

Hemorrhagic Fever Viruses as Biological Weapons

Medical and Public Health Management

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HEMORRHAGIC FEVER VIRUSES (HFVs) are the subject of the sixth article in a series on medical and public health management of civilian populations following use of biological weapons.¹⁻⁵ Historically, the term *viral hemorrhagic fever* (VHF) has referred to a clinical illness associated with fever and a bleeding diathesis caused by a virus belonging to 1 of 4 distinct families: Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae (TABLE 1).

Objective To develop consensus-based recommendations for measures to be taken by medical and public health professionals if hemorrhagic fever viruses (HFVs) are used as biological weapons against a civilian population.

Participants The Working Group on Civilian Biodefense included 26 representatives from academic medical centers, public health, military services, governmental agencies, and other emergency management institutions.

Evidence MEDLINE was searched from January 1966 to January 2002. Retrieved references, relevant material published prior to 1966, and additional sources identified by participants were reviewed.

Consensus Process Three formal drafts of the statement that synthesized information obtained in the evidence-gathering process were reviewed by the working group. Each draft incorporated comments and judgments of the members. All members approved the final draft.

Conclusions Weapons disseminating a number of HFVs could cause an outbreak of an undifferentiated febrile illness 2 to 21 days later, associated with clinical manifestations that could include rash, hemorrhagic diathesis, and shock. The mode of transmission and clinical course would vary depending on the specific pathogen. Diagnosis may be delayed given clinicians' unfamiliarity with these diseases, heterogeneous clinical presentation within an infected cohort, and lack of widely available diagnostic tests. Initiation of ribavirin therapy in the early phases of illness may be useful in treatment of some of these viruses, although extensive experience is lacking. There are no licensed vaccines to treat the diseases caused by HFVs.

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The HFVs are transmitted to humans via contact with infected animal reservoirs or arthropod vectors (the natural reservoirs and vectors of the

Ebola and Marburg viruses are unknown). The mode of transmission, clinical course, and mortality of these illnesses vary with the specific virus, but

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each is capable of causing a hemorrhagic fever syndrome. Clinical and epidemiological data are limited; outbreaks are sporadic and unanticipated, and there are few case series or clinical trials involving human subjects.

The Working Group on Civilian Bio-defense previously established a list of key features that characterize biological agents that pose particularly serious risks if used as biological weapons against civilian populations: (1) high morbidity and mortality; (2) potential for person-to-person transmission; (3) low infective dose and highly infectious by aerosol dissemination, with a commensurate ability to cause large outbreaks; (4) effective vaccine unavailable or available only in limited supply; (5) potential to cause public and health care worker anxiety; (6) availability of pathogen or toxin; (7) feasibility of large-scale production; (8) environmental stability; and (9) prior research and development as a biological weapon. Some HFVs exhibit a significant number of these key characteristics and pose serious risk as biological weapons, including Ebola and Marburg viruses (Filoviridae), Lassa fever and New World arenaviruses (Arenaviridae), Rift Valley fever (Bunyaviridae), and yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease (Flaviviridae).

Several viruses that can cause VHF will not be considered further in this analysis. Dengue is excluded because it is not transmissible by small-particle aerosol,⁷ and primary dengue causes VHF only rarely. Crimean-Congo hemorrhagic fever (CCHF) and the agents of hemorrhagic fever with renal syndrome (HFRS) also have been excluded after much deliberation. Although these pathogens can cause VHF and may be transmissible by small-particle aerosol, the working group noted that technical difficulties (ie, barriers to large-scale production) currently preclude their development as mass casualty weapons. Crimean-Congo hemorrhagic fever and the agents of HFRS do not readily replicate to high concentrations in cell cultures, a prerequisite for weaponization of an infectious organism. However, CCHF, the agents of HFRS, and dengue may carry great morbidity and mortality in naturally occurring outbreaks. In particular, CCHF may be transmitted from person to person, has a high case-fatality rate, and is endemic in central Asia and southern Africa. We acknowledge that technical difficulties may be overcome with advances in technology and science, and these excluded viruses may become a greater threat in the future. Other sources provide information on the viruses not addressed herein.⁸⁻¹²

The consequences of an unannounced aerosol attack with an HFV are the primary focus of this analysis. A variety of attack scenarios with these agents are possible. This analysis does not attempt to forecast the most likely but focuses on perhaps the most serious scenario. Understanding and planning for a covert aerosol attack with HFVs will improve preparedness for other scenarios as well.

CONSENSUS METHODS

The working group for this article was composed of 26 professionals from academic medical centers, public health, military services, governmental agencies, and emergency management institutions. MEDLINE databases were searched from January 1966 to January 2002 for the Medical Subject Headings *viral hemorrhagic fever, Ebola, Marburg, Lassa, arenavirus, Junin, Guanarito, Machupo, Sabia, CCHF, Rift Valley fever, hantavirus, dengue, yellow fever, Omsk hemorrhagic fever, Kyasanur Forest disease, biological weapons, biological terrorism, biological warfare, and biowarfare*. The references were reviewed and relevant materials published prior to 1966 were identified. The working group also identified other published and unpublished references for review.

Table 1. Hemorrhagic Fever Viruses*

| Family | Genus | Virus | Disease | Vector in Nature | Geographic Distribution |
|--------------|-------------|---|---|------------------|---|
| Filoviridae | Filovirus | Ebola† | Ebola hemorrhagic fever | Unknown | Africa |
| | | Marburg | Marburg hemorrhagic fever | Unknown | Africa |
| Arenaviridae | Arenavirus | Lassa | Lassa fever | Rodent | West Africa |
| | | New World Arenaviridae‡ | New World hemorrhagic fever | Rodent | Americas |
| Bunyaviridae | Nairovirus | Crimean-Congo hemorrhagic fever | Crimean-Congo hemorrhagic fever | Tick | Africa, central Asia, eastern Europe, Middle East |
| | Phlebovirus | Rift Valley fever | Rift Valley fever | Mosquito | Africa, Saudi Arabia, Yemen |
| | Hantavirus | Agents of hemorrhagic fever with renal syndrome | Hemorrhagic fever with renal syndrome | Rodent | Asia, Balkans, Europe, Eurasia§ |
| Flaviviridae | Flavivirus | Dengue | Dengue fever, Dengue hemorrhagic fever, and Dengue shock syndrome | Mosquito | Asia, Africa, Pacific, Americas |
| | | Yellow fever | Yellow fever | Mosquito | Africa, tropical Americas |
| | | Omsk hemorrhagic fever | Omsk hemorrhagic fever | Tick | Central Asia |
| | | Kyasanur Forest disease | Kyasanur Forest disease | Tick | India |

*Bold indicates hemorrhagic fever viruses that pose serious risk as biological weapons (addressed in this consensus statement).

†There are 4 subtypes of Ebola: Zaire, Sudan, Ivory Coast, and Reston.

‡The New World Arenaviridae include Machupo, the cause of Bolivian hemorrhagic fever; Junin, the cause of Argentine hemorrhagic fever; Guanarito, the cause of Venezuelan hemorrhagic fever; and Sabia, the cause of Brazilian hemorrhagic fever. An additional arenavirus has been isolated following 3 fatal cases of hemorrhagic fever in California, 1999-2000.⁹

§Additionally, the agents of hantavirus pulmonary syndrome have been isolated in North America.

A first draft resulted from the synthesis of information obtained during the evidence-gathering process. Members of the working group were convened to discuss the first draft of the formulated guidelines on January 10, 2002. Subsequently, a second draft was produced incorporating comments and judgments of the working group. They reviewed the second draft and submitted comments, which were incorporated into a third and final draft of the document.

HISTORY AND POTENTIAL AS BIOLOGICAL WEAPONS

Hemorrhagic fever viruses have been weaponized by the former Soviet Union, Russia, and the United States.¹³⁻¹⁵ There are reports that yellow fever may have been weaponized by North Korea.¹⁴ The former Soviet Union and Russia produced large quantities of Marburg, Ebola, Lassa, and New World arenaviruses (specifically, Junin and Machupo) until 1992.^{13,15} Soviet Union researchers quantified the aerosol infectivity of Marburg virus for monkeys, determining that no more than a few virions are required to cause infection.¹⁶ Yellow fever and Rift Valley fever viruses were developed as weapons by the US offensive biological weapons program prior to its termination in 1969.¹⁴ The Japanese terrorist cult Aum Shinrikyo unsuccessfully attempted to obtain Ebola virus as part of an effort to create biological weapons.¹⁷

Several studies have demonstrated successful infection of nonhuman primates by aerosol preparations of Ebola,¹⁸ Marburg,¹⁹ Lassa,²⁰ and New World arenaviruses.²¹ Arguments asserting that the absence of effective antiviral therapy and vaccines would make these viruses too dangerous to develop as weapons are not supported by the historical record.

In 1999, the Centers for Disease Control and Prevention (CDC) classified the HFVs as category A bioweapon agents, based on the potential to cause widespread illness and death, ease of dissemination or person-to-person transmission, potential for major public health impact, and requirement of special action for public health preparedness.²²

EPIDEMIOLOGY OF DISEASE TRANSMISSION

In nature, HFVs reside in animal hosts or arthropod vectors. The natural reservoir of filoviruses is unknown. Humans are infected incidentally, acquiring the disease by the bite of an infected arthropod, via aerosol generated from infected rodent excreta, or by direct contact with infected animal carcasses.²³ With the exception of Rift Valley fever and the diseases caused by flaviviruses (yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease), which are not transmissible from person to person, infected humans can spread the disease to close contacts, which may result in community outbreaks and nosocomial infections. Limited knowledge exists about transmission because outbreaks of these diseases are sporadic and unpredictable and often occur in areas without adequate medical and public health infrastructure. Outbreaks are usually well under way or have subsided by the time data gathering begins. The risks associated with various modes of transmission are not well defined because most persons who acquire these infections have a history of multiple contacts by multiple modes. Infections acquired percutaneously are associated with the shortest incubation period and highest mortality. Person-to-person airborne transmission appears to be rare but cannot be ruled out.

Filoviridae: Ebola and Marburg

Since 1967, when the first outbreak of VHF caused by Marburg virus occurred in Germany and Yugoslavia, there have been 18 reports of human outbreaks of VHF secondary to Ebola or Marburg viruses, resulting in approximately 1500 cases to date.²⁴ Most have occurred in Africa. Epidemiological investigation indicates that most cases occurred after direct contact with blood, secretions, or tissues of infected patients or nonhuman primates.

Several cases have followed needle-stick injuries. During the 1976 Ebola epidemic in Zaire (now Democratic Republic of the Congo), 85 (26.7%) of 318 cases occurred in individuals who had re-

ceived an injection, and every case of disease acquired by contaminated syringes resulted in death.²⁵ Mortality was substantially higher when the disease was acquired percutaneously. Evidence suggests that percutaneous exposure to very low inocula can result in infection.²⁶

Filoviruses can also be transmitted by mucosal exposure. Experiments in non-human primates have documented transmission of infection after direct administration of Marburg virus into the mouths and noses of experimental animals²⁷ and after direct administration of Ebola virus into the mouths or conjunctiva²⁸ of experimental animals. Human infections might occur through contact of contaminated fingers with oral mucosa or conjunctiva,²⁹ but direct evidence is lacking.

Copious numbers of Ebola viral particles found in human skin and lumina of sweat glands have raised concern that disease transmission may occur from touching an infected patient or corpse.³⁰ In the 1995 Ebola outbreak in Kikwit, Democratic Republic of the Congo, several persons preparing bodies for burial acquired the infection.³¹⁻³³ According to local custom, burial practices may involve washing the body and cutting the hair and nails of the corpse.³⁴ However, a study using guinea pigs was unable to document Marburg virus transmission through intact skin, while infection through skin lesions did occur.³⁵

A few cases of disease transmission by uncertain mechanisms described in 2 recent Ebola outbreaks,^{36,37} and findings from animal studies^{16,18,38} and 1 outbreak of Ebola in nonhuman primates,³⁹ raise concern about the potential for person-to-person transmission by way of small-droplet airborne nuclei. However, to date, Ebola epidemics in Africa were ultimately controlled and ended without use of specific airborne precautions. (HICPAC's definitions of standard, contact, droplet, and airborne precautions are at <http://www.cdc.gov/ncidod/hip/isolat/isopart2.htm>.)

Airborne transmission of Marburg virus was not observed in the 1967 outbreak in Germany and Yugoslavia fol-

lowing the importation of infected African green monkeys from eastern Africa.⁴⁰ In 1975, only 1 of 35 health care workers who cared for 2 patients with Marburg disease in South Africa without any barrier precautions became ill.⁴¹ In 1979, an outbreak of Ebola in southern Sudan infected 34 people. Although direct physical contact could not be established in 2 instances, 29 cases resulted from direct physical contact with an infected person and there were no cases of illness among 103 persons who were exposed to cases in confined spaces without any physical contact.⁴² In 1994, only 1 of 70 contacts of a patient with Ebola acquired the disease despite lack of airborne precautions.⁴³ In 1996, none of the 300 contacts of 2 patients with Ebola acquired the disease⁴⁴ despite involvement in numerous hazardous procedures prior to the patients' diagnosis, protected only by standard blood and bodily fluid precautions.

In 1995, 316 people became ill with Ebola in the Democratic Republic of the Congo; 25% of the cases involved health care workers. When barrier precautions were instituted, only 3 health care workers became infected. One was non-adherent to barrier precautions, the second had a needlestick injury, and it is speculated that the third, who always used protective equipment, became infected after touching her eyes with a contaminated glove.⁴⁵ None of the 78 household members who did not have direct physical contact with an infected person developed disease.³¹ However, in this outbreak, the only risk factor identified for 5 patients was visiting an infected patient in the absence of physical contact. These few cases led researchers to conclude that airborne transmission could not be ruled out³⁷ but seemed to be, at most, a minor mode of transmission.

In 2000, 224 people died in Uganda during an Ebola outbreak.³⁷ Fourteen (64%) of 22 medical personnel were infected after institution of isolation wards and infection control measures³⁷ including donning gowns, gloves, and shoe covers, standard surgical masks, and either goggles or eye glasses.⁴⁶ It is

not clear whether lack of adherence to guidelines contributed to nosocomial cases in this outbreak, but airborne transmission could not be ruled out.

Although Marburg virus has been isolated from healthy-appearing infected monkeys several days before clinical signs appear,²⁷ no transmission has been observed in this stage.⁴⁰ In humans, transmission of Ebola during the incubation period does not appear to be common.³¹ Transmissibility of Ebola increases with the duration of disease, and direct physical contact with an ill person during the late phase of clinical illness confers an additional risk.³¹ There has been only 1 reported case, during the outbreak in Zaire in 1976, in which the only possible source of infection was contact with an unconfirmed case hours before the patient developed symptoms.²⁵ The preponderance of evidence suggests that transmission of Ebola and Marburg virus rarely, if ever, occurs before the onset of signs and symptoms.

In several studies after the 1995 Kikwit outbreak, Ebola was detected in the seminal fluid of convalescing patients by reverse transcriptase polymerase chain reaction (RT-PCR) up to 101 days after disease onset,^{47,48} and virus was isolated 82 days after disease onset in the seminal fluid of 1 patient.⁴⁸ Marburg has been isolated 83 days after disease onset from the seminal fluid of a patient who may have sexually transmitted the disease to his spouse.⁴⁰

Arenaviridae: Lassa Fever and New World Arenaviruses

In nature, arenaviruses are transmitted to humans via inhalation of aerosols present in rodent urine and feces,⁴⁹ by ingestion of food contaminated with rodent excreta, or by direct contact of rodent excreta with abraded skin and mucous membranes.⁵⁰ Like filoviruses, person-to-person transmission of the arenaviruses occurs predominantly by direct contact with infectious blood and bodily fluids. A number of nosocomial outbreaks of Lassa fever⁵¹⁻⁵³ and of New World arenaviruses⁵⁴ have occurred via this mecha-

nism. As with filoviruses, person-to-person airborne transmission has been suspected in a few instances.

In 1969, during a nosocomial outbreak in Nigeria, an index patient with severe pulmonary involvement caused 16 secondary cases in persons who shared the same hospital ward with her. Airborne transmission was believed to have contributed to this outbreak, as there were no tertiary cases of Lassa fever in the hospital, despite the admission of Lassa fever-infected patients to other hospital wards.⁵¹ However, there is no definitive evidence of airborne transmission and the exact mechanisms of disease transmission during that outbreak remain unknown. Conversely, in the case of 1 Lassa fever-infected individual who traveled from Sierra Leone to the United States, no cases were detected in 522 contacts, even prior to initiating additional barrier precautions beyond standard precautions.⁵⁵ In another instance, in which an infected individual originated in Nigeria and traveled to St Thomas in the US Virgin Islands, none of the 159 people who had direct contact with the patient developed clinical or serological evidence of infection, even though they attended to the patient, without barrier precautions, during a 5-day period before the diagnosis.⁵⁶

Airborne transmission of Bolivian hemorrhagic fever has been implicated after a student became infected after watching a nursing instructor demonstrate the changing of bed linens of an infected patient, although the student did not touch the patient or any objects in the room and kept a distance of greater than 6 ft from the patient.⁵⁴ Conversely, approximately 80 involved health care workers who did not use airborne precautions remained healthy. Definitive evidence of person-to-person airborne transmission is lacking but, in these rare instances, there have been no plausible alternative explanations.

There have been no reports documenting transmission of arenaviruses by infected persons during the incubation period.^{54,57} However, Lassa fever virus can be detected in semen up to 3 months

Table 2. Microbiology of Hemorrhagic Fever Viruses⁷¹

| Family | Diameter, nm | Morphology | Presence of Envelope | Genome | | |
|--------------|--------------|---------------------------|----------------------|-----------|-----------------------|----------------------------|
| | | | | Size, kbp | Nature* | Configuration* |
| Filoviridae | 80 | Bacilliform (filamentous) | Yes | 19 | Single-strand RNA (-) | Nonsegmented (1 - segment) |
| Arenaviridae | 110-130 | Spherical | Yes | 11 | Single-strand RNA (±) | 2 ± Segments |
| Bunyaviridae | 80-120 | Spherical | Yes | 11-19 | Single-strand RNA (-) | 3 - Segments |
| Flaviviridae | 40-50 | Isometric | Yes | 10-12 | Single-strand RNA (+) | Nonsegmented (1 + segment) |

*Minus sign indicates negative-strand genome; plus sign, positive-strand genome; and plus/minus sign, ambisense genome.

after acute infection⁵⁸ and in urine 32 days after disease onset,⁵⁹ and Argentine hemorrhagic fever has been transmitted to spouses of convalescent patients 7 to 22 days after onset of illness.⁶⁰

Bunyaviridae: Rift Valley Fever

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.⁶¹ Ingestion of contaminated raw animal milk has been implicated epidemiologically.⁶² Despite high levels of viremia and isolation of low titers of virus from throat washings, there are no reported cases of person-to-person transmission of Rift Valley fever.⁶² However, laboratory technicians are at risk of acquiring the disease by inhalation of infectious aerosols generated from specimens.^{61,63}

If Rift Valley fever were used as a biological weapon, susceptible domestic livestock (sheep, cattle, buffalo, and goats) could also be infected. Infected livestock develop high levels of viremia, sufficient to infect susceptible mosquito vectors and lead to establishment of the disease in the environment⁶¹ and large epizootic epidemics, as occurred in Egypt in 1977⁶⁴ and the Arabian peninsula in 2000.⁶⁵ Several genera of mosquitoes (eg, *Aedes*, *Anopheles*, and *Culex*) in the United States have the capacity to act as vectors of Rift Valley fever.^{66,67}

Flaviviridae: Yellow Fever, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease

Humans acquire yellow fever virus from the bite of an infected mosquito⁶⁸ and acquire Omsk hemorrhagic fever and Kyasanur Forest disease viruses from the

bite of an infected tick.⁶⁹ There are no reported cases of person-to-person transmission or nosocomial spread of flaviviruses. Infection of laboratory personnel via inhalation of aerosols during cultivation of these viruses has been reported.^{69,70} As with Rift Valley fever, there is a theoretical risk of flaviviruses becoming established in an environment following infection of susceptible arthropod vectors.

MICROBIOLOGY AND PATHOGENESIS

All of the HFVs are small RNA viruses with lipid envelopes. Specific microbiological characteristics of these viruses are listed in TABLE 2.

Information regarding the pathogenesis of these agents following infection in humans is incomplete. Most data have been derived from clinical observations and experimentally induced disease in nonhuman primates. Interpretation of data derived from animal studies may be confounded by a series of factors, such as the species of the animal, the route of inoculation, and the virus dose.⁴⁰

All of the viruses of concern may lead to thrombocytopenia, and data suggest that platelet dysfunction is present in Ebola, Lassa fever, and Argentine hemorrhagic fever.⁷² Reduced levels of coagulation factors may be secondary to hepatic dysfunction and/or disseminated intravascular coagulation and are most prominent in Rift Valley fever and yellow fever.⁷² In addition, Ebola and Marburg viruses may lead to a hemorrhagic diathesis through direct damage of cells involved in hemostasis (such as platelets and endothelial cells) and/or indirectly through immunological and inflammatory pathways.⁷²

Filoviruses are extremely virulent in nonhuman primates and humans.⁷³ Necrosis of visceral organs (such as liver, spleen, and kidneys) has been associated with both direct viral-induced cellular damage and impairment of the microcirculation. Filoviruses are cytotoxic to cells. In general, inflammatory infiltration is absent in the affected visceral organs.⁷⁴ Even when viral titers in the lungs of monkeys are elevated, the virus is not apparent in the alveoli or airways, occurring primarily in the vascular structures.²⁸ All experimentally infected monkeys develop disseminated intravascular coagulation. Ebola, but not Marburg virus, makes a secreted form of its glycoprotein that has been suggested to have a role in virulence.⁷³ Endothelial cells support Marburg virus replication, and their destruction may contribute to the associated hemorrhagic diathesis and shock.⁷⁵

Infection with arenaviruses is initiated in nasopharyngeal mucosa.⁷⁶ Arenaviruses produce carrier states in rodents, their natural hosts, and viral multiplication is not associated with extensive cell damage. In vitro infections with Arenaviridae show that virus spreads throughout a variety of different cellular monolayers, with little or absent cytopathic effects⁷⁷; hence, it is believed that these viruses may exert their effects (at least in part) by inducing the secretion of inflammatory mediators from macrophages. Following experimental infection of nonhuman primates with arenaviruses, virtually all tissues become infected, with little histologic evidence of damage.⁷⁸ Hemorrhage following arenavirus infection appears to be associated with the presence of a circulating inhibitor of platelet aggregation and thrombocytopenia.

However, disseminated intravascular coagulation does not appear to be a central pathogenic mechanism.⁷⁹ Lassa fever appears to be terminated by a cellular, not humoral, immune response,⁷⁷ whereas in New World arenaviruses, recovery is preceded by cellular and humoral immune responses.⁸⁰

In contrast with arenaviruses, Rift Valley fever virus leads to destruction of infected cells.⁷⁷ The hemostatic derangements in Rift Valley fever are poorly understood, and a combination of vasculitis and hepatic necrosis has been postulated.^{81,82} Interferon alfa given shortly before or after experimental infection with Rift Valley fever virus has been

shown to protect rhesus monkeys from viremia and hepatocellular damage.⁸³ Clinical recovery is associated with appearance of neutralizing antibodies, and passive immunization prevented development of viremia in nonhuman primates inoculated with the virus.⁸³

Like Rift Valley fever, yellow fever virus leads to destruction of infected cells. Hepatocyte infection and degeneration is a late event in the course of infection,⁸⁴ associated with virtually no inflammation.⁶⁸ Neutralizing antibodies correlate with clearance of viremia, and paradoxically, with the second phase of illness, when patients may develop hemorrhage and shock.⁶⁸

Little is known about the pathogenesis of Omsk hemorrhagic fever and Kyasanur Forest disease viruses. Findings from postmortem examinations of 3 individuals who died of Kyasanur Forest disease showed degeneration of the larger visceral organs (especially liver and spleen) and hemorrhagic pneumonia.⁸⁵

CLINICAL MANIFESTATIONS

Information on the clinical manifestations of these diseases is derived from naturally occurring outbreaks. Although data derived from experimentally infected animals do not support marked differences in the clinical presentation according to route of expo-

Table 3. Clinical Characteristics of Hemorrhagic Fever Viruses Noted in Past Case Series or Outbreaks

| Virus | Distinctive Clinical Features | Person-to-Person Transmission | Incubation Period, d | Mortality, % | Treatment |
|---|--|-------------------------------|----------------------|--------------|-----------------------|
| Ebola ^{25,42-44,47,86,99} | High fever and severe prostration. A diffuse maculopapular rash may occur by day 5 of illness. Bleeding and disseminated intravascular coagulation are common. | Yes | 2-21 | 50-90* | Supportive |
| Marburg ^{40,41,87,102} | High fever, myalgias. Nonpruritic maculopapular rash of the face, neck, trunk, and arms may develop. Bleeding and disseminated intravascular coagulation are common. | Yes | 2-14 | 23-70† | Supportive |
| Lassa fever ^{52,88-91,100,101,110} | Gradual onset of fever, nausea, abdominal pain, severe sore throat, cough, conjunctivitis, ulceration of buccal mucosa, exudative pharyngitis, and cervical lymphadenopathy. Late signs include severe swelling of head and neck; pleural and pericardial effusions. Hemorrhagic complications less common. | Yes | 5-16 | 15-20 | Ribavirin, supportive |
| New World Arenaviruses ^{54,92,128} | Gradual onset of fever, myalgias, nausea, abdominal pain, conjunctivitis, flushing of face and trunk, and generalized lymphadenopathy. May develop petechiae, bleeding, and central nervous system dysfunction (tremors of the tongue and upper extremities, myoclonic movements, dysarthria, and generalized seizures). | Yes | 7-14 | 15-30 | Ribavirin, supportive |
| Rift Valley fever ^{61,93-96} | Fever, headache, retro-orbital pain, photophobia, and jaundice. Less than 1% develop hemorrhagic fever or encephalitis. Retinitis affects approximately 10%, which may occur at time of acute febrile illness or up to 4 weeks later. | No | 2-6 | <1 | Ribavirin, supportive |
| Yellow fever ^{68,97} | Fever, myalgias, facial flushing, and conjunctival injection. Patients either recover or enter a short remission followed by fever, relative bradycardia, jaundice, renal failure, and hemorrhagic complications. | No | 3-6 | 20 | Supportive |
| Omsk hemorrhagic fever ^{69‡} | Fever, cough, conjunctivitis, papulovesicular eruption on the soft palate, marked hyperemia of the face and trunk (but no rash), generalized lymphadenopathy, and splenomegaly. Some patients may develop pneumonia and central nervous system dysfunction. | No | 2-9 | 0.5-10 | Supportive |
| Kyasanur Forest disease ^{69,98} | Similar to Omsk but biphasic illness: first phase lasts 6-11 days and is followed by an afebrile period of 9-21 days. Up to 50% of patients relapse and develop meningoencephalitis. | No | 2-9 | 3-10 | Supportive |

*Reported Ebola data are for Sudan (50%) and Zaire (90%) subtypes. The Ivory Coast subtype has an indeterminate case-fatality rate, as there has been a single nonfatal human case. The Reston subtype causes subclinical infection in humans.

†Mortality ranges from 23% in the 1967 outbreak in Germany to 70% in the largest outbreak of 1999 in the Democratic Republic of the Congo.

‡Also Sergey Netesov, MD, written communication, February 27, 2002.

sure (parenteral vs aerosol),^{18,21} it is not possible to be certain that the same manifestations would follow bioweapons attacks on humans.

There are a variety of potential clinical manifestations following infection with these viruses, and not all patients develop the classic VHF syndrome. Clinical manifestations are nonspecific and may include fever, myalgias, rash, and encephalitis. The propensity to cause the classic VHF syndrome also differs among agents. Therefore, in the event of a bioterrorist attack with one of these agents, infected patients may have a variety of clinical presentations, complicating early detection and management. It may not be possible to differentiate among these diseases on clinical grounds alone, although a number of specific clinical features may be useful clues to diagnosis (TABLE 3).

The overall incubation period for HFVs ranges from 2 to 21 days. Patients initially exhibit a nonspecific prodrome, which typically lasts less than 1 week. Symptoms typically include high fever, headache, malaise, arthralgias, myalgias, nausea, abdominal pain, and nonbloody diarrhea. Filoviruses, Rift Valley fever, and flaviviruses are characterized by an abrupt onset, while arenaviruses have a more insidious onset.^{40,54,61,68,69,99,100}

Early signs typically include fever, hypotension, relative bradycardia, tachypnea, conjunctivitis, and pharyngitis. Most diseases are associated with cutaneous flushing or a skin rash (FIGURE 1 and FIGURE 2), but the specific characteristics of the rash vary with each disease (Table 3). Later, patients may show signs of progressive hemorrhagic diathesis, such as petechiae, mucous membrane and conjunctival hemorrhage (FIGURE 3); hematuria; hematemesis; and melena. Disseminated intravascular coagulation and circulatory shock may ensue. Central nervous system dysfunction may be present and manifested by delirium, convulsions, cerebellar signs, or coma and imparts a poor prognosis.

The differential diagnosis includes a variety of viral and bacterial diseases:

influenza, viral hepatitis, staphylococcal or gram-negative sepsis, toxic shock syndrome, meningococemia, salmonellosis and shigellosis, rickettsial diseases (such as Rocky Mountain spotted fever), leptospirosis, borreliosis, psittacosis, dengue, hantavirus pulmonary syndrome, malaria, trypanosomiasis, septicemic plague, rubella, measles, and hemorrhagic smallpox. Noninfectious processes associated with bleeding diathesis that should be included in the differential diagnosis include idiopathic or thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acute leukemia, and collagen-vascular diseases.

Laboratory abnormalities include leukopenia (except in some cases of Lassa fever, in which leukocytosis occurs), anemia or hemoconcentration, thrombocytopenia, and elevated liver enzymes. Jaundice is typical in Rift Valley fever and yellow fever.^{61,68} In addition, coagulation abnormalities may include prolonged bleeding time, prothrombin time, and activated partial thromboplastin time; elevated fibrin degradation products; and decreased fibrinogen. Urinalysis may reveal proteinuria and hematuria, and patients may develop oliguria and azotemia.^{26,40,54,61,68,100,101}

Convalescence may be prolonged and complicated by weakness, fatigue, anorexia, cachexia, alopecia, and arthralgias.^{43,45} Reported clinical sequelae include hearing or vision loss, impaired motor coordination, transverse myelitis, uveitis, pericarditis, orchitis, parotitis, and pancreatitis.^{40,36,52,54,61,102}

The case-fatality rate varies markedly among these agents, ranging from as low as 0.5% for Omsk hemorrhagic fever⁶⁹ to as high as 90% for Ebola (subtype Zaire).³³ Death is typically preceded by hemorrhagic diathesis, shock, and multiorgan system failure 1 to 2 weeks following onset of symptoms.

DIAGNOSIS

A high index of suspicion will be required to diagnose VHF among persons exposed to a covert bioterrorist attack. In naturally occurring cases, patients are likely to have risk factors

Figure 1. Maculopapular Rash in Marburg Disease



A nonpruritic maculopapular rash (resembling the rash of measles) may occur in up to 50% of patients infected with the Ebola or Marburg viruses within the first week of illness. The rash is more common in light-colored skin and desquamates on resolution. Reprinted with permission from Thieme (Martini GA, Knauff HG, Schmidt HA, et al. A hitherto unknown infectious disease contracted from monkeys. *Ger Med Mon.* 1968;13:457-470).

Figure 2. Erythematous Rash in Bolivian Hemorrhagic Fever



This macular, flushed, erythematous rash that blanches with pressure may be associated with infections caused by arenaviruses. The rash most commonly involves the face and thorax and may desquamate on convalescence. Reprinted with permission from Current Science/Current Medicine (Peters CJ, Zaki SR, Rollin PE. Viral hemorrhagic fevers. In: Fekety R, vol ed. *Atlas of Infectious Diseases, Volume VIII.* Philadelphia, Pa: Churchill Livingstone; 1997:10.1-10.26).

Figure 3. Ocular Manifestations in Bolivian Hemorrhagic Fever



Ocular manifestations associated with hemorrhagic fever viruses range from conjunctival injection to subconjunctival hemorrhage, as seen in this patient. Reprinted with permission from Current Science/Current Medicine (Peters CJ, Zaki SR, Rollin PE. Viral hemorrhagic fevers. In: Fekety R, vol ed. *Atlas of Infectious Diseases, Volume VIII.* Philadelphia, Pa: Churchill, Livingstone; 1997:10.1-10.26).

such as travel to Africa or Asia, handling of animal carcasses, contact with sick animals or people, or arthropod

Box 1. Key Medical and Public Health Interventions After Identification of Suspected Index Case of VHF

Identification

Identify suspected index case using these clinical criteria:* temperature $\geq 101^{\circ}\text{F}$ (38.3°C) of < 3 weeks' duration; severe illness, and no predisposing factors for hemorrhagic manifestations; and at least 2 of the following hemorrhagic symptoms: hemorrhagic or purple rash, epistaxis, hematemesis, hemoptysis, blood in stools, other, and no established alternative diagnosis.

Reporting

1. Report immediately to local and/or state health department.
2. Report immediately to infection control professional and laboratory personnel.

Treatment

1. Initiate supportive and ribavirin therapy (see Table 4) immediately while diagnostic confirmation is pending.
2. If infection with arenavirus or bunyavirus is confirmed, continue 10-day course of ribavirin.
3. If infection with filovirus or flavivirus is confirmed, or if the diagnosis of VHF is excluded or an alternative diagnosis is established, discontinue ribavirin.

Infection Control Measures

1. Initiate VHF-specific barrier precautions.
2. Initiate airborne precautions, with negative-pressure rooms if resources are available.

Public Health Measures

1. Confirm or exclude diagnosis via Laboratory Response Network.
2. Designated public health authority begins epidemiologic investigation.
3. Identify close and high-risk contacts and place under medical surveillance for 21 days from day of suspected/known exposure.
4. If contact does not have temperature $\geq 101^{\circ}\text{F}$ (38.3°C) or signs or symptoms of VHF by the end of 21 days, discontinue medical surveillance.
5. If contact has temperature $\geq 101^{\circ}\text{F}$ (38.3°C) or signs or symptoms consistent with VHF, initiate diagnostic workup and treatment, infection control, and public health interventions described for index case.

*Criteria are adapted from the World Health Organization's surveillance standards for acute hemorrhagic fever syndrome.¹⁰³

bites within 21 days of onset of symptoms. No such risk factors would be associated with a bioterrorist attack. The variable clinical presentation of these diseases presents a major diagnostic challenge. Clinical microbiology and public health laboratories are not currently equipped to make a rapid diagnosis of any of these viruses, and clinical specimens would need to be sent to the CDC or the US Army Medical Research Institute of Infectious Diseases (USAMRIID; Frederick, Md), the only 2 level D laboratories in the Laboratory Response Network. There are future plans to decentralize the process required for the laboratory confirmation of these viruses by equipping selected US

public health laboratories in the Laboratory Response Network with standard diagnostic reagents. This would likely expedite laboratory confirmation of suspected cases in the event of an outbreak (Michael Ascher, MD, written communication, February 26, 2002).

All suspected cases of HFV disease should be immediately reported to local and/or state health departments (BOX 1), who would then notify the CDC. The World Health Organization has developed surveillance standards for acute VHF syndrome with the aim of early detection of naturally occurring outbreaks and notification of cases, even before identification of the causal agent.¹⁰³ This includes prompt report-

ing to public health authorities of any patient with acute onset of fever of less than 3 weeks' duration who is severely ill, has no known predisposing host factors for hemorrhagic manifestations, and has any 2 of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in stool, or other hemorrhagic symptom. This broad definition may be useful in the early period following a confirmed bioterrorist-related case of VHF as well. Public health authorities may develop more specific case definitions after the etiologic agent is identified.

Public health authorities, in consultation with the CDC, should provide assistance and detailed instructions to clinical laboratories and to clinicians for processing and transport of laboratory specimens required for diagnosis of these agents. (See "Packaging Protocols for Biological Agents/Diseases" at <http://www.bt.cdc.gov/Agent/VHF/VHF.asp>.)

Methods of diagnosis at specialized laboratories include antigen detection by antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM antibody detection by antibody-capture ELISA, RT-PCR, and viral isolation. Antigen detection (by ELISA) and RT-PCR are the most useful diagnostic techniques in the acute clinical setting. Viral isolation is of limited value because it requires a biosafety level 4 (BSL-4) laboratory. (A full description of BSL-4 criteria is available at <http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s3.htm>.) There are only 2 BSL-4 facilities in the United States, located at the CDC and the USAMRIID, with in-depth diagnostic capability. Either the presence of IgM or a 4-fold rise in titer of IgG antibody between acute- and convalescent-phase serum samples are diagnostic of these viral illnesses, but antibody-capture ELISA is of limited value in early diagnosis because antibodies to these viruses usually do not appear until onset of recovery, approximately at the second week of illness. The CDC requires approximately 1 working day (with prior notification of arrival) to offer a preliminary laboratory diagnosis following receipt of patient specimens.

The diagnosis of VHF should be based initially on clinical criteria and judgment, with laboratory testing used to confirm or exclude this clinical diagnosis. Laboratory testing will require time and, in the event of a large attack, may be delayed or perhaps not possible given current laboratory capacities.

TREATMENT

The mainstay of treatment of VHF is supportive, with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. Because in some cases intravenous fluids have not reversed hypotension and may have contributed to pulmonary edema,¹⁰⁴ consideration should be given to early vasopressor support with hemodynamic monitoring. Mechanical ventilation, renal dialysis, and antiseizure therapy may be required. Intramuscular injections, aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulant therapies are contraindicated. Steroids are not indicated.⁹

Drug Therapy

There are no antiviral drugs approved by the US Food and Drug Administration (FDA) for treatment of HFVs. Ribavirin, a nucleoside analog, has some in vitro and in vivo activity against Arenaviridae and Bunyaviridae (including CCHF) but no utility against Filoviridae or Flaviviridae. Oral ribavirin, in combination with interferon alfa, is FDA-approved for treatment of chronic hepatitis C virus infection. Intravenous ribavirin is of limited availability in the United States. It is produced by ICN Pharmaceuticals Inc (Costa Mesa, Calif) for compassionate use under an investigational new drug (IND) application. Although a risk of human teratogenicity has not been demonstrated for ribavirin, its pharmacologic action and its teratogenicity and embryolethality in several animal species raise concern that such a risk may exist with maternal therapy during pregnancy. Therefore, ribavirin is classified as a pregnancy category X drug, and is contraindicated in pregnancy.¹⁰⁵ The primary adverse effect caused by riba-

Table 4. Recommendations for Ribavirin Therapy in Patients With Clinically Evident Viral Hemorrhagic Fever of Unknown Etiology or Secondary to Arenaviruses or Bunyaviruses*

| | Contained Casualty Setting | Mass Casualty Setting† |
|-----------------|---|---|
| Adults | Loading dose of 30 mg/kg intravenously (IV) (maximum, 2 g) once, followed by 16 mg/kg IV (maximum, 1 g per dose) every 6 hours for 4 days, followed by 8 mg/kg IV (maximum, 500 mg per dose) every 8 hours for 6 days | Loading dose of 2000 mg orally once, followed by 1200 mg/d orally in 2 divided doses (if weight >75 kg), or 1000 mg/d orally in 2 doses (400 mg in AM and 600 mg in PM) (if weight ≤75 kg) for 10 days‡ |
| Pregnant women§ | Same as for adults | Same as for adults |
| Children | Same as for adults, dosed according to weight | Loading dose of 30 mg/kg orally once, followed by 15 mg/kg per day orally in 2 divided doses for 10 days |

*Recommendations are not approved by the US Food and Drug Administration for any of these indications and should always be administered under an investigational new drug protocol. However, in a mass casualty setting, these requirements may need to be modified to permit timely administration of the drug.

†The threshold number of cases at which parenteral therapy becomes impossible depends on a variety of factors, including local health care resources.

‡Although a similar dosage (1000 mg/d in 3 divided doses) has been used in a small number of patients with Lassa fever,¹⁰⁶ this regimen would be impractical because the current formulation of oral ribavirin in the United States consists of 200-mg capsules, and ribavirin capsules may not be broken open.

§Refer to the section in text on treatment of pregnant women for details.

virin is a dose-related, reversible, hemolytic anemia. However, a range of cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients treated with combination ribavirin-interferon therapy for hepatitis C.¹⁰⁵

Small trials have shown that ribavirin may reduce mortality after infection with Lassa fever¹⁰⁶ and select New World arenaviruses.^{57,107} Ribavirin does not penetrate the brain well; therefore, it is not expected to be particularly effective against the neurological effects of these pathogens.^{57,108} Intravenous ribavirin given within the first 6 days of fever to patients with Lassa fever who had high levels of viremia decreased mortality from 76% to 9%.¹⁰⁷ A controlled trial of 18 patients with Argentine hemorrhagic fever resulted in 12.5% mortality in treated patients compared with 40% in untreated patients.¹⁰⁸

Recommendations for drug therapy by the working group are not approved by the FDA for any of these indications and should always be administered under an IND protocol. In a mass casualty situation, these requirements may need to be modified to permit timely administration of the drug. In addition, treatment of other suspected possible causes, such as bacterial sepsis, should not be withheld while await-

ing confirmation or exclusion of the diagnosis of VHF.

In a contained casualty situation (in which a modest number of patients require therapy), the working group recommends that an intravenous regimen of ribavirin be given as described in TABLE 4, in accordance with CDC's recommendations for treating patients with suspected VHF of unknown cause, pending identification of the agent.¹⁰⁹ A similar dose has been used in the treatment of Lassa fever.¹⁰⁶

In a mass casualty situation (in which the number of persons requiring therapy is sufficiently high that delivery of intravenous therapy is no longer possible), an oral regimen of ribavirin as described in Table 4 is recommended. This dose is currently licensed for treatment of chronic hepatitis C infection in the United States.¹⁰⁵ Although it is substantially lower than that in the intravenous regimen, a similar dose has been used to treat a few patients with Lassa fever,¹⁰⁶ and there are no available studies on tolerability or efficacy of higher doses of oral ribavirin.

Ribavirin is contraindicated in pregnancy. However, in the context of infection with VHF of unknown cause or secondary to an arenavirus or Rift Valley fever, the working group believes that the benefits appear likely to outweigh

any fetal risk of ribavirin therapy, and ribavirin is therefore recommended. The associated mortality of VHF tends to be higher in pregnancy.¹¹⁰

The use of oral or intravenous ribavirin is not approved by the FDA for children, and proper doses have not been established. Only aerosolized ribavirin has been approved by the FDA for children, to treat respiratory syncytial virus infection. However, in the context of infection with VHF of unknown cause or secondary to an arenavirus or Rift Valley fever, the working group believes that the benefits likely outweigh the risks of ribavirin therapy, and it is therefore recommended as described in Table 4. Similar doses have been used to treat children with adenovirus pneumonia¹¹¹ and hepatitis C¹¹² and were well tolerated. Ribavirin capsules may not be broken open and are only available in 200-mg doses. However, Schering-Plough Corp (Kenilworth, NJ) produces a pediatric syrup formulation (which is not commercially available) for use under an IND application.

For infections caused by filoviruses or flaviviruses, the working group recommends supportive medical care only. Ribavirin has been shown to have no clinical utility against these groups of viruses.

Passive Immunization

Studies and case reports evaluating convalescent plasma as therapy (or prophylaxis) of the diseases caused by HFVs have yielded mixed results depending on the disease, with some reports suggesting clinical utility^{26,80,82,101,113-117} and other studies showing no benefit.^{52,106,118} Passive immunization has also been associated with enhanced viral replication in experimentally infected animals.¹¹⁹ The logistics of collection, testing, and storing immune convalescent plasma are formidable. In the United States, the paucity of survivors of these diseases and the lack of a national program that collects and stores HFV immune plasma preclude its use in the initial response to a bioterrorist attack. Development of methods to manufacture monoclonal an-

tibodies and recent advances in selecting highly effective human-derived or humanized products may provide new approaches to therapy in the future.

POSTEXPOSURE PROPHYLAXIS

Effective prophylaxis following exposure to an HFV is hampered by the absence of effective vaccines and antiviral medications. The working group does not recommend preemptive administration of ribavirin in the absence of signs of infection to persons with known or suspected exposures to the HFVs. Ribavirin has no utility against filoviruses or flaviviruses. For arenaviruses, there is limited experimental evidence that post-exposure prophylaxis with ribavirin will delay onset of disease but not prevent it.^{120,121} Furthermore, the effectiveness of ribavirin as postexposure prophylaxis for arenaviruses or Rift Valley fever virus has never been studied in humans. While 1995 CDC guidelines recommend ribavirin to high-risk contacts of patients with Lassa fever,¹⁰⁹ a review and possible revision of these recommendations is to be shortly undertaken (James Hughes, MD, oral communication, January 10, 2002). However, public health professionals suggest that stratification of risk groups into high-risk and close contacts may facilitate counseling and outbreak investigation. High-risk contacts are those who have had mucous membrane contact with a patient (such as during kissing or sexual intercourse) or have had a percutaneous injury involving contact with the patient's secretions, excretions, or blood. Close contacts are those who live with, shake hands with, hug, process laboratory specimens from, or care for a patient with clinical evidence of VHF prior to initiation of appropriate precautions.

Persons considered potentially exposed to HFVs in a bioterrorist attack and all known high-risk and close contacts of patients diagnosed with VHF should be placed under medical surveillance. All such individuals should be instructed to record their temperatures twice daily and report any temperature of 101°F (38.3°C) or higher (or any

symptom noted in Table 3) to a clinician, hospital epidemiologist, or public health authority designated with surveillance. Surveillance should be continued for 21 days after the person's deemed potential exposure or last contact with the ill patient.

If a temperature of 101°F (38.3°C) or higher develops, ribavirin therapy should be initiated promptly as presumptive treatment of VHF, as described in Table 4, unless an alternative diagnosis is established or the etiologic agent is known to be a filovirus or a flavivirus. In the case of close and high-risk contacts of patients diagnosed with Rift Valley fever or a flavivirus, only those who process laboratory specimens from a patient prior to initiation of appropriate precautions require medical surveillance, as these specific viruses are not transmitted from person to person but may be transmitted in the laboratory setting.

VACCINE

With the exception of yellow fever live attenuated 17D vaccine, which is highly effective when administered to travelers to endemic areas,⁶⁸ there is no licensed vaccine for any of the HFVs. The yellow fever vaccine is produced in limited supply, and world stocks are not sufficient to meet a surge.¹²² This vaccine would not be useful in preventing disease if given in the postexposure setting because yellow fever has a short incubation period of 3 to 6 days, and neutralizing antibodies take longer to appear following vaccination.⁶⁸

INFECTION CONTROL

Given the lack of licensed or effective therapies and vaccines against the HFVs, efforts to prevent transmission of infection must rely on the meticulous implementation of and compliance with strict infection control measures. Filoviruses and arenaviruses are highly infectious after direct contact with infected blood and bodily secretions. A suspected case of VHF must be immediately reported to the hospital epidemiologist (or infection control professional) and to the local or state health department. The epi-

demiologist (or infection control professional) should, in turn, notify the clinical laboratory (so that additional precautions are put in place) as well as other clinicians and public health authorities.

Isolation Precautions

Direct contact with infected blood and bodily fluids has accounted for the majority of person-to-person transmission of filoviruses and arenaviruses. Therefore, we recommend that in the case of any patient with suspected or documented VHF, VHF-specific barrier precautions should be implemented immediately (BOX 2). These precautions do not reflect HICPAC's isolation guidelines terminology and are defined here as strict hand hygiene plus use of double gloves, impermeable gowns, face shields, eye protection, and leg and shoe coverings (given the copious amounts of infected material, such as vomitus and liquid stool, that may be present in the environment).

Airborne transmission of HFVs appears to be a rare event but cannot be conclusively excluded. Given the inability to completely exclude this potential, the lack of preventive vaccines, and, in the case of filoviruses, the lack of effective drug therapy, we recommend that in addition to VHF-specific barrier precautions, airborne precautions also be instituted. Airborne precautions entail the use of a high-efficiency particulate respirator for any person entering the room and, as required by HICPAC standards,¹²³ the patient should be placed in a room with negative air pressure, 6 to 12 air changes per hour, air exhausted directly to the outdoors or passage through a high-efficiency particulate air (HEPA) filter before recirculation, and doors kept closed. There are many circumstances in which the use of negative-pressure rooms may not be possible, including mass casualty situations. In such conditions, all other infection control measures should be taken (ie, VHF-specific barrier precautions and a HEPA respirator for any person entering the room), which would, in combination, substantially reduce the risk of nosoco-

Box 2. Recommendations for Protective Measures Against Nosocomial Transmission of Hemorrhagic Fever Viruses

Strict adherence to hand hygiene:

Health care workers should clean their hands prior to donning personal protective equipment for patient contact. After patient contact, health care workers should remove gown, leg and shoe coverings, and gloves and immediately clean their hands. Hands should be clean prior to the removal of facial protective equipment (ie, personal respirators, face shields, and goggles) to minimize exposure of mucous membranes with potentially contaminated hands, and once again after the removal of all personal protective equipment

Double gloves

Impermeable gowns

N-95 masks or powered air-purifying respirators, and a negative isolation room with 6-12 air changes per hour, as required by Healthcare Infection Control Practices Advisory Committee standards for airborne precautions*

Leg and shoe coverings

Face shields†

Goggles for eye protection†

Restricted access of nonessential staff and visitors to patient's room

Dedicated medical equipment, such as stethoscopes, glucose monitors, and, if available, point-of-care analyzers

Environmental disinfection with an Environmental Protection Agency-registered hospital disinfectant or a 1:100 dilution of household bleach

If there are multiple patients with viral hemorrhagic fever in one health care facility, they should be cared for in the same part of the hospital to minimize exposures to other patients and health care workers

*These resources may not be possible in many health care facilities or in a mass casualty situation. In this case, all other measures should be taken and would, in combination, be expected to substantially diminish the risk of nosocomial spread.

†Face shields and eye protection may be already incorporated in certain personal protective equipment, such as powered air-purifying respirators.

mial transmission. Available evidence suggests that in the great preponderance of historical cases, these measures were sufficient to prevent transmission of disease to health care workers, family members, and other patients. Non-essential staff and visitors should have restricted access to patients' rooms. If there are multiple patients with VHF in a health care facility, they should be cared for in the same part of the hospital to minimize exposure to other persons.

All persons, including health care workers and laboratory personnel who have had a close or high-risk contact with a patient infected with a filovirus or an arenavirus within 21 days of the patient's onset of symptoms, prior to the institution of appropriate infection control precautions, should be placed under medical surveillance and managed as described in the section on postex-

posure prophylaxis. Laboratory personnel who have processed laboratory specimens from a patient with any HFVs (including Rift Valley fever and the flaviviruses) within 21 days of the patient's onset of symptoms, prior to the institution of appropriate infection control precautions, should also be placed under medical surveillance.

Because some of these viruses may remain present in bodily fluids for long periods following clinical recovery, convalescent patients continue to pose a risk of disease transmission.^{40,60} Therefore, patients convalescing from a filoviral or an arenaviral infection should refrain from sexual activity for 3 months after clinical recovery.

Personal Protective Equipment

Powered air-purifying respirators (PAPRs) are theoretically more effica-

cious than N-95 disposable masks in providing respiratory protection from small-particle aerosols, mostly due to issues related to proper fitting of the masks.¹²⁴ However, no data exist to support higher efficacy of PAPRs over N-95 masks in preventing airborne transmission of infection in the health care setting.¹²⁵ PAPRs are more expensive (\$300-\$600 vs less than \$1 for disposable N-95 masks), are bulky, require maintenance, and impair voice communication to a higher degree than disposable N-95 masks.¹²⁶ One study has shown that PAPRs are associated with a higher incidence of needlestick injuries.¹²⁷ Disadvantages of the N-95 masks include the difficulty in ensuring a reliable face-mask seal with each use and impossibility of effective use by bearded individuals. The theoretical advantage of PAPRs over N-95 masks may be offset by the danger of increased needlestick or sharp injuries to those using PAPRs in these settings. The N-95 masks (in combination with face shields and goggles) are likely equivalent in protection to PAPRs in the health care setting.

Therefore, we recommend that clinicians caring for patients with a VHF use either N-95 masks or PAPRs, depending on their familiarity with one or the other, the suitability for the individual, and availability at a given institution. Some experts have advocated that PAPRs be used during cough-inducing procedures (ie, endotracheal intubations, bronchoscopies), autopsies, and centrifugation or pipetting of laboratory specimens. While there are no data to support this recommendation, we would concur as long as the health care workers are familiar with the use of PAPRs and are not subjecting themselves to the risk of inadvertent needlestick injury.

Laboratory Testing

The HFVs described herein (including Rift Valley fever and the flaviviruses) are highly infectious in the laboratory setting and may be transmitted to laboratory personnel via small-particle aerosols. The risk is especially high during aerosol-generating procedures, such as

centrifugation. To minimize the possibility of small-particle aerosol generation, all laboratory staff must be alerted to any suspected diagnosis of VHF. Designated laboratory workers should receive training in handling specimens from any suspected VHF patients in advance of such an event. Laboratory workers should wear personal protective equipment that ensures VHF-specific barrier and airborne precautions (Box 2). All specimens should be handled, at a minimum, in a class 2 biological safety cabinet following BSL-3 practices.¹²⁷ (A detailed description of class 2 biological safety cabinets is available at <http://www.cdc.gov/od/ohs/biosfty/bmbl4/b4aa.htm>, and a detailed description of BSL-3 practices is available at <http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s3.htm>.) Most clinical facilities are not equipped with a BSL-3 laboratory. Virus isolation should only be attempted in a BSL-4 laboratory.

Potential hazards associated with handling of clinical specimens from patients infected with an HFV pose great problems in hospital facilities. Laboratory tests should be limited to critical diagnostic tests. If adequate resources are available, point-of-care analyzers for routine laboratory analysis of infected patients should be used. Point-of-care analyzers are small, portable devices that may be used at the bedside, require only a few drops of fresh whole blood, display test results in a few minutes, limit the exposure of laboratory personnel to infectious clinical specimens, do not disrupt the clinical laboratory routine, and do not contaminate clinical laboratory equipment.

If point-of-care analyzers are not available, clinical specimens need to be processed in a clinical laboratory. Precautions that parallel those of a US hospital's successful efforts to care for a patient infected with a New World arenavirus should be followed.¹²⁸ Laboratory specimens should be clearly identified, double bagged, and hand carried to the laboratory at prescheduled times, preferably prior to equipment maintenance to enable decontamination of instruments af-

ter testing. Specimens should never be transported in pneumatic tube systems. Only dedicated, trained laboratory personnel should process clinical specimens from patients with VHF, wearing protective equipment to ensure airborne and VHF-specific barrier precautions. Serum should be pretreated with the detergent Triton X-100 (10 µL of 10% Triton X-100 per 1 mL of serum for 1 hour). Pretreatment with Triton X-100 may reduce the titers of these enveloped viruses, but efficacy has not been tested.¹⁰⁹ Pretreatment with Triton X-100 does not significantly alter serum electrolytes, urea nitrogen, creatinine, and glucose or liver function test results.¹²⁸ Additional guidelines for clinical specimen transport, processing, and disposal have been described by Armstrong et al.¹²⁸

Postmortem Practices

In the event of an outbreak of VHF, special provisions will be required for burial practices. Contact with cadavers has been implicated as a source of transmission in the Kikwit Ebola outbreak of 1995³⁶ and in Uganda in 2000.³⁷ We recommend that trained personnel, using the same infection control precautions as those used to transport ill patients, handle the bodies of patients who die of VHF. Autopsies should be performed only by specially trained persons using VHF-specific barrier precautions and HEPA-filtered respirators (N-95 masks or PAPRs) and negative-pressure rooms, as would be customary in cases in which contagious biological aerosols, such as *Mycobacterium tuberculosis*, are deemed a possible risk.¹²⁹ We recommend prompt burial or cremation of the deceased, with minimal handling. Specifically, no embalming should be done. Surgery or postmortem examinations are associated with increased risks of transmission and should be done only when absolutely indicated and after consultation with experts.

Environmental Decontamination

Linen handlers and workers involved in environmental decontamination should wear personal protective equipment that

ensures VHF-specific barrier precautions (Box 2). We recommend that contaminated linens be placed in double bags and washed without sorting in a normal hot water cycle with bleach. Alternatively, they may be autoclaved or incinerated.¹⁰⁹ Detailed instructions on handling and disinfection of contaminated linens are available from the CDC.¹⁰⁹ Environmental surfaces in patients' rooms and contaminated medical equipment should be disinfected with an Environmental Protection Agency-registered hospital disinfectant or a 1:100 dilution of household bleach.¹⁰⁹

It has been suggested that excreta should be disinfected with 0.6% sodium hypochlorite before disposal.¹³⁰ Although a theoretical concern remains that the disposal of contaminated human excreta may contaminate sewage systems, the working group does not recommend the addition of disinfectants to human excreta prior to disposal. Disinfectants are not effective in sterilizing solid waste, the indiscriminate addition of hypochlorite may damage septic tanks, and these viruses are not likely to survive standard sewage treatment in the United States.

In general, in their natural state, these lipid-enveloped viruses are not environmentally stable and are not expected to persist in the environment for prolonged periods.⁷ Decisions regarding the need for and methods of decontamination following an attack with an HFV should be made following expert analysis of the contaminated environment and the weapons used in the attack, in consultation with experts in environmental remediation.

ONGOING RESEARCH AND PROPOSED AGENDA

Mechanisms of disease transmission in human outbreaks of HFVs are still poorly understood. Clarification of the role of airborne transmission is vital. Rapid diagnostic methods need to be developed for all of the HFVs, including those that have been excluded from this article and made available to selected state health departments for the expedient diagnosis of suspected cases. Meth-

ods to safely handle potentially infected specimens in a clinical laboratory should be developed.

The diagnostic and therapeutic armamentarium urgently needs to be augmented. There also is an urgent need to develop vaccines and drug therapy. A live attenuated vaccine against Argentine hemorrhagic fever (candid No. 1) developed at the USAMRIID¹³¹ is available as an IND. This vaccine has been shown to be safe and effective in protecting agricultural workers in South America¹³² and may provide cross-protection against Bolivian hemorrhagic fever.⁹ There are 2 vaccines against Rift Valley fever also available as INDs. One is formalin inactivated and appears to be safe and effective when administered to laboratory workers. However, it is available only in limited supply, and the manufacturing capacity for producing additional vaccine no longer exists in the United States.^{133,134} Lastly, a formalin-inactivated Kyasanur Forest disease vaccine exists and has been shown to be protective in field trials in India.¹³⁵ There are several promising vaccines in development for prevention of filoviruses and Lassa fever, some in nonhuman primate models.¹³⁶⁻¹³⁹ Passive immunization strategies using recombinant human monoclonal antibodies should be pursued, given the potential benefit of passive immunization in a series of reports.^{80,114,116,117,140} Research with these agents is hampered by the requirement of conducting experiments in BSL-4 laboratories. More BSL-4 laboratories would expand research opportunities.

Ribavirin is the only potentially effective drug available for selected hemorrhagic fever because it is approved by the FDA for another indication. However, it is not effective against all of the HFVs and it is not widely available. The supply of ribavirin should be rapidly augmented, and studies to demonstrate its efficacy and safety against selected HFVs should be conducted to support an FDA approval for those indications. We also recommend the addition of intravenous and oral formulations of ribavirin to the US National Pharmaceutical Stockpile (a reposi-

tory of antibiotics, chemical antidotes, and other medical supplies managed by the CDC that may be emergently sent to the site of a disaster anywhere in the United States). New antiviral therapies should be pursued for the treatment of all HFVs, including those excluded from this article. The effects of any developed therapy in pediatric populations should also be evaluated.

Disclaimer: The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Health and Human Services, US Department of Defense, or US Department of Army positions, policies, or decisions unless so designated by other documentation. The recommendations on the use of drugs for uses not approved by the FDA do not represent the official views of the FDA or of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.

Additional Articles: This article is the sixth in a series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense*. See references 1 through 5.

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