Viral Hemorrhagic Fever Hazards for Travelers in Africa

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This short review covers 6 viral hemorrhagic fevers (VHFs) that are known to occur in Africa: yellow fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, Lassa fever, Marburg virus disease, and Ebola hemorrhagic fever. All of these have at one time or another affected travelers, often the adventurous kind who are “roughing it” in rural areas, who should therefore be made aware by their physicians or travel health clinics about their potential risk of exposure to any VHF along their travel route and how to minimize the risk. A significant proportion of VHF cases involving travelers have affected expatriate health care workers who were nosocomially exposed in African hospitals or clinics. The VHFs are associated with a high case-fatality rate but are readily prevented by well-known basic precautions.

Epidemiology of Viral Hemorrhagic Fevers in Africa

Viral hemorrhagic fevers (VHFs) prevalent in Africa comprise the arboviral infections yellow fever, Rift Valley fever, and Crimean-Congo hemorrhagic fever; the arenaviral infection Lassa fever; and the filoviral infections Marburg virus disease and Ebola hemorrhagic fever.

Yellow fever (YF). YF is caused by a mosquitoborne flavivirus found in the tropical zones of Africa and South America. Its urban cycle is maintained with humans as the reservoir host, whereas monkeys are the main reservoir host in the jungle cycle, with humans becoming accidentally involved when venturing into forested areas. In Africa, several species of Aedes mosquitoes serve as vectors, depending on geographic location and type of transmission cycle. Despite international regulations requiring vaccination, nonvaccinated travelers to areas of endemicity still slip through this control net. For example, YF recently proved fatal for 2 travelers who were not vaccinated: 1 had returned to Germany from Côte d’Ivoire (Ivory Coast) [1] and the other to California from Venezuela [2]. The German patient repeatedly claimed to have been vaccinated against YF 6 years earlier, but had probably confused the German term Gelbsucht (hepatitis) for Gelbfieber (YF). In support of this assumption, postmortem findings of antibodies to hepatitis B surface antigen indicated probable vaccination against hepatitis B, and his vaccination certificate showed no evidence of YF vaccination.

The other patient, prior to his trip, had been vaccinated against tetanus, typhoid fever, and hepatitis A, but not against YF. One of his 6 travel companions remained well but had no YF antibodies and also had not been vaccinated. Although such cases are uncommon, they serve to underline that YF must be suspected in any traveler with a febrile illness after returning from an area where YF is endemic and whose vaccination cannot be verified.

Rift Valley fever (RVF). RVF was first recognized as a viral zoonosis in Kenya in 1930 [3]. Several massive epizootics affecting domestic livestock have since been reported in widely separated parts of the African continent. As a major cause of abortion in livestock, RVF, caused by a phlebovirus, has serious economic implications. The last big RVF epizootic, which typically followed heavy rainfalls and floods in 1997–1998, killed large numbers of livestock in East Africa, especially Kenya, although several other livestock infections contributed to the serious extent of these losses [4]. The incidence of human cases in this outbreak was estimated to be 89,000. During 2000, RVF spread for the first time beyond the African continent to Saudi
Arabia and Yemen, affecting both livestock and humans [5]. Further, such exports of RVF to new areas beyond Africa, with establishment of new maintenance cycles, are not unlikely.

RVF may affect herders, farm workers, veterinarians, and abattoir workers as an occupational hazard by direct handling of infected animals and their products. Depending on locally prevailed mosquito species and their habits, RVF may also be transmitted by mosquito bites to children, soldiers, and other persons who have no contact with infected animals [6]. Although the risk to travelers of acquiring RVF is generally low, travel-associated cases have been reported [7, 8] and may increase in number in view of the increased incidence of RVF and of travel to RVF-affected regions.

Consumption of raw milk is another potential means of infection with the virus. Laboratory infections are common, either through handling of infectious materials or by inhalation of infectious aerosols [6].

**Crimean-Congo hemorrhagic fever (C-CHF).** C-CHF is a tickborne bunyavirus infection that was independently documented in Russia as Crimean hemorrhagic fever in 1945 and in the Democratic Republic of Congo (DRC, formerly the Belgian Congo) as Congo virus infection in 1956. The similarity of the subsequently isolated causative agents was established in 1969, and the 2 diseases, jointly renamed C-CHF, were since considered to be identical [9]. The virus transiently affects animals—from rodents and other small mammals to large animals such as antelopes and livestock (mainly cattle, sheep, and goats)—as well as birds, including migrating birds capable of transporting and thus spreading infected ticks over large distances. Ticks also act as reservoir hosts, as the virus is passed down transovarially from one generation of ticks to the next.

It is not surprising, therefore, that C-CHF occurs in large areas of eastern Europe, the Mediterranean region, western Asia (including the Arabian peninsula), and Africa, wherever ticks of the genus *Hyalomma* are prevalent [10]. Natural routes of transmission from animals to humans include direct contact between damaged human skin and the blood and tissues of infected animals, as well as inoculation of the virus by infected ticks. The latter is more commonly seen in persons who are exposed during recreational activities to C-CHF, whereas transmission by direct contact is frequent in persons who are exposed during occupational activities, such as farmers, herdsmen, veterinarians, and abattoir workers. Nosocomial transmission is common and often results in small outbreaks. Travelers sporadically have been infected, most likely by ticks. One of these was a young boy infected by a tick bite during a trip in South Africa, where he decided to sleep outdoors on the ground [11]. Another case involved a South African medical student on a walking trip in East Africa. Several other cases involving expatriate health care workers occurred in Dubai but were the result of nosocomial transmission [12]. Sporadic cases are probably underdiagnosed.

**Lassa fever (LF).** LF was first recognized in Lassa, Nigeria, in 1969, when its occurrence in several American missionary nurses led to the isolation from their blood of a hitherto unknown species of arenavirus, subsequently named “Lassa virus” [13]. LF has since also occurred in other West African countries, especially Sierra Leone, Liberia, and Guinea. From time to time, sporadic cases have been imported into Britain, the United States, Japan, and Canada [14], and at least 4 such imported cases, all fatal, were reported during 2000 [15]. One of these patients was a German student, and 2 patients were expatriate workers, of whom one was a British national working in Sierra Leone and the other a Dutch surgeon who may have been nosocomially infected. The fourth patient was a Nigerian, flown to Europe for treatment purposes.

LF is a frequent cause of nosocomial infection when preventive measures are inadequate or not practiced. Its reservoir host is a common African semidomestic rodent of the *Mastomys* species complex. Experimental infection of *Mastomys* resulted in lifelong excretion of the virus [16]. African grain crops and stores are thus commonly contaminated with the virus and often serve as the direct sources of local human infections, either by inhalation or by direct contact and entry of the virus through damaged skin.

**Marburg virus disease (MVD) and Ebola hemorrhagic fever (EHF).** MVD and EHF were first recognized in Germany in 1967 and in the DRC (formerly Zaire) and Sudan in 1976, respectively. Since then, <1500 cases (total for MVD/EHF combined) have been clinically recognized and recorded. Travelers are at very low risk of exposure, but occasional cases involving travelers have been imported into countries where they are not endemic. One such incident involved a young Australian backpacker who, in 1975, died with MVD that was thought to have been acquired in Zimbabwe. He was hospitalized in South Africa, where secondary cases occurred in his female travel companion and a nursing sister, both of whom survived [17]. A case involving a French expatriate engineer working in West Kenya offers another example of fatal MVD in a traveler. An outbreak of MVD that started during 1998 in a community of gold miners in war-torn DRC was still in progress in 2000 [18].

In 1976, the occurrence of an unknown fatal VHF in several Belgian missionaries in Yambuku, DRC, first drew international attention to an outbreak of what subsequently became known as “Ebola virus disease.” Italian missionaries were infected in 1995 in a similar Ebola virus disease outbreak.

However, incidents of these uncommon diseases continue to be associated with excessive media speculation and alarm. This is probably fueled by our lack of knowledge concerning the natural host and routes of transmission of these infections, as well as their dramatic clinical presentation, high case-fatality
rates (up to 88%), and lack of effective specific treatment. Although vervet monkeys and apes, such as chimpanzees, have clearly been established as immediate sources of human filoviral infections in some outbreaks [19, 20], their role in the ecology of these viruses is probably similar to that of humans, i.e., that of incidental hosts. The true reservoir hosts and arthropod vectors, if any, remain to be identified.

Without measurements, the 2 causative agents—Marburg virus and Ebola virus, respectively—are morphologically indistinguishable but antigenically distinct and are grouped together in the family Filoviridae [21]. Several subtypes of Ebola virus are recognized, all except one being of African origin and highly pathogenic to humans. The exception is the Reston strain, which has been traced to the Philippines and is pathogenic to cynomolgus monkeys. However, on the basis of the cases of several Ebola antibody–positive but healthy monkey-handlers in a facility housing numerous Ebola Reston–infected monkeys, this subtype appears to be capable of infecting humans without causing clinical illness [22]. Overall, the vast majority of recorded filovirus infections have been artificially generated in hospitals by exposure of inadequately protected health care workers to bleeding patients, by inoculation, or by vaccination of staff or patients with unrelated conditions by means of nonsterile, filovirus-contaminated syringes, needles, and other instruments.

**CLINICAL FEATURES**

**YF.** After an incubation period of 3–6 days, this biphasic illness presents initially with sudden onset of fever, rigors, headache, myalgia, nausea, vomiting, and a relative bradycardia. Jaundice is usually mild at this stage of yellow fever, and clinical improvement toward the end of the first week may indicate recovery. In some patients, this remission is followed within days by a second phase with signs and symptoms of increasing renal and hepatic failure, accompanied by intense jaundice and a generalized hemorrhagic state, with a case-fatality rate of 25%–50%. Leukopenia is a typical finding.

**RVF.** Asymptomatic infections with Rift Valley fever virus are common. In symptomatic cases, after a short incubation period of usually 2–6 days (occasionally longer), RFV presents with abrupt onset of a nonspecific flu-like illness with fever, headache, flushing, photophobia, retro-orbital pain, myalgia, rigors, and joint pain. Nausea and vomiting are frequent, and a faint maculopapular rash occurs in some patients [23]. The fever is often biphasic, returning to normal after ~1 week but recurring for a brief spell, after a further interval of a few days. Most patients recover spontaneously, but in <5% of cases, complications develop relatively late in the course of illness, or in early convalescence. These manifest in the form of encephalitis, retinitis [8, 24], or a generalized hemorrhagic state [25]. Bleeding usually presents within the first week of illness and is a common cause of RVF-associated deaths, estimated to occur in <1% of cases. Encephalitis may leave the patient with residual brain damage, whereas retinitis, which presents with a typical cotton-wool exudate on the macula, may in some cases result in permanently defective vision or blindness.

**C-CHF.** The symptoms and signs of Crimean-Congo hemorrhagic fever are similar to those of other viral VHFs. After an incubation period ranging from ~2 to 9 days, there is a very abrupt onset of illness, with fever, headache, myalgia, rigors, nausea, vomiting, abdominal pain, and conjunctival injection [10]. There may also be diarrhea, sore throat, photophobia, painful eyes, and meningism with confusion and aggression. Bleeding, in the form of a petechial rash or frank ecchymoses, epistaxis, and bleeding from various other organ systems, occurs in most cases and usually begins several days after the onset of illness. Lymphadenopathy is occasionally seen. The case-fatality rate is ~25%–33%.

**LF.** Unlike the other VHFs discussed here, Lassa fever is gradual in onset, with fever, headache, myalgia, sore throat with a patchy tonsillar exudate, dysphagia, dry cough, chest pain, and cramping abdominal pains with nausea, vomiting, and diarrhea. Some patients complain of severe retrosternal or epigastric pains. Gradual deterioration is associated with edema of the face and neck, respiratory distress, pleural and pericardial effusions, encephalopathy, and hemorrhage from various sites. Hypotension and shock, not related to blood loss, are a feature in ~17% of cases [26]. LF tends to be more severe during pregnancy. Deafness, thought to be an immune-mediated injury, may develop suddenly or gradually over a few hours during convalescence [27]. The case-fatality rate of LF is <2% overall, but it is 15%–20% for untreated hospitalized cases.

**MVD and EHF.** Marburg virus disease and Ebola hemorrhagic fever have very similar clinical features. After an incubation period that usually ranges from 5 to 14 days, there is sudden onset of illness with fever, headache, malaise, myalgia, arthralgia, abdominal pain, nausea, conjunctival injection, and a relative bradycardia. Other common symptoms include diarrhea, which may be bloody, vomiting, and anorexia. Despite severe hepatic involvement, overt jaundice is not common until the terminal stage of illness [28]. A prominent feature is a severe sore throat associated with marked edematous swelling of the soft tissues at the back of the throat, dysphagia, and, in more severe cases, dyspnea.

A short-lived, profuse, nonitchy maculopapular rash against an intensely erythematous background, which blanches on pressure, is often seen in white-skinned patients around the fifth day of illness. It is followed by desquamation of the affected skin during the early convalescent phase. On dark skins, the appearance of desquamation without a prior rash may be the only visible indication of skin involvement. Late eye compli-

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**CID 2001:33 (15 November) • 1709**
cations in the form of a unilateral uveitis have been noted in one case of MVD, in which viable virus was isolated from the anterior chamber of the eye 1 week after onset of ocular symptoms (87 days after onset of MVD) [29], and in 1 patients with EHF, in 1 of whom the presence of Ebola virus in a conjunctival swab specimen was suggested by reverse-transcriptase–PCR 22 days after onset of EHF [30].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the VHFs is extensive and based on other infections associated with features such as fever, rash, jaundice (or other evidence of hepatic and renal involvement), hemorrhage from multiple sites (including needle puncture wounds), leukopenia, and thrombocytopenia. Infections such as falciparum malaria, the acute form of African trypanosomiasis, typhoid fever, leptospirosis, relapsing fever, meningo-coccidial meningitis, and other bacterial meningitis, and other arboviral infections must therefore be considered.

LABORATORY CONFIRMATION OF VHF

Samples to be submitted for laboratory confirmation include blood, throat washings, urine, and various postmortem tissue specimens, especially of the liver. Laboratory confirmation of a VHF is usually based on electron microscopy, virus isolation, and serological demonstration of viral antigens and antibody in the form of specific IgM and IgG. Several serological techniques, including ELISA, immunofluorescence, RIAs, and western blotting, are available in specialized laboratories.

An immunohistochemical assay was recently developed to detect Ebola virus in formalin-fixed skin biopsy samples and provided a simple, safe, and sensitive method for laboratory confirmation of Ebola virus disease [31]. Reverse transcriptase PCR assays have been developed to diagnose all of the VHFs discussed in this review. Confirmatory investigations should be carried out in a specialized virology laboratory with maximum containment facilities (biosafety level 4).

SAFE MANAGEMENT

Available evidence indicates that the majority of nosocomial VHF cases have been acquired by inoculation with virus-contaminated instruments or by direct contact with blood or body fluids from infected patients. Isolation of VHF patients whenever possible is strongly recommended. Strict barrier nursing and universal precautions with blood, body fluids, and potentially contaminated objects are highly effective. These measures must be activated as soon as a diagnosis of a VHF is suspected. The use of a facial shield or mask and goggles is useful in avoiding entry of virus-contaminated blood or secretions through conjunctivae, nose, or mouth when a patient suddenly vomits, coughs, or sneezes. These measures should never be delayed until laboratory confirmation of a VHF is obtained, as secondary virus transmission is most likely to occur in the interim, when appropriate precautions are not practiced.

Patients with YF or RVF should be nursed in mosquito-protected premises. Nonimmune YF contacts should be immunized without delay. Preventive measures should apply to doctors, nurses, and anyone else (such as visitors, technicians, clerks, cleaners, messengers, and laboratory personnel) who may come into contact with a patient infected with a VHF or with potentially infectious blood or body fluids.

Healthy persons who have already been in contact with the patient when a VHF diagnosis is being considered should be subject to daily medical surveillance, but without quarantine or isolation, for a period of 21 days from the date of last contact. All samples for laboratory investigations should be clearly labeled, securely packaged, and forwarded by trained messengers. The receiving virology laboratory, as a matter of routine, is likely to practice all necessary containment measures during specimen processing. However, the same is not necessarily the case with all clinical pathology laboratories where regular monitoring of the patient’s microbiological, hematologic, and chemical parameters may be performed. Such laboratories should be fully informed about the patient’s diagnosis and its implications at the earliest opportunity.

Serum samples containing Lassa, Marburg, or Ebola viruses may be rendered considerably less infectious by heating to 60°C for 1 h, which allows for safe determinations of serum electrolyte, glucose, and blood urea nitrogen levels. Dilution of blood from such patients in 3% acetic acid renders it safe for WBC counts [32].

ANTIVIRAL THERAPY

Treatment of most VHFs is mainly supportive, and availability or lack of facilities for regular monitoring and support of vital functions may affect the course and outcome of illness. Treatment with ribavirin has significantly reduced the mortality rate associated with Lassa fever, with best results obtained when the drug is started early in the course of illness [33]. For C-CHF, because of its relative rarity and high mortality rate, placebo-controlled trials with ribavirin have not been appropriate. Although iv ribavirin is the preferred formulation, this has not always been readily available. However, the use of oral ribavirin early in the course of this disease appeared to result in a higher survival rate than had been observed among untreated patients [34]. Ribavirin is ineffective against filoviruses.

The results of administration of immunoglobulin to laboratory animals infected with Ebola virus generally have been
disappointing, as have results with IFN [35]. In a small, non-controlled trial, transfusion of blood from patients convalescing from Ebola virus infection resulted in a markedly lower case-fatality rate (12.5%) among 8 transfused patients in comparison with the overall case-fatality rate of 80% during the 1995 DRC epidemic [36]. However, these patients generally received better care than the nontreated patients who had presented earlier during the course of the outbreak. In addition, they were transfused late in the course of illness, when they probably were already on the way to recovery [37].

Recent studies suggest that certain nucleoside analog inhibitors of S-adenosylhomocysteine hydrolase inhibited replication of Ebola virus. One of these compounds, carbocyclic 3-deazaadenosine (Ado, John Montgomery, Southern Research Institute), conferred significant protection on laboratory mice when they were treated by the second day after experimental Ebola virus infection [38]. This is the first compound capable of protecting animals infected with Ebola virus from this otherwise lethal infection. Although much more work is needed, these results may herald the advent of a much-needed specific therapeutic drug for filovirus infections.

**PREVENTIVE MEASURES FOR TRAVELERS**

In terms of the International Health Regulations, YF remains the only disease subject to control by compulsory vaccination of international travelers from areas of endemicity or infection. The YF vaccine consists of a live attenuated 17D strain of the virus and has proved to be very safe and effective. However, infants, pregnant women, and immunocompromised persons are generally excepted from this regulation, provided they are issued a medical certificate specifying the reasons for nonvaccination. Nevertheless, when the risk of YF exposure is significant, vaccination may be the less harmful option. Vaccination certificates must be issued 10 days before arrival in a YF-affected area and remain valid for 10 years [39].

RVF vaccination is not recommended for the average traveler, but although it is not generally available, it may be indicated for those who are traveling to participate in international RVF-outbreak investigations or are otherwise at high risk of exposure.

Mosquito-avoidance measures should be routinely practiced by travelers to prevent not only YF and RVF but also malaria, dengue, and other mosquito-borne infections. Such measures include the wearing of long sleeves and long trousers, as well as the use of mosquito repellents, bed nets (ideally impregnated with a residual insecticide, such as permethrin), insecticide-spraying of sleeping quarters (unless air conditioned), and screening of windows and doors.

Tick-avoidance measures are important in the prevention of C-CHF, especially for backpackers and hikers, and include the use of protective clothing, with trousers tucked into socks and boots, and tick repellents. Frequent body searches should be made to find and remove ticks.

No specific measures are needed by the average traveler to prevent LF. Avoiding contact with rodents and avoiding sleeping in potentially rodent-infested premises in rural areas are recommended.

The natural animal host(s) and vector(s), if any, of MVD and EHF are unknown. Contact with nonhuman primates, the only immediate animal source of filovirus infections implicated thus far, should be avoided.

Expatriate health care workers in African clinics or hospitals should, in addition, practice barrier precautions when in doubt about a patient’s diagnosis. Standard precautions should be practiced at all times and with all patients.

**References**


