Viral Hemorrhagic Fevers Caused by Arenaviruses

Lassa Fever,
South American Hemorrhagic Fever,
Argentine Hemorrhagic Fever,
Bolivian Hemorrhagic Fever,
Venezuelan Hemorrhagic Fever

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IOWA STATE UNIVERSITY®

College of Veterinary Medicine
Iowa State University
Ames, Iowa 50011
Phone: 515.294.7189
Fax: 515.294.8259
cfsph@iastate.edu
www.cfsph.iastate.edu

INSTITUTE FOR INTERNATIONAL COOPERATION IN ANIMAL BIOLOGICS

Iowa State University
College of Veterinary Medicine
www.cfsph.iastate.edu/IICAB/

Importance

Viral hemorrhagic fevers (VHFs) are a group of infectious diseases with similar symptoms in people; the causative viruses affect the vascular system and can produce a severe multisystemic illness in some patients. Arenaviruses known to cause VHF include Lassa virus (Lassa fever), Junin virus (Argentine hemorrhagic fever), Machupo and Chapare viruses (Bolivian hemorrhagic fever), Guanarito virus (Venezuelan hemorrhagic fever), Sabia virus and Lujo virus. Some of the causative arenaviruses have probably not been identified yet; the South American arenaviruses emerged as agents of VHF within the last 60 years, and Lujo virus was discovered in Africa in 2008.

Arenavirus-associated VHFs are zoonotic diseases, with humans acting as accidental hosts. The viruses are carried in asymptomatic animal reservoirs, typically rodents. Nonhuman primates can be experimentally infected, but there is no evidence that these viruses are pathogenic in livestock, cats or dogs. In humans, the illness may be mild to severe or fatal. Bleeding tendencies, which are not usually life-threatening, occur in a proportion of the serious cases. The mortality rate for some VHFs may be as high as 30%. VHFs can be difficult to diagnose, particularly in the early stages when treatment is most effective. There are also fears that arenaviruses could be weaponized and used in bioterrorism.

Etiology

VHFs can be caused by viruses in the families Filoviridae, Arenaviridae, Bunyaviridae and Flaviviridae. There are more than 20 recognized members of the Arenaviridae, but fewer than half of these viruses have been linked to human illness. Arenaviruses that are known to cause viral hemorrhagic fever include Lassa virus (Lassa fever), Junin virus (Argentine hemorrhagic fever), Machupo and Chapare viruses (Bolivian hemorrhagic fever), Guanarito virus (Venezuelan hemorrhagic fever) and Sabia virus, as well as a recently discovered virus in Africa, which has been provisionally named Lujo virus. Junin, Machupo, Chapare, Guanarito and Sabia viruses are all found in South America, and the diseases they cause are known collectively as the South American hemorrhagic fevers. Whether other arenaviruses found in rodents can cause VHF is unknown. Flexal virus in South America, and Tacaribe virus in the Caribbean have each caused one or two non-fatal febrile illnesses in laboratory workers. Whitewater Arroyo virus has been linked to two fatal cases of hemorrhagic fever in California.

Taxonomy

The family Arenaviridae contains a single genus, *Arenavirus.* This genus is divided into two groups: the Tacaribe serocomplex and the Lassa-Lymphocytic choriomeningitis serocomplex. The Lassa-Lymphocytic choriomeningitis serocomplex, which is also called the Old World complex, contains Lassa virus and Lujo virus, which cause VHF in Africa. Other viruses in this complex include lymphocytic choriomeningitis virus (LCMV; see related factsheet), which is a human pathogen but does not cause hemorrhagic fever, as well as some African viruses that have not been linked to human disease, such as Ippy virus, Mobala virus, Mopeia virus, Morogoro virus and Merino Walk virus.

The Tacaribe serocomplex, which is also called the New World complex, contains arenaviruses that are endemic in the Western Hemisphere. There are three or four clades within this complex. Clade A contains Pirital, Pichinde, Flexal, Parana and Allpahuayo viruses. Junin, Machupo, Guanarito, Amapari, Tacaribe, Sabia, Cupixi and Chapare viruses are found in clade B, while clade C contains Oliveros, Latino and Pinhal virus. A fourth cluster, called A/Rec, consists of a group of North American arenaviruses that have genetic similarities to more than one clade; their taxonomic position is unresolved. The currently recognized viruses in A/Rec are Whitewater Arroyo, Tamiami, Bear Canyon, Skinner Tank, Catarina, Tonto Creek and Big Brushy Tank viruses. The most important Tacaribe serocomplex viruses, in terms of human disease, belong to clade B. This clade also contains some viruses that have not been linked to human illness.

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Geographic Distribution

Each arenavirus is maintained in one or a few animal reservoir hosts, and is limited by the distribution of that host. The occurrence of these viruses is patchy, with higher infection rates among the rodents in "hot spots." For example, the rodent host for Lassa virus is widespread in sub-Saharan Africa, but Lassa fever has been reported only from West Africa. This disease has been documented mainly in Nigeria, Liberia, Guinea and Sierra Leone, with isolated cases or serological evidence of the virus's presence in some other West African countries. Lujo virus was isolated recently from a cluster of hemorrhagic fever cases in southern Africa. The index case became infected in Zambia, and transmitted the infection to medical personnel in Zambia and South Africa.

In South America, viral hemorrhagic fever is caused by Junin virus in central Argentina, Machupo and Chapare viruses in Bolivia, Guanarito virus in western Venezuela, and Sabia virus in Brazil. In each case, the disease tends to occur in a limited region of the country.

Other arenaviruses

Old World arenaviruses that are found in rodents and have not been linked to human illness include Ippy virus and Mobala virus in the Central African Republic, Merino Walk virus in South Africa, Morogoro virus in Tanzania, and Mopeia virus in Mozambique and Zimbabwe. Serology suggests that Mopeia virus might also occur in the Central African Republic.

A number of Tacaribe serocomplex arenaviruses have been isolated from South American rodents. They include Amapari virus, Cupixi virus and Flexal virus in Brazil, Oliveros virus in Argentina, Latino virus in Bolivia, Pirital virus in Venezuela, Pichinde virus in Colombia, Parana virus in Paraguay, and Allpahuayo virus in Peru. Tacaribe virus occurs on Trinidad in the Caribbean. Although a number of arenaviruses have been isolated in North America, only Whitewater Arroyo virus in California has been characterized as a possible VHF pathogen. Arenaviruses that cause viral hemorrhagic fever have not been detected in Eurasia.

Transmission

Rodents become chronically infected with arenaviruses, and can shed these viruses for a lifetime. The viruses can be found in many secretions and excretions including urine, saliva and respiratory secretions. How they are transmitted between rodents is incompletely understood. Vertical transmission of Lassa virus is thought to be important in its reservoir host, *Mastomys natalensis*; young mice might become infected either transplacentally or soon after birth. A recent epidemiological study suggests that horizontal transmission might also be significant in these rodents. Horizontal transmission is thought to be important in maintaining Junin virus in rodent populations. Arenaviruses might be spread between animals during various forms of close contact such as fighting, allogrooming, mating or huddling, or from environmental contamination via aerosols. In one experiment, there was no evidence that fetuses became infected with Junin virus *in utero*; however, half of the pups from infected dams carried the virus by the time they were weaned.

Humans can be infected when arenaviruses contact mucous membranes or broken skin. This may occur during direct contact with rodents, including bites, or by indirect contact such as the inhalation of aerosolized excretions and secretions, or contact with contaminated food. Rodent urine is often thought to be the source of the virus. In parts of Africa, the rodent host for Lassa virus frequently invades homes. This rodent can also be part of the diet, and humans may become infected when they hunt the mice or prepare them to cook. Agricultural activities have been linked to infections with some South American arenaviruses. Junin virus infections (Argentine hemorrhagic fever), for example, peak during the corn harvest, when workers may be exposed to aerosolized virus from harvesting machinery. Aerosols generated during virus manipulation are often implicated in laboratories. Person-to-person transmission of arenaviruses can occur during close contact (e.g., between family members), and in the hospital setting when barrier nursing techniques are not used. The risk is particularly high when improperly sterilized needles are used for multiple patients, or when there is a safety breach, especially a scalpel cut, during an autopsy. Humans can shed arenaviruses in many body secretions and excretions including blood, urine, feces, saliva, vomitus and semen. Lassa virus can be found in the urine and semen for several weeks after the patient has recovered. Some arenavirus infections may have been venereally transmitted.

Disinfection

Arenaviruses can be inactivated by most detergents and disinfectants including 1% sodium hypochlorite and 2% glutaraldehyde, The viruses are also susceptible to ultraviolet light and gamma irradiation, and they can be inactivated by temperatures of 56°C (133°F) and by pH less than 5.5 or greater than 8.5.

Infections in Humans

Incubation Period

Arenavirus infections become apparent in approximately one to three weeks. The incubation period is usually 6 to 14 days for Argentine hemorrhagic fever (Junin virus). It can be 7 to 16 days for Bolivian hemorrhagic fever caused by Machupo virus, and 3 to 21 days for Lassa fever. Exposure to very high doses of an arenavirus may result in an incubation period as short as 2 days.

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Clinical Signs

Arenaviruses may cause subclinical infections or mild to fatal disease. Viral hemorrhagic fevers are clinically similar. They begin with a prodromal period characterized by a nonspecific flu-like illness. Some patients recover, while others develop more severe symptoms that may include hemorrhages, edema, hypotension, circulatory collapse and neurological signs. Some cases are fatal.

Lassa fever

Lassa fever usually begins gradually, as a nonspecific illness with fever, malaise, headache, myalgia, anorexia and weakness. Gastrointestinal signs including nausea, vomiting, abdominal pain or tenderness, and diarrhea may also be seen. Light-skinned patients can have a maculopapular or petechial rash over the chest, face and arms. Other symptoms may include a sore throat (with or without signs of pharyngitis), arthralgia, lymphadenopathy, conjunctival injection, a dry cough and chest pain. Many patients recover after this prodromal stage, but up to 10% develop a more severe illness with severe prostration, edema (especially on the face and neck), hypotension, shock, hepatitis and/or multiorgan failure. Mucosal hemorrhages or bleeding tendencies, most often seen as mild oozing from the nose or mouth, occur in approximatey 15-20% of these cases. Pleural and pericardial effusions are also possible late. Pregnant women often miscarry. Neurological signs such as confusion, disorientation, locomotor dysfunction, tremors, convulsions and coma are common in critically ill patients. The clinical picture can vary, and some people may not show the classical signs. For example, encephalopathy was the most prominent syndrome in one published case. Severely ill patients may die; the mortality rate is particularly high among pregnant women. Convalescence can be prolonged in patients who recover. Transient or permanent deafness often occurs during this stage, and can be seen in both mild and severe cases.

In infants, Lassa fever can appear as “swollen baby syndrome,” which is characterized by generalized edema, abdominal distention and bleeding. Many affected infants die. Other concurrent health risks might contribute to this syndrome.

Lujo virus infection

Lujo virus was isolated from a cluster of hemorrhagic fever cases in southern Africa in 2008. Like other VHFs, the illness began with nonspecific flu-like signs such as fever, headache and muscle pain. The clinical signs worsened over the following week, and gastrointestinal signs (vomiting, diarrhea) and pharyngitis developed, followed by rapid deterioration with neurological signs, respiratory distress and circulatory collapse. Liver dysfunction and a rash were also reported. The case fatality rate was unusually high, with four of five cases ending in death.

South American hemorrhagic fevers

South American hemorrhagic fevers resemble Lassa fever, but hemorrhages and neurological signs are more likely to be seen in severe cases. The initial symptoms may include fever, headache, anorexia, malaise and myalgia, with pain especially in the lower back. Nausea or dizziness, abdominal pain, vomiting, diarrhea, sore throat, hyperesthesia of the skin, flushing of the head and torso, and lymphadenopathy can also be seen. Most patients improve after a week or two, but approximately one-third of untreated cases become severe and life-threatening. Bleeding tendencies can occur in some of these cases. Petechiae may be seen on the skin, and the gums may bleed spontaneously or with slight pressure. Hemorrhages from the vagina or gastrointestinal tract are also possible. Blood loss is usually minor, but capillary leak syndrome can lead to hypotension and hypovolemic clinical shock. Neurological signs may be the predominant syndrome in some patients, and death can occur without significant capillary leak or hemorrhages. Secondary bacterial infections may result in pneumonia and septicemia. Although convalescence can take one to three months, survivors usually recover completely. Temporary hair loss may occur due to the high fever.

Only minor differences in clinical signs have been reported between the South American arenaviruses. Pharyngitis, vomiting and diarrhea were reported to be more common in patients infected with Guanarito virus, while erythema, petechiae, facial edema and shock may be seen more often in patients infected with Junin or Machupo viruses. Approximately 10% of Argentine hemorrhagic fever patients that are treated with immune plasma develop a late onset neurological syndrome after a symptom-free period. This syndrome is characterized by fever, cerebellar signs, cranial nerve palsies and/or other CNS signs. Its cause is not known.

Infections with other arenaviruses

Very little is known about the effects of infection with many arenaviruses. Three fatal illnesses were attributed to possible Whitewater Arroyo virus infection in California in 1999 and 2000. Further laboratory testing from one patient, who had positive PCR results alone, did not confirm the diagnosis; however, Whitewater Arroyo virus-associated VHF remains a possibility in the other two cases. The clinical signs were similar in all three patients: an initial, non-specific febrile illness with headache and myalgia was followed by acute respiratory distress syndrome. Thrombocytopenia, liver failure and hemorrhagic signs were also seen. Febrile illnesses have been reported in two laboratory workers infected with Flexal virus, and one laboratory worker infected with Tacaribe virus. The person infected with Tacaribe virus also had mild neurological signs. A number of people who have been exposed to Pichinde virus have seroconverted, but this virus has not been linked to human illness.

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Communicability

Person-to-person transmission of arenaviruses can occur in blood, urine, feces, saliva, vomitus, semen and other secretions or excretions. Lassa virus can be detected in the urine and semen for several weeks after the patient has recovered. Clinical samples such as tissues also contain virus. Person-to-person transmission usually occurs only during close contact, or in the hospital setting when good barrier nursing is not used. The greatest risk is via parenteral transmission (e.g., on improperly sterilized needles). Some arenaviruses, such as Guanarito virus (Venezuelan hemorrhagic fever), might be transmitted infrequently between people. One study reported only one possible case of secondary transmission among 165 patients with this disease, although many were initially nursed in open wards where isolation procedures were minimal. In contrast, Lujo virus infected several people who cared for the index case, including one person who cleaned a room after a patient died. Arenaviruses can be carried to non-endemic areas during the incubation period, which can be as long as three weeks.

Diagnostic Tests

Viral hemorrhagic fevers are often diagnosed by serology. Enzyme-linked immunosorbent assays (ELISAs), which can detect IgM or IgG, and indirect fluorescent antibody (IFA) tests can be used. A fourfold rise in the titer should be seen, or specific IgM should be detected. Cross-reactions can occur between arenaviruses in these tests. In contrast, virus neutralization tests are highly specific, but these antibodies may appear too late to be useful in immediate diagnosis. For example, patients with Lassa fever do not usually develop neutralizing antibodies until weeks after they became ill.

Arenaviral antigens can be detected in blood or tissues, using antigen-capture ELISAs. Diagnostic RT-PCR tests are available or have been published; however, there is limited clinical experience with these assays. Some PCR tests detect a wide range of arenaviruses, while others are more specific.

Virus isolation can also be used for diagnosis if a biosafety level 4 laboratory is available. Arenaviruses can be recovered in cell cultures, particularly Vero cells. The presence of the virus can be confirmed with immunohistochemical assays or RT-PCR. Arenaviruses can also be isolated in laboratory rodents such as sucking mice, guinea pigs or newborn hamsters.

Treatment

Supportive treatment is used for all VHFs. Specific therapies are also available for some viruses. The antiviral drug ribavirin has been used in cases of Lassa fever; treatment is most effective when it is started early in the course of the disease. Ribavirin can significantly reduce the mortality rate from severe Lassa fever, but it does not prevent deafness. Some other arenaviruses also seem to be sensitive to this drug, but clinical experience is limited and only anecdotal reports and/or animal studies may be available.

Human immune plasma is used to treat Argentine hemorrhagic fever (Junin virus), and plasma banks have been established. Treatment is most effective if it is started soon after the onset of the clinical signs; early treatment can decrease the mortality rate from 20-30% to 1-2%. Immune plasma might also be effective in patients with Bolivian hemorrhagic fever (Machupo virus); however, finding a source could be difficult, as relatively few cases are seen and there is no program to collect immune plasma.

Prevention

The risk of arenavirus infections can be decreased by avoiding contact with the reservoir host and its excretions. In endemic areas, food should be placed in rodent-proof containers to prevent contamination, and rodents should be discouraged from entering homes. This is particularly important when the reservoir host is one that will readily enter houses, such as *Mastomys natalensis*, the host for Lassa virus. Complete avoidance of contact with this common rodent can be difficult or impractical, although trapping may reduce populations around homes. The use of *Mastomys* spp. as a food source is not recommended. In South America, preventative measures may include replacing crops and burning areas that contain tall grasses. In urban locations, Bolivian hemorrhagic fever has been controlled with programs to trap *Calomys callosus*, the reservoir host for Machupo virus.

Guidelines for the safe cleaning of rodent-infested areas in homes have been published. Particular care should be taken to avoid aerosolizing droppings during cleaning; areas should be wetted with disinfectant, and activities such as sweeping, dusting and vacuuming should be avoided. Precautions should also be taken in laboratories when working with rodents, particularly those captured from the wild. Current personal protective equipment recommendations should be followed. Veterinarians outside the endemic area should be aware of potential risks from exotic rodents imported as pets.

Barrier nursing precautions, including the use of appropriate personal protective measures such as gloves, masks and gowns should be employed when caring for patients with VHFs. Good hygiene and appropriate sterilization of equipment should be practiced. The highest-risk of transmission occurs during unprotected contact with body fluids or excreta from an infected person. There is a low risk of transmission from unprotected contact when exposure to body fluids is unlikely (e.g., skin to skin contact)

A live attenuated vaccine is available in endemic areas for Argentine hemorrhagic fever (Junin virus). In animal studies, this vaccine also provided some protection against Bolivian hemorrhagic fever (Machupo virus) but not Venezuelan hemorrhagic fever (Guanarito virus) or VHF

caused by Sabia virus. No Lassa fever vaccine is licensed for humans, but experimental vaccines have shown promise in non-human primate models. Prophylaxis with ribavirin should be considered for people who are at high risk of having been infected with arenaviruses. However, it should be noted that this drug is teratogenic.

Morbidity and Mortality

VHFs may occur either as sporadic cases or in outbreaks. Recreational activities or occupational exposure (e.g., agricultural pursuits or handling of rodents) increase the risk of infection. Cases can also be seen after contact with rodents or their excretions in the home. Some outbreaks have been associated with nosocomial transmission. Health care workers who are not protected by barrier precautions are at an increased risk of exposure.

Lassa fever and Lujo virus infections

Lassa virus infections are common in West Africa; seroprevalence rates of 7% to 55% have been reported among humans. Approximately 100,000 to 300,000 Lassa virus infections and about 5000 deaths are estimated to occur each year. Because mild cases resemble other illnesses, and adequate medical and diagnostic facilities may not be available, this disease is probably underreported. Cases tend to be more common in February to April. Most Lassa virus infections are subclinical or characterized by a mild flu-like illness; 5-20% of cases may become severe. The overall case fatality rate is 1-2% for all patients with this disease, but 15–25% in those who have been hospitalized. Higher case fatality rates have also been reported; in some outbreaks, up to half of the patients have died. Lassa fever tends to be more severe in pregnant women, with case fatality rates up to 30-50%. There is evidence that some strains of Lassa virus might be more pathogenic than others.

Little is known about Lujo virus, the only other arenavirus known to cause VHF in Africa. In the single known outbreak, four medical workers became infected after exposure to the index case or to secondary cases. The only survivor was a patient who was treated with ribavirin.

South American arenaviruses

Argentine hemorrhagic fever (Junin virus) was first recognized in the early 1950s. The region where this disease occurs has gradually been expanding, and by 1988, several hundred cases were being reported each year. Vaccination has decreased this number to fewer than 100 cases a year. Argentine hemorrhagic fever is usually seasonal, with cases peaking during the fall harvest season, when agricultural workers are exposed in aerosols. Many infections have been associated with corn harvesting equipment. The case fatality rate is approximately 15-30% if specific therapy is not given, but the use of immune plasma can decrease this rate to 1-2%.

Bolivian hemorrhagic fever (Machupo virus) emerged when new settlements were established in an area near the Amazon River. From 1959 to the early 1960s, more than a thousand cases were reported. In some towns, 18-21% of the inhabitants became ill, and the case fatality rate was as high as 18-41%. The overall case fatality rate for this disease is estimated to be approximately 20%. Most of the early infections occurred in people who worked on farms. Later, infections were also acquired within urban areas; *C. callosus*, the rodent host for Machupo virus, has a tendency to invade villages. Rodent control within affected villages was able to control this disease, and Bolivian hemorrhagic fever was not reported between 1976 and 1992. Nineteen cases were documented during an outbreak in the 1990s.

Chapare virus was discovered in 2003-2004. This virus was recovered from a fatal case of hemorrhagic fever in rural Bolivia, outside the area where Machupo virus is endemic. Additional cases were reported from this outbreak, but details and laboratory confirmation were unavailable for most patients.

Venezuelan hemorrhagic fever (Guanarito virus) is found in an agricultural area of northwestern Venezuela. This disease was first recognized in 1989, but sporadic cases probably occurred much earlier. It might have emerged due to increased contact with infected rodents after deforestation and human encroachment into rodent habitats. Venezuelan hemorrhagic fever is seasonal, peaking in November to January; approximately 200 cases have been confirmed. According to anecdotal reports, Guanarito virus might cause somewhat more severe disease than Junin or Machupo viruses. The case fatality rate can be as high as 33%.

Some Tacaribe serocomplex virus infections have been recognized rarely in people. Sabia virus was first isolated in 1994, from an agricultural worker who died of the disease. No other naturally acquired cases, and two laboratory acquired cases have been reported. Whitewater Arroyo virus has been tentatively linked to at least two fatal illnesses in California in 1999 and 2000. The infected individuals were prevously healthy. Two symptomatic Flexal virus infections, and a single Tacaribe virus infection have been documented in laboratory workers. Seroconversion to Pichinde virus has been reported frequently, but this virus has not been linked to hemorrhagic fever.

Infections in Animals

Arenaviruses in Rodents

With the exception of Tacaribe virus, which occurs in fruit-eating bats (*Artibeus* sp.), the reservoir hosts for the arenaviruses are rodents. Each virus is usually carried subclinically by one species. Old World arenaviruses are found in rodents in the subfamily Murinae and family Muridae, while New World arenaviruses have been detected in rodents from the subfamilies Sigmodontinae and Neotominae in the family Cricetidae. The reservoir hosts

for the viruses that cause VHFs are *Mastomys natalensis* (natal multimammate mouse) for Lassa virus, *Calomys callosus* (large vesper mouse) for Machupo virus, and *Zygodontomys brevicauda* (short-tailed cane mouse) for Guanarito virus. *Calomys musculinus*, the drylands vesper mouse or corn mouse, is the primary host for Junin virus. Evidence for Junin virus infections has also been reported in other rodents including *C. laucha* (small vesper mouse), *Akodon azarae* (grass field mouse) and *Bolomys obscurus* (dark field mouse), as well as in the predatory carnivore *Galictis cuja* (lesser grison, a member of the Mustelidae). The mammalian hosts for Chapare virus, Sabia virus and Lujo virus are not yet known.

The infection rate among rodents varies between sites and over time. The prevalence of Junin virus in *C. musculinus* is 5-10% in areas where Argentine hemorrhagic fever outbreaks are seen. Outside these areas, the infection rate is lower or the virus is absent. Limited surveys suggest that the distribution of Lassa virus may also be patchy; in one study, the prevalence in *M. natalensis* was 0-9%. Human exposure can be influenced by the behavior of the reservoir host. The rodent host for Junin virus, for example, occurs almost exclusively along linear habitats such as fence lines and roadsides. In contrast, the reservoir host for Lassa virus is widespread. Although the latter species, *M. natalensis*, is found throughout sub-Saharan Africa, its population dynamics and tendency to enter houses may vary with the region.

Arenaviruses can be carried lifelong in apparently healthy rodents; overt clinical signs have not been reported in naturally infected animals. Limited evidence from experimentally infected rodents suggests that some arenaviruses might affect fertility or survival. *C. musculinus* that were inoculated intranasally at birth with Junin virus had decreased weight gain while nursing and up to 60 days after inoculation. The mortality rate in these animals, examined 24-40 days after virus inoculation, was as high as 70%. They also became persistently infected and had fewer offspring than uninfected mice. Another study reported anemia, splenomegaly and decreased fertility in *Calomys callosus* that became persistently infected with Machupo virus, but not in animals that cleared the virus.

Arenaviruses in Other Mammals

Domesticated livestock, dogs and cats do not seem to be important in the epidemiology of arenavirus infections; however, their susceptibility to these viruses has not been fully investigated.

Experimental infections with Lassa, Junin and Machupo viruses have been established in nonhuman primates. Some species that are susceptible to Lassa virus include baboons (*Papio* spp.), rhesus macaques (*Macaca mulatta)* and squirrel monkeys (*Saimiri* spp.). In rhesus monkeys inoculated with this virus, the clinical signs included lethargy, anorexia, constipation, fever, conjunctivitis and a skin rash. In two experiments, the mortality rate was 53-60%. In baboons, Lassa virus can cause an illness resembling the severe form of Lassa fever in humans, with fever, lethargy and hemorrhages.

Rhesus macaques infected with Junin virus developed clinical signs including anorexia, lethargy, gastrointestinal signs and vascular phenomena similar to VHFs in humans. Ribavirin decreased the severity of the illness, but some treated animals had late onset neurological signs. Marmosets (*Callithrix jacchus)* infected with Junin virus had an acute illness with anemia, leukopenia and thrombocytopenia, with death in approximately 17–24 days. Immune serum treatment decreased the mortality rate in these animals from 100% to 25%, but late onset neurological signs were seen. Ribavirin also increased the survival rate in Junin virus-infected marmosets.

Machupo virus infections have been established in rhesus macaques, Geoffroy's tamarins (*Saguinus geoffroyi*), African green monkeys (*Chlorocebus sabaeus*) and marmosets. The clinical signs in African green monkeys, rhesus macaques and marmosets included anorexia, fever, conjunctivitis, depression, diarrhea, dehydration, shock, tremors, hemorrhages and an erythematous skin rash. The mortality rate was 80%-100%. Neurological signs such as tremors, nystagmus, incoordination, convulsions, muscle atrophy and paresis were reported in some rhesus macaques that survived. Whether any arenavirus infections occur naturally among non-human primates in endemic areas is unknown.

Laboratory rodents including mice and guinea pigs (*Cavia porcella*) can also be infected with arenaviruses. An unnatural route such as intracerebral injection is often used. In guinea pigs inoculated intraperitoneally with Junin virus, the illness resembles Argentine hemorrhagic fever in humans. Some strains of this virus cause severe disease, with fever, weight loss, hypothermic shock, signs of encephalitis or paralysis, and death in up to 100% of the animals. Other strains seem to be much less virulent, with little or no weight loss, no clinical signs other than occasional fever, and no deaths. Machupo virus infections have also been reported in guinea pigs. As of 2010, arenavirus infections have not been seen in pet rodents; however, veterinarians should be aware that imported exotic rodents might carry these viruses asymptomatically.

Internet Resources

Arenaviruses. in eMedicine
http://emedicine.medscape.com/article/212356-overview

Centers for Disease Control and Prevention (CDC) –Viral Hemorrhagic Fevers
http://www.cdc.gov/ncidod/diseases/virlfvr/virlfvr.htm

Medical Microbiology
http://www.ncbi.nlm.nih.gov/books/NBK7627

The Merck Manual
http://www.merck.com/pubs/mmanual/

Public Health Agency of Canada. Material Safety Data Sheets
http://www.phac-aspc.gc.ca/msds-ftss/index.html

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*Link defunct as of 2010

Viral Hemorrhagic Fevers Caused by Arenaviruses

Table 1: Selected arenaviruses and their known rodent hosts

Virus	Rodent Host(s)
Amapari	*Oryzomys gaeldi* (rice rat); Neacomys guianae (bristly mouse)
Bear Canyon	*Peromyscus californicus* (California mouse)
Catarina	*Neotoma micropus* (southern plains woodrat)
Chapare	unknown
Guanarito	*Zygodontomys brevicauda* (short-tailedcane mouse)
Ippy	*Arvicanthus* sp. (Nile grass rat)
Lassa	*Mastomys* (*Praomys*) *natalensis* (natal multimammate mouse)
Latino	*Calomys callosus* (large vesper mouse)
Lujo	unknown
Junin	*Calomys musculinus* (drylands vesper mouse or corn mouse); also other species
Merino Walk	*Myotomis unisulcatus*
Machupo	*Calomys callosus* (large vesper mouse)
Mobala	*Praomys* sp. (soft-furred rats)
Mopeia	*Mastomys* sp. (multimammate mice)
Morogoro	*Mastomys* sp. (multimammate mice)

Virus	Rodent Host(s)
Oliveros	*Bolomys* sp. (bolo mice)
Pinhal	*Calomys tener* (delicate vesper mouse)
Pirital	*Sigmodon alstoni* (Alston's cotton rat)
Sabia	unknown
Skinner Tank	*Neotoma mexicana* (Mexican woodrat)
Tacaribe	*Artibeus* sp. bats
Tamiami	*Sigmodon hispidus* (hispid cotton rat)
Whitewater Arroyo	*Neotoma albigula* (white-throated wood rat).