

# Viral Hemorrhagic Fevers Caused by Arenaviruses including Lassa, Junin, Machupo, Guanarito, Chapare, Sabia and Lujo viruses

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

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## Importance

Viral hemorrhagic fevers (VHFs) are infectious diseases that can result in vascular disruption and bleeding tendencies in a proportion of serious cases. The causative agents are diverse and include certain filoviruses, bunyaviruses, flaviviruses and arenaviruses. Arenaviruses known to cause VHFs include Lassa virus (Lassa fever), Junin virus (Argentine hemorrhagic fever), Machupo and Chapare viruses (Bolivian hemorrhagic fever), Guanarito virus (Venezuelan hemorrhagic fever), Sabia virus (Brazilian hemorrhagic fever) and Lujo virus. All are carried in wild rodents, which usually appear healthy, and humans are accidental hosts. Some frequently affect humans; others are known only from a handful of clinical cases, sometimes as a single index case that spread to a few close contacts. Wild rodents also carry many other arenaviruses, many of which are poorly understood, and additional VHF agents probably exist among them.

Human clinical cases caused by arenaviruses are generally similar, and range in severity from a mild flu-like illness to a life-threatening disease that can affect a number of body systems and may include neurological signs, mild to severe hemorrhagic signs, or both. They resemble many other illnesses common in endemic areas, such as dengue or malaria, and misdiagnoses are possible. In particular, some novel arenaviral VHFs were originally thought to be other diseases and only diagnosed after several healthcare workers or family members in close contact with the patient became ill or died. VHF-associated arenaviruses are not known to affect any domestic animals, though they might cause disease in nonhuman primates and/or some rodents.

## Etiology

Arenaviruses that infect mammals, previously placed in the genus *Arenavirus* in the family *Arenaviridae*, order *Bunyavirales*, have all been transferred to the new genus *Mammarenavirus* in this family. Mammarenaviruses are divided into two genetically distinct groups, which circulate in different hemispheres. The members of the Lassa-lymphocytic choriomeningitis complex are endemic in the Eastern Hemisphere, while the New World or Tacaribe complex occurs in the Western Hemisphere. Although more than 40 mammarenaviruses have been identified in animals, only a few have been linked to human illnesses.

The Old World complex arenaviruses currently known to cause VHFs are Lassa virus (official species name *Lassa mammarenavirus*), which causes Lassa fever, and Lujo virus (*Lujo mammarenavirus*). VHFs can also be caused by members of the New World/Tacaribe complex including Junin virus (*Junin mammarenavirus*; Argentine hemorrhagic fever), Guanarito virus (*Guanarito mammarenavirus*; Venezuelan hemorrhagic fever), Sabia virus (*Sabia mammarenavirus*; Brazilian hemorrhagic fever), Machupo virus (*Machupo mammarenavirus*; Bolivian hemorrhagic fever) and Chapare virus (*Chapare mammarenavirus*). As Chapare virus also circulates in Bolivia, some authors consider it to also be an agent of Bolivian hemorrhagic fever. The diseases caused by Junin, Machupo, Chapare, Guanarito and Sabia viruses are collectively known as the South American hemorrhagic fevers.

Some VHF-causing arenaviruses, in particular Lujo virus, Sabia virus and Chapare virus, are known from only a few clinical cases and are poorly understood. It is likely that there are also other mammarenaviruses in rodents that can cause VHFs. In 2022, a report described a fatal VHF-like illness in Brazil, which was caused by an apparently novel arenavirus that had 87-89% identity to Sabia virus in two of its gene segments. Whitewater Arroyo virus was linked to two fatal cases of hemorrhagic fever in California, and is currently the only North American arenavirus that might be a VHF pathogen. Others arenaviruses either do not seem to be pathogenic to humans or are of uncertain disease potential. Flexal virus in South America and Tacaribe virus in the Caribbean have each caused one or two febrile illnesses in laboratory workers. None was severe or accompanied by hemorrhagic signs; however, this is not necessarily inconsistent with the virus being a potential VHF pathogen. Pichinde virus, found in Colombia, appears to be nonpathogenic. While a number of people exposed to Pichinde virus have seroconverted, none became ill.

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Lymphocytic choriomeningitis virus, an Old World/Tacaribe complex mammarenavirus of rodents not discussed in this factsheet, can affect humans but does not cause VHF. A description of lymphocytic choriomeningitis can be found in a factsheet at <http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php>.

## Species Affected

### Reservoir hosts, other rodents and bats

Almost all of the currently known mammarenaviruses circulate in rodents. Until recently, each virus was thought to be mostly limited to one or two hosts with which it had co-evolved. It now appears that, while each virus has primary reservoir hosts, it can also occur in other rodents.

The hosts for Old World mammarenaviruses are mainly members of the subfamily Murinae in the family Muridae. *Mastomys natalensis*, the natal multimammate mouse, is the primary reservoir host for Lassa virus. Evidence for Lassa virus infections has also been reported in other African rodents (e.g., *Hylomyscus pamfi*, *Lemniscomys striatus*, and mice and rats in the genera *Mus*, *Praomys* and *Rattus*), as well as shrews (*Corcidura* spp.). The host(s) of Lujo virus are currently unknown.

New World mammarenaviruses reservoirs are rodents in the subfamilies Sigmodontinae and Neotominae in the family Cricetidae. Junin virus is thought to be maintained primarily in *Calomys musculinus*, the drylands vesper mouse or corn mouse, and *C. laucha*, the small vesper mouse. There are reports of Junin virus antigens and/or antibodies in other species including *Akodon azarae* (grass field mouse), *Bolomys obscurus* (dark field mouse), *Mus musculus* (house mouse) and *Oligoryzomys flavescens* (yellow pigmy rice rat). *Calomys callosus*, the large vesper mouse, is known to carry Machupo virus. This mouse can also become chronically infected with Junin virus after experimental inoculation, though this is not known to occur outside the laboratory.

*Zygodontomys brevicauda*, the short-tailed cane mouse, appears to be a reservoir host for Guanarito virus. This virus is also found occasionally in *Sigmodon alstoni* (Alston's cotton rat), which often lives in close proximity to *Z. brevicauda*, and one study found antibodies in a small number of *Rattus rattus* (the black rat). The hosts for Chapare virus and Sabia virus are not yet known, but they are assumed to be rodents as well. Nucleic acids of Chapare virus were recently found in *Oligoryzomys microtis*, the small-eared pigmy rice rat, which was proposed as a possible reservoir host. *Oryzomys* spp. are reservoirs for Flexal virus, and Whitewater Arroyo virus has been found in *Neotoma albigula* (white-throated wood rat), *N. mexicana*, *N. micropus* and *N. cinerea*.

Laboratory mice (*Mus musculus*) and domestic guinea pigs (*Cavia porcella*) are used as experimental models for human VHFs. Guinea pig studies often use strain 13 animals, an inbred laboratory line that is particularly susceptible to mammarenaviruses, but outbred guinea pigs can also be infected. Highly artificial routes such as intracerebral or

intraperitoneal injection are often employed in these studies; however, there are reports of animals infected by aerosols and intranasal, subcutaneous or intramuscular inoculation, suggesting that naturally acquired infections might be possible. Machupo virus can infect newborn hamsters, though not adults, via intranasal inoculation.

Bats can host some mammarenaviruses, but whether they are reservoir hosts is currently unclear. Tacaribe virus was originally isolated from Jamaican fruit bats (*Artibeus jamaicensis*) and great fruit-eating bats (*A. lituratus*), which were thought to be its reservoirs. This has recently been questioned, based on a study of experimentally infected Jamaican fruit bats which suggested these animals might not readily transmit the virus to each other, as well as the isolation of Tacaribe virus from several pools of *Amblyomma americanum* ticks, which do not commonly feed on bats. Antibodies to this virus have also been detected in some other bats including vampire bats (*Desmodus rotundus*). Tacaribe virus was the only arenavirus known to infect bats at one time, but researchers recently found a novel virus called Tiete mammarenavirus in *Carollinus* spp. bats.

### Incidental hosts

Non-human primates have long been used as animal models for human arenaviral VHFs. However, there was no evidence for naturally occurring infections in these animals until a 2019 study found Lassa virus antibodies and antigens in mona monkeys (*Cercopithecus mona*) and antibodies in Anubis baboons (*Papio anubis*) during surveillance of zoo, pet and peridomestic primates in Nigeria. Several other primate species were all seronegative, and the authors suggested that mona monkeys, which had higher seroprevalence rates than the baboons, may be disproportionately exposed to rodents due to their habit of scavenging in human trash dumps.

A wide variety of primates can be infected with mammarenaviruses in the laboratory. Lassa virus infections have been established in baboons (*Papio* spp.), rhesus macaques (*Macaca mulatta*), cynomolgus macaques (*Macaca fascicularis*), common marmosets (*Callithrix jacchus*), African green monkeys (*Chlorocebus sabaeus*), squirrel monkeys (*Saimiri* spp.) and capuchin monkeys (*Cebus* spp.), among others. There are reports of experimental Junin virus infections in rhesus macaques, common marmosets, capuchin monkeys and other species; Machupo virus infections in rhesus and cynomolgus macaques, Geoffroy's tamarins (*Saguinus geoffroyi*) and African green monkeys; Guanarito virus infections in rhesus macaques; and Tacaribe virus infections in common marmosets.

Mammarenaviruses do not seem to cause any illnesses in livestock, dogs or cats, though antibodies to Lassa virus were found in some dogs in Africa. One study that reported seropositive dogs could not detect antibodies to this virus in sheep, goats, cattle or guinea pigs. A wild mustelid, the lesser grison (*Galictis cuja*) was found to have antibodies to Junin virus in Argentina. Horses, cats and rabbits experimentally

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infected with Machupo virus seroconverted but did not become ill, while pigs, chickens, turtles and opossums (*Didelphus* spp.) remained seronegative.

## Zoonotic potential

Lassa, Lujo, Junin, Machupo, Chapare, Guanarito, Sabia and Whitewater Arroyo viruses, as well as a Sabia-like virus described in Brazil in 2020, can cause VHFs in humans. Tacaribe and Flexal viruses have rarely caused illnesses in people, and are currently not known to cause any VHF-like signs.

## Geographic Distribution

Mammarenaviruses can be found in rodents in many locations worldwide, but the viruses that cause VHFs have mainly been reported in parts of Africa and South America. They seem to be restricted by the distribution of their primary rodent reservoir host(s) and, in many cases, by poorly understood factors that limit them to only part of that host's geographic range.

Lassa fever has been reported only from West Africa and is most common in Nigeria, Liberia, Guinea and Sierra Leone, though *M. natalensis* is widespread in sub-Saharan Africa. The distribution of Lujo virus is uncertain. One person became infected from an unknown source in Zambia, and the only other known cases were medical personnel exposed to this person in Zambia and South Africa.

In South America, VHFs have been caused by Junin virus in Argentina, Machupo and Chapare viruses in Bolivia, Guanarito virus in western Venezuela, and Sabia virus and a new Sabia-like virus in Brazil. While a number of mammarenaviruses have been isolated in North America, only Whitewater Arroyo virus in California is reported to be a possible VHF pathogen.

Of the zoonotic viruses with uncertain VHF potential, Flexal virus was detected in Brazil, while Tacaribe virus has been found in the Caribbean and Florida. Antibodies to the latter virus were also detected in a bat in Guatemala, raising the possibility that its range includes parts of the South American mainland, though cross-reactive antibodies to another virus cannot be ruled out.

## Transmission

Infected rodents can shed mammarenaviruses in many secretions and excretions including urine, saliva and respiratory secretions. They are thought to spread these viruses to each other during close contact (e.g., fighting, mating, huddling), and might also acquire them from contaminated environments. Aerosol transmission also seems to occur in some cases. Lassa and Machupo viruses have been transmitted between guinea pigs in different cages, and Lassa virus spread from caged guinea pigs to monkeys kept in the same room. *M. natalensis* can transmit Lassa virus vertically to its offspring *in utero*, as well as after birth; however, this seems to be limited or absent for Junin virus, Machupo virus and Guanarito virus, which are reported to decrease the fertility of their reservoir hosts

and/or kill fetuses *in utero*. Nevertheless, many pups born to Junin or Machupo virus-infected dams carry the virus by the time they are weaned. Offspring of guinea pigs experimentally infected with Junin virus were sometimes infected at birth.

Tacaribe virus has been isolated from the salivary glands of naturally infected *Artibeus* spp. bats, and viral nucleic acids were found in the oral secretions and feces of experimentally infected Jamaican fruit bats. Despite this, there was no clear evidence that experimentally infected bats transmitted the virus to uninfected bats placed in their cages.

Humans are thought to become infected with mammarenaviruses through mucous membranes or broken skin. Exposure may occur via bites, during the preparation of certain species (e.g., *M. natalensis*) for food, or other forms of direct contact with rodents, but in many cases the virus is thought to be acquired from an environment contaminated with rodent excretions and secretions, often via aerosols or contaminated food. In humans, mammarenaviruses and/or their nucleic acids have been found in urine, feces, saliva/respiratory secretions, ocular secretions, breast milk, colostrum and semen, as well as blood. Prolonged shedding has been reported in some hospitalized patients. Person-to-person transmission seems to occur mainly during close contact, though there are reports of some viruses infecting hospital workers who had only indirect patient contact, e.g., people who cleaned patient's rooms. Venereal transmission is also suspected to occur. Infectious Lassa virus has been detected in the semen of some men for up to 9 months and infectious Chapare virus for up to 3 months, with viral RNA found for longer periods, Mammarenaviruses can also be transmitted to the fetus *in utero*.

Mammarenaviruses are not normally transmitted by arthropods; however, Tacaribe virus was isolated several times from *Amblyomma americanum* ticks in Florida. Earlier, it was isolated from one pool of 344 mosquitoes, out of more than a million mosquitoes processed. The significance of these findings is still uncertain, as ticks and mosquitoes can acquire a virus in a recent blood meal without being competent vectors.

## Disinfection

Arenaviruses can be inactivated by most detergents and disinfectants including sodium hypochlorite, phenolic compounds, some acids (e.g., 3% acetic acid, peracetic acid), glutaraldehyde and formaldehyde. Experiments on some viruses also reported susceptibility to 70% alcohol, hydrogen peroxide, quaternary ammonium compounds, iodophors and/or lipid solvents. Junin and Machupo viruses are susceptible to temperatures of 56°C (133°F) for 30 minutes, while Lassa virus in serum was inactivated by heating serum at 60°C (140°F) for one hour. Ultraviolet light or gamma irradiation, and pH less than 5.5 or greater than 8.5 can also inactivate mammarenaviruses.



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## Infections in Animals

### Rodent Reservoirs

Many of the rodent hosts of arenaviruses seem to remain infected and shed these viruses for long periods, possibly lifelong. Neonates often seem to become tolerant and persistently infected. Adults can clear these viruses more readily, though some individuals remain infected for several months or more before eliminating the virus, and others might remain infected for life. Persistently infected reservoir hosts may or may not be seropositive.

Clinical signs have not been reported in the natural rodent hosts of arenaviruses in the wild, but experimental infections suggest that Junin, Machupo and Guanarito viruses affect fertility and can cause lethal infections in the fetus. Junin virus infections of neonatal *C. musculus* and Machupo virus infections of *C. callosus* were also found to slow their growth and increase mortality in growing pups. *C. callosus* that became persistently infected with Machupo virus developed anemia and splenomegaly. Certain laboratory strains of Junin virus have been reported to cause neurological signs in young *C. musculus* and some intranasally inoculated adults, though other strains, including viruses isolated from wild rodents, did not. Survival and recovery from neurological signs varied. One study found consistent microscopic evidence for moderate meningoencephalitis in *M. natalensis* inoculated with Lassa virus as adults, though no overt clinical signs were mentioned.

### Laboratory Rodents

Guinea pigs, mice and hamsters are most readily infected with mammarenaviruses during the neonatal period. Adults are often resistant. Many studies use strain 13 guinea pigs, which tend to have more severe illnesses, but other guinea pigs can also develop clinical signs, with lower morbidity and mortality rates.

Lassa virus infected guinea pigs can develop nonspecific signs of illness, sometimes accompanied by respiratory insufficiency. Mortality varies with the viral dose and route of inoculation and the animal's genetic background, but it is sometimes > 50% in strain 13 animals. Gross lesions included pulmonary edema and consolidation, pleural effusion, myocarditis, ascites, and focal calcifications in the heart and liver. Lujo virus inoculated intraperitoneally into strain 13 guinea pigs resulted in fever and other nonspecific signs of illness, with 100% mortality. At necropsy, the liver was often pale and friable, with reticular patterns suggestive of hepatic congestion and/or pale necrotic areas with a hyperemic rim. Other reported lesions were congested and hemorrhagic lymph nodes, pale yellow to hemorrhagic ascitic fluid, a distended jejunum, moderately to severely enlarged flaccid hearts, and petechiae and other hemorrhages on the serosa and/or mucosa of some abdominal organs (e.g., distal cecum, urinary bladder), with signs of profound coagulopathy terminally.

The effects of Junin virus in guinea pigs range from subclinical infections and mild illnesses, consisting of occasional fever, little or no weight loss, and few or no deaths, to severe disease with up to 100% mortality. In severe cases, the clinical signs may include fever, weight loss, hemorrhages and/or signs of encephalitis or paralysis, particularly progressive hindleg paralysis. Neurological signs tend to be seen mainly in animals that survive longer. Pregnant guinea may have reproductive losses, including stillbirths, and elevated mortality has been reported during the first 3 weeks in offspring born alive. Gross lesions reported in guinea pigs include petechiae and other hemorrhages in internal organs and subcutaneous tissues, interstitial pneumonia, and signs of inflammation and necrosis in the liver. Machupo and Guanarito viruses can also be lethal to guinea pigs, but guinea pigs inoculated with Tacaribe virus did not become ill. Mortality rates in Machupo virus-infected animals ranged from 20% to 80%.

### Bats and Tacaribe Virus

Some Tacaribe virus-infected Jamaican fruit bats and great fruit-eating bats found in the wild exhibited clinical signs similar to bat rabies (e.g., unusual behavior, difficulty flying) while others appeared healthy. Experimental inoculation of Jamaican fruit bats with low viral doses resulted in subclinical infections, while some bats given higher doses developed neurological signs (tremors, incoordination and/or inability to fly), with substantial mortality. Affected bats had CNS lesions (lymphocytic leptomeningitis, mild to moderate multifocal gliosis in the brainstem and prosencephalon, mild neutrophilic encephalitis of the prosencephalon), and in some cases, interstitial pneumonia, myocardial lesions, splenitis, mild to moderate multifocal hepatocellular necrosis, and mild to moderate neutrophilic enteritis.

### Nonhuman Primates

No clinical signs were reported in Lassa virus-infected rhesus monkeys or baboons found in Africa but, with the possible exception of one animal that had viral antigens, serology indicated that all of these animals had been infected some time before the study.

Experiments suggest that some species of nonhuman primates are relatively resistant to mammarenaviruses. Some animals, such as howler monkeys (*Alouetta caraya*), squirrel monkeys and three-striped owl monkeys (*Aotus trivirgatus*) inoculated with Junin virus, or capuchin and owl monkeys inoculated with Machupo virus, did not become ill, though they seroconverted. Others developed various mild to moderate clinical signs, often with full recovery. In one study, one of four squirrel monkeys inoculated with Lassa virus remained asymptomatic; another suddenly became severely depressed, with drooling and episodic tremors, but recovered completely after 2 days; the third had anorexia, polydipsia and lassitude for 10 days, and was beginning to recover at the end of the experiment; and the fourth had a prolonged, progressive illness with anorexia, depression and

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polydipsia, and eventually became moribund. The incubation period in this study varied from 8 to 18 days. Several capuchin monkeys inoculated with Lassa virus experienced “mild infections” with no mortality, though more susceptible primate species given the same viral dose often died. Wild-caught capuchin monkeys administered several different Junin virus strains sometimes had intermittent mild lethargy, mild anorexia or elevated body temperature, but did not become overtly ill. A similar study that used a laboratory-derived Junin strain reported mild illnesses with lymphadenopathy, weight loss and thrombocytopenia, with a late onset neurological syndrome in one of four animals.

Other species, such as rhesus and cynomolgus macaques, African green monkeys, marmosets and Geoffrey’s tamarins infected with various mammarenaviruses develop more severe illnesses. The incubation period ranges from about 5-6 days to 2-3 weeks. In addition to fever, lethargy, anorexia and weight loss, some animals may have facial edema, diarrhea, a macular rash, oral ulcerations and a nasal discharge. Thrombocytopenia is common, though generally more severe in animals inoculated with South American arenaviruses, and some animals develop various hemorrhagic signs. Purulent conjunctivitis from secondary bacterial infections has also been reported, and labored breathing may be seen in animals inoculated via aerosols. Blood chemistries often indicate damage to the liver. Neurological signs (e.g., tremors, nystagmus, ataxia, limb paresis, convulsions) often develop late, and can affect animals that appear to be recovering. Gross lesions are variable but liver lesions (e.g., congestion, enlargement, pale discoloration, increased friability, pale foci) are common, and some animals have petechiae or other hemorrhages on the mucosa or serosa of internal organs. Some studies have reported only mild histopathological lesions in various organs, and no gross lesions.

Mortality rates of 50-100% are common in highly susceptible primates, though this may be partly due to the viral dose they are given. However, there are occasional studies reporting milder outcomes. While Junin virus infections of rhesus macaques are often severe, isolates that cause only mild illnesses in this species, with recovery of all animals, have been described. Guanarito virus inoculated subcutaneously into rhesus macaques caused fever, reduced appetite and lethargy, but the animals all recovered.

Tacaribe virus did not cause any clinical signs in common marmosets, though they developed cross-protective immunity to Junin virus.

## Infections in Humans

### Incubation Period

The incubation period is usually around 1-2 weeks, but ranges from 2-3 days to 3 weeks. Very short incubation periods usually occur after high dose exposures, typically in a laboratory accident.

### Clinical Signs

Arenaviruses can cause subclinical infections as well as mild to fatal disease in humans. Clinical cases usually begin with a flu-like illness, after which some patients recover, while others develop more severe symptoms that can include vascular effects such as hemorrhages and capillary leak syndrome, as well as neurological signs.

#### *Lassa fever and Lujo virus infection*

Lassa fever usually begins as a nonspecific flu-like illness of variable severity, with fever and other nonspecific signs such as malaise, anorexia, headache and myalgia. Some patients also develop gastrointestinal signs (e.g., diarrhea, nausea, vomiting or abdominal discomfort), a sore throat, conjunctival injection, arthralgia, a dry cough, chest pain, or a maculopapular or petechial rash. The rash usually affects the chest, face and arms, and is most easily discerned in those with lighter skin.

Most patients recover after this stage, but some progress to a more severe illness that may include edema, especially on the face and neck, pleural or pericardial effusion, hypotension or hypovolemic shock, and signs of organ dysfunction (e.g., hepatitis, multiorgan failure). Bleeding tendencies occur in approximately 15-20% of serious cases, and most often appear as mild oozing from the nose or mouth, though melena, hematemesis, hematuria, vaginal bleeding and other hemorrhages are also reported. Critically ill patients often have neurological signs such as confusion, disorientation, locomotor dysfunction, tremors and convulsions. Fetal losses are common in pregnant women, especially during the third trimester, with septic abortion reported to be common in West Africa. In infants, Lassa fever is often characterized by generalized edema, abdominal distention and bleeding, and is frequently fatal. Convalescence can be prolonged in severely ill patients who recover. Transient or permanent deafness is a common sequela of Lassa fever, regardless of disease severity. Other complications, such as orchitis or uveitis, are rare.

A small cluster of five cases caused by Lujo virus resembled severe Lassa fever, with most patients developing various hemorrhagic signs, edema and/or a rash, and one with neurological signs from cerebral edema. Four of these cases were fatal.

#### *South American hemorrhagic fevers*

Only minor differences have been reported between the South American hemorrhagic fevers. These illnesses resemble Lassa fever, though hemorrhages and/or neurological signs appear to be more common. During the early flu-like stage, myalgia is reported to be most severe in the lower back. Most people improve after a week or two, but an estimated 25-30% of untreated cases become severe, with some patients developing edema, hypotension or hypovolemic shock, organ dysfunction, bleeding tendencies, neurological signs and other signs similar to severe Lassa fever. Blood loss is usually minor, though life-threatening internal bleeding has been reported. Petechiae are reported to

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be common in the pharynx and on the skin, especially the chest, arms and axillae. Pulmonary edema can be a significant cause of death. Pregnant women often abort, though there is at least one report of a woman who recovered later giving birth to a healthy child. Junin virus has been reported to cause congenital malformations. Survivors usually recover completely, though convalescence may take several weeks or months in severe cases.

Approximately 10% of Argentine hemorrhagic fever patients treated with immune plasma develop a late onset neurological syndrome about 4-5 weeks later. Common clinical signs in this condition include headache, dizziness, cerebellar ataxia, dysarthria, nystagmus, diplopia and vomiting, accompanied by fever. The illness is usually self-limiting with complete recovery within a few months; however, one patient died from ascending paralysis that resulted in respiratory failure.

## Infections with other arenaviruses

Three fatal VHF-like illnesses were attributed to possible Whitewater Arroyo virus infections in California in 1999 and 2000. All three cases were similar and characterized by an initial non-specific febrile illness with headache and myalgia, followed by acute respiratory distress syndrome, thrombocytopenia, liver failure and hemorrhagic signs. Further laboratory testing did not confirm the diagnosis in one patient, however, Whitewater Arroyo virus-associated VHF remains a possibility in the other two.

Febrile illnesses without hemorrhages were documented in two laboratory workers infected with Flexal virus, and one laboratory worker infected with Tacaribe virus, who reportedly had an influenza-like illness with fever and mild CNS signs. None of these cases was life-threatening. A number of people exposed to Pichinde virus have seroconverted, but there are no reports of any clinical cases from this virus.

## Diagnostic Tests

Mammarenaviruses, their nucleic acids and antigens can be found in blood, saliva/ oropharyngeal fluid, urine, and in some cases, cerebrospinal fluid (CSF). They can also be detected in various tissues after death.

RT-PCR tests have been validated for some diseases, and are frequently used to diagnose Lassa fever. Some assays detect a wide range of arenaviruses, while others are specific for one or more agents. Test availability varies, and RT-PCR tests for some of the rarer viruses, such as Sabia virus, may be difficult or impossible to find. Some Lassa fever PCR tests may not detect all Lassa virus isolates.

Arenaviral antigens can be detected with antigen-capture ELISAs, though this test is sometimes negative in the later stages of the illness. Various rapid tests have also been described, and a lateral flow assay for Lassa fever is available in some countries. Immunohistochemistry can be employed post-mortem on tissues. Mammarenaviruses can be isolated in Vero cells or other cell lines, but this requires biosafety level 4 laboratories and it is rarely done. Virus isolation in

laboratory rodents was mainly used in the past and also requires high biosafety conditions.

Serology can also be employed in the diagnosis of arenavirus VHFs, and is particularly useful in Lassa fever. Lassa virus-specific IgM can usually be found by the second week of illness, and many patients are seropositive on presentation. Antibodies usually appear more slowly in South American hemorrhagic fevers, typically in the third week. ELISAs, which can detect either IgM or IgG, are the most commonly used serological tests, but indirect fluorescent antibody (IFA) tests and virus neutralization may also be available. Cross-reactivity between different mammarenaviruses can be an issue in ELISAs and IFA, while virus neutralization tests, are highly specific. However, patients with Lassa fever do not usually develop neutralizing antibodies until weeks after they became ill. In general, serological diagnosis requires a fourfold rise in titer or the detection of specific IgM. However, there are reports of IgM in some people without Lassa fever symptoms, and some authors suggest also documenting the development of specific IgG.

## Treatment

In addition to symptomatic treatment, human immune plasma can significantly increase survival in Argentine hemorrhagic fever. It is most effective if started early. Specific immune plasma has also been suggested for Bolivian hemorrhagic fever, but finding a source is likely to be difficult, as relatively few cases are seen and there are no plasma banks. Plasma has generally been disappointing in treating Lassa fever.

Ribavirin is often given to Lassa fever patients, and it has also been employed in some clinical cases caused by other arenaviruses. However, the routine use of this drug in Lassa fever has recently become controversial. There is very limited experience with other antiviral drugs.

## Prevention

The risk of infection with an arenavirus can be decreased by avoiding contact with the reservoir hosts, their secretions and excretions, and potentially contaminated food or water. Rodent trapping programs and other measures to reduce exposure in and around homes (e.g., the use of rodent-proof containers for food) are particularly useful for viruses such as Lassa virus, which is often acquired inside the home. Guidelines for cleaning rodent-infested areas are available from various agencies. In particular, care should be taken to avoid aerosolizing dust and droppings during clean-up.

A live attenuated vaccine is available for Junin virus, which is often acquired during agricultural activities. Animal studies suggest that this vaccine might also provide some protection against Machupo virus, though not against Guanarito virus or Sabia virus. Various rodent control measures have been suggested for reducing human exposures to arenaviruses that tend to be acquired outdoors, though their efficacy is unclear.



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Barrier nursing precautions, including the use of appropriate personal protective measures, should be employed when caring for arenavirus-infected patients. Additional precautions, such as the use of N95 respirators, are recommended for procedures such as endotracheal intubation that may generate aerosols.

## Morbidity and Mortality

### *Lassa fever and Lujo virus infections*

Lassa fever is a common disease in West Africa, where 100,000 or more cases are estimated to occur each year. It is seasonal to some extent, with cases most common between January and April. Most infections are thought to be acquired in houses infested by the rodent reservoir. Seroprevalence rates in this region range from 7% to 55%, and the disease, which often resembles other illnesses when mild, is probably underreported. Approximately 80-95% of Lassa virus infections are thought to be subclinical or mild, and the overall mortality rate is thought to be < 5%, though higher rates have been reported in some outbreaks or certain groups, such as pregnant women, which have a high incidence of septic abortion, and infants, which often die. Overall, the case fatality rate in seriously ill people admitted to West African hospitals is estimated to be about 10-20%.

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 ill after exposure to the index case, a healthy 36-year old, or other infected patients. The only survivor was a medical worker who received intensive care and ribavirin. More than 90 additional hospital workers, including at least 30 estimated to have had high risk-contact with these patients, were monitored but did not become ill.

### *South American arenaviruses*

Argentine hemorrhagic fever was first recognized in the early 1950s. This disease is usually seasonal, with cases peaking during the fall harvest season, when agricultural workers are exposed to Junin virus in aerosols from harvesting equipment. The region where it has been recognized has gradually been expanding, and by 1988, several hundred cases were being reported each year. However, this number decreased significantly after a vaccine became available. Venezuelan hemorrhagic fever, which was first recognized in 1989, also occurs in an agricultural region. It might have emerged after increased encroachment into the habitats of Guanarito virus-infected rodents, though sporadic cases are thought to have occurred earlier. Its incidence is unclear, but at least 600 clinical cases had been documented as of 2006. Cases seem to be most common between November and January.

Bolivian hemorrhagic fever emerged when new settlements were established in an area near the Amazon River. More than a thousand cases were reported between 1959 and the early 1960s, and affected 18-21% of the inhabitants of some towns. While most early cases were acquired on farms, they also occurred later in urban areas.

Some reports suggest that the outbreaks may have been facilitated by a drop in the feline population, thought to have been caused by neurological disease from DDT. Bolivian hemorrhagic fever was not documented between 1976 and 1992, but 19 cases were seen during an outbreak in the 1990s. Chapare virus was discovered in 2003-2004, in a cluster of Bolivian hemorrhagic fever cases outside the area where Machupo virus is usually seen. It was found again in a cluster of 5 cases in 2019, and increased awareness resulted in the identification of four more cases in 2019 and 2020.

Some South American arenaviruses have been recognized very rarely in people. Sabia virus was first detected in 1994, in a 25-year-old agricultural worker who died of the disease. Another fatal case was seen in a 32-year-old, while two additional cases occurred in laboratory workers. One mainly had prolonged influenza-like signs and recovered with relatively limited medical support; the other was hospitalized but survived. A recent case caused by a Sabia-like virus in a healthy 52-year-old was fatal.

South American hemorrhagic fevers appear to have a relatively high mortality rate, and can cause deaths in young, healthy people as well as those who are elderly or in poor health. The case fatality rate in Argentine hemorrhagic fever has been estimated to be about 15-30% if specific therapy is not given, though the use of immune plasma can decrease this rate to 1-2%. The other South American viruses seem to have similar case fatality rates, with an estimate of about 20% in Bolivian hemorrhagic fever, though there are reports of deaths in up to 41% of the cases in some towns during the initial outbreaks, and 23% in Venezuelan hemorrhagic fever. Reports of Chapare virus infections are limited, but 8 of the 17 known cases were fatal. However, it is possible that milder illnesses and asymptomatic infections with these viruses are underdiagnosed. Antibodies to Guanarito virus or related viruses were found in approximately 10% of unaffected family members during the Venezuelan hemorrhagic fever outbreak in 1989, while later surveillance detected antibodies in 3.6% of the community. Antibodies to Junin virus were detected in some unvaccinated migrant workers with no history of this disease, and unpublished serological studies suggests that Machupo virus can cause some milder cases and asymptomatic infections.

Neither Flexal nor Tacaribe virus is known to have caused any severe illnesses, to date, though few cases are known.

## Internet Resources

[Medscape eMedicine Arenaviruses](#)

[Public Health Agency of Canada. Pathogen Safety Data Sheets](#)

[The Merck Manual](#)

[World Health Organization. Lassa fever](#)

# Viral Hemorrhagic Fevers Caused by Arenaviruses

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## References

- Atkin S, Anaraki S, Gothard P, Walsh A, Brown D, Gopal R, Hand J, Morgan D. The first case of Lassa fever imported from Mali to the United Kingdom, February 2009. *Euro Surveill*. 2009;14. pii: 19145.
- Baskin GB. Pathology of nonhuman primates [online]. Primate Info Net. Wisconsin Primate Research Center; 2002 Feb. Available at: <http://www.primate.wisc.edu/pin/pola6-99.html>. \* Accessed 23 Oct 2002.
- Bell TM, Shaia CI, Bunton TE, Robinson CG, Wilkinson ER, Hensley LE, Cashman KA. Pathology of experimental Machupo virus infection, Chicava strain, in cynomolgus macaques (*Macaca fascicularis*) by intramuscular and aerosol exposure. *Vet Pathol*. 2015;52(1):26-37.
- Bentim Góes LG, Fischer C, Almeida Campos AC, de Carvalho C, Moreira-Soto A, Ambar G, Ruckert da Rosa A, de Oliveira DC, Jo WK, Cruz-Neto AP, Pedro WA, Queiroz LH, Minoprio P, Durigon EL, Drexler JF. Highly diverse arenaviruses in neotropical bats, Brazil. *Emerg Infect Dis*. 2022;28(12):2528-33.
- Bird BH, Dodd KA, Erickson BR, Albariño CG, Chakrabarti AK, McMullan LK, Bergeron E, Ströeher U, Cannon D, Martin B, Coleman-McCray JD, Nichol ST, Spiropoulou CF. Severe hemorrhagic fever in strain 13/N guinea pigs infected with Lujo virus. *PLoS Negl Trop Dis*. 2012;6(8):e1801.
- Bossi P, Tegnell A, Baka A, Van Loock F, Hendriks J, Werner A, Maidhof H, Gouvras G; Task Force on Biological and Chemical Agent Threats, Public Health Directorate, European Commission, Luxembourg. Bichat guidelines for the clinical management of haemorrhagic fever viruses and bioterrorism-related haemorrhagic fever viruses. *Euro Surveill*. 2004;9(12):E11-2.
- Cajimat MN, Milazzo ML, Rollin PE, Nichol ST, Bowen MD, Ksiazek TG, Fulhorst CF. Genetic diversity among Bolivian arenaviruses. *Virus Res*. 2009;140(1-2):24-31.
- Callis RT, Jahrling PB, DePaoli A. Pathology of Lassa virus infection in the rhesus monkey. *Am J Trop Med Hyg*. 1982;31(5):1038-45.
- Carballal G, Cossio PM, Oubina IR, De La Vega MT, Nagle C, Casanova MB, Gonzales PH, Arana RM. Infeccion experimental de un primate sudamericano, el *Cebus* sp., con la cepa XI de virus Junin. *Medicina (B Aires)*. 1983;43:639-46.
- Carballal G, Videla CM, Merani MS. Epidemiology of Argentine hemorrhagic fever. *Eur J Epidemiol*. 1988;4(2):259-74.
- Carrion R, Brasky K, Mansfield K, Johnson C, Gonzales M, Ticer A, Lukasevich I, Tardif S, Patterson J. Lassa virus infection in experimentally infected marmosets: liver pathology and immunophenotypic alterations in target tissues. *J Virol*. 2007;81(12):6482-90.
- Centers for Disease Control and Prevention (CDC). Fatal illnesses associated with a new world arenavirus--California, 1999-2000. *MMWR Morb Mortal Wkly Rep*. 2000;49(31):709-11.
- Centers for Disease Control and Prevention (CDC). Lassa fever [online]. CDC; 2004 Dec. Available at: <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/lassaf.htm>. \* Accessed 13 Feb 2010.
- Centers for Disease Control and Prevention (CDC). Viral hemorrhagic fevers [online]. CDC; 2004 Aug. Available at: <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/vhf.htm>. \* Accessed 13 Feb 2010.
- Charrel RN, de Lamballerie X. Arenaviruses other than Lassa virus. *Antiviral Res*. 2003;57(1-2):89-100.
- Charrel RN, de Lamballerie X. Zoonotic aspects of arenavirus infections. *Vet Microbiol*. 2010;140(3-4):213-20.
- Charrel RN, de Lamballerie X, Emonet S. Phylogeny of the genus *Arenavirus*. *Curr Opin Microbiol*. 2008;11(4):362-8.
- Cheng HY, French CE, Salam AP, Dawson S, McAleenan A, McGuinness LA, Savović J, Horby PW, Sterne JAC. Lack of evidence for ribavirin treatment of Lassa fever in systematic review of published and unpublished studies. *Emerg Infect Dis*. 2022;28(8):1559-68.
- Chinel LV. South American haemorrhagic fevers. In: Proceedings of an international colloquium on Ebola virus infection and other hemorrhagic fevers [online]. 1977 Dec 6-8; Antwerp, Belgium. Available at: <http://www.itg.be/ebola/ebola-50.htm>. \* Accessed 23 Oct 2002.
- Cogswell-Hawkinson A, Bowen R, James S, Gardiner D, Calisher CH, Adams R, Schountz T. Tacaribe virus causes fatal infection of an ostensible reservoir host, the Jamaican fruit bat. *J Virol*. 2012;86(10):5791-9.
- Delgado S, Erickson BR, Agudo R, Blair PJ, Vallejo E, Albariño CG, Vargas J, Comer JA, Rollin PE, Ksiazek TG, Olson JG, Nichol ST. Chapare virus, a newly discovered arenavirus isolated from a fatal hemorrhagic fever case in Bolivia. *PLoS Pathog*. 2008;18;4(4):e1000047.
- de Manzione N, Salas RA, Paredes H, Godoy O, Rojas L, Araoz F, Fulhorst CF, Ksiazek TG, Mills JN, Ellis BA, Peters CJ, Tesh RB. Venezuelan hemorrhagic fever: clinical and epidemiological studies of 165 cases. *Clin Infect Dis*. 1998;26(2):308-13.
- de Mello Malta F, Amgarten D, Nastri ACSS, Ho YL, Boas Casadio LV, Basqueira M, Selegatto G, Cervato MC, Duarte-Neto AN, Higashino HR, Faustino Medeiros FA, Gendler JLPL, Levin AS, Pinho JRR. Sabiá virus-like mammarenavirus in patient with fatal hemorrhagic fever, Brazil, 2020. *Emerg Infect Dis*. 2020;26(6):1332-4.
- Downs WG, Anderson CR, Spence L, Aitken THG, Greenhall AH. Tacaribe virus, a new agent isolated from *Artibeus* bats and mosquitos in Trinidad, West Indies. *Am J Trop Med Hyg*. 1963;12:640-6.



# Viral Hemorrhagic Fevers Caused by Arenaviruses

- Drosten C, Gottig S, Schilling S, Asper M, Panning M, Schmitz H, Gunther S. Rapid detection and quantification of RNA of Ebola and Marburg viruses, Lassa virus, Crimean-Congo hemorrhagic fever virus, Rift Valley fever virus, dengue virus, and yellow fever virus by real-time reverse transcription-PCR. *J Clin Microbiol.* 2002;40(7): 2323-30.
- Drosten C, Kümmerer BM, Schmitz H, Günther S. Molecular diagnostics of viral hemorrhagic fevers. *Antiviral Res.* 2003;57(1-2):61-87.
- Eberhardt KA, Mischlinger J, Jordan S, Groger M, Günther S, Ramharter M. Ribavirin for the treatment of Lassa fever: A systematic review and meta-analysis. *Int J Infect Dis.* 2019;87:15-20.
- Ellwanger JH, Chies JA. Keeping track of hidden dangers - The short history of the Sabiá virus. *Rev Soc Bras Med Trop.* 2017;50(1):3-8.
- Emonet SF, de la Torre JC, Domingo E, Sevilla N. Arenavirus genetic diversity and its biological implications. *Infect Genet Evol.* 2009;9(4):417-29.
- Emonet S, Lemasson JJ, Gonzalez JP, de Lamballerie X, Charrel RN. Phylogeny and evolution of old world arenaviruses. *Virology.* 2006;350(2):251-7.
- Enria DA, Briggiler AM, Sánchez Z. Treatment of Argentine hemorrhagic fever. *Antiviral Res.* 2008;78(1):132-9.
- Escalera-Antezana JP, Rodríguez-Villena OJ, Arancibia-Alba AW, Alvarado-Arnez LE, Bonilla-Aldana DK, Rodríguez-Morales AJ. Clinical features of fatal cases of Chapare virus hemorrhagic fever originating from rural La Paz, Bolivia, 2019: A cluster analysis. *Travel Med Infect Dis.* 2020;36:101589.
- Evseev AA., Dvoretkaia VI, Bogatikov GV, Pshenichnov VA, Mustafin RM. Experimental Lassa fever in hamadryas baboons. *Vopr Virusol.* 1991;36(2): 150-2.
- Fernandes J, de Oliveira RC, Guterres A, Barreto-Vieira DF, Terças ACP, Teixeira BR, da Silva MAN, Caldas GC, de Oliveira Coelho JMC, Barth OM, D'Andrea PS, Bonvicino CR, de Lemos ERS. Detection of Latino *virus* (Arenaviridae: Mammarenavirus) naturally infecting *Calomys callidus*. *Acta Trop.* 2018;179:17-24.
- Fichet-Calvet E, Lecompte E, Koivogui L, Daffis S, ter Meulen J. Reproductive characteristics of *Mastomys natalensis* and Lassa virus prevalence in Guinea, West Africa. *Vector Borne Zoonotic Dis.* 2008;8(1):41-8.
- Fisher Hoch SP, McCormick JB. Pathophysiology and treatment of Lassa fever. *Curr Top Microbiol Immunol.* 1987;134:231-9.
- Forbes KM, Voutilainen L, Jääskeläinen A, Sironen T, Kinnunen PM, Stuart P, Vapalahti O, Henttonen H, Huitu O. Serological survey of rodent-borne viruses in Finnish field voles. *Vector Borne Zoonotic Dis.* 2014;14(4):278-83.
- Frank MG, Beitscher A, Webb CM, Raabe V; members of the Medical Countermeasures Working Group of the National Emerging Special Pathogens Training and Education Center's (NETEC's) Special Pathogens Research Network (SPRN). South American hemorrhagic fevers: A summary for clinicians. *Int J Infect Dis.* 2021;105:505-15.
- Fulhorst CF, Cajimat MN, Milazzo ML, Paredes H, de Manzione NM, Salas RA, Rollin PE, Ksiazek TG. Genetic diversity between and within the arenavirus species indigenous to western Venezuela. *Virology.* 2008;378(2):205-13.
- Fulhorst CF, Ksiazek TG, Peters CJ, Tesh RB. Experimental infection of the cane mouse *Zygodontomys brevicauda* (family *Muridae*) with Guanarito virus (*Arenaviridae*), the etiologic agent of Venezuelan hemorrhagic fever. *J Infect Dis.* 1999;180(4):966-9.
- Gandsman EJ, Aaslestad HG, Ouimet TC, Rupp WD. Sabia virus incident at Yale University. *Am Ind Hyg Assoc J.* 1997;58(1):51-3.
- Garnett LE, Strong JE. Lassa fever: With 50 years of study, hundreds of thousands of patients and an extremely high disease burden, what have we learned? *Curr Opin Virol.* 2019;37:123-31.
- Georges AJ, Gonzalez JP, Abdul-Wahid S, Saluzzo JF, Meunier DMY, McCormick JB. Antibodies to Lassa and Lassa-like viruses in man and mammals in the Central African Republic. *Trans R Soc Trop Med Hyg.* 1985;79: 78-9.
- Goeijenbier M, Wagenaar J, Goris M, Martina B, Henttonen H, Vaheri A, Reusken C, Hartskeerl R, Osterhaus A, Van Gorp E. Rodent-borne hemorrhagic fevers: under-recognized, widely spread and preventable - epidemiology, diagnostics and treatment. *Crit Rev Microbiol.* 2013;39(1):26-42.
- Gómez RM, Jaquenod de Giusti C, Sanchez Vallduvi MM, Friks J, Ferrer MF, Schattner M. Junín virus. A XXI century update. *Microbes Infect.* 2011;13(4):303-11.
- Gompf SA. Arenaviruses [online]. eMedicine; 2019 May. Available at: <https://emedicine.medscape.com/article/212356-overview>. Accessed 23 Jan 2023.
- Gonder E, Eddy G. Indirect immunofluorescence, serum neutralization, and viremia responses of rhesus monkeys (*Macaca mulatta*) to Machupo virus. *J Med Virol.* 1986;19(2):187-92.
- Gryseels S, Rieger T, Oestereich L, Cuypers B, Borremans B, Makundi R, Leirs H, Günther S, Göüy de Bellocq J. Gairo virus, a novel arenavirus of the widespread *Mastomys natalensis*: Genetically divergent, but ecologically similar to Lassa and Morogoro viruses. *Virology.* 2015;476:249-56.
- Happi AN, Happi CT, Schoepp RJ. Lassa fever diagnostics: past, present, and future. *Curr Opin Virol.* 2019;37:132-8.
- Happi AN, Olumade TJ, Ogunson OA, Sijuwola AE, Ogunleye SC, et al. Increased prevalence of Lassa fever virus-positive rodents and diversity of infected species found during human Lassa fever epidemics in Nigeria. *Microbiol Spectr.* 2022;10(4):e0036622.
- Haun BK, Kamara V, Dweh AS, Garalde-Machida K, Forkay SSE, Takaaze M, Namekar M, Wong TAS, Bell-Gam Woto AER, Humphreys P, Weeks OI, Fallah MP, Berestecky JM, Nerurkar VR, Lehrer AT. Serological evidence of Ebola virus exposure in dogs from affected communities in Liberia: A preliminary report. *PLoS Negl Trop Dis.* 2019;13(7):e0007614.
- Hensley LE, Smith MA, Geisbert JB, Fritz EA, Daddario-DiCaprio KM, Larsen T, Geisbert TW. Pathogenesis of Lassa fever in cynomolgus macaques. *Virol J.* 2011;8:205.
- Ivanov AP, Bashkirtsev VN, Tkachenko EA. Enzyme-linked immunosorbent assay for detection of arenaviruses. *Arch Virol.* 1981;67(1):71-4.
- Jahrling PB, Hesse RA, Eddy GA, Johnson KM, Callis RT, Stephen EL. Lassa virus infection of rhesus monkeys: pathogenesis and treatment with ribavirin. *J Infect Dis.* 1980;141(5):580-9.

# Viral Hemorrhagic Fevers Caused by Arenaviruses

- Jahrling PB, Peters CJ. Passive antibody therapy of Lassa fever in cynomolgus monkeys: importance of neutralizing antibody and Lassa virus strain. *Infect Immun*. 1984;44:528-33.
- Jay MT, Glaser C, Fulhorst CF. The arenaviruses. *J Am Vet Med Assoc*. 2005;227(6):904-15.
- Joseph AA, Fasipe OJ, Joseph OA, Olatunji OA. Contemporary and emerging pharmacotherapeutic agents for the treatment of Lassa viral haemorrhagic fever disease. *J Antimicrob Chemother*. 2022;77(6):1525-31.
- Kastello MD, Eddy GA, Kuehne RW. A rhesus monkey model for the study of Bolivian hemorrhagic fever. *J Infect Dis*. 1976;133(1):57-62.
- Kaye KM. Lassa fever. In: Porter RS, Kaplan JL, editors. *The Merck manual* [online]. 18<sup>th</sup> ed. Whitehouse Station, NJ: Merck and Co.; 2009. Available at: <http://www.merck.com/mmpe/sec14/ch191/ch191d.html>. \* Accessed 13 Feb 2010.
- Keeton C. South African doctors move quickly to contain new virus. *Bull World Health Organ*. 2008;86(12):912-3.
- Kenmoe S, Tchatchouang S, Ebogo-Belobo JT, Ka'e AC, Mahamat G, et al. Systematic review and meta-analysis of the epidemiology of Lassa virus in humans, rodents and other mammals in sub-Saharan Africa. *PLoS Negl Trop Dis*. 2020;14(8):e0008589.
- Kernéis S, Koivogui L, Magassouba N, Koulemou K, Lewis R, Aplogan A, Grais RF, Guerin PJ, Fichet-Calvet E. Prevalence and risk factors of Lassa seropositivity in inhabitants of the forest region of Guinea: a cross-sectional study. *PLoS Negl Trop Dis*. 2009 17;3(11):e548.
- Khan SH, Goba A, Chu M, Roth C, Healing T, Marx A, Fair J, Guttieri MC, Ferro P, Imes T, Monagin C, Garry RF, Bausch DG; Mano River Union Lassa Fever Network. New opportunities for field research on the pathogenesis and treatment of Lassa fever. *Antiviral Res*. 2008;78(1):103-15.
- Kortepeter M, Christopher G, Cieslak T, Culpepper R, Darling R, Pavlin J, Rowe J, McKee K, Eitzen E, editors. *Medical management of biological casualties handbook* [online]. 4th ed. United States Department of Defense; 2001. Viral hemorrhagic fevers. Available at: <http://www.vnh.org/BIOCASU/15.html>. \* Accessed 24 Oct 2002.
- Larson EW, Stephenson EH, Dominik JW. Aerosol stability and respiratory infectivity of Lassa virus. Available at: <https://apps.dtic.mil/sti/pdfs/ADA114671.pdf>. Accessed 12 Feb 2023.
- Lecompte E, ter Meulen J, Emonet S, Daffis S, Charrel RN. Genetic identification of Kodoko virus, a novel arenavirus of the African pigmy mouse (*Mus Nannomys minutoides*) in West Africa. *Virology*. 2007;364(1):178-83.
- Loayza Mafayle R, Morales-Betoulle ME, Romero C, Cossaboom CM, Whitmer S. Chapare hemorrhagic fever and virus detection in rodents in Bolivia in 2019. *N Engl J Med*. 2022;386(24):2283-94.
- Maiztegui J, Vocfrey J, Fernandez M, Barrera Oro J. Aislamiento de virus Junin a partir de leche materna. *Medicina (Buenos Aires)*. 1973;33(6):659-60.
- McCormick JB. Epidemiology and control of Lassa fever. *Curr Top Microbiol Immunol*. 1987;134:69-78.
- McKee KT, Green DE, Mahlandt BG, Bagley LR, Lyerly WH, Peters CJ, Eddy GA. Infection of *Cebus* monkeys with Junin virus. *Medicina (B Aires)*. 1985;45(2):144-52.
- McLeod CG, Stookey JL, Eddy GA, Scott K. Pathology of chronic Bolivian hemorrhagic fever in the rhesus monkey. *Am J Pathol*. 1976;84(2):211-24.
- McLeod CG, Stookey JL, White JD, Eddy GA, Fry GA. Pathology of Bolivian hemorrhagic fever in the African green monkey. *Am J Trop Med Hyg*. 1978;27(4):822-6.
- Mills JN, Ellis BA, Childs JE, McKee KT Jr, Maiztegui JI, Peters CJ, Ksiazek TG, Jahrling PB. Prevalence of infection with Junin virus in rodent populations in the epidemic area of Argentine hemorrhagic fever. *Am J Trop Med Hyg*. 1994;51(5):554-62.
- Mills JN, Ellis BA, McKee KT Jr, Calderon GE, Maiztegui JI, Nelson GO, Ksiazek TG, Peters CJ, Childs JE. A longitudinal study of Junin virus activity in the rodent reservoir of Argentine hemorrhagic fever. *Am J Trop Med Hyg*. 1992;47(6):749-63.
- Ogbo O, Ajuluchukwu E, Uneke CJ. Lassa fever in West African sub-region: an overview. *J Vector Borne Dis*. 2007;44(1):1-11.
- Ogunro BN, Olugasa BO, Kayode A, Ishola OO, Kolawole ON, Odigie EA, Happi C. Detection of antibody and antigen for Lassa virus nucleoprotein in monkeys from southern Nigeria. *J Epidemiol Glob Health*. 2019;9(2):125-7.
- Paessler S, Walker DH. Pathogenesis of the viral hemorrhagic fevers. *Annu Rev Pathol*. 2013;8:411-40.
- Palacios G, Savji N, Hui J, Travassos da Roas A, Popov V, Briese T, Tesh R, Lipkin WI. Genomic and phylogenetic characterization of Merino Walk virus, a novel arenavirus isolated in South Africa. *J Gen Virol*. 2010;91(Pt 5):1315-24.
- Patterson M, Grant A, Paessler S. Epidemiology and pathogenesis of Bolivian hemorrhagic fever. *Curr Opin Virol*. 2014;5:82-90.
- Peters CJ. Emerging infections: lessons from the viral hemorrhagic fevers. *Trans Am Clin Climatol Assoc*. 2006;117:189-96.
- Peters CJ, Jahrling PB, Liu CT, Kenyon RH, McKee KT Jr, Barrera Oro JG. Experimental studies of arenaviral hemorrhagic fevers. *Curr Top Microbiol Immunol*. 1987;134:5-68.
- Pfau CJ. Arenaviruses. In: Baron S., editor. *Medical microbiology*. 4th ed. New York: Churchill Livingstone; 1996. Available at: Available at: <http://www.gsbs.utmb.edu/microbook/ch057.htm>. \* Accessed 11 Oct 2002.
- Public Health Agency of Canada [PHAC]. Pathogen Safety Data Sheets: Infectious Substances – Lassa virus. Centre for Biosecurity, PHAC; 2010 Sep. Available at: <https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/lassa-virus.html>. Accessed 23 Jan 2023.
- Public Health Agency of Canada [PHAC]. Pathogen Safety Data Sheets: Infectious Substances – Junin virus. Centre for Biosecurity, PHAC; 2010 Aug. Available at: <https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/junin-virus.html>. Accessed 23 Jan 2023.
- Public Health Agency of Canada [PHAC]. Pathogen Safety Data Sheets: Infectious Substances – Machupo virus. Centre for Biosecurity, PHAC; 2010 Sep. Available at: <https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/machupo-virus.html>. Accessed 23 Jan 2023.

# Viral Hemorrhagic Fevers Caused by Arenaviruses

- Raabe V, Koehler J. Laboratory diagnosis of Lassa fever. *J Clin Microbiol.* 2017;55(6):1629-37.
- Raabe V, Mehta AK, Evans JD; Science Working Group of the National Emerging Special Pathogens Training and Education Center (NETEC) Special Pathogens Research Network (SPRN). Lassa virus infection: a summary for clinicians. *Int J Infect Dis.* 2022;119:187-200.
- Salam AP, Duvignaud A, Jaspard M, Malvy D, Carroll M, Tarning J, Oliario PL, Horby PW. Ribavirin for treating Lassa fever: A systematic review of pre-clinical studies and implications for human dosing. *PLoS Negl Trop Dis.* 2022;16(3):e0010289.
- Salu OB, Amoo OS, Shaibu JO, Abejegah C, Ayodeji O, Musa AZ, Idigbe I, Ezechi OC, Audu RA, Salako BL, Omilabu SA. Monitoring of Lassa virus infection in suspected and confirmed cases in Ondo State, Nigeria. *Pan Afr Med J.* 2020;36(253). 10.11604/pamj.2020.36.253.22104
- Sangiorgio P, Weissenbacher MC. Congenital and perinatal infection with Junin virus in guinea pigs. *J Med Virol.* 1983;11(2):161-5.
- Sayler KA, Barbet AF, Chamberlain C, Clapp WL, Alleman R, Loeb JC, Lednicky JA. Isolation of Tacaribe virus, a Caribbean arenavirus, from host-seeking *Amblyomma americanum* ticks in Florida. *PLoS One.* 2014;9(12):e115769.
- Sewlall NH, Richards G, Duse A, Swanepoel R, Paweska J, Blumberg L, Dinh TH, Bausch D. Clinical features and patient management of Lujo hemorrhagic fever. *PLoS Negl Trop Dis.* 2014;8(11):e3233.
- Silva-Ramos CR, Faccini-Martínez ÁA, Calixto OJ, Hidalgo M. Bolivian hemorrhagic fever: a narrative review. *Travel Med Infect Dis.* 2021;40:102001.
- Silva-Ramos CR, Montoya-Ruíz C, Faccini-Martínez ÁA, Rodas JD. An updated review and current challenges of Guanarito virus infection, Venezuelan hemorrhagic fever. *Arch Virol.* 2022;167(9):1727-38.
- Sironi M, Forni D, de la Torre JC. Mammarenavirus genetic diversity and its biological implications. *Curr Top Microbiol Immunol.* 2023;439:265-303.
- Tesh RB, Jahrling PB, Salas R, Shope RE. Description of Guanarito virus (Arenaviridae: Arenavirus), the etiologic agent of Venezuelan hemorrhagic fever. *Am J Trop Med Hyg.* 1994;50(4):4529.
- Thielebein A, Ighodalo Y, Taju A, Olorok T, Omiunu R et al. Virus persistence after recovery from acute Lassa fever in Nigeria: a 2-year interim analysis of a prospective longitudinal cohort study *Lancet Microbe.* 2022;3(1):e32-e40.
- Ubico SR, McLean RG. Serologic survey of neotropical bats in Guatemala for virus antibodies. *J Wildl Dis.* 1995;31(1):1-9.
- Vitullo AD, Hodara VL, Merani MS. Effect of persistent infection with Junin virus on growth and reproduction of its natural reservoir, *Calomys musculus*. *Am J Trop Med Hyg.* 1987;37(3):663-9.
- Vitullo AD, Merani MS. Vertical transmission of Junin virus in experimentally infected adult *Calomys musculus*. *Intervirology.* 1990;31(6):339-44.
- Wagner FS, Eddy GA, Brand OM. The African green monkey as an alternate primate host for studying Machupo virus infection. *Am J Trop Med Hyg.* 1977;26(1):159-62.
- Walker DH, Wulff H, Lange JV, Murphy FA. Comparative pathology of Lassa virus infection in monkeys, guinea-pigs, and *Mastomys natalensis*. *Bull World Health Organ.* 1975;52(4-6):523-34.
- Walker DH, Wulff H, Murphy FA. Experimental Lassa virus infection in the squirrel monkey. *Am J Pathol.* 1975;80(2):261-78.
- Webb PA, Justines G, Johnson KM. Infection of wild and laboratory animals with Machupo and Latino viruses. *Bull World Health Organ.* 1975; 52(4-6): 4939.
- Weissenbacher MC, Coto CE, Calello MA, Rondinone SN, Damonte EB, Frigerio MJ. Cross-protection in nonhuman primates against Argentine hemorrhagic fever. *Infect Immun.* 1982;35(2):425-30.
- Weissenbacher MC, Laguens RP, Coto CE. Argentine hemorrhagic fever. *Curr Top Microbiol Immunol.* 1987;134: 79-116.
- Yun NE, Linde NS, Dziuba N, Zacks MA, Smith JN, Smith JK, Aronson JF, Chumakova OV, Lander HM, Peters CJ, Paessler S. Pathogenesis of XJ and Romero strains of Junin virus in two strains of guinea pigs. *Am J Trop Med Hyg.* 2008;79(2):275-82.
- Zadeh VR, Afowowe TO, Abe H, Urata S, Yasuda J. Potential and action mechanism of favipiravir as an antiviral against Junin virus. *PLoS Pathog.* 2022;18(7):e1010689.

\*Link defunct