

The arenaviruses

Michele T. Jay, DVM, MPVM, DACVPM; Carol Glaser, DVM, MD; Charles F. Fulhorst, DVM, DrPH

The virus family *Arenaviridae* is a diverse group of RNA viruses and includes the etiologic agents of several emerging zoonoses that are characterized by high case-fatality rates. Murid rodents (rats and mice) are the principal reservoirs of the arenaviruses for which natural host relationships have been studied extensively. Six arenaviruses are known to cause human disease: Guanarito virus (causes Venezuelan hemorrhagic fever), Junin virus (Argentine hemorrhagic fever), lymphocytic choriomeningitis virus (lymphocytic choriomeningitis), Lassa virus (Lassa fever), Machupo virus (Bolivian hemorrhagic fever), and Sabiá virus (human disease [not yet named]).

The purpose of this article is to review the major features of the zoonotic arenaviruses, which are important for several reasons: the viruses cause severe disease in humans in the geographic regions where the viruses are endemic, infections may be diagnosed in humans outside of areas in which the viruses are endemic as a result of travel or exposure in research settings, laboratory and pet animals (mice and hamsters) and wild-caught rodents may harbor arenaviruses and pose a risk to their handlers, legal or illegal importation of wild rodents for the pet trade could result in introduction of arenaviruses into locations in which the viruses are not endemic, and arenaviruses are classified as Category A bioterrorism pathogens by the CDC because of the extremely serious consequences to public health associated with their use in a terrorist attack.

Taxonomy and Classification

Arenavirus particles are spherical to pleomorphic and approximately 50 to 300 nm in diameter. Virions possess a lipid-containing envelope that is covered with distinct, spikelike projections distributed evenly over the surface. Host-cell ribosomes are accumulated in variable numbers within the envelope. In fact, the name "arena" originates from the Latin word for sandy (arenosus), which describes the granular appearance of these host-cell ribosomes when viewed by use of an electron microscope.¹ The *Arenaviridae* genome consists

of 2 single-stranded RNA molecules designated L (large) and S (small). The S segment encodes gene sequences for 2 structural proteins: the nucleocapsid protein and the envelope glycoprotein precursor, which is posttranslationally cleaved into the GP-1 and GP-2 subunits. Notably, partial sequence analysis of the nucleocapsid protein has been extensively used to study the evolution and genetic diversity of the *Arenaviridae*.

The *Arenaviridae* has only 1 unique genus, *Arenavirus*, which currently includes 22 species (Appendix).^{1,2} Many novel arenaviruses have been reported in the literature³⁻⁷ over the last decade, especially in the Americas, but the natural history and clinical importance of most of these viruses remain unclear. The family comprises 2 serocomplexes: the lymphocytic choriomeningitis-Lassa (Old World) complex and the Tacaribe (New World) complex. Members of the former are associated with the subfamily Murinae (Old World rats and mice), whereas members of the latter are associated with the subfamily Sigmodontinae (New World rats and mice). Undoubtedly, the number of recognized arenaviruses will continue to increase as more potential rodent-virus relationships are examined.

The lymphocytic choriomeningitis-Lassa complex is grouped into 2 monophyletic lineages that appear to correlate with monophyletic genera within the rodent subfamily Murinae.⁸ The South American members of the Tacaribe complex are classified into 3 distinct lineages (designated A, B, and C), and in some instances, the lineages appear to correlate with monophyletic genera within the rodent subfamily Sigmodontinae.⁸⁻¹⁰ Results of recent phylogenetic studies^{11,12} by Charrel et al indicate that the North American arenaviruses (Bear Canyon, Tamiami, and Whitewater Arroyo) comprise a fourth lineage in the Tacaribe complex and are the product of recombination between 2 South American arenaviruses, one from lineage A and one from lineage B. All of the pathogenic viruses in the Tacaribe complex are classified in lineage B (Guanarito, Junin, Machupo, and Sabiá viruses), perhaps suggesting an as yet unrecognized genetic factor that is causally associated with the pathogenic phenotype of the New World arenaviruses.¹⁰

Findings of phylogenetic studies have also suggested that there is an ancient evolutionary relationship between the arenaviruses and their specific rodent hosts. The Muridae-*Arenaviridae* relationship may be an example of host-virus codivergence, at least in some instances in which the phylogeny of the virus species

From the California Department of Health Services, Division of Communicable Disease Control, 1616 Capitol Ave, Sacramento, CA 95899-7413 (Jay); the California Department of Health Services, Division of Communicable Disease Control, 805 Marina Bay Pkwy, Richmond, CA 94804 (Glaser); and the Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555-0144 (Fulhorst). Dr Jay's present address is Western Institute for Food Safety and Security, University of California, Davis, CA 95616. Address correspondence to Dr. Jay

appears to match the phylogeny of its specific rodent host.⁸⁻¹⁰ Although intriguing, the codivergence model for rodent and arenavirus evolution is difficult to prove, especially because the taxonomy of the Muridae remains controversial. Interestingly, a similar phylogenetic relationship has been observed between murid rodent reservoirs and hantaviruses, another emerging group of rodent-borne RNA viruses; many epidemiologic and ecologic parallels exist between these otherwise unrelated rodent-borne viruses.^{13,14}

Partial sequence analysis (primarily based on the nucleocapsid protein) has revealed a remarkable genetic diversity within the genus as a whole and among different strains of those arenaviruses that have been studied in detail. For example, Lassa virus strains vary as much as 27% at the nucleotide level and 15% at the amino acid level.¹⁵ Genetic diversity among strains may also vary by host and geographic location. Results of a study¹⁶ of Guanarito virus isolates collected from western Venezuela identified higher sequence variation among strains isolated from rodents, compared with human isolates. In the southwestern United States, findings of sequence analyses of Whitewater Arroyo virus strains isolated from wood rats have suggested that this species varies genetically by geographic location.^{17,18} In addition, considerable genetic diversity has been found among Whitewater Arroyo virus strains that have been isolated from different species of wood rat (*Neotoma* spp). Whether some of these isolates represent novel arenaviral species remains to be elucidated.

Epidemiology and Ecology

Each arenaviral species is usually associated with a single rodent species or closely related species. All of the arenaviruses that cause disease are rodent-borne (the reservoir of Sabiá virus is unknown, but presumed to be a South American rodent). Therefore, the epidemiologic and ecologic characteristics of these viruses depend primarily on rodent-host population dynamics and human behavior that increases the likelihood of exposure to infected rodents or their excreta. The single exception to the association between the *Arenaviridae* and rodents may be Tacaribe virus (the prototypical New World arenavirus). This virus, which has not been associated with human disease, was isolated in 1956 from salivary glands and other tissues of frugivorous bats (*Artibeus* spp) captured on the island of Trinidad.¹⁹ There is a paucity of information on the susceptibility of other nonrodent hosts to infection with arenaviruses. Rhesus macaques and guinea pigs develop disease after experimental inoculation with some arenaviruses and have been used as animal models of arenaviral diseases in humans. In addition, naturally occurring outbreaks and deaths among captive marmosets and tamarinds have been attributed to infection with lymphocytic choriomeningitis virus following exposure to infected wild mice.^{20,21} To the authors' knowledge, the role of nonrodent domestic mammal species (dogs, cats, and livestock) in the transmission of the arenaviruses has not been investigated, but epidemiologic evidence supports their unimportance as reservoirs. Arthropod vectors have not been implicated in the transmission of the arenaviruses.

Although much has been learned about the epidemiologic and ecologic characteristics of the arenaviruses since the discovery of lymphocytic choriomeningitis virus more than 70 years ago, there are still many gaps in our understanding of this complex group of viruses. Arenaviruses and their associated human diseases are difficult to study for several reasons. First, surveillance systems for arenaviral infections in human and rodent populations are poor or nonexistent in the countries where these viruses are endemic. Second, population-based, longitudinal studies are challenging to conduct because most of these viruses circulate in remote and sometimes inaccessible locations of developing countries; investigations are hampered by the lack of roads and other infrastructure and by political unrest, among other factors. For this reason, there is a bias toward collecting data from outbreaks or conducting studies in areas in which the disease is hyperendemic. Third, safe handling of these viruses requires high-level containment facilities (biosafety level 4 for the hemorrhagic fever viruses). Serologic surveys are commonly performed in lieu of studies that involve handling live virus, but the results from such investigations can be difficult to interpret because testing methods vary widely between laboratories. Finally, interpretation of epidemiologic data is further complicated by an incomplete understanding of the genetic diversity of the genus and strain differences within the individual species, circulation of different arenaviral species and coinfections in the same geographic region, and the fact that the taxonomy of many of the rodent reservoirs is in flux.

Despite these limitations, some generalizations can be made about the epidemiology of the arenaviruses. The geographic distribution of each arenavirus subsumes the geographic range of its principal host. In the Americas, the distribution of the arenaviruses identified to date has been assessed (Figure 1). The disease patterns in human populations range from hyper-



Figure 1—The known distribution in the Americas of arenaviruses of the Tacaribe complex.

endemic to endemic to rare or unknown, depending on the specific virus and geographic location. A striking feature of the arenaviruses is the heterogeneity in their geographic distribution. The viruses almost always have a patchy distribution within the range of their rodent reservoirs²²⁻²⁵; compared with other areas, the so-called hot spots are characterized by greater infection rates in rodent hosts and may correlate with more frequent reports of human outbreaks. Additionally, most of the arenaviral diseases are characterized by seasonal peaks that are perhaps associated with increased rodent populations or periods when contact between humans and rodents is more frequent. For example, the number of reported cases of Argentine hemorrhagic fever increases during the harvest season, and a disproportionate number of reported cases are among agricultural workers. The overall temporal and spatial variability within human and rodent populations most likely relates to a combination of factors such as rodent density, virus survival, human behavior, and other virus-host factors that may influence infection rates.²² In the following portions of text, the major epidemiologic features of the specific zoonotic arenaviral species and the arenaviruses detected in the United States are summarized.

Lymphocytic choriomeningitis virus—The prototypical arenavirus lymphocytic choriomeningitis virus was discovered in 1933 by Armstrong and Lillie²⁶ while they were investigating an outbreak of St Louis encephalitis in humans. Presently, lymphocytic choriomeningitis virus is recognized more for its contribution to fundamental research in the fields of immunology and virology than as a cause of human disease. Although not within the scope of this update, the value of the murine model of lymphocytic choriomeningitis virus infection and disease to basic medical research cannot be overstated and has been reviewed in several recent publications.²⁷⁻²⁹

In humans, lymphocytic choriomeningitis virus is a cause of acute aseptic meningoencephalitis and congenital malformations of the CNS and eye. Both sexes and all age groups are susceptible, but infections are more common in young adults.³⁰ Persons with a suppressed immune system and women in the first or second trimester of pregnancy are at increased risk of developing severe illness following infection. Solid organ transplants from infected donors represent a rare but serious risk for recipients as recently described in the United States.^{31,32} Lymphocytic choriomeningitis virus has near worldwide distribution, which coincides with the geographic distribution of its principal host, the ubiquitous house mouse (*Mus musculus*). The house mouse and other members of the genus *Mus* readily enter human dwellings in search of food and shelter. In previous studies²² of wild-caught mice, the seroprevalence of antibodies against lymphocytic choriomeningitis virus ranged from zero to 60%. Most people infected with the virus are probably exposed to infectious rodents in their homes^{22,30}; numbers of infections with lymphocytic choriomeningitis virus in humans peak in the fall, possibly because more mice are entering homes. Poor sanitation and other conditions that favor invasion of

human dwellings by mice may increase the risk of human exposure to lymphocytic choriomeningitis virus.

In humans, the incidence of infection with lymphocytic choriomeningitis virus is unknown, but most experts believe the disease is under-recognized or under-reported. Nonspecific clinical signs, challenging diagnostic algorithms, and a general lack of awareness on the part of health care providers all combine to make recognition of lymphocytic choriomeningitis virus infections and the associated diseases in humans unlikely. Serosurveys, syndromic surveillance for neurologic disease, and reports of sporadic cases provide some information about the incidence of infection with lymphocytic choriomeningitis virus in human populations. In studies^{33,34} conducted in the early 1990s among residents of Baltimore and Alabama, the seroprevalence of antibodies against lymphocytic choriomeningitis virus was 4.7% and 5.1%, respectively; results of a subsequent serosurvey in Birmingham, Ala, determined that the seroprevalence had decreased (3.5%), perhaps as a result of improved sanitation.³⁵

In a recent review of hospitalized individuals with viral encephalitis in England, lymphocytic choriomeningitis virus infection was diagnosed in only 7 of 2,574 (< 1.0%) people who had disease of known viral etiology.³⁶ No cases of lymphocytic choriomeningitis virus infection were identified among 91 patients evaluated in a similar encephalitis surveillance project in California.³⁷ In contrast, some of the older reviews of patients with neurologic disease revealed a higher percentage (8% to 11%) of individuals infected with lymphocytic choriomeningitis virus.²² The low number of cases in the more recent studies may represent a true decrease in incidence or may be explained by the focus on individuals with encephalitis, for whom a more severe and uncommon outcome is generally expected.

Historically, large outbreaks of lymphocytic choriomeningitis virus infections were linked to infected mice and Syrian hamsters used for research or sold as pets; tumor cell lines harvested from infected rodents were also implicated.^{38,39} The outbreaks ended after the distributors destroyed infected stocks of mice, infected stocks of hamsters, and contaminated cell lines. In 1989, laboratory-associated lymphocytic choriomeningitis virus infections reappeared when researchers were exposed to infected nude mice and tumor cell lines.⁴⁰

In 2005, lymphocytic choriomeningitis virus re-emerged as a zoonotic concern for pet stores and owners of pet rodents.^{32,41} An epidemiologic investigation of transplant-associated lymphocytic choriomeningitis virus infections among organ recipients traced the source of the virus to a donor's pet hamster. The donor purchased the hamster at a local pet store shortly before becoming ill. The investigation implicated a single distributor as the supplier of the infected rodent. Subsequent testing revealed lymphocytic choriomeningitis virus infections among the index hamster and 2 other hamsters and a guinea pig from the pet store. Approximately 3% of the hamsters at the distributor also yielded positive results on testing. As a result of the outbreak, the CDC issued interim guidance for minimizing risk for human lymphocytic choriomeningitis virus infection associated with rodents.⁴¹

Other recent reports of lymphocytic choriomeningitis virus infections in the United States include 6 individuals with congenital lymphocytic choriomeningitis virus infections identified in Arizona, Nebraska, and Texas.⁴² In 1999, the Arizona State Health Department issued a report⁴³ that described a 17-year-old female with signs of viral meningitis for whom a presumptive diagnosis of lymphocytic choriomeningitis virus infection was made. Two of 5 *M. musculus* trapped at the girl's school were seropositive for antibodies against lymphocytic choriomeningitis virus. Public health officials determined that the patient's exposure was most likely a result of inhalation of contaminated dust while cleaning up mouse droppings in a classroom 11 days prior to the onset of illness.

Lassa virus—Lassa virus is the causative agent of Lassa fever, 1 of the 5 viral hemorrhagic fevers caused by arenaviruses. The term viral hemorrhagic fever describes a potentially fatal clinical syndrome characterized by an insidious onset of nonspecific signs followed by bleeding manifestations and shock. Lassa virus was first described in 1969 during an investigation of a hemorrhagic illness that affected persons working as missionaries in Nigeria.^{44,45} Nosocomial transmission was identified during the outbreak and was subsequently recognized as a serious risk for health care personnel working with Lassa fever patients and clinical specimens in the absence of standard barrier precautions.

At present, Lassa fever is an important cause of febrile illness in West Africa; it is estimated that 100,000 to 300,000 cases and several thousand Lassa virus-associated deaths occur each year.⁴⁶ The cases are primarily reported from hyperendemic or endemic foci in the West African countries of Guinea, Liberia, Nigeria, and Sierra Leone. Infections are reported equally among both sexes and all age groups. There is a seasonal peak in the incidence of Lassa fever during the late rainy or early dry season (February to April). The background prevalence of Lassa fever in regions in which the disease is endemic is unknown, but the disease (especially with regard to mild illness) is almost certainly under-recognized and under-reported. Prevalence of serum antibodies against Lassa virus among health care workers ranges from 1% to 40%, based on findings of serosurveys conducted in hyperendemic areas where nosocomial infections were previously reported.⁴⁷⁻⁴⁹ Bausch et al⁵⁰ recently reported results from a prospective cohort study in Guinea, where Lassa fever is believed to be relatively uncommon. Acute Lassa fever was confirmed in 22 of 311 (7%) patients with compatible signs of illness who were evaluated at several hospitals in different regions of the country. In addition, serum IgG antibodies against Lassa virus indicative of past exposure were detected in 14% of the patients assessed. Those investigators suggested that their findings probably represent the true picture of Lassa fever in West Africa, in which affected individuals are difficult to differentiate clinically from persons with febrile illness resulting from other causes.

The natal multimammate mouse (*Mastomys natalensis*) is the reservoir of Lassa virus and is usually the

predominant rodent in the regions where the virus is present in Africa. Like the house mouse (*M. musculus*), the multimammate mouse readily invades human dwellings. The prevalence of Lassa virus in reservoir host populations across West Africa is unknown. Results of limited studies^{22,24,46,51} suggest that the distribution of the virus is spatially patchy and some mouse populations appear to be free of virus, whereas others have high infection rates. The prevalences of Lassa virus in human and mouse populations vary from house to house in African villages where Lassa fever outbreaks have been reported.⁵² A recent prevalence study⁵¹ of Lassa virus infection in small mammals in Guinea revealed variation in the proportion of multimammate mice (range, 0% to 9%) infected with the virus, depending on geographic location; the infection rates in savannah and forest zones were higher than rates in the coastal and urban zones. The study also found an important correlation between the overall spatial distribution of seropositive mice and the prevalence of serum IgG antibodies against Lassa virus in humans from Guinea.

Lassa virus is the most frequently imported arenaviral disease. Cases have been reported from numerous areas in which the virus is not endemic, including the United States.⁵³⁻⁵⁸ For example, in October 2004, a New Jersey resident died of Lassa fever after returning from a visit to West Africa.⁵⁸ As a result, an intensive public health investigation was conducted to identify and monitor high-risk contacts because of the risk of person-to-person transmission. No secondary cases were identified, but the incident emphasizes the potential for development of Lassa fever in persons outside of West Africa, especially as international travel increases.

Tacaribe complex viruses in South America—Four members of the Tacaribe complex naturally cause severe disease in humans: Junin, Machupo, Guanarito, and Sabiá viruses.

Junin virus, the most extensively studied of the South American hemorrhagic fever viruses, is the causative agent of Argentine hemorrhagic fever. Junin virus was identified in 1957 during a hemorrhagic fever outbreak investigation in Buenos Aires.^{59,60} An estimated 200 to 2,000 cases of Argentine hemorrhagic fever/y are reported in the north-central Argentine Pampas. There is a distinct seasonal peak in the fall (February to May) during the agriculture harvest.³⁰ Adult men are disproportionately affected, presumably because of the occupational risk associated with agricultural work; however, all age groups and both sexes are susceptible. The drylands vesper mouse (*Calomys musculinus*) is considered the primary host of Junin virus. However, there is serologic evidence for Junin virus infection in other sigmodontine rodent species that inhabit the region in which Argentine hemorrhagic fever is endemic; the contribution of these other rodent species to the ecology of Junin virus is unclear.²² Mills et al⁶¹ documented a correlation between increasing rodent population density and prevalence of Junin virus infections in humans. Results of ecologic studies^{22,61} also indicate that the reservoir host has a predis-

position toward stable linear habitats such as fence lines, roadsides, and railroads, an observation that could have implications for prevention programs.

Guanarito virus, the causative agent of Venezuelan hemorrhagic fever, also affects rural populations and has a limited geographic distribution. Venezuelan hemorrhagic fever has been reported in or near the Portuguesa State in northwestern Venezuela, an intensively cultivated agricultural region.⁶² Prior to its recognition as a distinct clinical entity in 1989, sporadic cases of Venezuelan hemorrhagic fever were probably misdiagnosed as dengue fever. Notably, deforestation and human encroachment into rodent habitat may have resulted in increased human exposure to infected rodents and a concomitant increase in human illness. This increase in illness among humans likely contributed to the recognition of Guanarito virus as a new cause of viral hemorrhagic fever.⁶³ Results of an epidemiologic study⁶⁴ of 165 cases of Venezuelan hemorrhagic fever indicated that the disease is seasonal and the number of affected people peaks in November to January. Infections among adult men are more common; however, infections among women and children also develop, suggesting that exposure may take place inside or outside of the home. The reservoir of Guanarito virus is a grassland rodent, the short-tailed cane mouse (*Zygodontomys brevicauda*).⁶⁵ Initially, on the basis of seroepidemiologic findings, the primary rodent host was thought to be another rodent species, the cotton rat (*Sigmodon alstoni*). However, subsequent evaluation of arenaviral isolates from both of those rodent species revealed that *Z. brevicauda* was the principal rodent host of Guanarito virus, whereas *S. alstoni* was the principal rodent host of a newly recognized viral species, Pirital virus.⁶⁵ Pirital virus is not known to cause human illness, but the virus circulates in the same geographic region as Guanarito virus. The initial misidentification of the reservoir of Guanarito virus illustrates the confusion that can arise as a result of the extensive serologic cross-reactivity among arenaviruses, especially when multiple arenaviruses coexist in the same geographic location.

Machupo virus, the causative agent of Bolivian hemorrhagic fever, was discovered in 1962 during an outbreak of viral hemorrhagic fever in San Joaquin in northeastern Bolivia.⁶⁶ Outbreaks of Bolivian hemorrhagic fever have occurred in cities and towns, possibly related to factors that favored the infestation of human dwellings by rodents. Successful control of outbreaks has been accomplished through implementation of intensive rodent trapping and exclusion programs.⁶⁷ Cases of Bolivian hemorrhagic fever were not reported from 1976 to 1992, but the disease reemerged in 1994 when a household of family members was affected.⁶⁸ The large vesper mouse (*Calomys callosus*) is the reservoir of Machupo virus. The geographic range of the large vesper mouse includes southeastern South America, but the Machupo virus appears to be limited to northeastern Bolivia. The discrepancy may be explained by genetic differences between vesper mouse populations in northeastern Bolivia, compared with mouse populations in other areas of South America.²⁵

Sabiá virus, an agent of hemorrhagic fever in Brazil, is the least understood of the South American hemorrhagic fever viruses. Sabiá virus was isolated in 1994 from a Brazilian patient who was originally thought to have yellow fever; later, viral hemorrhagic fever was diagnosed. No subsequent cases of naturally acquired human disease caused by Sabiá virus have been described. The reservoir of this virus has yet to be determined, but is presumed to be a South American rodent.³ Infections with Sabiá virus have been reported among laboratory workers in Brazil and the United States.^{3,69} In 1994, a virologist acquired Sabiá virus infection following a centrifuge accident at a university laboratory in Connecticut. This individual did not report the accident until 12 days later while being examined at an emergency room for a febrile illness. This delay caused significant concern about secondary infections in the community, especially among close contacts such as family, coworkers, and health care workers. The patient recovered after treatment with ribavirin (an antiviral compound), and no secondary cases were identified. The incident illustrates the risk of aerosol transmission of Sabiá virus during centrifugation of infected cell culture or other infected materials and the potential consequences if laboratory accidents are not promptly reported to the appropriate authorities. Enhanced precautions for the management of patients hospitalized with suspected viral hemorrhagic fever were recommended as a result of this event.⁷⁰

Tacaribe complex viruses in North America—Three arenaviral species that are naturally associated with New World rodent species indigenous to North America are known to exist: Tamiami, Whitewater Arroyo, and Bear Canyon. The hispid cotton rat (*Sigmodon hispidus*) in southern Florida is the principal host of Tamiami virus.⁷¹ The geographic range of this rodent species extends from the Midwestern United States southward to northern South America.⁷² Although common in grassland and agricultural habitats, cotton rats do not live commensally with people; thus, human interaction should be minimal. No human disease has been attributed to Tamiami virus.

The white-throated wood rat (*Neotoma albigula*) in northwestern New Mexico is the principal host of Whitewater Arroyo virus.⁵ Recent studies^{17,18,73-75} have revealed that Tacaribe complex viruses antigenically and phylogenetically most closely related to Whitewater Arroyo virus are widely distributed geographically throughout the southwestern United States in association with various *Neotoma* spp, including *Neotoma micropus* (southern plains wood rat), *Neotoma mexicana* (Mexican wood rat), *Neotoma stephensi* (Stephen's wood rat), and *Neotoma cinerea* (bushy-tailed wood rat). In 2002, a novel arenavirus (proposed name Bear Canyon virus) was isolated from several California mice (*Peromyscus californicus*) captured in southern California.⁷ Bear Canyon virus, like Tamiami virus, is not known to cause human disease.

The zoonotic potential of Whitewater Arroyo virus is unclear. In August 2000, the California Department of Health Services and the University of Texas Medical Branch reported fatal illnesses in 3 California residents

that were possibly associated with Whitewater Arroyo infection.⁷⁶ The patients were 14-, 30-, and 52-year-old females. Although Whitewater Arroyo virus was never previously linked to human illness, the diagnosis was considered because the illnesses and clinical laboratory findings were compatible with those described for South American hemorrhagic fever viruses; the patients reported no history of travel to areas in which South American hemorrhagic fever viruses are endemic and no other risk factors such as working in a laboratory; researchers had recently reported serologic evidence of Whitewater Arroyo-like virus in wood rat populations in the Los Angeles basin, thus raising the possibility of human exposure within California; and the results of numerous tests for other causes were negative. Reverse transcriptase-polymerase chain reaction assays of RNA isolated from clinical specimens from all 3 women revealed Whitewater Arroyo virus-specific RNA, and infectious arenavirus was isolated in culture of Vero E6 cells inoculated with clinical materials from the 14-year-old patient. However, results of further laboratory evaluation of clinical specimens from the 30-year-old woman did not confirm the diagnosis. It remains uncertain whether the other 2 deaths in California were related to infection with Whitewater Arroyo virus. No additional Whitewater Arroyo virus-associated cases have since been identified. Regardless, discovery of previously unrecognized rodent-borne viral zoonoses in the United States would not be surprising; unusual illnesses or clusters of disease should be reported to public health officials and thoroughly investigated.

Mode of Transmission

Transmission to humans—Rodent-to-human transmission of arenaviruses is believed to occur via inhalation of aerosolized virus or via direct contact with the virus through mucosal or cutaneous routes. Infected rodents shed virus in their urine, saliva, oropharyngeal excretions, and other bodily excreta and secretions, which may then contaminate the environment.

Consumption of mice has also been reported as a risk factor associated with Lassa virus infection in humans.⁷⁷ Person-to-person transmissions of Lassa virus and the South American hemorrhagic viruses have been documented in hospital and household settings.^{3,30,78,79} However, secondary spread within the community at large appears to be uncommon. Person-to-person transmission may occur via direct contact with blood, tissues, secretions, and excretions of infected patients or via inhalation of aerosolized virus from clinical specimens. Lassa fever patients may shed virus in urine and semen for several weeks after recovery, and there is evidence that sexual activity has resulted in secondary cases.^{46,80} Intrauterine transmission of arenaviruses is well documented and may result in severe congenital malformation or death of the fetus or newborn.^{30,43} Transmission of lymphocytic choriomeningitis virus by solid organ transplantation was recently described in the United States.^{31,32}

Rodent-to-rodent transmission—Results of a laboratory study²² involving rodents have indicated that exposure to infective virus particles early in life (ie, at or near birth) usually results in development of a

chronic carrier state. Indeed, the ability to establish chronic infections in their respective principal rodent hosts is the hallmark of the arenaviruses. Vertical (dam-to-progeny) virus transmission is critical to the long-term maintenance of lymphocytic choriomeningitis virus in wild *M musculus* populations. In nature, perpetuation of Lassa virus is probably similar. In contrast, horizontal transmission is thought to be the dominant mode of intraspecific transmission of the New World arenaviruses. Horizontal transmission can occur via allogrooming, fighting, venereal contact, or possible inhalation of infective aerosols.^{22,61}

Clinical Signs

In humans, the zoonotic arenaviruses cause a spectrum of clinical illness ranging from subclinical infection to severe disease and death. The case-to-infection ratio is not known for these viruses, but it is believed that infection with Lassa virus or the South American hemorrhagic fever viruses usually results in development of disease. Illness caused by arenaviral infection generally begins with a prodrome that is characterized by a gradual onset of nonspecific signs and symptoms most often including fever, headache, myalgia, and malaise. The disease may then progress to more severe illness depending on the specific arenaviral species causing the infection.

Lymphocytic choriomeningitis virus infections have the lowest reported mortality rate (< 1%) of the pathogenic arenaviruses. In humans, most infections are probably asymptomatic or result in a mild febrile illness. The incubation period is typically 8 to 13 days, but may be as long as 21 days (eg, in neurologic cases). The illness is biphasic and usually begins with development of fever, headache, malaise, myalgia, and gastrointestinal tract signs.³⁰ Less commonly, pharyngitis, cough, and joint pain are reported. The first phase of illness lasts approximately 1 week and is followed by a short period of remission from clinical signs. Approximately 10% to 20% of individuals with lymphocytic choriomeningitis virus infection will develop neurologic disease. The CNS signs become apparent during the second phase and may include meningitis or encephalitis. Rarely, lymphocytic choriomeningitis virus causes hydrocephalus, myelitis, and possibly myocarditis. Clinicopathologic findings usually include leukopenia and thrombocytopenia during the first phase. Abnormalities in samples of CSF (for example, high protein concentration, high WBC count, and low glucose concentration) are detected during the second phase. Intrauterine infection with lymphocytic choriomeningitis virus has resulted in fetal or neonatal death; some infected infants may develop hydrocephalus, microcephaly, or chorioretinitis.⁴³

Lassa virus and the South American hemorrhagic fever viruses may cause viral hemorrhagic fever, a syndrome that is associated with high case-fatality rates. Lassa virus is a major cause of febrile illness in people in West Africa. In < 10% of Lassa fever cases, severe illness will develop, but the case-fatality rate for hospitalized patients is 15% to 25%; mortality rates during nosocomial outbreaks can be much higher.^{30,78-80} Clinical signs of Lassa fever include a febrile prodrome that is followed by retrosternal chest pain, pharyngitis,

back pain, cough, gastrointestinal tract illness, or hepatitis. As disease becomes more severe, hypotension, peripheral vasoconstriction, decreased urinary output, facial and pulmonary edema, mucosal hemorrhage, severe prostration, or shock may develop. Clinical laboratory findings in Lassa fever patients may include changes in leukocyte concentration, thrombocytopenia, albuminuria, or proteinuria and high serum aspartate aminotransferase activity.^{81,82} Continued viremia in the absence of an effective immune response and high serum aspartate aminotransferase activity (> 150 U/L) indicate a grave prognosis. Lassa fever is also a significant cause of pediatric illness in sub-Saharan Africa.⁸³ Infants may develop swollen baby syndrome, which is characterized by edema, abdominal distention, bleeding, and frequently death. Lassa virus infection acquired during pregnancy is linked to abortion and high case-fatality rates; a mortality rate of 30% has been reported in women infected during the third trimester of pregnancy.^{84,85} The duration of acute illness is approximately 2 to 3 weeks, but convalescence may be prolonged and complicated by development of hearing loss in 20% of Lassa fever patients.⁸⁶ The cause of the deafness is not known, but about half of those persons affected never regain their hearing.

The South American hemorrhagic fever viruses (Guanarito, Junin, Machupo, and Sabiá) generally cause more visible signs of hemorrhage and neurologic disease, compared with Lassa virus. Case-fatality rates range from 15% to 30%, but mortality rates attributed to Argentine hemorrhagic fever and possibly Bolivian hemorrhagic fever can be reduced to 1% to 2% through administration of human immune plasma.⁸⁰ Severe disease caused by the South American hemorrhagic fever viruses may involve the cardiovascular, gastrointestinal, renal, or nervous systems. Clinical features of Argentine hemorrhagic fever—the disease that has been studied in the most detail—may include hypotension, shock, flushing of the head and torso, petechiae, ecchymoses, bleeding, and neurologic signs (eg, tremors, dysarthria, and seizures).⁸⁷ In some patients, neurologic symptoms predominate. Infection in humans is characterized by a triad of clinicopathologic findings including leukopenia, thrombocytopenia, and proteinuria. In a case series study⁶⁴ of Venezuelan hemorrhagic fever, the major clinical signs in patients were fever, malaise, headache, sore throat, vomiting, abdominal pain, diarrhea, convulsions, and hemorrhagic manifestations; leukopenia and thrombocytopenia were common, and the case-fatality rate (33%) in that study was high despite hospitalization and intensive treatment of patients. The clinical features of Bolivian hemorrhagic fever and disease as a result of Sabiá virus infection appear to be similar to those associated with Argentine hemorrhagic fever and Venezuelan hemorrhagic fever, but far fewer cases have been studied. The duration of acute illness caused by the South American hemorrhagic fever viruses is approximately 10 to 15 days after onset, but convalescence may be prolonged. Similar to lymphocytic choriomeningitis virus and Lassa virus, infection during pregnancy in humans can result in intrauterine infection and abortion.

Pathogenesis and Pathologic Features

Humans—Previous studies²⁸⁻³⁰ have established that acute CNS disease caused by lymphocytic choriomeningitis virus is mediated by a cellular immune response. In contrast, the pathogenesis and pathophysiologic features of Lassa fever and the South American hemorrhagic fevers are not well understood. Lassa fever infections result in the early appearance of serum IgG and IgM antibodies, but their presence does not seem to correlate with clinical improvement; serum neutralizing antibodies do not appear until late in the course of disease and do not appear to be therapeutic against severe disease.⁸⁸ Recovery from Lassa fever correlates to the resolution of viremia. In contrast, the cellular and humoral responses probably both play a role in recovery from infection with the South American hemorrhagic fever viruses. Production of binding and neutralization antibodies during acute infection with Junin virus correlates with clearance of virus from the blood and clinical improvement.

Infection in humans presumably follows entry of virus via the respiratory, gastrointestinal, or reproductive tracts or through cuts and abrasions of the skin. Primary replication of virus in the reticuloendothelial system is followed by viremia. In severely affected individuals, endothelial cell damage causes erythrocyte and platelet dysfunction, which leads to increased vascular permeability, capillary leakage, and altered cardiac function. Cytokines and other soluble mediators probably contribute to the pathogenesis of the dysfunction of the vascular endothelium.³⁰ Death is believed to be due to hypovolemic shock and vascular leakage. Overall, the pathologic changes observed do not explain the fatal outcome. Gross lesions may include petechiae, ecchymoses, and mucosal bleeding, but these findings are not always present. Histologic examination of tissue specimens obtained postmortem may reveal focal necrosis in the liver, kidneys, and other organs.

Rodents—The hallmark of the arenaviruses is their ability to establish chronic infections in their respective principal rodent hosts. Persistent infection in individual rodents is critical to the long-term maintenance of arenaviruses in nature. It is commonly assumed that chronic infections are subclinical, but some arenaviruses cause a decrease in fitness (eg, reduced longevity or fecundity) of the rodent host. Lymphocytic choriomeningitis virus causes glomerulonephritis in mice and shortens their lifespan by a few months, especially if they were infected after birth. Renal deposition of virus-antibody complexes is believed to be the underlying cause of the kidney disease.⁸⁹ Results of laboratory experiments involving Machupo virus infection in *Calomys* mice suggest that intraspecific transmission of virus may lead to decreased population numbers and result in reduced fitness.²² Some researchers speculate that the seasonal fluctuations of Bolivian hemorrhagic fever and Argentine hemorrhagic fever may be attributed to decreased populations of reservoir hosts caused by lowered fecundity in subsequent generations of rodents following chronic infection with Machupo and Junin virus, respectively.

Diagnosis

In humans, nonspecific clinical signs and laboratory findings combined with a history of travel to an area in which an arenavirus is endemic or contact with rodents are suggestive of arenaviral disease. Diagnosis of arenaviral infections in humans is challenging because many other diseases present with similar nonspecific clinical signs. The list of differential diagnoses is lengthy and may include influenza, leptospirosis, malaria, shigellosis, typhoid fever, or other viral hemorrhagic fevers (eg, yellow fever and dengue). For patients with neurologic disease, tests for other causes of meningitis or encephalitis (eg, infection with enteroviruses or arboviruses) should be conducted.

Because there are no pathognomonic clinical features associated with arenaviral disease, specialized laboratory tests are necessary for a definitive diagnosis. The gold standard diagnostic test is virus isolation. Virus can be isolated from samples of serum, throat washings, urine, and various tissues. However, diagnostic tests that require handling of hemorrhagic fever virus-infected specimens represent a high exposure risk and should only be performed in high-level containment areas—specifically, biosafety level-4 laboratories—by trained personnel.⁹⁰ For these reasons, public health officials must be consulted immediately when arenaviral disease is suspected. Recently, immunohistochemical assays for detection of arenaviral antigen, various reverse transcriptase-polymerase chain reaction assays for arenavirus-specific RNA, and other laboratory assays have been developed as useful adjuncts to virus isolation. Some of the methods may be adapted for use in biosafety level-3 laboratories in the future, thus obviating the restriction of diagnostic assessments to the few biosafety level-4 laboratories that are operational presently in the Americas and Europe.

Serologic evaluation is the most practical, rapid, and widely utilized method used to diagnose arenaviral disease. In a patient with compatible signs and symptoms, a positive result of an ELISA to detect viral-specific antigen or IgM antibody, a rising serum IgG antibody titer (determined via an ELISA), or positive results of specific immunofluorescence tests are indicative of a presumptive diagnosis.^{80,91} Positive results of immunofluorescence assays and the ELISA are usually obtained during illness or early convalescence. Cross-reactivity between arenaviral strains lowers the specificity of the ELISA and immunofluorescence tests. Neutralizing serum antibody tests are highly specific; such tests are useful for retrospective surveys but not particularly useful in practice for diagnostic purposes. Furthermore, patients infected with Lassa virus generally do not develop serum neutralizing antibodies until weeks after onset of illness.

Treatment

Management of arenaviral infections in humans involves supportive treatments primarily. Maintenance of correct fluid and electrolyte balance is imperative. Administration of the antiviral drug ribavirin (a ribonucleoside analog) is often recommended, but limited quantities of this drug are available, and its use is often not feasible for most of the patients in Africa and

South America.⁹² The exact mode of action of ribavirin is not known, but treatment must be started early in the illness; the drug has no effect on deafness associated with Lassa fever.³⁰ More research is needed to evaluate the effectiveness of ribavirin in treating humans infected with South American viral hemorrhagic fever viruses. Anecdotally, 2 patients infected with Machupo virus recovered after treatment with ribavirin.⁹³ The drug was also used to treat the person with laboratory-acquired Sabiá virus infection discussed earlier in this article, and the patient recovered.⁶⁹

Immune therapy has been used successfully to treat Argentine hemorrhagic fever cases, but the limited availability of biologically safe plasma or serum restricts the use of this treatment modality. Human immune plasma must be given to patients within 8 days of onset, and treatment may be complicated by development of a transient late-onset neurologic syndrome.^{94,95} Immune therapy may also be effective against Machupo virus infection, but there are too few cases to maintain a reliable source of immune plasma.

Prevention and Control

Vaccination—A live attenuated strain of Junin virus is the basis of the only arenaviral vaccine (Candid #1) that has been evaluated in humans. This vaccine also appears to cross-protect against Machupo virus challenge in guinea pigs and nonhuman primates, but not Guanarito virus or Sabiá virus challenge.⁹⁵ A recombinant vaccinia virus vaccine derived from Lassa virus proteins was developed in the 1980s and was shown to have efficacy in guinea pigs and nonhuman primates; however, vaccine trials in humans have not been initiated despite the considerable death and illness attributed to Lassa fever.^{96,97} Progress in development of arenaviral vaccines has been slow because of many challenges. Although no notable safety issues have been reported after vaccination with the live attenuated Junin virus vaccine, there is a general concern about administering live attenuated arenaviral vaccines to humans because of the theoretical possibility of reversion of the virus to virulence and the severe effects of natural arenaviral infection in pregnant women and their fetuses. The advent of recombinant vaccine technology may alleviate these concerns.⁹⁸ Even more daunting than the scientific issues related to arenaviral vaccine development are the social, economic, and political barriers in the countries where these diseases are prevalent.

Rodent control—Eradication of arenaviruses is not a feasible goal because these pathogens are entrenched in wild rodent populations. However, exposure to infected rodents may be reduced through environmental modification. For example, crop replacement or periodic burning of tall grassy areas that are in close proximity to agricultural fields and human habitation has been recommended to control South American hemorrhagic fever viruses in regions in which the viruses are endemic.²² Trapping and other rodent control measures such as proper food storage can be effective, but require a sustained effort that is often impractical, especially in developing countries. After a large Bolivian hemorrhagic fever outbreak in the city of San Joaquin, an intensive trapping

program was considered successful; however, rodent control efforts in African villages have not been as effective in decreasing the number of Lassa fever cases.

Occupational risk reduction—Occupational exposures among researchers that handle rodents are prevented by adherence to guidelines and procedures that effectively prevent exposure to rodent-borne diseases.^{99,100} Because of the potential for aerosolization, special care must be taken to avoid laboratory accidents while handling live virus, especially during centrifugation. Researchers working with rodents or cell lines susceptible to lymphocytic choriomeningitis virus should only purchase animals from reputable commercial suppliers that use serologic tests to screen and eliminate carriers, and wild rodents should be excluded from animal research facilities. Screening protocols for arenaviral infections other than lymphocytic choriomeningitis virus are not routinely available. Precautions for safe cleaning of rodent-infested areas have also been published.¹⁰⁰ Arenaviruses, like other enveloped RNA viruses, are killed by heat, UV light, or γ irradiation and by most detergents and disinfectants. Efforts should be made to prevent aerosolization of virus particles while cleaning potentially contaminated areas (ie, use liquid disinfectants and avoid sweeping, dusting, or vacuuming).

Patient management—Prevention of person-to-person transmission in health care and household settings depends on appropriate patient management.⁹⁰ Implementation of standard precautions while caring for patients considerably decreases development of nosocomial infections. Isolation precautions for patients with suspected viral hemorrhagic fever have been published in the United States and other countries.^{56,57,70,90} Caregivers must be educated regarding the proper use of barrier precautions to prevent contact with infectious materials, especially blood and urine from patients.

Public Health Implications

Laboratory animal veterinarians—The lymphocytic choriomeningitis virus outbreaks during the 1970s that involved mice and hamsters underscore the risk of exposure to rodent-borne viruses in research settings. Fortunately, control measures implemented by commercial rodent distributors have markedly decreased this risk. However, the potential for exposure to zoonotic diseases associated with the handling of wild-caught rodents may be underappreciated by the scientific community. In addition to the pathogenic arenaviruses described in this review, wild rodents are known to harbor many other human pathogens, depending on the rodent species and geographic location (eg, hantaviruses, *Yersinia pestis*, and *Francisella tularensis*).^{13,101,102} Researchers that use wild rodents for studies or class demonstrations unrelated to infectious diseases may be unaware of the potential for rodent-to-human disease transmission. Rodents infected with arenaviruses usually have no clinical signs, yet the excretions and tissues may contain high concentrations of virus.²² Institutional veterinarians should be aware of these risks and provide appropriate counsel to researchers in their universities. Personal protective equipment and other safety measures must be used according to current

recommendations to protect researchers and their students.^{99,100} Given the rapidly expanding number of novel rodent-borne infectious agents, every study involving wild-caught rodents should receive careful consideration with regard to human health before commencement.

Lymphocytic choriomeningitis virus infection from pet rodents—Pet rodents (hamsters, mice, guinea pigs, and possibly other rodents) are potential carriers of lymphocytic choriomeningitis virus. Interim guidelines to prevent human exposure to lymphocytic choriomeningitis from pet rodents were recently published.⁴¹ Serologic testing of individual pet rodent species is generally unreliable and not recommended as a strategy to minimize risk of exposure to the virus. Educational materials on safe handling of pet rodents should be made available at pet stores. Pet stores with potentially infected rodents in stock should contact public health authorities for additional information and guidance.

Importation of arenaviruses into areas in which the viruses are not endemic—Several countries have reported imported Lassa fever cases among patients returning from areas of Africa in which the disease is endemic, including a recent case in New Jersey.⁵⁸ Public health officials must be notified immediately if arenaviral infection is suspected in a patient returning from a region in which such viruses are endemic. Because of the potential for person-to-person transmission, adherence to appropriate isolation precautions and laboratory protocols is critical. International travel has also enhanced the potential for importation of cases of other arenaviruses such as South American hemorrhagic fever viruses into nonendemic areas.

Importation of wild rodents for the pet trade represents another possible means of introduction of an exotic arenavirus into an area in which the virus is not endemic. The remarkable occurrence of monkeypox infections in the United States in 2003 resulting from contact between imported African wild rodents and pet prairie dogs illustrates the potential for a similar incident involving other rodent-borne diseases such as arenaviral infections.¹⁰³ Although prohibition of the importation of African wild rodents into the United States following the monkeypox outbreak represents an important control measure, enforcement of the ban may be difficult.¹⁰⁴ Furthermore, the ban does not specifically include wild rodent hosts of the South American hemorrhagic fever viruses. As “pocket pets” (primarily domestic and wild rodents) become increasingly popular, the threat of exposure to zoonotic pathogens harbored by these species increases. Veterinarians should be aware of these risks and communicate any concerns to their clients and public health officials.

Bioterrorism—There is a consensus among experts that Lassa virus and the South American hemorrhagic fever arenaviruses are high-priority bioterrorism agents.¹⁰⁵ The hemorrhagic fever viruses are classified by the National Institute of Health and the CDC as Category A pathogens, which are defined as high-priority biological

agents with the greatest potential to damage the medical or public health system. Hemorrhagic fever viruses classified as Category A pathogens include Lassa virus and the 4 pathogenic South American hemorrhagic fever viruses (Junin, Guanarito, Machupo, and Sabiá), as well as the filoviruses (Ebola and Marburg). Arenaviruses are especially dangerous in the context of terrorism for several reasons, including high infectivity by aerosol; high case-fatality rates (15% to 30%); potential for person-to-person transmission, especially in health care settings; lack of or limited availability of treatments and vaccinations; reservoir hosts that represent a source to obtain virus; and the potential for viral hemorrhagic fever to cause significant alarm and disruption in the general population and among health care workers.^{105,106}

Overview

The arenaviruses are a diverse group of viruses that includes agents of severe human disease. Outbreaks of lymphocytic choriomeningitis virus infection among humans have been associated with interactions with laboratory and pet rodents. Veterinarians need to be aware of the risks associated with handling rodents that may harbor arenaviruses or other rodent-borne pathogens. In addition, arenaviruses that cause viral hemorrhagic fever are classified as high-priority bioterrorism pathogens.

References

- Buchmeier MJ, Bowen MD, Peters CJ. *Arenaviridae: the viruses and their replication*. In: Knipe DM, Howley PM, eds. *Fields virology*. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001;1635–1668.
- Charrel RN, de Lamballerie X. Arenaviruses other than Lassa virus. *Antiviral Res* 2003;57:89–100.
- Lisieux T, Coimbra M, Nassar ES, et al. New arenavirus isolated in Brazil. *Lancet* 1994;343:391–392.
- Tesh RB, Jahrling PB, Salas R, et al. Description of Guanarito virus (*Arenaviridae*: Arenavirus), the etiologic agent of Venezuelan hemorrhagic fever. *Am J Trop Med Hyg* 1994;50:452–459.
- Fulhorst CF, Bowen MD, Salas RA, et al. Isolation and characterization of Whitewater Arroyo virus, a novel North American arenavirus. *Virology* 1996;224:114–120.
- Fulhorst CF, Bowen MD, Salas RA, et al. Isolation and characterization of Pirital virus, a newly discovered South American arenavirus. *Am J Trop Med Hyg* 1997;56:548–553.
- Fulhorst CF, Bennett SG, Milazzo ML, et al. Bear Canyon virus: an arenavirus naturally associated with the California mouse (*Peromyscus californicus*). *Emerg Infect Dis* 2002;8:717–721.
- Clegg JC. Molecular phylogeny of the arenaviruses. *Curr Top Microbiol Immunol* 2002;262:1–24.
- Bowen MD, Peters CJ, Nichol ST. The phylogeny of New World (Tacaribe complex) arenaviruses. *Virology* 1996;219:285–290.
- Bowen MD, Peters CJ, Nichol ST. Phylogenetic analysis of the *Arenaviridae*: patterns of virus evolution and evidence for cospeciation between arenaviruses and their rodent hosts. *Mol Phylogenet Evol* 1997;8:301–316.
- Charrel RN, Feldmann H, Fulhorst CF, et al. Phylogeny of New World arenaviruses based on the complete coding sequences of the small genomic segment identified an evolutionary lineage produced by intrasegmental recombination. *Biochem Biophys Res Commun* 2002;1118–1124.
- Charrel RN, de Lamballerie X, Fulhorst CF. The Whitewater Arroyo virus: natural evidence for genetic recombination among Tacaribe serocomplex viruses (family *Arenaviridae*). *Virology* 2001;283:161–166.
- Calisher CH, Mills JN, Root JJ, et al. Hantaviruses: etiologic agents of rare, but potentially life-threatening zoonotic diseases. *J Am Vet Med Assoc* 2003;222:163–166.

- Hjelle B, Yates T. Modeling Hantavirus maintenance and transmission in rodent communities. *Curr Top Microbiol Immunol* 2001;256:77–90.
- Bowen MD, Rollin PE, Ksiazek TG, et al. Genetic diversity among Lassa virus strains. *J Virol* 2000;74:6992–7004.
- Weaver SC, Salas RA, de Manzione N, et al. Guanarito virus (*Arenaviridae*) isolates from endemic and outlying localities in Venezuela: sequence comparisons among and within strains isolated from Venezuelan hemorrhagic fever patients and rodents. *Virology* 2000;266:189–195.
- Fulhorst CF, Charrel RN, Weaver SC, et al. Geographic distribution and genetic diversity of Whitewater Arroyo virus in the southwestern United States. *Emerg Infect Dis* 2001;7:403–407.
- Fulhorst CF, Milazzo ML, Carroll DS, et al. Natural host relationships and genetic diversity of Whitewater Arroyo virus in southern Texas. *Am J Trop Med Hyg* 2002;67:114–118.
- Downs WG, Anderson CR, Spense L, et al. Tacaribe virus, a new agent isolated from *Artibeus* bats and mosquitoes in Trinidad, West Indies. *Am J Trop Med Hyg* 1963;12:640–646.
- Montali RJ, Ramsay EC, Stephensen CB, et al. A new transmissible viral hepatitis of marmosets and tamarins. *J Infect Dis* 1989;160:759–765.
- Stephensen CB, Jacob JR, Montali RJ, et al. Isolation of an arenavirus from a marmoset with callitrichid hepatitis and its serologic association with disease. *J Virol* 1991;65:3995–4000.
- Childs JE, Peters CJ. Ecology and epidemiology of arenaviruses and their hosts. In: Salvato MS, ed. *The Arenaviridae*. New York: Plenum Press, 1993;331–384.
- Mills JN, Ellis BA, McKee KT, et al. A longitudinal study of Junin virus activity in the rodent reservoir of Argentine hemorrhagic fever. *Am J Trop Med Hyg* 1992;47:749–763.
- Demby AH, Inapogui A, Kargbo K, et al. Lassa fever in Guinea: II. Distribution and prevalence of Lassa virus infection in small mammals. *Vector Borne Zoonotic Dis* 2001;1:283–297.
- Salazar-Bravo J, Dragoo JW, Bowen MD, et al. Natural nidality in Bolivian hemorrhagic fever and the systematics of the reservoir species. *Infect Genet Evol* 2002;1:191–199.
- Armstrong C, Lillie RD. Experimental lymphocytic choriomeningitis of monkeys and mice produced by a virus encountered in studies of the 1933 St. Louis encephalitis epidemic. *Public Health Rep* 1934;49:1019–1027.
- Oldstone MB. Arenaviruses. I. The epidemiology molecular and cell biology of arenaviruses. Introduction. *Curr Top Microbiol Immunol* 2002;262:V–XII.
- Slifka MK. Mechanisms of humoral immunity explored through studies of LCMV infection. *Curr Top Microbiol Immunol* 2002;263:67–81.
- Zinkernagel RM. Lymphocytic choriomeningitis virus and immunology. *Curr Top Microbiol Immunol* 2002;263:1–5.
- Peters CJ. *Arenaviridae*. Lymphocytic choriomeningitis virus, Lassa virus, and the South American hemorrhagic fevers. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 6th ed. Philadelphia: Churchill Livingstone, 2000;1855–1862.
- Paddock C, Ksiazek T, Comer JA, et al. Pathology of fatal lymphocytic choriomeningitis virus infection in multiple organ transplant recipients from a common donor. *Mod Pathol* 2005;18(suppl):163A–264A.
- Lymphocytic choriomeningitis virus infection in organ transplant recipients—Massachusetts, Rhode Island, 2005. *MMWR Morb Mortal Wkly Rep* 2005;54:537–539.
- Childs JE, Glass GE, Ksiazek TG, et al. Human-rodent contact and infection with lymphocytic choriomeningitis and Seoul viruses in an inner-city population. *Am J Trop Med Hyg* 1991;44:117–121.
- Stephensen CB, Blount SR, Lanford RE, et al. Prevalence of serum antibodies against lymphocytic choriomeningitis virus in selected populations from two US cities. *J Med Virol* 1992;38:27–31.
- Park JY, Peters CJ, Rollin PE, et al. Age distribution of lymphocytic choriomeningitis virus serum antibody in Birmingham, Alabama: evidence of a decreased risk of infection. *Am J Trop Med Hyg* 1997;57:37–41.
- Davison KL, Crowcroft NS, Ramsay ME, et al. Viral

encephalitis in England, 1989–1998: what did we miss? *Emerg Infect Dis* 2003;9:234–240.

37. Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998–2000. *Clin Infect Dis* 2003;36:731–742.

38. Gregg MB. Recent outbreaks of lymphocytic choriomeningitis in the United States of America. *Bull World Health Organ* 1975;52:549–553.

39. Biggar RJ, Deibel R, Woodall JP. Implications, monitoring, and control of accidental transmission of lymphocytic choriomeningitis virus within hamster tumor cell lines. *Cancer Res* 1976;36:551–553.

40. Dykewicz CA, Dato VM, Fisher-Hoch SP, et al. Lymphocytic choriomeningitis outbreak associated with nude mice in a research institute. *JAMA* 1992;267:1349–1353.

41. Update: interim guidance for minimizing risk for human lymphocytic choriomeningitis virus infection associated with pet rodents. *MMWR Morb Mortal Wkly Rep* 2005;54(dispatch):1–3.

42. Barton LL, Peters CJ, Ksiazek TG. Lymphocytic choriomeningitis virus: an unrecognized teratogenic pathogen. *Emerg Infect Dis* 1995;1:152–153.

43. Levy C. Lymphocytic choriomeningitis. *Vector Ecology Newsletter* 1999;30(2):20.

44. Buckley SM, Casals J. Lassa fever, a new virus disease of man from West Africa. III. Isolation and characterization of the virus. *Am J Trop Med Hyg* 1970;19:680–691.

45. Frame JD, Baldwin JM, Glocke DJ, et al. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. *Am J Trop Med Hyg* 1970;19:670–676.

46. McCormick JB, Webb PA, Krebs JW, et al. A prospective study of the epidemiology and ecology of Lassa Fever. *J Infect Dis* 1987;155:437–444.

47. Frame JD, Hahrling PB, Yalley-Ogunro, et al. Endemic Lassa fever in Liberia. II. Serological and virological findings in hospital patients. *Trans R Soc Trop Med Hyg* 1984;78:656–660.

48. Fabiyi A, Tomori O, Pinneo P. Lassa fever antibodies in hospital personnel in the Plateau State of Nigeria. *Niger Med J* 1979;9:23–25.

49. Bajani MD, Tomori O, Rollin PE, et al. A survey of antibodies to Lassa virus among health workers in Nigeria. *Trans R Soc Trop Med Hyg* 1997;91:379–381.

50. Bausch DG, Demby AH, Mamadi C, et al. Lassa fever in Guinea: I. Epidemiology of human disease and clinical observations. *Vector Borne Zoonotic Dis* 2001;1:269–281.

51. Demby AH, Inapogui A, Kargbo K, et al. Lassa fever in Guinea: II. Distribution and prevalence of Lassa virus infection in small mammals. *Vector Borne Zoonotic Dis* 2001;1:283–297.

52. Keenlyside RA, McCormick JB, Webb PA, et al. Case-control study of *Mastomys natalensis* and humans in Lassa virus-infected households in Sierra Leone. *Am J Trop Med Hyg* 1983;32:829–837.

53. Mahdy MS, Chiang W, McLaughlin B, et al. Lassa fever: the first confirmed case imported into Canada. *Can Dis Wkly Rep* 1989;15:193–198.

54. Lassa fever imported to England. *Commun Dis Rep CDR Wkly* 2000;10:99.

55. Lassa fever, imported case, Netherlands. *Wkly Epidemiol Rec* 2000;75:265.

56. Colebunders R, Van Esbroeck M, Moreau M, et al. Imported viral haemorrhagic fever with a potential for person-to-person transmission: review and recommendations for initial management of a suspected case in Belgium. *Acta Clin Belg* 2002;57:233–240.

57. Haas WH, Breuer T, Pfaff G, et al. Imported Lassa fever in Germany: surveillance and management of contact persons. *Clin Infect Dis* 2003;36:1254–1258.

58. Imported Lassa fever—New Jersey, 2004. *MMWR Morb Mortal Wkly Rep* 2004;53:894–897.

59. Parodi AS, Greenway DJ, Ruggiero HR, et al. Concerning the epidemic outbreak in Junin. *Dia Med* 1958;30:2300–2301.

60. Molteni HD, Guarinos HC, Petrillo CO, et al. Clinico-statistical study of 338 patients with epidemic hemorrhagic fever in the northwest of the province of Buenos Aires. *Sem Med* 1961;118:839–855.

61. Mills JN, Ellis BA, Childs JE, et al. Prevalence of infection with Junin virus in rodent populations in the epidemic area of Argentine hemorrhagic fever. *Am J Trop Med Hyg* 1994;51:554–562.

62. Salas R, de Manzione N, Tesh RB, et al. Venezuelan hemorrhagic fever. *Lancet* 1991;338:1033–1036.

63. Doyle TJ, Bryan RT, Peters CJ. Viral hemorrhagic fevers and hantavirus infections in the Americas. *Infect Dis Clin North Am* 1998;12:95–110.

64. de Manzione N, Salas RA, Paredes H, et al. Venezuelan hemorrhagic fever: clinical and epidemiological studies of 165 cases. *Clin Infect Dis* 1988;26:308–313.

65. Fulhorst CF, Bowen MD, Salas RA, et al. Natural rodent host associations of Guanarito and Piritaval viruses (Family *Arenaviridae*) in central Venezuela. *Am J Trop Med Hyg* 1999;61:325–330.

66. Johnson KM, Wiebenga NH, Mackenzie RB, et al. Virus isolations from human cases of hemorrhagic fever in Bolivia. *Proc Soc Exp Biol Med* 1965;118:113–118.

67. Kuns ML. Epidemiology of Machupo virus infection. II. Ecological and control studies of hemorrhagic fever. *Am J Trop Med Hyg* 1965;14:813–816.

68. Bolivian hemorrhagic fever—El Beni Department, Bolivia, 1994. *MMWR Morb Mortal Wkly Rep* 1994;43:943–946.

69. Gandsman EJ, Aaslestad HG, Ouimet TC, et al. Sabiá virus incident at Yale University. *Am Ind Hyg Assoc J* 1997;58:51–53.

70. Armstrong LR, Dembry LM, Rainey PM, et al. Management of a Sabia virus-infected patient in a US hospital. *Infect Control Hosp Epidemiol* 1999;20:176–182.

71. Calisher CH, Tzianabos T, Lord RD, et al. Tamiami virus, a new member of the Tacaribe group. *Am J Trop Med Hyg* 1970;19:520–526.

72. Smithsonian National Museum of Natural History Web site. North American mammals: *Sigmondon hispidis*. Available at: web4.si.edu/mna/image_info.cfm?species_id=307. Accessed Dec 5, 2004.

73. Kosoy MY, Elliott LH, Ksiazek TG, et al. Prevalence of antibodies to arenaviruses in rodents from the southern and western United States: evidence for an arenavirus associated with the genus *Neotoma*. *Am J Trop Med Hyg* 1996;54:570–576.

74. Bennett SG, Milazzo ML, Webb JP, et al. Arenavirus antibody in rodents indigenous to coastal southern California. *Am J Trop Med Hyg* 2000;62:626–630.

75. Calisher CH, Nabity S, Root JJ, et al. Transmission of an arenavirus in white-throated woodrats (*Neotoma albigula*), southeastern Colorado, 1995–1999. *Emerg Infect Dis* 2001;7:397–402.

76. Fatal illnesses associated with a new world arenavirus—California, 1999–2000. *MMWR Morb Mortal Wkly Rep* 2000;49:709–711.

77. Ter Meulen J, Lukashevich I, Sidibe K, et al. Hunting of peridomestic rodents and consumption of their meat as possible risk factors for rodent-to-human transmission of Lassa virus in the Republic of Guinea. *Am J Trop Med Hyg* 1996;55:661–666.

78. McCormick JB, Fisher-Hoch SP. Lassa fever. *Curr Top Microbiol Immunol* 2002;262:75–109.

79. Leifer E, Gocke DJ, Bourne H. Lassa fever, a new virus disease of man from West Africa. II. Report of a laboratory-acquired infection treated with plasma from a person recently recovered from the disease. *Am J Trop Med Hyg* 1970;19:677–679.

80. Peters CJ, Zaki SR. Viral hemorrhagic fever: an overview. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical infectious diseases: principles, pathogens, & practice*. New York: WB Saunders Co, 1999; 1180–1188.

81. Johnson KM, McCormick JB, Webb PA, et al. Clinical virology of Lassa fever in hospitalized patients. *J Infect Dis* 1987;155:456–464.

82. McCormick JB, King IJ, Webb PA, et al. A case-control study of the clinical diagnosis and course of Lassa fever. *J Infect Dis* 1987;155:445–455.

83. Webb PA, McCormick JB, King J, et al. Lassa fever in children in Sierra Leone, West Africa. *Trans R Soc Trop Med Hyg* 1986;80:577–582.

84. McCormick JB. Clinical, epidemiologic, and therapeutic aspects of Lassa fever. *Med Microbiol Immunol* 1986;175:153–155.

85. Price ME, Fisher-Hoch SP, Craven RB, et al. A prospective study of maternal and fetal outcome in acute Lassa fever infection during pregnancy. *BMJ* 1988;297:584–587.

86. Cummins D, McCormick JB, Bennett D, et al. Acute sensorineural deafness in Lassa fever. *JAMA* 1990;264:2093–2096.

87. Maiztegui JI. Clinical and epidemiologic patterns of Argentine haemorrhagic fever. *Bull World Health Organ* 1975;52:567–574.

88. Peters CJ. Pathogenesis of viral hemorrhagic fevers. In: Nathanson N, Ahmed R, Gonzalez-Scarano F, et al, eds. *Viral pathogenesis*. Philadelphia: Lippincott-Raven Publishers, 1997;779–799.

89. Oldstone MB. Biology and pathogenesis of lymphocytic choriomeningitis virus infection. *Curr Top Microbiol Immunol* 2002;263:83–117.

90. Update. Management of patients with suspected viral hemorrhagic fever—United States. *MMWR Morb Mortal Wkly Rep* 1995;44:475–499.

91. Bausch DG, Rollin PE, Demby AH, et al. Diagnosis and clinical virology of Lassa fever as evaluated by enzyme-linked immunosorbent assay, indirect fluorescent-antibody test, and virus isolation. *J Clin Microbiol* 2000;38:2670–2677.

92. Damonte EB, Coto CE. Treatment of arenavirus infections: from basic studies to the challenge of antiviral therapy. *Adv Virus Res* 2002;58:125–155.

93. Kilgore PE, Ksiazek TG, Rollin PE, et al. Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis* 1997;24:718–722.

94. Enria D, Franco SG, Ambrosio A, et al. Current status of the treatment of Argentine hemorrhagic fever. *Med Microbiol Immunol* 1986;175:173–176.

95. Enria DA, Barrera Oro JG. Junin virus vaccines. *Curr Top Microbiol Immunol* 2002;263:239–261.

96. Auperin DD. Construction and evaluation of recombinant virus vaccines for Lassa fever. In: Salvato MS, ed. *The Arenaviridae*. New York: Plenum Press, 1993;259–280.

97. Fisher-Hoch SP, Hutwagner L, Brown B, et al. Effective vaccine for Lassa fever. *J Virol* 2000;74:6777–6783.

98. Baize S, Marianneau P, Georges-Courbot MC, et al. Recent advances in vaccines against viral hemorrhagic fevers. *Curr Opin Infect Dis* 2001;14:513–518.

99. CDC Web site. Methods for trapping and sampling small mammals for virologic testing. Available at: www.cdc.gov/ncidod/dvrd/spb/mnpages/rodentmanual.htm. Accessed Dec 5, 2004.

100. Mills JN, Corneli A, Young JC, et al. Hantavirus pulmonary syndrome: United States: updated recommendations for risk reduction. *MMWR Recomm Rep* 2002;51(RR-9):1–12.

101. Orloski KA, Lathrop SL. Plague: a veterinary perspective. *J Am Vet Med Assoc* 2003;222:444–448.

102. Feldman KA. Tularemia. *J Am Vet Med Assoc* 2003;222:725–730.

103. Multistate outbreak of monkeypox—Illinois, Indiana, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep* 2003;52:537–540.

104. Control of communicable diseases; restrictions on African rodents, prairie dogs, and certain other animals. Interim final rule; opportunity for public comment. *Fed Regist* 2003;68:62353–62369.

105. Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA* 2002;287:2391–2405.

106. Peters CJ. Are hemorrhagic fever viruses practical agents for biological terrorism? In: Scheld WM, Craig WA, Hughes JM, eds. *Emerging infections 4*. Washington, DC: American Society for Microbiology, 2000;201–209.

Appendix

Arenaviral serocomplexes and their reservoir hosts, geographic distribution, and associated human diseases.

Serocomplex	Virus	Reservoir host (common name)	Geographic distribution	Human disease
Lymphocytic choriomeningitis-Lassa virus serocomplex	Ippy	<i>Arvicanthus</i> spp	Central African Republic Nigeria, Ivory Coast, Guinea, Sierra Leone	Lassa fever
	Lassa	<i>Mastomys natalensis</i> (natal multimammate mouse)		
	Lymphocytic choriomeningitis	<i>Mus musculus</i> (house mouse)	Europe, Asia, and the Americas	Aseptic meningitis, congenital anomalies
Mobala	Mopeia	<i>Praomys</i> spp	Central African Republic Mozambique	
		<i>Mastomys natalensis</i> (natal multimammate mouse)		
Tacaribe serocomplex*				
Group A	Allpahuayo	<i>Oecomys bicolor</i> (bicolored arboreal rice rat)	Peru	
	Bear Canyon	<i>Peromyscus californicus</i> (California mouse)	USA (California)	
	Flexal	<i>Oryzomys</i> spp	Brazil	
	Pichindé	<i>Oryzomys albigularis</i> (Tomes' rice rat)	Colombia	
	Parana	<i>Oryzomys buccinatus</i> (Paraguayan rice rat)	Paraguay	
	Pirital	<i>Sigmodon alstoni</i> (Alston's cotton rat)	Venezuela	
	Tamiami	<i>Sigmodon hispidus</i> (hispid cotton rat)	USA (Florida)	
	Whitewater Arroyo	<i>Neotoma albigula</i> (white-throated wood rat)	USA (New Mexico)	
Group B	Amapari	<i>Oryzomys capito</i> (large-headed rice rat), <i>Neacomys guianae</i> (Guiana bristly mouse)	Brazil	Venezuelan hemorrhagic fever
	Cupixi	<i>Oryzomys capito</i> (large-headed rice rat)	Brazil	
	Guanarito	<i>Zygodontomys brevicauda</i> (short-tailed cane mouse)	Venezuela	
	Junin	<i>Calomys musculus</i> (drylands vesper mouse), <i>Calomys laucha</i> (small vesper mouse)	Argentina	
	Machupo	<i>Calomys callosus</i> (large vesper mouse)	Bolivia	
	Sabiá	Unknown	Brazil	
Tacaribe	<i>Artibeus</i> spp (frugivorous bats)	Trinidad		
Group C	Latino	<i>Calomys callosus</i> (large vesper mouse)	Bolivia	Argentine hemorrhagic fever Bolivian hemorrhagic fever Viral hemorrhagic fever
	Oliveros	<i>Bolomys obscurus</i> (dark bolo mouse)	Argentina	

*Groups A, B, and C denote phylogenetic groupings that are based on analyses of viral nucleocapsid protein gene sequences.