CTMI (2007) 315:253–288

Arenaviruses

J. P. Gonzalez[1,3] (✉) · S. Emonet[1] · X. de Lamballerie[2,3] · R. Charrel[2,3]

[1]IRD U178, Conditions et Territoires d'Emergence des Maladies, Thaïlande, *frjpg@mahidol.ac.th*
[2]Unité des Virus Emergents (EA3292, IFR48), Université de la Méditerranée, Marseille, France
[3]Unité Pathologies Virales Emergentes, Univ Méditerranée-IRD

Abstract The *Arenaviridae* family contains 22 recognized virus species, each of them strongly associated with a rodent species (except Tacaribe virus which is associated with a species of bat), suggesting an ancient co-evolutionary process. Although the concept of co-evolution between rodents and arenaviruses is now largely accepted, little has been uncovered in terms of dating the phenomenon and the mechanisms of evolution, including speciation and pathogenicity. These questions are targeted in the present chapter. Old World arenaviruses are associated with the Eurasian rodents in the family Muridae. New World arenaviruses are associated with American rodents in the subfamily Sigmodontinae. The correlation between the rodent host phylogeny and the viruses suggests a long association and a co-evolutionary process. Furthermore, three distinct New World arenaviruses share a common ancestor, demonstrating a unique recombination event that probably occurred in that ancestor. This shows that recombination among arenaviruses of different lineages might occur in nature. Recombination and co-evolutionary adaptation appear as the main mechanisms of

arenavirus evolution, generating a high degree of diversity. The diversity among rodent host reservoir and virus species and the potential to exchange genomic material provide a basis for the emergence of new viruses and the risk of these becoming pathogenic for humans.

1 Introduction

The *Arenaviridae* family consists of a unique *Arenavirus* genus that currently contains 22 recognized virus species (Salvato et al. 2005). Arenaviruses are enveloped single-stranded RNA viruses, with a genome consisting of two RNA segments, designated large (L) and small (S). The L genomic segment (~7.2 kb) encodes the viral RNA-dependent RNA polymerase and a zinc-binding protein. The S genomic segment (~3.5 kb) encodes the nucleocapsid protein and envelope glycoproteins in nonoverlapping open reading frames of opposite polarities. The genes on both S and L segments are separated by an intergenic noncoding region with the potential of forming one or more hairpin configurations. The 5′ and 3′ untranslated terminal sequences of each RNA segment possess a relatively conserved reverse complementary sequence spanning 19 nucleotides at each extremity. Nucleocapsid antigens are shared by most arenaviruses, and quantitative relationships show the basic split between viruses of Africa and viruses of the Western Hemisphere. Individual viruses are immunologically distinct by neutralization assays, which depend on the specificity of epitopes contained in the envelope glycoproteins (Salvato et al. 2005).

Virions are spherical to pleomorphic with a diameter of 50–300 nm (average diameter for spherical particles is 120 nm). They possess a dense lipid-containing envelope covered with 8- 10-nm-long club-shaped projections. Host cell ribosomes present in the viral particles, are responsible for the sandy appearance of the virus by electron microscopy, hence the name arenavirus (Latin: *arena*, sand). Buoyant density is 1.17–1.18 g/cm^3 in sucrose and 1.19–1.20 g/cm^3 in CsCl. Virus is rapidly inactivated at 56°C, at pH below 5.5 or above 8.5, or by exposure to UV and gamma irradiation (Table 1).

Lymphocytic choriomeningitis virus (LCMV) was first isolated in the 1930s (Armstrong and Lillie 1934) but it is only in the late 1960s that LCMV was found to be related to the already existing Tacaribe group, which then led to the creation of the *Arenaviridae* family (Murphy et al. 1969). The arenaviruses have been classified into two groups according to their antigenic properties: (1) the Tacaribe serocomplex (including viruses indigenous to rodents of the New World) and the prototype Tacaribe virus (TCRV) isolated from *Artibeus* bats in Trinidad (Downs et al. 1963), and (2) the Lassa-lymphocytic choriomeningitis (LCM) serocomplex (including the viruses indigenous to rodents of Africa and the ubiquitous lymphocytic choriomeningitis virus (LCMV), recognized as the Old World group) (Fig. 1).

Table 1 The *Arenaviridae* family

Virus		Acronym	Country of prototype virus isolate	Human significance[a]	Historical reference
1	Allpahuayo	ALLV	Peru	NE	Moncayo et al. 2001
2	Amapari	AMAV	Brazil	NE	Pinheiro et al. 1966
3	Bear canyon	BCNV	USA, California	NE	Peters et al. 1996
5	Cupixi	CPXV	Brazil	NE	Charrel et al. 2002
6	Flexal	FLEV	Brazil	LI	Pinheiro et al. 1977
7	Guanarito	GTOV	Venezuela	HF, LI	Salas et al. 1991
8	Ippy	IPPYV	Central African Republic	NE	Swanepoel et al. 1985
9	Junin	JUNV	Argentina	HF	Parodi et al.1958
10	Lassa	LASV	Nigeria	HF	Buckley et al. 1970
11	Latino	LATV	Bolivia	NE	Webb et al. 1973
12	Lymphocytic choriomeningitis	LCMV	Europe, USA	NS	Amstrong and Lilly 1934
13	Machupo	MACV	Bolivia	HF, LI	Johnson et al. 1965
14	Mobala	MOBV	Central African Republic	NE	Gonzalez et al. 1983
15	Mopeia	MOPV	Mozambique	NE	Wulff et al. 1977
16	Oliveros	OLVV	Argentina	NE	Mills et al. 1996
16[b]	Pampa		Argentina	NE	Lozano et al. 1997
17	Parana	PARV	Paraguay	NE	Webb et al. 1970
18	Pichinde	PICV	Colombia	LI	Trapido and Sanmartin 1971
19	Pirital	PIRV	Venezuela	NE	Fulhorst et al. 1997
20	Sabia	SABV	Brazil	HF, LI	Lisieur et al. 1994
21	Tacaribe	TCRV	Trinidad	LI	Downs et al. 1963
22	Tamiami	TAMV	USA Florida	NE	Calisher et al. 1970
23	Whitewater Arroyo	WWAV	USA, south West	NE	Fulhorst et al. 1996

Acronyms are attributed by the ICTV (Salvato et al. 2000). Countries are where the virus was first isolated and the associated reference is also the first report of the prototype virus. For arenaviruses known to be human pathogens virus, the primary clinical syndrome is indicated

[a] *BSL* biosafety level

[b] *HF* hemorrhagic fever; *NS* neurological syndrome; *LI* laboratory infection; *NE* No evidence of natural human infection

[c] Pampa virus should be considered as a genotype of Oliveros virus

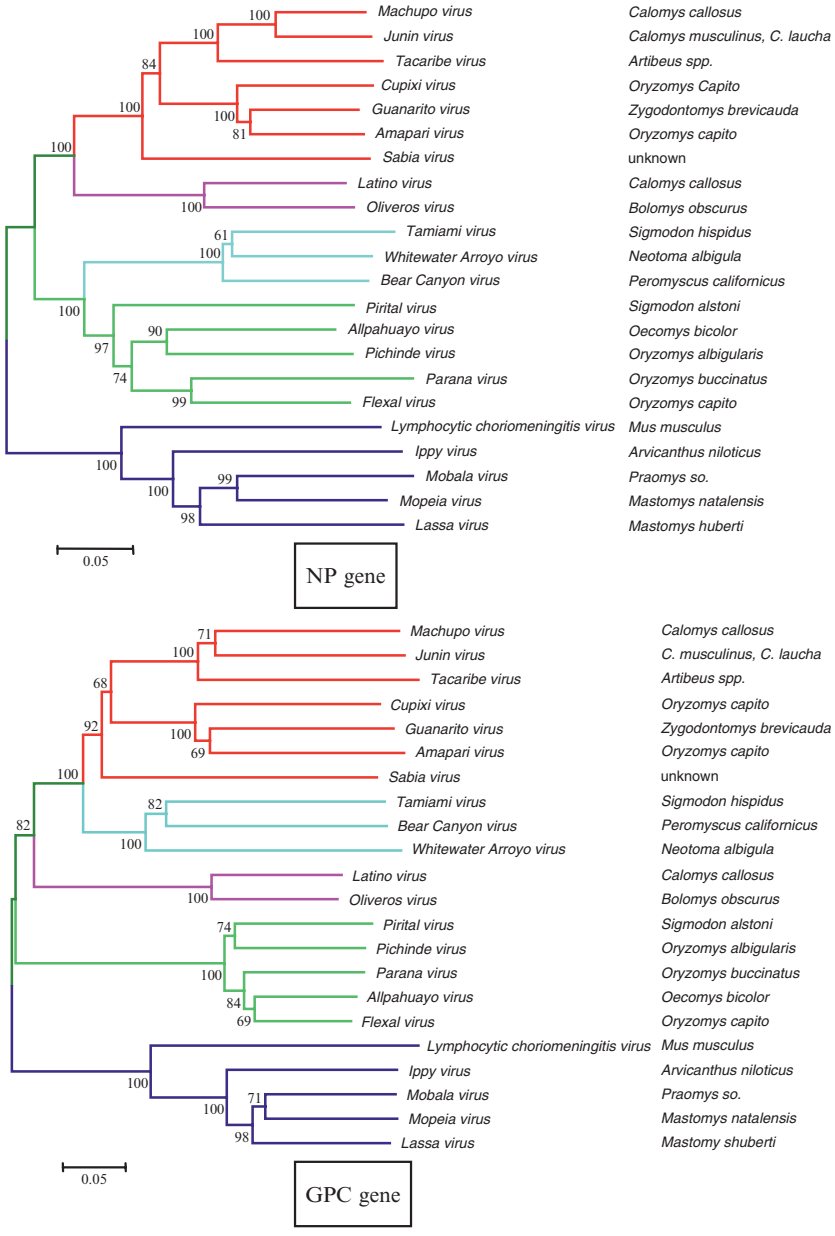

Fig. 1 *Arenavirus* phylogeny and rodent reservoir

Genetic studies of arenaviruses are congruent with comparative serological analyses. Both methods indicate that the 22 arenaviruses represent four phylogenetic lineages. The Old World (Lassa-LCM serocomplex) lineage comprises five viruses: LCMV, Lassa (LASV), Mopeia (MOPV), Mobala (MOBV) (Buckley et al. 1970; Wulff et al. 1977; Gonzalez et al. 1983), and Ippy (IPPYV) (Swanepoel et al. 1985) and is deeply rooted to the three New World (Tacaribe serocomplex) lineages, designated A, B, and C. Lineage A includes five South American viruses, Pirital (PIRV), Pichindé (PICV) (Fulhorst et al. 1997; Trapido and Sanmartin 1971), Flexal (FLEV), Paraná (PARV), and Allpahuayo (ALLV) (Pinheiro et al. 1977; Webb et al. 1970; Moncayo et al. 2001). Lineage B includes seven South American viruses including Sabiá (SABV), Junín (JUNV), Machupo (MACV), Guanarito (GTOV), Amapari (AMAV) (Lisieux et al. 1994; Parodi et al. 1958, Johnson et al. 1965; Salas et al. 1991; Pinheiro et al. 1966), Tacaribe (TCRV) (Downs et al. 1963), and Cupixi (CPXV) (Charrrel et al. 2002). Lineage C comprises three South American viruses: Oliveros (OLVV) (Mills et al. 1996), Latino (LATV) (Webb et al. 1975), and Pampa (PAMV), which is a genotype of OLVV and does not represent a taxonomic species (Salvato et al. 2005). Phylogenetic studies conducted with complete gene sequences recently demonstrated that discrepancies observed in the topology of phylograms reconstructed from nucleoprotein and envelope glycoprotein genes are attributed to the recombinant nature of the S RNA segment of the three North American viruses: Whitewater Arroyo (WWAV), Tamiami (TAMV), and Bear Canyon (BCNV) (Fulhorst et al. 1996; Calisher et al. 1970; Fulhorst et al. 2002) (Table 2).

LASV, JUNV, MACV, GTOV, and SABV are known to cause a severe hemorrhagic fever, in western Africa, Argentina, Bolivia, Venezuela, and Brazil, respectively (Peters et al. 1996), and were first recovered during investigations of human disease in 1969 (Buckley et al. 1970), 1958 (Parodi et al.1958), in 1963 (Johnson et al. 1965), 1989, (Salas et al. 1991), and 1990 (Coimbra et al. 1994), respectively. They are included in the Category A Pathogen List as defined by the CDC, and listed as Biosafety Level 4 (BSL-4) agents. The family prototype, LCMV, was first isolated in 1933 during serial monkey passage of human material obtained from a fatal infection in the first documented epidemic of St. Louis encephalitis. LCMV is an agent of acute central nervous system disease (Barton and Hyndman 2000) and is also responsible for congenital malformations (Barton et al. 1993). FLEV and TCRV viruses have caused febrile illnesses in laboratory workers. WWAV has been associated with three fatal cases of infection in California in 2000 (CDC 2000), but further cases have not been documented since.

LCMV, LASV, and related viruses from the Old World are associated with rodents from the family *Muridae*, subfamily *Murinae*. New World arenaviruses are associated with New World rodents in the family Muridae, subfamily

Table 2 Geographic and reservoir characteristics of arenaviruses

Acronym	Evolutionary lineage[a]	Distribution[b]	Biogeographic domain	Reservoir
Old World arenaviruses				
LASV	OW	Nigeria, Guinea, Liberia, Sierra Leone[c]	Paleartic	*Mastomys huberti*
MOBV	OW	Central African Republic	Paleartic	*Praomys* spp.
MOPV[d]	OW	Mozambique, Tanzania	Paleartic	*Mastomys natalensis*
IPPYV	OW	Central African Republic	Paleartic	*Arvicanthus niloticus.*
LCMV	OW	Eurasia, USA, Canada	Holoartic	*Mus musculus*
New World arenaviruses (North Central America)				
BCNV[e]	NW-rec-A/B	USA, California	Neartic	*Peromyscus californicus*
TAMV[e]	NW-rec-A/B	USA, Florida Everglades	Neartic	*Sigmodon hispidus*
WWAV[e]	NW-rec-A/B	Southwestern USA	Neartic	*Neotoma albigula*
New World arenaviruses (South America)				
Lineage A				
ALLV[e]	NW-A	Peru	Neotropic	*Oecomys bicolor*
FLEV	NW-A	Brazil	Neotropic	*Oryzomys capito*
PARV	NW-A	Paraguay	Neotropic	*Oryzomys buccinatus*
PICV	NW-A	Colombia	Neotropic	*Oryzomys albigularis*
PIRV	NW-A	Venezuela	Neotropic	*Sigmodon alstoni*
Lineage B				
AMAV	NW-B	Brazil	Neotropic	*Oryzomys capito*
CPXV	NW-B	Brazil, northeastern	Neotropic	*Oryzomys capito*
JUNV	NW-B	Argentina	Neotropic	*Calomys musculinus*
GTOV	NW-B	Venezuela	Neotropic	*Zygodontomys brevicauda*

(*Continued*)

Table 2 Phylogeny and rodent vector reservoir —cont'd.

Acronym	Evolutionary lineage[a]	Distribution[b]	Biogeographic domain	Reservoir
MACV	NW-B	Bolivia	Neotropic	*Calomys callosus*
SABV	NW-B	Brazil	Neotropic	unknown
TCRV	NW-B	Trinidad	Neotropic	*Artibeus spp.* (bat)
Lineage C				
LATV	NW-C	Bolivia	Neotropic	*Calomys callosus*
OLVV	NW-C	Argentina	Neotropic	*Bolomys obscurus*

[a] *OW* Old World; *NW* New World
[b] Listed countries are included on the basis of virus isolation only, no serology
[c] One case was probably generated between Ivory Coast and Burkina Faso; the place of origin remains unknown
[d] Morogoro virus, which is a genotype of Mopeia virus, has recently been isolated from Mastomys rodents in Tanzania and is under study (Gunther et al., unpublished data)
[e] Recombinant lineage as previously reported (Charrel et al. 2001)

Sigmodontinae Wilson and Reeder 2005). The correspondence between the phylogeny of the hosts and of the viruses suggests a long association and co-evolution (Gonzalez 1986a, 1986b; Bowen et al. 1998). TCRV isolated from bats is the only member of the family that is not known to be a chronic, inapparent infection of rodents (Fig. 2).

2 Arenaviruses and Their Natural Hosts

Arenavirus species and rodent species are strongly associated in a specific manner, suggestive of a possible co-evolutionary process. Although the concept of co-evolution between rodents and arenaviruses is now largely accepted within the scientific community, little information has been found in terms of dating the phenomenon and detailed leading mechanisms (Gonzalez et al. 1986b; Bowen et al. 1997, 1998; Charrel et al. 2001) (Table 3).

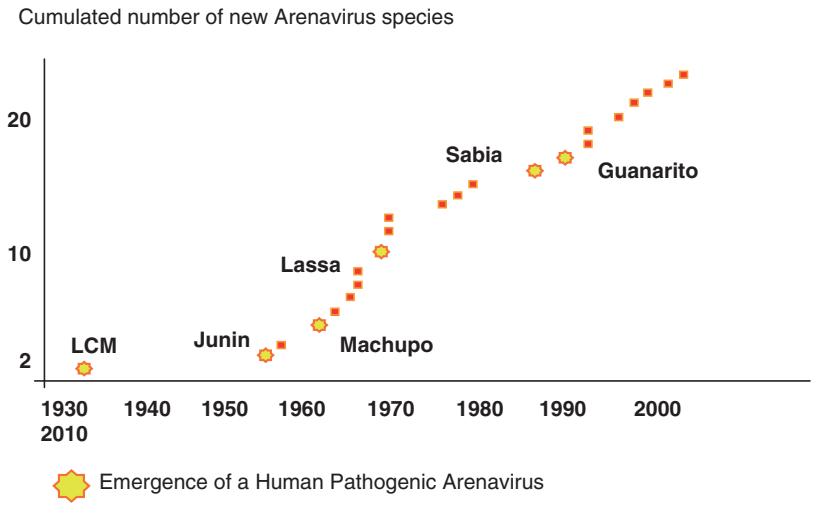

Fig. 2 The time scale of *Arenavirus* emergence. Each *red circle* represents the time of the first isolation of a new arenavirus; *stars* are those pathogenic for humans

Table 3 Arenaviruses and their natural reservoir hosts

Virus	Place of isolation	Primary host[a], Hp/ host reservoir, Hr	Secondary host[a]	Hr, main biotope
Old World Arenaviruses				
LCMV	Worldwide	*Mus musculus*	*Apodemus sylvaticus*; *Mus domesticus*	Domestic environment
LASV	Nigeria	*Mastomys huberti*	*Mastomys erythroleucus*	Savannah and forest galleries
IPPYV	Central African Republic (north)	*Arvicanthis niloticus*	*Lemniscomys striatus*	Sudanese dry savanna
MOBV	Central African Republic (south)	*Praomys jacksoni*	*Mastomys erythroleucus*	Sub-Sudanese wet savanna
MOPV	Mozambique, Tanzania	*Mastomys natalensis*	*Mastomys huberti*	Dry savannah
New World Arenaviruses (North Central America)				
BCNV	USA, California	*Peromyscus californicus*	*Neotoma fuscipes*; *Peromyscus boylii*	
TAMV	USA, Florida Everglades	*Sigmodon hispidus*		Marshes

(*Continued*)

Table 3 Arenaviruses and their natural reservoir hosts —cont'd.

Virus	Place of isolation	Primary host[a], Hp / host reservoir, Hr	Secondary host[a]	Hr, main biotope
WWAV	USA, southwest	*Neotoma albigula*	*Neotomys mexicana N. cinerea, N. micropus, N. fuscipes*	
New World Arenaviruses (South America)				
ALLV	Peru	*Oecomys bicolor*	*Oecomys paricola*	
AMAV	Brazil, north-eastern Amapa	*Oryzomis capito*	*Neacomys guianae, Oryzomis gaeldi*; *Neacomys spinosus*	Amazonian tropical forest
CPXV	Brazil, north-eastern Amapa	*Oryzomis megacephalus*	*Oryzomys capito*	Forest
FLEV	Brazil	*Oryzomys capito*	*Oryzomys* spp.	Tropical forest
JUNV	Argentina	*Calomys musculinus Calomys laucha*	*Calomys musculinus*; *Akodon azarae*	Extensive agricultural area (corn fields)
GTOV	Venezuela	*Zygodontomys brevicaudata*	*Sigmodon alstoni*; *Zygodon longicaudatus*	
LATV	Bolivia, Brazil	*Calomys callosus*		Low tropical savanna
MACV	Bolivia, eastern	*Calomys callosus*		Low tropical savanna
OLVV	Argentina	*Bolomys obscurus*		Pampa
PARV	Paraguay	*Oryzomys buccinatus*	*Bolomys obscurus*	
PICV	Colombia: Cali, Medellin, Popaya	*Oryzomys albigularis*	*Thomasomys fuscatus*, *Zygodontomys* spp.	Primary fog forest (elevation 1,500 m)
PIRV	Venezuela	*Sigmodon alstoni*	*Zygodontomys brevicaudata*	
SABV	Brazil, central	unknown	unknown	Secondary clearing forest
TCRV	Trinidad	*Artibeus lituratus palmarum*	*Artibeus jamaicensis trinitatus*	Tropical forest

[a]Primary hosts are those most commonly infected in nature by the virus, secondary hosts are those that have been accidentally infected or have been consistently found with reactive antibody to specific arenaviral antigens. The habitat refers to that of the primary host

2.1
Co-evolution Process

Specific rodents are the principal hosts of arenaviruses (Childs and Peters 1993; Bowen et al. 1997). Usually one rodent species, less often two closely related species, act as the principal host(s) (virus reservoir) of each arenavirus species, in which natural infection is usually a chronic mild or inapparent infection. The only exception is Tacaribe virus, which has only been associated with a chronic infection of bats. It is now widely recognized that the diversity of arenaviruses is the result of a long-term, shared evolutionary relationship (termed co-evolution or co-speciation) between viruses of the family *Arenaviridae* and rodents of the family *Muridae* (Johnson et al. 1965; Gonzalez 1986a; Bowen et al. 1996). The time scale of the co-evolutionary divergence of specific arenaviruses and their rodent hosts is still under discussion. From our observations and analyses, we strongly favor an ancient co-evolutionary process with several transfers, parallel and diffuse evolution. Our hypothesis is that an ancestral arenavirus type was chronically infecting a common rodent ancestor before New World sigmodontine and Old World murids diverged, approximately 35 million years before the present (Mybp). Each lineage (i.e., New World sigmodontine and Old World murid rodents) evolved independently with their own arenaviruses (co-evolution and co-speciation) resulting in a specific association between rodent species and arenavirus type, as we see today. In addition, when rodent and virus phylogenies are compared, major rodent subfamilies (*Sigmontinae* and *Murinae*) correspond with the major arenavirus clades (i.e., New World arenaviruses vs Old World arenaviruses). A similar association is also evident among South American arenavirus strains and among the South American neotropical *Sigmodontiae* due to the same evolutionary processes. However, discrepancies from the general hypothesis of co-evolution have also been observed, suggesting that spillover from one species or genus to another might occur, and that genomic segments might also be exchanged in some instances (Gonzalez et al. 1986b, 1996a, 1996b; Hugot et al. 2001). Thus the emergence of new virus types and pathogen transmission to humans appears likely to be associated with specific rodent species and their ecology and behavior (Figs. 3, 4).

2.2
A Brief Ancient History of Rodents

We use the most common theory on rodent radiation to support part of our hypothesis. From the Eurasian continent, cricetid rodents, ancestors of murid rodents, spread into the Americas, and then, from Asia, murid rodents spread to Europe and Africa. The term "murid" corresponds to the *Murinae* subfamily of the family *Muridae* (Wilson and Reeder 2005). The term "sigmodontine"

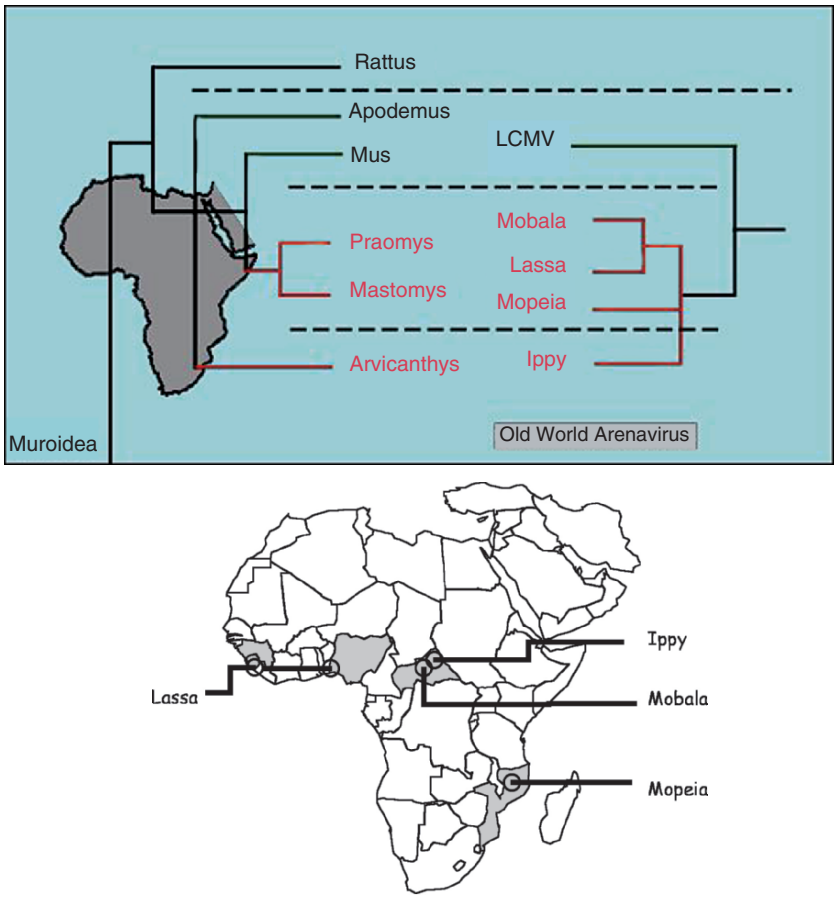

Fig. 3 Phylogeography of Old World arenaviruses and hosts. A specific association between virus and rodent host is exemplified by a diffuse co-evolution process of Old World arenaviruses and their murid rodent hosts

refers specifically to New World rodents of the subfamily *Sigmodontinae* of the family *Muridae* (previously classified as being in the family *Cricetidae*) and includes the New World rats and mice. As early as the Eocene, 65 Mybp, a rodent ancestor bearing *Muridae* characters, *Simimys* , was recognized within North America. During the Oligocene (37 Mybp), the *Muridae* distribution became holoartic. The New World *Sigmodontinae* colonized the Americas by waves of migration northward and southward. As a result, the sigmodontine fauna of South America derived from North America and today, the South

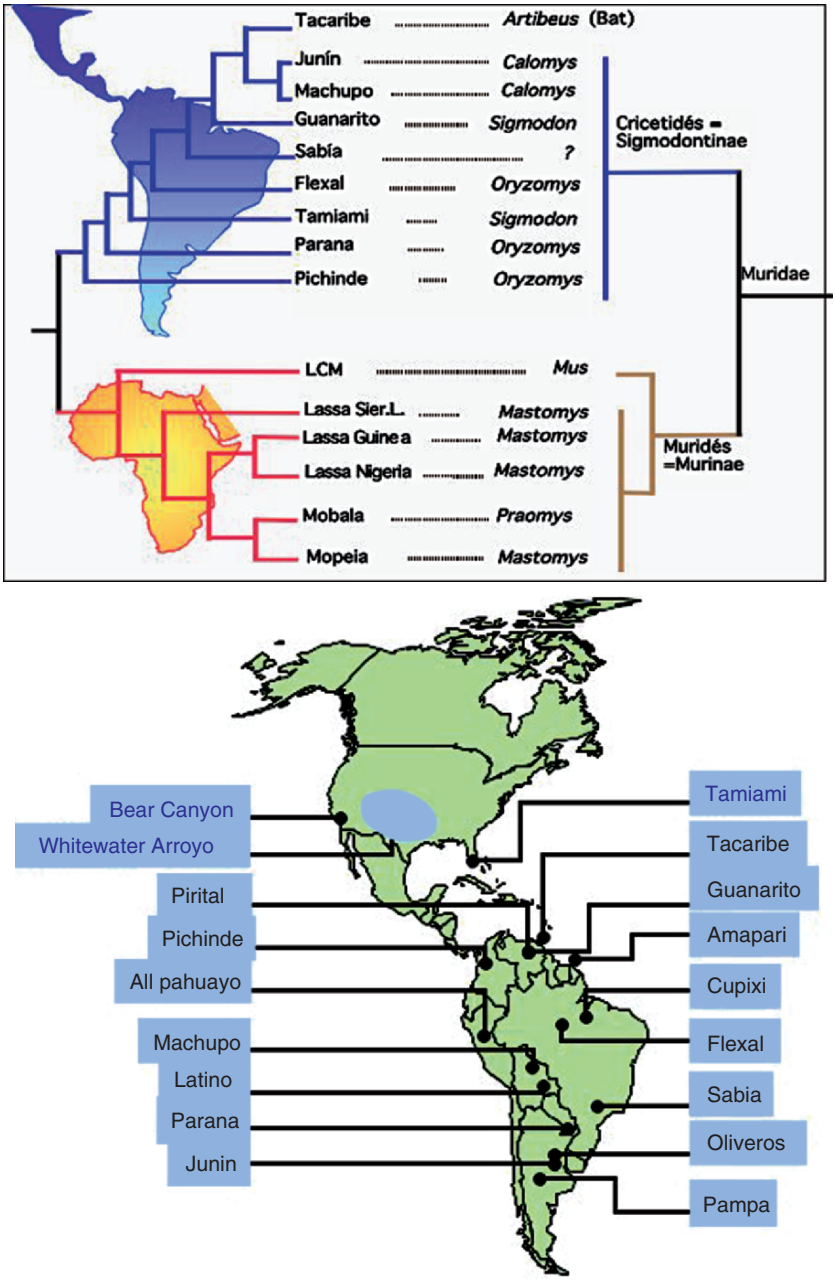

Fig. 4 Phylogeography of New World arenaviruses. The geographic distribution is shown for three indigenous arenaviruses from North America and 14 indigenous arenavirus types from of South America

American group can be distinguished from the less diversified sigmodontine rodents of genera such as *Neotoma* and *Peromyscus* of North America.

In Asia, murid rodents probably came from North America and were present during the Oligocene (35 Mybp). Arising from an original pool, successive waves of murids spread to Europe during the late Miocene (15 Mybp), but there was only a limited extension into Africa where they became underrepresented.

From Asia, murid rodents spread around the Mediterranean basin to Europe approximately 14 Mybp. During that period, the subfamily Murinae extended from Europe into North Africa and rapidly became the most widely distributed rodents in Africa.

From the Pleistocene era (2 Mybp), murid rodents were present in northern Africa. They then spread southward, although their species radiation was severely influenced by arid climate and geomorphology. During that time, speciation reached its highest point influenced by climate variation and physical isolation because of physical barriers such as the Rift Valley and the division of the African continent by the Sahara. More recently, humans have played an important role in the spread of rodents, particularly commensal species such as *Mus*. Some rodent genera from the Pleistocene are still present in East Africa, while others from North Africa have disappeared. However, it likely that murid ancestors were very closely related to the present extant genera (Gonzalez 1996a) (Fig. 5).

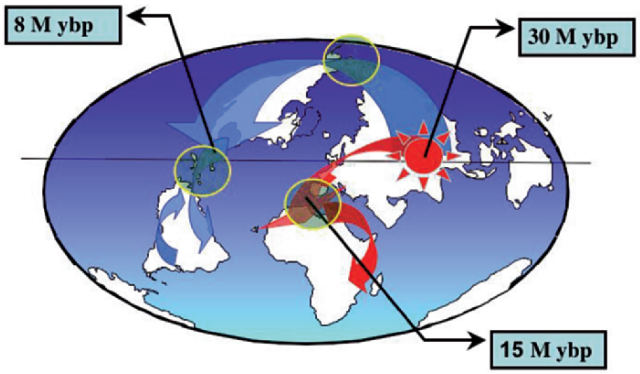

Fig. 5 The rodent migration and emergence and spread of arenaviruses and their rodent hosts. Rodent expansion shows the path of virus dispersion. The subfamilies *Murinae* and *Sigmodontinae* are indicated by *red* and *blue*, respectively, by the approximate time of expansion and speciation. After 34 Mybp (Oligocene), the Eurasian continent became colder and arid with a general shrinking of forest cover; 30 Mybp, rodents probably emerged from Central Eastern Asia and started their Asian radiation journey through Europe. Temperature changes and warmer periods (15 Mybp) would have helped separate the original rodent lineages of Asia and Europe and further their spread in Africa and the Americas. However, back-migrations occurred by way of the Bering Strait and other land bridges such as the Panamanian isthmus in the Americas

2.3
Rodent Migration Within the Americas and an Astonishing Diversity

Comparative phylogenetic analyses of N and GPC proteins showed that the three North American arenaviruses (Whitewater Arroyo, Tamiami, Bear Canyon) group together; however, depending upon the gene used for analysis, these viruses group within different lineages. They are more closely related to lineage A viruses in N protein-based analyses, whereas they are more closely related to lineage B viruses in GPC protein-based phylograms. This suggests that WWAV, TAMV, and BCNV share a common ancestor, which must have been a recombinant of lineages A and B (Fig. 6).

According to the history of rodent migrations within America, rodents migrated across the Panamanian isthmus, from North America to South America, where rodent diversification was able to expand explosively because of the absence of predators and highly favorable ecological conditions. It is postulated that recombination events among arenaviruses most likely occurred in South America and the resulting chimeric viruses were then introduced into North America during the back migration of certain rodent populations

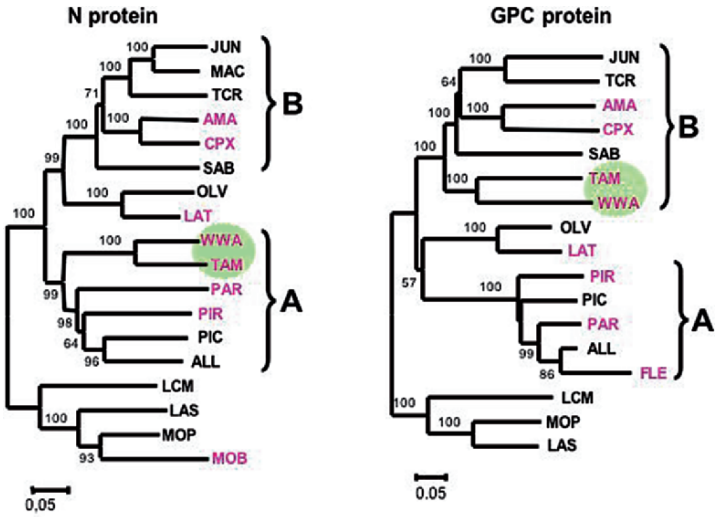

Fig. 6 Comparative New World *Arenavirus* phylogeny using N and GPC sequences demonstrating recombination processes in evolution. *Left*, the capsid protein (N gene) of TAMV and WWAV are inherited from an ancestor virus belonging to lineage A; *right*, the GPC protein of TAMV and WWAV are inherited from an ancestor that belonged to lineage B

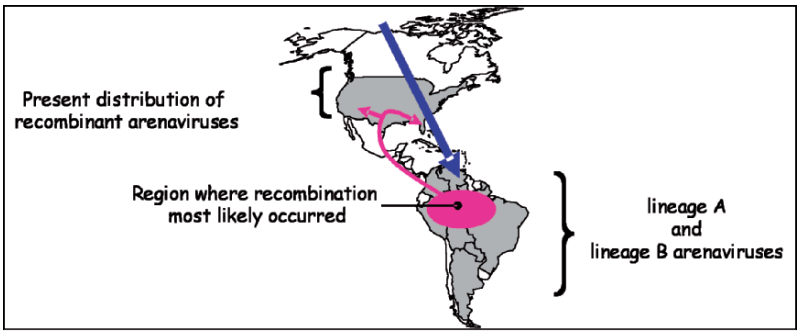

Fig. 7 Rodent migration and American arenavirus recombinations. Rodent diffusion in the Americas. *Blue arrow* shows the first migration of murids from North to South America, corresponding to the split between Old World and New World rodents, estimated at 35 Mybp. First migration from North to South America estimated at 15 Mybp. *Purple ovals* indicate rodent speciation in South America (an explosive radiation of species, 10 Mybp), and *arrows* indicate the back-migration (across the Panamanian land bridge between 10 and 8.6 Mybp) of extant rodent species into Central and North America harboring recombinant arenaviruses (Fig. 8)

(e.g., *Sigmodon* spp.) across the Panamanian land bridge. Although dating the period of recombination is difficult because of controversial data for time estimation of rodent migrations, the paleobiogeography of sigmodontines suggests that recombination could have occurred as far as back as10 Mybp (Engel et al. 1998) (Fig. 7, 8).

2.4 Mechanisms of Virus Evolution

There are three possible mechanisms driving the evolution of arenaviruses: (1) accumulation of point mutations; (2) intersegmental reassortment; and (3) intrasegmental recombination.

2.4.1 Accumulation of Mutations

In the *Arenaviridae* family, the accumulation of mutations appears to be the mechanism most often responsible for virus diversity observed between isolates within a given viral species. By analogy to other RNA viruses, it is believed that mutations are caused by the absence of proofreading activity of the viral RNA-dependent RNA polymerase during virus replication. With respect to the

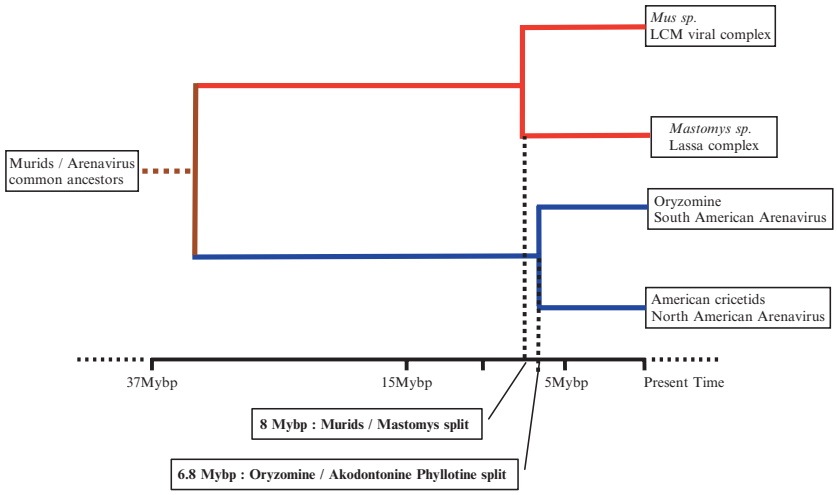

Fig. 8 Proposed time scale of *arenavirus* and rodent co-evolution/cospeciation

rate at which rate mutations are produced and accumulated in arenaviruses, experimental data generated in vitro with a partial region of the polymerase of LCMV suggest mutation frequencies ranging from 1.2 to 3.5×10^{-4} substitutions per nucleotide per genome replication (Grande-Perez et al. 2005). These mutations lead to the generation of virions exhibiting various fitness patterns, and only the best-adapted virions are presumably selected and maintained. The factors driving the selection are multiple and complex and change over time. The occurrence of mutations together with natural selection account for the creation of the genetic diversity observed within a virus species.

2.4.2 Intersegmental Recombination (Reassortment)

Reassortants of arenaviruses have been generated experimentally (Lukashevich et al. 1992; Rivière and Oldstone 1986), with the genome of the reassortant virus containing one genomic segment from each parent. This mechanism has not been described in nature so far for arenaviruses. Experimental generation of a reassortant arenaviruses consisting of the L RNA segment of Mopeia virus and the S RNA segment of Lassa virus has demonstrated that an exchange of genetic material is possible despite a genetic diversity of 28% at the amino acid level (Lukashevich et al. 1992). It is worth noting that these reassortant viruses

were produced by co-cultivation on Vero cell monolayers, without the use of sophisticated equipment or complicated molecular techniques. During the current atmosphere of heightened bioterrorism surveillance, this data would suggest that the generation of chimeric viruses is not so complicated and may be attempted with very basic equipment.

Recently, fatal cases of acute hemorrhagic fever in Kenya and Somalia have been attributed to a reassortant bunyavirus—the family *Bunyaviridae* contain tri-segmented genomes—comprising genomic segments from Bunyamwera virus and from a novel bunyavirus; both were previously unknown as etiologic agents of hemorrhagic fever (Gerrard et al. 2004; Bowen et al. 2001). Bunyavirus reassortment under laboratory conditions had previously documented that exchange of M segments of LaCrosse (LACV) and Snowshoe Hare (SSH) viruses created chimeric viruses; those containing the M segment of LACV, irrespective of S and L segments of SSHV, showed an enhanced capability to disseminate and be transmitted by *Aedes trisereriatus* mosquitoes (Beaty et al. 1982; Beaty et al. 1981). These field and laboratory findings highlight the ability of viral reassortment in creating a chimeric new virus that exhibits increased pathogenicity for humans (as compared to the two parental strains) or specific, novel biologic properties (not displayed by the parental strains).

To identify virus reassortment, complete sequence characterization of viral genomes is a necessary prerequisite. Until recently, the lack of genetic data for the L segment of arenaviruses in all but a handful of virus species hampered the quest for identifying natural reassortment. Recently, however, large genomic programs dedicated to arenaviruses have provided significant sequence data sets containing the complete genomes of almost all arenaviruses. Subsequent sequence analyses and phylogenetic studies, however, were unable to detect any evidence of the natural occurrence of reassortment among arenavirus species, despite an exhaustive search using full-length genomes. Thus, although demonstrated experimentally, it is believed that reassortment may not play a major role in evolution of the *Arenaviridae*.

2.4.3 Intrasegmental Recombination

Intragenic recombination is one of the well-documented mechanisms of evolution of positive-strand, double-stranded and negative-strand RNA viruses (Lai 1992; Hahn et al. 1998; Worobey et al. 1999; Desselberg et al. 1986; Suzuki et al. 1998; Bergman et al. 1992; Orlich et al. 1994; Sibold et al. 1999). Intrasegmental recombination was recently demonstrated for the three North American arenaviruses (WWAV, TAMV, and BCNV) (Charrel et al. 2001, 2002, Archer and Rico-Hesse 2002), indicating common derivation from a recombinational

event between ancestors in both lineage A and lineage B viruses. Analysis of complete genome sequences for all recognized members of the genus *Arenavirus* suggest that there are no other examples of intrasegmental recombination. Since these three viruses possess a common ancestor as demonstrated by phylogeny, recombination most likely occurred in this ancestor. It is important to note that recombinant arenaviruses are able to infect humans (Kosoy et al. 1996). Whether they cause disease in infected individuals is still not clearly established; however, three cases of fatal human infections associated with Whitewater Arroyo virus have been reported in California (CDC 2000).

2.4.4 Evolutive Significance of Interspecies Recombination

The evidence for recombination deduced from the genetic analysis of the genomic S RNA raises major questions concerning the nature of situations that may be conducive to intragenic recombination:

2.4.4.1 Co-infection of the Same Rodent by Two Different Arenaviruses Belonging to Distinct Phylogenetic Lineages

In nature, since arenaviruses can establish chronic infections among their rodent hosts, the more likely scenario for interspecific genome recombination would involve superinfection of a rodent already chronically infected with one arenavirus by a second distinct arenavirus. This hypothesis requires the co-existence of distinct arenaviruses in the same geographic area and this situation is present within several regions of a number of countries. For example, the principal hosts of OLLV, JUNV, and LCMV are rodents of the species *Necromys benefactus* (formerly *Bolomys obscurus;* Wilson and Reeder 2005), *Calomys musculinus* and *Mus musculus*, respectively. These three species and three other common rodent species exist sympatrically in rural regions of Argentina (Mills et al. 1996). Studies of the dynamics of OLLV infection among rodents indicate that dual infections by JUNV and OLLV viruses may occur at low frequency among three species of rodents (*N. benefactus*, *Akodon azarae* , and *M. musculus*) based on comparative IFA titers obtained against specific arenaviral antigens.

Additionally, there is evidence that the principal host for a specific arenavirus can be naturally infected with a different arenavirus associated with a sympatric rodent species. For example, *Sigmodon alstoni* , the principal host of PIRV (lineage A) can naturally be infected with GTOV (lineage B) (Fulhorst et al. 1999b). Moreover, experimental data have shown that immunization of rodents

with a virus belonging to a given lineage is poorly protective against infection by viruses belonging to different lineages (Weissenbacher et al. 1975). Consequently, although mixed infections of rodents with distinct arenaviruses have not been reported in the literature, field and experimental data suggest that infections by arenaviruses of different lineages are plausible.

2.4.4.2 Co-infection of One Cell by Two Viruses

Experiments performed in cell cultures have clearly established that co-infection of a single cell by two distinct arenaviruses is possible (Bishop et al. 1980; Rivière et al. 1985; Rivière and Oldstone 1986; Whitton et al. 1988; Lukashevitch 1992). This co-infection could potentially allow the generation of recombinant RNA molecules by template switching of the RNA polymerase. According to this mechanism, the RNA polymerase would jump from one template to another during RNA processing, generating a chimeric RNA molecule including sequences inherited from the two parental strains.

Thus, in summary, our current knowledge concerning the ecology of rodents infected by arenaviruses and the natural circulation of these viruses in the New World, together with experimental data, would suggest that recombination between arenaviruses belonging to different lineages could potentially occur in nature. Furthermore, the recombinant nature of the genome of the 3 arenavirus indigenous to North America (WWAV, TAMV, BCNV) suggests that their ancestor may have been endowed with a selective advantage, facilitating the maintenance and transmission of the recombinant over time. This finding reinforces the fact that future phylogenetic analyses of arenaviruses should be based on complete genomic sequences to allow the identification of recombination and/or reassortment events and therefore a better understanding of the processes of co-speciation and the occurrence of crossing-over or reciprocal recombination.

3 From Enzootic to Epidemic: *Arenavirus* Ecology and Human Health

Persistent infection of the rodent host appears to be a crucial phenomenon in the long-term persistence of the arenaviruses in nature. Infection in the rodent host is associated with a chronic or sporadic viremia and/or viruria and sometimes a life-long shedding of the virus into the environment. The course of the infection is determined by factors such as the age, genetic make-up, immunological resistance, and history of prior infection within the rodent host, but also by the infecting virus strain. Neonatally infected rodents

usually become chronic carriers of virus and excrete the virus for a long time (throughout life) in their urine. Virus transmission within rodent populations can occur through three mechanisms: (1) vertical (dam to progeny) transmission, (2) horizontal transmission through direct or indirect contacts, and (3) a balanced combination of both mechanisms. Female rodents infected as neonates with certain arenaviruses (JUNV, MACV) may show reduced fertility or suffer decreased litter sizes (Childs and Peters 1993; Webb et al. 1975); additionally, neonates born to infected dams may experience stunted growth. Accordingly, the persistence of these arenaviruses within a rodent population requires some degree of horizontal transmission. In contrast, other arenaviruses that do not cause infertility, such as certain strains of LCMV (Childs and Peters 1993), can be maintained in a rodent population exclusively by vertical transmission.

Humans usually become infected by arenaviruses through direct contact with infected rodents, including bites, through inhalation of infectious rodent excreta and secreta. The domestic and peridomestic behavior of several species of rodent reservoir hosts is a major contributing factor facilitating viral transmission from rodent to human. Transmission of arenaviruses to humans occurs following recreational or agricultural incursions into environments providing critical habitat for rodent hosts. Additionally, professionals handling infected rodents in the field or laboratory are at increased risk of infection (Sewell 1995). Modifications of the environment driven either by human activities, such as modern farming practices, or ecological changes, such as flooding, have been implicated in the emergence of human disease caused by arenaviruses.

Nine arenaviruses are associated with human diseases. LASV, JUNV, MACV, GTOV, and SABV are known to cause a severe hemorrhagic syndrome, in western Africa, Argentina, Bolivia, Venezuela, and Brazil, respectively (Peters et al. 1996). They are highly infectious, virulent pathogens and all are listed on the Category A Pathogen List (as defined by the CDC); such agents can only be handled in Biosafety Level 4 (BSL-4) laboratories. Infection by LCMV can result in acute central nervous system disease and congenital malformations (Barton and Hyndman 2000; Barton et al. 1993). Very little is known about the health consequences of infection with the other arenaviruses: PICV infection has resulted in numerous seroconversions among humans without any notable clinical significance; FLEV has resulted in two symptomatic laboratory infections and should be regarded as dangerous (F. Pinheiro, unpublished data); TCRV virus has caused a single case of a febrile disease with mild CNS symptomatology (J. Casals, unpublished data) (Peters et al. 1996; Karabatsos 1985; Buchmeier et al. 1974). WWAV has recently been associated with three fatal cases of infection in California (CDC 2000).

3.1
Lymphocytic Choriomeningitis Virus

The first arenavirus to be isolated was LCMV, which was discovered in 1933 during the investigation of an epidemic of St. Louis encephalitis in the USA. In regions where LCMV is known to exist, infection in the two closely related reservoir species hosts, *Mus domesticus* and *M. musculus*, is highly focal (Lehmann-Grube 1971). Studies conducted in Baltimore, Boston, and Washington, DC, revealed a spotty distribution of virus-positive mice in houses (Farmer et al. 1942; Childs et al. 1991, 1992). Similarly, in Germany, much higher infection rates prevail among *Mus* in the west-central region than in the southern or northern portions of the country (Ackermann et al. 1964). Human cases of LCMV infection are most common in autumn. This pattern is the result of peak seasonal population densities of rodents and the movement of house mice into homes and barns with the onset of cold weather. In addition, seasonal variation in infection rates of *Mus* sp. may occur. Situations associated with transmission of virus from infected wild mice to humans include substandard housing such as mobile homes or inner city dwellings, the cleaning of rodent-infested barns or outbuildings, and the autumn entry of wild mice into dwellings. Most human LCMV infections occur among young adults, although persons of all ages have been affected. The mode of transmission in most sporadic human infections is not definitely known; however, experimental and epidemiologic observations implicate aerosols, direct contact with rodents, and rodent bites (in that order) as the most likely vehicles (Enria et al. 1999; Farmer et al. 1942; Hinman et al. 1975). Although most sporadic LCM cases are attributed to contact with infected wild mice, outbreaks of disease have been traced to infected laboratory mice and Syrian hamsters *(Mesocricetus auratus*) (Dykewitz et al. 1992). Individual cases or outbreaks of LCM in the United States and Europe have resulted from exposures to infected pet hamsters (Biggar et al. 1975; Ackermann et al. 1972). Recently, a case of LCMV infection in France was traced back to a population of urban *Mus musculus*; virus isolates were obtained from 60% of the mice trapped in the patient's home (R. Charrel et al).

Although LCMV infection may occur worldwide wherever the house mouse has been introduced, human infection has been conclusively demonstrated only in Europe and the Americas (Lehmann-Grube 1971). LCM cases present most commonly as febrile illnesses with headache and systemic symptoms; leukopenia and thrombocytopenia are usually noted (Peters et al. 1995). After 3–5 days of nonspecific illness, the fever subsides, but it frequently recurs in 2–4 days with several days of even more severe headache. Patients may exhibit meningitis during this second febrile period. In approximately one-third of the cases, cerebrospinal fluid (CSF) exhibits lymphocytic pleocytosis, an elevated protein

content, and hypoglycorrhachia. Sometimes there is more severe damage to the central nervous system (CNS) and transient hydrocephalus has been described. Chorioretinitis and congenital hydrocephalus may occur in fetal infections. The second febrile episode, as well as some of the complications of convalescence, have long been thought to represent immunopathologic phenomena, and antibodies detectable by immunofluorescence appear at about this time (Peters et al. 1995). The prevalence of antibody to LCMV is approximately 5% among adults living in large cities of the United States (Childs et al. 1991). Both CNS and congenital infections caused by LCMV may be more common than appreciated and are undoubtedly underdiagnosed (Enria et al 1999; Barton 1996, 2001).

In 2005, LCMV caused an outbreak of infection among four patients who had received solid organ transplants from an infected donor. Severe illness developed in all four patients, three of whom died (CDC 2005). The donor was probably infected from his pet hamster.

3.1.1 South American Arenaviral Hemorrhagic Fever

The clinical picture of the South American arenaviral hemorrhagic fever is almost identical regardless of the virus responsible for the disease. Argentine, Bolivian, and Venezuelan arenaviral hemorrhagic fevers are remarkably similar clinically, and mortality in each is about 15%–30% (Sabattini et al. 1970; Maiztegui et al. 1975; Stinebaugh et al.1966). The disease caused by all three viruses can include neurological symptoms, hemorrhage, and shock; these clinical findings herald a poor prognosis.

3.1.1.1 Argentine Hemorrhagic Fever: Junin Virus

The rodent host reservoir of JUNV is *Calomys musculinus*, a small field rodent of Argentina (Sabattini and Maiztegui 1970). *Calomys* populations reach their highest densities in cornfields and the surrounding weedy fence lines during the austral fall. In the 1950s, a new disease (Argentinean Hemorrhagic Fever, AHF) emerged in the Buenos Aires province of Argentina, a rich farming region, and was associated with intensive deforestation and intensive agricultural practices that considerably increased the contacts between humans and rodents. Most of the infected persons were male agricultural workers engaged in harvesting corn. Transmission from the rodent is by inhalation of infected aerosols produced from rodent excreta or from rodents caught and shredded in mechanical harvesters (Maiztegui 1975). As a consequence, infection with JUNV is strongly seasonal and peaks during the harvest season in autumn. Since the emergence

of AHF, a progressive geographic expansion of epidemic outbreaks, occurring a variable intervals, has been observed (Maiztegui 1975; Maiztegui et al. 1986). After its first isolation in 1959, human cases were initially recorded within a 16,000-km^2 area of the rich agricultural pampas north of Buenos Aires province, but AHF progressively expanded to become endemic in a 150,000-km^2 area in southern of Santa Fé, southeastern Cordoba, and northeastern La Pampa provinces (Enria and Feuillade 1998). To date, the human population at risk is estimated to be about 5 million. Several hypotheses were proposed to explain this expansion. Since 1958, cases have been annually recorded, ranging from several hundred to 3,500. An epidemic outbreak of human AHF in southern Santa Fé and northern Buenos Aires provinces was shown to coincide, with a lag of 1–2 months, with the peak density in a rapidly increasing population of *C. musculinus*. The maximum prevalence of JUNV antigen-positive rodents, approximately 25% of adult *C. musculinus*, coincided with peak rodent population density (Mills et al. 1992).

Although human cases present with either neurologic or hemorrhagic manifestations (or a combination of both), molecular studies of JUNV have not associated either syndrome with a particular JUNV genotype (Albarino et al. 1997). Studies of the genetic diversity among JUNV strains circulating in central Argentina demonstrated a high degree of genetic similarity among isolates from the same locale. However, no cluster of related JUNV strains was associated with clinically different forms of AHF (Garcia et al. 2000). Mortality among patients with confirmed AHF was 14%–17% before the routine initiation of immune plasma was implemented (Maiztegui et al. 1979); treatment has reduced the mortality to less than 1%. Introduction of an effective vaccine, using a live-attenuated virus (Candidate#1) (Maiztegui et al. 1998), has decreased the incidence of the AHF to fewer than 100 cases per year (Enria et al. 2002).

3.1.1.2 Bolivian Hemorrhagic Fever: Machupo Virus

The rodent species *Calomys callosus* is the reservoir host of MACV, the agent of Bolivian hemorrhagic fever (BHV) (Johnson et al. 1966). As with JUNV, the dynamics of the rodent population determine the epidemiological features of disease outbreaks among humans (Mercado et al. 1975). In contrast to the rodent host of JUNV, *C. callosus* invades houses during the rainy season, resulting in human cases with identical attack rates among all ages. However, on remote ranches and in fields, adult male patients predominate. A series of outbreaks from 1962 to 1964 in the sparsely populated province of El Beni in northeast Bolivia, involved more than 1,000 patients, 180 of whom died; an increase of rodents invading small towns was coincidentally reported . Transmission was interrupted by a targeted campaign to reduce the rodent population within affected towns.

Bolivian hemorrhagic fever is restricted to the tropical savanna of Beni province and recent investigations have shown that the populations of rodents responsible for the maintenance and transmission of MACV are an independent monophyletic lineage, different from those in other areas of South America (Salazar-Bravo et al. 2002).

The incidence of BHF cases is greatest between April and July (late rainy and early dry season), but the dominant epidemiologic feature is that of small outbreaks in different villages and ranches, with several years of quiescence thereafter. Transmission is thought to occur by aerosols from infected rodents or possibly by contact with food contaminated by infected rodent urine. Most of the recorded infections were acquired by direct contact with *C. laucha* or by aerosol through infected excreta. However, nosocomial transmission of MACV has been clearly demonstrated (Peters et al. 1971; Kilgore et al. 1995). Nosocomial outbreaks have been associated with a single index case who had visited a BHF endemic region. The only recognized hospital-based outbreak resulted in four secondary cases followed by a tertiary case acquired from a necropsy incident; all but one person died. Recently, an epidemic was reported in which seven members of the same family were infected, six of whom died (CDC 1994).

3.1.1.3
Venezuelan Hemorrhagic Fever: Guanarito Virus

In 1989, cases of hemorrhagic fever in the central plains of Venezuela were associated with a new *Arenavirus*, designated Guanarito virus after the region where the first outbreak occurred (Salas et al. 1991). The main affected population was settlers moving into cleared forest areas to practice small-scale agriculture. Since its discovery, GTOV has been responsible for at least 200 cases of VHF. For unknown reasons, the number of reported human cases has spontaneously dropped since 1992, although rodent infection can still be readily demonstrated within and beyond the boundaries of the original endemic zone (Weaver et al. 2001). Natural and experimental data initially suggested that two different rodent species were involved in the transmission cycle of GTOV in nature; the cane rat (*Zygodontomys brevicauda*) and the cotton rat (*Sigmodon alstoni*) (Fulhorst et al. 1999a, 1999b; Tesh et al. 1993). Recently, *Z. brevicauda* has been shown to be the primary reservoir host as it develops a persistent infection with lifelong viruria, accompanied by either low or undetectable levels of antibody. In contrast, the cotton rat has characteristics of an intermediate host infected by spillover of GTOV from cane rats, as it produces neutralizing antibodies and excretes virus for only a limited time.

Research undertaken to better understand the geographic distribution and potential variation in GTOV circulating in the VHF-epidemic area of western Venezuela resulted in the genetic sequencing of 29 isolates of GTOV obtained

from rodents and humans (Weaver et al. 2000). Nine genotypes of GTOV were distinguished, all of which, with the exception of the dominant genotype, were restricted to very small geographic areas. All but one of the strains obtained from humans belonged to the dominant genotype. Closely related strains of the dominant GTOV genotype were obtained from a large area covering approximately 75,000 km^2 (Tesh et al. 1993, 1999). A single rodent could be infected by a virus population varying less than 0.5% at the nucleotide level<CHFAN (a low-diversity quasispecies). In contrast, the dominant GTOV strain infecting humans was invariant. Human disease was not associated with a unique genotype restricted to a particular rodent host species. However, overall, the available data are insufficient to conclude whether or not certain genotypes are more pathogenic and/or infectious for humans than others. The limited mobility of rodents in isolated metapopulations could account for the coexistence of independent virus lineages without mixing and competitive exclusion.

3.1.1.4
Brazilian Hemorrhagic Fever: Sabia Virus

Sabia virus has caused a single natural human infection that was fatal, and also two none fatal laboratory infections (Coimbra et al. 1994; Barry et al. 1995). No reservoir host has yet been identified.

3.1.1.5
Lassa Fever: Lassa Virus

Lassa fever is named after a small town in Nigeria, where the first epidemic was described in 1969 (Buckley and Casals 1970). LASV is associated with rodents belonging to the genus *Mastomys* (sometimes referred to as *Praomys*), which are widely distributed in sub-Saharan Africa. In the regions where LASV is endemic, up to 30% of *Mastomys* rodents can carry the virus (Keenlyside 1983). Lassa virus is responsible for an estimated 100,000–300,000 infections and approximately 5,000 deaths annually (McCormick et al. 1987). To date, cases have been reported from Nigeria, Liberia, Sierra Leone, Guinea, Burkina Faso, Ivory Coast, Ghana, Senegal, Gambia, and Mali. Among hospitalized patients, mortality is estimated at 15%–20% (Webb et al. 1986). Serologic surveys suggest that subclinical cases also occur (McCormick et al. 1987). Lassa fever occurs through direct or indirect contact with infected rodents. A number of cases acquired by local residents have been associated with the capture and handling of rodents for consumption (Ter Meulen et al. 1996).

Imported cases of LASV infection among travelers returning from endemic locations have been reported from England, Germany, Japan, the Netherlands, Israel, and the United States.

Nosocomial transmission is a common feature of Lassa fever, and many hospital-based outbreaks have been described (Keenlyside et al. 1983, Fischer-Hoch et al. 1995). However, it is apparent that this aspect of Lassa fever has been overestimated in reports based on infections in hospitals. The additional risk to hospital workers within the endemic zone is not great, as judged by serosurveys, providing that basic hygiene measures are maintained in hospitals dealing with suspected cases (Helmick et al. 1986). Nosocomial cases have been reported only in hospital settings where basic hygiene measures were not enforced. Arenaviruses readily invade the fetus, whether in their natural rodent reservoir, laboratory animals, or humans. Pregnant women infected with LASV often abort and have a high mortality rate; similar observations have been made for Argentinian and Bolivian HFs (Price et al. 1988).

4
Prevention and Control

Prevention of arenaviral disease consists of interrupting the transmission of virus from rodents to humans, from humans to humans, and from infected specimens to laboratory personnel. Strategies for reducing contact between rodents and humans have been effective in the control of outbreaks of BHF; trapping and removal of *C. callosus* in towns reduced the incidence of disease to essentially zero. Rodent intervention strategies have proven more difficult for preventing AHF as conditions under which human exposure occurs are primarily rural and associated with the harvesting of corn. The geographic distribution *C. musculinus* (reservoir host of JUNV) is much wider than *C. callosus* (reservoir of MACV), and Argentinian agricultural practices continue to place workers at risk of exposure to reservoir hosts.

A collaborative effort undertaken by the US and Argentine governments led to the production of a live attenuated Junín virus vaccine named Candid#1. Its efficacy was proven in a double-blind trial in 15,000 agricultural workers at risk to natural infection in Argentina. Subsequently, more than 100,000 people were immunized with JUNV vaccine in Argentina. A prospective study conducted over two epidemic seasons among 6,500 male agricultural workers in Argentina showed that Candid #1 vaccine efficacy was greater or equal to 84%, and no serious adverse effects were detected (Maiztegui et al 1998).

Recent animal protection studies suggest that the JUNV vaccine could be protective against MACV infections as well. However, attenuated JUNV strains do not protect experimental animals against GTOV challenge. Rhesus monkeys (*Cercopithecus aethiops*) challenged with purified inactivated LASV developed humoral antibody responses comparable to that among humans who recovered from Lassa fever. However, these monkeys were not protected when

challenged with LASV and died following exposure. A naturally attenuated strain of MOPV from Mozambique protects rhesus monkeys against LASV challenge, but field studies are required to establish the extent and nature of natural human infections with this virus before it can seriously be considered a candidate for human vaccine development. Alternative approaches, including the use of vaccinia virus vectors bearing the LASV GPC or N genes, are being actively investigated and show promising preliminary results.

5 Conclusion

Arenaviruses and their rodent hosts share a common ancient history and the extant diversity of arenaviruses probably evolved through the processes of co-evolution, co-speciation and virus recombination. One can clearly distinguish four major clades of extant arenaviruses which are distributed either in the Old World (including Europe, Africa, and Asia) or the Americas. These observations are congruent with the ancient history of rodents mirroring the ancient paths and spread of *Arenavirus* ancestors. Such a model of co-evolution between parasite and specific hosts appears to apply to other viral groups such as the hantaviruses (Gonzalez 1996a) and Simian immunodeficiency virus (Kuhman et al. 2001). Two new arenaviruses have been recently discovered in Africa: the Morogoro virus isolated from *Mastomys natalensis* in Tanzania, and related to Mopeia virus, and the Kodoko virus detected in pigmy mice (*Mus Nannomys minutoides*) from Guinea. This findings together with the fact that arenavirus have coevolved with their rodent hosts strongly supports that many arenaviruses remain to be discovered not only in Europe, Americas and Africa, but also in Asia and Oceania.

Arenaviruses infect a variety of rodent hosts in which they are often nonpathogenic, whereas several are highly pathogenic for humans, resulting in severe hemorrhagic or neurological syndromes in that accidental host. Since their discovery in the early 1930s, new arenaviruses have been discovered and/or have emerged as human pathogens. As co-evolution and co-speciation occur over a long geological period, recombination appears more likely to occur in the short term and may be potentially most important in giving rise to human pathogenic strains.

References

Ackermann R, Bloedhorn H, Kupper B, Winkens I, Scheid W (1964) Über die Verbreiting des Virus der lymphocytaren Choriomeningitis unter den Mausen in Westdeutschland. I Utersuchungen uberwiegend an Hausmauden *(Mus musculus)*. Zentrabl Bakteriol 194:407–430

Ackermann R, Stille W, Blumenthal W, Helm EB, Keller K, Baldus O (1972) Syrische Goldhamster als Ubertrager von lymphozytarer Choriomeningitis. Dtsch Med Wochenschr 97:1725–1731

Ahmed R, Hahn CS, Somasundaram T, Villarete L, Matloubian M, Strauss JH (1991) Molecular basis of organ-specific selection of viral variants during chronic infection. J Virol 65:4242–4247

Albarino CG, Ghiringhelli PD, Posik DM, Lozano ME, Ambrosio AM, Sanchez A, Romanowski V (1997) Molecular characterization of attenuated Junin virus strains. J Gen Virol 78:1605–1610

Amman BR, Pavlin BI, Albariño CG, Comer JA, Erickson BR, Oliver JB, et al. Pet rodents and fatal lymphocytic choriomeningitis in transplant patients. Emerg Infect Dis [serial on the Internet]. 2007 May [*date cited*]. Available from http://www.cdc.gov/EID/content/13/5/719.htm

Archer AM, Rico-Hesse R (2002) High genetic divergence and recombination in Arenaviruses from the Americas. Virology 20:304:274–281

Armstrong C, Lillie RD (1934) Experimental lymphocytic choriomeningitis of monkeys and mice produced by a virus encountered in studies of the 1933 St Louis encephalitis epidemic. Public Health Rep 49:1019–1027

Banner LR, Lai MM (1991) Random nature of coronavirus RNA recombination in the absence of selection pressure. Virology 185:441–445

Barry M, Russi M, Armstrong L, Geller D, Tesh R, Denbry L, Gonzalez JP, Khan A, Peters CJ (1995) Treatment of a laboratory-acquired Sabia virus infection. N Eng J Med 333:294–296

Barton LL (1996) Lymphocytic choriomeningitis virus: a neglected central nervous system pathogen. Clin Infect Dis 22:197

Barton LL, Hyndman NJ (2000) Lymphocytic choriomeningitis virus: reemerging central nervous system pathogen. Pediatrics 105:E35

Barton LL, Budd SC, Morfitt WS, Peters CJ, Ksiazek TG, Schindler RF, Yoshino MT (1993) Congenital lymphocytic choriomeningitis virus infection in twins. Pediatr Infect Dis J 12:942–946

Beaty BJ, Holterman M, Tabachnick W, Shope RE, Rozhon EJ, Bishop DHL (1981) Molecular basis of bunyavirus transmission by mosquitoes: role of the middle-sized RNA segment. Science 211:1433–1435

Beaty BJ, Miller BR, Shope RE, Rozhon EJ, Bishop DHL (1982) Molecular basis of bunyavirus per os infection of mosquitoes: role of the middle-sized RNA segment. Proc Natl Acad Sci U S A 79:1295–1297

Bergmann M, Garcia-Sastre A, Palese P (1992) Transfection-mediated recombination of influenza A virus. J Virol 66:7576–7580

Biggar RJ, Woodall JP, Walter PD, Haughie GE (1975) Lymphocytic choriomeningitis outbreak associated with pet hamsters: fifty-seven cases from New York State. JAMA 232:494–500

Bishop DH, Beaty BJ, Shope RE (1980) Recombination and gene coding assignments of bunyaviruses and arenaviruses. Ann N Y Acad Sci 354:84–106

Bockstahler LE, Carney PG, Bushar G, Sagripanti JL (1992) Detection of Junin virus by the polymerase chain reaction. J Virol Methods 39:231–235

Bowen MD, Peters CJ, Nichol ST (1996) The phylogeny of New World (Tacaribe complex) arenaviruses. Virology 219:285–290
Bowen MD, Peters CJ, Nichol ST (1997) Phylogenetic analysis of the Arenaviridae: patterns of virus evolution and evidence for cospeciation between arenaviruses and their rodent hosts. Mol Phylogenet Evol 8:301–316
Bowen MD, Rollin PE, Ksiazek TG, Hustad HL, Bausch DG, Demby AH, Bajani MD, Peters CJ, Nichol ST (2000) Genetic diversity among Lassa virus strains. J Virol 74:6992–7004
Bowen MD, Trappier SG, Sanchez AJ, Meyer RF, Goldsmith CS, Zaki SR, Dunster LM, Peters CJ, Ksiazek TG, Nichol ST, the RVF Task Force (2001) A reassortant bunyavirus isolated from acute hemorrhagic fever cases in Kenya and Somalia. Virology 291:185–190
Buckley SM, Casals J (1970) Lassa fever: a new virus disease of man from West Africa. III. Isolation and characterization of the virus. Am J Trop Med Hyg 19:680–691
Buchmeier M, Adam E, Rawls WE (1974) Serologic evidence of infection by Pichinde virus among laboratory workers. Infect Immun 9:821–823
Calisher CH, Tzianabos T, Lord RD, Coleman PH (1970) Tamiami virus, a new member of the TaCaribe group. Am J Trop Med Hyg 19:520–526
Centers for Disease Control and Prevention (1994) Bolivian hemorrhagic fever – El Beni department Bolivia, 1994. Morb Mortal Wkly Rep 43:943–946
Centers for Disease Control and Prevention (2000) Fatal illnesses associated with a New World arenavirus – California, 1999–2000. Morb Mortal Wkly Rep 49:709–711
Centers for Disease Control and Prevention (2005) Lymphocytic choriomeningitis virus infection in organ transplant recipients, Massachusetts Rhode Island, 2005. Morb Mortal Wkly Rep 54:537–539
Charrel RN, de Lamballerie X, Fulhorst CF (2001) The Whitewater Arroyo virus: natural evidence for genetic recombination among Tacaribe serocomplex viruses (family Arenaviridae). Virology 283:161–166
Charrel RN, Feldmann H, Fulhorst CF, Khelifa R, de Chesse R, de Lamballerie X (2002) 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 296:1118–1124
Charrel RN, Retornaz K, Emonet S, Noel G, Chaumoitre K, Minodier P, Girard N, Garnier JM, de Lamballerie X. Acquired hydrocephalus caused by a variant lymphocytic choriomeningitis virus. Arch Intern Med. 2006; 166:2044–2046
Childs JE, Peters CJ (1993) Ecology and epidemiology of arenaviruses and their hosts. In: Slavato MS (ed) The arenaviruses. Plenum, New York, pp 331–384
Childs JE, Glass GE, Ksiazek TG, Rossi CA, Oro JG, Leduc JW (1991) Human-rodent contact and infection with lymphocytic choriomeningitis and Seoul viruses in an inner-city population. Am J Trop Med Hyg 44:117–121
Childs JE, Glass GE, Korch GW, Ksiazek TG, Leduc JW (1992) Lymphocytic choriomeningitis virus infection and house mouse *(Mus musculus)* distribution in urban Baltimore. Am J Trop Med Hyg 47:27–34
Clegg JCS, Bowen MD, Buchmeier MJ, Gonzalez JP, Lukashevich IS, Peters CJ, Rico-Hesse R, Romanowski V (2000) Arenaviridae. In: Van Regenmortel MHV, Fauquet CM, Bishop

DHL, Carsten EB, Estes MK, Lemon SM, Maniloff J, Mayo MA, McGeoch DJ, Pringle DR, Wickner RB (eds) Virus taxonomy. Seventh Report of the International Committee for the Taxonomy of Viruses, Academic, New York, pp 633–640

Cummins D (1990) Lassa fever. Br J Hosp Med 43:186–192

Demby AH, Chamberlain J, Brown DW, Clegg CS (1994) Early diagnosis of Lassa fever by reverse transcription-PCR. J Clin Microbiol 32:2898–2903

Desport M, Collins ME, Brownlie J (1998) Genome instability in BVDV: an examination of the sequence and structural influences on RNA recombination. Virology 246:352–361

Desselberger U, Hung T, Follett EA (1986) Genome analysis of human rotaviruses by oligonucleotide mapping of isolated RNA segments. Virus Res 4:357–368

Downs WG, Anderson CR, Spoence L, Aitken THG, Green Hall AH (1963) Tacaribe virus a new agent isolated from *Artibeus* bats and mosquitoes in Trinidad West Indies. Am J Trop Med Hyg 12:640–646

Dropulic LK, Hardwick JM, Griffin DE (1997) A single amino acid change in the E2 glycoprotein of Sindbis virus confers neurovirulence by altering an early step of virus replication. J Virol 71:6100–6105

Dubuisson J, Lustig S, Ruggli N, Akov Y, Rice CM (1997) Genetic determinants of Sindbis virus neuroinvasiveness. J Virol 71:2636–2646

Dykewicz CA, Dato VM, Fisher-Hoch SP, Howarth MV, Perez-Oronoz GI, Ostroff SM, Gary H Jr, Schonberger LB, McCormick JB (1992) Lymphocytic choriomeningitis outbreak associated with nude mice in a research institute. JAMA 267:1349–1353

Emonet S, Retornaz K, Gonzalez J-P, de Lamballerie X, Charrel RN. Mouse-to-human transmission of variant lymphocytic choriomeningitis virus. Emerg Infect Dis [serial on the Internet]. 2007 Mar [*date cited*]. Available from http://www.cdc.gov/EID/content/13/3/472.htm

Engel SR, Hogan KM, Taylor JF, Davis SK (1998) Molecular systematics and paleobiogeography of the South American sigmodontine rodents. Mol Biol Evol 15:35–49

Enria D, Feuillade MR (1998) Argentine haemorrhagic fever (Junin virus-Arenaviridae): a review on clinical, epidemiological, ecological, treatment and preventive aspects of the disease. In: Travassos da Rosa APA, Vasconcelos PFC, Travassos da Rosa JFS (eds) An overview of arbovirology in Brazil and neighboring countries. Instituto Evandro Chaggas Belem Brazil, pp 219–232

Enria D, Bowen M, Mills JN, Shieh WJ, Bausch D, Peters CJ (1999) Arenaviruses. In: Guerrant RL, Walker DH, Weller PF(eds) Tropical infectious diseases: principles pathogens, and practice. Churchill Livingstone; Philadelphia, chapter 111

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

Fischer SA, Graham MB, Kuehnert MJ, Kotton CN, Srinivasan A, Marty FM, Comer JA, Guarner J, Paddock CD, DeMeo DL, Shieh WJ, Erickson BR, Bandy U, DeMaria A Jr, Davis JP, Delmonico FL, Pavlin B, Likos A, Vincent MJ, Sealy TK, Goldsmith CS, Jernigan DB, Rollin PE, Packard MM, Patel M, Rowland C, Helfand RF, Nichol ST, Fishman JA, Ksiazek T, Zaki SR; LCMV in Transplant Recipients Investigation Team. Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med. 2006; 354:2235–2249

Fisher-Hoch SP, Tomori O, Nasidi A, Perez-Oronoz GI, Fakile Y, Hutwagner L, McCormick JB (1995) Review of cases of nosocomial Lassa fever in Nigeria: the high price of poor medical practice. BMJ 311:857–859

Fulhorst CF, Bowen MD, Ksiazek TG, Rollin PE, Nichol ST, Kosoy MY, Peters CJ (1996) Isolation and characterization of Whitewater Arroyo virus, a novel North American arenavirus. Virology 224:114–120

Fulhorst CF, Bowen MD, Salas RA, Duno G, Utrera A, Ksiazek TG, De Manzione NM, De Miller E, Vasquez C, Peters CJ, Tesh RB (1999a) Natural rodent host associations of Guanarito and pirital viruses (family Arenaviridae) in central Venezuela. Am J Trop Med Hyg 61:325–330

Fulhorst CF, Ksiazek TG, Peters CJ, Tesh RB (1999b) Experimental infection of the cane mouse *Zygodontomys brevicauda* (family Muridae) with Guanarito virus (Arenaviridae), the etiologic agent of Venezuelan hemorrhagic fever. J Infect Dis 180:966–969

Fulhorst CF, Charrel RN, Weaver SC, Ksiazek TG, Bradley RD, Milazzo ML, Tesh RB, Bowen MD (2001) Geographic distribution and genetic diversity of Whitewater Arroyo virus in the southwestern United States. Emerg Infect Dis 7:403–407

Fulhorst CF, Bennett SG, Milazzo ML, Murray HL Jr, Webb JP Jr, Cajimat MNB, Bradley RB (2002) Bear canyon virus: an arenavirus naturally associated with the California mouse (*Peromyscus californicus*). Emerg Infect Dis 8:717–721

Garcia JB, Morzunov SP, Levis S, Rowe J, Calderon G, Enria D, Sabattini M, Buchmeier MJ, Bowen MD, St Jeor SC (2000) Genetic diversity of the Junin virus in Argentina: geographic and temporal patterns. Virology 272:127–136

Georgescu MM, Balanant J, Macadam A, Otelea D, Combiescu M, Combiescu AA, Crainic R, Delpeyroux F (1997) Evolution of the Sabin type 1 poliovirus in humans: characterization of strains isolated from patients with vaccine-associated paralytic poliomyelitis. J Virol 71:7758–7768

Grande-Perez A, Gomez-Mariano G, Lowenstein PR, Domingo E (2005) Mutagenesis-induced, large fitness variations with an invariant arenavirus consensus genomic nucleotide sequence. J Virol 79:10451–10459

Gritsun TS, Desai A, Gould EA (2001) The degree of attenuation of tick-borne encephalitis virus depends on the cumulative effects of point mutations. J Gen Virol 82:1667–1675

Gunther S, Emmerich P, Laue T, Kuhle O, Asper M, Jung A, Grewing T, Ter Meulen J, Schmitz H (2000) Imported lassa fever in Germany: molecular characterization of a new lassa virus strain. Emerg Infect Dis 6:466–476

Gerrard SR, Li L, Barrett AD, Nichol ST (2004) Ngari virus is a Bunyamwera virus reassortant that can be associated with large outbreaks of hemorrhagic fever in Africa. J Virol 78:8922–8926

Gonzalez JP (1986) Les arénavirus d'Afrique : un nouveau paradigme d'évolution. Bull Institut Pasteur 84:67–85

Gonzalez JP, McCormick JB, Herve JP, Jonhson KM, Georges AJ (1983) An arenavirus isolated from wild-caught rodents in the Central African Republic. Intervirology 19:105–112

Gonzalez JP (1996) Coevolution of rodent and viruses: Arenaviruses and Hantaviruses. *In* New Dimension *in* Parasitology M. Ali Ozcel edit. Acta Parasitologica Turcica. 20, supp. 1:617–638

Gonzalez JP, Bowen M, Nicholl S, Rico-Hesse R (1996) Genetic characterization of Sabiá arenavirus an emerging human pathology, 1996. J Gen Virol 221:218–324

Gonzalez JP, Georges AJ, Kiley MP, Meunier DMY, Peters CJ, McCormick JB (1986) Evolutionary biology of a Lassa virus complex. Med Microbiol Immunol 175:157–159

Gonzalez JP, Sanchez A, Rico-Hesse (1995) Venezuelan molecular phylogeny of Guanarito virus, an emerging human arenavirus. J Am Soc Trop Med Hyg 53:1–6

Hahn CS, Lustig S, Strauss EG, Strauss JH (1988) Western equine encephalitis virus is a recombinant virus. Proc Natl Acad Sci U S A 85:5997–6001

Helmick CG, Webb PA, Scribner CL, Krebs JW, McCormick JB (1986) No evidence for increased risk of Lassa ferver infection in hospital staff. Lancet 2:1202–1205

Hinman AR, Fraser DW, Douglas RG et al (1975) Outbreak of lymphocytic choriomeningitis virus infection in medical center personnel. Am J Epidemiol 101:103

Hirabayashi Y, Oka S, Goto H, Shimada K, Kurata T, Fisher-Hoch SP, McCormick JB (1988) An imported case of Lassa fever with late appearance of polyserositis. J Infect Dis 158:872–875

Hugot JP, Denys CH, Gonzalez JP (2001) Evolution of the Old World Arenaviridae and their rodent hosts: generalized host-transfer or association by descent? Infect Genet Evol 1:22–25

Jarvis TC, Kirkegaard K (1992) Poliovirus RNA recombination: mechanistic studies in the absence of selection. EMBO J 11:3135–3145

Johnson KM, Wiebenga NH, Mackenzie RB, Kuns ML, Tauraso NM, Shelekov A, Webb PA, Justines G, Beye HK (1965) Virus isolations from human cases of hemorrhagic fever in Bolivia. Proc Soc Exp Biol Med 118:113–118

Karabatsos N (1985) International Catalogue of Arboviruses Including Certain Other Viruses of Vertebrates, 3rd edn. American Society of Tropical Medicine and Hygiene, San Antonio

Keenlyside RA, McCormick JB, Webb PA, Smith E, Elliott L, Johnson KM (1983) Case-control study of Mastomys natalensis and humans in Lassa virus-infected households in Sierra Leone. Am J Trop Med Hyg 32:829–837

Kilgore PE, Peters CJ, Mills JN, Rollin PE, Armstrong L, Khan AS, Ksiazek TG (1995) Prospects for the control of Bolivian hemorrhagic fever. Emerg Infect Dis 1:97–100

Kosoy MY, Elliott LH, Ksiazek TG, Fulhorst CF, Rollin PE, Childs JE, Mills JN, Maupin GO, Peters CJ (1996) 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 54:570–576

Kuhmann SE, Madani N, Diop OM, Platt EJ, Morvan J, Muller-Trutwin MC, Barre-Sinoussi F, Kabat D (2001) Frequent substitution polymorphisms in African green monkey CCR5 cluster at critical sites for infections by simian immunodeficiency virus SIVagm, implying ancient virus-host coevolution. J Virol 75:8449–8460

Lai MM (1992) RNA recombination in animal and plant viruses. Microbiol Rev 56:61–79

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 Mar 22; [Epub ahead of print]

Lehmann-Grube F (1971) Lymphocytic choriomeningitis virus. Springer, New York
Lisieux T, Coimbra M, Nassar ES, Burattini MN, de Souza LT, Ferreira I, Rocco IM, da Rosa AP, Vasconcelos PF, Pinheiro FP et al (1994) New arenavirus isolated in Brazil. Lancet 343(8894):391–392
Lozano ME, Ghiringhelli PD, Romanowski V, Grau O (1993) A simple nucleic acid amplification assay for the rapid detection of Junin virus in whole blood samples. Virus Res 27:37–53
Lozano ME, Enria D, Maiztegui JI, Grau O, Romanowski V (1995) Rapid diagnosis of Argentine hemorrhagic fever by reverse transcriptase PCR-based assay. J Clin Microbiol 33:1327–1332
Lozano ME, Posik DM, Albarino CG, Schujman G, Ghiringhelli PD, Calderon G, Sabattini M, Romanowski V (1997) Characterization of arenaviruses using a family-specific primer set for RT-PCR amplification and RFLP analysis. Its potential use for detection of uncharacterized arenaviruses. Virus Res 49:79–89
Lukashevich IS (1992) Generation of reassortants between African arenaviruses. Virology 188:600–605
Lunkenheimer K, Hufert FT, Schmitz H (1990) Detection of Lassa virus RNA in specimens from patients with Lassa fever by using the polymerase chain reaction. J Clin Microbiol 28:2689–2692
Maiztegui JI (1975) Clinical and epidemiological patterns of Argentine haemorrhagic fever. Bull World Health Organ 52:567–576
Maiztegui JI, Sabattini MS, Barrera Oro JG (1972) Activity of lymphocytic choriomeningitis virus (LCM) in the endemic area of Argentine hemorrhagic fever (AHF). I. Serological studies in rodents captured in the City of Pergamino. Medicina (B Aires) 32:131–137
Maiztegui JI, Fernandez NJ, de Damilano AJ (1979) Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. Lancet 2:1216–1217
Maiztegui J, Feuillade M, Briggiler A (1986) Progressive extension of the endemic area and changing incidence of Argentine hemorrhagic fever. Med Microbiol Immunol (Berl) 175:149–152
Maiztegui JI, McKee KT Jr, Barrera Oro JG, Harrison LH, Gibbs PH, Feuillade MR, Enria DA, Briggiler AM, Levis SC, Ambrosio AM, Halsey NA, Peters CJ (1998) Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. AHF Study Group. J Infect Dis 177:277–283
McCormick JB, Webb PA, Krebs JW, Johnson KM, Smith ES (1987) A prospective study of the epidemiology and ecology of Lassa fever. J Infect Dis 155:437–444
McKee KT Jr, Mahlandt BG, Maiztegui JI, Eddy GA, Peters CJ (1985) Experimental Argentine hemorrhagic fever in rhesus macaques: viral strain-dependent clinical response. J Infect Dis 152:218–221
Mercado R (1975) Rodent control programmes in areas affected by Bolivian haemorrhagic fever. Bull World Health Organ 52:691–695
Meyer H, Johnson R, Crawford I, Dascomb H, Rogers N (1960) Central nervous systems syndromes of "viral" etiology: a study of 713 cases. Am J Med 29:334–347

Mills JN, Ellis BA, McKee KT Jr, Ksiazek TG, Oro JG, Maiztegui JI, Calderon GE, Peters CJ, Childs JE (1991) Junin virus activity in rodents from endemic and non endemic loci in control Argentina. Am J Trop Med Hyg 44:589–597

Mills JN, Ellis BA, McKee KT, Calderón GE, Maiztegui JI, Nelson GO, Ksiazek TG, Peters CJ, Childs JE (1992) A longitudinal study of Junín virus activity in the rodent reservoir of Argentine hemorrhagic fever. Am J Trop Med Hyg 47:749–763

Mills JN, Barrera Oro JG, Bressler DS, Childs JE, Tesh RB, Smith JF, Enria DA, Geisbert TW, McKee KT Jr, Bowen MD, Peters CJ, Jahrling PB (1996) Characterization of Oliveros virus, a new member of the Tacaribe complex (Arenaviridae: *Arenavirus*). Am J Trop Med Hyg 54:399–404

Moncayo AC, Hice CL, Watts DW, Travassos da Rosa AP, Guzman H, Russell KL, Calampa C, Gozalo A, Popov VL, Weaver SC, Tesh RB (2001) Allpahuayo virus: a newly recognized arenavirus (Arenaviridae) from arboreal rice rats (Oecomys bicolor and Oecomys paricola) in northeastern Peru. Virology 284:277–286

Murphy FA, Webb PA, Johnson KM, Whitfield SG (1969) Morphological comparison of Machupo virus with lymphocytic choriomeningitis: basis for a new taxonomic group. J Virol 535:541

Musser GG, Carleton MD (1993) Family Muridae In: Wilson DE, Reeder DM (eds) Mammals species of the world. Smithsonian Institution, Washington, DC

Orlich M, Gottwald H, Rott R (1994) Nonhomologous recombination between the hemagglutinin gene and the nucleoprotein gene of an influenza virus. Virology 204:462–465

Park JY, Peters CJ, Rollin PE, Ksiazek TG, Gray B, Waites KB, Stephensen CB (1997) Development of a reverse transcription-polymerase chain reaction assay for diagnosis of lymphocytic choriomeningitis virus infection and its use in a prospective surveillance study. J Med Virol 51:107–114

Parodi AS Greenway DJ, Rugiero HR (1958) Sobre la etiologia del brote epidemico de Junin. El Dia Medico 30:2300–2301

Peters CJ (1995) Arenavirus diseases. In: Porterfield JS (ed) Kass handbook of infectious diseases. Exotic viral infections. Chapman and Hall Medical, New York, pp 227–246

Peters CJ, Kuehne RW, Mercado R, Le Bow RH, Spertzel RO, Webb PA (1974) Hemorrhagic fever in Cochabamba Bolivia, 1971. Am J Epidemiol 99:425–433

Peters CJ, Buchmeier M, Rollin PE, Ksiazek TG (1996) Arenaviruses. In: Fields BN, Knipe DM, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman R, Straus SE (eds) Fields virology, 3 rd edn. Lippincott-Raven, Philadelphia, pp 1521–1551

Pinheiro FP, Woodal JP, Travassos da Rosa APA, Ravassos da Rosa JF (1977) Studies on arenvairus in Brazil. Medicina B Aires [Suppl 3] 175:197

Price ME, Fisher-Hoch SP, Craven RB, McCormick JB (1988) A prospective study of maternal and fetal outcome in acute Lassa fever infection during pregnancy. BMJ 297:584–587

Riviere Y, Oldstone MB (1986) Genetic reassortants of lymphocytic choriomeningitis virus: unexpected disease and mechanism of pathogenesis. J Virol 59:363–368

Riviere Y, Ahmed R, Southern PJ, Buchmeier MJ, Oldstone MB (1985) Genetic mapping of lymphocytic choriomeningitis virus pathogenicity: virulence in guinea pigs is associated with the L RNA segment. J Virol 55:704–709

Sabattini MS, Maiztegui JI (1970) Fiebre hemorrhagica argentina. Medicina (Buenos Aires). 30 [Suppl]:111

Salas R, de Manzione N, Tesh RB, Rico-Hesse R, Shope RE, Betancourt A, Godoy O, Bruzual R, Pacheco ME, Ramos B et al (1991) Venezuelan hemorrhagic fever. Lancet 338:1033–1036

Salvato M, Borrow P, Shimomaye E, Oldstone MB (1991) Molecular basis of viral persistence: a single amino acid change in the glycoprotein of lymphocytic choriomeningitis virus is associated with suppression of the antiviral cytotoxic T-lymphocyte response and establishment of persistence. J Virol 65:1863–1869

Salvato M, Clegg JCS, Bowen MD, Buchmeier MJ, Gonzalez JP, Lukashevich IS, Peters CJ, Rico-Hesse R, Romanowski V (2005) Arenaviridae. In: Van Regenmortel MHV, Fauquet CM, Bishop DHL, Carsten EB, Estes MK, Lemon SM, Maniloff J, Mayo MA, McGeoch DJ, Pringle DR, Wickner RB (eds) Virus Taxonomy. 8 th ICTV Report of the International Committee for the Taxonomy of Viruses. Academic, New York, pp 633–640

Salazar-Bravo J, Dragoo JW, Bowen MD, Peters CJ, Ksiazek TG, Yates TL (2002) Natural nidality in Bolivian hemorrhagic fever and the systematics of the reservoir species. Infect Genet Evol 1:191–199

Schlaeffer F, Bar-Lavie Y, Sikuler E, Alkan M, Keynan A (1988) Evidence against high contagiousness of Lassa fever. Trans R Soc Trop Med Hyg 82:311

Sewell DL (1995) Laboratory-associated infections and biosafety. Clin Microbiol Rev 8:389–405

Sibold C, Meisel H, Kruger DH, Labuda M, Lysy J, Kozuch O, Pejcoch M, Vaheri A, Plyusnin A (1999) Recombination in Tula hantavirus evolution: analysis of genetic lineages from Slovakia. J Virol 73:667–675

Skinner HH, Knight EH, Buckley LS (1976) The hamster as a secondary reservoir host of lymphocytic choriomeningitis virus. J Hyg (Lond) 76:299–306

Stephensen CB, Blount SR, Lanford RE, Holmes KV, Montali RJ, Fleenor ME, Shaw JF (1992) Prevalence of serum antibodies against lymphocytic choriomeningitis virus in selected populations from two US cities. J Med Virol 38:27–31

Stinebaugh BJ, Schloeder FX, Johnson KM, Mackenzie RB, Entwisle G, De Alba E (1966) Bolivian hemorrhagic fever: a report of four cases. Am J Med 40:217–230

Suzuki Y, Gojobori T, Nakagomi O (1998) Intragenic recombinations in rotaviruses. FEBS Lett 427:183–187

Swanepoel R, Leman PA, Shepherd AJ, Shepherd SP, Kiley MP, McCormick JB (1985) Identification of Ippy as a Lassa-fever-related virus. Lancet 1(8429):639

Ter Meulen J, Lukashevich I, Sidibe K, Inapogui A, Marx M, Dorlemann A, Yansane ML, Koulemou K, Chang-Claude J, Schmitz H (1996) 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 55:661–666

Tesh RB, Wilson ML, Salas R, De Manzione NM, Tovar D, Ksiazek TG, Peters CJ (1993) Field studies on the epidemiology of Venezuelan hemorrhagic fever: implication of the cotton rat Sigmodon alstoni as the probable rodent reservoir. Am J Trop Med Hyg 49:227–235

Tesh RB, Salas RA, Fulhorst CF, de Manzione N, Duno G, Weaver SC, Utrera A, Parades H, Ellis BA, Mills JN, Bowen MD, Ksiazek TG (1999) Epidemiology of arenaviruses in the Americas. In: Saluzzo JE, Dodet B (eds) Rodent-borne viral Diseases (hantaviruses and arenaviruses). Elsevier, Paris, pp 213–221

Trapido H, Sanmartin C (1971) Pichinde virus: a new virus from Colombia. Am J Trop Med Hyg 20:631–664

Trappier SG, Conaty AL, Farrar BB, Auperin DD, McCormick JB, Fisher-Hoch SP (1993) Evaluation of the polymerase chain reaction for diagnosis of Lassa virus infection. Am J Trop Med Hyg 49:214–221

Van der Heide RM (1982) A patient with Lassa fever from Burkina Faso (formerly Upper Volta), diagnosed in the Netherlands. Ned T Geneesk 126:1–7

Weaver SC, Salas RA, de Manzione N, Fulhorst CF, Duno G, Utrera A, Mills JN, Ksiazek TG, Tovar D, Tesh RB (2000) 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 266:189–195

Weaver SC, Salas RA, de Manzione N, Fulhorst CF, Travasos da Rosa APA, Duno G, Utrera A, Mills JN, Ksiazek TG, Tovar D, Guzman H, Kang W, Tesh RB (2001) Extreme genetic diversity among Pirital virus (Arenaviridae) isolates from Western Venezuela. Virology 285:110–118

Webb PA, Johnson KM, Hibbs JB, Kuns ML (1970) Parana, a new Tacaribe complex virus from Paraguay. Arch Gesamte Virusforsch 32:379–388

Webb PA, Justines G, Johnson KM (1975) Infection of wild and laboratory animals with Machupo and Latino viruses. Bull World Health Organ 52:493–499

Webb PA, McCormick JB, King IJ, Bosman I, Johnson KM, Elliott LH, Kono GK, O'Sullivan R (1986) Lassa fever in children in Sierra Leone West Africa. Trans R Soc Trop Med Hyg 80:577–582

Weissenbacher MC, Coto CE, Calello MA (1975) Cross-protection between Tacaribe complex viruses. Presence of neutralizing antibodies against Junin virus (Argentine hemorrhagic fever) in guinea pigs infected with Tacaribe virus. Intervirology 6:42–49

Whitton JL, Southern PJ, Oldstone MB (1988) Analyses of the cytotoxic T lymphocyte responses to glycoprotein and nucleoprotein components of lymphocytic choriomeningitis virus. Virology 162:321–327

Wilson DE, Reeder DM (2005) Mammal Species of the World, 2nd edn. Johns Hopkins University Press, Baltimore

Worobey M, Rambaut A, Holmes EC (1999) Widespread intras-serotype recombination in natural populations of dengue virus. Proc Natl Acad Sci U S A 96:7352–7357

Wulff H, McIntosh BM, Hammer DB, Johnson KM (1977) Isolation of arenavirus closely related to Lassa virus from *Mastomys natalensis* in South East Africa. Bull World Health Organ 55:441–444