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Review

Emerging infectious diseases: The *Bunyaviridae*

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The *Bunyaviridae* are a large group of viruses that infect a diversity of arthropod vectors and animal hosts. They have a worldwide distribution and can be the cause of human illness ranging from mild asymptomatic infection to hemorrhagic fever and fatal encephalitis. The growth of the human population, the expansion of agricultural and economic development, climatic changes, and the speed and frequency of global transportation all favor the emergence of bunyaviruses and other arthropod borne viruses. International monitoring of the *Bunyaviridae* and a greater understanding of their ecology and biology are needed to prepare for future outbreaks. *Journal of NeuroVirology* (2005) **11,** 412–423.

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Introduction: the family *Bunyaviridae*

The *Bunyaviridae* are a diverse group of RNA viruses divided into five genera (*Orhobunyavirus*, *Hantavirus*, *Nairovirus*, *Phlebovirus*, and *Tospovirus*), and encompassing over 300 viral species (Calisher, 1996). The family was characterized in 1975 to classify viruses with morphological and structural similarities, but with diverse life cycles (Schmaljohn, 1996). The bunyavirus genome is comprised of three negative-sense RNA segments that employ a variety of coding strategies to generate a limited set of structural and non-structural proteins (Schmaljohn, 1996). The L or large RNA segment encodes the virus polymerase, the medium or M segment encodes the glycoproteins G1 and G2 and a nonstructural protein NSm, and the S or small RNA codes for both the nucleocapsid and the NSs nonstructural protein. Within the family *Bunyaviridae*, distinctions between the genera are based on antigenic, serological, molecular, and structural differences (Calisher, 1996). The terminal 10 to 15 nucleotides of each RNA segment, which are highly conserved and partially complementary, play a major role in delineating the groupings (Calisher, 1996).

Members of the family *Bunyaviridae* are found worldwide, and some are significant pathogens in animals, or in the case of the genus *Tospovirus*, plants. Most are spread through sylvatic transmission cycles between susceptible vertebrate hosts and hematophagous arthopods, including mosquitos, phlebotomine flies, and ticks (Figure 1A). Viruses in the genus *Hantavirus* are unique among the *Bunyaviridae* in that they do not infect insect vectors. Instead, hantaviruses are maintained in nature through persistent, mostly benign infection of their natural rodent hosts (Figure 1B). In addition, an alternative route of nonvectored transmission has been reported for some nairoviruses and phleboviruses, including Crimean-Congo hemorrhagic fever virus and Rift Valley fever virus (Al-Hazmi *et al*, 2003; Burney *et al*, 1980; Chapman *et al*, 1991; Mundel and Gear, 1951; Nabeth *et al*, 2001). These viruses can also be spread by exposure to infected animal tissues or body fluids.

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Bunyavirus diseases of the central nervous system (CNS)

Orthobunyaviruses: La Crosse virus and Cache Valley virus

The genus *Orthobunyavirus* (formerly termed *Bunyavirus*) is the largest of the *Bunyaviridae* and is named after the prototype virus of this

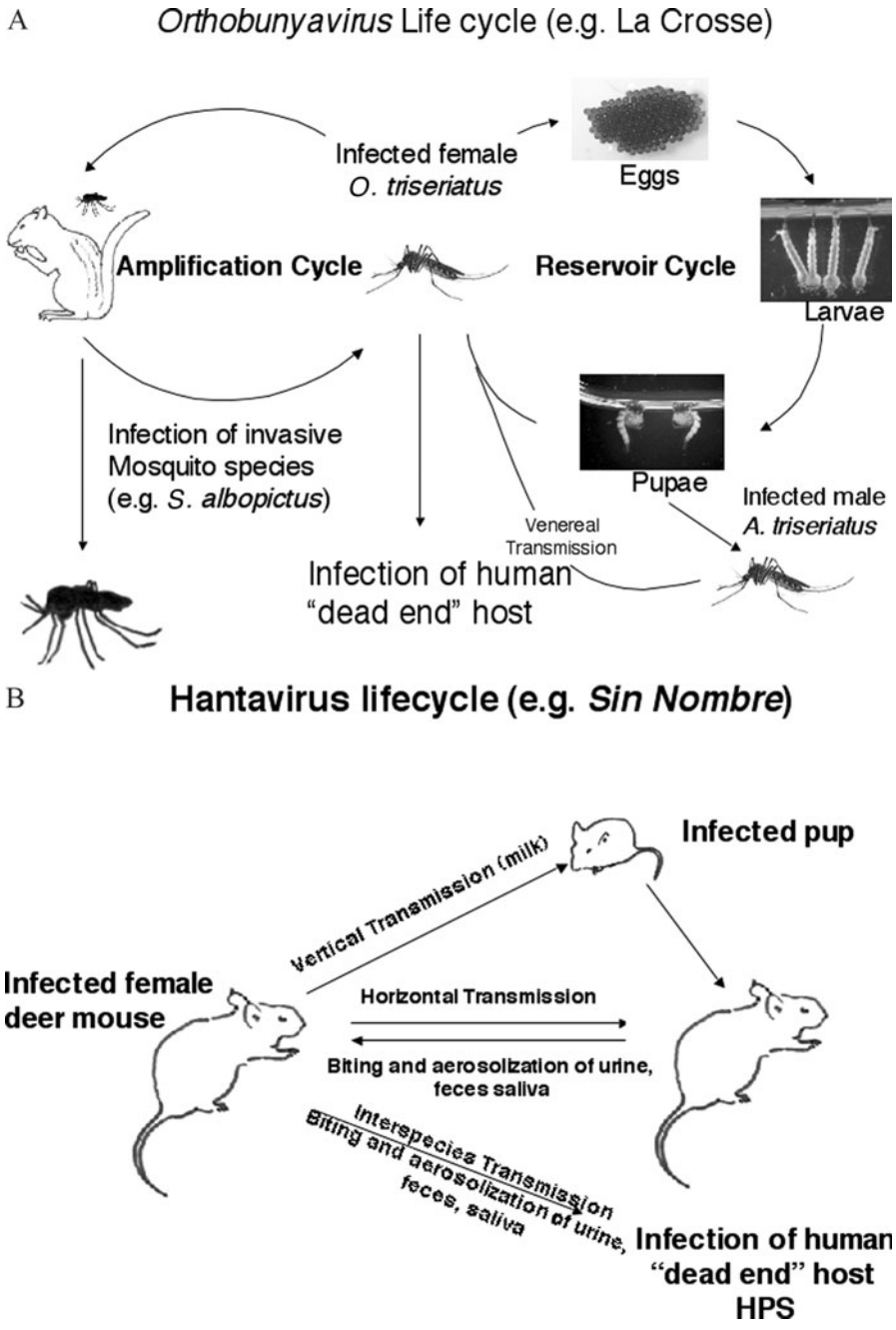

Figure 1 Representative lifecycles of the *Bunyaviridae*. **A**, *Orthobunyavirus* lifecycle (e.g., La Crosse). La Crosse virus is maintained in nature through a mosquito reservoir cycle and a mammalian amplification cycle. The primary vector for La Crosse is the woodland mosquito, *O. triseriatus*, and the principal vertebrate hosts are small rodents including squirrels and chipmunks. In the mosquito reservoir cycle, vertical transmission from an infected female mosquito to her progeny occurs via transovarial infection of eggs, which provides an overwintering mechanism for the virus. In addition, infected male mosquitoes can transmit LACV during mating, thereby spreading infection within the mosquito population. Upon taking a blood meal, infected mosquitoes may transmit LACV to small mammals which develop brief but high viremias that may lead to subsequent infection of hematophagous mosquitoes, either uninfected *O. triseriatus* or invasive mosquito species such as *S. albopictus*. **B**, *Hantavirus* lifecycle (e.g., Sin Nombre). Unlike LACV, Sin Nombre is exclusively rodent born and uses the deer mouse, *Peromyscus maniculatus*, as its primary vector. Infected females may transmit the virus through breast milk. In addition, horizontal and interspecies transmission may occur through biting or aerosolization of urine, feces, and saliva.

Table 1 Representative members of the *Bunyaviridae* associated with diseases of vertebrates

Virus	*Genus*	*Distribution*	*Host/associated illness*	*Arthropod vector*	*Primary host*	*References*
Cache Valley	*Orthobunyavirus*	North America	Sheep, cattle, human (rare)/congenital musculoskeletal and CNS defects	Mosquitoes (*Aedes* species, *Culiseta inornata, Culex tarsalis*)	Livestock, deer	(Chung *et al*, 1990) (Sexton *et al*, 1997)
La Crosse	*Orthobunyavirus*	North America	Human/encephalitis and aseptic meningitis Canine/panencephalitis (rare)	Mosquitoes (*Aedes triseriatus, Aedes albopictus*)	Chipmunks, squirrels	(Thompson *et al*, 1965; Gonzalez-Scarano *et al*, 1996; Tatum *et al*, 1999)
Tahyna	*Orthobunyavirus*	Europe	Human/febrile illness	Mosquitoes (*Aedes vexans, Culiseta inornata*)	Rabbits, domestic animals	(Traavik *et al*, 1978)
Hantaan	*Hantavirus*	Asia, Europe	Human/HFRS[1]	N/A	Field mice	(Lee *et al*, 1978)
Puumala	*Hantavirus*	Asia, Europe	Human/HFRS (mild)	N/A	Bank voles	(Yanagihara *et al*, 1985)
Sin Nombre	*Hantavirus*	North America	Human/HPS[2] (30–50% mortality)	N/A	Deer mice	(Morzunov *et al*, 1995; Nichol *et al*, 1993)
Crimean-Congo hemorrhagic fever	*Nairovirus*	Asia, Africa, Europe	Human/hemorrhagic fever (10–50% mortality)	Ticks (primarily *Hyalomma* species) culicoid flies	Domestic and wild animals and birds	(Hoogstraal, 1979; Swanepoel, 1994)
Nairobi sheep disease	*Nairovirus*	Africa, Asia	Sheep, goats/hemorrhagic gastroenteritis, abortion (75% mortality in sheep)	Ixodid Ticks (*Rhipicephalus appendiculatus*), culicoid flies	Sheep and goats	(Daubney and Hudson, 1931; Davies, 1978; Davies, 1997; Terpstra, 1994)
Rift Valley fever	*Phlebovirus*	Africa	Human/hepatitis, hemorrhagic disease, retinitis, meningoencephalitis (3% mortality) Livestock/abortion, fever, hepatitis (30% mortality)	Mosquitoes (*Aedes* species*and Culex* species)	Sheep and cattle	(Daubney *et al*, 1931; Mundel and Gear, 1951; Zeller and Bouloy, 2000)
Sandfly fever (Toscana)	*Phlebovirus*	Europe	Human/fever, arthralgia, aseptic meningitis, meningoencephalitis	Phlebotomine flies	Unkown, bat?	(Dionisio *et al*, 2003; Verani *et al*, 1988; Verani *et al*, 1984)

[1]Hemorrhagic fever with renal syndrome; [2]Hantavirus pulmonary syndrome.

group, Bunyamwera virus (González-Scarano and Nathanson, 1996). *Orthobunyaviruses* are grouped together based on serological and molecular relationships, and over 172 individual viruses are classified within the 18 *Orthobunyavirus* serogroups (Calisher, 1996). They have been identified in every continent of the world with the exception of Antarctica (Calisher, 1996, González-Scarano and Nathanson, 1996). In addition, most members of the genus are transmitted by mosquitoes (González-Scarano and Nathanson, 1996). Several members, including La Crosse (LACV), Cache Valley, Jamestown Canyon, and Akabane viruses, have been associated with diseases in animals and humans (González-Scarano and Nathanson, 1996) (Table 1). Of these, the members of the California serogroup have been studied most intensively (González-Scarano and Nathanson, 1996). The serogroup was named after California encephalitis virus, the first member described (Hammon and Reeves, 1952; Hammon *et al*, 1952). Originally identified in conjunction with three clinical cases of encephalitis; California encephalitis virus has since been rarely implicated in CNS disease, or for that matter in any symptomatic infection (Eldridge *et al*, 2001). However, other members of the California serogroup, including LACV and Tahyna virus, are important human pathogens (González-Scarano *et al*, 1996; González-Scarano and Nathanson, 1996).

LACV was first recovered from a fatal case of encephalitis in a 4-year-old girl who died in La Crosse, Wisconsin, after acquiring the infection in Minnesota (Thompson *et al*, 1965). After the initial description of the virus, LACV was recognized as a major cause of encephalitis and aseptic meningitis in children residing in the midwestern United States, the area where its principal vector, the woodland mosquito *Aedes triseriatus* is endemic. Small mammals, predominantly chipmunks and squirrels, are the amplifying host for LACV (Figure 1A). These animals develop brief but sufficiently high viremias during infection to transmit virus to hematophagous mosquitoes (Figure 1A), which serve not only to mediate further spread of the virus, but also as a reservoir. In endemic areas, a large proportion of squirrels (30%) and chipmunks (60%) are seropositive (Gauld *et al*, 1974; Thompson *et al*, 1983). Humans are less likely to transmit virus back to mosquitoes and are probably "dead-end" hosts, particularly because

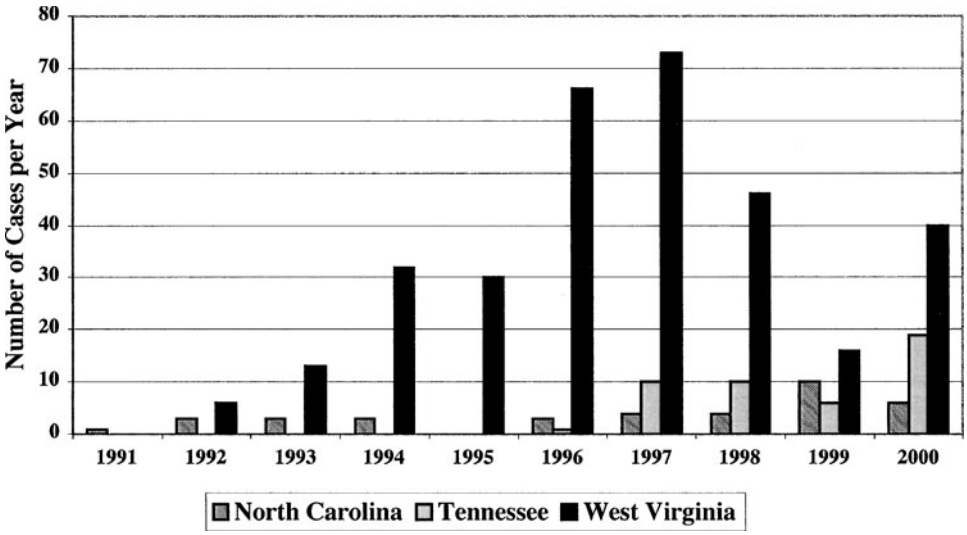

Figure 2 Confirmed and probable California serogroup viral (mainly La Crosse) encephalitis cases in states where it is emerging, 1991–2000.

symptomatic infection is generally confined to children (Figure 1A). Since systematic reporting began in the mid 1960s, the range and annual number of documented cases of LACV infection has remained constant at around 100 per year, which probably reflects little variation in the population of *O. triseriatus* (Kappus *et al*, 1983), although as shown in Figure 2, there has been spread to other areas, possibly as a result of the emergence of a new vector.

LACV overwinters by transmission from female mosquitoes to their larvae (Figure 1A) (Patrican and DeFoliart, 1987). Venereal transmission from transovarially infected males to uninfected females also occurs (Figure 1A) (Thompson and Beaty, 1978). In the late 1990s, LACV encephalitis activity increased significantly in West Virginia, Tennessee, and North Carolina (Gerhardt *et al*, 2001; Jones *et al*, 2000; Utz *et al*, 2003). Between 1996 and 1999 West Virginia accounted for more than half of the reported cases of LACV encephalitis (Gerhardt *et al*, 2001). LACV has been isolated in Tennessee and North Carolina from naturally infected Asian tiger mosquitoes (*S. albopictus)* a species introduced from Asia to the United States in used tire casings (Moore and Mitchell, 1997). Recently, LACV was also identified in transovarially infected populations of *S. albopictus,* suggesting that the Asian tiger mosquito may become an important accessory vector of LACV and facilitate the expansion of the virus into new areas (Gottfried *et al*, 2002).

Clinically, LACV causes a nonspecific febrile illness with an estimated incubation period of one week; this is followed by acute encephalitis in a small proportion of children, almost exclusively younger than 16 years (Kalfayan, 1983). As expected from an arboviral disease, it is most frequent in late summer and early fall corresponding to the lifecycle of *O. triseriatus* (Wurtz and Paleologos, 2000). Symptoms associated with LACV encephalitis include stiff neck, seizures, lethargy, and, rarely, coma. These may persist for up to 10 days (Kalfayan, 1983; González-Scarano *et al*, 1996). Seizures are present in approximately half of the children with LACV encephalitis, and about 10% of children will develop epilepsy. A smaller proportion (≈2%) may have persistent paresis, learning disabilities, or cognitive deficits (Kalfayan, 1983; González-Scarano *et al*, 1996). Fortunately, in spite of the index, case LACV encephalitis rarely results in death (González-Scarano *et al*, 1996). Temporal lobe abnormalities, a finding commonly associated with herpes simplex virus encephalitis, have been described in LACV encephalitis (Wurtz and Paleologos, 2000; Sokol *et al*, 2001). In view of this, it has been suggested that LACV encephalitis may mimic herpes encephalitis, indicating that LACV may be underreported (Sokol *et al*, 2001).

Cache Valley virus (CVV), another Orthobunyavirus with CNS implications, is a member of the Bunyamwera serogroup. First isolated in Utah in 1956 (Holden and Hess, 1959), CVV infects a number of mosquitoes including those of the genera *Culiseta*, *Aedes*, and *Anopheles* (Table 1). Along with several other members of the genus *Orthobunyaviruses*, including Main Drain, Akabane, and Tensaw viruses, CVV has been reported to cause congenital CNS abnormalities (McGowan *et al*, 1973; Emmons *et al*, 1983). CVV has been isolated from mosquitoes and animals throughout much of North, Central, and South America (Calisher *et al*, 1986; González-Scarano *et al*, 1996). Antibodies to CVV have also been detected in many domestic and wild mammals including swine, goats, cattle, elk, white-tailed deer, domesticated caribou, horses, and jackrabbits (Blackmore and Grimstad, 1998; Hoff *et al*, 1970; McLean *et al*, 1987). The virus has been demonstrated to affect fetuses principally, and to

cause various birth defects including arthrogryposis, hydrancephaly, and hydrocephalus in sheep, cattle, and possibly in humans (Calisher and Sever, 1995; Chung *et al*, 1990; Edwards *et al*, 1989; Edwards, 1994). Cache Valley virus is a significant veterinary pathogen in North American ruminants and in addition to the aforementioned congenital abnormalities, the virus has been associated with infertility in livestock (Edwards *et al*, 1998). Antibodies to CVV have been reported in humans, and the virus may be associated with a febrile illness (Mangiafico *et al*, 1988). More recently, CVV was isolated from a North Carolina patient with severe encephalitis and multiorgan failure (Sexton *et al*, 1997). Further studies are necessary to determine if CVV has a role in cases of unexplained human viral encephalitis and congenital abnormalities (Sexton *et al*, 1997).

Phleboviruses: Toscana virus and Rift Valley fever virus

The *Phlebovirus* genus is comprised of at least 51 viruses, 23 of which are in the sandfly fever group (Calisher, 1996). Members of this genus use a diverse range of arthopod vectors including phlebotomine flies, mosquitoes, and ticks (Calisher, 1996). Of interest, the *Phlebovirus* genome structure is similar to that of the *Tospoviruses* in that the nonstructural (NS) protein is transcribed using an ambisense strategy (Giorgi *et al*, 1991).

The sandfly fever viruses are transmitted by phlebotomine flies and generally cause an acute, nonfatal influenza-like illness in humans known as phlebotomus fever or sandly fever. Descriptions of a flulike illness in the Mediterranean that likely corresponded to sandfly fever can be traced back to the Napoleonic wars. However, it was not until 1905 that the connection between this illness and sandflies was realized (Sabin *et al*, 1944). In the sandfly fever group, only Toscana virus, which was first isolated in 1971 from *Phlebotomus perniciousus* sandflies in central Italy, exhibits neurotropic activity (Verani *et al*, 1980). Since its initial isolation, Toscana virus has been recovered from *P. perniciousus* and *P. perfiliewi* sandflies in other Mediterranean countries, including Spain, Portugal, Greece, Cyprus, and southern France (Mendoza-Montero *et al*, 1998; Ehrnst *et al*, 1985; Eitrem *et al*, 1990, 1991a, 1991b; Dobler *et al*, 1997). The primary mammalian reservoir for Toscana virus is unknown (Table 1), but the virus was recovered from the brain of a bat captured in an endemic area, which suggests a possible role for this species in its ecology (Verani *et al*, 1988).

Populations living in endemic areas have a high prevalence of antibodies against Toscana virus. This, together with reports of sporadic asymptomatic infections indicates that as with other arboviruses, systemic infection is more common than is appreciated (Braito *et al*, 1997; Nicoletti *et al*, 1980). Moreover, in a small proportion of infected individuals, infection with Toscana virus leads to aseptic meningitis and meningoencephalitis typically characterized by severe headache, muscle aches, and high fever, from which patients generally make a full recovery in 7 to 10 days. Although rare, severe meningoencephalitis with systemic involvement associated with Toscana virus has been reported (Mendoza-Montero *et al*, 1998; Schwarz *et al*, 1996; Nicoletti *et al*, 1991; Schwarz *et al*, 1995; Braito *et al*, 1998; Baldelli *et al*, 2004).

Toscana virus related cases of aseptic meningitis and meningoencephalitis typically occur in the summer and peak in August, which correlates with the life cycle of *P. perniciosus* and *P. perfiliewi* (Valassina *et al*, 2000). A serologic study of 104 cases of viral meningitis in southern Tuscany demonstrated that 81% were caused by Toscana virus infection, implicating Toscana virus as a frequent and highly relevant etiologic agent of meningitis in central Italy (Valassina *et al*, 2000).

Rift Valley fever virus (RVFV) is a phlebovirus responsible for recurrent epizootics and human epidemics in Africa. First isolated in 1930 during an epizootic involving ewes and lambs on a farm near Lake Naivasha in the Great Rift Valley of Kenya (Daubney *et al*, 1931), RVFV has been retrospectively traced to epizootics as far back as 1912 (Eddy *et al*, 1981). However, RVFV was not classified as a member of the genus *Phlebovirus* until 1980 when serologic tests demonstrated its antigenic relationship to the phlebotomus fever viruses (Shope *et al*, 1980). RVFV has been demonstrated to infect a wide variety of mosquito species, especially members of the genera *Culex* and *Aedes* (Diallo *et al*, 2000; Eddy *et al*, 1981; Fontenille *et al*, 1998; Turell *et al*, 1984). These RVFV epizootics result from dramatic increases in mosquito populations following periods of high rainfall (Bicout and Sabatier, 2004). The interepizootic reservoir for RVFV is not known. However, the namaqua rock rat and various species of bats have been suggested as candidate reservoirs (Oelofsen and Van der Ryst, 1999). Moreover, it has been suggested that transovarial transmission of RVFV may occur (Gargan *et al*, 1988; Linthicum *et al*, 1985), potentially bypassing the need for an interepizootic reservoir. Originally endemic in the flood plains that occur in natural depressions in the grasslands of sub-Saharan Africa, the geographic range of RVFV has expanded substantially in the last century (Davies *et al*, 1985), as will be discussed later in this review.

RVFV can cause severe disease in infected livestock; sheep, cattle, Asian water buffalo, camels, and goats are susceptible. In livestock, the incubation period lasts 2 to 4 days; this is followed by symptoms that include fever, hepatitis, and frequent abortion. In fact, farmers may become aware of RVFV in their sheep flocks by an increase in miscarriages rather than other signs of infection (Balkhy and Memish, 2003). Among livestock, sheep are most susceptible to RVFV and frequently develop high levels of

viremia. In lambs, the mortality rates can be as high as 90%, lower in adults (Daubney *et al*, 1931; Zeller and Bouloy, 2000).

RVFV infection of humans occurs most frequently in individuals who are in contact with livestock including herdsmen, abattoir workers, and veterinary personnel (Abu-Elyazeed *et al*, 1996; Mundel and Gear, 1951). Human transmission is thought to occur via mosquito vectors, unpasteurized milk, aerosols of bloods, or amniotic fluid, or through other direct contact with infected animals. Human RVFV is associated with a broad spectrum of disease ranging from asymptomatic infection and a benign febrile illness to a more severe disease course including retinitis, hepatitis, necrotic encephalitis, and in 1% to 3% of those infected, hemorrhagic fever (Madani *et al*, 2003). Increased mortality due to RVFV infection is associated with advanced age. Clinically, RVFV encephalitis leads to symptoms such as disorientation, drowsiness, severe headache, neck stiffness, hemi- or paraparesis, convulsions, and coma (Madani *et al*, 2003). A recent study of a RVFV epidemic in Saudi Arabia reported a relatively high (14%) mortality rate and high incidence of neurological manifestations (17.1%) in infected persons (Balkhy and Memish, 2003; Madani *et al*, 2003).

Vaccines against RVFV have been developed; however, deleterious effects of vaccination, incomplete protection, and vaccine shortages have limited their success (Caplen *et al*, 1985; Morrill *et al*, 1997a, 1997b; Morrill and Peters, 2003; Randall *et al*, 1964). In addition to causing illness and fatalities in human populations, the devastation caused by RVFV outbreaks is compounded by economic losses due to its effects on livestock in agrarian societies (Balkhy and Memish, 2003; Davies, 1975).

Emerging Bunyaviruses

Rift Valley Fever virus

Since its identification in 1931, there have been over 30 outbreaks of disease caused by RVFV (Madani *et al*, 2003). Extensive human epidemics of RVFV were first reported in 1951 when an estimated 20,000 persons were infected during an epizootic of cattle and sheep in South Africa (Mundel and Gear, 1951). Outbreaks of RVFV were restricted to sub-Saharan Africa until 1977 when 18,000 persons were infected and 598 related deaths were reported in Egypt (El-Akkad, 1978). The continuous movement of livestock from endemic countries in Africa to Egypt may have been a source for this outbreak, as suggested by the high degree of similarity between M segment nucleic acid and amino acid sequences in Egyptian and endemic African livestock isolates (Balkhy and Memish, 2003; Battles and Dalrymple, 1988; Gad *et al*, 1986). In addition, it is believed that the 1977 Egyptian outbreak was related to the construction of the Aswan Dam, which increased flooding of the riverbanks after heavy rains and resulted in increased mosquito reproduction (Balkhy and Memish, 2003). Ten years later, a major RVFV outbreak occurred in Mauritania after the construction of the Diama dam on the Senegal River led to extensive flooding (Jouan *et al*, 1988). Throughout the late twentieth century, outbreaks of RVFV continued in Africa (Arthur *et al*, 1993; Jouan *et al*, 1988; Nabeth *et al*, 2001; Durand *et al*, 2003). After heavy rainfall in late 1997, the virus infected 27,500 individuals and claimed 170 human lives in the Garissa District of Kenya, constituting the largest recorded outbreak of RVFV in East Africa (Woods *et al*, 2002). This outbreak extended to four of Kenya's six provinces and, in addition, the World Health Organization surveillance program confirmed human disease in parts of Tanzania and, for the first time, Somalia (Woods *et al*, 2002).

In September 2000, the first cases of RVFV outside of Africa were reported in Yemen and in the Jizan region of Saudi Arabia (Balkhy and Memish, 2003; Madani *et al*, 2003). Whether RVFV will become endemic in the Arabian Peninsula remains to be determined. It has been suggested that because of agricultural development, climate change, and movement of livestock, there is a high probability of recurring outbreaks of RVFV in Africa as well as the potential for spread by either natural or intentional means to non–disease-endemic areas (Woods *et al*, 2002). Furthermore, the occurrence of RVFV outside of Africa highlights the potential for this disease to spread to nonendemic areas. In addition, the ability of this virus to infect a large number of mosquito species (Thonnon *et al*, 1999; Diallo *et al*, 2000) underscores the potential for RVFV to increase its geographic range given the right environmental or man-made conditions. Remote sensing satellite technology predicting rainfall patterns that are likely to result in the emergence of arthropod vector-borne diseases, particularly during the warm phase of the El Niño/Southern Oscillation (ENSO) phenomenon, may constitute a viable means to monitor RVFV activity and to target specific areas for vaccination and surveillance (Anyamba *et al*, 2001; Linthicum *et al*, 1999; Woods *et al*, 2002). Control of mosquito populations during and after heavy rains is essential in the prevention of both animal and human infection.

Hantaviruses

In contrast to other members of the family *Bunyaviridae*, hantaviruses are exclusively rodent-borne. Hantaviruses cause a persistent infection in their rodent reservoirs; the animals do not demonstrate any overt clinical signs, although pathological examination has demonstrated some changes in the lung and liver (Netski *et al*, 1999). Infected rodents shed the virus in urine, saliva, and feces (Figure 1B), and transmission to humans occurs through the inhalation of small particle aerosols from contaminated

excreta in areas of high rodent concentration. Exposure has therefore been associated with entering or cleaning rodent-infested structures (Douglass *et al*, 2003). Hantaviruses are found worldwide and the distribution of hantavirus associated diseases is determined by the geographic distribution of the rodent reservoirs for each hantavirus (Schmaljohn and Hjelle, 1997).

Two major clinical disorders are associated with hantavirus infections in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) (Schmaljohn and Hjelle, 1997; Papadimitriou, 1995). HFRS is associated with Old World hantaviruses including Puumala, Dobrava, Hantaan, and Seoul, and with rodent reservoirs of the subfamily *Muridae*. Approximately 100,000 cases of HFRS are reported annually in Europe and Asia (Johnson, 1999). The clinical symptoms of HFRS range from mild to severe and include fever, hemorrhages, and renal impairment. The case-fatality rates range from <1% for Puumala virus to 5% to 15% for Hantaan virus (Wichmann *et al*, 2002). In addition to HFRS (also known as nephropathia epidemica), Puumala virus has been associated with perimyocarditis and neurological manifestations, including severe headache, blurred vision, meningism, cerebral hemorrhage, and encephalitis (Alexeyev and Morozov, 1995; Ahlm *et al*, 1998; Bergmann *et al*, 2002). Although not typically associated with disorders of the CNS in humans, Hantaan virus has been demonstrated to cause acute encephalitis in experimentally infected adult laboratory mice (Wichmann *et al*, 2002).

HPS is caused by New World hantaviruses including Andes virus and Sin Nombre virus (SNV), and rodents of the subfamily *Sigmodontinae* are the principal reservoirs. Characterized by fever, vascular leakage, noncardiogenic pulmonary edema, and shock, HPS fatality rates for SNV and Andes viruses range from 30% to 50%. Currently, there are no effective antiviral drugs or vaccines against this rapidly progressive and often fatal disease (Custer *et al*, 2003).

HPS emerged as a new infectious disease in the United States in 1993 when a cluster of previously healthy young adults succumbed to an acute respiratory illness preceded by an abrupt onset of fever, headache, cough, and myalgia (Duchin *et al*, 1994; Hughes *et al*, 1993). This acute respiratory illness was initially termed "Four Corners disease" because of its localization to the Four Corners area where Arizona, Colorado, New Mexico, and Utah intersect; this name was rapidly discarded once the etiologic agent was identified through serological studies that showed cross-reactivity with Old World hantaviruses and with Prospect Hill virus (Hjelle *et al*, 1994b). Subsequently, hantavirus antibody positivity and hantavirus sequences were identified in deer mice, *Peromyscus maniculatus*, which are native to most of the continental United States and parts of Canada and Mexico (Nichol *et al*, 1993). The virus implicated with the Four Corners HPS outbreak was named Sin Nombre virus (SNV) (Spanish for virus without a name) when regional naming was felt to be confusing (Simonsen *et al*, 1995). Although its prevalence varies temporally and geographically, approximately 10% of deer mice tested are infected with SNV (Douglass *et al*, 2001; Root *et al*, 2003).

After the identification of SNV, several other hantaviruses with the potential to cause HPS in humans have been isolated or identified through other means such as polymerase chain reaction (PCR) amplification of the genomes. These include El Moro Canyon, Isla Vista, Black Creek Canal, Bayou, and Muleshoe viruses (Torrez-Martinez and Hjelle, 1995; Torrez-Martinez *et al*, 1995; Song *et al*, 1995; Papa *et al*, 2000). Meadow voles, cotton rats, rice rats, and white footed mice have been demonstrated to serve as primary reservoirs for these New World hantaviruses. Evidence of infection has been reported in predators including dogs, cats, and coyotes (Leighton *et al*, 2001; Malecki *et al*, 1998), indicating that a wide variety of mammalian species coming into contact with infected rodents are potentially at risk. Although there is no evidence for transmission to other animals or to humans from these "dead-end" hosts, domestic cats and dogs may bring infected rodents into contact with humans.

HPS remains a rare disorder. A number of ecological factors contributed to the Four Corners outbreak in 1993 (Engelthaler *et al*, 1999; Glass *et al*, 2002). To wit, unusually high precipitation caused by the El Niño, a climatic phenomenon that occurs cyclically in the Western Pacific, led to increased vegetation and a 10-fold increase in the rodent populations of New Mexico (Engelthaler *et al*, 1999; Glass *et al*, 2000, 2002). This dramatic rise in the density of the rodent population may have facilitated transmission of SNV between rodents (Engelthaler *et al*, 1999; Morse, 1994). In addition, more rodents would have theoretically entered human dwellings, thereby increasing rodent contact and the abundance of rodent feces in close proximity to people (Calisher *et al*, 2002; Hjelle *et al*, 1994a). In 1999, an HPS outbreak in Panama with a 25% fatality rate marked the first cases of HPS identified in Central America (Vincent *et al*, 2000). This outbreak led to the identification of another hantavirus, Choclo virus, which is associated with the rodent host *Oligoryzomys fulvescens* (Vincent *et al*, 2000). The broad geographic distribution of Sigmodontine rodents in the New World suggests that human cases of HPS have the potential to occur throughout the Americas, especially as climate changes affect weather patterns and human populations continue to encroach upon the natural habitats of hantavirus infected rodents (Engelthaler *et al*, 1999; Morse, 1994).

Conclusions

The *Bunyaviridae* are a unique group of viruses whose members are able to infect invertebrates, vertebrates and plants. In this era of rapidly changing local and global environments (Nichol *et al*, 2000), several factors, including their promiscuous use of arthropod vectors and vertebrate hosts, have made the *Bunyaviridae* prominent among emerging and reemerging infectious agents. Increased awareness of bunyaviruses in endemic areas, education regarding modes of disease transmission and necessary precautions, and implementation of vector control are paramount in the prevention of future outbreaks.

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