Chapter 10
Family *Bunyaviridae*

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Core Message The family *Bunyaviridae* is one of the largest and most diverse of the established viral families. Viruses within this family infect a wide range of organisms including invertebrates, vertebrates, and plants. Bunyaviruses are transmitted by mammals or arthropods, including ticks, mosquitoes, biting midges, sandflies, and thrips. Some viruses within this family are important pathogens causing encephalitis or hemorrhagic fever in humans, abortions in pregnant animals, or devastating disease in economically important plants.

1 Introduction

The large family *Bunyaviridae* includes more than 400 distinct members (bunyaviruses) that are grouped into five genera—*Hantavirus*, *Nairovirus*, *Orthobunyavirus*, *Phlebovirus*, and *Tospovirus*. Bunyaviruses possess a tripartite, single-stranded RNA genome that encodes four structural and, in some cases, one or two additional

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nonstructural proteins in a mostly negative-sense (i.e., anti-message) manner. Exemplifying the great diversity of the family *Bunyaviridae*, viruses in this family are known to infect invertebrates, vertebrates, and plants. Indeed, most viruses of the family are arthropod-borne, and various mosquitoes, ticks, biting flies, and thrips are vectors for transmission of orthobunyaviruses, nairoviruses, phleboviruses, and tospoviruses, respectively. Small mammals serve as amplifying hosts for most bunyaviruses, although some members (hantaviruses) use small mammal reservoirs and are transmitted via aerosolized excreta. Bunyaviruses have a worldwide geographic distribution, and some of these viruses are associated with significant human illnesses, including encephalitides and viral hemorrhagic fevers. Other bunyaviruses cause diseases in domestic animals and plants that are associated with significant economic impact.

2 History and Classification

Undoubtedly, many bunyaviral diseases were known long before viruses were discovered in the late nineteenth century. As far back as 960 A.D., the Chinese described illnesses closely resembling hemorrhagic fever with renal syndrome (HFRS) [1, 2], which is now known to be caused by certain hantaviruses. During the Napoleonic Wars (1803–1815), soldiers suffered from an epidemic of febrile illness, named Mediterranean fever that had symptoms similar to sandfly fever [3] that is caused by a phlebovirus. Sandfly fever was first clinically described by Alois Pick in 1886 in the Balkans region where the disease was prevalent in an endemic form [4].

In 1943, Smithburn and colleagues initially isolated Bunyamwera virus from *Aedes* mosquitoes during studies of yellow fever in Uganda [5] that is now classified in the genus *Orthobunyavirus*. Early classification of arboviruses (arthropod-borne viruses) relied mostly on serological relatedness, using methods such as complement fixation and neutralization tests. By 1960, eastern equine encephalitis virus, western equine encephalitis virus, and certain other viruses were known to be related to each other and were referred to as group A arboviruses (which are now classified in the genus *Alphavirus* in the family *Togaviridae*). Japanese encephalitis virus, yellow fever virus, St. Louis encephalitis virus, West Nile virus, and certain other viruses were also known to be related to each other and were referred to as group B arboviruses (which are now classified in the family *Flaviviridae*). Following the isolation of Bunyamwera virus, several other arboviruses were isolated that clearly did not fit into these two antigenic groups. These viruses were subsequently assigned to what became known as the group C arboviruses [6]. The family *Bunyaviridae* was formally established in 1975 to incorporate this group [7], and its members are now grouped into five genera—*Hantavirus*, *Nairovirus*, *Orthobunyavirus*, *Phlebovirus*, and *Tospovirus*. Viruses in all genera infect vertebrates, except for those in the genus *Tospovirus*, which infect plants [8].

3 Physical Properties

Bunyavirion morphology varies among viruses of each of the five genera; however, virions are generally spherical, 80–120 nm in diameter, and possess surface glycoprotein projections of 5–10 nm. These peplomers are embedded in a lipid bilayered envelope approximately 5 nm thick and are thought to mostly consist of heterodimers of the two viral glycoproteins (Fig. 10.1). The previous designations of these glycoproteins, G1 and G2, were based on their relative migration in polyacrylamide gels. Today, these proteins are referred to as Gn and Gc, referring to the amino-terminal and carboxy-terminal coding of the proteins [9]. Orthobunyavirions have surfaces covered with closely packed, knob-like morphologic units with no detectable order. Similarly, no obvious order is found for the small surface structures with central cavities observed on nairovirions [10]. In contrast, hantavirions have a surface structure that is distinctly ordered in a square grid-like pattern [10]. Phlebovirions have round, closely packed subunits approximately 10–11 nm in diameter with central cavities approximately 5 nm in diameter [10]. The appearances of tospovirions are similar to those of nairovirions in which, other than the presence of glycoprotein spikes, distinctive surface structures have not been observed.

Bunyavirions consist of 2 % RNA, 58 % protein, 33 % lipid, and 7 % carbohydrate (estimated for Uukuniemi virus of the genus *Phlebovirus*) and are sensitive to heat, lipid solvents, detergents, and formaldehyde [11]. Treatment with lipid solvents or detergents removes the viral envelope, resulting in loss of infectivity in arthropods and mammals [11]. Interestingly, however, the envelope is not required for viral entry or replication in plant cells of the plant-infecting tomato spotted wilt virus [12].

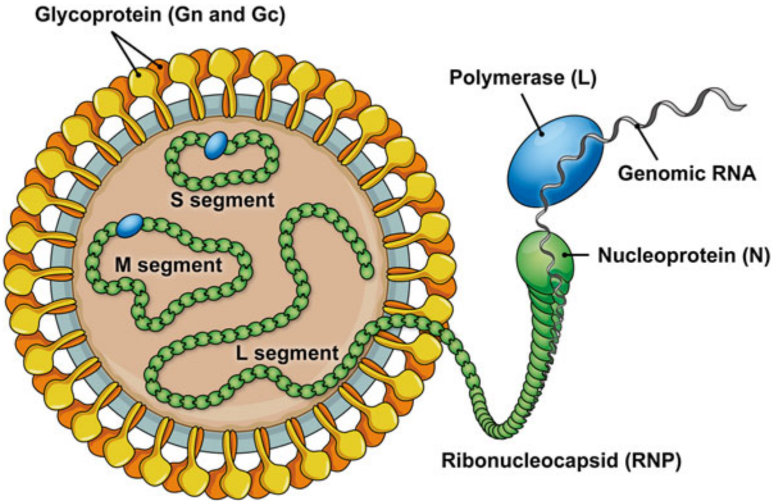

Fig. 10.1 Schematic enveloped, spherical bunyavirion, 80–120 nm diameter. Image courtesy of ViralZone, SIB Swiss Institute of Bioinformatics, with permission

4 Genome Structure

The bunyaviral genome comprises three segments of negative or ambisense single-stranded RNA designated as small (S), medium (M), and large (L). The lengths of the genomic segments vary among the genera, with the total genome lengths of approximately 11–19 kb (Table 10.1). The 3′ and 5′ terminal nucleotides of each genomic segment are highly conserved among viruses of a given genus, but differ among viruses of different genera (Table 10.2). Stretches of the 3′ and 5′ termini are complementary. Thus, the termini of each segment base-pair, forming noncovalently closed, panhandle-like RNAs. Direct support for base-pairing comes from electron microscopy studies of extracted RNA from Uukuniemi virions, in which three sizes of circular RNAs are evident [13].

5 Protein Coding and Viral Replication Strategies

The S, M, and L genome segments of all bunyaviruses encode a nucleocapsid protein (N), two envelope glycoproteins (Gn and Gc), and an RNA-dependent RNA polymerase (L), respectively (Fig. 10.2).

The S segment is approximately 1.0–3.0 kb and has one open reading frame (ORF) in the negative-sense orientation that codes for N. N is the most abundant component of virions and viral product in infected cells. N plays several important roles in viral replication, including protecting the RNA from degradation. The S segment of the orthobunyaviruses encodes for both the N protein and a nonstructural (NS)s protein in overlapping reading frames. Likewise, some hantavirus

Table 10.1 Approximate length (kb) of the genomic RNA segments of viruses belonging to the five genera included in the family *Bunyaviridae*

	Genus				
RNA segment	*Orthobunyavirus*	*Hantavirus*	*Nairovirus*	*Phlebovirus*	*Tospovirus*
S	1.0	1.7	1.7	1.7	2.9
M	4.5	3.9	4.9	3.2	4.8
L	6.9	6.5	12.2	6.4	8.9
Total	12.4	12.1	18.8	11.3	16.6

Table 10.2 Bunyavirus genus-specific consensus 3′ and 5′ terminal nucleotide sequences of the viral genomic RNAs

Orthobunyavirus	3′-UCAUCACAUGA…………………..UCGUGUGAUGA-5′
Hantavirus	3′-AUCAUCAUCUG…………………………AUGAUGAU-5′
Nairovirus	3′-AGAGUUUCU…………………………..AGAAACUCU-5′
Phlebovirus	3′-UGUGUUUC………………………………GAAACACA-5′
Tospovirus	3′-UCUCGUUA……………………………CUAACGAGA-5′

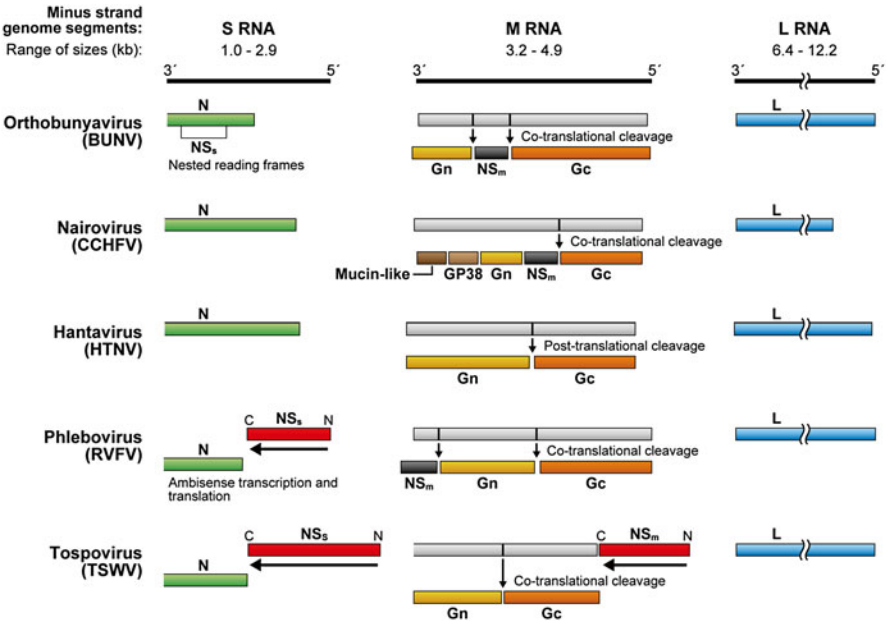

Fig. 10.2 Genome organization of viruses of the five bunyavirus genera. Structural proteins are N (nucleocapsid) and the two viral glycoproteins, Gn and Gc, named according to their proximity to the N or C termini of the precursor polyprotein, respectively. The L protein possesses RNA-dependent RNA polymerase activity. Virus abbreviations: *BUNV* Bunyamwera virus, *CCHFV* Crimean-Congo hemorrhagic fever virus, *HTNV* Hantaan virus, *RVFV* Rift Valley fever virus, *TSWV* tomato spotted wilt virus

genomes have an ORF within the N ORF, and an NSs protein has been detected in cells infected with some hantaviruses [14, 15].

A single, continuous ORF in the M RNA segment encodes the polyprotein precursor of the glycoproteins, which is co-translationally cleaved by a cellular protease into mature Gn and Gc. The M segment of nairoviruses is 30–50 % larger than M segments of viruses of the other genera and has the coding potential of up to 240 kDa of protein [16]. The M segment of Crimean-Congo hemorrhagic fever virus (CCHFV) encodes a precursor Gn (preGn) that undergoes posttranslational cleavage to two proteins of unknown functions, a mucin-rich protein, and glycoprotein GP38 [17]. The M segments of some bunyaviruses (but not those of hantaviruses) also encode a NSm protein. NSm is encoded in negative-sense orientation in the case of orthobunyaviruses and phleboviruses, but in positive-sense orientation in the case of tospoviruses. The nairovirus CCHFV also encodes NSm [18]. This integral membrane protein is cleaved off from the C-terminal region of preGn and is detected in cells infected with CCHFV, but not in virion pellets [18]. The function of this protein is currently unknown. In fact, the only M segment NS protein to have a defined role is the NSm of tospoviruses, which aids viral cell-to-cell movement

Table 10.3 Approximate mass (kDa) of structural proteins of viruses belonging to the five bunyavirus genera

	Genus				
Protein	*Orthobunyavirus*	*Hantavirus*	*Nairovirus*	*Phlebovirus*	*Tospovirus*
N	25	50	50	30	30
Gn	35	70	35	55–70	45
Gc	110	55	75	65	75
L	250	250	450	250	330

(see below). The L segment uses a conventional negative-sense (i.e., complementary to mRNA) coding strategy.

The bunyaviral L segments encode the RNA-dependent RNA polymerase (L). Hantaviral, orthobunyaviral, and phleboviral L is of similar mass ≈250 kDa, whereas tospoviral and nairoviral L is considerably larger (330 kDa and 450 kDa, respectively) (Table 10.3).

Bunyavirions gain entry into host cells by mechanisms similar to many other enveloped viruses. The viral glycoproteins, Gn and Gc, are primarily responsible for attachment to host cells and fusion with cellular membranes. Attachment to the host cell is followed by virion endocytosis. Most bunyaviruses assemble and bud into the Golgi apparatus (visualized by electron microscopy in the case of Bunyamwera virus) [19]. After budding into the Golgi cisternae, maturing virions are transported to the plasma membrane in small vesicles. By a process that resembles normal exocytosis, virion release occurs after fusion of the vesicles with the plasma membrane [20].

6 Ecology and Epidemiology

6.1 *Orthobunyaviruses*

The genus *Orthobunyavirus* includes ≈53 species and contains more than 193 viruses. Most of these viruses are grouped into ≈20 serogroups based on antigenic relationships (Table 10.4) [8, 21]. The vast majority of the viruses are vectored by mosquitoes; however, some orthobunyaviruses have culicoid flies (i.e., biting midges of the genus *Culicoides*) or ticks as vectors. These viruses are distributed worldwide; however, the majority of these viruses are not well studied. The exceptions are those viruses that have medical (e.g., La Crosse and Oropouche viruses) or veterinary importance (e.g., the newly emerged Schmallenberg virus).

La Crosse virus (LACV) is a member of the California serogroup and one of the most significant bunyaviruses in terms of causing human encephalitis. LACV is transmitted by its primary vector, the forest-dwelling, tree-hole-breeding mosquito *Aedes triseriatus* [22] (Fig. 10.3). This mosquito is found throughout the northern, midwestern, and northeastern USA. LACV is maintained in these mosquitoes by

Table 10.4 Viruses in the genus *Orthobunyavirus*

Virus species (in italics) and their member viruses	Vector	Distribution	Disease host
Anopheles A serogroup			
Anopheles A virus			
Anopheles A virus (ANAV)	Mosquitoes	South America	–
Arumateua virus (ARTV)	Mosquitoes	South America	–
Caraipé virus (CPEV)	Mosquitoes	South America	–
Las Maloyas virus (LMV)	Mosquitoes	South America	–
Lukuni virus (LUKV)	Mosquitoes	South America	–
Trombetas virus (TRMV)	Mosquitoes	South America	–
Tucuruí virus (TUCV)	Mosquitoes	South America	–
Tacaiuma virus			
Tacaiuma virus (TCMV)	Mosquitoes	South America	Human
CoAr 1071 virus	Mosquitoes	South America	–
CoAr 3627 virus	Mosquitoes	South America	–
Virgin River virus (VRV)	Mosquitoes	North America	–
Anopheles B serogroup			
Anopheles B virus			
Anopheles B virus (ANBV)	Mosquitoes	South America	–
Boracéia virus (BORV)	Mosquitoes	South America	–
Bakau serogroup			
Bakau virus			
Bakau virus (BAKV)	Mosquitoes	Asia	–
Ketapang virus (KETV)	Mosquitoes	Asia	–
Nola virus (NOLAV)	Mosquitoes		–
Tanjong Rabok virus (TRV)	ND	Asia	–
Telok Forest virus (TFV)	ND	Asia	–
Bunyamwera serogroup			
Bunyamwera virus			
Batai virus (BATV)	Mosquitoes	Asia	Human
Birao virus (BIRV)	Mosquitoes	Africa	–
Bozo virus (BOZOV)	Mosquitoes	Africa	–
Bunyamwera virus (BUNV)	Mosquitoes	Africa	Human
Cache Valley virus (CVV)	Mosquitoes	North America	Sheep, cattle, human
Fort Sherman virus (FSV)	Mosquitoes	South America	Human
Germiston virus (GERV)	Mosquitoes	Africa	Human
Iaco virus (IACOV)	Mosquitoes	South America	–
Ilesha virus (ILEV)	Mosquitoes	Africa	Human
Lokern virus (LOKV)	Mosquitoes/culicoid flies	North America	–
Maguari virus (MAGV)	Mosquitoes	South America	–
Mboke virus (MBOV)	Mosquitoes	Africa	–
Ngari virus (NRIV)[a]	Mosquitoes	Africa	Human

(continued)

Table 10.4 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease host
Northway virus (NORV)	Mosquitoes	North America	–
Playas virus (PLAV)	Mosquitoes	South America	–
Potosi virus (POTV)	Mosquitoes	North America	–
Santa Rosa virus (SARV)	Mosquitoes	North America	–
Shokwe virus (SHOW)	Mosquitoes	Africa	Human
Stanfield virus	Mosquitoes	North America	–
Tensaw virus (TENV)	Mosquitoes	North America	–
Tlacotalpan virus (TLAV)	Mosquitoes	North America	–
Tucunduba virus (TUCV)	Mosquitoes	South America	–
Xingu virus (XINV)	Mosquitoes	South America	Human
Guaroa virus			
Guaroa virus (GROV)	Mosquitoes	North America, South America	Human
Kairi virus			
Kairi virus (KRIV)	Mosquitoes	South America	Horse
Main Drain virus			
Main Drain virus (MDV)	Mosquitoes/culicoid flies	North America	Horse
Bwamba serogroup			
Bwamba virus			
Bwamba virus (BWAV)	Mosquitoes	Africa	Human
Pongola virus (PGAV)	Mosquitoes	Africa	Human
California serogroup			
California encephalitis virus			
California encephalitis virus (CEV)	Mosquitoes	North America	Human
Chatanga virus	Mosquitoes	Asia, Europe	–
Inkoo virus (INKV)	Mosquitoes	Europe	Human
Jamestown Canyon virus (JCV)	Mosquitoes	North America	Human
Jerry Slough virus			
Keystone virus (KEYV)	Mosquitoes	North America	–
La Crosse virus (LACV)	Mosquitoes	North America	Human
Lumbo virus (LUMV)	Mosquitoes	Africa	Human
Melao virus (MELV)	Mosquitoes	South America	–
Morro Bay virus (MBV)			
San Angelo virus (SAV)	Mosquitoes	North America	–
Serra do Navio virus (SDNV)	Mosquitoes	South America	–
Snowshoe hare virus (SSHV)	Mosquitoes	North America	Human
South River virus (SORV)	Mosquitoes	North America	–
Tahyña virus (TAHV)	Mosquitoes	Europe	Human
Trivittatus virus (TVTV)	Mosquitoes	North America	–
Capim serogroup			
Acara virus			
Acara virus (ACAV)	Mosquitoes	North America, South America	–
Moriche virus (MORV)	Mosquitoes	South America	–

(continued)

Table 10.4 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease host
Benevides virus			
Benevides virus (BVSV)	Mosquitoes	South America	–
Capim virus			
Capim virus (CAPV)	Mosquitoes	South America	–
Gamboa serogroup			
Alajuela virus			
Alajuela virus (ALJV)	Mosquitoes	North America	–
San Juan virus (SJV)	Mosquitoes	South America	–
Gamboa virus			
Gamboa virus (GAMV)	Mosquitoes	North America	–
Pueblo Viejo virus (PVV)	Mosquitoes	South America	–
Group C serogroup			
Caraparú virus			
Apeú virus (APEUV)	Mosquitoes	South America	Human
Bruconha virus (BRUV)	Mosquitoes	South America	–
Caraparú virus (CARV)	Mosquitoes	North America, South America	Human
Ossa virus (OSSAV)	Mosquitoes	North America	Human
Vinces virus (VINV)	Mosquitoes	South America	–
Madrid virus			
Madrid virus (MADV)	Mosquitoes	North America	Human
Marituba virus			
Gumbo Limbo virus (GLV)	Mosquitoes	North America	–
Marituba virus (MTBV)	Mosquitoes	South America	Human
Murutucú virus (MURV)	Mosquitoes	South America	Human
Nepuyo virus (NEPV)	Mosquitoes	North America, South America	Human
Restan virus (RESV)	Mosquitoes	South America	Human
Zungarococha virus (ZUNV)	ND	South America	Human
Oriboca virus			
Itaquí virus (ITQV)	Mosquitoes	South America	Human
Oriboca virus (ORIV)	Mosquitoes	South America	Human
Guama serogroup			
Bertioga virus			
Bertioga virus (BERV)	ND	South America	–
Cananeia virus (CNAV)	Mosquitoes	South America	–
Guaratuba virus (GTBV)	Mosquitoes	South America	–
Itimirim virus (ITIV)	ND	South America	–
Mirim virus (MIRV)	Mosquitoes	South America	–
Bimiti virus			
Bimiti virus (BIMV)	Mosquitoes	South America	–
Guama virus			
Ananindeua virus (ANUV)	Mosquitoes	South America	–

(continued)

Table 10.4 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease host
Guama virus (GMAV)	Mosquitoes	North America, South America	Human
Mahogany Hammock virus (MHV)	ND	North America	–
Moju virus (MOJUV)	Mosquitoes	South America	–
Kongool serogroup			
Koongol virus			
Koongol virus (KOOV)	Mosquitoes	Australia	–
Wongal virus (WONV)	Mosquitoes	Australia	–
Minatitlan serogroup			
Minatitlan virus			
Minatitlan virus (MNTV)	ND	North America	–
Palestina virus (PLSV)	Mosquitoes	South America	–
Nyando serogroup			
Nyando virus			
Nyando virus (NDV)	Mosquitoes	Africa	Human
Eretmapodites virus (ERETV)	Mosquitoes	Africa	–
Olifantsvlei serogroup			
Bomtambi virus			
Bomtambi virus (BOTV)	Mosquitoes	Africa	–
Olifantsvlei virus			
Bobia virus (BIAV)	Mosquitoes	Africa	–
Dabakala virus (DABV)	Mosquitoes	Africa	–
Olifantsvlei virus (OLIV)	Mosquitoes		–
Oubi virus (OUBIV)	Mosquitoes	Africa	–
Patois serogroup			
Patois virus			
Abras virus (ABRV)	Mosquitoes	South America	–
Babahoya virus (BABV)	Mosquitoes	South America	–
Pahayokee virus (PAHV)	Mosquitoes	North America	–
Patois virus (PATV)	Mosquitoes	North America	–
Shark River virus (SRV)	Mosquitoes	North America	–
“Sedlec serogroup”			
Sedlec virus			
I612045 virus	ND	Asia	–
Oyo virus	ND	Africa	–
Sedlec virus (SEDV)	ND	Europe	–
Simbu serogroup			
Akabane virus			
Akabane virus (AKAV)	Mosquitoes/culicoid flies	Africa, Asia, Australia	Cattle
Sabo virus (SABOV)	Culicoid flies	Africa	–

(continued)

Table 10.4 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease host
Tinaroo virus (TINV)	Culicoid flies	Australia	–
Yaba-7 virus (Y7V)	ND	Africa	–
"*Leanyer virus*"			
Leanyer virus (LEAV)	Mosquitoes	Australia	–
Oropouche virus			
Facey's Paddock virus (FPV)	ND	Australia	–
Madre de Dios virus	ND	South America	–
Oropouche virus (OROV)	Mosquitoes/culicoid flies	South America	Human
Pintupo virus	ND	North America	–
Utinga virus (UTIV)	ND	South America	–
Utive virus (UVV)	ND	North America	–
Sathuperi virus			
Douglas virus (DOUV)		Australia	–
Sathuperi virus (SATV)	Mosquitoes/culicoid flies	Africa, Asia	–
Simbu virus			
Simbu virus (SIMV)	Mosquitoes/culicoid flies	Africa	–
Shamonda virus			
Peaton virus (PEAV)	Culicoid flies	Australia	–
Sango virus (SANV)	Mosquitoes/culicoid flies	Africa	–
Shamonda virus (SHAV)	Culicoid flies	Africa	–
Shuni virus			
Aino virus (ANOV)	Mosquitoes/culicoid flies	Asia, Australia	–
Kaikalur virus (KAIV)	Mosquitoes	Asia	–
Shuni virus (SHUV)	Mosquitoes/culicoid flies	Africa	–
Thimiri virus			
Thimiri virus (THIV)	ND	Africa, Asia	–
Iquitos virus (IQTV)[b]	ND	South America	Human
Jatobal virus (JATV)[b]	ND	South America	–
Schmallenberg virus (SBV)[b]	Culicoid flies	Europe	Cattle
Tete serogroup			
Batama virus			
Batama virus (BMAV)	ND	Africa	–
Tete virus			
Bahig virus (BAHV)	Ticks	Asia, Europe	–
Matruh virus (MTRV)	Ticks	Africa, Asia	–
Tete virus (TETEV)	ND	Africa	–
Tsuruse virus (TSUV)	ND	Asia	–
Weldona virus (WELV)	Culicoid flies	North America	–
Turlock serogroup			
M'Poko vius			
M'Poko virus (MPOV)	Mosquitoes	Africa	–
Yaba-1 virus (Y1V)	Mosquitoes	Africa	–

(continued)

Table 10.4 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease host
Turlock virus			
Lednice virus (LEDV)	Mosquitoes	Europe	–
Turlock virus (TURV)	Mosquitoes	North America, South America	–
Umbre virus (UMBV)	Mosquitoes	Asia	–
Wyemoyia serogroup			
Wyeomyia virus			
Anhembi virus (AMBV)	Mosquitoes	South America	–
BeAr 328208 virus (BAV)	Mosquitoes	South America	–
Cachoeira Porteira virus (CPOV)			
Iaco virus (IACOV)			
Macaua virus (MCAV)	Mosquitoes	South America	–
Sororoca virus (SORV)	Mosquitoes	South America	–
Taiassui virus (TAIAV)	Mosquitoes	South America	–
Tucunduba virus (TUCV)			
Wyeomyia virus (WYOV)	Mosquitoes	South America	Human
Ungrouped			
Bushbush virus			
Benfica virus	Mosquitoes	South America	–
Bushbush virus (BSBV)	Mosquitoes	South America	–
Juan Diaz virus (JDV)	ND	North America	–
Catu virus			
Catu virus (CATUV)	Mosquitoes	South America	Human
Estero Real virus			
Estero Real virus (ERV)	Ticks	North America	–
Guajara virus			
Guajara virus (GJAV)	Mosquitoes	North America, South America	–
Kaeng Khoi virus			
Kaeng Khoi virus (KKV)	Nest bugs	Asia	–
Manzanilla virus			
Buttonwillow virus (BUTV)	Culicoid flies	North America	–
Cat Que virus	Mosquitoes	Asia	–
Ingwavuma virus (INGV)	Mosquitoes	Africa, Asia	Pig
Inini virus (INIV)	ND	South America	–
Manzanilla virus (MANV)	ND	South America	–
Mermet virus (MERV)	Mosquitoes	North America	–
Timboteua virus			
Timboteua virus (TBTV)	Mosquitoes	South America	–
Zegla virus			
Zegla virus (ZEGV)	ND	North America	–

(continued)

Table 10.4 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease host
Unclassified			
Abbey Lake bunyavirus (Ab-BUNV)	Mosquitoes	Asia	–
Brazoran virus	Mosquitoes	North America	–
Enseada virus (ENSV)	Mosquitoes	South America	–
Khurdun virus (KHURV)	ND	Europe	–
Kowanyama virus (KOWV)	Mosquitoes	Australia	–
Mojuí dos Campos virus (MDCV)	ND	South America	–
Murrumbidgee virus (MURBV)	Mosquitoes	Australia	–
Salt Ash virus (SASHV)	Mosquitoes	Australia	–
Termeil virus (TERV)	Mosquitoes	Australia	–

ND not determined

[a] Includes Garissa virus

[b] It is currently unclear to which species these reassortant Simbu serogroup viruses belong

Fig. 10.3 *Aedes triseriatus*, commonly known as the "treehole mosquito," obtaining a blood meal from a human hand (courtesy of James Gathany, obtained from the Centers for Disease Control and Prevention (CDC) Public Health Image Library at http://phil.cdc.gov/phil/home.asp [accessed Feb 25, 2014])

transovarial transmission, which allows overwintering of the virus in mosquito eggs [23]. Squirrels, chipmunks, foxes, and woodchucks often serve as amplifying reservoir hosts [24]. Most cases of La Crosse encephalitis occur in the summer and early fall when risk of being bitten by infected mosquitoes is highest. The majority of cases occur in the Mississippi and Ohio River basins with over 90 % of cases reported from Wisconsin, Minnesota, Iowa, Indiana, Ohio, and Illinois; however, cases also occur throughout most of the eastern half of the USA (Fig. 10.4).

Oropouche virus (OROV) was first identified from Trinidad in 1955 [25] and was later isolated from the blood of a pale-throated sloth (*Bradypus tridactylus*) in 1960 [26]. Recently, OROV has become the second most frequent cause of arboviral infection in Brazil, surpassed only by dengue viruses [26]. OROV has been associated with large and explosive outbreaks of febrile disease in South and Central

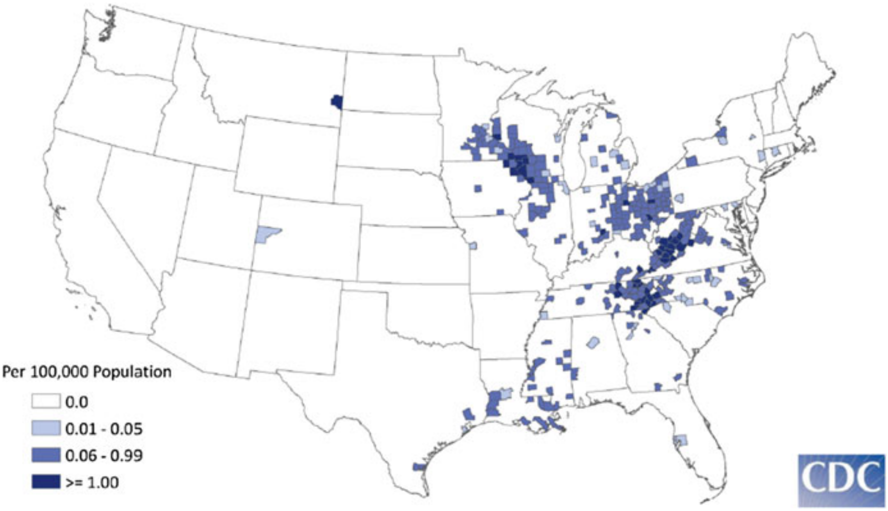

Fig. 10.4 Most reported cases of California serogroup virus neuroinvasive disease (encephalitides, meningoencephalitides, or meningitides) are due to La Crosse virus (LACV). Counties are *shaded* according to incidence ranging from less than 0.06, 0.06–0.99, and greater than 1.00 per 100,000. Most of the counties with the highest incidence are located along the Appalachian range and the upper Mississippi River basin (Obtained from the CDC website at http://www.cdc.gov/lac/tech/epi.html [accessed Feb 25, 2014])

America, especially in the Amazon Basin. More than half a million cases have been reported in the Americas [26]. In addition to outbreaks, OROV can also cause sporadic human infections [27]. OROV is transmitted to sloths, marsupials, primates, and birds by *Aedes serratus* and *Culex quinquefasciatus* mosquitoes. Notably, OROV has adapted to an urban cycle involving man, with biting midges (*Culicoides paraensis*) as the primary vector [28, 29].

In addition to human pathogens, the genus *Orthobunyavirus* also contains pathogens of significant veterinary importance. One example is the recently emerged Schmallenberg virus (SBV). In late 2011, a nonspecific febrile syndrome occurred in dairy cattle that was characterized by decreased milk production and watery diarrhea [30]. The affected farms were located along the German-Dutch boarder in North Rhine-Westphalia, near the city of Schmallenberg, Germany. Next-generation sequencing and metagenomic analysis was used to identify the novel orthobunyavirus from blood samples of deceased cows from a farm in Schmallenberg [30]. Since the first detection in Germany, SBV has spread rapidly over large parts of northern and western Europe (Fig. 10.5). In addition to the febrile syndrome initially described for the virus, transplacental infection often results in the birth of malformed calves, lambs, and goat kids [31, 32]. Based on similarities to other related viruses affecting livestock, researchers suspected that Schmallenberg virus was transmitted by biting midges (*Culicoides*). In fact, several studies have detected the virus in field-collected midges [33–36], and viral replication and dissemination in *C. sonorensis* midges

Fig. 10.5 Distribution of Schmallenberg virus by country in Europe as of February 2013 (courtesy of O. Smooth, obtained at http://en.wikipedia.org/wiki/Schmallenberg_virus [accessed Feb 27, 2014])

have been observed under laboratory conditions [37]. Interestingly, SBV appears to be a reassortant virus, with the M segment from Sathuperi virus and the S and L segments from Shamonda virus, both members of the Simbu serogroup of orthobunyaviruses [38].

6.2 Nairoviruses

The genus *Nairovirus* includes ≈50 predominantly tick-borne viruses in eight established and four proposed species [39, 40] (Table 10.5). The pathogenicity of many of these viruses is not known. However, two nairoviruses are known to be serious pathogens: Crimean-Congo hemorrhagic fever virus (CCHFV) and Nairobi sheep disease virus (NSDV). CCHFV causes severe hemorrhagic fever in humans, and NSDV causes severe gastroenteritis in sheep and goats. Case-fatality rates of infections with either virus can reach 90 % [41, 42]. CCHF is the most widespread tick-borne viral infection of humans, occurring across a vast area including western China through Southern Asia, the Middle East to southeastern Europe, and most of Africa [43]. CCHFV is

Table 10.5 Viruses in the genus *Nairovirus*

Virus species (in italics) and their member viruses	Original source	Year of description
“*Ahun virus*”[a]		
Ahun virus	Common pipistrelle (*Pipistrellus pipistrellus*), whiskered myotis (*Myotis mystacinus*)	2014
“*Artashat virus*”		
Artashat virus (ARTSV)	Ticks: *Ornithodoros alactagalis*	1972
Crimean-Congo hemorrhagic fever virus		
Crimean-Congo hemorrhagic fever virus (CCHFV)	Humans	1967
Hazara virus (HAZV)	Ticks: *Ixodes redikorzevi*	1970
Khasan virus (KHAV)	Ticks: *Haemaphysalis longicornis*	1978
Dera Ghazi Khan virus		
Abu Hammad virus (AHV)	Ticks: *Argas hermanni*	1971
Abu Mina virus (AMV)	Ticks: *Argas streptopelia*	1963
Dera Ghazi Khan virus (DGKV)	Ticks: *Hyalomma dromedarii*	1970
Kao Shuan virus (KSV)	Ticks: *Argas robertsi*	1970
Pathum Thani virus (PTHV)	Ticks: *Argas robertsi*	1970
Pretoria virus (PREV)	Ticks: *Argas africolumbae*	1973
Dugbe virus		
Dugbe virus (DUGV)	Ticks: *Amblyomma variegatum*	1970
Ganjam virus (GANV)[b]	Ticks: *Haemaphysalis intermedia*	1969
Kupe virus	Ticks: *Amblyomma gemma*, *Rhipicephalus pulchellus*	2009
Nairobi sheep disease virus (NSDV)	Domestic sheep	1910
Hughes virus		
Caspiy virus (CASV)[c]	Ticks: *Ornithodoros maritimus*	1970
Farallon virus (FARV)	Ticks: *Carios capensis*	1964
Fraser Point virus (FPV)	ND	ND
Great Saltee virus (GRSV)	Ticks: *Ornithodoros* maritimus	1976
Hughes virus (HUGV)	Ticks: *Ornithodoros capensis*	1962
Puffin Island virus (PIV)	Ticks: *Ornithodoros maritimus*	1979
Punta Salinas virus (PSV)	Ticks: *Ornithodoros* sp.	1967
Raza virus (RAZAV)	Ticks: *Carios denmarki*	1962
Sapphire II virus (SAPV)	Ticks: *Argas cooley*	ND
Soldado virus (SOLV)	Ticks: *Ornithodoros* sp.	1963
Zirqa virus (ZIRV)	Ticks: *Ornithodoros* sp.	1969
“*Issyk-kul virus*”		
Issyk-kul virus (ISKV)	Bats: noctule (*Nyctalus noctula*); ticks: *Argas* sp.	1973
Kasokero virus (KASV)	Bats: Egyptian rousettes (*Rousettus aegyptiacus*)	1986
Keterah virus (KTRV)	Bats: lesser Asiatic yellow house bat (*Scotophilus kuhli temminckii*)	1976

(continued)

Table 10.5 (continued)

Virus species (in italics) and their member viruses	Original source	Year of description
Yogue virus (YOGV)	Bats: Egyptian rousettes (*Rousettus aegyptiacus*)	1986
Qalyub virus		
Bakel virus (BAKV)	ND	ND
Bandia virus (BDAV)	Multimammate rat (*Mastomys* sp.)	1965
Chim virus (CHIMV)	Ticks: *Ornithodoros tartakovskyi*	1971
Omo virus (OMOV)	Multimammate rat (*Mastomys* sp.)	1971
Qalyub virus (QYBV)	Ticks: *Ornithodoros erraticus*	1952
Sakhalin virus		
Avalon virus (AVAV)[d]	Ticks: *Ixodes* uriae	1972
Clo Mor virus (CMV)	Ticks: *Ixodes* uriae	1973
Finch Creek virus	Ticks: *Ixodes uriae*	2009
Kachemak Bay virus (KBV)	Ticks: *Ixodes signatus*	1974
Sakhalin virus (SAKV)	Ticks: *Ixodes putus*	1970
Taggert virus (TAGB)	Ticks: *Ixodes* uriae	1972
Tillamook virus (TILLV)	Ticks: *Ixodes uriae*	1970
"*South Bay virus*"		
South Bay virus (SBV)	Ticks: *Ixodes scapularis*	2014
Tamdy virus		
Tamdy virus (TDY)	Ticks: *Hyalomma* sp.	1976
Thiafora virus		
Erve virus (ERVEV)	Greater white-toothed shrew (*Crocidura russula*)	1982
Thiafora virus (TFAV)	White-toothed shrew (*Crocidura* sp.)	1971

ND not determined

[a] Viruses in quotation marks represent proposed species

[b] Some consider GANV to be an Asian variant of NSDV

[c] Exact taxonomic position is currently unclear

[d] Also known as Paramushir virus (PRMV)

maintained through vertical and horizontal transmission in ixodid (hard) ticks of several genera, which spread the virus to a variety of wild and domestic mammals. Affected mammals develop transient viremia without signs of illness. Human infections occur through tick bite or exposure to the blood or other body fluids from infected animals or humans. Ticks of the genus *Hyalomma* (Fig. 10.6) are the principal source of human infection, probably because both the immature and the adult forms of the tick actively seek hosts for their obligate blood meals. Of note, during a recent viral metagenomics study, novel nairovirus sequences were detected in France in bats belonging to two different species [44]. These sequences diverge significantly from all known nairovirus genomes and thus represent a new nairovirus, Ahun virus, which will probably to be assigned to a novel species.

Fig. 10.6 *Hyalomma marginatum rufipes* tick, a known vector of Crimean-Congo hemorrhagic fever. This specimen was collected from Kenya and has the characteristic banded coloration pattern on the legs, typical of *Hyalomma* ticks (courtesy of Alan R. Walker, obtained at http://en.wikipedia.org/wiki/Ticks_of_domestic_animals [accessed Feb 26, 2014])

6.3 Hantaviruses

The *Hantavirus* genus contains 36 viruses classified into 24 species and an additional ≈67 unclassified viruses (Table 10.6). Unlike all other members of the family *Bunyaviridae*, hantaviruses are not arboviruses, but infect rodents, eulipotyphla (shrews and moles), and bats [45]. Human hantavirus infection is thought to occur following exposure to excretions from infected mammalian hosts. Researchers generally agree that hantaviruses have co-evolved with their hosts over the course of several hundreds of thousands to millions of years [46]. Phylogenetic trees visualize that most hantaviruses clearly group according to their mammalian hosts (Fig. 10.7) [47]. Rodent-borne hantaviruses form two basic lineages, Old World and New World, which primarily reflect the geographic distribution of their rodent hosts. Significant human pathogens among the Old World viruses include Hantaan, Seoul, Puumala, and Dobrava-Belgrade viruses, which cause HFRS. Hantaan virus, named after the Hantaan River in Korea, is the prototype hantavirus and was first isolated from the striped field mouse (*Apodemus agrarius*) in 1976 [48]. After this discovery, other related viruses were characterized and classified including Puumala virus from the bank vole (*Myodes glareolus*) [49], Seoul virus from brown and roof rats (*Rattus norvegicus* and *R. rattus*) [50], and Dobrava-Belgrade virus from the yellow-necked field mouse (*Apodemus flavicollis*) [51].

Hantaviruses were first recognized in the New World in 1982 (Prospect Hill virus) and then again in 1993 when Sin Nombre virus was identified as the causative agent of an outbreak of acute respiratory distress, today called hantavirus (cardio-) pulmonary syndrome (HCPS), in the Four Corners area of the US Southwest [52]. Sin Nombre virus (Fig. 10.8) was ultimately isolated from North American deermice (*Peromyscus maniculatus*), which were confirmed as the primary rodent reservoirs for this hantavirus [53]. Since the first detection of this Sin Nombre virus in

Table 10.6 Viruses in the genus *Hantavirus*

Virus species (in italics) and their member viruses	Host	Distribution	Disease in humans
Andes virus			
Andes virus (ANDV)	Argentine akodont (*Necromys benefactus*), long-tailed colilargo (*Oligoryzomys longicaudatus*)	South America	HCPS
Bermejo virus (BMJV)	Chacoan colilargo (*Oligoryzomys chacoensis*)	South America	HCPS
Lechiguanas virus (LECV)	Flavescent colilargo (*Oligoryzomys flavescens*)	South America	HCPS
Maciel virus (MCLV)	Dark-furred akodont (*Necromys obscurus*)	South America	HCPS
Orán virus (ORNV)	Long-tailed colilargo (*Oligoryzomys longicaudatus*)	South America	HCPS
Pergamino virus (PRGV)	Azara's akodont (*Akodon azarae*)	South America	HCPS
Tunari virus (TUNV)	Unknown	South America	HCPS
Bayou virus			
Bayou virus (BAYV)	Marsh oryzomys (*Oryzomys palustris*)	North America	HCPS
Black Creek Canal virus			
Black Creek Canal virus (BCCV)	Hispid cotton rat (*Sigmodon hispidus*)	North America	HCPS
Caño Delgadito virus			
Caño Delgadito virus (CADV)	Alston's cotton rat (*Sigmodon alstoni*)	South America	Unknown
Dobrava-Belgrade virus			
Dobrava-Belgrade virus (DOBV)	Yellow-necked field mouse (*Apodemus flavicollis*)	Europe	HFRS
Kurkino virus	Striped field mouse (*Apodemus agrarius*)	Europe	HFRS
Sochi virus	Caucasus field mouse (*Apodemus ponticus*)	Europe	HFRS
El Moro Canyon virus			
El Moro Canyon virus (ELMCV)	Sumichrast's harvest mouse (*Reithrodontomys sumichrasti*), western harvest mouse (*Reithrodontomys megalotis*)	North America	HCPS
Hantaan virus			
Amur/Soochong virus (AMRV/SOOV)	Korean field mouse (*Apodemus peninsulae*)	Asia	HFRS
Hantaan virus (HTNV)	Striped field mouse (*Apodemus agrarius*)	Asia	HFRS

(continued)

Table 10.6 (continued)

Virus species (in italics) and their member viruses	Host	Distribution	Disease in humans
Isla Vista virus			
Isla Vista virus (ISLAV)	Californian vole (*Microtus californicus*)	North America	Unknown
Khabarovsk virus			
Khabarovsk virus (KHAV)	Reed vole (*Microtus fortis*), Maximowicz's vole (*Microtus maximowiczii*)	Asia	Unknown
Laguna Negra virus			
Laguna Negra virus (LANV)	Big laucha (*Calomys callosus*), little laucha (*Calomys laucha*)	South America	HCPS
Muleshoe virus			
Muleshoe virus (MULV)	Hispid cotton rat (*Sigmodon hispidus*)	North America	HCPS
New York virus			
New York virus (NYV)	White-footed deermouse (*Peromyscus leucopus*)	North America	HCPS
Prospect Hill virus			
Bloodland Lake virus (BLLV)	Prairie vole (*Microtus ochrogaster*)	North America	Unknown
Prospect Hill virus (PHV)	Meadow vole (*Microtus pennsylvanicus*)	North America	Nonpathogenic[a]
Puumala virus			
Hokkaido virus (HOKV)	Gray red-backed vole (*Myodes rufocanus*)	Asia	Unknown
Muju virus (MUJV)	Korean red-backed vole (*Myodes regulus*)	Asia	HFRS
Puumala virus (PUUV)	Bank vole (*Myodes glareolus*), gray red-backed vole (*Myodes rufocanus*)	Europe	HFRS/HCPS
Río Mamoré virus			
Maripa virus	Unknown	South America	HCPS
Río Mamoré virus (RIOMV)	Small-eared colilargo (*Oligoryzomys microtis*)	South America	HCPS
Río Segundo virus			
Río Segundo virus (RIOSV)	Mexican harvest mouse (*Reithrodontomys mexicanus*)	North America	Unknown
Saaremaa virus			
Saaremaa virus (SSAV)	Striped field mouse (*Apodemus agrarius*)	Europe	HFRS

Seoul virus			
Seoul virus (SEOV)	Brown rat (*Rattus norvegicus*), Losea rat (*Rattus losea*), roof rat (*Rattus rattus*)	Worldwide[b]	HFRS
Sin Nombre virus			
Blue River virus (BRV)	White-footed deermouse (*Peromyscus leucopus*)	North America	HCPS
Monongahela virus (MGLV)	North American deermouse (*Peromyscus maniculatus*)	North America	HCPS
Sin Nombre virus (SNV)	North American deermouse (*Peromyscus maniculatus*)	North America	HCPS
Thailand virus			
Anjozorobe virus	Major's tufted-tailed rat (*Eliurus majori*), roof rat (*Rattus rattus*)	Africa	Unknown
Jurong virus	Oriental house rat (*Rattus tanezumi*)	Asia	Unknown
Serang virus (SERV)	Oriental house rat (*Rattus tanezumi*)	Asia	Unknown
Thailand virus (THAIV)	Greater bandicoot rat (*Bandicota indica*), Savile's bandicoot rat (*Bandicota savilei*)	Asia	Unknown
Thottapalayam virus			
Thottapalayam virus (TPMV)	Asian house shrew (*Suncus murinus*)	Asia	Nonpathogenic[c]
Topografov virus			
Topografov virus (TOPV)	Siberian brown lemming (*Lemmus sibiricus*)	Asia	Unknown
Tula virus			
Tula virus (TULV)	Common vole (*Microtus arvalis*), East European vole (*Microtus levis*), Eurasian water vole (*Arvicola amphibius*), field vole (*Microtus agrestis*)	Europe	HFRS/HCPS
Unclassified			
Altai virus (ALTV)	Common shrew (*Sorex araneus*)	Asia	Unknown
Alto Paraguay virus (ALPAV)	Chacoan marsh rat (*Holochilus chacarius*)	South America	Unknown
Anajatuba virus (ANJV)	Fornes' colilargo (*Oligoryzomys fornesi*)	South America	HCPS
Ape Aime virus (AAIV)	Montane akodont (*Akodon montensis*)	South America	Unknown
Araraquara virus (ARAV)	Hairy-tailed akodont (*Necromys lasiurus*)	South America	HCPS
Araucária virus (ARAUV)	Black-footed colilargo (*Oligoryzomys nigripes*)	South America	HCPS
Artybash/Amga virus (ARTV/MGAV)	Laxmann's shrew (*Sorex caecutiens*)	Asia, Europe	Unknown
Asama virus (ASAV)	Japanese shrew mole (*Urotrichus talpoides*)	Asia	Unknown

(continued)

Table 10.6 (continued)

Virus species (in italics) and their member viruses	Host	Distribution	Disease in humans
Ash River virus (ARRV)	Cinereus shrew (*Sorex cinereus*)	North America	Unknown
Asikkala virus (ASIV)	Eurasian pygmy shrew (*Sorex minutus*)	Europe	Unknown
Azagny virus (AZGV)	West African pygmy shrew (*Crocidura obscurior*)	Africa	Unknown
Boginia virus (BOGV)[d]	Eurasian water shrew (*Neomys fodiens*)	Europe	Unknown
Bowé virus (BOWV)	Doucet's musk shrew (*Crocidura douceti*)	Africa	Unknown
Calabazo virus	Short-tailed zygodont (*Zygodontomys brevicauda*)	North America	Unknown
Camp Riley virus (RPLV)	Northern short-tailed shrew (*Blarina brevicauda*)	North America	Unknown
Cao Bang virus (CBNV)[e]	Chinese mole shrew (*Anourosorex squamipes*)	Asia	Unknown
Carrizal virus (CARV)	Sumichrast's harvest mouse (*Reithrodontomys sumichrasti*)	North America	Unknown
Castelo dos Sonhos virus (CASV)	Brazilian colilargo (*Oligoryzomys eliurus*)	South America	HCPS
Catacamas virus (CATV)	Coues' oryzomys (*Oryzomys couesi*)	North America	Unknown
CGRn9415 virus[f]	Brown rat (*Rattus norvegicus*)	Asia	Unknown
Choclo virus (CHOV)	Fulvous colilargo (*Oligoryzomys fulvescens*)	North America	HCPS
Da Bie Shan virus (DBSV)	Confucian niviventer (*Niviventer confucianus*)	Asia	Unknown
Dahonggou Creek virus (DHCV)	Long-tailed mole (*Scaptonyx fusicaudus*)	Asia	Unknown
Gou virus (GOUV)	Brown rat (*Rattus norvegicus*), roof rat (*Rattus rattus*), Oriental house rat (*Rattus tanezumi*)	Asia	HFRS
Huangpi virus (HUPV)	Japanese pipistrelle (*Pipistrellus abramus*)	Asia	Unknown
Huitzilac virus (HUIV)	Western harvest mouse (*Reithrodontomys megalotis*)	North America	Unknown
Iamonia virus (AMNV)	Southern short-tailed shrew (*Blarina carolinensis*)	North America	Unknown
Imjin virus (MJNV)	Ussuri white-toothed shrew (*Crocidura lasiura*)	Asia	Unknown
Itapúa virus	Black-footed colilargo (*Oligoryzomys nigripes*)	South America	Unknown
Jaborá virus (JABV)	Montane akodont (*Akodon montensis*), Paraná akodont (*Akodon paranaensis*), Serra do Mar akodont (*Akodon serrensis*)	South America	Unknown
Jeju virus (JJUV)	Asian lesser white-toothed shrew (*Crocidura shantungensis*)	Asia	Unknown
Jemez Springs virus (JMSV)[g]	Dusky shrew (*Sorex monticolus*)	North America	Unknown

Juquitiba virus (JUQV)	Black-footed colilargo (*Oligoryzomys nigripes*), Fornes' colilargo (*Oligoryzomys fornesi*)	South America	HCPS
Kenkeme virus (KKMV)	Flat-skulled shrew (*Sorex roboratus*)	Asia	Unknown
Kilimanjaro virus (KMJV)	Kilimanjaro mouse shrew (*Myosorex zinki*)	Africa	Unknown
Lena River virus (LNAV)?	Laxmann's shrew (*Sorex caecutiens*)	Europe	Unknown
Limestone Canyon virus (LSCV)	Brush deermouse (*Peromyscus boylii*)	North America	Unknown
Longquan virus (LQUV)	Chinese Rufous horseshoe bat (*Rhinolophus sinicus*), Formosan lesser horseshoe bat (*Rhinolophus monoceros*), intermediate horseshoe bat (*Rhinolophus affinis*)	Asia	Unknown
Luxi virus (LUXV)	Yunnan red-backed vole (*Eothenomys miletus*)	Asia	Unknown
Magboi virus (MGBV)	Hairy slit-faced bat (*Nycteris hispida*)	Africa	Unknown
Makokou virus (MAKV)	Noack's roundleaf bat (*Hipposideros ruber*)	Africa	Unknown
Maporal virus (MAPV)	Fulvous colilargo (*Oligoryzomys fulvescens*)	South America	Unknown
Montano virus (MTNV)	Orizaba deermouse (*Peromyscus beatae*)	North America	Unknown
Mouyassué virus (MOYV)	Banana pipistrelle (*Neoromicia nanus*)	Africa	Unknown
Nova virus (NVAV)	European mole (*Talpa europaea*)	Europe	Unknown
Oxbow virus (OXBV)	American shrew mole (*Neurotrichus gibbsii*)	North America	Unknown
Paranoá virus	Unknown	South America	HCPS
Playa de Oro virus (OROV)	Coues' oryzomys (*Oryzomys couesi*)	North America	Unknown
Qian Hu Shan virus (QHSV)[h]	Stripe-backed shrew (*Sorex cylindricauda*)	Asia	Unknown
Rockport virus (RKPV)	Eastern mole (*Scalopus aquaticus*)	North America	Unknown
Sangassou virus (SANGV)	Allen's hylomyscus (*Hylomyscus alleni*)	Africa	Unknown
Sarufutsu virus (SFSV)	Long-clawed shrew (*Sorex unguiculatus*)	Asia	Unknown
Seewis virus (SWSV)	Common shrew (*Sorex araneus*), Eurasian pygmy shrew (*Sorex minutus*), Siberian large-toothed shrew (*Sorex daphaenodon*), tundra shrew (*Sorex tundrensis*)	Europe, Asia	Unknown
Tanganya virus (TGNV)	Therese's shrew (*Crocidura theresae*)	Africa	Unknown
Tatenale virus (TATV)	Field vole (*Microtus agrestis*)	Europe	Unknown

(continued)

Table 10.6 (continued)

Virus species (in italics) and their member viruses	Host	Distribution	Disease in humans
Tigray virus (TIGV)	White-footed stenocephalemys (*Stenocephalemys albipes*)	Africa	Unknown
Uluguru virus (ULUV)	Geata mouse shrew (*Myosorex geata*)	Africa	Unknown
Vladivostok virus (VLAV)	Reed vole (*Microtus fortis*)	Asia	Unknown
Xinyi virus (XYIV)	Taiwanese mole shrew (*Anourosorex yamashinai*)	Asia	Unknown
Xuan Son virus (XSV)	Pomona leaf-nosed bat (*Hipposideros pomona*)	Asia	Unknown
Yakeshi virus (YKSV)	Taiga shrew (*Sorex isodon*)	Asia	Unknown
Yuanjiang virus (YUJV)	Reed vole (*Microtus fortis*)	Asia	Unknown

HCPS hantavirus (cardio-)pulmonary syndrome, *HFRS* hemorrhagic fever with renal syndrome

[a] PHV is considered nonpathogenic to humans based on the lack of reported human cases, despite widespread distribution of the virus in indigenous rodents [135]

[b] SEOV has a worldwide distribution likely due to the spread of brown rats from Asia that follow humans [136]

[c] Data on specific cellular receptor usage of TPMV suggest that the virus is not pathogenic to humans [137]

[d] Includes strain “Laihi virus (LAIV)” found in Eurasian water shrews (*Neomys fodiens*)

[e] Also known as Lianghe virus (LHEV)

[f] Natural reassortant of HTNV and SEOV

[g] Includes the genotypes “Fox Creek virus (FXCV)” found in American water shrews (*Sorex palustris*), “Powell Butte virus (PWBV)” found in vagrant shrews (*Sorex vagrans*), and “Tualatin River virus (TLNV)” found in Trowbridge’s shrews (*Sorex trowbridgii*)

[h] Also known as Qiandao Lake (QDLV)

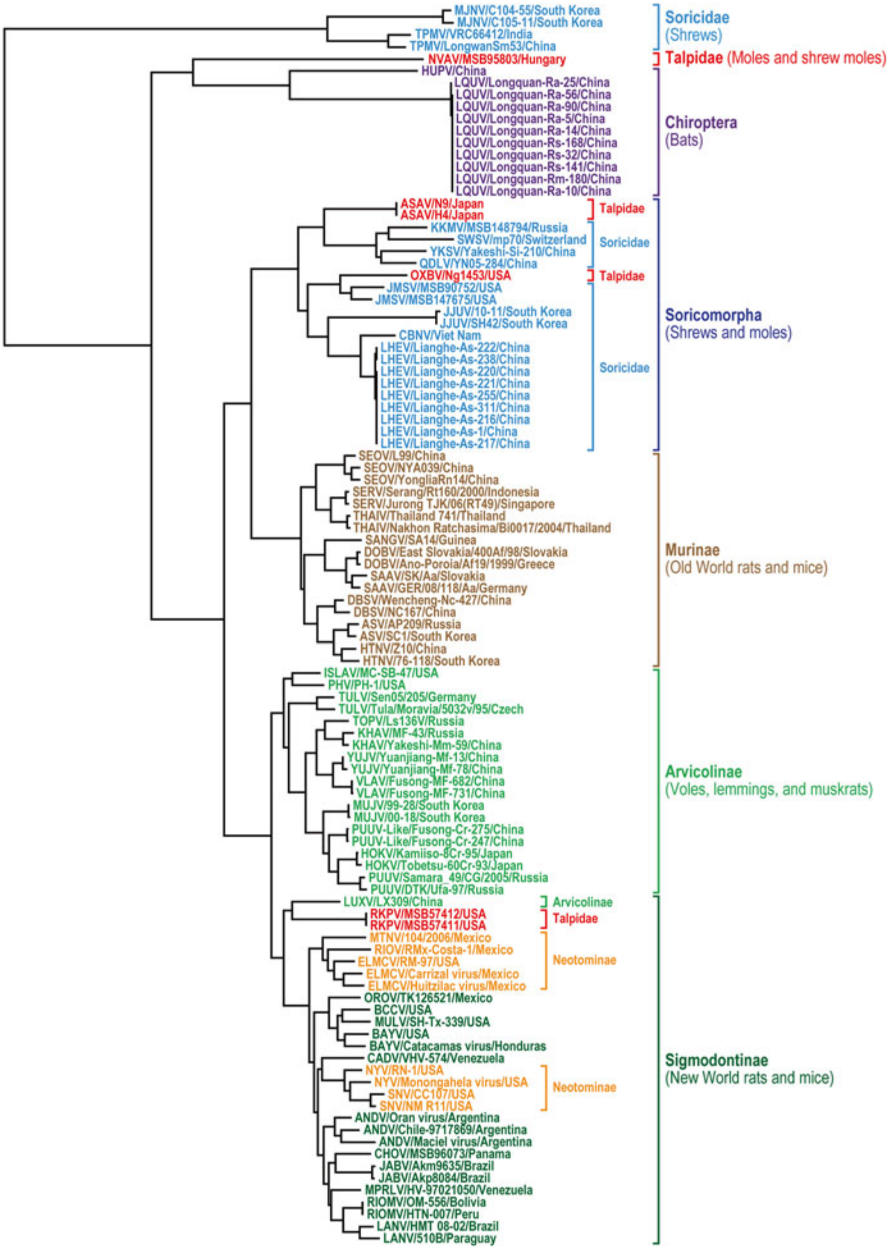

Fig. 10.7 Phylogenetic tree based on the coding sequence of the S segments of hantavirus genomes showing coevolution with their mammalian reservoir hosts. Image modified from Guo et al. [47]

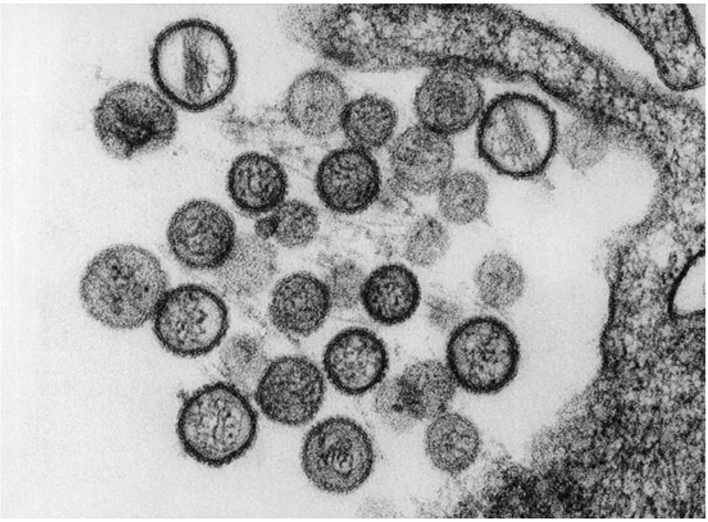

Fig. 10.8 Transmission electron micrograph showing the ultrastructure of virions of the hantavirus Sin Nombre virus (courtesy of CDC/Brian W.J. Mahy and Luanne H. Elliott, obtained from CDC's Public Health Image Library at http://phil.cdc.gov/phil/home.asp [accessed Feb 11, 2014])

the USA, numerous additional hantaviruses have been discovered throughout the Americas, some of which (e.g., Andes virus) are clearly pathogenic to humans and cause HCPS [54].

Thottapalayam virus was isolated from an Asian house shrew in India in 1964 [55], but was not classified as a hantavirus until 1989 [56]. Since 2006, at least 26 new hantaviruses have been identified from eulipotyphla [8, 57]. In addition, more recently, hantaviruses have been identified in bats from diverse geographic locations, including Africa [58, 59] and Asia [47, 60]. Until now, none of the non-rodent-borne hantaviruses has been associated with disease.

6.4 Phleboviruses

The genus *Phlebovirus* includes ≈24 species and ≈115 viruses (Table 10.7) that can be classified based on their antigenic similarities, arthropod vectors, and the presence of an open reading frame in M segments coding for a non-structural protein. Phleboviruses are transmitted by arthropod vectors, namely, sandflies, mosquitoes, biting midges of the *Culicoides* genus, or ticks [8]. Infection of the vector is frequently persistent and lifelong. Within the vectors, the viruses multiply and spread transovarially (i.e., vertical transmission) and venereally (i.e., horizontal transmission) [61–63]. Generally, phleboviruses are specific with regard to arthropod vectors and vertebrate hosts. However, some phleboviruses infect multiple vectors, with

Table 10.7 Viruses in the genus *Phlebovirus*

Virus species (in italics) and their member viruses	Vector	Distribution	Disease in humans
“*Aguacate virus*”[a]			
Aguacate virus (AGUV)	Sandflies	South America	–
Armero virus (ARMV)	Sandflies	South America	–
Durania virus (DURV)	Sandflies	South America	–
Ixcanal virus (IXCV)	Sandflies	South America	–
“*Bhanja virus*”			
Bhanja virus (BHAV)	Ticks	Eurasia, Africa	Encephalitis, febrile illness
Forécariah virus (FORV)	Ticks	Africa	–
Heartland virus (HRTV)	Ticks	North America	Febrile illness
Hunter Island group virus (HIGV)	Ticks	Australia	–
Kisemayo virus (KISV)	Ticks	Africa	–
Lone Star virus (LSV)	Ticks	North America	–
Malsoor virus	ND	Asia	–
Palma virus (PALV)	Ticks	Europe	–
Razdan virus (RAZV)	Ticks	Asia	–
Severe fever with thrombocytopenia virus (SFTSV)	Ticks	Asia	Febrile illness, hemorrhagic fever
Bujaru virus			
Bujaru virus (BUJV)	ND	South America	–
Munguba virus (MUNV)	Sandflies	South America	–
Candiru virus			
Alenquer virus (ALEV)	ND	South America	Febrile illness
Ariquemes virus (ARQV)	Sandflies	South America	–
Candiru virus (CDUV)	ND	South America	Febrile illness
E(s)charate virus (ESVC)	ND	South America	Febrile illness
Itaituba virus (ITAV)	ND	South America	–
Jacunda virus (JCNV)	ND	South America	–
Maldonado virus (MLOV)	ND	South America	Febrile illness
Morumbi virus (MRMBV)	ND	South America	Febrile illness
Mucura virus (MCRV)	Mosquitoes	South America	–
Nique virus (NIQV)	Sandflies	South America	–
Oriximiná virus (ORXV)	Sandflies	South America	–
Serra Norte virus (SRNV)	ND	South America	Febrile illness
Turuna virus (TUAV)	Sandflies	South America	–
Chilibre virus			
Cacao virus (CACV)	Sandflies	South America	–
Chilibre (CHIV)	Sandflies	South America	–
Frijoles virus			
Frijoles virus (FRIV)	Sandflies	South America	–
Joa virus (JOAV)	Sandflies	South America	–

(continued)

Table 10.7 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease in humans
“*Grand Arbaud virus*”			
Grand Arbaud virus (GAV)	Ticks	Europe	–
“*Icoaraci virus*”			
Belterra virus (BELTV)	ND	South America	–
Icoaraci virus (ICOV)	Mosquitoes, sandflies	South America	–
“*Karimabad virus*”			
Gabek Forest virus (GFV)	Sandflies	Africa	–
Karimabad virus	Sandflies	Asia	–
“*Manawa virus*”			
Manawa virus (MWAV)	Ticks	Asia	–
“*Murre virus*”			
Murre virus (MURV)	ND	North America	–
RML-105-105455 virus (RMLV)	Ticks	North America	–
Sunday Canyon virus	Ticks	North America	–
“*Precarious Point virus*”			
Catch-me-cave virus	Ticks	Australia	–
Precarious Point virus (PPV)	Ticks	Australia	–
“*Provencia virus*”			
Provencia virus	Sandflies	Europe	–
Punta Toro virus			
Buenaventura virus (BUEV)	Sandflies	South America	–
Punta Toro virus (PTV)	Sandflies	South America	Febrile illness
Rift Valley fever virus			
Rift Valley fever virus (RVFV)	Mosquitoes	Africa, Asia	Encephalitis, febrile illness, hemorrhagic fever
Salehabad virus			
Adria virus (ADRV)	Sandflies	Europe	–
Arbia virus (ARBV)	Sandflies	Europe	–
Arumowot virus (AMTV)	Mosquitoes	Africa	–
Odrenisrou virus (ODRV)	Mosquitoes	Africa	–
Olbia virus	Sandflies	Europe	–
Salehabad virus (SALV)	Sandflies	Asia	–
Sandfly fever Naples virus			
Fermo virus	Sandflies	Europe	–
Gordil virus	ND	Africa	–
Granada virus (GRV)	ND	Europe	–
Massila virus	Sandflies	Europe	–
Punique virus (PUNV)	Sandflies	Africa	–
Saint-Floris virus (SAFV)	ND	Africa	–
Sandfly fever Naples virus (SFNV)	Sandflies	Asia	Febrile illness

(continued)

Table 10.7 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease in humans
Tehran virus (THEV)	Sandflies	Asia	–
Toscana virus (TOSV)	Sandflies	Eurasia	Febrile illness, meningoencephalitis
“*Sandfly fever Sicilian virus*”			
Chagres virus (CHGV)	Sandflies	South America	Febrile illness
Chios virus	ND	Europe	Encephalitis
Corfou virus (CFUV)	Sandflies	Europe	–
Sandfly fever Cyprus virus	Sandflies	Eurasia	Febrile illness
Sandfly fever Sicilian virus (SFSV)	Sandflies	Eurasia	Febrile illness
Sandfly fever Turkey virus	Sandflies	Asia	Febrile illness
Uukuniemi virus			
Chizé virus (CHZV)	Ticks	Europe	–
EgAN 1825-61 virus	ND	Africa	–
Fin V 707 virus	Ticks	Europe	–
Khasan virus (KHAV)	Ticks	Asia	–
Oceanside virus (OCV)	Ticks	North America	–
Ponteves virus (PTVV)	Ticks	Europe	–
Rukutama virus (RUKV)	Ticks	Europe	–
St. Abbs Head virus (SAHV)	Ticks	Europe	–
Tunis virus (TUNV)	Ticks	Africa	–
Uukuniemi virus (UUKV)	Ticks	Eurasia	Febrile illness
Zaliv Terpenyia virus (ZTV)	Ticks	Eurasia	–
Unclassified			
Ambe virus (AMBEV)	Sandflies	South America	–
American dog tick phlebovirus (ADTPV)	Ticks	North America	–
Anhanga virus (ANHV)	ND	South America	–
Arboledas virus (ADSV)	Sandflies	South America	–
Blacklegged tick phlebovirus (BTPV)	Ticks	North America	–
Caimito virus (CAIV)	Sandflies	South America	–
Itaporanga virus (ITPV)	Mosquitoes	South America	–
Komandory virus (KOMV)	Ticks	Asia	–
Leticia virus (LTCV)	Sandflies	South America	–
Mariquita virus (MRQV)	Sandflies	South America	–
Morolillo virus (MOLV)	ND	South America	–
Otter fecal phlebovirus	ND	Eurasia	–
Pacui virus (PACV)	Sandflies	South America	–
Phasi Chaeron-like virus (PCLV)	Flies	Asia	–
Phasi Chaeron virus (PhaV)	Flies	Asia	–
Red fox fecal phlebovirus	ND	Eurasia	–
Rio Grande virus (RGV)	ND	South America	–

(continued)

Table 10.7 (continued)

Virus species (in italics) and their member viruses	Vector	Distribution	Disease in humans
Salanga virus	ND	Africa	–
Salobo virus (SBOV)	ND	South America	–
Tapara virus (TAPV)	Sandflies	South America	–
Uriurana virus (URIV)	Sandflies	South America	–
Urucuri virus (URUV)	ND	South America	–

ND not determined

[a]Viruses in quotation marks represent proposed species

Fig. 10.9 *Phlebotomus papatasi* sandfly, a known vector of sandfly fever Naples and sandfly fever Sicilian viruses, taking a blood meal (photo courtesy of CDC/James Gathany, obtained from CDC's Public Health Image Library at http://phil.cdc.gov/phil/home.asp [accessed March 18, 2014])

several distinct phleboviruses using the same vectors. This multivirus infection provides considerable opportunity for reassortment of the genome segments and therefore results in the evolution of new viruses. The vertebrate hosts or reservoirs of most phleboviruses have not been characterized to date. However, the role of the amplifying hosts might be minimal or secondary in regard to the horizontal amplification of the viruses in vectors [64].

Phleboviruses occupy broad geographic and ecologic niches, defined by the distribution, host competency, and biological behavior of their vectors. Phleboviruses are endemic in Europe, Africa, Central Asia, and the Americas, and have even been found on a subantarctic island [65, 66]. There is considerable evidence that phlebovirus habitats, especially for sandfly-borne viruses and Rift Valley fever virus, are expanding, possibly due to climate change and thereby changing ranges of vectors [64, 67].

Sandfly-borne phleboviruses are transmitted by the sandflies in the family *Psychodidae*, which are present in the warm zones of Asia, Africa, Australia, Southern Europe, and the Americas [68]. In the Old World (Figs. 10.9 and 10.10), the most important human pathogens are sandfly fever Sicilian virus (SFSV), sandfly fever Naples virus (SFNV), and Toscana virus (TOSV), all of which are

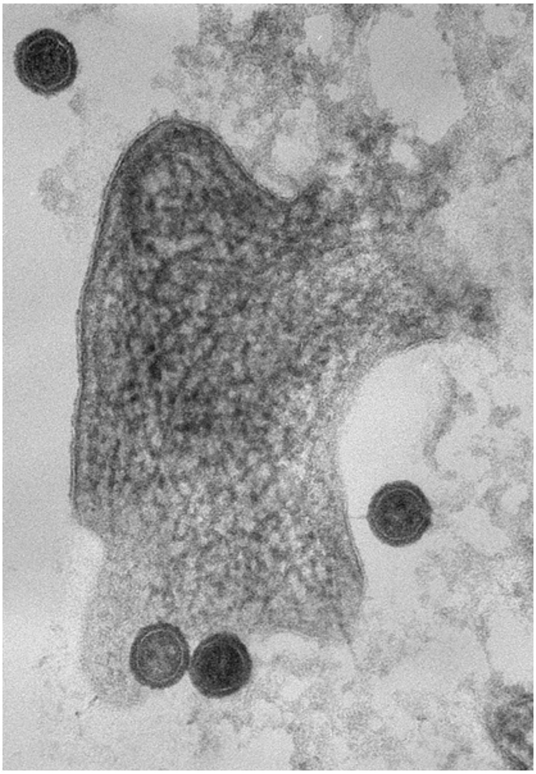

Fig. 10.10 Transmission electron micrograph of virions of the phlebovirus sandfly fever Turkey virus (50,000× magnification, courtesy of Dr. Stefan Frey, Bundeswehr Institute of Microbiology, Munich, Germany)

transmitted by *Phlebotomus* sandflies and cause febrile disease [64]. The risk for phlebovirus exposure via sandflies is high in populations residing in regions south and east of the Mediterranean Sea [64]. Little is known about the epidemiology of sandfly-borne phleboviruses of the New World that are transmitted by *Lutzomyia* sandflies. Several viruses, such as Alenquer, Candiru, Chagres, E(s)charate, Morumbi, Punta Toro, and Serra Norte viruses, were isolated from humans with clinical febrile disease in Brazil, Panama, Columbia, Peru, and regions of northern South America. The phleboviral diseases of tropical America are probably associated with rodents living in forests that may act as amplifying hosts [69, 70].

Transmission of sandfly-borne phleboviruses to susceptible humans and animals occurs during the blood meal of female sandflies, which are the primary reservoirs for these viruses [64, 65]. Vertical and horizontal transmissions, demonstrated experimentally and in natural habitats, are contributing mechanisms that assure long-term maintenance of phleboviruses in these vectors [71]; however, the exact role and efficiency of these mechanisms in the transmission cycles of various phleboviruses have not been fully explored. Researchers generally agree that humans or other large vertebrates are dead-end hosts that do not participate in the natural virus transmission cycle. Horizontal transmission among infected vertebrates does not occur. Toscana virus was isolated from a Kuhl's pipistrelle (*Pipistrellus kuhli*) in Italy [72], but the role of bats in virus circulation remains clear. Direct aerosol or parenteral transmission of sandfly-borne phleboviruses has not been demonstrated.

Rift Valley fever virus (RVFV) is the best characterized mosquito-borne phlebovirus. RVFV is the causative agent of Rift Valley fever (RVF), an acute disease of domestic ruminants characterized by deaths of newborn animals and abortion in pregnant sheep, goats, and cattle. RVF was initially described in British Kenya in 1931 [73]. The disease is endemic in sub-Saharan Africa and has caused major outbreaks in several African countries including Egypt, Kenya, Madagascar, Mauritania, Tanzania, Senegal, Somalia, South Africa, and Sudan [74, 75]. The largest human epidemic occurred in Egypt in 1977–1978, when there were an estimated 200,000 human infections, with some 18,000 cases of illness and 600 deaths. In 2000, an outbreak occurred in Saudi Arabia and Yemen, the first outbreak occurring outside of Africa. This outbreak raises concern that the disease could spread further into Asia or Europe, or even to the Western Hemisphere where susceptible mosquitoes may be present [76, 77]. In its enzootic regions, RVFV persists in the environment through vertical transmission in mosquitoes and horizontal transmission by mosquitoes among domestic and wild herbivores, including cattle, buffalo, sheep, and goats. The principal hosts for RVFV have not been identified but presumably involve native ungulates and rodents [76, 78]. Bats can also be infected experimentally [79]. RVFV may replicate in a number of potential vectors, including ticks and a variety of flies [80–82]. However, various mosquitoes, including *Aedes* and *Culex* mosquitoes, are the main arthropod vectors in the natural environment [77]. RVFV is transmitted to vertebrates by the bites of infected mosquitoes or by direct contact with infected tissues, blood, body fluids, and fomites, particularly if associated with abortions. Aborted materials and placental membranes contain high numbers of virions, which can either contaminate the local environment or infect animals or humans in close contact. In vitro experiments have described the relatively long-term persistence of RVFV in the environment [77, 83]. Because of this persistence and the potential for aerosol transmission, biosafety level 3/4 laboratory conditions are recommended for handling the virus. Due to habitat expansion of competent vectors, increases in live animal trade, and impact of climatic and environmental changes, the risk of an introduction of RVFV into naive zones and preparedness for a probable emergence have been considered by several national and international agencies [77, 84].

Tick-borne phleboviruses [8] are transmitted via competent hematophagous hard (ixodid) or soft (argasid) ticks to various warm-blooded vertebrates [51]. Uukuniemi virus (UUKV) is the prototype tick-borne phlebovirus in the Old World and was originally isolated from a pool of *Ixodes ricinus* ticks collected in southern Finland [85]. Subsequently, UUKV was detected in Scandinavia and central and Eastern Europe and from Azerbaijan in Central Asia. Vertebrate hosts for UUKV are forest rodents (e.g., bank voles) and ground-feeding passerine birds [86]. Serological surveys suggest that humans have been exposed to UUKV without serious consequences. In fact, other than UUKV, which has been associated with a self-limiting acute febrile disease in individuals from southern Russia, no human illness has been reported with the other Uukuniemi group viruses [86, 87].

Bhanja virus (BHAV) is another tick-borne phlebovirus that was initially isolated from *Haemaphysalis intermedia* ticks collected from a paralyzed goat in India. BHAV has subsequently been isolated in Europe and Africa from ticks of several other species, domestic animals, and humans, and has been associated with febrile disease in domestic animals (sheep, goats, and cows) and meningoencephalitis in humans [86].

Novel tick-borne phleboviruses causing disease in humans have recently emerged in China and the USA. These include severe fever with thrombocytopenia syndrome virus (SFTSV; also known as Huaiyangshan virus or Henan fever virus) and Heartland virus [88–91]. SFTSV causes a severe and potentially fatal febrile illness with thrombocytopenia and hemorrhagic manifestations. SFTSV mainly occurs in the rural areas of eastern, central, and northeastern China, but SFTSV has also been reported from South Korea and Japan [92]. SFTSV has been detected in *Haemaphysalis longicornis* and *Rhipicephalus microplus* ticks collected in the endemic region of China [93]. A wide range of animals, including sheep, goats, cattle, pigs, dogs, chickens, and rodents have tested positive for antibodies against SFTSV [94]. Incidence of livestock infection was significantly higher than the incidence in poultry, humans, and rats, suggesting livestock might serve as amplifying hosts in human transmission. Heartland virus (HRTV) has been associated with human cases of severe febrile illness with thrombocytopenia after tick exposure in the central USA [88]. Ticks are implicated as potential vectors, as the virus was recently detected in field-collected *Amblyomma americanum* ticks [95]. Preliminary investigations also suggest exposure to HRTV or an antigenically similar virus in cattle, sheep, goats, deer, and elk [96]. Genetically, Bhanja group virus and its close relatives form a clade distinct from those of SFTSV/HRTV and UUKV.

7 Clinical Features of Human and Animal *Bunyaviridae* Infections

7.1 *Orthobunyaviruses*

At least 36 orthobunyaviruses have been associated with human disease (Table 10.4), causing a range of syndromes such as febrile illnesses, encephalitides, or hemorrhagic fevers. California serogroup viruses are important causes of disease among humans in the USA. For example, La Crosse virus (LACV) is a common cause of arboviral encephalitis in children in the midwestern USA, whereas Jamestown Canyon virus commonly causes encephalitis in adults [97]. The onset of illness is usually sudden and characterized by fever, headache, malaise, nausea, and vomiting. Within a few days, these signs and symptoms are accompanied by meningeal signs and lethargy. In severe forms, the disease may progress to seizures (approximately 50 %) and coma (about 10 %) [97]. The case-fatality rate is approximately 1 % or less, and the total duration of the illness rarely exceeds 2 weeks [97]. Most infected individuals do not experience neurologic sequelae. Other orthobunyaviruses (e.g., Cache Valley virus) cause abortion or teratogenic effects in pregnant livestock.

7.2 Nairoviruses

Crimean-Congo hemorrhagic fever virus (CCHFV) is the most important of the nairoviruses in terms of human disease [42, 43]. CCHFV infection can result in a severe hemorrhagic syndrome with a 5–30 % case-fatality rate. The course of the disease is divided into four phases: incubation period, prehemorrhagic phase, hemorrhagic phase, and convalescent phase. The length of the incubation period appears to depend in part on the mode of acquisition of virus. Following a tick bite, the incubation period ranges from 1 to 5 days, whereas it is usually 5–7 days (maximum 13 days) following contact with infected blood or tissues [98]. The prehemorrhagic phase begins as a sudden and nonspecific prodrome that is characterized by fever, myalgia, arthralgia, and lower back and abdominal pain [98]. In patients who progress to hemorrhagic signs, the start of the hemorrhagic phase is abrupt and begins approximately 3–6 days following the onset of signs and symptoms. Bleeding occurs at various sites, including the brain and respiratory, gastrointestinal, and urogenital tracts. At this phase, the most common manifestation is a petechial rash of the skin, conjunctivae, and other mucous membranes, which progresses to large cutaneous ecchymoses. In those patients who succumb to infection, death occurs approximately 6–10 days after the first signs and symptoms from irreversible shock (e.g., loss of blood pressure, elevated levels of proinflammatory cytokines, and disseminated intravascular coagulation) [98, 99]. In patients who survive CCHF, full recovery may take up to a year [98].

7.3 Hantaviruses

Hantavirus infections are associated with two clinical disorders in humans: HFRS and HCPS. HFRS is associated with Old World viruses (e.g., Hantaan, Seoul, Dobrava, and Puumala viruses), whereas, HCPS is associated with New World viruses (e.g., Sin Nombre and Andes viruses) (Table 10.6). In general, the severity of HFRS varies with the causative agent. HFRS caused by Hantaan and Dobrava viruses are more severe, while disease caused by Seoul virus is more moderate and disease caused by Puumala virus is mild ("nephropathia epidemica"). Hantaan virus-associated HFRS, which first came to the attention of western physicians during the Korean War, is among the most severe forms of HFRS, resulting in a case-fatality rate of 5–15 % [100]. Classically, the clinical course of HFRS occurs in five distinct phases. First, a febrile phase consists of headache, high fever, and chills. A hypotensive phase then follows during which blood platelet numbers drop and petechial hemorrhage can be observed. Abdominal pain and tachycardia are also observed during this stage. An oliguric phase may occur next in which decreased urine production, proteinuria and may progress to kidney failure. Urine production is then increased in the diuretic phase, which can last for months before the patient enters the convalescent phase and recovery [101].

In contrast, HCPS is a severe acute disease associated with a rapid onset of respiratory failure and cardiogenic shock [102]. HCPS bears some resemblance to HFRS except that the lungs are targeted for capillary leakage, instead of the kidneys [101]. As with HFRS, the clinical presentation and case-fatality rate depends on the etiological hantavirus [101]. The onset of HCPS in the Americas is generally characterized by nonspecific symptoms such as fever, myalgia, cough, gastrointestinal symptoms, chills, and headache. HCPS evolves rapidly (1–3 days) to a lung capillary leak syndrome, resulting in respiratory distress, followed by respiratory failure and then cardiogenic shock. These clinical signs are responsible for the majority of deaths (case-fatality rate up to 50 %) [100].

Although in general the Old World hantaviruses target the kidneys (resulting in HFRS) and New World hantaviruses target the lungs and heart (resulting in HCPS), this distinction is far from absolute. Indeed, controversy exists among hantavirologists whether the terms HFRS and HCPS should be abandoned in favor of the more generic single designation, “hantavirus fever” [103]. In the last few years, cases of hantavirus infection with divergent symptomatology have been reported. For example, cases of Puumala virus infection with pulmonary involvement were observed in Europe, and acute renal failure has been recognized in patients infected with New World hantaviruses [104, 105]. Similarly, in a recent study in China, investigators examined the clinical characteristics and outcome of 48 patients with HFRS who also had acute respiratory distress syndrome [106]. Patients in this study were in critical condition, with 21 succumbing to the disease (43.8 % case-fatality rate).

7.4 Phleboviruses

The best-known clinical condition associated with phleboviruses is a febrile illness known as sandfly fever (also known as phlebotomus, papatacci, or 3-day fever in the Old World). Sandfly fever is prevalent in the countries in the Mediterranean Basin, Northern Africa, and parts of Central, Western, and Southern Asia [65]. Cases and outbreaks of sandfly fever still occur in non-immune individuals in endemic regions [107, 108]. Sandfly fever has also been described as an important travel-related infection, and several cases of imported sandfly fever have been reported in patients following visits to endemic regions [107, 109]. Sandfly fever is characterized by high fever, headache, retroorbital pain, photophobia, generalized aches, malaise, and chills. Abdominal pain, discomfort, diarrhea, or constipation may also occur. The duration of fever is usually 2–4 days, but may be extended in some cases. Following the febrile stage, the affected patients frequently suffer from fatigue and weakness. Convalescence may require a few days to several weeks and can be incapacitating. The prognosis is favorable without any complications, sequelae, or lethality. In infected individuals, viral replication is controlled by the immune response. The immunity to sandfly fever phleboviruses is specific to the virus, and neutralizing antibodies produced during exposure are sufficient to suppress the occurence of symptoms upon rechallenge with homotypic agent [110, 111]. In the Old World, phleboviruses responsible for sandfly fever are sandfly fever Sicilian virus (SFSV) and sandfly fever Naples Virus (SFNV) [64, 110]. Regional SFSV variants, sandfly fever Cyprus virus (SFCV) and sandfly fever Turkey virus (SFTV), are also associated with the clinical picture of sandfly fever similar to that caused by SFSV and SFNV, but induce more prominent gastrointestinal symptoms, including elevation of hepatic enzymes and thrombocytopenia, with a more emphasized post-infectious asthenic syndrome [112–114]. In the New World, primarily Alenquer, Chagres, Candiru, and Punta Toro viruses have been detected in individuals with febrile diseases [61, 70]. Tick-borne Uukuniemi virus has also been identified in a limited number of cases of acute illness characterized by fever, headache, muscle and joint pain, facial hyperemia, and body rash [86, 87].

Toscana virus (TOSV), another sandfly-borne phlebovirus, transmitted by the bites of *Phlebotomus perniciosus* and *P. perfiliewi* sandflies, is a significant human pathogen due to its distinct neurotropism, causing central nervous system infections in endemic regions around the Mediterranean Sea [115]. TOSV has been pinpointed as a major agent of seasonal aseptic meningitis or meningoencephalitis, especially occurring during spring-summer months when the activity of vectors increase. TOSV infection is also a travel-associated infection in individuals leaving endemic regions [115]. Similar to the other phleboviral infections, the majority of the TOSV exposures result in an asymptomatic seroconversion or subclinical infection. Clinical manifestations in symptomatic TOSV infections are frequently characterized by high fever, severe headache, myalgia, and neurological symptoms of cortical and/or meningeal involvement from which patients generally recover within 7–10 days [64, 110, 115]. Central nervous system involvement in most cases is associated with a favorable outcome, but severe and lethal infections have also been reported [116]. Moreover, a variety of clinical signs and symptoms including hydrocephalus, impaired speech, paresis, hearing loss, diffuse intravascular coagulation, myositis-fasciitis, and testicular manifestations have also been reported [116–120].

RVF is the clinical manifestation of infection with the mosquito-borne RVFV, affecting ruminant animals and humans. Outbreaks of RVF in ruminants are often recognized initially as an abortion storm in herds of pregnant animals. Sheep are the most susceptible mammals, while cattle, goats, and camels demonstrate variations in susceptibility. Forty to 100 % of pregnant RVFV-infected sheep abort, and the fetuses often have malformations [76]. Newborn lambs suffer from an acute disease, characterized by necrotic hepatitis with 95–100 % lethality. Some breeds of adult sheep also exhibit hemorrhagic signs, similar to those seen in humans. In humans, exposure to RVFV frequently remains asymptomatic. In those with clinical signs, the disease presents with an influenza-like febrile disease without complications. However, severe manifestations such as hepatitis, retinitis, encephalitis, and hemorrhagic disease have been observed in a small number of cases with RVF, with the overall case-fatality rate estimated to be between 0.5 and 2 % [77, 121].

Severe fever with thrombocytopenia syndrome (SFTS) is a recently described human clinical disease caused by the emerging tick-borne phlebovirus SFTSV [90]. The disease is characterized by high fever, fatigue, anorexia, vomiting, and diarrhea, as well as laboratory findings of thrombocytopenia, leukocytopenia, and elevation of certain serum enzymes, including alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, and creatine kinase. The symptoms of SFTS frequently resolve after a week. However, in some cases, the patient's condition progresses to multiorgan dysfunction, disseminated intravascular coagulation, shock, and/or acute respiratory distress syndrome, with neurologic and hemorrhagic manifestations [122, 123]. Case-fatality rates as high as 30 % have been reported [124]. HRTV infections present similar to SFTS. However, the prognosis is favorable, with no respiratory or kidney involvement or coagulation abnormalities [88].

8 General Features of Plant-Infecting Tospoviruses

Currently, 11 species are included in the genus *Tospovirus*, each of which has one member virus. Many other tospoviruses have yet to be classified into species (Table 10.8) [8]. Thrips of numerous species (Fig. 10.11) of the genera *Frankliniella*, *Thrips*, *Scirtothrips*, and *Ceratothripoides* have been reported to transmit tospoviruses to a wide variety of plant species [8]. Transmission can also occur by mechanical means via infected plant sap. Tomato spotted wilt virus (TSWV) is the prototype tospovirus, and, contrary to its name, has a broad host range with susceptible plants belonging to more than 925 species of 70 botanical families [8]. Spotted wilt disease of tomato was first described in 1915 in Australia. The disease was later shown to be transmitted by thrips and caused by TSWV in 1930 [125]. The worldwide dispersal in the 1980s of the western flower thrip (*Frankliniella occidentalis*), a major vector of TSWV, led to a reemergence of the disease. By 1994, worldwide losses of tomato were estimated to be in excess of US $1 billion annually [126]. In addition to tomatoes, other economically important plants affected by TSWV include peppers, lettuce, peanuts, and chrysanthemums [127]. Tospoviruses cause variable signs, including necrotic or chlorotic rings and flecking on leaves, stems and fruits, with early infections leading to one-sided growth, drooping or deformed leaves, wilting, stunting, and death [127] (Fig. 10.12). Late in TSWV infection, tomatoes produce unmarketable fruit with necrotic ringspots that often appear only when the fruit reaches full color (Fig. 10.13).

Molecular and structural studies, mostly performed on TSWV, have shown many similarities with animal-infecting bunyaviruses, including particle morphology, genomic organization, and replication and transcription cycles [128]. The presence of an envelope membrane is relatively unique among plant viruses, and is only found on tospovirions and plant-adapted rhabdovirions [128]. In contrast to the many similarities tospoviruses have with animal-infecting bunyaviruses, some interesting differences reflect tospovirus adaptation to plants. Unlike all other bunyaviruses, the NSm protein of tospoviruses is translated using a genomic ambi-

Table 10.8 Viruses in the genus *Tospovirus*

Virus species Member viruses	Vector	Distribution
Groundnut bud necrosis virus		
Groundnut bud necrosis virus (GBNV)[a]	Thrips: *Frankliniella schultzei*, *Scirtothrips dorsalis*,*Thrips palmi*	Asia
Groundnut ringspot virus		
Groundnut ringspot virus (GRSV)	Thrips: *Frankliniella gemina*, *Frankliniella intonsa*, *Frankliniella occidentalis*, *Frankliniella schultzei*	Africa, North America, South America
Groundnut yellow spot virus		
Groundnut yellow spot virus (GYSV)[b]	Thrips: *Scirtothrips dorsalis*	Asia
Impatiens necrotic spot virus		
Impatiens necrotic spot virus (INSV)	Thrips: *Frankliniella fusca*, *Frankliniella intonsa*, *Frankliniella occidentalis*, *Frankliniella schultzei*	Africa, Asia, Australia, Europe, North America, South America
Polygonum ringspot virus		
Polygonum ringspot virus (PolRSV)	Thrips: *Dictyothrips betae*	Europe
Tomato chlorotic spot virus		
Tomato chlorotic spot virus (TCSV)	Thrips: *Frankliniella intonsa*, *Frankliniella occidentalis*, *Frankliniella schultzei*	Puerto Rico, South America
Tomato spotted wilt virus		
Tomato spotted wilt virus (TSWV)	Thrips: *Frankliniella bispinosa*, *Frankliniella cephalica*, *Frankliniella fusca*, *Frankliniella gemina*, *Frankliniella intonsa*, *Frankliniella occidentalis*, *Frankliniella schultzei*, *Thrips palmi, Thrips setosus*, *Thrips tabaci*	Africa, Asia, Australia, Europe, North America, South America
Watermelon silver mottle virus		
Watermelon silver mottle virus (WSMoV)	Thrips: *Thrips palmi*	Asia
Zucchini lethal chlorosis virus		
Zucchini lethal chlorosis virus (ZLCV)	Thrips: *Frankliniella zucchini*	South America
Unclassified		
Alstroemeria necrotic streak virus (ANSV)	Thrips: *Frankliniella occidentalis*	South America
Bean necrotic mosaic virus (BeNMV)	ND	Central America, South America
Calla lily chlorotic spot virus (CCSV)	Thrips: *Thrips palmi*	Asia
Capsicum chlorosis virus (CaCV)[c]	Thrips: *Ceratothripoides claratris*, *Frankliniella schultzei*, *Thrips palmi*	Asia, Australia
Chrysanthemum stem necrosis virus (CSNV)	Thrips: *Frankliniella gemina*, *Frankliniella occidentalis*, *Frankliniella schultzei*	Asia, Europe, South America

(continued)

Table 10.8 (continued)

Virus species Member viruses	Vector	Distribution
Hippeastrum chlorotic ringspot virus (HCRV)	ND	Asia
Iris yellow spot virus (IYSV)	Thrips: *Frankliniella fusca*, *Thrips tabaci*	Africa, Asia, Australia, Europe, Hawaii, North America, South America,
Lisianthus necrotic ringspot virus (LNRV)	ND	Asia
Melon severe mosaic virus (MeSMV)	ND	North America, South America
Melon yellow spot virus (MYSV)[d]	Thrips: *Thrips palmi*	Asia
Mulberry vein banding virus (MuVBV)	ND	Asia
Peanut chlorotic fan-spot virus (PCFV)[e]	Thrips: *Scirtothrips dorsalis*	Asia, South America
Pepper necrotic spot virus (PNSV)[f]	ND	South America
Soybean vein necrosis-associated virus (SVNaV)	ND	North America
Tomato necrotic ringspot virus (TNRV)	Thrips: *Ceratothripoides claratris*, *Thrips palmi*	Thailand
Tomato yellow (fruit) ring virus (TYRV)	Thrips: *Thrips tabaci*	Asia, Africa
Tomato zonate spot virus (TZSV)	Thrips: *Frankliniella occidentalis*, *Thrips palmi*, *Thrips tabaci*	Asia
Watermelon bud necrosis virus (WBNV)	*Thrips palmi*	Asia

ND not determined

[a] Also known as peanut bud necrosis virus (PDNV)

[b] Also known as peanut yellow spot virus (PYSV)

[c] Also known as Gloxinia tospovirus, tomato necrosis virus (TNRV), or Thailand tomato tospovirus

[d] Also known as Physalis severe mottle virus (PhysSMV)

[e] Also known as groundnut chlorotic fan-spot virus (GCFSV)

[f] Also known as pepper Peruvian necrotic virus

sense strategy [129] (Fig. 10.2). Also, the NSm protein of tospoviruses is the only NSm in the family for which a well-defined function is known. Unlike the animal-infecting bunyaviruses, tospovirus particles accumulate in large vesicles within the cell and are not secreted from plant cells. Spread of the viruses to neighboring plants only occurs after larval-stage thrips have acquired the virus after feeding on infected plants [130]. After a latency period, thrips can transmit the tospovirus during the adult stage. Furthermore, due to the presence of a rigid cell wall in plants, plant viruses can only spread to neighboring cells through channels connecting the plant

Fig. 10.11 A thrip on a person's finger. Thrips are small insects with a distinctive cigar-shaped body. They are the primary vectors of plant diseases caused by tospoviruses (courtesy of OpenCage, obtained at http://en.wikipedia.org/wiki/Thrips [accessed March 18, 2014])

Fig. 10.12 Pepper plant infected with tomato spotted wilt virus showing the initial development of necrotic spots on the leaves (courtesy of Carlos Gonzalez, obtained at http://en.wikipedia.org/wiki/Tospovirus [accessed March 18, 2014])

Fig. 10.13 Tomato infected with tomato spotted wilt virus showing the development of necrotic ringspots on the fruit (obtained at http://en.wikipedia.org/wiki/Tospovirus [accessed March 18, 2014])

cells called plasmodesmata. As TSWV and most other plant viruses have a diameter of 80–120 nm, these virus cannot pass through the plasmodesmata that have a diameter in the range of only 5 nm. Thus, to facilitate movement, many plant viruses have adapted and encode cell-to-cell movement proteins (MPs) that modify plasmodesmata to allow passage of macromolecules, including virions [131]. The NSm protein of TSWV has been identified as the cell-to-cell MP that allows virus to move between plant cells [132–134].

9 Unclassified Bunyaviruses

At least 28 viruses, mostly isolated from mosquitoes or ticks and with unknown pathogenic potential for humans, are possible bunyaviruses, but currently remain unclassified (Table 10.9).

Table 10.9 Unclassified Bunyaviruses

Virus	Host	Distribution	Disease in humans
Antequera virus (ANTV)	Mosquitoes	South America	Unknown
Bangui virus (BGIV)	Humans?	Africa	Fever/rash
Barranqueras virus (BQSV)	Mosquitoes	South America	Unknown
Belem virus (BLMV)	Birds	South America	Unknown
Belmont virus (BELV)	Mosquitoes	Australia	Unknown
Bobaya virus (BOBV)	Birds	Africa	Unknown
Caddo Canyon virus (CDCV)	Ticks	North America	Unknown
Chim virus (CHIMV)	Ticks	Asia	Unknown
Cumutu virus (CUMV)	Mosquitoes	North America	Unknown
Gan Gan virus (GGV)	Mosquitoes	Australia	Arthritis/rash
Gouléako virus (GOLV)	Mosquitoes	Africa	Unknown
Herbert virus (HEBV)	Mosquitoes	Africa	Unknown
Hissar virus	Ticks	Asia	Unknown
Kaisodi virus (KSOV)	Ticks	Asia	Unknown
KF298274 virus	Mosquitoes	Europe	Unknown
Kibale virus (KIBV)	Mosquitoes	Africa	Unknown
Kigluaik phantom virus (KIGV)	Biting midges	North America	Unknown
Lanjan virus (LJNV)	Ticks	Asia	Unknown
Mapputta virus (MAPV)	Mosquitoes	Australia	Unknown
Maprik virus (MPKV)	Mosquitoes	Australia	Unknown
Nome phantom virus (NOMV)	Biting midges	North America	Unknown
Okola virus (OKOV)	Mosquitoes	Africa	Unknown
Pacora virus (PCAV)	Mosquitoes	North America	Unknown
Para virus (PARAV)	Mosquitoes	South America	Unknown
Resistencia virus (RTAV)	Mosquitoes	South America	Unknown

(continued)

Table 10.9 (continued)

Virus	Host	Distribution	Disease in humans
Santarem virus (STMV)	Mosquitoes	South America	Unknown
Silverwater virus (SILV)	Ticks	North America	Unknown
Sunday Canyon virus (SCAV)	Ticks	North America	Unknown
Taï virus (TAIV)	Mosquitoes	Africa	Unknown
Tanga virus (TANV)	Mosquitoes	Africa	Unknown
Tataguine virus (TATV)	Mosquitoes, humans	Africa	Febrile illness
Trubanaman virus (TRUV)	Mosquitoes	Australia	Arthritis/rash
Wanowrie virus (WANV)	Ticks, humans	Asia	Unknown
Witwatersrand virus (WITV)	Mosquitoes	Africa	Unknown
Yacaaba virus (YAVC)	Mosquitoes	Australia	Unknown

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