Bunyaviruses

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Abstract

The family Bunyaviridae, the most numerous family of RNA viruses, was established in 1975. In these days, it is integrated by more than 350 worldwide viral species, grouped into five genera: *Orthobunyavirus*; *Hantavirus*; *Nairovirus*; *Phlebovirus*, which infect vertebrates; and *Tospovirus* which are viruses that infect plants. From these four genera that infect vertebrates, only *Hantavirus* is not considered an arthropod-borne virus (arbovirus). *Orthobunyavirus* is the largest one, including 48 viral species, which in turn have different variants and strains. This family includes important viral pathogens, which cause diseases of veterinary and human concern such as Rift Valley fever (*Phlebovirus*), Akabane (*Orthobunyavirus*) and Nairobi sheep disease (*Nairovirus*), Oropouche (*Orthobunyavirus*), and Crimean-Congo hemorrhagic fever (*Nairovirus*). Many bunyaviruses are considered emergent, since they have increased their influence in new populations and geographic areas around the world. Examples of this are the viruses Crimean-Congo hemorrhagic fever and Rift Valley fever that emerged in parts of Europe due to the migration of their vectors possibly under the influence of climate change. The study of these emerging viruses is of great importance, whereas they have no preventive treatments and/or therapy, and it is necessary to know deeply its behavior in order to implement efficient control measures. This chapter deals aspects of molecular and cellular biology, cycle of transmission, ecological and epidemiological aspects, pathogenesis, clinical aspects, and diagnosis of the major bunyavirus species of medical and veterinary concern in different regions of the world.

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10.1 Introduction

The family Bunyaviridae was established in 1975 to cover a large number of arthropod-borne viruses that share morphological, morphometric, and antigenic features (Schmaljohn and Nichol 2006). The family name derives from Bwamba (Uganda, South Africa), where it was isolated for the first time from mosquito *Aedes* sp., Bunyamwera virus (BUNV), the prototype virus of the family (Monath and Heinz 1996). The classification of members of this family has historically relied on genetic, structural, and antigenic relationships between different viruses.

Currently, this family comprises 97 viral species distributed worldwide and is grouped into five genera: *Orthobunyavirus*, *Nairovirus*, *Phlebovirus*, *Hantavirus*, and *Tospovirus* (Table 10.1) (Plyusnin et al. 2012). The first four genera infect animals, whereas the latter infects many plant species (Plyusnin et al. 2012). The different members of these families exhibit diverse modes of transmission; however, within each family, they are similar. Members of the genera *Orthobunyavirus*, *Phlebovirus*, and *Nairovirus* are transmitted by arthropods (mosquitoes, ticks, sand flies, and biting midges) and kept in a vector-vertebrate cycle (Plyusnin et al. 2012).

Members of this family are widely distributed in the world and have public health importance because of their pathogenicity for both humans and domestic and wild animals (Table 10.2).

10.2 Virus Structure

Bunyavirus are enveloped viruses with a helical and oval or spherical capsid of 80–120 nm of diameter. The envelope consists of a lipid bilayer of 5–7 nm in which two viral glycoproteins called Gn and Gc are embedded. These glycoproteins are heterodimers that extend across the surface forming projections or spikes of 5–10 nm in length, which can be observed by electron microscopy (Fig. 10.1). The chemical composition is about 2 % RNA, 58 % protein, 33 % lipid, and 7 % carbohydrate, varying among species. Treatment with lipid solvents or nonionic detergents removes lipid envelope resulting in loss of infectivity of these viruses (Schmaljohn and Nichol 2006).

10.2.1 Viral Genome

The genome consists of single-stranded RNA of negative polarity divided into three segments called small (S), medium (M), and large (L), reflecting the relative length of nucleotides (Fig. 10.1) (Schmaljohn and Nichol 2006).

Genetic organization of the segments is similar in all genera, each one possessing non-translated

Table 10.1 Bunyaviridae family taxonomy

Genus	Viral species	Virus prototype	Geographical distribution	Vector/host
Orthobunyavirus	48	Bunyamwera	Africa, America, Asia, Australia, Europe	Mosquitoes, *Culicoides*
Phlebovirus	9	Fiebre del Valle de Rift	Africa, America, Asia, Europe	Sand flies, mosquitoes, ticks
Nairovirus	7	Hemorrhagic fever de Crimean-Congo	Africa, America, Asia, Europe	*Culicoides*, ticks, mosquitoes, flies
Hantavirus	24	Hantaan	Africa, America, Asia, Europe	Rodents
Tospovirus	9	Marchitez manchada del tomate	Africa, America, Asia, Europe	Thrips

Table 10.2 Medical and veterinary importance of viral species of *Orthobunyavirus*, *Phlebovirus*, and *Nairovirus* genera

Genus	Viral species	Geographical distribution	Vector	Disease	Affects to
Orthobunyavirus	Akabane	Africa, Asia, Australia	Mosquitoes	Congenital malformations, abort	Animals
	Aino	Africa, Asia, Australia	*Culicoides*, mosquitoes	Congenital malformations, abort	Animals
	Bunyamwera	Africa, America	Mosquitoes	Febrile syndrome, nervous syndrome, Congenital malformations, abort	Animals, human
	Bwamba	Africa	Mosquitoes	Febrile syndrome	Human
	California encephalitis	America, Asia	Mosquitoes	Nervous syndrome	Human
	Caraparu	America	Mosquitoes	Febrile syndrome	Human
	Guaroa	Central America and South America	Mosquitoes	Febrile syndrome	Human
	Inkoo	Europe, Asia	Mosquitoes	Nervous syndrome	Human
	Ilesha	Africa	Mosquitoes	Febrile syndrome, nervous syndrome	Human
	Kairi	America	Mosquitoes	Febrile syndrome	Animals
	Jamestown Canyon	North America	Mosquitoes	Nervous syndrome	Human
	La Crosse	North America	Mosquitoes	Nervous syndrome	Human
	Madrid	America	Mosquitoes	Febrile syndrome	Human
	Main Drain	America	*Culicoides*, mosquitoes	Congenital malformations, febrile syndrome	Animals
	Marituba	America	Mosquitoes	Febrile syndrome	Human
	Oriboca	America	Mosquitoes	Febrile syndrome	Human
	Oropouche	Central America and South America	*Culicoides*, mosquitoes	Febrile syndrome	Human
	Schmallenberg	Europe	*Culicoides*, mosquitoes	Congenital malformations, abort	Animal
	Tahyna	Africa, Asia, Europe	Mosquitoes	Febrile syndrome	Human
	Wyeomyia	Central America and South America	Mosquitoes	Febrile syndrome	Human
Phlebovirus	Candiru	South America	Sand flies	Febrile syndrome	Human
	Punta Toro	South America	Sand flies	Febrile syndrome	Human
	Rift Valley fever	Africa, Asia	Mosquitoes	Febrile syndrome	Human
	Sandfly fever virus	Asia, Europe	Sand flies	Febrile syndrome	Human
Nairovirus	Crimean-Congo hemorrhagic fever	Africa, Asia, Europe	Ticks	Hemorrhagic fever	Human
	Nairobi sheep disease	Africa, Asia	Ticks	Hemorrhagic disease	Human

regions (NTRs) located at the terminal 5′ and 3′ ends surrounding a single transcription unit. These NTRs are highly conserved within each genus and have specific sequences in their terminal ends, which are involved in RNA synthesis and packaging. The viruses within each genus in this family have segments of similar lengths and a common strategy for the general expression of their products (Schmaljohn and Nichol 2006).

Viruses belonging to *Orthobunyavirus*, *Hantavirus*, and *Nairovirus* genera have shown genetic reassortment, which may occur in cells

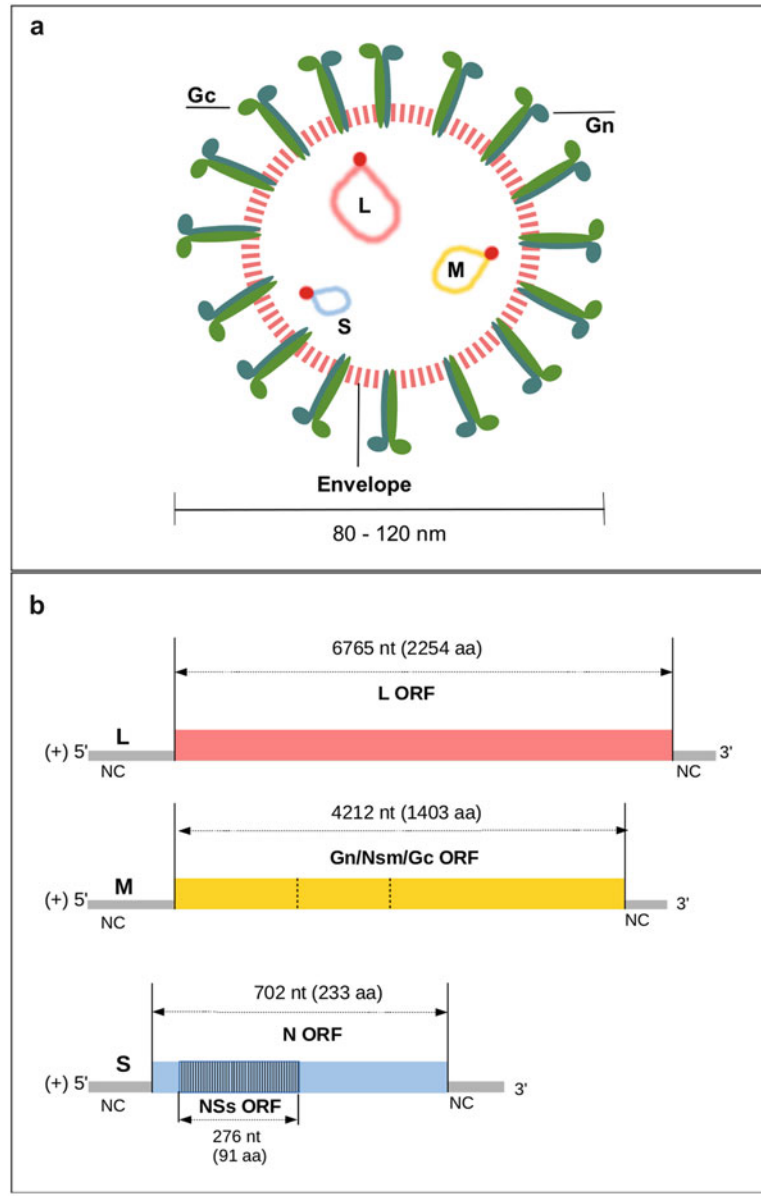

Fig. 10.1 Schematic representation of a virion (**a**) and genomic RNAs (**b**) belonging to prototypic members of family Bunyaviridae

with dual infection by related viruses (same genus) (Reese et al. 2008). Two viruses replicate in the same cell, where the segments of the genome can be rearranged and to be packaged into the virion. For example, in regions where two genotypes of La Crosse virus (LCV) are circulating, a third genotype containing genome segments from the other two genotypes was detected (Reese et al. 2008).

10.2.2 Viral Proteins

The replication strategy varies among genera, being in the negative sense in *Orthobunyavirus*, *Nairovirus*, and *Hantavirus* and ambisense in *Phlebovirus* (Schmaljohn and Nichol 2006).

The S segment encodes the N (nucleocapsid) protein. Its main role is to encapsidate the viral RNA replication products to form ribonucleoprotein

complexes. Moreover, this segment encodes a nonstructural protein called NSs in the most of orthobunyaviruses and phleboviruses. Its primary role is to modulate the antiviral response of the host cell. In orthobunyaviruses, the N and NSs proteins are translated from the same messenger RNA (mRNA) encoded by the S segment; however, in phleboviruses, these proteins are translated from different mRNA transcripts (Schmaljohn and Nichol 2006).

The M segment encodes two envelope glycoproteins called Gn and Gc. They are involved in the virus attachment to the cell and the fusion of the viral and cellular membrane. Some viruses from *Orthobunyavirus* and *Phlebovirus* genera encode a third protein, NSm. Its function is unclear and varies with the virus; for example, in orthobunyaviruses, NSm participates in the assembly of viral particles, while in phleboviruses, it would be involved in the regulation of apoptosis (Schmaljohn and Nichol 2006).

Finally, the L segment encodes a single protein called L or RNA-dependent RNA polymerase (RdRp) using a negative-sense transcription-translation strategy. This protein has a weight of 200 KDa and functions as viral transcriptase (Schmaljohn and Nichol 2006).

10.2.3 Viral Replication

As in most of RNA viruses, in bunyaviruses, the replication process takes place in the cytoplasm of the host cell. The first step is the attachment of the virus to the cell surface, a process that is mediated by the Gn and Gc glycoproteins and cellular receptors (Schmaljohn and Hooper 2001). The function of these two glycoproteins varies among viruses of the same genus, and for some of these viruses, the union to mammalian cells is mediated by Gc, whereas in mosquito cells, it is mediated by Gn, although in some cases also by Gc. Furthermore, the Gn glycoprotein has been associated with the ability of the bunyaviruses (excepting *Hantavirus*) to produce high viral loads in peripheral circulation. It has also been associated with their ability to invade nervous tissue. The host cell receptors involved in this step are unknown for most of bunyaviruses. However, evidence suggests that members of the integrin (in hantaviruses) and lectins (in phleboviruses) families are incriminated. In a second step, the virion enters into the target cell by endocytosis, and as a result, it is enclosed into an endosome. It is believed that acidification of the endosome induces a conformational change in Gn and Gc proteins facilitating fusion of viral and cell membranes. This produces the emergence of viral genome into the cytoplasm, where the L protein expressed by the viral genome acts as polymerase (Schmaljohn and Hooper 2001).

The primary transcription of the mRNA from viral RNA (vRNA) of negative polarity (mold) occurs in the cytoplasm. This process is mediated by the viral polymerase and the N protein; the latter protein is involved in the initiation of transcription. The next step is the translation of mRNA into the necessary structural and nonstructural proteins for viral replication; in the case of L and S segments, the translation is performed in free ribosome, whereas in the M segment, it occurs in ribosomes attached to the membrane of the rough endoplasmic reticulum (Schmaljohn and Hooper 2001).

Then the viral replication process takes place, which is mediated by the viral polymerase. Right after that, the process of morphogenesis and maturation of viral particle assembly occurs in the Golgi apparatus. Virions are packed in vesicles from the Golgi apparatus and are released through exocytosis mechanism from the cells as new mature viral particles (Schmaljohn and Hooper 2001).

Differences in the replication process were observed between vertebrate and invertebrate host cells, particularly in mosquitoes. Apparently, some processes associated with transcription regulation of the viral genome into mRNA are tightly controlled by the mosquito ovary metabolism. These processes allow a very effective transovarian transmission, thereby generating an infected progeny (Schmaljohn and Hooper 2001).

10.3 Clinical Manifestations

Most of infections by members of this family in humans and in domestic and wild animals are asymptomatic; however, there are some bunyaviruses that produce various kinds of pathologies

(Beaty and Calisher 1991). Clinical manifestations are diverse and include febrile syndrome, affection of the nervous system (encephalitis, meningitis), hemorrhagic fever, congenital malformations, abortions, and death (Table 10.2) (Beaty and Calisher 1991; Pinheiro et al. 1981). The most common symptoms in the bunyavirus (BUNV, Oropouche virus (OROV), Rift Valley fever virus (RVFV)) are the febrile syndrome. It usually starts suddenly and acutely with high fever, headache, myalgia, retro-orbital pain, nausea, vomiting, and anorexia. Symptoms usually persist for 3–5 days, and in the most severe cases between 7 and 10 days, normally without sequelae. CNS infection is caused by viruses like BUNV, LCV, and California encephalitis virus (CEV) with the most common being encephalitis. The beginning is dominated by symptoms like high fever, holocranial headache, fatigue, stiff neck and followed by myalgia, nausea, vomiting, weakness, and conjunctival congestion. Then, the neurological manifestations characterized by mental confusion, meningeal irritation, motor problems and reflexes, and brain injuries appear. The most severe forms evolve to coma and death. In some cases, neurological sequelae such as paresthesias, motor incoordination, balance problems, visual, olfactory and/or hearing, and memory loss occur. On the other hand, some viruses act as teratogens, producing different birth defects during gestation, such as arthrogryposis, scoliosis, torticollis, hydranencephaly, hydrocephalus, porencephaly, microcephaly, and cerebral and muscular hyperplasia. This is very common in ruminants caused by BUNV, AKAV, and AINV infections but also has been observed in humans caused by BUNV.

10.4 Bunyaviruses of Public Health Concern

10.4.1 *Orthobunyavirus*

This is the largest genus of the Bunyaviridae family and consists of 48 viral species with their strains/isolates distributed worldwide (Table 10.2) (Plyusnin et al. 2012). The delimitation of each virus within each genus is quite difficult because of the little or null virus or strain biochemical and molecular characterization (Schmaljohn and Nichol 2006). Based on serological criteria (FC, NT, and IHA), most of these viruses have been placed in 18 serogroups; however, some viral species are not included in any of them (Schmaljohn and Nichol 2006).

The 18 serogroups are Anopheles A, Anopheles B, Bakau, Bunyamwera, Bwamba, group C, California, Gamboa, Guama, Koongol, Minattian, Nyando, Olifantsvlei, Potosi, Simbu, Tete, Turlock, and Wyeomyia (Schmaljohn and Nichol 2006). Within each serogroup, the antigenic relationships between different members vary greatly, and one reason is the occurrence of natural reassortments among them. Therefore, different viruses within each serogroup may be more or less related to the others and to members of other serogroups, depending on the serological technique used for the study.

The main vectors of orthobunyaviruses are mosquitoes of the genera *Culex* and *Ochlerotatus*; small mammals and birds are regarded as possible vertebrate hosts. Humans and domestic mammals in general are dead-end hosts. Humans serve as host for the maintenance of orthobunyaviruses only in very few cases (i.e., OROV) (Soldano and González-Scarano 2005).

10.4.2 Bunyamwera Serogroup

10.4.2.1 Bunyamwera Virus (BUNV)

BUNV was originally isolated from *Aedes*[1] sp. in Uganda (Africa) in 1943 during a yellow fever virus (YFV) outbreak (Smithbum et al. 1946). Subsequently, it was also recovered from humans with febrile syndrome (Uganda, Nigeria, and South Africa) and hemorrhagic fever (Somalia and Kenya). It is widely distributed across sub-Saharan Africa and is an important etiological

[1]Although several taxonomic modifications have been proposed on Culicidae genera, mostly splitting *Aedes* by Reinert et al. (2009) (and accepted by CBM), this taxonomy has been used in the chapters according to authors' preference. To facilitate utilization by health personnel, all new aedine genera can be considered *Aedes* (CBM).

agent of acute febrile syndrome and CNS pathologies in humans. High prevalence of neutralizing antibodies (NTAb) (>82 %) in humans was detected in some regions (Smithbum et al. 1946). This virus was also isolated from various mosquito *Aedes* species, so it is believed to be the primary vector in nature (Smithbum et al. 1946). Moreover, NTAb against BUNV has also been detected in domestic animals, monkeys, rodents, and birds. Although laboratory inoculations showed that rodents, bats, and primates develop enough viremia to infect mosquito, whether any of these would meet the requirements to be considered a host in nature is unknown (Smithbum et al. 1946).

In the Americas, the first *Orthobunyavirus* isolated closely related to BUNV is the Cache Valley virus (CVV), recovered from *Culiseta inornata* (USA, 1956) (Holden and Hess 1959). Currently, according to the classification of the International Committee on Taxonomy of Viruses, CVV is considered a strain or an isolate of BUNV (Plyusnin et al. 2012). This virus is endemic to Canada, the USA, Mexico, and Argentina.

Several strains have been recovered from different species of mosquitoes of the genera *Anopheles*, *Culex*, *Culiseta*, *Ochlerotatus*, and *Psorophora* in Argentina, Brazil, Colombia, Ecuador, Mexico, Panama, and the USA (Plyusnin et al. 2012). Neutralizing antibodies against this virus have been detected in humans, domestic animals (cows, horses, goats, and sheep), and wildlife (moose, deer, caribou, hares, birds, and mice) across all America (McConnell et al. 1987; McLean et al. 1987).

BUNV is considered the causative agent of neural pathologies (encephalitis, meningitis, and febrile syndrome) and CNS defects in humans (Campbell et al. 2006; Mangiafico et al. 1988; Sexton et al. 1997). The first record of infection by BUNV was detected in a human with febrile syndrome in Brazil (1980). Later, in Panama (1985), another strain was recovered from a soldier who had a clinical presentation of malaise, fever, muscle pain, and throat; the patient recovered perfectly after 10 days without apparent sequelae (Mangiafico et al. 1988). In the USA, BUNV was isolated from three severe human cases; two were fatal meningitis and encephalitis (Sexton et al. 1997; Campbell et al. 2006). In Argentina (2009), a fever case was confirmed as a BUNV infection by serology. Interestingly, this case was presumptively diagnosed as dengue fever virus (Tauro et al. 2012). Finally, various seroepidemiological studies suggest that BUNV could be the etiologic agent of congenital malformations in humans, because a correlation was established between the occurrence of malformations in newborns and detection of NTAb against this virus in their mothers (Edwards 1993).

In the USA, BUNV was found associated with the occurrence of febrile and neurologic disease in domestic and wild animals. The subclinical infections result in most of the cases. Clinical manifestations can range from short periods of malaise, fever, loss of appetite, and lack of mobility to encephalitis. Congenital malformations in animals that become infected when being pregnant were also reported (Edwards 1993).

The association between infection with BUNV and the occurrence of congenital malformations were studied for the first time in Texas, USA (1987). Several BUNV strains were isolated during a congenital malformation outbreak in sheep. The observed malformations included CNS and skeletal muscle, such as arthrogryposis, scoliosis, torticollis, hydranencephaly, hydrocephalus, porencephaly, microcephaly, and cerebral and muscular hyperplasia. A high percentage of abortions were also recorded. Neutralizing antibodies were detected in 100 % of sheep with malformed offspring (Chung et al. 1991; McConnell et al. 1987; McLean et al. 1987). Experimental inoculations in sheep have revealed that the teratogenic effect of the virus depends on the stage of pregnancy in which maternal infection occurs. Thus, if infection occurs between 28 and 36 days, the CNS and skeletal muscle occur defects; however, if it occurs between days 37 and 42, it is evident only in the skeletal muscle. Infection after 50 days of pregnancy does not cause injury, and after 76 days, the fetus is immunocompetent and produces antibodies (Chung et al. 1991).

During the 1950s and 1960s, two strains were recovered from equine encephalitis cases in Guyana and Colombia; in Argentina, two new

BUNV strains were isolated from equine encephalitis and one from equine abortion in 2013 (Santamartin et al. 1973; Spence and Downs 1968; Tauro et al. 2013).

There are no vaccines or treatments to protect animals from BUNV infection. One of the possible solutions is to make reproductive crosses outside the period of greatest activity of vectors, thus reducing the risk of infection during pregnancy. However, in places where winter is moderate or there are unexpected weather changes, vector activity can be extended, increasing the risk of infection.

10.4.2.2 Kairi Virus (KRIV)

KRIV is a virus exclusively found in the Americas. It was first isolated in 1955 from *Oc. scapularis* mosquitoes collected in Trinidad (Anderson et al. 1961). KRIV was later recovered in the Amazon region from *Oc. scapularis* mosquitoes and monkeys. In Mexico (Yucatan Peninsula), a strain of KRIV was isolated from mosquitoes *Oc. taeniorhynchus* during a study conducted in 2007; this is the most current isolation of this virus and the only record of activity of KRIV in North America.

In Argentina, this virus was isolated from *Ochlerotatus* sp. mosquito (Córdoba province) in 1966 (Sabattini et al. 1998). KRIV NTAb has been detected in humans, domestic animals (cows, horses, goats, and sheep) and wildlife (birds and rodents) in different provinces. Later, in 1974, another strain was recovered from febrile horses from the province of Buenos Aires. NTAb were detected in 67.6 % of cohabiting horses. However, since horses infected with Western equine encephalitis virus also occurred in the same area simultaneously, it is difficult to attribute the observed febrile syndrome to KRIV infection (Calisher and Shape 1998).

Serological cross-reactions were observed between KRIV and BUNV. Therefore, it is essential to include both viruses in differential diagnosis and serological surveillance. There are no vaccines currently available against KRIV.

10.4.2.3 Main Drain Virus (MDV)

This virus is limited to North America and was first isolated in California from the biting midge *Culicoides variipennis* (Schmaljohn and Nichol 2006). It was also recovered from the brain of an equine that presented incoordination and ataxia, stiff neck, inability to swallow, fever, and tachycardia. In nature, MDV is maintained through transmission between this *Culicoides* vector and rabbits and rodents as hosts (Schmaljohn and Nichol 2006). Experimental studies in sheep during early gestation showed the teratogenic potential of this virus (Edwards et al. 1997). As for the rest of the viruses belonging to this serogroup currently, there are no vaccines on the market.

10.4.2.4 Ilesha Virus (ILEV)

ILEV was isolated for the first time from a 9-year-old girl with fever and rash in the town of Ilesa, West of Nigeria in 1957 (Okuno 1961). Later, different strains were recovered from patients mostly with fever and erythema in Central and Eastern Africa; there was also a case of meningoencephalitis reported in the Central African Republic and a case of hemorrhagic fever in Madagascar (Morvan et al. 1994). The main vector of ILEV is *Anopheles gambiae*, which was recovered in the Central African Republic (Digoutte et al. 1980). Serological studies in Nigeria detected high prevalence of infection in humans (children and adults) and domestic animals (cattle and goats).

10.4.3 Simbu Serogroup

10.4.3.1 Oropouche Virus (OROV)

OROV was first isolated from a rural worker in Trinidad in 1955 (Anderson et al. 1961). This virus is associated with several major epidemics of febrile illness in the Amazon region of Brazil and Peru and in Panama. The high prevalence of antibodies detected in inhabitants of forest and rural regions of Amazon region suggests an endemic circulation of this virus. In terms of geographic distribution, the activity of OROV has been documented in Argentina, Brazil, Panama, and Peru (Pinheiro et al. 1981). In humans, OROV infection can produce Oropouche fever (OROF), which manifests as an acute clinical infection, along with headache, myalgia, arthralgia among other systemic manifestations (LeDuc and Pinheiro 1988). The presence of rash is rare. Some patients present

meningitis. The incubation period is 4–8 days and symptoms last from 2 to 7 days. Viremia in humans may be detected between 2 and 3 days after the onset of symptoms. Recovery from the disease is complete without apparent sequelae even in the most severe cases. No mortality records produced by this virus were documented (Pinheiro et al. 1981). Due to a large number of OROF cases recorded in the last 45 years in humans, OROV is considered the most important emergent viral disease in tropical areas of Central and South America.

OROV has been isolated from various vertebrate sources (humans, monkeys, and edentates) and arthropods (mosquitoes *Cx. quinquefasciatus*, *Coquillettidia venezuelensis*, *Oc. serratus*, and biting midges *Culicoides paraensis*). Studies have shown that OROV is maintained in nature by two cycles (Fig. 10.2): an enzootic cycle characterized by monkeys, sloths, and birds as potential hosts and an unknown vector. In urban settings, an alternative epidemic cycle can take place where human generated high viremia enough to infect *C. paraensis*. This arthropod is the principal urban vector involved in OROV epidemics (Pinheiro et al. 2013).

Recent phylogenetic studies indicate the presence of three different OROV lineages: lineage I, which is the prototype strain recovered in Trinidad and in the western Amazon; lineage II, which contains strains isolated in Peru and eastern Amazon; and lineage III, which includes isolates made in Panama, and more recently, in 2000, isolated strains from *Callithrix* sp. marmosets in the Brazilian state of Minas Gerais (Brazil). These studies suggest movements of strains through Amazon regions of Brazil and Peru (Pinheiro et al. 2013).

In the Brazilian Amazon, OROV is the second most common arbovirus after DENV. Between 1960 and 1980 thousands of people became infected with OROV in the Amazonian areas of Pará state and nearby regions. Later, viral activity was recorded in the states of Acre, Amapá, Maranhão, and Rondônia. In 2003 and 2004, two epidemics were recorded in the state of Pará, and strains belonging to lineages I and II were recovered.

The recent isolation of OROV from *Callithrix* sp. in the southeastern state of Minas Gerais is a fact to consider. Southeastern Brazil is one of the most populated areas of the Americas, with important cities like Belo Horizonte, Rio de Janeiro, and São Paulo. The proximity of OROV to this area represents a serious risk for their inhabitants due to its potential urbanization and development of serious outbreaks (Pinheiro et al. 2013).

In the North of Argentina (Formosa, Jujuy, Salta, and Tucumán), OROV IgM antibodies were detected in febrile humans (North). Molecular phylogenetic analyses indicated the presence of a fourth monophyletic lineage (lineage IV). It was not possible to isolate the virus so far (Pinheiro et al. 2013).

10.4.3.2 Akabane Virus (AKAV)

AKAV is widely distributed in tropical and temperate regions of Oceania, Asia, Middle East, and Africa and is transmitted by different species of biting midges (Kurogi et al. 1987). This virus has great economic importance because it affects

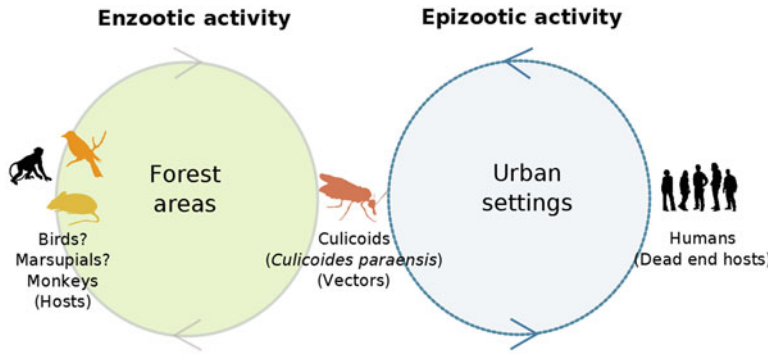

Fig. 10.2 Enzootic and epidemic cycles of Oropouche virus in tropical regions of South America

cattle, sheep, and goats (Kurogi et al. 1987). Sporadic outbreaks with abortions, premature births, and congenital anomalies characterized by arthrogryposis and hydrancephaly were reported, with Australia, Israel, Taiwan, Korea, and Turkey being among the most affected countries by such outbreaks in ruminants (Kurogi et al. 1987). Infection by AKAV in adult animals is usually subclinical, but in cattle, infections are particularly associated with encephalitis production (Kurogi et al. 1987).

Currently, there are two vaccines to immunize domestic animals: a monovalent (AKAV) and a trivalent one (AKAV-AINV-Chuzan virus (CHUV)) (Hechinger et al. 2013). CHUV belongs to the family Reoviridae (genus *Orbivirus*) and is teratogen for ruminants. Given the current epidemiological situation in countries where these viruses circulate, vaccination of young females is an important measure to eliminate the risk of infection of animals during fetal development (Hechinger et al. 2013).

10.4.3.3 Aino Virus (AINV)

This virus has been detected by serological surveys and isolates in Japan, Korea, Taiwan, Israel, Turkey, and Australia. AINV is transmitted by mosquitoes and biting midges and affects ruminants and birds (Tsuda et al. 2004).

Infection in domestic mammals generally causes a subclinical and short viremia. In pregnant animals, the virus can infect the fetus by invading the CNS and/or skeletal muscle tissues, causing hydrancephaly, hydrocephalus, microcephaly, encephalomyelitis, or arthrogryposis (Tsuda et al. 2004). It is very common to observe mixed outbreaks by both AINV and AKAV, so the differential diagnosis is essential to identify the etiologic agent causing disease in animals. The only vaccine available against this virus is trivalent (AKAV-AINV-CHUV) (Hechinger et al. 2013).

10.4.3.4 Schmallenberg Virus (SBV)

SBV has been the *Orthobunyavirus* with greatest veterinary relevance in Europe in the last years (Wu et al. 2014). This virus was originally recovered from clinical samples obtained from cattle with fever, diarrhea, loss of appetite, and decreased milk production in Germany and the Netherlands during the summer and fall of 2011 (Hoffmann et al. 2012). Later, as in infections by other members of the Simbu serogroup, SBV was associated with the occurrence of abortions, stillbirths, and congenital malformations (Wu et al. 2014).

The disease was first observed in cattle, sheep, and goats, but it was also detected in deer, bison, alpaca, moose, and other wild ruminants infected with this virus. Currently, isolations and outbreaks by SBV have been reported in a large area of Europe (Germany, the Netherlands, Belgium, Luxembourg, France, the UK, Italy, and Spain). *Culicoides* species are involved in the transmission of SBV in nature (Rasmussen et al. 2012).

As an effective tool for controlling disease caused by SBV, different inactivated vaccines have been developed and tested; some of which are marketed in some countries, like France and the UK (Wu et al. 2014).

10.4.4 California Serogroup

10.4.4.1 California Encephalitis Virus (CEV)

CEV serogroup prototype was isolated from mosquitoes *Oc. dorsalis* and *Cx. tarsalis* in California in 1943 (Hammon and Reeves 1952). During 1945, also in California, this virus was listed as the etiologic agent causing disease in two children and one adult hospitalized for encephalitis. NTAb were detected in 11 % of patients admitted to the same hospital with nervous syndrome. The last record of isolation for this virus was in 2001. Antibodies against this virus have been detected in rabbits, hares, squirrels, horses, and cows (Schmaljohn and Nichol 2006)

10.4.4.2 La Crosse Virus (LVC)

LCV is the most pathogenic virus in this serogroup and the virus of greatest epidemiological importance in the USA. It was first isolated from the brain of a 4-year-old boy who died of encephalitis in the county of La Crosse (Wisconsin, USA) (Rust et al. 1999).

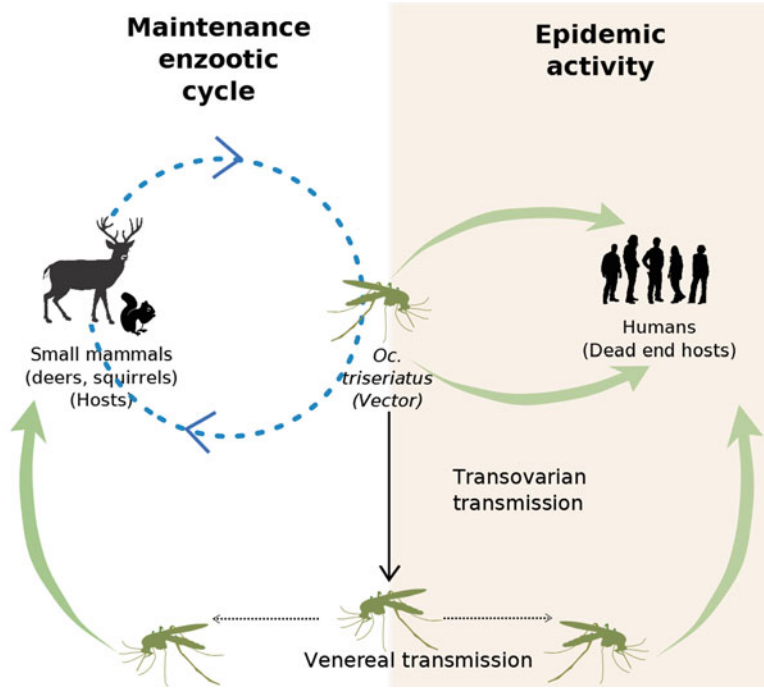

Fig. 10.3 Transmission and maintenance cycle of La Crosse virus in the USA

It is mainly transmitted by the mosquito *Oc. triseriatus*, in which there has been transovarian transmission as a strategy for the winter. Mammal species, such as squirrels (*Sciurus carolinensis*), marmots (*Tamias striatus*), and foxes, act as virus sources in summer, becoming important hosts for LCV amplifiers (Fig. 10.3).

LCV infection is considered a major cause of encephalitis and meningitis in children in the USA; however, in adults, the virus causes only mild fever without neurological involvement (Rust et al. 1999). The incubation period is about 3–7 days, and in most patients, it starts with a rapid rise in temperature followed by stiff neck, lethargy, headache, nausea, and vomiting which generally sharpen the seventh day postinfection. Stroke occurs in 50 % of the patients, and up to 30 % can reach the coma. About 65 % of patients develop meningitis with the presence of mononuclear cells and/or polymorphonuclear cells in the cerebrospinal fluid. Neurological sequelae such as epilepsy occurred in 10–15 % of children who had stroke during the acute phase of the disease. Additionally, about 2 % of patients remain with permanent paresis (Rust et al. 1999).

In 1958, a strain of LCV previously called Snowshoe virus (SSHV) was isolated from the snowshoe hare (*Lepus americanus*) in Montana, USA. This strain has a wide distribution, covering Alaska, Canada, North of USA, and some parts of Asia. The natural cycle develops through mosquitoes and wild animals. In Canada, the snowshoe hare is considered an important host, although other wild animals may be also involved in the cycle. There is evidence of infection in at least 16 species of wild animals (rabbits, rodents, carnivores, and ungulates) and four species of domestic animals (chickens, horses, cows, and dogs). Furthermore, infection was detected in several species of mosquitoes belonging to the genera *Aedes*, *Ochlerotatus*, *Culex*, and *Culiseta*. Human infection with this strain has been associated with the occurrence of encephalitis and meningitis. Domestic and wild animals are often found infected but rarely develop disease (Hubálek et al. 2014).

10.4.4.3 Jamestown Canyon Virus (JCV)

JCV is responsible for encephalitis in humans in the USA, where it is widely distributed. It was isolated from the mosquito *Culiseta inornata* in

California in 1961 (Grimstad 1988). It is mainly transmitted by the bite of *Cs. inornata* and several species of *Ochlerotatus*, in which transovarian transmission was observed. The white deer (*Odocoileus virginianus*) is the amplifier host in nature. This virus recently was isolated from vesicular lesions in horses (Grimstad 1988).

Even though this virus causes neurological disease like LCV in humans, the main difference is related to the severity of the disease, depending on age of the patient. Therefore, LCV infection is always more severe in children, whereas JCV is more severe in adults. The disease can generally range from asymptomatic through a feverish syndrome to fatal cases of encephalitis. Given that there are serological cross-reactions among different virus serogroups and co-circulate in some regions, it is important to make a differential diagnosis to determine the virus causing the disease (Grimstad 1988).

10.4.4.4 Guaroa Virus (GROV)

GROV was first isolated from a human without signs of disease in Colombia in 1959; subsequently, numerous strains of this virus have been recovered from febrile patients in Brazil and mosquitoes in Colombia, Panama, and Brazil. Several studies suggest that GROV is widely distributed in Central and South America, since antibodies have been detected in humans in Brazil, Argentina, Peru, and Guatemala (Groseth et al. 2015).

Since most isolates were made from the mosquito *An. neivai*, it has been incriminated as a potential vector of GROV.

In Brazil, GROV infections were detected in patients with fever and other symptoms, such as headache, myalgia, and prostration. Moreover, a strain was isolated from a liver biopsy performed on a patient with paralysis. The last records of the disease are those obtained in Peru and Bolivia, where 17 cases were confirmed in patients with acute self-limited febrile syndrome; nine were recovered in Peru in 2007 and two from Bolivia in 2007 and 2009. The most common clinical symptoms in patients with GROV were chills, malaise, bone pain, headache, retro-orbital pain, myalgia, and arthralgia (Groseth et al. 2015).

10.4.4.5 Tahyna Virus (TAHV)

TAHV is the first arbovirus isolated in Europe from mosquitoes. Published evidences confirm its circulation in Asia, Africa, and Europe (Hubálek et al. 2014).

In nature, its main vector is *Ae. vexans*, a mosquito species from which most of viral strains were isolated; field work complementary to the laboratory evidence has demonstrated that other mosquito species may also act as vectors: *Oc. cantans*, *Oc. caspius*, *Oc. dorsalis*, *Ae. cinereus*, *Oc. sticticus*, and *Culiseta annulata*. Rabbits, hares, hedgehogs, and pigs are considered the primary hosts (Hubálek et al. 2014).

Infection with this virus is associated mainly with the production of febrile syndrome in children, particularly in European countries (Hubálek et al. 2014).

10.4.4.6 Inkoo Virus (INKV)

INKV was first isolated in Finland in 1964. This virus is mainly distributed in Europe and Russia, and it is transmitted by *Oc. communis* and *Oc. punctor* in Scandinavia. In Russia, it was isolated from *Oc. hexodontus* and *Oc. punctor*. The disease associated with INKV infection has not been well characterized, but a few records suggest this virus as a causative agent of CNS disease in children and young adults in Finland (Putkuri et al. 2007)

10.4.4.7 Group C Serogroup

This serogroup includes Marituba virus (MTBV), Oriboca virus (ORIV), Caraparu virus (CARV), and Madrid virus (MADV); all of them were described for the first time in the Brazilian Amazon during the 1950s. Isolates have been made from humans, wild animals (mainly rodents, marsupials, and bats), and mosquitoes. Geographically, group C is present in American countries, including the USA, Mexico, Panama, Honduras, Guatemala, Trinidad, Brazil, Peru, Ecuador, Venezuela, and French Guiana (Plyusnin et al. 2012).

These viruses have been associated with a human disease that generally occurs as a self-limited dengue-like illness with fever, headache, myalgia, nausea, vomiting, and weakness and

lasts for 2–5 days. Despite the public health concern posed by these viruses, they have received little attention, and studies are scarce (Pinheiro and da Rosa 1994)

10.4.5 Wyeomyia Serogroup

10.4.5.1 Wyeomyia Virus (WYOV)

Different strains of WYOV have been recovered exclusively in Central and South America (Colombia, Trinidad, Panama, and Brazil) from different species of mosquitoes collected in rainforest areas of the New World (*Wyeomyia melanocephala*, *Ps. albipes*, *Wy. pilicauda*, *Sabethes soperi*, *Wyeomyia* spp., *Sabethes* spp., and *Sa. glaucadaemon*). The prototype strain of the virus was first isolated from a human and mosquitoes *Wy. melanocephala* and *Ps. albipes* in Colombia in 1940 (Plyusnin et al. 2012).

The range of vertebrate hosts has not been defined. Evidences support involvement of rodents and birds as host. Two viral strains were isolated from *Proechimys guyannensis* and *P. iheringi*. Antibodies were detected in birds (Chowdhary et al. 2012).

The role of WYOV as causal agent of disease in humans is not entirely clear: only two strains have been recovered from ill patients, one with febrile syndrome and the other with a fever accompanied by symptoms of encephalitis (Chowdhary et al. 2012).

10.4.6 Bwamba Serogroup

10.4.6.1 Bwamba Virus (BWAV)

BWAV is transmitted by mosquitoes of the species *An. gambiae*, *An. funestus*, *Ae. furcifer*, *Aedes* spp., *An. coustani*, and *Mansonia uniformis*. The main anthropophilic species of mosquitoes acting as vectors are *An. funestus* and *An. gambiae*. Several strains of BWAV have been recovered from humans in Nigeria, Cameroon, Central African Republic, Kenya, Tanzania, and South Africa (Lutwama et al. 2002).

The disease developed by BWAV was described as a relatively severe generalized infection of short duration (4–5 days) and benign, since no fatalities have been recorded so far. Often, when a meningeal involvement occurs, it is accompanied by rash. Other common symptoms are fever, headache, and arthralgia. In some cases, digestive tract diseases, especially diarrhea, also occur. The convalescent stage is characterized by a marked fatigue that lasts 8–10 days. The viremia in humans is of short duration (2–4 days), which makes virus isolation very difficult (Lutwama et al. 2002).

10.4.6.2 *Phlebovirus*

Viruses belonging to this genus are widely distributed throughout the world, except in Australia, and are the most diverse with respect to the arthropod vectors involved in its natural cycle (Table 10.2) (Plyusnin et al. 2012).

This genus has nine virus species with more than 70 antigenically different strains or isolates divided in complexes according to the transmitted vectors. While most viruses are transmitted by sand flies of the genera *Phlebotomus*, *Lutzomyia*, and *Sergentomyia*, some are transmitted by mosquitoes (Rift Valley fever virus – RVFV) and ticks (Sandfly[2] fever Naples virus – SFNV) (Plyusnin et al. 2012).

10.4.6.3 Rift Valley Fever Virus (RVFV)

RVFV was first identified in Great Rift Valley in Kenya in 1931 during an outbreak that affected thousands of small ruminants causing abortions in sheep and mortality in newborn lambs. This virus is characterized by producing large explosive epidemics across Africa, as in the Arabian Peninsula. RVFV mainly affects ruminants (goats, sheep, cows, and camels) and humans. In ruminants, particularly sheep, RVFV infection is characterized by a high rate of abortion, high mortality rate in young animals (~70 %), and significant mortality in adult animals (20–30 %) (Arum et al. 2015).

[2]Even being "sandfly fever" more usual than "sand fly fever" in the scientific literature, the last form was utilized for the sake of standardization in American English (CBM).

In humans, the virus is transmitted by mosquito bites or exposure to blood and body fluids or spray when handling infected animals themselves. Clinical infection in humans is self-limited and is manifested by fever, headache, weakness, muscle pain, and photophobia. In a very small number of human patients (1–3 %), the virus causes hepatitis, retinitis, blindness, encephalitis, and hemorrhagic fever (Arum et al. 2015).

In nature, RVFV is transmitted by various species of mosquitoes of the genera *Aedes* s.l., *Culex*, and *Anopheles*. Ruminants act as amplifier hosts in epizootic/epidemic cycles, transmitting the virus to other mosquitoes and therefore causing amplification and virus spread as well (Arum et al. 2015).

Due to the ability of RVFV to infect and replicate in different mosquito species, the virus shows great potential to spread to other parts of the world, such as America, Asia, and Europe, which could cause serious economic and health problems (Arum et al. 2015).[3]

Currently, an attenuated virus vaccine has been proven safe for both adults and young animals and very effective in sheep, cows, and monkeys. However, it cannot be used in pregnant individuals because it has teratogenic effect on the fetus (Miller et al. 2015).

10.4.6.4 Sandfly Fever Naples Virus (SFNV)

Numerous strains of SFNV are responsible for most of the cases of febrile syndrome produced by sand flies in Europe and Asia. Previously classified as a separate species, currently Toscana is the strain with greatest impact on health. It was isolated from *Phlebotomus perniciosus* collected in Monte Argentario (Grosseto, Italy) in 1971 (Plyusnin et al. 2012). SFNV is widely distributed, covering Italy, France, Spain, Slovenia, Turkey, Portugal, Sweden, and Greece. It is transmitted by *Ph. perniciosus* and *Ph. perfiliewi*, which also act as reservoirs. Transovarian transmission has been demonstrated in laboratory studies and by virus isolation in *Phlebotomus* males. Although this virus has been isolated from human patients and wild animals, it is not known which vertebrates are involved in its maintenance. In humans, the infection produces mostly a moderate febrile illness, with neurological involvement (aseptic meningitis), sometimes with complete recovery. After an incubation period of up to 2 weeks, the onset of symptoms is abrupt (headache, fever, nausea, vomiting, and myalgia). Other frequent symptoms are leukopenia, stiff neck, and low level of consciousness, tremors, and paresis. Viremia developed in both humans and laboratory animals is low and short-lasting.

10.4.6.5 *Phlebovirus* in the Americas

In the American continent, there is little information regarding epidemiology and ecology of phleboviruses. Punta Toro virus (PTV) and Candiru virus (CANV) are associated with febrile syndrome in humans (Plyusnin et al. 2012). PTV was isolated in Panama and Colombia from sand flies and humans. Seroprevalence detected in Panama ranged from 5 % in children to 27–40 % in adults. PTV produces an acute febrile illness lasting 2–5 days in humans. In the Brazilian Amazon, numerous strains of CANV have been recovered from arthropods and a human febrile case. The disease caused by these Amazonian phleboviruses is acute, self-limited flu-like, and lasts for 2–5 days. It is characterized by a sudden start with high fever, frontal headache, back pain, myalgia, retro-orbital pain, and photophobia (Palacios et al. 2011).

10.4.7 *Nairovirus*

Nairoviruses (Table 10.2) have a worldwide distribution and are transmitted almost exclusively by ticks, but few representatives have been recovered from biting midges, mosquitoes, and flies (mechanical vector). There are seven viral species with numerous strains that exhibit a large geographical distribution, probably due to widely dispersed amplifier host, mostly birds.

[3]This virus (and CCHFV, see below) is cited as a potential for bioterrorism (Lockwood 2009) (see Chap. 3) (CBM).

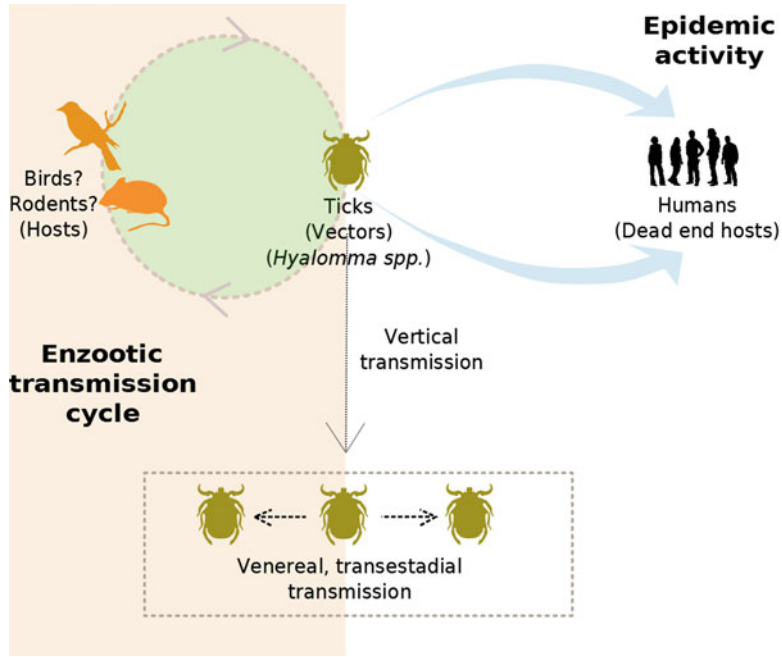

Fig. 10.4 Transmission cycle of Crimean-Congo hemorrhagic fever virus in Congo

10.4.7.1 Crimean-Congo Hemorrhagic Fever Virus (CCHFV)

CCHFV is the *Nairovirus* of health importance. This virus is present across many geographic regions of Asia, Africa, and Europe, overlapping with the distribution of its vector: *Hyalomma* ixodid ticks. Although the virus has been isolated from more than 30 different tick species, *Hyalomma marginatum* is considered the main vector. Transovarian, transestadial, and venereal transmission of the virus has been observed in ticks (Fig. 10.4). Domestic and wild animals that serve as hosts for ticks often develop significant viremia and antibody without appreciable clinical manifestations (Appannanavar and Mishra 2011).

CCHFV is transmitted to humans by the bite of an infected tick or by direct contact with blood or tissues of an infected person. The virus first replicates locally in the entry area, and then it spreads via the lymphatic and hematic systems to the liver, reticuloendothelial system, or other target organs where it replicates massively. CCHFV produces cytopathic effects on endothelial cells, hepatocytes, and macrophages. The disease is characterized by endothelial damage determined by capillary fragility that is evidenced by immune complex formation and complement activation. Moreover, the reduction of thrombocytopenia and thrombosis in bone marrow is observed. Tissue damage in the liver causes the release of procoagulant factors, leading to circulatory collapse by intravenous coagulations. Liver injury also prevents synthesis and replacement of coagulation factors, ultimately leading to hemorrhage (Appannanavar and Mishra 2011).

The incubation period is short (1–13 days), depending on the infection route. The disease onset is sudden, with chills, fever, severe headache, irritability, sore throat, retro-ocular pain, photophobia, myalgia, and back pain. Other usual initial symptoms are nausea, sore throat, vomiting, abdominal pain, and diarrhea. During the first 2 days, the fever appears intermittently, and the patient has mood swings, confusion, and aggression, followed by lassitude, depression, and somnolence between the second and fourth day, accompanied by flushing, tachycardia, and mild hypotension. Between the fourth and fifth day, bleeds appear (epistaxis, hematemesis, hematuria, and gingival and vaginal bleeding). In the most severe cases, patients may develop hep-

atorenal and pulmonary collapse from the fifth day and can progressively get drowsiness and stupor, leading to coma and death. Case fatality rates ranged from 30 to 50 %. Slow recovery begins at day 9 or 10. Full recovery can take a month or longer (Appannanavar and Mishra 2011).

The infections occur most often among field-workers after being bitten by an infected tick, and to a lesser extent, among workers exposed to contaminated tissues from livestock (e.g., slaughter-house), and between health workers through contact with the body fluids of infected patients (Appannanavar and Mishra 2011).

Prophylaxis must be based on surveillance programs involving ticks and animals through which endemic or high-risk areas can be defined. The application of chemical products to animals for tick control at a large scale is quite limited because of the development of chemical resistance (Appannanavar and Mishra 2011).

Alternative strategies such as vaccines against ticks, semiochemicals, and the use of biocontrol agents are currently being developed. The main mode of personal protection is to avoid contact with ticks or contaminated tissues, which requires the use of proper clothing (gloves, closed work clothes) and repellents on clothing (Appannanavar and Mishra 2011).

Even though several vaccines have been developed, their use has been rather restricted geographically. The development of a safe and effective vaccine (inactivated virus) is currently limited by the low availability of necessary infrastructure for development and potential demand due to the number of cases that exist today (Appannanavar and Mishra 2011).

10.4.7.2 Nairobi Sheep Disease Virus (NSDV)

NSDV causes a severe hemorrhagic disease in domestic animals with high morbidity and mortality. It was first isolated in 1917 in Nairobi (Africa) and is endemic in Eastern and Central Africa and India. In nature, NSDV is transmitted by ixodid ticks *Rhipicephalus appendiculatus*, the main vector in Africa and *Haemaphysalis intermedia* in India. Goats and sheep are the only host mammals known for NSDV in nature; other animals like cows and horses are refractory to the disease (Marczinke and Nichol 2002).

The incubation period is of 4–15 days. Clinical manifestations begin with high fever (40–41°C), leucopenia, and anorexia; animals are listless and motionless, with gastrointestinal bleeding and hemorrhagic mucopurulent nasal discharge, conjunctivitis, and painful dyspnea. In pregnant animals, NSDV can cause abortions. Animals that survive become immune (Marczinke and Nichol 2002).

NSDV has a limited effect on animals born in enzootic areas because of the acquired immunity across the maternal antibodies. However, the virus has a great impact, causing significant economic losses when infected animals are brought to new free areas of this virus or healthy animals are introduced in enzootic areas (Marczinke and Nichol 2002)

Human infections are rare and generally subclinical; mild flu symptoms, fever, and arthralgias are manifested in rare cases. There are no vaccines available (Marczinke and Nichol 2002).

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