

# Lesser-known bunyavirus infections

W.C. Wilson <sup>(1)\*</sup>, N.N. Gaudreault <sup>(1)</sup>, M.M. Hossain <sup>(2)</sup> & D.S. McVey <sup>(1)</sup>

(1) United States Department of Agriculture, Agricultural Research Service, Arthropod-Borne Animal Diseases Research Unit, Manhattan, Kansas, United States of America

(2) Kansas State University, School of Veterinary Medicine, Diagnostic Medicine and Pathobiology, Manhattan, Kansas, United States of America

\*Corresponding author: william.wilson@ars.usda.gov

## Summary

This paper reviews less well-known or less widely distributed viruses of the *Bunyaviridae* family that are nonetheless of significant veterinary and public health concern. These include: Cache Valley fever, Main Drain, Ingwavuma, Bhanja and Heartland viruses. A description of the agents, clinical signs of infection, epidemiology, and insect transmission is provided for each, and the authors discuss current diagnostic strategies plus the lack of control measures.

## Keywords

*Bunyaviridae* – Bunyavirus – Nairovirus – Orthobunyavirus – Phlebovirus.

## Introduction

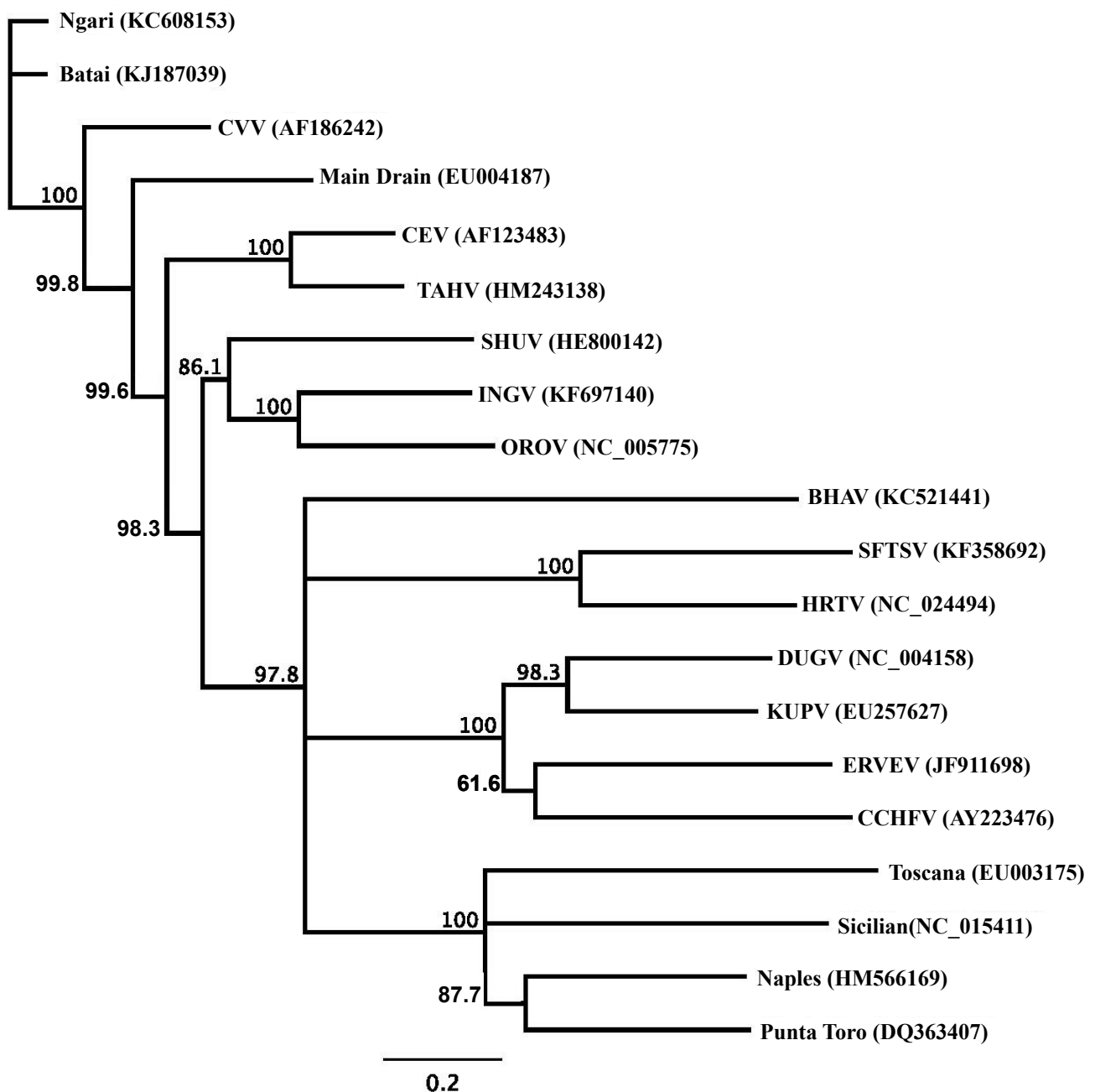
The family *Bunyaviridae* contains at least five genera, three of which, *Orthobunyavirus*, *Phlebovirus* and *Nairovirus*, infect vertebrates and are transmitted by arthropods, including mosquitoes, midges, sandflies and ticks (1, 2). Many of the viruses in this family are of medical and veterinary importance and those of greatest concern are dealt with elsewhere in this issue. The paper discusses less well-known or less widely distributed bunyaviruses. The emphasis is on viruses of veterinary concern, but human pathogens, with unknown or potential veterinary significance (1), are also included. The genus *Orthobunyavirus* comprises over 174 viruses (3) (new members are constantly being discovered), and various mosquitoes, midges and vertebrates serve as amplifying hosts. Approximately 25 orthobunyaviruses are known to cause human disease, including febrile illness, encephalitis and haemorrhagic fever. The genus *Phlebovirus* comprises no fewer than 60 viruses, at least eight of which are associated with human disease. Phleboviruses are mainly transmitted by sandflies and mosquitoes, but there are some important tick-borne viruses in the genus. Febrile illnesses and 'sandfly fever' are the most common manifestations of phlebovirus infection in humans. Sandfly fever is characterised by a sudden-onset fever, rash, photophobia, anorexia and malaise. Infection with a highly pathogenic novel phlebovirus, known as Huaiyangshan virus (4), or severe fever with thrombocytopenia syndrome virus (SFTSV) (5), is characterised by high fever and haemorrhagic signs. Nairoviruses are globally distributed, primarily tick borne, and are known to be pathogenic for humans and animals.

Altogether, 34 nairoviruses have been identified. The most recently identified nairovirus is Kupe virus (KUPV), associated with ticks feeding on livestock in Kenya (6). Nairobi sheep disease and Crimean-Congo haemorrhagic fever (CCHFV) viruses are reviewed elsewhere in this issue, and the limited information available on the remaining nairoviruses is discussed here.

In this paper, the authors primarily discuss emerging or recently identified agents. Little is known about their distribution, pathogenicity, epidemiology and impact on animal and public health. Furthermore, outbreaks of infection are often sporadic, diagnostic procedures are limited, and there is little surveillance for most of these viruses. Re-evaluation of these neglected bunyaviruses is warranted, given the continuing emergence of new members and discovery of pathogenic roles for existing viruses.

## Aetiological agent

The historic classification of bunyaviruses into genera and serogroups on the basis of antigenic relationships coincides remarkably well with the results of modern phylogenetic analysis, as can be seen for the viruses considered in this paper (Fig. 1). The genus *Orthobunyavirus* currently has 18 serogroups, of which the Bunyamwera, California and Simbu serogroups contain medically relevant viruses that are discussed here (Table I). The California group contains the important human pathogens of California encephalitis, La Crosse, Jamestown Canyon and Tahyna viruses. The Simbu and Bunyamwera serogroups contain at least



**Fig. 1**  
**Representative phylogenetic organisation of bunyaviruses**

The tree was generated using Geneious® Muscle multiple sequence alignment, the Tamura-Nei genetic distance model and the neighbour-joining tree-building method

20 viruses on several continents, including the animal pathogens such as Akabane, Schmallenberg and Cache Valley viruses. From the Simbu group, Akabane virus has been associated with congenital problems in domestic ruminants in Australia, Japan, Africa and the Middle East, and Oropouche virus (OROV) is known to cause febrile illness in humans in South America (Brazil). Ingwavuma virus (INGV) is a member of the Manzanilla subgroup of the Simbu serogroup and has been found in Africa,

Indonesia and Asia. Infections with INGV have not yet been associated with clinical disease (26, 27, 28, 29). Shuni virus of the Simbu group has been associated with neurological disease in horses (30). Cache Valley virus (CVV) belongs to the Bunyamwera serogroup and is known for causing reproductive losses in sheep, cattle and horses, as well as disease in humans (14). CVV infection in sheep is teratogenic, causing fetal malformations and deaths. In humans, CVV is most commonly associated with febrile

illness and neurological disease. Other animal pathogens in the Bunyamwera group include the viruses Main Drain and Ngari. Main Drain virus has been associated with encephalitis in horses and teratogenic effects in sheep (8, 18). Ngari virus, a reassortant bunyavirus of Bunyamwera and Batai viruses, has been implicated in epidemic haemorrhagic disease in Africa (21, 22, 49).

The genus *Phlebovirus* is divided into the Sandfly fever and Uukuniemi serogroups (50). The Sandfly fever group viruses are primarily transmitted by mosquitoes and sandflies, and include important pathogens such as Rift Valley fever virus (RVFV) and other viruses listed in Table I. The Uukuniemi group includes the tick-borne, animal and human pathogens Bhanja virus (BHAV), SFTSV (37, 51), and Heartland virus (HRTV) (52), which are closely related yet distinct viruses (2, 50). BHAV and two other antigenically related unassigned bunyaviruses, Forecariah virus and Kismayo virus, form a distinct genetic type that is different from SFTSV and HRTV. While similar to SFTSV and HRTV in the way in which they are transmitted, they nonetheless appear to differ by host pathobiology, since BHAV is primarily associated with disease in young domestic ruminants (cattle and sheep) (53) and only sporadic cases of disease in humans (33), while SFTSV and HRTV have only been associated with outbreaks of life-threatening disease in humans (34, 38, 54). There is serological evidence that SFTSV and HRTV may infect domestic animals, including sheep, goats, cattle, pigs, dogs, and chickens, as well as rodents; however, whether these viruses cause disease in animals or what role animals play in the epidemiology of the disease is not yet known (38). An SFTSV- and HRTV-like virus, named Hunter Island group virus (HIGV), was isolated in Australia during a 2002 investigation of a disease outbreak among shy albatrosses (*Thalassarche cauta*) (42). However, at present there is no evidence that HIGV causes disease, and the ecology of this virus is yet to be determined.

The *Nairovirus* genus has been classified into seven serological groups: Crimean-Congo haemorrhagic fever, Dera Ghazi Khan, Hughes, Nairobi sheep disease, Qalyub, Sakhalin and Thiafora. The prototypic members of two groups, CCHFV and Nairobi sheep disease, are not discussed here. Dugbe virus (DUGV) and KUPV of the Nairobi sheep disease group have been associated with livestock hosts but are typically asymptomatic (23); however, DUGV has been associated with febrile illness leading to prolonged thrombocytopenia in humans (55). Erve virus (ERVEV) of the Thiafora serogroup has been associated with human infection resulting in severe headache and intracerebral haemorrhage (31).

## Epidemiology

The distribution of bunyaviruses is determined by the distribution of their vectors and vertebrate hosts. Many

bunyaviruses have emerged or been detected with new technologies over the last few decades and it is often speculated that climate change may affect the epidemiology of these vector-borne viruses (56). Of the bunyaviruses that are able to multiply in arthropod vectors, transovarial transmission (vertical transmission) is a potential mechanism for the maintenance of these viruses in the arthropod (57). Typically, these viruses require transmission by an arthropod, although animal-to-animal transmission can occur through direct exposure to infected body fluids. One example is CCHFV, where nosocomial infection has occurred during surgical procedures on infected individuals (58). In general, humans are 'dead-end hosts' (i.e. not associated with transmission to vector arthropods) for bunyaviruses, except for some viruses of the genus *Phlebovirus*. Why humans are dead-end hosts is not clear. For example, humans circulate high levels of RVFV, but generally do not contribute significantly to infecting vectors. This could be associated with less exposure to arthropod feeding.

Orthobunyaviruses of the California serogroup, such as Snowshoe hare virus and La Crosse virus, have been associated with human disease in North America since the early 1970s (8, 9, 59). Another significant orthobunyavirus of the Americas associated with disease in both animals and humans is CVV. This virus was initially identified in Utah in 1954 (60), and has since been detected throughout the United States (USA) and Canada (19), as well as in Mexico (61), Panama (62), Ecuador (63), Jamaica (64) and Argentina (15). More recently, a new member of this serological group was isolated in Finland; the five new isolates have been described as Mohko isolates of the Chatanga virus (7). The related Tahyna virus has been found in Asia, Africa and Europe (12, 13, 65). INGV has been isolated from birds, pigs and *Culex* species mosquitoes from Thailand, Indonesia, India and Africa (27, 28, 29). There is also serological evidence of INGV infection of water buffalo, goats and sheep in Indonesia and Java (26). The clinical significance of INGV is not known.

Bhanja virus, of the Uukuniemi group of phleboviruses, was first identified in India in 1954 (66), and has since been detected in regions of southern and central Asia, Africa and Europe (33, 67, 68). SFTSV and HRTV are examples of newly emerged phleboviruses. SFTSV was identified in 2010 and confirmed to be responsible for causing an outbreak of acute febrile illness in China throughout 2009 (37, 51). It has now been detected throughout Central and north-eastern China (38), Japan (69) and South Korea (70). In North America, HRTV was originally isolated and identified from residents of Missouri in 2009, and then later from a febrile patient in Tennessee in 2013 (34, 52). A serological survey of domestic animals and livestock suggests that HRTV or a similar virus may be circulating in Minnesota (35).

**Table I**  
**Antigenic classification of lesser-known and less widely distributed bunyaviruses with the potential to affect livestock**

Genus/virus (abbreviation)	Distribution	Vertebrate host	Vector	Signs of infection		Reference
				Human	Livestock	
<b>Orthobunyavirus</b>						
<b>California serogroup</b>						
California encephalitis	North America	Humans	Mosquito	Fever, vomiting, headache	NR	1, 7
La Crosse virus	North America	Humans	Mosquito	Febrile, neuroinvasive	Teratogenic experimentally in sheep	8, 9
Snowshoe hare virus	North America	Snowshoe hare		Rare, meningitis and encephalitis	Asymptomatic	10, 11
Tahyna virus (TAHV)	Asia, Europe, Africa	Humans, rodents	Mosquito	Fever, headache, nausea, malaise and pharyngitis	NR	12, 13
<b>Bunyamwera serogroup</b>						
Cache Valley virus (CVV)	The Americas	Ruminants and humans	Mosquito	Encephalitis, multi-organ failure	Abortion	14, 15, 16, 17
Main Drain virus (MDV)	North America	Horses, sheep	<i>Culicoides</i>	NR	Horses: ataxia, fever, tachycardia Sheep: teratogenic	8, 18, 19, 20
Batai virus and Ngari virus (BATV, NRIV)	Africa	Humans	Mosquito, tick	Haemorrhagic fever	NR	21, 22, 23, 24
<b>Simbu serogroup</b>						
Oropouche virus (OROV)	South America: Brazil	Humans	Mosquito	Fever, joint pain	NR	25
Ingwavuma virus (INGV)	Africa, Asia, India and Indonesia	Pigs, birds and ruminants	Mosquito	NR	Seroprevalence	26, 27, 28, 29
Shuni virus	South Africa	Horses	Mosquito	NR	Neurological disease	30
<b>Nairovirus</b>						
<b>Thiafora serogroup</b>						
Erve virus (ERVEV)	Europe	Humans	Tick	Severe headache	NR	31
<b>Nairobi sheep disease group</b>						
Dugbe virus (DUGV)	Africa	Humans, cattle, sheep	Tick	NR	Seroprevalence	23, 32
Kupe virus (KUPV)	Africa	Humans, cattle	Tick	NR	Seroprevalence	6, 23
<b>Phlebovirus</b>						
<b>Uukuniemi serogroup</b>						
Bhanja virus (BHAV)	Africa, Asia, Europe and India	Humans, young animals	Tick	Febrile, central nervous system symptoms	Febrile, central nervous system signs	33
Heartland virus (HRTV)	North America	Humans, ruminants	Tick	Fever, headache, diarrhoea and muscle joint aches	Infection reported	34, 35, 36
Severe fever with thrombocytopenia syndrome virus (SFTSV)	Asia	Humans	Tick	Haemorrhagic fever	NR	4, 37, 38, 39, 40, 41
Hunter Island group virus	Australia	Shy albatrosses ( <i>Thalassarche cauta</i> )	Tick	NR	NR	42
<b>Sandfly fever serogroup</b>						
Punta Toro	North and South America	Humans	Mosquito	Febrile illness	NR	43, 44
Sandfly fever Naples (SFNS)	Europe	Humans	Sandfly	Febrile illness	NR	45, 46
Sandfly fever Sicilian (SFSV) (Cyprus virus)	Europe	Humans	Sandfly	Febrile illness	NR	45, 47
Toscana	Europe	Humans	Sandfly	Aseptic meningitis and meningoencephalitis	NR	48

NR: none reported

Crimean-Congo haemorrhagic fever virus is the best known of the *Nairovirus* genus. Other nairoviruses include DUGV and KUPV, found in Africa (23), and ERVEV (31), found in Europe (Table I).

## Transmission

Mosquito transmission has long been associated with the California group viruses (7, 59). Similarly, the initial isolation of CVV of the Bunyamwera group was made from *Culiseta inornata* mosquitoes in the USA (60), and subsequent isolations have been made from a number of different species of *Aedes*, *Anopheles*, *Culex* and *Coquillettidia* mosquitoes (19, 71). Transmission of the Simbu group of viruses varies. *Culicoides* are considered the primary vectors of OROV (25). The transmission of INGV has not been clearly demonstrated but it has been isolated from the *Culex* species and thus is presumably mosquito borne (26, 27, 28, 29). Shuni virus has been isolated from *Culicoides* spp. and *Culex theileri* mosquitoes, and so is probably also vector borne (30).

The BHA, SFTS and HRT viruses are members of an expanded Uukuniemi group (2) and are considered to be tick-borne pathogens, given that these viruses have been isolated from ticks, and are associated with disease in animals and humans with a history of exposure to tick bites. BHAV was first isolated from *Haemaphysalis intermedia* ticks found on a paralysed goat (66), and has since been reported from a number of different species of *Ixodes*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Rhipicephalus* and *Amblyomma* ticks (33). SFTSV has been detected in the presumed tick vectors *Haemaphysalis longicornis* and *Rhipicephalus microplus* (37, 51). It may also be transmitted person to person by direct contact with infectious bodily fluids and secretions (39, 72, 73, 74, 75). HRTV was isolated from the Lone Star tick (*Amblyomma americanum*) during a field survey of arthropods (36). The ecological life cycles of these viruses are not well understood, and the effects of SFTSV, HRTV and similar viruses on animal health and the animals' role in transmission is still unclear. Members of the Sandfly fever group viruses are transmitted by either mosquitoes or sandflies (see Table I).

All of the nairoviruses appear to be tick borne. A survey of arboviruses in ticks associated with Kenyan livestock found most isolates of DUGV in *R. pulchellus* from sheep and cattle, while KUPV was found in ticks, including *R. pulchellus*, that had been captured from livestock in Isiolo (23). KUPV has also been isolated from *A. gemma* (6). The transmission of ERVEV is unclear. Although it is distantly related to CCHFV, no association with that virus's tick

vector, *Borrelia burgdorferi*, was noted in ERVEV-infected humans (76). Other insect vector species or rodents are the putative reservoir hosts of this virus.

## Clinical signs

The California group of viruses has been associated primarily with encephalitis in humans and has been extensively studied and reviewed (1). TAHV has been associated with fever, headache, nausea, malaise and pharyngitis in humans (12, 13). Of the Bunyamwera group, CVV is primarily pathogenic for young domestic ruminants, with subclinical disease being most common in adult animals (14, 33). CVV infection in sheep primarily targets the fetal central nervous and musculoskeletal systems, resulting in embryonic and fetal death and congenital defects, including arthrogryposis with hydrocephalus or hydranencephaly, spinal column deformities, fetal mummification and stillbirths (36, 74, 75, 76, 77). Histological lesions associated with CVV consist primarily of areas of necrosis and loss of paraventricular neuropil and motor neurons in the central nervous system (CNS), and a resolving myositis with poorly developed myotubular myocytes in skeletal muscle (77). The development of fetal lesions depends on fetal age when infected, with pathology developing between 28 and 48 days of gestation, but not if infection occurs after 48 days of gestation (78). The virus is cleared from the tissues within a few weeks of infection, presumably by innate and adaptive immune responses (79). Reported human cases of CVV infection are rare, but febrile illness, meningitis and encephalitis have been reported (15, 80). Although Main Drain virus was first associated with encephalomyelitis in horses (18), it has also been shown to induce fetal malformations in sheep (8). The Ngari virus is a genetic reassortment of Bunyamwera and Batai viruses and has been associated with severe febrile illness in humans (22, 24). Although other members of the Simbu serogroup are associated with clinical disease in animals and/or humans, there is no clear clinical description for INGV infection (26, 27, 28, 29).

Bhanja virus is associated with sporadic febrile illness in humans (2) and has been shown to cause febrile and CNS signs in sheep (81). HRTV and SFTSV are most commonly associated with human infections, with disease manifestations including fever, thrombocytopenia, leukocytopenia, and, in some cases, multi-organ failure and death (38, 54). SFTSV is responsible for causing death in 12–30% of reported cases (38), whereas only one fatality has been reported out of eight known human HRTV cases (34, 54). Fatalities related to SFTSV or HRTV infections have generally occurred in patients >70 years of age (34, 40). It is not yet clear if SFTSV or HRTV cause disease in animals; although it does appear that animals can

become infected by these viruses, especially domestic and wild ruminants (35, 38).

The pathogenesis of SFTSV infection remains to be elucidated as there is currently no fully compatible experimental animal model. However, experimental studies in cell culture and mice (4, 5, 82) indicate that SFTSV-induced thrombocytopenia is caused by the clearance of circulating virus-bound platelets promoted by splenic macrophages, which might resemble the disease features of SFTSV infection in humans (38). An autopsy of a fatal case of HRTV revealed positive immunohistochemistry (IHC) staining of the spleen and lymph tissues consistent with the features of SFTSV pathology, while other organs tested negative for reactivity with the viral nucleocapsid protein (34). The sandfly-transmitted viruses are primarily associated with febrile and encephalitic disease of humans and no livestock involvement has been reported (Table I).

Dugbe virus and KUPV are known to infect cattle (6, 23) but no clinical disease has been clearly associated with these viruses. Antibody responses to DUGV were found in a patient in South Africa with prolonged thrombocytopenia (32). ERVEV is associated with severe headache in humans (31).

## Diagnosis

The diagnosis of infection caused by those viruses discussed here is generally based on detection by reverse transcription polymerase chain reaction and sequencing, virus isolation, and the demonstration of an immune response by virus neutralisation or enzyme-linked immunosorbent assay (53). There are no commercially available or standardised tests to diagnose these infections. Diagnostics are usually conducted at specialised reference laboratories. Anti-SFTSV nucleoprotein (NP) antibodies cross-react with HRTV NP and have therefore been used in serological screening for SFTSV- and HRTV-like viruses (35, 83), and for IHC detection of antigen in the tissues of HRTV patients (34).

## Control measures

Surveillance data indicate that the incidence of SFTSV is growing, and closely related viruses have been detected on several continents. Although outbreaks of infection with these viruses appear to be sporadic, the resulting lack of

testing and absence of ongoing surveillance are probably responsible for a significant degree of under-diagnosis and underestimation of their prevalence. Thus, the true impact of these viruses on animal and public health remains undefined.

There are currently no vaccines for any of the viruses discussed. Because these are vector-borne viruses, the best means of control is to prevent exposure to the bites of the arthropod vectors; namely, ticks and mosquitoes. Direct contact with body fluids, secretions or other tissues of infected animals or individuals should be avoided, as this may be another route of viral transmission (as appears to be the case with SFTSV).

## Conclusion

The *Bunyaviridae* family of viruses is diverse and versatile. Most of these viruses are transmitted by arthropods (mosquitoes, biting midges, sandflies or ticks) but some are rodent borne. Many of the viruses in this family are of major veterinary and public health concern, and research has understandably been focused on those associated with large outbreaks of disease. Nevertheless, the lesser-known viruses reviewed in this paper also pose potential risks to veterinary and public health. Research which uses unbiased new diagnostic or virus discovery tools in the surveillance of vectors, livestock and wildlife should be encouraged. Such research is likely to provide a better understanding of known bunyaviruses and to identify new viruses, facilitating better disease control and improvement of public health and food security.



## Infecciones dues à des bunyavirus moins connus

W.C. Wilson, N.N. Gaudreault, M.M. Hossain & D.S. McVey

### Résumé

Cet article passe en revue un certain nombre de virus moins connus ou moins largement représentés de la famille des *Bunyaviridae*, dont l'importance pour la santé publique ou la santé vétérinaire est néanmoins significative. C'est le cas notamment du virus de la vallée Cache, du virus Main Drain, du virus Ingwavuma, du virus Bhanja et du virus Heartland. Pour chacun d'eux, les auteurs décrivent l'agent pathogène, les signes cliniques, l'épidémiologie et le mode de transmission par les insectes, ainsi que les stratégies de diagnostic envisageables et les problèmes soulevés par l'absence de mesures de contrôle.

### Mots-clés

*Bunyaviridae* – Bunyavirus – Nairovirus – Orthobunyavirus – Phlebovirus.



## Infecciones por bunyavirus menos conocidos

W.C. Wilson, N.N. Gaudreault, M.M. Hossain & D.S. McVey

### Resumen

Los autores pasan revista a una serie de virus de la familia *Bunyaviridae* menos conocidos, o de distribución menos extensa, que sin embargo revisten importancia para la salud pública y veterinaria, en particular: virus del Valle de Cache, virus Main Drain, virus Ingwavuma, virus Bhanja y virus Heartland. Tras describir el agente, los signos clínicos de infección, la epidemiología y la transmisión por insectos de cada uno de estos virus, los autores examinan los actuales procedimientos de diagnóstico y los problemas derivados de la ausencia de medidas de lucha.

### Palabras clave

*Bunyaviridae* – Bunyavirus – Nairovirus – Orthobunyavirus – Phlebovirus.



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