Genetic Diversity and Geographic Distribution of Bat-borne Hantaviruses

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Abstract

The recent discovery that multiple species of shrews and moles (order Eulipotyphla, families Soricidae and Talpidae) from Europe, Asia, Africa and/or North America harbour genetically distinct viruses belonging to the family *Hantaviridae* (order *Bunyavirales*) has prompted a further exploration of their host diversification. In analysing thousands of frozen, RNAlater®-preserved and ethanol-fixed tissues from bats (order Chiroptera) by reverse transcription polymerase chain reaction (RT-PCR), ten hantaviruses have been detected to date in bat species belonging to the suborder Yinpterochiroptera (families Hipposideridae, Pteropodidae and Rhinolophidae) and the suborder Yangochiroptera (families Emballonuriade, Nycteridae and Vespertilionidae). Of these, six hantaviruses are from Asia (Xuân Sơn virus and Đakrông virus in Vietnam; Láibīn virus in China and Myanmar; Huángpí virus and Lóngquán virus in China; and Quezon virus in the Philippines); three are from Africa (Mouyassué virus in Côte d'Ivoire and Ethiopia; Magboi virus in Sierra Leone; and Makokou virus in Gabon); and one from Europe (Brno virus in the Czech Republic). Molecular identification of many more bat-borne hantaviruses is expected. However, thus far, none of these newfound viruses has been isolated in cell culture and it is unclear if they cause infection or disease in humans. Future research must focus on myriad unanswered questions about the genetic diversity and geographic distribution, as well as the pathogenic potential, of bat-borne viruses of the family *Hantaviridae*.

Introduction

As recently as a decade ago, the single exception to the strict rodent association of hantaviruses was Thottapalayam virus, a long-unclassified virus originally isolated from the Asian house shrew (*Suncus murinus*) (Carey *et al.*, 1971). Analysis of the genome of Thottapalayam virus strongly supported an ancient non-rodent host origin and an early evolutionary divergence from rodent-borne hantaviruses (Song *et al.*, 2007a; Yadav *et al.*, 2007). Equipped with this information and employing reverse transcription polymerase chain reaction (RT-PCR), genetically distinct hantaviruses were detected in multiple species of shrews (order Eulipotyphla, family Soricidae) from widely separated geographic regions in Asia, Europe, Africa and North America. In addition to challenging the conventional view that rodents are the sole or principal reservoirs of hantaviruses, the discovery of soricid-borne hantaviruses suggested that moles (order Eulipotyphla, family Talpidae) might also harbour hantaviruses, and as predicted, several talpid-borne hantaviruses have been found in Europe, Asia and North America (Yanagihara *et al.*, 2014).

Acquisition of new knowledge about the spatial and temporal distribution, host range and genetic diversity of hantaviruses in shrews and moles, and more recently in bats, has been made possible largely through the generosity of museum curators and field mammalogists, who willingly granted access to their archival tissue collections. The availability of such well-curated specimens provides strong justification for the continued long-term maintenance and near-term expansion of archival tissue repositories for future investigations and innovative applications (Dunnum *et al.*, 2017).

Phylogenetic analyses of these newfound hantaviruses indicate at least four distinct clades, with the most divergent lineage comprising hantaviruses harboured by the European mole (*Talpa europaea*) (Kang *et al.*, 2009c) and several bat species (Sumibcay *et al.*, 2012; Weiss *et al.*, 2012; Arai *et al.*, 2013; Guo *et al.*, 2013; Gu *et al.*, 2014c; Xu *et al.*, 2015; Arai *et al.*, 2016b; Witkowski *et al.*, 2016; Straková *et al.*, 2017; Těšíková *et al.*, 2017; Arai *et al.*, 2019a; Arai *et al.*, 2019b). On the basis of intensive phylogenetic analysis of the full-length S- and M-genomic segments, a new taxonomic classification has been proposed, which includes four newly defined subfamilies in the family *Hantaviridae* (Maes *et al.*, 2019). In addition, the realization that these Eulipotyphla- and Chiroptera-borne hantaviruses are more genetically diverse than those found in rodents, as well as the discovery of hantavirus-like sequences in fish and reptile hosts, suggests that the evolutionary history of the *Hantaviridae* is far more complex than previously conjectured. Thus, the dawn of a new era in hantavirology is focused on exploring the inconvenient evidence that rodents may not be the original mammalian hosts of primordial hantaviruses. Also, the once-growing complacency and indifference towards rodent-borne hantaviruses is being replaced by renewed zeal to fill major gaps in our understanding about the ecology, transmission dynamics and pathogenic potential of these newly discovered, still-orphan hantaviruses, before the emergence of the next new hantavirus disease outbreak occurs (Yanagihara *et al.*, 2015).

The history of research on this once-obscure group of rodent-borne viruses has been marked by rediscovery and new beginnings (Yanagihara *et al.*, 2014). In this brief review, the genetic diversity and geographic distribution of hantaviruses from bats will be summarized in the context of hantaviruses harboured by rodents, shrews and moles to provide insights into their evolutionary origins and future risk and disease emergence.

Taxonomy

Previously classified in an unassigned order and in the genus *Hantavirus* of the family *Bunyaviridae*, hantaviruses have been recently reclassified and reassigned to a new family, designated *Hantaviridae*, in the order *Bunyavirales* (Adams *et al.*, 2017; Maes *et al.*, 2018). Viruses belonging to the four other genera formerly in the family *Bunyaviridae* (namely, *Nairovirus*, *Orthobunyavirus*, *Phlebovirus*, and *Tospovirus*) are now members of new viral families: *Feraviridae*, *Fimoviridae*, *Jonviridae*, *Nairoviridae*, *Peribunyaviridae*, *Phasmaviridae*, *Phenuiviridae*, and *Tospoviridae*.

The family *Hantaviridae* has been further classified into four subfamilies (*Actantavirinae*, *Agantavirinae*, *Mammantavirinae* and *Repantavirinae*) (Table 6.1). The subfamily *Mammantavirinae* comprises four genera (*Loanvirus*, *Mobatvirus*, *Orthohantavirus* and *Thottimvirus*), based on DEmARC analysis, using concatenated complete S and M amino acid-coding regions (Maes *et al.*, 2019). Virus members of each genus in the subfamily *Mammantavirinae*, with their mammalian reservoir host category (rodent, shrew, mole and bat), are summarized in Table 6.1. In addition, recently published hantavirus-like sequences from fish and reptile, which are closely related and ancestral to hantaviruses harboured by mammals (Shi *et al.*, 2018), have been classified into the newly created subfamilies of *Actantavirinae* and *Agantavirinae* and *Repantavirinae*, respectively (Table 6.1).

All rodent-borne hantaviruses belong to the genus *Orthohantavirus*, which also comprises nearly all of the genetically distinct hantaviruses recently detected in shrews and moles (Table 6.1). The exceptions are members of the genus *Thottimvirus*: Thottapalayam virus in the Asian house shrew (*Suncus murinus*) (Carey *et al.*, 1971; Song *et al.*, 2007a; Kang *et al.*, 2011c) and Imjin virus in the Ussuri white-toothed shrew (*Crocidura lasiura*) (Song *et al.*, 2009), as well as probably Uluguru virus in the Geata mouse shrew (*Myosorex geata*) (Kang *et al.*, 2014) and Kilimanjaro virus in the Kilimanjaro mouse shrew (*Myosorex zinki*) (Kang *et al.*, 2014). By contrast, all newfound hantaviruses

Table 6.1 Taxonomic classification of viruses belonging to the family *Hantaviridae* and their reservoir host category

Subfamily	Genus	Host	Virus name[a]
Actantavirinae	*Actinovirus*	Fish	Hagfish
Agantavirinae	*Agnathovirus*	Fish	Batfish, Goosefish, Spikefish
Mammantavirinae	*Loanvirus*	Bat	Brno, *Huángpí*, *Lóngquán*, *Magboi*, *Mouyassué*
	Mobatvirus	Bat	Đakrông, Láibīn, *Makokou*, Quezon, Xuân Sơn
		Mole	Nova
	Orthohantavirus	Rodent	Andes, Bayou, Black Creek Canal, Cano Delgadito, Choclo, Dàbiéshān, Dobrava, El Moro Canyon, Fugong, Hantaan, Khabarovsk, Laguna Negra, Lúxī, Maporal, Montano, Necocli, Prospect Hill, Puumala, Sangassou, Seoul, Sin Nombre, Thailand, Tigray, Tula
		Shrew	*Ash River*, Asikkala, *Azagny*, *Boginia*, Bowé, Cao Bằng, Jeju, *Jemez Springs*, Kenkeme, *Qian Hu Shan*, Seewis, *Tanganya*, Yákèshí
		Mole	Asama, Bruges, Oxbow, Rockport
	Thottimvirus	Shrew	Imjin, *Kilimanjaro*, Thottapalayam, *Uluguru*
		Mole	*Dahonggou Creek*
Repantavirinae	*Reptillovirus*	Reptile	Gecko

[a] Virus names shown in italics indicate the presumptive taxonomic placement in the absence of full-length S- and M-segment sequences. The names for the viruses in the genera *Actinovirus*, *Agnathovirus* and *Reptillovirus* are tentative.

harboured by bats belong to the genera *Loanvirus* and *Mobatvirus* (Table 6.1).

To minimize unnecessary confusion, the viruses newly classified in the family *Hantaviridae* will be referred to in this review as hantaviruses, even if the genus *Hantavirus* no longer exists and is not part of the revised taxonomy. Members of the family *Hantaviridae* are enveloped viruses possessing a tripartite genome, comprising three single-stranded, negative-sense RNA segments, designated S (small), M (medium), and L (large), which encode the nucleocapsid protein, the envelope glycoproteins (Gn and Gc), and the viral RNA-dependent RNA polymerase, respectively (Plyusnin *et al.*, 1996; Guardado-Calvo and Rey, 2017).

Hantavirus disease

The clinical and public health significance of hantaviruses are attributed to two medically important syndromes, namely, haemorrhagic fever with renal syndrome (HFRS) (Myhrman, 1951; Smadel, 1953; Powell, 1954; Lähdevirta, 1971; Yanagihara and Gajdusek, 1988; Noh *et al.*, 2013; Jiang *et al.*, 2016; Zou *et al.*, 2016) and hantavirus cardiopulmonary syndrome (HCPS) (Duchin *et al.*, 1994; Ketai *et al.*, 1994; Llah *et al.*, 2018), which are caused by a few rodent-borne orthohantaviruses in Europe, Asia and the Americas (Lee *et al.*, 1979; Brummer-Korvenkontio *et al.*, 1980; Nichol *et al.*, 1993; Jonsson *et al.*, 2010; Jiang *et al.*, 2017). Humans are usually infected with orthohantaviruses by the respiratory route with inhalation of aerosolized excretions or secretions (Tsai, 1987; Yanagihara, 1990). In general, person-to-person transmission does not occur, the rare exceptions being a few HCPS cases with Andes virus in Argentina and Chile (Padula *et al.*, 1998; Toro *et al.*, 1998; Martinez *et al.*, 2005; Martinez-Valdebenito *et al.*, 2014).

A fundamental epidemiological factor in HFRS and HCPS cases is exposure to environments contaminated with urine, faeces and/or saliva from infected rodents. Thus, outbreaks of HFRS and HCPS are often associated with encroachment of rodent habitats or irruptions of reservoir rodent populations with invasion of human dwellings. Although HFRS and HCPS cases have also resulted from seemingly trivial exposures, the intimate handling of rodents does not necessarily constitute sufficient exposure. That is, while mammalogists have frequent occupational contact with rodents and are presumably at increased risk, several seroepidemiological studies have indicated insignificant prevalence of orthohantavirus infections (Yanagihara *et al.*, 1984; Vapalahti *et al.*, 1995; Lundkvist *et al.*, 2000; Fritz *et al.*, 2002).

This has been corroborated in a more recent study, in which only four of 757 persons who had handled neotomine or sigmodontine rodents in North America exhibited serum IgG antibodies against Sin Nombre virus (Fulhorst *et al.*, 2007). Also, during the height of the HCPS outbreak in the Four Corners region in 1993, forest and park service personnel showed no evidence of Sin Nombre virus infection (Vitek *et al.*, 1996). By contrast, studies in Europe show clear associations between orthohantavirus infection and exposure to rodent excreta among certain high-risk occupation groups, such as animal trappers, forestry workers and farmers (Groen *et al.*, 1995; Vapalahti *et al.*, 1999; Grygorczuk *et al.*, 2008; Mertens *et al.*, 2011; Wróblewska-Łuczka *et al.*, 2017; Wróblewska-Łuczkawroblewska *et al.*, 2017), and individuals, such as hunters, whose recreational activities encroach on wildlife habitats (Deutz *et al.*, 2003).

The principal symptoms and clinical features of both HFRS and HCPS include high fever, chills, headache, generalized myalgia, abdominal pain, and nausea and vomiting. Prominent shared characteristics of HFRS and HCPS also include thrombocytopenia (Connolly-Andersen *et al.*, 2015) and vascular leakage, or increased endothelial cell permeability (Gorbunova *et al.*, 2010). While HFRS varies in clinical severity, ranging from mild to severe and life threatening, with mortality ranging from < 1% to ≥ 15%, depending on the specific orthohantavirus (Yanagihara and Gajdusek, 1988; Vaheri *et al.*, 2013; Avšič-Županc *et al.*, 2016), HCPS is generally severe, and despite intensive care treatment, has mortality rates of 25% or higher (Jonsson *et al.*, 2010; Martinez *et al.*, 2010; MacNeil *et al.*, 2011). The clinical management of HFRS and HCPS is largely supportive, with careful fluid and electrolyte management and monitoring of cardiopulmonary and/or renal function. Dialysis may be required in some patients with severe HFRS. For HCPS patients, mechanical ventilation is frequently required, and other life-saving measures, such as extracorporeal membrane oxygenation, may be necessary (Duchin *et al.*, 1994; Mertz *et al.*, 2006).

Rodents as reservoir hosts

Orthohantaviruses are hosted by small mammals, unlike all other viruses in the order *Bunyavirales*, which are transmitted by arthropod vectors (mosquito, tick or sandfly). In particular, rodents (order Rodentia, families Muridae and Cricetidae) have long been known to serve as reservoir hosts of orthohantaviruses (Table 6.1). The seminal discovery that the striped field mouse (*Apodemus agrarius*) harboured Hantaan virus, the aetiological agent of Korean haemorrhagic fever (Lee *et al.*, 1978), made possible the detection of Puumala virus, the agent of nephropathia epidemica, in the bank vole (*Myodes glareolus*) (Brummer-Korvenkontio *et al.*, 1980). Subsequently, other murid rodent species, including the yellow-necked field mouse (*Apodemus flavicollis*) (Avšič-Županc *et al.*, 1992), Korean field mouse (*Apodemus peninsulae*) (Yashina *et al.*, 2001; Baek *et al.*, 2006), Black Sea field mouse (*Apodemus ponticus*) (Klempa *et al.*, 2008), brown rat (*Rattus norvegicus*) (Lee *et al.*, 1982), and Chinese white-bellied rat (*Niviventer confucianus*) (Wang *et al.*, 2000), as well as African wood mouse (*Hylomyscus simus*) in Guinea (Klempa *et al.*, 2006) and Ethiopian white-footed mouse (*Stenocephalemys albipes*) in Ethiopia (Goüy de Bellocq *et al.*, 2016), have been found to harbour genetically distinct orthohantaviruses.

Also, multiple cricetid rodent species of the subfamilies Arvicolinae, Sigmodontinae and Neotominae host orthohantaviruses. Examples include the meadow vole (*Microtus pennsylvanicus*) (Lee P-W *et al.*, 1982, 1985), California vole (*Microtus californicus*) (Song W *et al.*, 1995), common vole (*Microtus arvalis*) (Plyusnin *et al.*, 1994), deer mouse (*Peromyscus maniculatus*) (Nerurkar *et al.*, 1993; Nichol *et al.*, 1993), white-footed mouse (*Peromyscus leucopus*) (Song *et al.*, 1994), western harvest mouse (*Reithrodontomys megalotis*) (Hjelle *et al.*, 1994), hispid cotton rat (*Sigmodon hispidus*) (Rollin *et al.*, 1995), marsh rice rat (*Oryzomys palustris*) (Torrez-Martinez and Hjelle, 1995), Alston's cotton rat (*Sigmodon alstoni*) (Fulhorst *et al.*, 1997), long-tailed rice rat (*Oligoryzomys longicaudatus*) (Levis *et al.*, 1998), small-eared pygmy rice rat (*Oligoryzomys microtis*) (Powers *et al.*, 1999), hairy-tailed bolo mouse (*Necromys lasiurus*) (Suzuki *et al.*, 2004), large vesper mouse (*Calomys callosus*) (Levis *et al.*, 2004), short-tailed cane mouse (*Zygodontomys brevicauda*) (Ruedas *et al.*, 2004), and montane grass mouse (*Akodon montensis*) (Goodin *et al.*, 2009).

Previously, the conventional view posited that each genetically distinct orthohantavirus was harboured by a single rodent species, with which it co-evolved. Mounting evidence refutes this overly simplistic paradigm and instead supports the concepts of host sharing and host switching. That is, the same orthohantavirus species may be hosted by more than one reservoir rodent species. For example, Tula virus has been reported in the common vole, southern vole (*Microtus rossiaemeridionalis*), field vole (*Microtus agrestis*), Altai vole (*Microtus obscurus*), European pine vole (*Pitymys subterraneus*) and Eurasian water vole (*Arvicola amphibius*) (Plyusnin *et al.*, 1994; Song *et al.*, 2002; Song *et al.*, 2004; Schmidt-Chanasit *et al.*, 2010; Schlegel *et al.*, 2012a; Klempa *et al.*, 2013b; Polat *et al.*, 2018).

Host sharing seems to apply also to other rodent-borne orthohantaviruses, such as Thailand virus, which has been detected in the greater bandicoot rat (*Bandicota indica*) (Elwell *et al.*, 1985; Blasdell *et al.*, 2011) and lesser bandicoot rat (*Bandicota savilei*) in Thailand (Pattamadilok *et al.*, 2006), Asian house rat (*Rattus tanezumi*) in Indonesia (Plyusnina *et al.*, 2009) and Singapore (Johansson *et al.*, 2010), and black rat (*Rattus rattus*) in Madagascar (Reynes *et al.*, 2014; Raharinosy *et al.*, 2018). Moreover, genetic variants of Puumala virus, designated Hokkaido virus and Muju virus, have been reported in the grey red-backed vole (*Myodes rufocanus*) in Japan (Kariwa *et al.*, 1995) and Russia (Yashina *et al.*, 2015), northern red-backed vole (*Myodes rutilus*) in Russia (Yashina *et al.*, 2015) and royal vole (*Myodes regulus*) in Korea (Song K-J *et al.*, 2007; Lee JG *et al.*, 2014).

Apart from examples of the same orthohantavirus species being harboured by multiple rodent species, the same rodent species can also host more than one orthohantavirus species. Examples include the field vole which hosts Tula virus in Europe and a newly discovered orthohantavirus, named Tatenale virus, in the United Kingdom (Pounder *et al.*, 2013); and the striped field mouse, which serves as the reservoir of Hantaan virus in Asia, also hosts the Kurkino and Saaremaa genotypes of Dobrava-Belgrade virus in Europe (Nemirov *et al.*, 1999; Klempa *et al.*, 2013a; Németh *et al.*, 2013).

Shrews and moles as reservoir hosts

Although the isolation of Thottapalayam virus from an Asian house shrew predated the isolation of prototype Hantaan virus, and despite early reports of HFRS antigens in tissues of the Eurasian common shrew (*Sorex araneus*), Eurasian water shrew (*Neomys fodiens*) and European mole in Russia (Gavrilovskaya *et al.*, 1983; Tkachenko *et al.*, 1983) and the former Yugoslavia (Gligić *et al.*, 1992), shrews and moles (order Eulipotyphla, families Soricidae and Talpidae) have generally been dismissed as being unimportant in the phylogeography and evolution of hantaviruses.

However, guided by these long-ignored historical accounts and emboldened by the isolation of a novel hantavirus, named Imjin virus from the Ussuri white-toothed shrew captured along the Imjin River, near the demilitarized zone in the Republic of Korea (Song *et al.*, 2009; Gu *et al.*, 2011), an aggressive search was launched for hantavirus RNA, using a brute-force RT-PCR approach based on labour-intensive, time-consuming and trial-by-error oligonucleotide design. In analysing total RNA, extracted from more than 1500 tissues from 50 shrew species collected in Europe, Asia, North America and Africa, between 1982 and 2012, multiple genetically distinct soricid-borne orthohantaviruses have been detected (Table 6.1). These include Seewis virus in the Eurasian common shrew in Switzerland (Song *et al.*, 2007b), Hungary and Finland (Kang *et al.*, 2009a), Russia (Yashina *et al.*, 2010) and Poland (Gu *et al.*, 2014b); Ash River virus in the masked shrew (*Sorex cinereus*) and Jemez Springs virus in the dusky shrew (*Sorex monticolus*) in the USA (Arai *et al.*, 2008a); Kenkeme virus in the flat-skulled shrew (*Sorex roboratus*) (Kang *et al.*, 2010) and Artybash virus in the Laxmann's shrew (*Sorex caecutiens*) (Arai *et al.*, 2016a) in Russia; Sarufutsu virus in the long-clawed shrew (*Sorex unguiculatus*) in Japan (S. Arai *et al.*, unpublished data); Cao Bằng virus in the Chinese mole shrew (*Anourosorex squamipes*) in Vietnam (Song *et al.*, 2007c) and Taiwanese mole shrew (*Anourosorex yamashinai*) in Taiwan (Gu *et al.*, 2016a); Camp Ripley virus in the northern short-tailed shrew (*Blarina brevicauda*) in the USA (Arai *et al.*, 2007); Boginia virus in the Eurasian water shrew in Poland (Gu *et al.*, 2013a); Bowé virus in the Doucet's musk shrew (*Crocidura douceti*) in Guinea (Gu *et al.*, 2013b); Azagny virus in the West African pygmy shrew (*Crocidura obscurior*) in Côte d'Ivoire (Kang *et al.*, 2011b); and Jeju virus in the Asian lesser white-toothed shrew (*Crocidura shantungensis*) in Korea (Arai *et al.*, 2012). By contrast, Uluguru virus in the geata mouse shrew and Kilimanjaro virus in the Kilimanjaro mouse shrew in Tanzania (Kang *et al.*, 2014) appear to be more closely related to Thottapalayam virus and Imjin virus, which have been classified in the genus *Thottimvirus* (Table 6.1).

Host sharing or spillover has also been found for soricid-borne orthohantaviruses. Examples include Seewis virus in the Eurasian common shrew and Eurasian pygmy shrew (*Sorex minutus*) in the Czech Republic and Germany (Schlegel *et al.*, 2012b) and in Poland (Gu *et al.*, 2014b). Also, Seewis virus has been detected in the tundra shrew (*Sorex tundrensis*) and large-toothed Siberian shrew (*Sorex daphaenodon*) in Russia (Yashina *et al.*, 2010) and in the Mediterranean water shrew (*Neomys anomalus*) in Austria (N. Nowotny, unpublished data) and Poland (Gu *et al.*, 2014b). Moreover, Jemez Springs virus, which is harboured by the dusky shrew, has been found in the vagrant shrew (*Sorex vagrans*), Trowbridge's shrew (*Sorex trowbridgii*) and American water shrew (*Sorex palustris*) in the USA (H.J. Kang *et al.*, unpublished data).

In addition, other investigators have reported soricid-borne orthohantaviruses, including Seewis virus in the Eurasian common shrew in Austria (N. Nowotny, unpublished data), Finland (Ling *et al.*, 2014), Germany (Schlegel *et al.*, 2012b; Obiegala *et al.*, 2017), Slovakia (Schlegel *et al.*, 2012b) and Slovenia (Korva *et al.*, 2013; Resman *et al.*, 2013); Tanganya virus in the Therese's shrew (*Crocidura theresae*) in Guinea (Klempa *et al.*, 2007); Qian Hu Shan virus in the greater striped-back shrew (*Sorex cylindricauda*) (Zuo *et al.*, 2014) and Yákèshí virus in the taiga shrew (*Sorex isodon*) (Guo *et al.*, 2013) in China; and Asikkala virus in the Eurasian pygmy shrew in the Czech Republic and Germany (Radosa *et al.*, 2013). Moreover, Kenkeme virus was found to co-circulate with Hantaan and Khabarovsk viruses in Bolshoy Ussuriysky Island, in China (Wang *et al.*, 2014).

Testing more than 600 tissue samples from 12 of the approximately 40 extant mole species has yielded seven genetically distinct hantaviruses: Asama virus in the Japanese shrew mole (*Urotrichus talpoides*) from Japan (Arai *et al.*, 2008b); Oxbow virus in the American shrew mole (*Neurotrichus gibbsii*) (Kang *et al.*, 2009b) and Rockport virus in the eastern mole (*Scalopus aquaticus*) (Kang *et al.*, 2011a) from the USA; Nova virus in the European mole from Hungary (Kang *et al.*, 2009c), France (Gu *et al.*, 2014a), Poland (Gu *et al.*, 2014b) and Belgium (Laenen *et al.*, 2018); Bruges virus in the European mole from Belgium and United Kingdom (Laenen *et al.*, 2018); Asturias virus in the Iberian mole (*Talpa occidentalis*) from Spain (Gu *et al.*, 2016c); and Dahonggou Creek virus in the long-tailed mole (*Scaptonyx fusicaudus*) from China (Kang *et al.*, 2016). As in rodents, the same talpid host can harbour more than one hantavirus species, as exemplified by the European mole, which hosts Nova virus and Bruges virus in Belgium (Laenen *et al.*, 2018) and the Iberian mole, which appears to harbour Asturias virus, Bruges virus and Nova virus in Spain (Gu *et al.*, 2016c).

Because many mole species have been unavailable for testing and sample sizes were small, numbering fewer than 10 individuals for many of the species tested, the list of seven probably represents a gross underestimation of the actual number of talpid-borne hantaviruses. More targeted searches for hantavirus RNA in mole species, such as the Altai mole (*Talpa altaica*), blind or Mediterranean mole (*Talpa caeca*), Caucasian mole (*Talpa caucasica*), Roman mole (*Talpa romana*) and Balkan mole (*Talpa stankovici*), will likely lead to the discovery of additional hantaviruses and provide insights into host-switching events.

Nova virus, which represents among the most highly divergent lineages (Kang *et al.*, 2009c), has been classified in the genus *Mobatvirus* with several hantaviruses harboured by bats (Table 6.1). Recent studies have indicated high prevalence of Nova virus infection exceeding 50% in European moles from France and Poland, suggesting efficient enzootic virus transmission and a well-established, long-standing reservoir host–mobatvirus relationship (Gu *et al.*, 2014a; Gu *et al.*, 2014b). Much like Seewis virus, which is widespread in the Eurasian common shrew throughout Europe, Nova virus probably occurs throughout the vast distribution of the European mole.

Bats as reservoir hosts

Bats (order Chiroptera) represent the second largest order of mammals, with more than 1200 species or approximately 20% of all classified mammal species worldwide. Bats are found in all continents, except Antarctica. They are the only mammals capable of controlled and sustained flight. While most bats are insectivorous or frugivorous, three extant bat species, which are all native to the Americas, feed exclusively on the blood of birds or mammals. Bats serve as natural reservoirs of many microbial pathogens, and their mobility through flight, longevity and social structures contribute to the transmission and spread of zoonotic diseases.

The order Chiroptera was formerly divided in two suborders: Megachiroptera and Microchiroptera. However, due to the paraphyly of the Microchiroptera, a new taxonomic nomenclature has been proposed, comprising the suborder Yinpterochiroptera or Vespertilioniformes (megabats or fruit bats in the family Pteropodidae in Megachiroptera and a few Microchiroptera families) and the suborder Yangochiroptera or Pteropodiformes (the remaining Microchiroptera families) (Teeling, 2009). Irrespective of the classification, bat species in both suborders have been found to host viruses in the newly created genera of *Loanvirus* and *Mobatvirus*, within the subfamily *Mammantavirinae*, of the family *Hantaviridae*, suggesting that primordial hantaviruses may have emerged in an early common ancestor of bats.

Despite the more than 3000 tissue samples from approximately 100 bat species, representing 11 families (Emballonuridae, Hipposideridae, Megadermatidae, Miniopteridae, Molossidae, Mormoopidae, Nycteridae, Phylostomidae, Pteropodidae, Rhinopholidae, and Vespertilionidae), tested by RT-PCR, only 10 bat-borne hantaviruses have hitherto been reported (Table 6.2). Within the suborder Yinpterochiroptera, hantaviruses have been reported in bat species belonging to three

Table 6.2 Summary of bat-borne loanviruses and mobatviruses in the family *Hantaviridae*[a]

Authors	Tissues collected	Total tested	Genus species	Country	RNA positive	Virus name
Sumibcay *et al*. (2012)	2011–2012	213	*Neoromicia nanus*	Côte d'Ivoire	2/12	Mouyassué
Weiss *et al*. (2012)	2009–2011	417	*Nycteris hispida*	Sierra Leone	1/18	Magboi
Arai *et al*. (2013)	2012	51	*Hipposideros pomona*	Vietnam	1/5	Xuân Sơn
Guo *et al*. (2013)	2011–2012	605	*Rhinolophus monoceros*	China	1/4	Lóngquán
			Rhinolophus affinis	China	6/26	Lóngquán
			Rhinolophus sinicus	China	3/135	Lóngquán
			Pipistrellus abramus	China	1/5	Huángpí
Gu *et al*. (2014c)	1981–2012	533	*Hipposideros pomona*	Vietnam	5/44	Xuân Sơn
Xu *et al*. (2015)	2012	32	*Taphozous melanopogon*	China	1/32	Láibīn
Arai *et al*. (2016b)	2008–2013	376	*Rousettus amplexicaudatus*	Philippines	1/15	Quezon
Witkowski *et al*. (2016)	2009	324	*Hipposideros ruber*	Gabon	1/123	Makokou
Straková *et al*. (2017)	2008–2013	53	*Nyctalus noctula*	Czech Republic	2/12	Brno
Těšíková *et al*. (2017)	2009–2014	85	*Neoromicia capensis*	Ethiopia	1/25	Mouyassué
Arai *et al*. (2019a)	2013–2015	121	*Taphozous melanopogon*	Myanmar	2/13	Láibīn
Arai *et al*. (2019a)	2013–2015	156	*Hipposideros cineraceus*	Vietnam	3/6	Xuân Sơn
Arai *et al*. (2019b)	2012–2015	215	*Aselliscus stoliczkanus*	Vietnam	1/2	Đakrông

[a] Total number of bats tested: 3181 (representing 11 families) resulting in 32 positive bats by RT-PCR
Yinpterochiroptera: Hipposideridae, Megadermatidae, Pteropodidae, Rhinopholidae.
Yangochiroptera: Emballonuridae, Miniopteridae, Molossidae, Mormoopidae, Nycteridae, Phylostomidae, Vespertilionidae.
Unpublished data on approximately 2000 additional bats from Africa: Ponan virus in *Neoromicia nanus* from Côte d'Ivoire.
Lompole virus in unidentified bat species from Democratic Republic of Congo.

phylogenetically distant families, namely Hipposideridae (Old World leaf-nosed bats), Rhinolophidae (horseshoe bats) and Pteropodidae (Old World fruit bats) (Arai *et al.*, 2013; Guo *et al.*, 2013; Gu *et al.*, 2014c; Arai *et al.*, 2016b; Witkowski *et al.*, 2016; Arai *et al.*, 2019a; Arai *et al.*, 2019b), while within the suborder Yangochiroptera, bat species in the families Nycteridae (slit-faced or hollow-faced bats), Vespertilionidae (vesper bats) and Emballonuridae (sac-winged bats) have been shown to harbour hantaviruses (Sumibcay *et al.*, 2012; Weiss *et al.*, 2012; Xu *et al.*, 2015; Straková *et al.*, 2017; Těšíková *et al.*, 2017; Arai *et al.*, 2019a). The families Hipposideridae and Vespertilionidae are among the most speciose insectivorous bats, with member species distributed across Africa, Europe, Asia, the Americas and Australia. Their vast geographic distribution provides unlimited opportunities to search for other bat-associated hantaviruses.

To date, bat-borne hantaviruses include: Mouyassué virus in the banana pipistrelle (*Neoromicia nanus*) from Côte d'Ivoire (Sumibcay *et al.*, 2012) and cape serotine (*Neoromicia capensis*) from Ethiopia (Těšíková *et al.*, 2017); Magboi virus in the hairy slit-faced bat (*Nycteris hispida*) from Sierra Leone (Weiss et al., 2012); Xuân Sơn virus in the Pomona roundleaf bat (*Hipposideros pomona*) (Arai *et al.*, 2013; Gu et al., 2014c) and ashy roundleaf bat or least leaf-nosed bat (*Hipposideros cineraceus*) (Arai *et al.*, 2019a) from Vietnam; Đakrông virus in the Stoliczka's Asian trident bat (*Aselliscus stoliczkanus*) from Vietnam (Arai *et al.*, 2019b); Láibīn virus in the black-bearded tomb bat (*Taphozous melanopogon*) from China (Xu et al., 2015) and Myanmar (Arai *et al.*, 2019a); Huángpí virus in the Japanese house bat (*Pipistrellus abramus*) and Lóngquán virus in the Chinese horseshoe bat (*Rhinolophus sinicus*), Formosan lesser horseshoe bat (*Rhinolophus monoceros*) and intermediate horseshoe bat (*Rhinolophus affinis*) from China (Guo et al., 2013); Makokou virus in the Noack's roundleaf bat (*Hipposideros ruber*) from Gabon (Witkowski et al., 2016); Quezon virus in the Geoffroy's rousette (*Rousettus amplexicaudatus*) from the Philippines (Arai et al., 2016b); and Brno virus in the common noctule (*Nyctalus noctula*) from the Czech Republic (Straková et al., 2017).

Compared to the multitude of orthohantaviruses reported from more than half of the 50 Eulipotyphla species tested (Yanagihara *et al.*, 2014), the cumulative number of newly recognized bat-borne hantaviruses is exceedingly low (Sumibcay *et al.*, 2012; Weiss *et al.*, 2012; Arai *et al.*, 2013; Guo *et al.*, 2013; Gu *et al.*, 2014c; Xu *et al.*, 2015; Arai *et al.*, 2016b; Witkowski *et al.*, 2016; Straková *et al.*, 2017; Těšíková *et al.*, 2017; Arai *et al.*, 2019a; Arai *et al.*, 2019b). The reasons for the low success rates of detecting hantavirus RNA in bat tissues are not altogether clear. One possibility is the highly divergent nature of their genomes, as well as the very focal or localized nature of hantavirus infection in bats and the small sample sizes of bat species, as well as primer mismatches, suboptimal PCR cycling conditions, and variable tissue preservation with degraded RNA (Arai *et al.*, 2013; Gu *et al.*, 2014c). Alternatively, bats may be less susceptible to hantavirus infection or may have developed immune mechanisms to curtail viral replication and/or persistence. In any case, as shown in Table 6.3, the full genomes of bat-borne hantaviruses are largely incomplete. Suboptimal primer design, imperfect cycling conditions, low RNA yields and poor RNA integrity (particularly in poorly preserved archival tissues collected under harsh field conditions) may have thwarted amplification and genome sequencing efforts (Gu *et al.*, 2014c). However, while fewer bat species have been identified as reservoirs, the hantaviruses they harbour are among the most genetically diverse described to date.

Hantaviruses in bats of the suborder Yangochiroptera

The geographic distribution of four bat species belonging to the suborder Yangochiroptera, which harbour newfound orthohantaviruses, is shown in Fig. 6.1. A brief description of each hantavirus and its reservoir bat host is provided below and data are summarized in Table 6.2. Full genomes of Láibīn virus and Brno virus are available (Table 6.3).

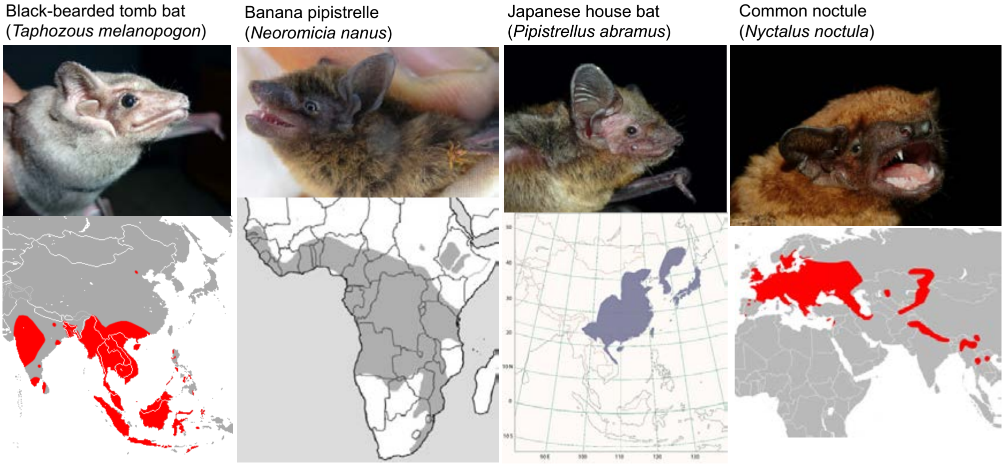
Mouyassué virus (MOYV) (genus *Loanvirus*). Detected in ethanol-fixed liver tissues from two of 12 banana pipistrelles captured near Mouyassué village (N 05°22'07", W 03°05'37") in Aboisso District, 130 km from Abidjan, in the extreme south-eastern region of Côte d'Ivoire during June 2011, MOYV was one of the first bat-borne hantaviruses reported (Sumibcay *et al.*, 2012). The originally proposed three-letter abbreviation was changed to MOYV to avoid confusion with Moussa

Table 6.3 Summary of available sequences for 10 bat-borne loanviruses and mobatviruses belonging to the suborders Yangochiroptera and Yinpterochiroptera

						Segment		
Suborder	Family	Genus and species	Country	Year trapped	Virus Name	S	M	L
Yangochiroptera	Emballonuridae	*Taphozous melanopogon*	China	2012	Láibīn	■ 1935 KM102247	■ 3908 KM102248	■ 6531 KM102249
			Myanmar	2015	Láibīn	■ 1776 MK064114	■ 3881 MK064115	■ 6531 MK064116
	Nycteridae	*Nycteris hispida*	Sierra Leone	2010	Magboi			░ 414 JN037851
	Vespertilionidae	*Neoromicia nanus*	Côte d'Ivoire	2011	Mouyassué			░ 1691 JQ287716
		Neoromicia capensis	Ethiopia	2014	Mouyassué			░ 237 KX184829
		Pipistrellus abramus	China	2011	Huángpí	▓ 1115 JX473273		░ 343 JX465369
		Nyctalus noctula	Czech Republic	2012	Brno	■ 1269 KX845678	■ 3408 KX845679	■ 6432 KX845680
Yinpterochiroptera	Hipposideridae	*Hipposideros pomona*	Vietnam	2012	Xuân Sơn	■ 1748 KC688335	■ 3756 KU976427	■ 6520 JX912953
		Hipposideros cineraceus	Vietnam	2013	Xuân Sơn	▓ 1660 MK393927	▓ 1754 MK393928	■ 6521 LC406451
		Hipposideros ruber	Gabon	2012	Makokou			▓ 3582 KT316176
		Aselliscus stoliczkanus	Vietnam	2013	Đakrông	■ 1746 MG663534	■ 3622 MG663535	■ 6535 MG663536
	Rhinolophidae	*Rhinolophus sinicus*	China	2011	Lóngquán	■ 1564 JX465422	■ 3619 JX465402	░ 324 JX465388
		Rhinolophus affinis	China	2011	Lóngquán	■ 1545 JX465416	■ 3618 JX465398	░ 324 JX465382
		Rhinolophus monoceros	China	2011	Lóngquán	■ 1564 JX465419		░ 324 JX465385
	Pteropodidae	*Rousettus amplexicaudatus*	Philippines	2009	Quezon	■ 1830 KU950713	■ 3772 KU950714	■ 6556 KU950715

The full-length genomes of one bat-borne loanvirus (Brno virus) and four bat-borne mobatviruses (Đakrông virus, Láibīn virus, Quezon virus and Xuân Sơn virus) have been sequenced. In addition, full-length S- and M-segment sequences are available for Lóngquán virus, a bat-borne loanvirus. The number of nucleotides for each segment sequenced to date, with GenBank number, is shown for each bat-borne loanvirus and mobatvirus.

Available Sequences ■ Full Length ▓ >50% ░ <50% □ None



Black-bearded tomb bat (*Taphozous melanopogon*)

Banana pipistrelle (*Neoromicia nanus*)

Japanese house bat (*Pipistrellus abramus*)

Common noctule (*Nyctalus noctula*)

Figure 6.1 Geographic distribution of four bat species, belonging to the suborder Yangochiroptera, which harbour newfound loanviruses and mobatviruses. The black-bearded tomb bat (*Taphozous melanopogon*) (family Emballonuridae) hosts Láibīn virus; the banana pipistrelle (*Neoromicia nanus*) (family Vespertilionidae) hosts Mouyassué virus; the Japanese house bat (*Pipistrellus abramus*) (family Vespertilionidae) hosts Huángpí virus; and the common noctule (*Nyctalus noctula*) (family Vespertilionidae) hosts Brno virus. Not shown are the hairy slit-faced bat (*Nycteris hispida*) (family Nycteridae) and cape serotine (*Neoromicia capensis*) (family Vespertilionidae), which host Magboi virus and Mouyassué virus, respectively.

virus (MOUV), a newly described rhabdovirus isolated from *Culex* mosquitoes in Côte d'Ivoire (Quan *et al.*, 2010). MOYV has also been found in one of nine cape serotines captured in Dhati Walel National Park (N 09°13'33", E 34°52'37"), at an elevation of 1427 m, in Ethiopia during February 2014 (Těšíková *et al.*, 2017). The successful amplification of MOYV from ethanol-fixed tissues augments the potential pool of archival tissues for future exploratory studies of hantaviruses in bats, as well as other insectivorous small mammals that have shared ancestry with bats. The banana pipistrelle and cape serotine, which are distributed widely in forests and savannas across sub-Saharan Africa (Monadjem *et al.*, 2017b, 2017c), are two of 13 species in the genus *Neoromicia* of the family Vespertilionidae. Like other vesper bats, the banana pipistrelle and cape serotine are insectivorous.

Magboi virus (MGBV) (genus *Loanvirus*). In analysing 525 tissue samples from 417 bats representing 28 genera for hantavirus RNA, a 414-nucleotide region of the L segment of a newfound orthohantavirus, named MGBV, was detected in one of 18 hairy slit-faced bats captured at Magboi River within Gola National Park (N 07°50.194', W 10°38.626') in Sierra Leone during 2009 (Weiss *et al.*, 2012). The host species (family Nycteridae) has a wide geographic range, encompassing much of sub-Saharan Africa, with the exception of the Horn of Africa and parts of southern Africa. There is an apparently disjunct population in western Mauritania close to the border with Senegal, and an isolated record from central Mali.

Huángpí virus (HUPV) (genus *Loanvirus*). Sequences from a 1115-nucleotide region of the S segment and a 343-nucleotide region of the L segment are available for HUPV, which was detected in one of five Japanese house bats, captured in Huángpí District (N 30°52'30", E 114°22'30"), one of 13 districts of Wuhan, the capital of Húběi Province in China during 2012 (Guo *et al.*, 2013). The Japanese house bat, a member of the family Vespertilionidae, is found in the southern Ussuri region (Russia and China), the western half of China including Taiwan, Japan, the Korean Peninsula, Vietnam, Myanmar, and India (Fig. 6.1) (Bates and Tsytsulina, 2008).

Láibīn virus (LAIV) (genus *Mobatvirus*). The full-length genome (1935 nucleotide S, 3908 nucleotide M and 6531-nucleotide L segment) is available for LAIV strain BT20 (Table 6.3), which was originally detected in one of 32 black-bearded tomb bats, captured in Láibīn City (N 23°44', E 109°14') in Guăngxī Province in China during July 2012 (Xu *et al.*, 2015). LAIV (strain BT33) has also been detected in one of 74 black-bearded tomb bats captured in May 2014 in Băisè, in Guăngxī Province, bordering Vietnam (Xu *et al.*, 2019), as well as in two of 15 black-bearded tomb bats (strains MM4377M17 and MM4378M18), trapped in November 2015 in Shwe Ba Hill Cave in the Sagaing Region of Myanmar (Arai *et al.*, 2019a). LAIV has the longest M segment, which includes a 504-nucleotide long 3′-non-coding region. The black-bearded tomb bat is widely distributed throughout Asia and Southeast Asia (Fig. 6.1), including Brunei, Cambodia, China, India, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Sri Lanka, Thailand, Timor-Leste and Vietnam (Csorba *et al.*, 2008).

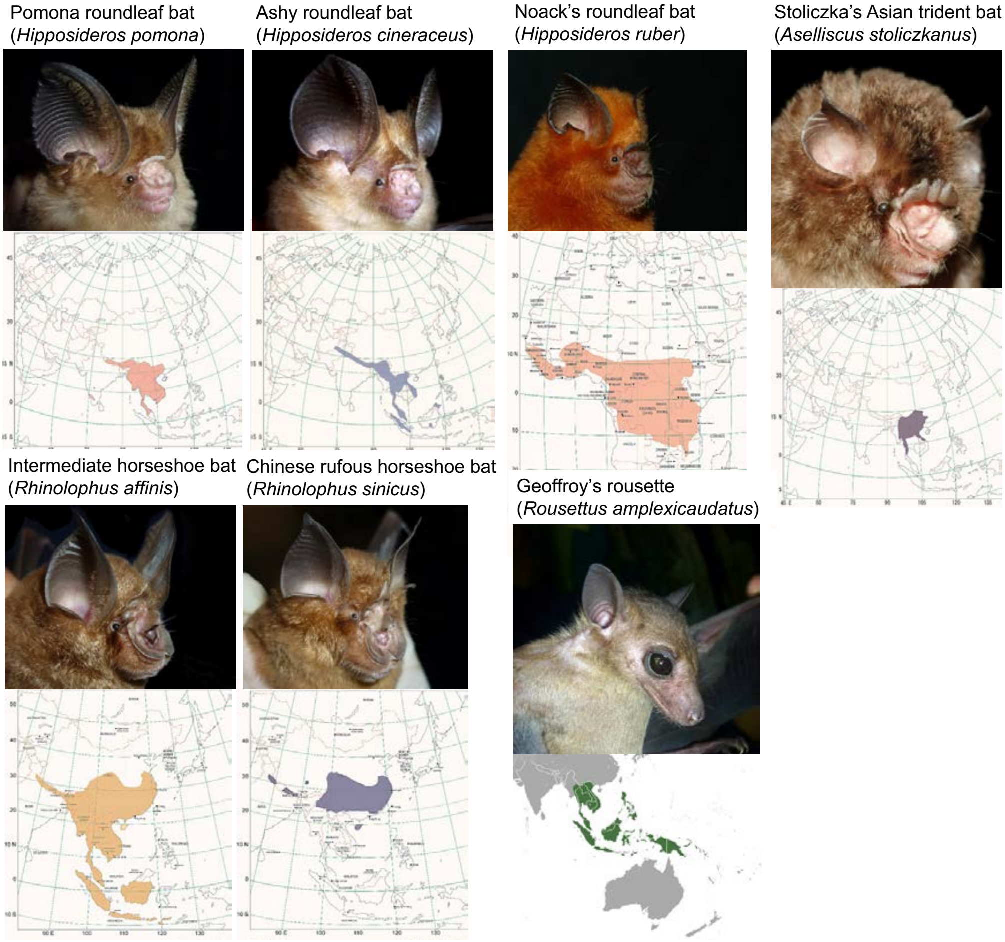
Brno virus (BRNV) (genus *Loanvirus*). In testing 53 bats, which had died accidentally or which were found dead, BRNV was detected in two of 12 common noctules in Brno (N 49°12', E 16°37'), the second largest city in the Czech Republic (Straková *et al.*, 2017). The entire genome of BRNV strain 7/2012 is available (1269-nucleotide S, 3408-nucleotide M and 6432-nucleotide L) (Table 6.3). To date, this is the only bat-borne hantavirus reported from Europe. Common noctules have a wide Palearctic distribution (Fig. 6.1), including Europe and southern Scandinavia to the Urals and Caucasus; Turkey to Israel and Oman; western Turkmenistan, western Kazakhstan, Uzbekistan, Kyrgyzstan, and Tajikistan to southwest Siberia and perhaps the Himalayas. Its occurrence in North Africa is questionable, and a record from Mozambique is considered dubious (Csorba and Hutson, 2016).

Hantaviruses in bats of the suborder Yinpterochiroptera

The geographic distribution of seven bat species belonging to the suborder Yinpterochiroptera, which harbour newfound orthohantaviruses is shown in Fig. 6.2. A brief description of each hantavirus and its reservoir bat host is provided below and data are summarized in Table 6.2. Full genomes of Xuân Sơn virus, Đakrông virus and Quezon virus are available.

Lóngquán virus (LQUV) (genus *Loanvirus*). LQUV was detected in six of 26 intermediate horseshoe bats (strains Ra-5, Ra-10, Ra-14, Ra-25, Ra-56 and Ra-90), three of 135 Chinese rufous horseshoe bats (strains Rs-32, Rs-141 and Rs-168), and one of four Formosan lesser horseshoe bats (strain Rm-180), captured in Lóngquán City (N 28°04', E 119°08') in southwestern Zhèjiāng Province in China during 2011 (Guo *et al.*, 2013). Intermediate horseshoe bats are widespread throughout South Asia (Fig. 6.2), southern and central China and Southeast Asia (Walston *et al.*, 2008); Chinese rufous horseshoe bats range from northern South Asia into northern Southeast Asia, and much of central, southern and southwestern China (Bates *et al.*, 2008); and Formosan lesser horseshoe bats are reported as a Taiwanese species, but it is very similar to least horseshoe bats (*Rhinolophus pusillus*) in body size, echolocation call frequency and mitochondrial gene sequences. Least horseshoe bats have a very wide range from South Asia eastward to Japan, occurring also in southern and southwestern China, including Taiwan, southward through mainland Southeast Asia to Indonesia and Borneo (Hutson *et al.*, 2008). Its ability to also host LQUV warrants study.

Xuân Sơn virus (XSV) (genus *Mobatvirus*). To date, six strains of XSV (VN1982B4, F42640, F42682, F44580, F44583 and F44601) have been detected in Pomona roundleaf bats, captured in Xuân Sơn National Park (N 21°07'26.75", E 104°57'29.98"), a nature reserve in Thanh Sơn District, of Phú Thọ Province, approximately 100 km west of Hanoi, during July 2012; in Na Hang Nature Reserve (N 22°7', E 105°15') in Tuyên Quang Province during May 1997; and in Noc Ong Toan (N 15.1400°, E 108.0200°) in Quảng Nam Province during March 1999 (Arai *et al.*, 2013; Gu *et al.*, 2014c). XSV-infected Pomona roundleaf bats have also been captured in the Sagaing Region and in Nay Pyi Taw Union Territory of Myanmar (Arai *et al.*, 2019a) and in Yúnnán Province of China (Xu *et al.*, 2019). And in Vietnam, XSV has been detected in ashy roundleaf bats captured in Bắc Hướng Hóa Nature Reserve (N 16°53'21", E 106°34'14") in Hướng Hóa District, Quảng Trị Province during August 2013; in Xuân Sơn National Park (N 21°07'23", E 104°57'36") in Tân Sơn District, Phú Thọ Province during August 2015; and in Me Linh Station for Biodiversity (N 21.3927°, E 105.7145°) in Phúc Yên District, Vĩnh Phúc Province during April 2016 (Arai *et*



Pomona roundleaf bat (*Hipposideros pomona*)

Ashy roundleaf bat (*Hipposideros cineraceus*)

Noack's roundleaf bat (*Hipposideros ruber*)

Stoliczka's Asian trident bat (*Aselliscus stoliczkanus*)

Intermediate horseshoe bat (*Rhinolophus affinis*)

Chinese rufous horseshoe bat (*Rhinolophus sinicus*)

Geoffroy's rousette (*Rousettus amplexicaudatus*)

Figure 6.2 Geographic distribution of seven bat species, belonging to the suborder Yinpterochiroptera, which harbour newfound loanviruses and mobatviruses. The Pomona roundleaf bat (*Hipposideros pomona*) and ashy roundleaf bat (*Hipposideros cineraceus*) (family Hipposideridae) hosts Xuân Sơn virus; the Noack's roundleaf bat (*Hipposideros ruber*) (family Hipposideridae) hosts Makokou virus; the Stoliczka's Asian trident bat (*Aselliscus stoliczkanus*) (family Hipposideridae) hosts Đakrông virus; the intermediate horseshoe bat (*Rhinolophus affinis*) and Chinese rufous horseshoe bat (*Rhinolophus sinicus*) (family Rhinolophidae) hosts Lóngquán virus; and the Geoffroy's rousette (*Rousettus amplexicaudatus*) (family Pteropodidae) hosts Quezon virus.

al., 2019a). Recently, XSV strains have also been reported in ashy roundleaf bats from Guǎngxī Province in China (Xu *et al.*, 2019). Pomona roundleaf bats and ashy roundleaf bats are sympatric, but the latter species usually occurs in much lower abundance. Nevertheless, they often roost in the same caves, which may account for spillover of XSV.

The genome of prototype XSV strain VN1982B4 consists of 1748-nucleotide S, 3756-nucleotide M and 6520-nucleotide L (Table 6.3). The *Hipposideros* genus of the family Hipposideridae is one of the most speciose of insectivorous bats, with more than 70 species distributed across Africa, Europe, Asia and Australia. The vast geographic distribution of the Pomona roundleaf bat throughout Vietnam (Fig. 6.2), as well as in Bangladesh, Cambodia, China, India, Laos, Malaysia, Myanmar, Nepal and Thailand, provides opportunities to ascertain the genetic diversity and phylogeography of XSV and XSV-related hantaviruses. In this regard, although hantavirus RNA was not detected in archival tissues from several other *Hipposideros* species (*H. cafer, H. cervinus, H. cyclops* and *H. gambianus*) (Sumibcay *et al.*, 2012; Weiss *et al.*, 2012), it is very likely that many more genetically divergent mobatviruses are harboured by bat species in this large family.

Makokou virus (MAKV) (genus *Mobatvirus*). A partial 3582-nucleotide region of the L segment is available for MAKV, which was detected in one of 123 Noack's roundleaf bats, trapped in a cave near the city of Makokou (N 0°34', E 12°52') in Gabon during 2009 (Witkowski *et al.*, 2016). A member of the family *Hipposideridae*, the Noack's roundleaf bat is one of the most common bat species in Africa (Fig. 6.2), ranging from west to east in central Africa, Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Republic of Congo, Democratic Republic of Congo, Côte d'Ivoire, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Malawi, Mali, Mozambique, Niger, Nigeria, Rwanda, São Tomé and Príncipe, Senegal, Sierra Leone, Sudan, Tanzania, Togo, Uganda and Zambia (Monadjem, 2017a).

Đakrông virus (DKGV) (genus *Mobatvirus*). The entire genome of DKGV strain VN2913B72 (1746-nucleotide S, 3622-nucleotide M and 6535-nucleotide L) (Table 6.3) has been detected in one of two Stoliczka's Asian trident bats, captured in Đakrông Nature Reserve (N 16°39'3", E 107°2'13") in Quảng Trị Province in Vietnam in August 2013 (Arai *et al.*, 2019b). The Stoliczka's Asian trident bat, one of three species in the genus *Aselliscus*, is found in northern Southeast Asia (Fig. 6.2), from Myanmar and southern China in the North through Thailand, Laos and Vietnam to Pulau Tioman Island, Peninsular Malaysia in the South. A closely related species, the Dong Bac's trident bat (*Aselliscus dongbacana*) (Tu *et al.*, 2015), overlaps in body size, geographic distribution, echolocation and habitat, but orthohantavirus RNA could not be detected in this species (S. Arai *et al.*, unpublished data).

Quezon virus (QZNV) (genus *Mobatvirus*). As the only hantavirus to date in a megabat, or flying fox species, QZNV, which was detected in one of 15 Geoffroy's rousettes, captured in Quezon National Park (N 13°59', E 121°55'), located approximately 130 km southeast of Manila, on Luzon Island, in the Philippines during 2009 (Arai *et al.*, 2016b), expands the host range of hantaviruses. The Geoffroy's rousette, one of 10 species in the genus *Rousettus*, is a megabat or Old World fruit bat typically roosting in caves and feeding on fruit, nectar and pollen throughout Southeast Asia and in the Malesia region of Oceania, in Myanmar, Thailand, Cambodia, Laos, Vietnam, Singapore, Indonesia, Borneo, East Timor, Solomon Islands, Bismarck Archipelago, Papua New Guinea and the Philippines (Fig. 6.2). Reproductive synchrony between Geoffroy's rousettes and two closely related species, long-tongued nectar bat (*Macroglossus minimus*) and lesser short-nosed fruit bat (*Cynopterus brachyotis*), has been documented in the Philippines (Heideman and Utzurrum, 2003).

Molecular phylogeny

Previously, the segregation of hantaviruses into clades that paralleled the molecular phylogeny of their rodent hosts suggested codivergence (Plyusnin *et al.*, 1996). Recently, this concept has been challenged on the basis of the disjunction between the evolutionary rates of the host and virus species. Preferential host switching and local host-specific adaptation have been proposed to account for the largely congruent phylogenies (Ramsden *et al.*, 2009). However, host-switching events alone do not completely explain the co-existence and distribution of genetically distinct hantaviruses among host species in three divergent taxonomic orders of small mammals spanning across four continents (Bennett *et al.*, 2014).

Phylogenetic analyses, based on S-, M- and L-genomic sequences, using maximum-likelihood and Bayesian methods, indicate that all bat-borne hantaviruses (or loanviruses and mobatviruses) share a common ancestry (Fig. 6.3). In all analyses, Nova virus from the European mole segregates with the bat-associated mobatviruses. The basal position of bat- and mole-borne mobatviruses and selected shrew-borne hantaviruses (or thottimviruses), such as Thottapalayam virus in the Asian house shrew and Imjin virus in the Ussuri white-toothed shrew, suggests that bats, moles and/or shrews, rather than rodents, may have served as the primordial mammalian hosts of ancestral hantaviruses (Fig. 6.3).

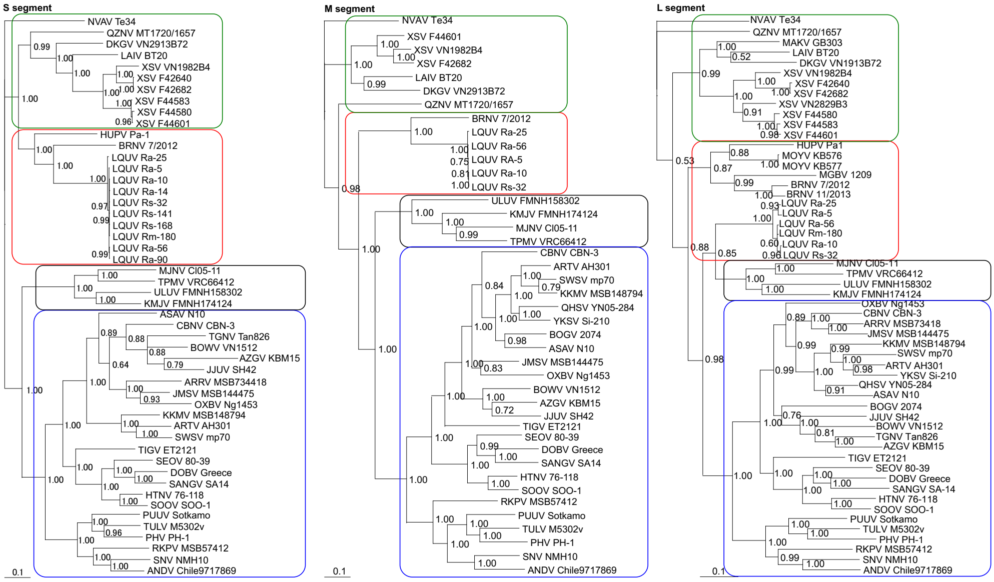


Figure 6.3 Phylogenetic trees, based sequences of the S-, M- and L-genomic segments, respectively, generated by the Bayesian Markov chain Monte Carlo estimation method, under the GTR + I + Γ model of evolution. The phylogenetic groupings of viruses belonging to the genera *Loanvirus* (red), *Mobatvirus* (green), *Orthohantavirus* (blue) and *Thottimvirus* (black) within the subfamily *Mammantavirinae* of the family *Hantaviridae* are shown. The numbers at each node are Bayesian posterior probabilities (> 0.7) based on 150,000 trees: two replicate Markov chain Monte Carlo runs, consisting of six chains of 10 million generations each sampled every 100 generations with a burn-in of 25,000 (25%). Scale bars indicate nucleotide substitutions per site. Loanviruses include Brno virus (BRNV) strains 7/2012 (S: KX845678; M: KX845679; L: KX845680) and 11/2013 (L: KR920360), Lóngquán virus (LQUV) strains Ra-5 (S: JX465416; M: JX465398; L: JX465382), LQUV Ra-10 (S: JX465413; M: JX465396; L: JX465379), LQUV Ra-14 (S: JX465414), LQUV Ra-25 (S: JX465415; M: JX465397), LQUV Ra-56 (S: JX465417; M: JX465399; L: JX465383), LQUV Ra-90 (S: JX465418) from *Rhinolophus affinis*, LQUV Rs-32 (S: JX465422; M: JX465402; L: JX465388), LQUV Rs-141 (S: JX465420), LQUV Rs-168 (S: JX465421) from *Rhinolophus sinicus*, LQUV Rm-180 (S: JX465419; L: JX465385) from *Rhinolophus monoceros*, Magboi virus (MGBV) strain 1209 (L: JN037851) from *Nycteris hispida*, Mouyassué virus (MOYV) strains KB576 (L: JQ287716) and KB577 (L: KJ000540) from *Neoromicia nanus*, and Huángpí virus (HUPV) strain Pa-1 (S: JX473273; L: JX465369) from *Pipistrellus abramus*. Mobatviruses include Đakrông virus (DKGV) strain VN2913B72 (S: MG663536; M: MG663535; L: MG663534) from *Aselliscus stoliczkanus*, Láibīn virus (LAIV) strain BT20 (S: KM102247; M: KM102248; L: KM102249) from *Taphozous melanopogon*, Xuân Sơn virus (XSV) strains VN1982B4 (S: KC688335; M: KU976427; L: JX912953), F42640 (S: KF704708; L: KF704713), F42682 (S: KF704709; M: KJ000538; L: KF704714), F44580 (S: KF704710; L: KF704715), F44583 (S: KF704711; L: KF704716), F44601 (S: KF704712; M: KJ000539; L: KF704717) from *Hipposideros pomona*, XSV strain VN2829B3 (L: LC406451) from *Hipposideros cineraceus*, Makokou virus (MAKV) strain GB303 (L: KT316176) from *Hipposideros ruber*, Quezon virus (QZNV) strain MT1720/1657 (S: KU950713; M: KU950714; L: KU950715) from *Rousettus amplexicaudatus*, and Nova virus (NVAV) strain Te34 (S: KR072621; M: KR072622; L: KR072623) from *Talpa europaea*. Orthohantaviruses include Cao Bằng virus (CBNV) strain CBN-3 (S: EF543524; M: EF543526; L: EF543525) from *Anourosorex squamipes*, Ash River virus (ARRV) strain MSB734418 (S: EF650086; L: EF619961) from *Sorex cinereus*, Jemez Springs virus (JMSV) strain MSB144475 (S: FJ593499; M: FJ593500; L: FJ593501) from *Sorex monticolus*, Seewis virus (SWSV) strain mp70 (S: EF636024; M: EF636025; L: EF636026) from *Sorex araneus*, Artybash virus (ARTV) strain AH301 (S: KF974360; M: KF974359; L: KF974361) from *Sorex caecutiens*, Kenkeme virus (KKMV) strain MSB148794 (S: GQ306148; M: GQ306149; L: GQ306150) from *Sorex roboratus*, Qian Hu Shan virus (QHSV) strain YN05–284 (M: GU566022; L: GU566021) from *Sorex cylindricauda*, Yákèshí virus (YKSV) strain Si210 (M: NC_038705; L: JX465389) from *Sorex isodon*, and Boginia virus (BOGV) strain 2074 (L: JX990965) from *Neomys fodiens*, Azagny virus (AZGV) strain KBM15 (S: JF276226; M: JF276227; L: JF276228) from *Crocidura obscurior*, Tanganya virus (TGNV) strain Tan826 (S: EF050455; L: EF050454) from *Crocidura theresea*, Bowé virus (BOWV) strain VN1512 (S: KC631782; M: KC631783; L: KC631784) from *Crocidura douceti*, Jeju virus (JJUV) strain SH42 (S: HQ663933; M: HQ663934; L: HQ663935) from *Crocidura shantungensis*, Asama virus (ASAV) strain N10 (S: EU929072; M: EU929075; L: EU929078) from *Urotrichus talpoides*, Oxbow virus (OXBV) strain Ng1453 (S: FJ5339166; M: FJ539167; L: FJ593497) from *Neurotrichus gibbsii*, and Rockport virus (RKPV) strain MSB57412 (S: HM015223; M: HM015222; L: HM015221) from *Scalopus aquaticus*. Other orthohantavirus taxa include Sin Nombre virus (SNV) strain NMH10 (S: NC_005216; M: NC_005215; L: NC_005217), Andes virus (ANDV) strain Chile9717869 (S: AF291702; M: AF291703; L: AF291704), Prospect Hill virus (PHV) stain PH-1 (S: Z49098; M: X55129; L: EF646763), Tula virus (TULV) strain M5302v (S: NC_005227; M: NC_005228; L: NC_005226), Puumala virus (PUUV) strain Sotkamo (S: NC_005224; M: NC_005223; L: NC_005225), Dobrava virus (DOBV) strain Greece (S: NC_005233; M: NC_005234; L: NC_005235), Hantaan virus (HTNV) strain 76-118 (S: NC_005218; M: NC_005219; L: NC_005222), Soochong virus (SOOV) strain SOO-1 (S: AY675349; M: AY675353; L: DQ056292), Sangassou virus (SANGV) strain SA14 (S: JQ082300; M: JQ082301; L: JQ082302), Tigray virus (TIGV) strain ET2121 (S: KU934010; M: KU934009; L: KU934008), and Seoul virus (SEOV) strain 80-39 (S: NC_005236; M: NC_005237; L: NC_005238). Thottimiviruses include Thottapalayam virus (TPMV) strain VRC66412 (S: AY526097; M: NC_010708; L: EU001330) from *Suncus murinus*, Imjin virus (MJNV) strain Cl05-11 (S: EF641804; M: EF641798; L: EF641806) from *Crocidura lasiura*, Uluguru virus (ULUV) strain FMNH158302 (S: JX193695; M: JX193696; L: JX193697) from *Myosorex geata*, and Kilimanjaro virus (KMJV) strain FMNH174124 (S: JX193698; M: JX193699; L: JX193700) from *Myosorex zinki*.

Geographic-specific clustering was evidenced by the close phylogenetic relationship between prototype XSV VN1982 from Phú Thọ Province and XSV F42640 and XSV F42682 from neighbouring Tuyên Quang Province in northern Vietnam. On the other hand, XSV F44583, XSV 44601 and XSV 44580 from Quảng Nam province in central Vietnam clustered together. Although limited differences are present in phylogenetic trees based on each segment, tree topologies are generally congruent and supported by significant bootstrap values (> 70%) and posterior node probabilities (> 0.70).

To compare the evolutionary relationships of loanviruses, mobatviruses, orthohantaviruses and thottimiviruses with their hosts, phylogenetic trees were reconstructed for co-phylogeny mapping, using consensus topologies based on amino acid sequences of the nucleocapsid protein, Gn and Gc glycoproteins and RNA-dependent RNA-polymerase. Such tanglegrams (Fig. 6.4), constructed using TreeMap 3b1243, exhibited congruent segregation of viruses within the family *Hantaviridae*, according to the subfamily of their reservoir hosts, with no evidence of host switching except for Asama virus, Oxbow virus, Nova virus and Rockport virus, which are all hantaviruses harboured by moles (Arai *et al.*, 2008b; Kang *et al.*, 2009b; Kang *et al.*, 2011a). Asama virus and Oxbow virus were more closely aligned to soricine shrew-borne orthohantaviruses, Rockport virus shared a common ancestry with orthohantaviruses hosted by cricetid rodents and Nova virus was phylogenetically related to bat-borne mobatviruses (Figs. 6.3 and 6.4). Genetic recombination and reassortment events have also played a significant role in the evolution and the currently recognized diversity of the family *Hantaviridae* (Lee SH *et al.*, 2017; Castel *et al.*, 2017; Klempa, 2018).

Based on exhaustive phylogenetic analyses, using multiple methods, all bat-borne loanviruses and mobatviruses reported to date share a common ancestry, which is consistent with their host phylogeny. However, recently, in testing blood samples, obtained from 53 bats captured in south-eastern Brazil, for hantavirus infection, the partial S segment of an orthohantavirus, showing very high sequence similarity with Araraquara virus, was amplified from a Seba's short-tailed bat (*Carollia perspicillata*), a widespread frugivorous bat species in the family Phyllostomidae (Sabino-Santos *et al.*, 2018). Also, partial S segment sequences of an Araraquara virus-like orthohantavirus was detected in the urine, heart, liver, lungs, spleen and kidneys of a common vampire bat (*Desmodus rotundus*), a sanguivorous phyllostomids species. Phylogenetic analysis showed that this Araraquara virus-like hantavirus formed a monophyletic group with Araraquara virus strain P5/Cajuru (GenBank EF571895), amplified from the blood of a HCPS patient in San Paulo (de Sousa *et al.*, 2008) and strain IB_SP_bol66/2171 (EU170223), amplified from a hairy-tailed bolo mouse (*Necromys lasiurus*) captured in San Paulo, Brazil, in June 2005 (Ramsden *et al.*, 2008). The detection of Araraquara virus-like orthohantavirus sequences in two phyllostomids species is decidedly unexpected. That a nearly identical sequence of an Araraquara virus-like orthohantavirus was amplified from two very different bat species in a laboratory known to work with Araraquara virus raises a high degree of suspicion that this surprising observation might represent laboratory contamination or PCR carryover.

That is, this observation is reminiscent of previously reported serological evidence of hantavirus infection in the common serotine (*Eptesicus serotinus*) and greater horseshoe bat (*Rhinolophus ferrumequinum*) captured in Korea (Kim *et al.*, 1994). Subsequent genetic analysis of hantavirus isolates from these bat species proved to be indistinguishable from prototype Hantaan virus (Jung and Kim, 1995), indicating laboratory contamination. Nevertheless, intensified investigations by independent groups are warranted to confirm if bats serve as reservoir hosts of Araraquara virus-like orthohantaviruses. If they do, this would be somewhat akin to Rockport virus, harboured by the fossorial eastern mole, which shares a most recent common ancestor with cricetid rodent-borne orthohantaviruses. The eastern mole is sympatric and syntopic with cricetid rodent species, which serve as reservoir hosts of orthohantaviruses, suggesting a host-switching event in the distant past (Kang *et al.*, 2011a).

Discussion

Because many emerging viral infectious diseases have their origins in mammalian reservoir hosts

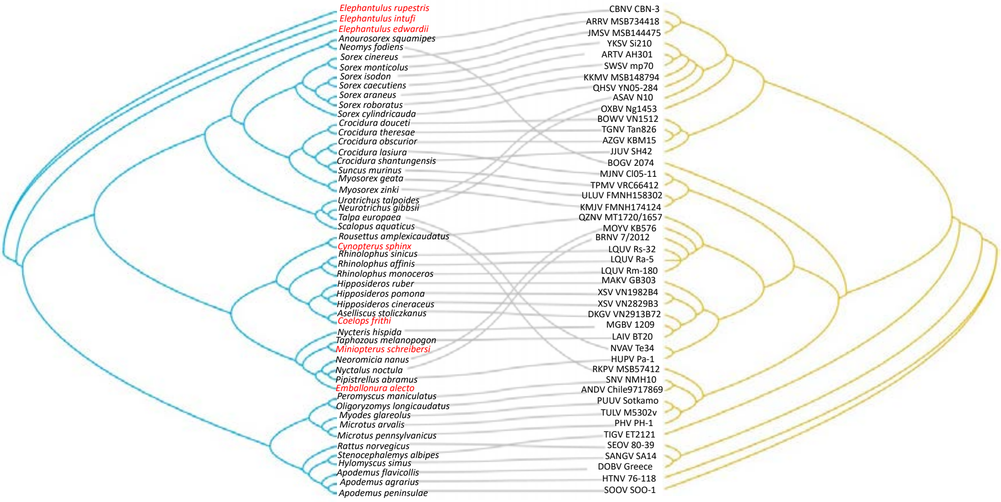


Figure 6.4 Tanglegram, generated by TreeMap 3b1243, comparing the phylogenies of orthohantaviruses and their Chiroptera, Eulipotyphla and Rodentia hosts. The host tree on the left was based on cytochrome *b* gene sequences, while the hantavirus tree on the right was based on the amino acid sequences of the RNA-dependent RNA polymerase, generated by the Bayesian Markov chain Monte Carlo estimation method. The phylogenetic positions of each reservoir host and respective orthohantavirus are shown: Đakrông virus (DKGV) strain VN2913B72 (L: MG663534) from *Aselliscus stoliczkanus* (KU161570), Brno virus (BRNV) strain 7/2012 (L: KX845680) from *Nyctalus noctula* (JX570902), Magboi virus (MGBV) strain 1209 (L: JN037851) from *Nycteris hispida* (HQ693722), Mouyassué virus (MOYV) strain KB576 (L: JQ287716) from *Neoromicia nanus* (EU797428), Huángpí virus (HUPV) strain Pa-1 (L: JX465369) from *Pipistrellus abramus* (JX465352), Lóngquán virus (LQUV) strain Ra-5 (L: JX465381) from *Rhinolophus affinis* (JX465358), LQUV Rs-32 (L: JX465381) from *Rhinolophus sinicus* (JX465362), LQUV Rm-180 (L: JX465381) from *Rhinolophus monoceros* (JX465359), Láibīn virus (LAIV) strain BT20 (L: KM102249) from *Taphozous melanopogon* (LC406449), Makokou virus (MAKV) strain GB303 (L: KT316176) from *Hipposideros ruber* (EU934474), Xuân Sơn virus (XSV) strain VN1982B4 (L: JX912953) from *Hipposideros pomona* (JX912954) and XSV VN2829B3 (L: LC406451) from *Hipposideros cineraceus* (LC406452), and Quezon virus (QZNV) strain MT1720/1657 (L: KU950715) from *Rousettus amplexicaudatus* (KU950716) are shown in TreeMap dendrogram. Also shown are Cao Bằng virus (CBNV) strain CBN-3 (L: EF543525) from *Anourosorex squamipes* (AB175090), Ash River virus (ARRV) strain MSB734418 (L: EF619961) from *Sorex cinereus* (FJ667512), Jemez Springs virus (JMSV) strain MSB144475 (L: FJ593501) from *Sorex monticolus* (FJ667514), Seewis virus (SWSV) strain mp70 (L: EF636026) from *Sorex araneus* (FJ667524), Artybash virus (ARTV) strain AH301 (L: KF974361) from *Sorex caecutiens* (KF974362), Kenkeme virus (KKMV) strain MSB148794 (L: GQ306150) from *Sorex roboratus* (AB175128), Qian Hu Shan virus (QHSV) strain YN05–284 (L: GU566021) from *Sorex cylindricauda* (AB175121), Yákèshí virus (YKSV) strain Si-210 (L: JX465389) from *Sorex isodon* (JX465364), and Boginia virus (BOGV) strain 2074 (L: JX990965) from *Neomys fodiens* (KC537797), as well as Thottapalayam virus (TPMV) strain VRC66412 (L: EU001330) from *Suncus murinus* (DQ630386), Imjin virus (MJNV) strain Cl05–11 (L: EF641806) from *Crocidura lasiura* (KJ004674), Azagny virus (AZGV) strain KBM15 (L: JF276228) from *Crocidura obscurior* (JF276229), Tanganya virus (TGNV) strain Tan826 (L: EF050454) from *Crocidura theresea* (DQ521043), Bowé virus (BOWV) strain VN1512 (L: KC631784) from *Crocidura douceti* (KC684929), Jeju virus (JJUV) strain SH42 (L: HQ663935) from *Crocidura shantungensis* (HQ663932), Uluguru virus (ULUV) strain FMNH158302 (L: JX193697) from *Myosorex geata* (JX193701), and Kilimanjaro virus (KMJV) strain FMNH174124 (L: JX193700) from *Myosorex zinki* (JX193702). Mole-borne orthohantaviruses include Asama virus (ASAV) strain N10 (L: EU929078) from *Urotrichus talpoides* (EU918371), Nova virus (NVAV) strain Te34 (L: KR072623) from *Talpa europaea* (FJ715340), Oxbow virus (OXBV) strain Ng1453 (L: FJ593497) from *Neurotrichus gibbsii* (FJ595237), and Rockport virus (RKPV) strain MSB57412 (L: HM015221) from *Scalopus aquaticus* (HM461914). Other taxa include Sin Nombre virus (SNV) strain NMH10 (L: NC_005217) from *Peromyscus maniculatus* (AF119261), Andes virus (ANDV) strain Chile9717869 (L: AF291704) from *Oligoryzomys longicaudatus* (AF346566), Prospect Hill virus (PHV) strain PH-1 (L: EF646763) from *Microtus pennsylvanicus* (AF119279), Tula virus (TULV) strain M5302v (L: NC_005226) from *Microtus arvalis* (AY220770), Puumala virus (PUUV) strain Sotkamo (L: NC_005225) from *Myodes glareolus* (JX477304), Dobrava virus (DOBV) strain Greece (L: NC_005235) from *Apodemus flavicollis* (JF819967), Hantaan virus (HTNV) strain 76–118 (L: NC_005222) form *Apodemus agrarius* (AB303225), Soochong virus (SOOV) strain SOO-1 (L: DQ056292) from *Apodemus peninsulae* (AB073811), Sangassou virus (SANGV) strain SA14 (L: JQ082302) from *Hylomyscus simus* (DQ212188), Tigray virus (TIGV) strain ET2121 (L: KU934008) from *Stenocephalemys albipes* (AF518346) and Seoul virus (SEOV) strain 80–39 (L: NC_005238) from *Rattus norvegicus* (AB355903). Outgroups include *Elephantulus edwardii* (DQ901019), *Elephantulus intufi* (DQ901206), *Elephantulus rupestris* (DQ901201) and no pair orthohantavirus host, *Coelops frithii* (DQ888674), *Emballonura alecto* (MK064108), *Miniopterus schreibersii* (MK064109) and *Cynopterus sphinx* (MK064110) are shown in red.

(Woolhouse and Gowtage-Sequeria, 2005), a better understanding about the geographic distribution of zoonotic viruses and their hosts is vital to assess risk and to predict future viral disease outbreaks, as well as to discover previously unrecognized disease associations in the case of still-orphan viruses harboured by small mammals (Han *et al.*, 2016; Dunnum *et al.*, 2017). While not all viruses in search of diseases, or orphan viruses, warrant investigations to ascertain their pathogenic potential and virulence at the time of their discovery, selected viruses, particularly those related to viruses known to cause severe and life-threatening syndromes, such as HFRS and HCPS, are worthy of high research priority. No one would have predicted that rodent-borne orthohantaviruses could cause acute renal insufficiency with varying degrees of haemorrhage and shock, as well as a rapidly progressive, frequently fatal respiratory disease.

The realization that rodent-borne orthohantaviruses are capable of causing HFRS and HCPS raises the possibility that one or more newfound soricid- and talpid-associated orthohantaviruses or thottimviruses, and possibly bat-borne loanviruses and mobatviruses, may similarly cause a wide spectrum of febrile illnesses. In this regard, prospective studies of neotomine and sigmodontine rodent-borne orthohantaviruses in the early 1980s might have provided important clues about their pathogenicity and virulence long before the abrupt recognition of HCPS in 1993. In much the same way, one or more of the newly identified non-rodent-borne viruses of the family *Hantaviridae* may cause outbreaks of human disease and/or serve as surrogate antigens for the diagnosis of previously unrecognized diseases. Robust serological assays and other sensitive rapid diagnostic technologies, now under development, will assist in establishing if these newest members of the family *Hantaviridae* are pathogenic for humans. Also, studies on the genetics, transmission dynamics and disease-causing potential of one or more of the newly identified viruses in shrews, moles and bats, as well as African rodents, may better prepare the next generation of health care workers to be vigilant for the next outbreak of hantaviral disease.

That viruses of the subfamily Mammantavirinae are distributed widely across three taxonomic orders of terrestrial mammals has changed previously held dogmas about hantavirus evolution and phylogeography (Bennett *et al.*, 2014). At the same time, although the global landscape of hantavirus distribution is far richer now than it was just a decade ago (Fig. 6.5), it is unclear if selection bias in the collection and availability, and subsequent testing of tissues from rodents, shrews, moles and bats, has distorted or unduly influenced our current concepts. For example, while rodents of multiple genera and species serve as reservoirs of orthohantaviruses, orthohantaviruses have been found in only two genera (*Hylomyscus* and *Stenocephalemys*) of rodents belonging to the subfamily Murinae in Africa, despite decades-long exploratory investigations. By contrast, in Eurasia, rodents belonging to genera in both the subfamilies Murinae (*Apodemus*, *Bandicota*, *Niviventer* and *Rattus*) and Arvicolinae (*Arvicola*, *Eothenomys*, *Lemmus*, *Microtus*, *Myodes* and *Pitymys*) are known to harbour orthohantaviruses. In the Americas, on the other hand, a dizzying diversity of orthohantaviruses has been found in rodent genera not only of the subfamilies Murinae (*Rattus*) and Arvicolinae (*Microtus* and *Myodes*), but also in the subfamilies Neotominae (*Peromyscus* and *Reithrodontomys*) and Sigmodontinae (*Akodon*, *Calomys*, *Holochilus*, *Necromys*, *Oligoryzomys*, *Oryzomys*, *Sigmondon* and *Zygodontomys*) (de Oliveira *et al.*, 2014; Yanagihara *et al.*, 2015). The caveat here is that rodents of the subfamilies Neotominae and Sigmodontinae do not exist in the Old World.

Multiple hantaviruses exhibiting far greater genetic diversity have been detected recently in shrews and moles representing genera in three subfamilies (Crocidurinae, Myosoricinae and Soricinae) of the family Soricidae and in two subfamilies (Talpinae and Scalopinae) of the family Talpidae, within the order Eulipotyphla, in Africa (*Crocidura*, *Myosorex*), Eurasia (*Anourosorex*, *Neomys*, *Scaptonyx*, *Sorex*, *Suncus*, *Talpa* and *Urotrichus*), and North America (*Blarina*, *Neurotrichus*, *Scalopus* and *Sorex*). Similarly, bat genera belonging to each of three families in both suborders of Chiroptera (Yinpterochiroptera and Yangochiroptera) host hantaviruses in Africa (*Hipposideros*, *Neoromicia* and *Nycteris*) and Eurasia (*Aselliscus*, *Hipposideros*, *Nyctalus*, *Pipistrellus*, *Rhinolophus*, *Rousettus* and *Taphozous*). To date, genetically distinct bat-borne hantaviruses have not been reported from the Americas.

Much work is obviously still needed to better understand the genetic diversity of viruses within the family *Hantaviridae* and the geographic distribution of their hosts. In particular, more intensive investigations are warranted to investigate beyond the more common families within the order Rodentia, as well as of the less well-known and low abundant genera within the order Eulipotyphla,

Figure 6.5 Global landscape of mammal-borne viruses within the family *Hantaviridae*. Representative hantaviruses harboured by rodents (grey) are shown, as are all hantaviruses detected to date in shrews (black), moles (green) and bats (blue).

and of the less speciose members of the suborders Yinpterochiroptera and Yangochiroptera.

Unlike the high prevalence of orthohantavirus infection reported in multiple species of shrews and moles, the absence of hantavirus infection in the majority of bat species analysed to date and the low prevalence of hantavirus RNA in only a few individuals of a given bat species would tend to argue against a long-standing hantavirus-bat host relationship, and instead support spillover or host-switching events. That is, the gleaning feeding behaviour of some bats, such as *Nycteris*, presents the possibility of acquired infection from excreta of well-established terrestrial reservoirs of orthohantaviruses. However, this seems highly improbable because bat-borne hantaviruses are among the most genetically diverse described to date and are phylogenetically distinct from hantaviruses harboured by rodents, shrews and moles.

With the discovery of divergent hantavirus lineages in three taxonomic orders of placental mammals, there is renewed interest in investigating their genetic diversity and geographic distribution. Newly acquired knowledge that bats harbour distinctly divergent lineages of hantaviruses emphasizes the truly complex evolutionary origins and phylogeography of a group of viruses once thought to be restricted to rodents. At this point, it would not be surprising if hantaviruses were found in small mammals belonging to other taxonomic orders, such as Erinaceomorpha (hedgehogs) and even Afrosoricida (tenrecs). Such discoveries may provide additional insights into the dynamics of hantavirus transmission, potential reassortment of genomes, and molecular determinants of hantavirus pathogenicity. As importantly, a sizable expansion of the *Hantaviridae* sequence database would provide valuable tools for refining diagnostic tests and enhancing preparedness for future outbreaks caused by still-orphan newfound hantaviruses.

Future research

Among the urgent questions for future research about the genetic diversity and geographic distribution of viruses within the family *Hantaviridae* are the following:

- What other taxonomic orders serve as reservoir hosts? That is, with the discovery of hantavirus-like sequences in reptile and fish, what is the host range of *Hantaviridae*? And do other terrestrial

mammals, such as hedgehogs and tenrecs, harbour hantaviruses?
- What do the reservoir hosts have in common? Are some hosts more permissive to being recipients of host switches? Are some loanviruses, mobatviruses, orthohantaviruses and thottimiviruses more likely to switch into new hosts?
- What are the possibilities of developing more sensitive and less labour-intensive, primer-independent molecular detection tools for discovering other members of the family *Hantaviridae*?
- What is driving the evolutionary diversification of loanviruses, mobatviruses, orthohantaviruses and thottimiviruses? How do we definitively date divergence? What are the host evolutionary relationships?

Another unanswered question is whether or not one or more of the recently detected or yet-to-be discovered shrew- and mole-borne orthohantaviruses, or bat-borne loanviruses and mobatviruses, cause infection or disease in humans. In this regard, progress has been hampered by the lack of virus isolates from non-rodent hosts. That is, while multiple orthohantaviruses have been isolated from many rodent species and adapted to growth in cell culture or laboratory-bred rodents, there are, to date, only two thottimivirus isolates from shrews, namely, Thottapalayam virus from the Asian house shrew (Carey *et al.*, 1971) and Imjin virus from the Ussuri white-tooted shrew (Song *et al.*, 2009), and a single mole-borne mobatvirus isolate, namely, Nova virus from the European mole (Gu *et al.*, 2016b). There are no isolates of loanviruses or mobatviruses from bats. Future virus-isolation attempts may benefit from more innovative approaches, such as the use of reservoir host-derived cell cultures from tissues of shrews and bats (Eckerle *et al.*, 2014).

Thus far, while there is suggestive evidence that Bowé virus and Uluguru virus (a shrew-borne orthohantavirus found in Guinea and a presumptive shrew-borne thottimivirus found in Tanzania, respectively) might cause infection in humans, as evidenced by serological tests using recombinant nucleocapsid proteins as antigens (Heinemann *et al.*, 2016), there is no definitive proof that these or any of the newfound non-rodent-associated loanviruses, mobatviruses, orthohantaviruses and thottimiviruses cause a clinically identifiable disease or syndrome in humans (Yanagihara *et al.*, 2015).

However, it would be premature to conclude that this would be true for other newfound and still-undiscovered soricid-, talpid- or Chiroptera-borne viruses of the family *Hantaviridae* for the very reason that the majority of rodent-borne orthohantaviruses do not cause infection or disease in humans. A significant shortcoming of any investigation in search of a rare infectious disease event is the failure to study individuals who are affected by that rare event. On the one hand, the inability to detect antibodies against a given non-rodent-borne loanvirus, mobatvirus, orthohantavirus or thottimivirus in a given study population may indicate that that particular virus does not cause infection in humans. On the other hand, this same (negative) result could mean that the study simply failed to enrol subjects exposed to that virus. In other words, if infection with a given non-rodent-borne loanvirus, mobatvirus, orthohantavirus or thottimivirus is associated with a rare or uncommon disease, one would be unable to show pathogenicity in humans. In this regard, even at the height of the 1993 HCPS outbreak in the Four Corners region, no serological evidence of Sin Nombre virus infection could be found in patients with a variety of diseases or in health care workers, parks service personnel and mammalogists. Only patients with HCPS had evidence of Sin Nombre virus infection. Thus, even with the most lethal infectious agent, one would erroneously conclude that the microbe is non-pathogenic or non-infectious, unless the 'right' patients were tested.

Sensitive serological tests have facilitated the rapid screening of wild rodents for evidence of orthohantavirus infection. And in large part, this type of pre-screening has allowed more focused RT-PCR testing of antibody-positive rodents. By contrast, there are virtually no data about the prevalence of IgG antibodies against loanviruses, mobatviruses, orthohantaviruses and thottimiviruses in shrews, moles and bats, primarily because of the unavailability of blood or serum specimens in archival collections and the lack of suitable immunological reagents. However, as in rodents, one would surmise that antibody-positive shrews, moles and bats would more likely have detectable viral RNA. To what extent the presence of neutralizing antibodies against loanviruses or mobatviruses in bats would more readily pre-select which bats to test by RT-PCR is unknown. As it now stands, this is a moot point because no hantavirus isolates are available from bats to be able to perform neutralization tests.

For answers to these questions, and myriad others, reagents need to be developed. And multidisciplinary collaborative studies must be designed to optimize specimen collection to facilitate the isolation and characterization of newfound bat-borne loanviruses and mobatviruses to better understand virus–host interactions.

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Note added in proof

Since the submission of this manuscript, a new orthohantavirus, named Academ virus, has been detected in the Altai mole (*Talpa altaica*) from Western Siberia.

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