Chapter 9
Expanded Host Diversity and Global Distribution of Hantaviruses: Implications for Identifying and Investigating Previously Unrecognized Hantaviral Diseases

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Core Message

- Discovery of genetically distinct hantaviruses in multiple species of shrews and moles (order Eulipotyphla) and insectivorous bats (order Chiroptera) heralds a new frontier in hantavirology.
- Acquisition of new knowledge about the spatial and temporal distribution, host range and genetic diversity of newfound hantaviruses harbored by shrews, moles, and bats was accelerated by having access to archival tissue collections.
- Newfound hantaviruses in shrews, moles, and bats are genetically more diverse than those hosted by rodents (order Rodentia), suggesting that the evolutionary origins of hantaviruses are more ancient and complex than previously contemplated.
- Phylogenetic analyses indicate four distinct hantavirus clades, with evidence of both co-divergence and host switching, and suggest that shrews, moles, and/or bats may have predated rodents as the early reservoir hosts of primordial hantaviruses.
- Detection of hantavirus RNA in ethanol-fixed tissues greatly expands the pool of specimens for future hantavirus-discovery efforts, particularly in other insectivorous small mammals, such as hedgehogs and tenrecs.
- The lack of cell culture isolates of the newly detected hantaviruses hosted by shrews, moles, and bats has hampered the identification and investigation of novel hantaviral diseases.

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1 Introduction

In the spring of 1993, four decades after their forefathers in Korea were faced with an epidemic febrile illness with renal failure, a disease then unknown to American medicine called Korean hemorrhagic fever [1–3], emergency room physicians and health-care workers in the Four Corners region of the southwestern USA were confronted with a terrifying outbreak of a rapidly progressive, frequently fatal respiratory disease, now known as hantavirus cardiopulmonary syndrome (HCPS) [4]. No one had the prescience to predict that this previously unrecognized disease would be caused by a once-exotic group of rodent-borne viruses, belonging to the *Hantavirus* genus of the *Bunyaviridae* family.

Present-day hantavirology dates to the seminal discovery of Hantaan virus (HTNV) as the prototype virus of hemorrhagic fever with renal syndrome (HFRS) in the striped field mouse (*Apodemus agrarius*) [5]. This milestone made possible the identification of other HFRS-causing hantaviruses, such as Puumala virus (PUUV) in the bank vole (*Myodes glareolus*) [6], Seoul virus (SEOV) in the brown rat (*Rattus norvegicus*) [7], and Dobrava virus (DOBV) in the yellow-necked field mouse (*Apodemus flavicollis*) [8]. Similarly, the identification of Sin Nombre virus (SNV) in the deer mouse (*Peromyscus maniculatus*) [9, 10] and Andes virus (ANDV) [11, 12] in the long-tailed colilargo (*Oligoryzomys longicaudatus*), as the causative agents of HCPS, marked the next major benchmark in hantavirology. Several other genetically distinct hantaviruses harbored by neotomine and sigmodontine rodents in the USA, such as New York virus (NYV) in the white-footed mouse (*Peromyscus leucopus*) [13–15], Bayou virus (BAYV) in the marsh rice rat (*Oryzomys palustris*) [16–18], and Black Creek Canal virus (BCCV) in the hispid cotton rat (*Sigmodon hispidus*) [19, 20], have been associated with HCPS.

Recently, a new frontier in hantavirology has been forged with the discovery of highly divergent lineages of hantaviruses in multiple species of shrews and moles (order Eulipotyphla) and insectivorous bats (order Chiroptera) from widely separated geographic regions. Phylogenetic analyses suggest that ancestral shrews and moles and/or bats may have predated rodents as the early reservoir hosts of primordial hantaviruses [21, 22]. However, to what extent one or more of these newfound non-rodent-borne hantaviruses might cause infection and disease in humans is unknown.

Nevertheless, both HFRS and HCPS are excellent examples of how the initial identification and subsequent investigation of previously unrecognized emerging infectious diseases are dependent on the coordinated efforts of collaborative teams, comprising clinicians, epidemiologists, microbiologists, mammalogists and field ecologists, and pathologists. In such outbreaks, the initial observational acumen and clinical experience of medical and paramedical personnel—whether they be in the best-equipped tertiary-care referral hospitals or in resource-constrained rural clinics or field settings in low-income countries—are critical to suspect that something out of the ordinary might be occurring. Moreover, the persistence or stubbornness and strong conviction of health-care practitioners, who refuse to readily accept negative laboratory tests, is an important prerequisite for identifying new, emerging and reemerging infectious diseases. Thus, effective early-warning systems are heavily

dependent on individual people, and the importance of this first step in recognition of new diseases cannot be over emphasized. Also vital is the unwavering support of human resources and public health infrastructure, which are increasingly aided by powerful social media applications and sophisticated data-sharing communications and information technology platforms.

In this chapter, we will not attempt to review the rich diversity of hantaviruses and their genotypes in myriad neotomine and sigmodontine rodents of various species in the Americas, largely because this has been elegantly summarized, with the clear demonstration that the majority of South American hantaviruses segregate into three phylogenetic clades, comprising ANDV and ANDV-like viruses, Laguna Negra virus (LANV) and LANV-like viruses, and Rio Mamore virus (RIOMV) and RIOMV-like viruses [23]. Instead, we focus mainly on reviewing the host diversity and geographic distribution of the newfound non-rodent-borne hantaviruses and summarize efforts to identify human infection and to investigate diseases that may be caused by these still-orphan hantaviruses. We draw from the detailed studies on the first rodent-borne hantavirus from sub-Saharan Africa, namely Sangassou virus (SANGV) harbored by the African wood mouse (*Hylomyscus simus*) [24], and the first shrew-borne hantavirus to be isolated in nearly four decades, namely Imjin virus (MJNV) hosted by the Ussuri white-toothed shrew (*Crocidura lasiura*) [25]. We also discuss some of the challenges associated with definitively linking newly described orphan viruses to previously unrecognized infectious diseases in humans.

2 Reservoir Host Diversity

Like all other members of the *Bunyaviridae* family, viruses in the *Hantavirus* genus possess a negative-sense, single-stranded RNA genome consisting of three segments, designated large (L), medium (M), and small (S), which encode an RNA-dependent RNA polymerase, envelope glycoproteins (Gn, Gc) and a nucleocapsid (N) protein, respectively [26, 27]. However, unlike the more than 400 other members in this virus family, hantaviruses are unique in that they are harbored by small mammals. Whether or not arthropod vectors, such as mites, are involved in the transmission dynamics and maintenance of the enzootic cycle have again been raised recently [28], and renewed investigations are now underway.

Initially, rodents were believed to serve as the exclusive reservoir hosts of hantaviruses [29]. Moreover, the conventional view held that each genetically distinct hantavirus is carried by a rodent of a single species, with which it coevolved. This now appears to be an overly simplistic paradigm, particularly in light of the expanded host range and genetic diversity of hantaviruses [21, 22]. Mounting evidence supports the concepts of host sharing and host switching. That is, as shown in Table 9.1, the same hantavirus may be harbored by more than one reservoir rodent, such as Tula virus (TULV) in the common vole (*Microtus arvalis*), Russian common vole (*Microtus rossiaemeridionalis*), field vole (*Microtus agrestis*), and European pine vole (*Pitymys subterrraneus*) [30–34]. TULV has also been reported in the Eurasian

Table 9.1 Hantaviruses and rodent-host and disease associations[a]

Family	Subfamily	Reservoir host species	Virus name	Disease
Muridae	Murinae	*Apodemus agrarius*	Hantaan	HFRS
		Apodemus agrarius	Dobrava (Kurkino)	HFRS
		Apodemus agrarius	Dobrava (Saaremaa)	HFRS?
		Apodemus flavicollis	Dobrava (Dobrava)	HFRS
		Apodemus ponticus	Dobrava (Sochi)	HFRS
		Apodemus peninsulae	Amur	HFRS
		Apodemus peninsulae	Soochong	HFRS
		Hylomyscus simus	Sangassou	Unknown
		Niviventer confucianus	Da Bie Shan	Unknown
		Rattus losea	Seoul	HFRS?
		Rattus norvegicus	Seoul	HFRS
		Rattus rattus	Seoul	HFRS
		Bandicota indica	Thailand	HFRS
		Bandicota savilei	Thailand-like	Unknown
		Rattus rattus	Thailand (Anjozorobe)	Unknown
		Rattus tanezumi	Thailand (Serang)	Unknown
		Rattus tanezumi	Thailand (Jurong)	Unknown
		Stenocephalemys albipes	Tigray	Unknown
Cricetidae	Arvicolinae	*Eothenomys miletus*	Luxi	Unknown
		Microtus agrestis	Tatenale	Unknown
		Microtus agrestis	Tula	Unknown
		Microtus arvalis	Tula	Unknown
		Microtus rossiaemeridionalis	Tula	Unknown
		Pitymys subterraneus	Tula	Unknown
		Arvicola amphibius	Tula	Unknown
		Microtus californicus	Isla Vista	Unknown
		Microtus ochrogaster	Bloodland Lake	Unknown
		Microtus fortis	Khabarovsk	Unknown
		Microtus maximowiczii	Khabarovsk	Unknown
		Microtus fortis	Vladivostok	Unknown
		Microtus fortis	Yuanjiang	Unknown
		Microtus pennsylvanicus	Prospect Hill	Unknown
		Myodes glareolus	Puumala	HFRS
		Myodes rufocanus	Puumala	HFRS
		Myodes rufocanus	Hokkaido	Unknown
		Myodes regulus	Muju	HFRS?
		Lemmus sibiricus	Topografov	Unknown
	Neotominae	*Peromyscus boylii*	Limestone Canyon	Unknown
		Peromyscus beatae	Montano	Unknown
		Peromyscus leucopus	Blue River	Unknown
		Peromyscus leucopus	New York	HCPS
		Peromyscus maniculatus	Sin Nombre	HCPS
		Reithrodontomys megalotis	El Moro Canyon	Unknown
		Reithrodontomys sumichrasti	El Moro Canyon	Unknown

(continued)

Table 9.1 (continued)

Family	Subfamily	Reservoir host species	Virus name	Disease
		Reithrodontomys mexicanus	Rio Segundo	Unknown
	Sigmodontinae	*Akodon azarae*	Pergamino	HCPS
		Akodon montensis	Ape Aime	Unknown
		Akodon montensis	Jaborá	Unknown
		Akodon paranaensis	Jabora	Unknown
		Akodon serrensis	Jabora	Unknown
		Bolomys lasiurus	Araraquara	HCPS
		Bolomys obscurus	Maciel	HCPS
		Calomys laucha	Laguna Negra	HCPS
		Calomys callosus	Laguna Negra	HCPS
		Holochilus chacoensis	Alto Paraguay	Unknown
		Oligoryzomys chacoensis	Bermejo	HCPS
		Oligoryzomys fornesi	Anajatuba	HCPS
		Oligoryzomys longicaudatus	Oran	HCPS
		Oligoryzomys longicaudatus	Andes	HCPS
		Necromys benefactus	Andes	HCPS
		Oligoryzomys nigripes	Araucária	HCPS
		Oxymycterus judex	Araucária	HCPS
		Oligoryzomys flavescens	Lechiguanas	HCPS
		Oligoryzomys delicatus	Maporal	Unknown
		Oligoryzomys fulvescens	Maporal	Unknown
		Oligoryzomys fulvescens	Choclo	HCPS
		Oligoryzomys costaricensis	Choclo	HCPS
		Oligoryzomys microtis	Rio Mamore	HCPS
		Oligoryzomys nigripes	Itapúa	Unknown
		Oligoryzomys nigripes	Juquitiba	HCPS
		Oligoryzomys fornesi	Juquitiba	HCPS
		Oligoryzomys utiaritensis	Castelo dos Sonhos	HCPS
		Oryzomys couesi	Catacamas	Unknown
		Oryzomys couesi	Playa de Oro	Unknown
		Oryzomys palustris	Bayou	HCPS
		Sigmodon alstoni	Cano Delgadito	Unknown
		Sigmodon hispidus	Muleshoe	Unknown
		Sigmodon hispidus	Black Creek Canal	HCPS
		Zygodontomys brevicauda	Calabazo	Unknown

[a]This table is not meant to be exhaustive or comprehensive. Rather its intent is to display the vast diversity of hantaviruses harbored by rodents in the Muridae and Cricetidae families. In particular, the large number of hantaviruses hosted by multiple sigmodontine rodent hosts in South America is emphasized. However, many of these viruses probably do not represent distinct species but fall into one of three phylogenetic clades: ANDV, LANV, and RIOMV. The rodent reservoirs of some HCPS-causing hantaviruses, such as Tunari virus, Maripa virus, and Paranoá virus, have not been identified. Disease associations, such as HFRS or HCPS, are shown, when known. Otherwise, the "Unknown" descriptor is used

ANDV Andes virus, *HCPS* hantavirus cardiopulmonary syndrome, *HFRS* hemorrhagic fever with renal syndrome, *LANV* Laguna Negra virus, *RIOMV* Rio Mamore virus

water vole (*Arvicola amphibius*) [35]. It is unclear if this represents spillover from common voles or a host switch. Host sharing and/or host switching seems to apply also to other rodent-borne hantaviruses, such as Thailand virus (THAIV) in the greater bandicoot rat (*Bandicota indica*) [36, 37] and Savile's bandicoot rat (*Bandicota savilei*) [38], as well as THAIV-like hantaviruses in the black rat (*Rattus rattus*) and tanezumi rat (*Rattus tanezumi*) [39, 40]. Moreover, genetic variants of PUUV, designated Hokkaido virus (HOKV) and Muju virus (MUJV), have been reported in the gray red-backed vole (*Myodes rufocanus*) in Japan [41] and the royal vole (*Myodes regulus*) in Korea [42, 43], respectively. In addition, as discussed in greater detail later, some hantaviruses harbored by soricine shrews and insectivorous bats have been detected in hosts belonging to more than one species, but further research is necessary to better understand these host–virus relationships.

Spillover of hantaviruses to syntopic rodents and host-switching events, on the one hand, are contrasted by the same rodents also hosting more than one hantaviruses. For example, the field vole hosts TULV in Europe and a newly discovered hantavirus, named Tatenale virus (TATV), in the UK [44]; and the striped field mouse, which serves as the reservoir of HTNV in Asia, also hosts the Kurkino and Saaremaa genotypes of DOBV in Europe [45]. It is noteworthy that the least virulent genotypes of DOBV are those harbored by the striped field mouse in Europe, whereas in Asia, the striped field mouse harbors the prototypic virulent hantavirus, known as HTNV. On the other hand, DOBV genotypes Dobrava and Sochi, which are hosted by the yellow-necked field mouse and the Caucasus field mouse (*Apodemus ponticus*), respectively, are more pathogenic and account for the majority of HFRS fatalities in Europe [45]. The molecular basis for this differential virulence is unknown.

Whereas HFRS- and HCPS-causing hantaviruses are only known to be harbored by rodents thus far, the global landscape of hantaviruses has been forever altered by the discovery of highly divergent lineages of hantaviruses in shrews, moles, and insectivorous bats [21, 22]. As such, the evolutionary origins and phylogeography are clearly ancient and far more complex than previously contemplated [21, 22, 46]. Although unimaginable a few years ago, the entire host diversity has presumably not been attained and many more genetically distinct hantaviruses, particularly those hosted by shrews, moles, and bats, still await discovery.

2.1 Hantaviruses in Rodents

A rich literature exists on hantaviruses harbored by rodents of the Muridae and Cricetidae families. Since most of the attention has understandably been paid to hantaviruses that cause HFRS and HCPS, the reader is often left with the mistaken impression that all hantaviruses are pathogenic. In fact, the majority of rodent-borne hantaviruses has not been associated with human infection and disease. This is particularly true for hantaviruses carried by arvicoline rodents, and in particular those harbored by members of the *Microtus* genus, the prototype being

Prospect Hill virus (PHV), the first hantavirus isolated from an indigenous wild rodent, the meadow vole (*Microtus pennsylvanicus*), in North America [47]. Other prominent examples include Khabarovsk virus (KHAV) and Vladivostok virus (VLAV), hosted by the Maximowicz's vole (*Microtus maximowiczii*) and reed vole (*Microtus fortis*), respectively, which do not appear to cause infection or disease in humans [48, 49]. Also, not all genetic variants or genotypes of the same hantavirus appear to have the identical degree of pathogenicity. For example, no human disease has been associated with HOKV, harbored by the gray red-backed vole in Japan, despite its close genetic and phylogenetic relationship with PUUV [41]. Also, the Saaremaa genotype of DOBV, carried by the striped field mouse in Estonia, seems non-pathogenic [45].

Table 9.1 lists the hantaviruses detected in rodents and indicates which hantaviruses are known to be pathogenic. As previously mentioned, extensive host sharing, in which the same hantavirus is harbored by rodents belonging to more than one species, is evident. It is not clear in every instance whether this has resulted from spillover or host-switching events and subsequent species-specific adaptation. Examples can be found in rodent-borne hantaviruses of the same rodent host family and subfamily. The bewildering constellation of rodents of divergent species and designations of hantaviruses, particularly in South America, have recently been simplified by in-depth analysis of hantavirus isolates from HCPS patients and rodents. As mentioned earlier, the majority of South American hantaviruses, and in particular ANDV, LANV, and RIOMV, belong to three distinct hantavirus species [23]. However, not all strains of ANDV, LANV, and RIOMV appear to cause HCPS. Also, hantaviruses carried by closely related rodent hosts, such as Choclo virus (CHOV) and Maporal virus (MAPV) in the Costa Rican pygmy rice rat (*Oligoryzomys costaricensis*) and the delicate pygmy rice rat (*Oligoryzomys delicatus*), respectively, exhibit vastly different pathogenic potential, with CHOV causing a full spectrum from subclinical infection to severe HCPS [50, 51], and MAPV showing no disease in humans [52]. Both CHOV and MAPV were previously thought to be hosted by the fulvous colilargo (*Oligoryzomys fulvescens*) [53–55].

Hantavirus infection in the rodent host is subclinical, generally with short-lived viremia but with dissemination of virus in multiple tissues, including lung, salivary gland and kidney [56–59]. The demonstration of virus antigen in brown fat of overwintering live-caught bank voles in the former Soviet Union suggests a possible mechanism of virus maintenance [60]. Virus excretion in urine and feces persists for months or possibly lifelong in infected rodents, despite high-titered serum neutralizing antibodies. There is no evidence of vertical transmission of hantaviruses in rodents [29, 61, 62]. Arthropod vectors do not appear to be involved in hantavirus infection among humans [29, 63], but questions have again been raised about the role of mites in the maintenance of the hantavirus enzootic cycle [28].

Hantavirus-infected reservoir rodents tend to be localized in small, circumscribed foci, rather than being uniformly distributed in any given geographical area [29]. As such, transmission and prevalence rates of rodent-borne hantavirus infections are regulated within reservoir host populations and typically vary in time and space [64].

Since the recognition of HCPS in the Americas, the epizootiology of SNV infection in deer mouse populations has been intensively studied. Among the more consistent findings have been the widespread nature of the SNV enzootic in the reservoir rodent species, the greater preponderance of infection in adult male deer mice, the decreasing antibody prevalence with age (suggesting passively acquired immunity in pups), the higher SNV antibody prevalence in peri-domestic compared to sylvan settings, and the correlation between population size and hantavirus-antibody prevalence [61, 65–71]. In addition, SNV RNA was repeatedly detected in serially collected blood samples, particularly in antibody-positive male deer mice, suggesting their role in virus shedding for prolonged periods [72].

2.2 Hantaviruses in Shrews

Shrews have been generally ignored in the transmission dynamics and evolutionary origins of hantaviruses, despite the fact that Thottapalayam virus (TPMV), a previously unclassified virus isolated from the Asian house shrew (*Suncus murinus*), captured near Vellore in Tamil Nadu, India [73, 74], predated the isolation of HTNV. Also, the early reports of the detection of HFRS antigens in tissues of the Eurasian common shrew (*Sorex araneus*), alpine shrew (*Sorex alpinus*), and Eurasian water shrew (*Neomys fodiens*) in Russia and the former Yugoslavia [60, 75, 76] went largely unnoticed.

The antigenic relationship between TPMV and 31 other hantavirus isolates has been investigated by cross-enzyme immunoassay (ELISA) and cross-plaque-reduction neutralization tests (PRNT) using antisera from experimentally infected animals [77]. Antisera prepared against strains of HTNV, PUUV, SEOV, THAIV, and PHV, exhibited 16-fold or lower ELISA titers to cell culture-derived TPMV antigen than to the homotypic hantaviral antigen [77]. Of the 32 hantaviruses examined by PRNT, TPMV was the only one that displayed no cross-neutralization with any other hantavirus; that is, none of the heterologous antisera neutralized TPMV and the antiserum to TPMV did not neutralize any other hantavirus [77].

Recently, TPMV strains have been detected in Asian house shrews captured in Nepal [78] and China [79]. Phylogenetic analysis of the partial and full genome sequences of prototype TPMV and other newfound TPMV strains demonstrate that they form a separate phylogenetic clade, suggesting an early evolutionary divergence from other hantaviruses [80–82]. Using oligonucleotide primers based on TPMV, a novel hantavirus, named MJNV, was detected in Ussuri white-toothed shrews (*Crocidura lasiura*) captured along the Imjin River, near the demilitarized zone in the Republic of Korea [25]. High prevalence of MJNV infection has been demonstrated within discrete foci during the autumn months, with evidence of marked male predominance [25]. The absence of cross neutralization between MJNV and rodent-borne hantaviruses indicates that it is antigenically distinct.

Empowered by the full genomes of TPMV and MJNV, we launched an opportunistic search for hantavirus RNA using reverse transcription polymerase chain reaction

(RT-PCR). Initially, we envisioned that the genomes of TPMV and MJNV would make finding new hantaviruses a trivial exercise. Instead, the unexpectedly vast genetic diversity of the shrew-borne hantaviruses posed considerable challenges in designing suitable primers for the amplification of their genes. Also, in the belief that the probability of success for finding novel hantaviruses would be highest in frozen tissues, we initially limited our search to such specimens. However, we soon learned that this approach placed unnecessary restrictions on our virus-discovery attempts, so we expanded our search to include tissues which were either preserved in RNAlater® RNA Stabilization Reagent or fixed in 90 % ethanol.

The generosity of museum curators and field mammalogists, who provided access to their valuable archival tissue collections, accelerated the acquisition of new knowledge about the host range and spatial and temporal distribution of hantaviruses. In analyzing RNA, extracted from more than 1,500 tissues from nearly 50 shrew species collected throughout Europe, Asia, North America, and Africa, between 1980 and 2012, we have discovered multiple genetically distinct hantaviruses, including Seewis virus (SWSV) in the Eurasian common shrew [83–86], Ash River virus (ARRV) in the masked shrew (*Sorex cinereus*) [87], Jemez Springs virus (JMSV) in the dusky shrew (*Sorex monticolus*) [87], Kenkeme virus (KKMV) in the flat-skulled shrew (*Sorex roboratus*) [88], Amga virus (MGAV) in the Laxmann's shrew (*Sorex caecutiens*) [89], Sarufutsu virus (SRFV) in the long-clawed shrew (*Sorex unguiculatus*) [90], Cao Bang virus (CBNV) in the Chinese mole shrew (*Anourosorex squamipes*) [91], Xinyi virus (XYIV) in the Taiwanese mole shrew (*Anourosorex yamanashi*) [92], Camp Ripley virus (RPLV) in the northern short-tailed shrew (*Blarina brevicauda*) [93], Iamonia virus (AMNV) in the southern short-tailed shrew (*Blarina carolinensis*) (unpublished), Boginia virus (BOGV) in the Eurasian water shrew [94], Azagny virus (AZGV) in the West African pygmy shrew (*Crocidura obscurior*) [95], Jeju virus (JJUV) in the Asian lesser white-toothed shrew (*Crocidura shantungensis*) [96], Bowé virus (BOWV) in the Doucet's musk shrew (*Crocidura douceti*) [97], Uluguru virus (ULUV) in the geata mouse shrew (*Myosorex geata*) [98], and Kilimanjaro virus (KMJV) in the Kilimanjaro mouse shrew (*Myosorex zinki*) [98] (Table 9.2).

As for rodent-borne hantaviruses, examples of host sharing or spillover have been found for SWSV in the Eurasian pygmy shrew [86, 99], tundra shrew

Table 9.2 Genetically distinct Hantaviruses detected in shrews (order Eulipotyphla, family Soricidae)

Virus name	Virus abbreviation	Reservoir host species	Country	Year of capture	References
Azagny	AZGV	*Crocidura obscurior*	Côte d'Ivoire	2009	[95]
Bowé	BOWV	*Crocidura douceti*	Guinea	2012	[97]
Imjin	MJNV	*Crocidura lasiura*	Korea	2004	[25]
Jeju	JJUV	*Crocidura shantungensis*	Korea	2007	[96]
Tanganya	TGNV	*Crocidura theresae*	Guinea	2004	[102]

(continued)

Table 9.2 (continued)

Virus name	Virus abbreviation	Reservoir host species	Country	Year of capture	References
Thottapalayam	TPMV	*Suncus murinus*	India	1964	[73, 81, 82]
			Nepal	1996	[78]
			China	2009	[79]
Kilimanjaro	KMJV	*Myosorex zinki*	Tanzania	2002	[98]
Uluguru	ULUV	*Myosorex geata*	Tanzania	1996	[98]
Cao Bang	CBNV	*Anourosorex squamipes*	Vietnam	2006	[91]
			China	2006	Unpublished
Xinyi	XYIV	*Anourosorex yamashinai*	Taiwan	1989	[92]
Camp Ripley	RPLV	*Blarina brevicauda*	USA	1998	[93]
			Canada	1983	Unpublished
Iamonia	AMNV	*Blarina carolinensis*	USA	1983	Unpublished
Amga	MGAV	*Sorex caecutiens*	Russia	2006	[89]
			Japan	2010	[89]
Ash River	ARRV	*Sorex cinereus*	USA	1994	[87]
Asikkala	ASIV	*Sorex minutus*	Czech Republic	2010	[104]
Boginia	BOGV	*Neomys fodiens*	Poland	2011	[94]
Jemez Springs	JMSV	*Sorex monticolus*	USA	1996	[87]
		Sorex palustris	Canada	2005	Unpublished
		Sorex trowbridgii	USA	1996	Unpublished
		Sorex vagrans	USA	1996	Unpublished
Kenkeme	KKMV	*Sorex roboratus*	Russia	2006	[88]
Sarufutsu	SRFV	*Sorex unguiculatus*	Japan	2006	[90]
Seewis	SWSV	*Sorex araneus*	Switzerland	2006	[83]
			Hungary	1997	[84]
			Finland	1982	[84]
			Germany	2007	[99]
			Czech Republic	2010	[99]
			Poland	2010	[86, 94]
			Slovakia	2008	[99]
			Slovenia	1990	[100, 101]
			Russia	2006	[85]
		Sorex daphaenodon	Russia	2006	[85]
		Sorex minutus	Germany	2005	[84]
			Poland	2012	[86]
		Sorex tundrensis	Russia	2006	[85]
			Mongolia	2010	Unpublished
		Neomys anomalus	Austria	2007	Unpublished
			Poland	2011	[86]
Qian Hu Shan	QHSV	*Sorex cylindricauda*	China	2005	[105]
Yakeshi	YAKV	*Sorex isodon*	China	2006	[103]

(*Sorex tundrensis*) [85], large-toothed Siberian shrew (*Sorex daphaenodon*) [85], and Mediterranean water shrew (*Neomys anomalus*) [86]. Also, JMSV, which is harbored 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 North America (unpublished). In addition, other investigators have independently reported SWSV among Eurasian common shrews in central Europe [99–101], well as additional shrew-borne hantaviruses, including Tanganya virus in the Therese's shrew (*Crocidura theresae*) [102], Yakeshi virus in the taiga shrew (*Sorex isodon*) [103], Asikkala virus (ASIV) in the Eurasian pygmy shrew (*Sorex minutus*) [104], and Qian Hu Shan virus in the stripe-backed shrew (*Sorex cylindricauda*) [105].

2.3 Hantaviruses in Moles

Tissues from moles belonging to 10 of the 40 extant species, tested to date, have yielded five genetically distinct hantaviruses, including Asama virus (ASAV) in the Japanese shrew mole (*Urotrichus talpoides*) [106], Oxbow virus (OXBV) in the shrew mole (*Neurotrichus gibbsii*) [107], Nova virus (NVAV) in the European mole (*Talpa europaea*) [108], Rockport virus (RKPV) in the eastern mole (*Scalopus aquaticus*) [109], and Dahonggou Creek virus (DHCV) in the long-tailed mole (*Scaptonyx fusicaudus*) (unpublished) (Table 9.3). Undoubtedly, this represents a gross underestimation of the number of talpid-borne hantaviruses, because many more moles belonging to other species were unavailable for testing and for the ten species tested, the sample sizes were small, numbering fewer than ten individuals. More targeted searches for hantavirus RNA in moles that share common ancestries with the known talpid reservoirs will likely lead to the discovery of additional hantaviruses and/or clarify whether or not host sharing occurs among moles. In addition, studies of moles, which are sympatric and syntopic with shrews and rodents, are warranted to ascertain host-switching events.

The most highly divergent lineage of hantaviruses is represented by NVAV [108]. Recent studies indicate high prevalences of NVAV infection exceeding 50 % in

Table 9.3 Genetically distinct Hantaviruses detected in moles (order Eulipotyphla, family Talpidae)

Virus name	Virus abbreviation	Reservoir host species	Country	Year	Reference
Asama	ASAV	*Urotrichus talpoides*	Japan	2008	[106]
Dahonggou Creek	DHCV	*Scaptonyx fusicaudus*	China	1989	Unpublished
Nova	NVAV	*Talpa europaea*	Hungary	1999	[108]
			France	1912	[110]
			Poland	2010	[86]
Oxbow	OXBV	*Neurotrichus gibbsii*	USA	2003	[107]
Rockport	RKPV	*Scalopus aquaticus*	USA	1986	[109]

European moles from France and Poland, suggesting efficient enzootic virus transmission and a well-established, long-standing reservoir host–hantavirus relationship [86, 110]. Much like SWSV is widespread in the Eurasian common shrew throughout Europe, NVAV probably occurs throughout the vast distribution of the European mole. The rodent-borne hantavirus counterparts are PUUV in the bank vole in Europe and PUUV-like hantaviruses, such as HOKV and MUJV, in other arvicoline rodent species in Far East Asia, as well as SNV in the deer mouse and SNV-like hantaviruses, such as NYV, in other neotomine rodents in North America.

2.4 *Hantaviruses in Bats*

Attempts by our group and others to find hantavirus RNA by RT-PCR in more than 1,500 tissue samples from insectivorous and frugivorous bats belonging to approximately 100 species have resulted in the identification of six hantaviruses (Table 9.4). These include Mouyassué virus (MOYV) in the banana pipistrelle from Côte d'Ivoire [111, 112], Magboi virus (MGBV) in the hairy slit-faced bat (*Nycteris hispida*) from Sierra Leone [113], Makokou virus (MAKV) in the Noack's round-leaf bat (*Hipposideros ruber*) from Gabon [114], Xuan Son virus (XSV) in the Pomona round-leaf bat (*Hipposideros pomona*) from Vietnam [112, 115], Huangpi virus (HUPV) in the Japanese pipistrelle (*Pipistrellus abramus*), and Longquan virus (LQUV) in the Chinese rufous horseshoe bat (*Rhinolophus sinicus*), Formosan lesser horseshoe bat (*Rhinolophus monoceros*), and intermediate horseshoe bat (*Rhinolophus affinis*) from China [103]. Thus far, hantaviruses have not been detected in fruit bats (flying foxes).

Compared to the much higher success rates of detecting hantavirus RNA in shrews and moles, the very low success rate of similar efforts in bat tissues may be attributed to several factors. For one, the genomes of bat-borne hantaviruses may be too different to be readily amenable to the current primer-based screening methodologies, and primer mismatches and suboptimal PCR cycling conditions need to be overcome [111, 112, 115]. Also, the very focal nature of hantavirus infection, small sample sizes from any given bat species and poorly preserved or degraded RNA may be contributory.

Table 9.4 Genetically distinct Hantaviruses detected in insectivorous bats (order Chiroptera)

Virus name	Virus abbreviation	Reservoir host species	Country	Year	References
Huangpi	HUPV	*Pipistrellus abramus*	China	2011	[103]
Longquan	LQUV	*Rhinolophus sinica*	China	2011	[103]
		Rhinolophus affinis	China	2011	[103]
		Rhinolophus monoceros	China	2011	[103]
Magboi	MGBV	*Nycteris hispida*	Sierra Leone	2010	[113]
Makokou	MAKV	*Hipposideros ruber*	Gabon	2012	[114]
Mouyassué	MOYV	*Neoromicia nanus*	Côte d'Ivoire	2011	[111, 112]
Xuan Son	XSV	*Hipposideros pomona*	Vietnam	2012	[112, 115]

Alternatively, bats may be less susceptible to hantavirus infection or may have developed immune mechanisms to curtail viral replication and/or viral persistence. While bats of fewer species might serve as reservoirs, the hantaviruses they harbor are among the most genetically diverse described to date [103, 111–115]. As such, intensified studies on the phylogeography and transmission dynamics of hantaviruses in bats may provide additional insights into their evolutionary origins.

Although frozen tissues are intuitively preferred in virus-discovery efforts, the successful detection of hantavirus RNA in ethanol-fixed tissue from bat tissues [111] should substantially expand the pool of specimens for hantavirus hunting, especially in tissues from bats and other small mammals, such as hedgehogs and tenrecs, which may also carry hantaviruses. Such studies, currently underway, will further explore the host range of hantaviruses.

3 Geographic Distribution

Hantaviruses have now been identified in rodents, shrews, moles, and bats from widely separated geographic regions. For rodents and shrews, hantaviruses have been found in members of multiple species in four continents. Although far from comprehensive, the geographic distribution of hantaviruses is shown in Table 9.5, and the geographic origins of hantaviruses detected in shrews, moles, and bats are shown in Figs. 9.2, 9.3, and 9.4. The hantaviruses in South America have been

Table 9.5 Geographic distribution of rodent-, shrew-, mole-, and bat-borne hantaviruses[a]

		Hantaviruses in			
Continent	Country	Rodent	Shrew	Mole	Bat
Asia	Cambodia	SEOV, THAIV			
	China	AMRV, DBSV, HTNV, KHAV, LUXV, PUUV, SEOV	CBNV, MJNV, QHSV, TPMV, YAKV	DHCV	HUPV, LQUV
	India	SEOV	TPMV		
	Indonesia	SEOV, THAIV	TPMV		
	Japan	HOKV, SEOV	SRFV	ASAV	
	Korea	HTNV, MUJV, SEOV, SOOV	JJUV, MJNV		
	Mongolia		SWSV		
	Nepal		TPMV		
	Russia	AMRV, DOBV, KHAV, PUUV, SEOV, TULV, VLAV	KKMV, MGAV, SWSV		
	Singapore	SEOV, THAIV			
	Taiwan	SEOV	XYIV		
	Thailand	SEOV, THAIV			
	Vietnam	SEOV	CBNV, TPMV		XSV

(continued)

Table 9.5 (continued)

		Hantaviruses in			
Continent	Country	Rodent	Shrew	Mole	Bat
Europe	Austria	PUUV, TULV	SWSV		
	Belgium	PUUV, SEOV			
	Czech Republic	DOBV, PUUV, TULV	ASIV, SWSV		
	Finland	PUUV	ASIV, SWSV		
	France	PUUV, SEOV, TULV		NVAV	
	Germany	DOBV, PUUV, TULV	ASIV, SWSV		
	Hungary	DOBV, PUUV, TULV	SWSV	NVAV	
	Poland	DOBV, PUUV, TULV	BOGV, SWSV	NVAV	
	Serbia	DOBV, PUUV, SEOV, TULV			
	Slovakia	DOBV, PUUV, TULV	SWSV		
	Slovenia	DOBV, PUUV, SEOV, TULV	SWSV		
	Switzerland	TULV	SWSV		
	UK	SEOV, TATV			
Africa	Cote d'Ivoire		AZGV		MOYV
	Ethiopia	TIGV			
	Gabon				MAKV
	Guinea	SANGV	BOWV, TGNV		
	Madagascar	THAIV			
	Sierra Leone				MGBV
	Tanzania		ULUV, KMJV		
North America	USA	BAYV, BCCV, BLLV, EMCV, ISLAV, MULV, NYV, PHV, SEOV, SNV	AMNV, ARRV, JMSV, RPLV	OXBV, RKPV	
	Canada	SNV	JMSV		

[a]This table is not meant to be exhaustive. For example, the hantaviruses in South America are not listed because reservoir hosts other than rodents are not known

Rodent-borne hantaviruses: *AMRV*, Amur virus; *BAYV*, Bayou virus; *BCCV*, Black Creek Canal virus; *BLLV*, Bloodland Lake virus; *DBSV*, Da Bie Shan virus; *DOBV*, Dobrava virus; *EMCV*, El Moro Canyon virus; *HTNV*, Hantaan virus; *HOKV*, Hokkaido virus; *ISLAV*, Isla Vista virus; *KHAV*, Khabarovsk virus; *LUXV*, Luxi virus; *MULV*, Muleshoe virus; *MUJV*, Muju virus; *NYV*, New York virus; *PHV*, Prospect Hill virus; *PUUV*, Puumala virus; *SANGV*, Sangassou virus; *SEOV*, Seoul virus; *SNV*, Sin Nombre virus; *SOOV*, Soochong virus; *TATV*, Tatenale virus; *THAIV*, Thailand virus; *TIGV*, Tigray virus; *TULV*, Tula virus; *VLAV*, Vladivostok virus. Several rodent-borne hantaviruses in North America, such as Blue River virus and Limestone Canyon virus, detected in *Peromyscus leucopus* and *Peromyscus boylii*, respectively, are not listed

Shrew-borne hantaviruses: *AMNV*, Iamonia virus; *ARRV*, Ash River virus; *ASIV*, Asikkala virus; *AZGV*, Azagny virus; *BOGV*, Boginia virus; *BOWV*, Bowé virus; *CBNV*, Cao Bang virus; *JJUV*, Jeju virus; *JMSV*, Jemez Springs virus; *KMJV*, Kilimanjaro virus; *MGAV*, Amga virus; *MJNV*, Imjin virus; *QHSV*, Qian Hu Shan virus; *RPLV*, Camp Ripley virus; *SRFV*, Sarufutsu virus; *SWSV*, Seewis virus; *TGNV*, Tanganya virus; *TPMV*, Thottapalayam virus; *ULUV*, Uluguru virus; *YAKV*, Yakeshi virus

Mole-borne hantaviruses: *ASAV*, Asama virus; *DHCV*, Dahonggou Creek virus; *NVAV*, Nova virus; *OXBV*, Oxbow virus; *RKPV*, Rockport virus

Bat-borne hantaviruses: *HUPV*, Huangpi virus; *LQUV*, Longquan virus; *MAKV*, Makokou virus; *MGBV*, Magboi virus; *MOYV*, Mouyassué virus; *XSV*, Xuan Son virus

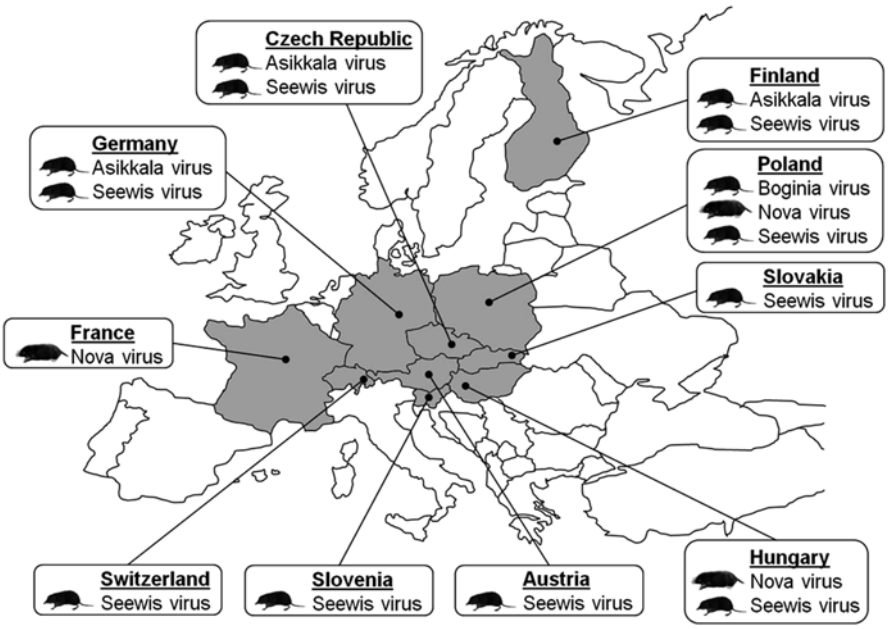

Fig. 9.1 Map of Europe, showing the countries where shrew- and mole-borne hantaviruses have been found. Table 9.5 provides a list of the hantaviruses harbored by rodents, shrews and moles in Europe

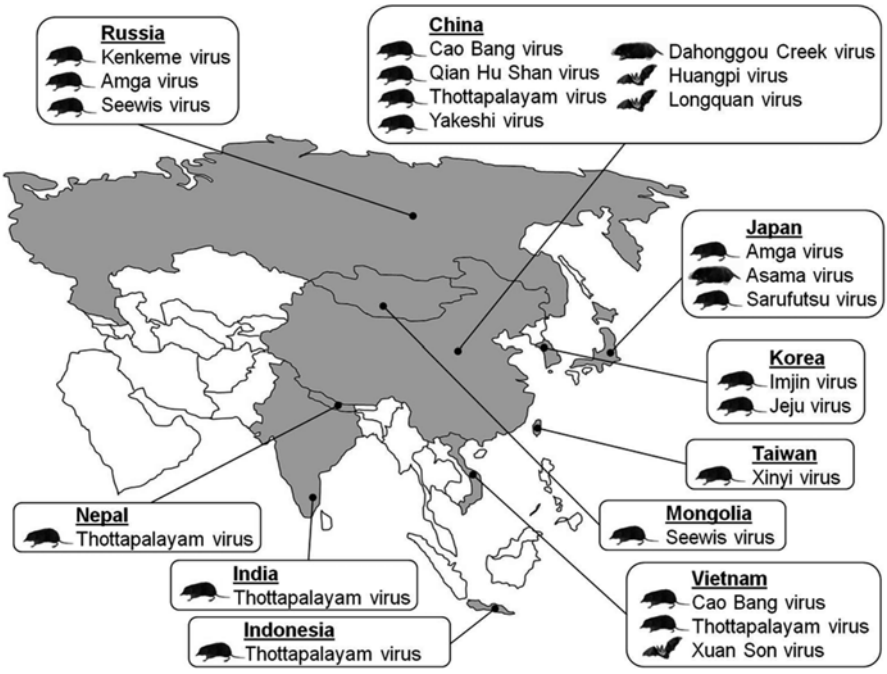

Fig. 9.2 Map of Asia, showing the countries where shrew-, mole-, and bat-borne hantaviruses have been found. Table 9.5 provides a list of the hantaviruses harbored by rodents, shrews, moles, and bats in Asia

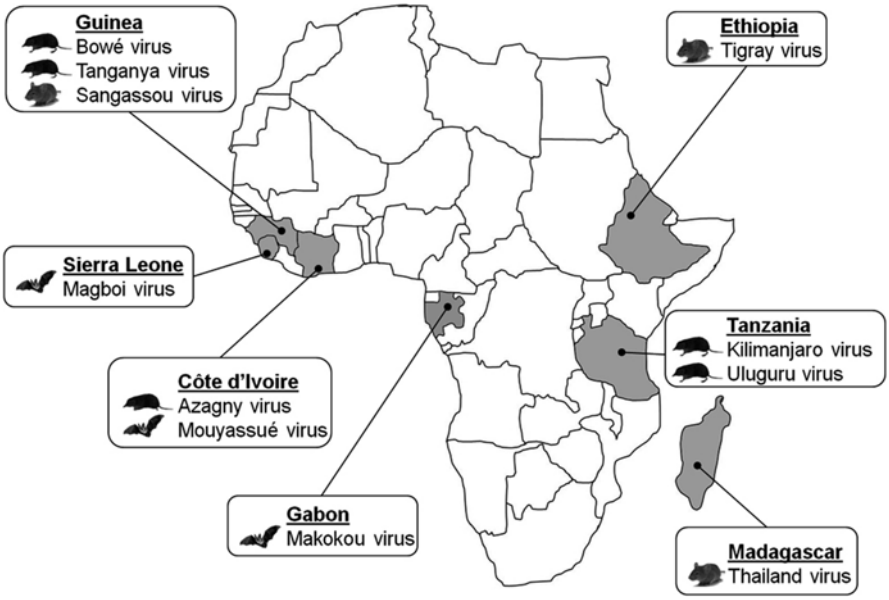

Fig. 9.3 Map of Africa, showing the countries where shrew- and bat-borne hantaviruses have been found. Table 9.5 provides a list of the hantaviruses harbored by rodents, shrews and bats in Africa

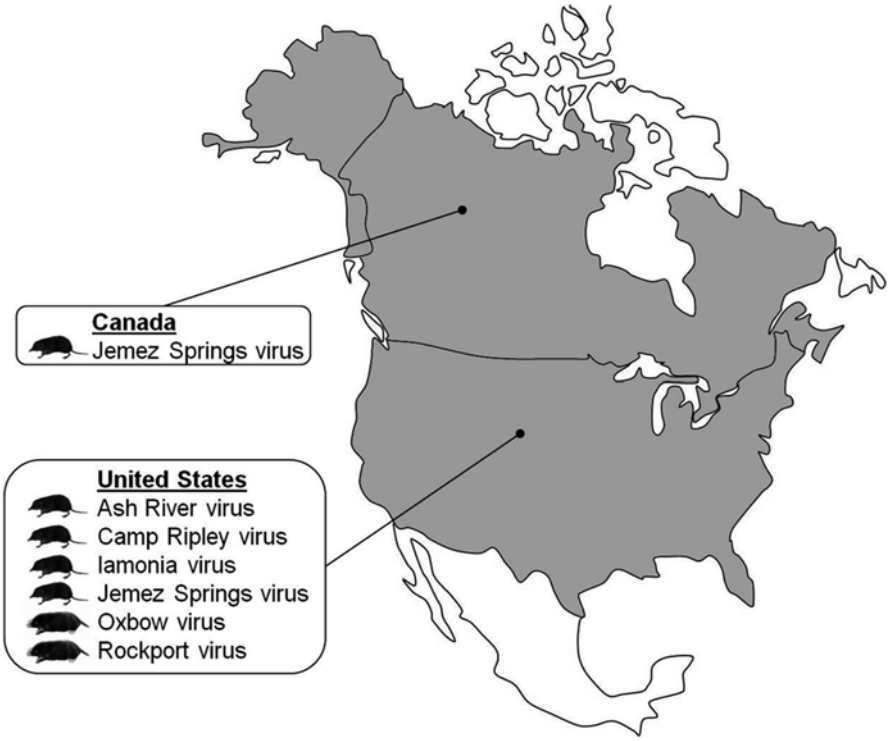

Fig. 9.4 Map of North America, showing the countries where shrew- and mole-borne hantaviruses have been found. Table 9.5 provides a list of the hantaviruses harbored by rodents, shrews and moles in North America

excluded intentionally because hosts other than rodents have not been identified. Similarly, countries in which only SEOV has been detected in rats are not included, in part because of their nearly global distribution, possibly accounted for by international shipping. The distribution of the reservoir host may also result from intentional anthropogenic activities. For example, it is highly likely that the present-day distribution of the Asian house shrew is due to human migration (S.D. Ohdachi, personal communication).

Of the 33 genetically distinct hantaviruses identified in shrews, moles, and bats (Tables 9.2, 9.3, and 9.4), each differs from known hantaviruses by more than 7 % in the amino acid sequence of the S segment-encoded nucleocapsid protein, suggesting that they may all represent new hantavirus species. However, in the absence of virus isolates in tissue culture, all of the current criteria mandated by the International Committee on Taxonomy of Viruses (ICTV) [116] cannot be met. Nevertheless, assuming for the moment that the 22 hantaviruses in shrews (Table 9.2), five in moles (Table 9.3), and six in bats (Table 9.4) represent distinct species, we can make the following observations: the preponderance of 15 hantaviruses in eulipotyphlya and chiropterans from Asia [25, 73, 88–92, 96, 103, 105, 106, 112] (Fig. 9.2), compared to the comparatively lower number of four from Europe [83, 94, 104, 108] (Fig. 9.1), eight from Africa [95, 97, 98, 102, 111, 113, 114] (Fig. 9.3), and six from North America [87, 93, 107, 109] (Fig. 9.4), and the far greater genetic diversity of hantaviruses hosted by Asian eulipotyphla and chiropterans and their basal positions in phylogenetic trees suggest that hantaviruses originated in Asia [22, 95]. An Asian origin was similarly concluded following an analysis of 190 S-segment sequences of rodent-borne hantaviruses, found in 30 countries during 1985–2010, retrieved from GenBank [117].

Previously, geographic-specific genetic variation has been demonstrated for HTNV in the striped field mouse [118], Soochong virus (SOOV) in the Korean field mouse (*Apodemus peninsulae*) [119], PUUV in the bank vole [120–124], MUJV in the royal vole [42, 43], TULV in the European common vole [32, 125], and ANDV in the long-tailed colilargo [23, 126]. Similarly, phylogenetic analyses show that hantaviruses harbored by shrews [84, 85, 99] and moles [86, 110] segregate along geographically specific lineages, suggesting long-standing associations between hantaviruses and their reservoir eulipotyphlan hosts.

While long suspected, novel hantaviruses have only recently been detected in rodents [24, 127] and shrews [95, 97, 98, 102], as well as insectivorous bats [111, 113, 114], in sub-Saharan Africa (Table 9.5 and Fig. 9.3). Notably, the five hantaviruses detected in African shrews and three detected in African bats, compared to only two hantaviruses reported from African rodents, despite the testing of tissues from many more rodents than shrews or bats, suggest that rodents may not have been the primordial mammalian hosts of ancestral hantaviruses [21, 22]. It is very probable that many more hantaviruses are extant in Africa, where unique lineages of shrews have diversified and evolved [95, 97, 98, 102]. Thus, more intensified investigations are warranted, not only in well-recognized biodiversity hotspots in West Africa but also in less-studied savannah and desert biomes.

4 Hantavirus Evolution

Before discussing the evolutionary dynamics of hantaviruses, it needs to be made clear that, while the newfound hantaviruses in shrews, moles, and bats are undoubtedly viruses, this does not infer that they have been adopted by the ICTV as hantavirus species (116). In fact, almost none of these viruses have been isolated in cell culture and their existence is inferred from partial or whole genome sequences. However, as evidenced by the extent of amino acid sequence differences observed compared to ICTV-classified hantaviruses and their unique ecological niches, it is likely that most of these newly reported hantaviruses will prove to be distinct hantavirus species.

Currently, the genomic database comprises sequences for 33 genetically distinct hantaviruses hosted by shrews, moles, and bats (Tables 9.2, 9.3, and 9.4). Whole genomes are available for only seven (BOWV, CBNV, JJUV, MJNV, RKPV, TPMV, YAKV), and full-length S-segment sequences have been completed for 20. None of the bat-borne hantaviruses have been fully sequenced, and full-length M-segment sequences are generally lacking. The paucity of whole-genome sequences of the newfound eulipotyphla- and chiroptera-borne hantaviruses has greatly hampered attempts at clarifying their evolutionary origins and phylogeography [21, 22]. And thus far, efforts at employing next-generation sequencing technology have been largely unsuccessful, primarily because of the limited availability of tissues and poor-quality of tissue RNA.

Phylogenetic analysis, based on partial or full genome sequences of all three segments, results in trees consisting of four distinct clades (Fig. 9.5). One clade comprises hantaviruses harbored by rodents of the Muridae family; a second by hantaviruses hosted by rodents of the Cricetidae family; a third by hantaviruses in eulipotyphlans of the Soricidae family; and a fourth by hantaviruses harbored by talpid moles (Talpinae subfamily) and insectivorous bats, which represent the most divergent hantaviruses found to date (Fig. 9.5). Eulipotyphla-borne hantaviruses are divided into two phylogenetic lineages: one that is paraphyletic with murid rodent-borne hantaviruses, includes soricine and crocidurine shrew-borne hantaviruses, and two hantaviruses carried by shrew moles (ASAV and OXBV); the other lineage includes TPMV and MJNV, two crocidurine shrew-associated hantaviruses that are phylogenetically more closely related to bat-borne hantaviruses (HUPV, LQUV, MGBV, MOYV, XSV).

Previously, the segregation of hantaviruses into clades that paralleled the molecular phylogeny of their rodent hosts in the Murinae, Arvicolinae, Neotominae, and Sigmodontinae subfamilies suggested the concept of co-divergence [128]. Recently, this concept has been challenged on the basis of the disjunction between the evolutionary rates of the hosts and viruses. Preferential host switching and local host-specific adaptation have been proposed to account for the largely congruent phylogenies [129]. However, host-switching events alone do not completely explain the coexistence and distribution of genetically distinct hantaviruses among hosts of different species in three divergent taxonomic orders of small mammals spanning across four continents [108]. Moreover, phylogenetic trees reconstructed for co-phylogeny mapping, using consensus topologies based on amino acid sequences

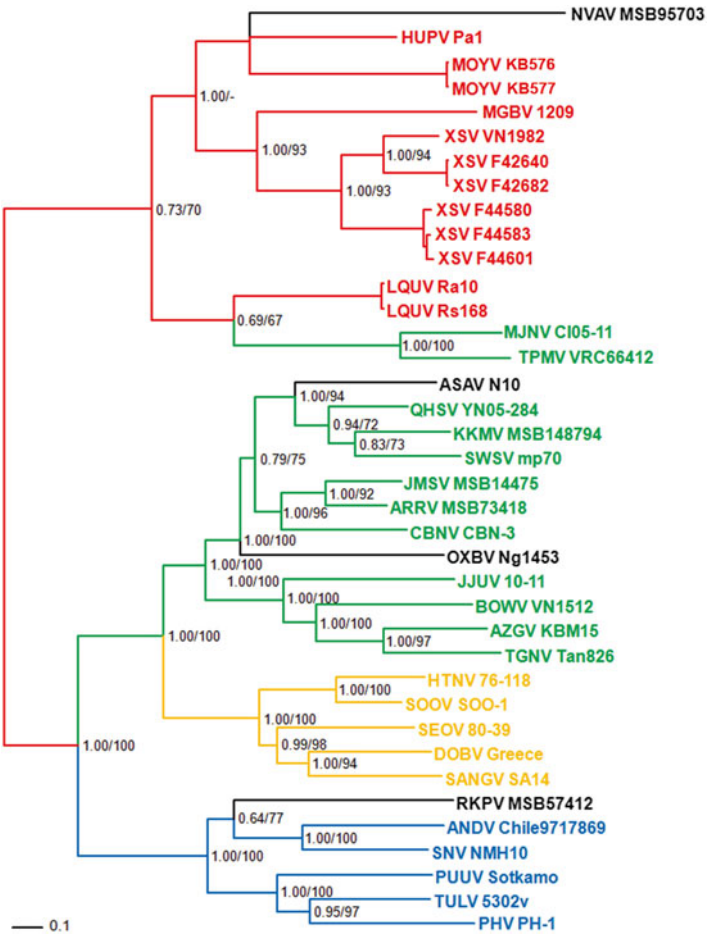

Fig. 9.5 Phylogenetic tree generated by maximum-likelihood and Bayesian methods, based on the alignment of the L-segment sequences of hantaviruses. The phylogenetic positions of Xuan Son virus (XSV) and Mouyassué virus (MOYV) are shown in relationship to other bat-borne hantaviruses (shown in *red*), including Magboi virus (MGBV), Longquan virus (LQUV) and Huangpi virus (HUPV), and representative shrew-borne hantaviruses (shown in *green*), including Thottapalayam virus (TPMV VRC66412), Imjin virus (MJNV Cl05-11), Seewis virus (SWSV mp70), Kenkeme virus (KKMV MSB148794), Cao Bang virus (CBNV CBN-3), Ash River virus (ARRV MSB 73418), Jemez Springs virus (JMSV MSB144475), Qian Hu Shan virus (QHSV YN05-284), Tanganya virus (TGNV Tan826), Azagny virus (AZGV KBM15), Jeju virus (JJUV 10-11), Bowé virus (BOWV VN1512); mole-borne hantaviruses (shown in *black*), including Asama virus (ASAV N10), Oxbow virus (OXBV Ng1453), Nova virus (NVAV MSB95703), and Rockport virus (RKPV MSB57412). Also shown are representative Murinae rodent-borne hantaviruses (shown in *orange*), including Hantaan virus (HTNV 76-118), Soochong virus (SOOV SOO-1), Dobrava virus (DOBV Greece), Seoul virus (SEOV 80-39), and Sangassou virus (SANG SA14); Arvicolinae rodent-borne hantaviruses (shown in *blue*), including Tula virus (TULV M5302v), Puumala virus (PUUV Sotkamo), and Prospect Hill virus (PHV PH-1); and Neotominae and Sigmodontinae rodent-borne hantaviruses (shown in *blue*), Sin Nombre virus (SNV NMH10) and Andes virus (ANDV Chile9717869). The numbers at each node are posterior node probabilities (*left*) based on 150,000 trees and bootstrap values (*right*) based 1,000 replicates executed on the RAxML BlackBox web server, respectively. The scale bar indicates nucleotide substitutions per site

of the nucleocapsid protein, Gn and Gc glycoproteins and RNA-dependent RNA-polymerase, exhibited congruent segregation of hantaviruses according to the subfamily of their eulipotyphlan reservoir hosts, with no evidence of host switching except for two hantaviruses carried by shrew moles [107].

Host-switching events in hantavirus evolution have been documented between hosts of the same family (Soricidae and Soricidae), of different families (Soricidae and Talpidae) and of separate orders (Eulipotyphla and Rodentia) [103, 106, 107]. The importance of such virus-host switching lies in the possible emergence of disease-causing hantaviruses. The close association between distinct hantaviruses and specific rodents, shrews, and moles probably resulted from alternating and periodic episodes of host/pathogen co-divergence through deep evolutionary time [95]. That is, as evidenced by the overall congruence between the phylogenies of hantavirus genes and their rodent and eulipotyphlan hosts, hantaviruses have likely co-diverged with specific reservoir hosts during part of their evolutionary history [108, 109].

5 Hantaviral Diseases

In a now classic volume, published in 1953, Gajdusek conjectured that Korean hemorrhagic fever in Asia and nephropathia epidemica in Scandinavia, while occurring in different geographic locations and exhibiting differential clinical severity, were manifestations of the same disease and were caused by the same virus or closely related viruses [1]. This conjecture, made more than a decade before the discovery of HTNV, was verified shortly after the isolation of HTNV in cell culture [130–133]. And while the literature contains more than 150 synonyms for this clinical syndrome, the designation of HFRS has been dominant since the isolation of HTNV. With the advent of HCPS, as a disease with predominantly cardiac and pulmonary involvement, the conventional view was that of two clinically distinguishable syndromes caused by hantaviruses harbored by rodents belonging to different rodent subfamilies in the Old and New Worlds. That is, HFRS was caused by hantaviruses carried by rodents of the Murinae and Arvicolinae subfamilies, while hantaviruses hosted by rodents in the Neotominae and Sigmondontinae subfamilies caused HCPS.

This tidy trans-Atlantic classification may have outlived its usefulness and is being subjected increasingly to intense scrutiny, particularly as clinicians in both the Old and New Worlds encounter cases of HFRS which lack renal involvement but exhibit prominent cardiopulmonary features, and conversely as cases of HCPS with renal insufficiency but without pulmonary involvement are documented [51, 134–138]. Once downplayed or sometimes intentionally ignored, the considerable overlap between HFRS and HCPS is challenging the long-accepted distinction of two separate clinical syndromes. A proposed nosology would entail the moniker “hantavirus fever” [51, 139]. Much more discussion is obviously needed for ultimate consensus and adoption, but this particular name might not necessarily solve the current conundrum. For instance, some diseases, caused by arboviruses, such as dengue

fever and West Nile fever, typically refer to the milder, non-life-threatening clinical forms of infections with dengue and West Nile viruses. For patients with clinically severe diseases with either flavivirus, different names are typically used, such as dengue hemorrhagic fever and dengue shock syndrome, or West Nile virus meningoencephalitis, respectively. For dengue, the World Health Organization (WHO) has recently issued revised guidelines for classifying dengue virus-infected patients, based on clinical severity and laboratory tests [140], into three levels: dengue; dengue with warning signs; and severe dengue.

Although there is no unanimity of opinion in accepting the new WHO guidelines for dengue [141, 142], a similar nosological approach may be contemplated for hantavirus-infected patients: namely, hantavirus fever; hantavirus fever with warning signs; and severe hantavirus fever. Irrespective of the resultant new classification, however, it is imperative that the guidelines are concise, clearly stated, easily implemented and relevant to the diagnosis and clinical management of patients with hantavirus disease. As with dengue, a list of warning signs to alert physicians to better identify severe cases, or potentially severe cases, and to make appropriate changes in clinical care, especially in resource-poor settings, would be valuable.

5.1 HFRS and HCPS

Outbreaks of HFRS usually follow encroachment of rodent habitats or irruptions of reservoir rodent populations with subsequent invasion of human dwellings. The respiratory droplet route of aerosolized rodent excreta constitutes the principal mode of viral transmission to humans [3, 29]. Humans infected with pathogenic hantaviruses usually develop mild to severe clinical disease, but subclinical infection also occurs to varying degrees depending on the hantavirus. In Scandinavia, HFRS is often still referred to as nephropathia epidemica, which, while usually mild, may run a more fulminant course [3]. Inapparent or subclinical hantavirus infection is not uncommon, depending on the particular virus, as with Choclo and Calabazo viruses on the Azuero peninsula of Panama [143]. Human population-based serosurveys in HFRS- and HCPS-endemic geographic areas indicate low (<1–5 %) to very high (>30 %) prevalences of anti-hantavirus antibodies [143–145]. Infections among children are uncommon, and seroprevalence tends to increase with age.

Vascular leak, or increased endothelial permeability, is the principal pathophysiological feature of severe HFRS and HCPS. The principal symptoms and clinical features of both syndromes include high fever, chills, headache, generalized myalgia, abdominal pain, and nausea and vomiting. In the classical descriptions of HFRS, five distinct phases were described [3, 29, 63, 146]. Febrile phase, which begins abruptly; hypotensive phase, on the fifth day of illness; oliguric phase, on the ninth day of illness, with associated thrombocytopenia, proteinuria, hemorrhage and plasma leakage; diuretic phase, usually between days 12 and 14; and convalescent phase, which is gradual over several months. Depending on the severity of disease, not all HFRS patients exhibit all phases, or the phases may overlap [147]. The early

stage of HCPS, which resembles the febrile phase of HFRS, is somewhat nondescript and can be easily confused with other, more common, acute-onset febrile infectious diseases. But at 4–10 days after the onset of illness, HCPS patients experience rapidly progressive respiratory distress, characterized by dry cough and extreme shortness of breath, or dyspnea [4, 148–150]. Multivariate analysis showed that the clinical features of dizziness, nausea and vomiting and absence of cough at the time of hospital admission, and the initial laboratory abnormalities of thrombocytopenia, low serum bicarbonate level and elevated hematocrit served to identify HCPS patients [151].

The clinical management of HFRS and HCPS is largely supportive, with careful fluid management and monitoring of cardiopulmonary and/or renal function, administered in an intensive care hospital setting. Dialysis may be required for 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 [4, 152]. The use of antiviral drugs is uncommon, despite the significant benefit from intravenous ribavirin, as demonstrated in a prospective, randomized, double-blind, placebo-controlled clinical trial involving 242 patients with serologically confirmed HFRS in China [153]. In a subsequent study, intravenous ribavirin significantly reduced the occurrence of oliguria and the severity of renal insufficiency in HFRS patients [154]. Similarly well-controlled trials of intravenous ribavirin in HCPS have not been conducted. However, because of the lack of clinical benefit in an open-label trial of ribavirin, conducted during the 1993 HCPS outbreak, a trial which was not designed to assess efficacy [155], and the partial results from a placebo-controlled, double-blind trial that was prematurely terminated because of inadequate patient accrual [156], ribavirin is currently not recommended in the treatment of HCPS or available for this use under any existing research protocol. Recent findings from *in vivo* studies in the Syrian hamster HCPS model, indicating that ribavirin provides effective post-exposure prophylaxis against HCPS-causing ANDV infection [157, 158], should prompt serious reconsideration of the current, possibly unjustified verdict against the use of ribavirin in HCPS. This is more than an academic issue, for while the lethality of HFRS ranges from <1 % to more than 20 % [3, 63], the lethality of HCPS is much higher, ranging from 30 to 50 % or more in the Americas [148–150]. As such, adjunct therapy with ribavirin, or other newly developed antiviral compound, could potentially reduce the number of HCPS-related deaths. A well-designed, properly controlled and sufficiently powered clinical trial of intravenous ribavirin for HCPS should be conducted in South America, where more than 4,000 HCPS cases have been diagnosed up until 2013 [150].

A fundamental epidemiological factor in HFRS and HCPS is exposure to rodent-infested habitats. Seemingly trivial exposure to environments contaminated with rodent excretions can lead to infection and disease. On the other hand, the intimate handling of rodents does not necessarily constitute sufficient exposure. Thus, although individuals, such as mammalogists, who have frequent occupational contact with rodents, are presumed at increased risk to rodent-borne pathogens, several studies have indicated insignificant prevalence of hantavirus infections [159–162]. This has been corroborated in a recent study, in which only four of 757 persons who had handled neotomine or sigmodontine rodents in North America exhibited serum

IgG antibodies against SNV [163]. Also, during the height of the HCPS outbreak in the Four Corners region, forest and park service personnel showed no evidence of SNV infection [164]. By contrast, studies in Eurasia show clear associations between hantavirus infection and exposure to rodent excreta among certain high-risk occupation groups, such as animal trappers, forestry workers and farmers [165–167], and individuals, such as hunters, whose recreational activities encroach on wildlife habitats [168].

No evidence of SNV or ANDV transmission was found among health-care workers exposed to patients with confirmed HCPS [169, 170]. Similarly, there are no reports of hantavirus transmission from HFRS patients to physicians or medical personnel or to family members. On the other hand, there are well-substantiated reports of person-to-person transmission of ANDV in Argentina and Chile [171–174]. In a study of household contacts of persons with HCPS in Chile, the risk was highest among sex partners [174]. Also, epidemiological data suggest that prolonged and close contact with HCPS patients during the prodromal phase of disease, before patients seek medical attention, may constitute the period of increased risk [173].

5.2 Identifying and Investigating Previously Unrecognized Hantaviral Diseases

Not all orphan viruses, or viruses in search of diseases, warrant investigations to ascertain their pathogenic potential at the time of discovery. However, selected viruses, particularly those related to viruses known to cause severe and life-threatening diseases, such as HFRS and HCPS, are worthy of high research priority. No one would have predicted that rodent-borne viruses, previously known to cause acute renal insufficiency with varying degrees of hemorrhage and shock, would also cause an acute respiratory disease. The realization that rodent-borne hantaviruses are capable of causing HFRS and HCPS raises the possibility that soricid-associated hantaviruses may similarly cause a wide spectrum of febrile illnesses. In this regard, prospective studies of neotomine and sigmodontine rodent-borne hantaviruses in the early 1980s might have provided important clues about their pathogenicity long before the recognition of HCPS in 1993. In much the same way, one or more of the newly identified soricid-borne hantaviruses may cause outbreaks of human disease and/or serve as surrogate antigens for the diagnosis of previously unrecognized hantaviral diseases. Robust serological assays and other sensitive technologies, now under development, will assist in establishing if these newest members of the *Hantavirus* genus are pathogenic for humans. Also, studies on the genetics, transmission dynamics and disease-causing potential of one or more of the newly identified hantaviruses in shrews, moles, and insectivorous bats, as well as African rodents, may better prepare the next generation of health-care workers before the next newly recognized hantaviral disease.

By focusing too heavily on the syndromic features of renal and/or cardiopulmonary dysfunction, the full spectrum of hantavirus disease may be obscured or missed. Possibly, a detailed examination of atypical cases of HFRS and HCPS may provide

clues about other previously unrecognized diseases caused by hantaviruses, particularly those newly discovered in shrews, moles, and bats. In this regard, before the recognition of HCPS, serological surveys were conducted for evidence of hantavirus infection among patients with fever of unknown etiology in the USA, including individuals with pneumonia, rickettsial-like illnesses and leptospirosis-negative tests [175]. However, as in any serosurvey, one can be misled into thinking that an orphan virus is nonpathogenic if the 'wrong' patient groups are studied. In the case of HCPS, only HCPS patients had evidence of SNV infection.

5.2.1 In Search of SANGV Infection and Disease

As summarized recently, many thousands of sera from randomly selected human populations in Algeria, Benin, Burkino Faso, Cameroon, Central African Republic, Chad, Djibouti, Egypt, Gabon, Nigeria, Senegal, and countries in South Africa have been tested for evidence of hantavirus infection [176]. In all such studies across the African continent, IgG antibodies against HTNV, and occasionally SEOV, PUUV, or PHV, were sought, using either enzyme-linked immunosorbent assay (ELISA) or immunofluorescent antibody test (IFA). Because confirmatory tests were not employed in nearly all of these studies, the reported seroprevalences, which ranged from 0.2 to 17 %, cannot be interpreted [162]. With the recent detection of rodent- and shrew-borne hantaviruses in both West and East Africa, and with improvements in serological testing, more accurate information about the true burden of hantavirus infection and disease in humans may be within reach.

In large part, this is being made possible by SANGV, which is the first hantavirus discovered in the African wood mouse in sub-Saharan Africa [24] and the only African hantavirus isolated in cell culture [177]. The whole genome of SANGV has been sequenced and studies indicate that SANGV uses β(1) integrin as a cell-entry receptor [177]. Previously, pathogenic hantaviruses, which cause HFRS (HTNV, SEOV, PUUV, DOBV) and HCPS (SNV, NYV), have been shown to utilize αvβ3 integrin for cell entry, compared to nonpathogenic hantaviruses (PHV) which use β1 integrin [178–181]. β1 integrin usage would suggest that SANGV is nonpathogenic. Nevertheless, detailed serological surveys have been conducted to ascertain if SANGV causes human infection and disease.

In analyzing 717 serum specimens from inhabitants of 29 villages in Forest Guinea (including 68 samples from residents of Sangassou village) by ELISA, with confirmation by IFA, western blot (WB), and focus-reduction neutralization test (FRNT), Klempa and colleagues found approximately 1 % of tested individuals to be antibody positive [182]. Also, in a separate study of 253 sera from residents of Upper Guinea [183] and in a survey of 1,442 samples from the Republic of South Africa [176], the seroprevalence was 1 %. However, the prevalence was much higher (4.4 %) among 68 patients from Sangassou village, who had fever of unknown origin [183]. Two of the three seropositive children had neutralizing antibodies against SANGV and had an illness compatible with HFRS [183]. Although HFRS is usually uncommon in children [184–187], SANGV may differ in this regard from other HFRS-causing

hantaviruses. Alternatively, the selection of febrile study participants in Sangassou village might have skewed the findings.

5.2.2 In Search of MJNV Infection and Disease

The isolation of MJNV from the Ussuri white-toothed shrew also raised questions about its pathogenic potential. From one standpoint, however, the objective of demonstrating MJNV infection in humans might be considered ill conceived for the simple reason that shrew populations are generally much smaller than rodent populations, making the probability of contact between humans and shrews (and their excretions) extremely low. Also, the Ussuri white-toothed shrew is not found in peri-domestic habitats, unlike the Asian house shrew, which carries a closely related hantavirus known as TPMV, making even less likely exposure to MJNV-infected fomites. While this line of thinking is logical, zoonotic microbes, in general, tend to rarely infect humans, but they are nevertheless of significant medical importance. In this regard, HCPS itself is a rare disease. And quite likely, in the absence of an outbreak of human disease caused by MJNV, one would be looking for such a rare event. Placed in proper perspective, therefore, HCPS would have probably gone unnoticed, had cases not clustered in time and space and had a closely knit group of dedicated and astute health-care workers not recognized that something very unusual was happening.

Our search for evidence of MJNV infection was focused almost entirely on patients with acute febrile illnesses, and in whom other zoonotic infectious diseases (such as leptospirosis, scrub typhus, murine typhus and HFRS caused by HTNV and SEOV) had been ruled out. A summary of the study populations, comprising 2,800 participants, is shown in Table 9.6. Acute-phase sera from clinic and hospitalized patients, as well as sera from individuals with HFRS-like symptoms, were screened

Table 9.6 Serological survey of MJNV infection

	Serum	ELISA MJNV		IFA				
Study Population	Tested	IgM+	IgG+	MJNV+	TPMV+	RT-PCR +	WB +	PRNT +
Paju Adult and Pediatric Clinic	52	0	ND	0	0	ND	ND	ND
Guro Hospital	327	1	ND	3	2	0	ND	ND
HFRS-like disease 2003	593	2	ND	2	0	ND	ND	ND
HFRS-like disease 2004	1074	0	ND	7	7	0	ND	ND
HFRS-like disease 2006	656	5	2	6	3	0	3	0
HFRS-like disease 2011	30	0	ND	0	0	ND	ND	ND

Abbreviations: *HFRS*, hemorrhagic fever with renal syndrome; *IFA*, indirect immunofluorescence antibody test; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *MJNV*, Imjin virus; *ND* = test not done; *PRNT*, plaque-reduction neutralization test; *RT-PCR*, reverse transcription polymerase chain reaction; *TPMV*, Thottapalayam virus; *WB*, western blot

Table 9.7 Serological testing of individuals with suspected MJNV infection

Study group	Patient	Age Sex	ELISA MJNV IgM	ELISA MJNV IgG	IFA MJNV	IFA TPMV	RT-PCR L	RT-PCR M	RT-PCR S	RT-PCR WB	RT-PCR PRNT
Guro Hospital	1	37 M	–	–	64	–	ND	–	ND	ND	ND
	2	24 M	200	–	–	–	ND	–	ND	ND	ND
	3	49 F	–	–	256	–	–	–	–	ND	ND
	4	58 F	–	–	32	–	–	–	–	ND	ND
HFRS-like disease 2003	5	79 F	–	ND	32	–	–	–	–	ND	ND
	6	69 F	–	ND	32	–	–	–	–	ND	ND
	7	40 M	400	ND	–	–	–	–	–	ND	ND
	8	56 M	400	ND	–	–	–	–	–	ND	ND
HFRS-like disease 2004	9	34 M	–	–	64	–	–	–	–	ND	ND
	10	35 M	–	–	128	–	ND	–	ND	ND	ND
	11	22 M	–	–	256	–	–	–	–	ND	ND
	12	35 M	–	–	128	–	–	–	–	ND	ND
	13	UNK	–	–	256	–	–	–	–	ND	ND
	14	80 M	–	–	128	–	–	–	–	ND	ND
	15	UNK	–	–	64	–	–	–	–	ND	ND
HFRS-like disease 2006	16	33 M	200	–	64	32	ND	–	ND	–	–
	17	36 M	400	–	–	32	ND	–	ND	–	–
	18	53 F	400	–	64	–	ND	–	ND	+	–
	19	26 M	800	–	256	–	ND	–	ND	–	–
	20	65 F	800	–	32	128	ND	–	ND	–	–
	21	UNK	–	400	128	–	ND	–	ND	+	–
	22	45 M	–	400	1024	–	ND	–	ND	+	–

Definitions: ELISA IgM and IgG: defined as <200; IFA MJNV and TPMV: defined as <32; PCR: defined as undetectable hantavirus RNA; WB: defined as <40; PRNT: defined as <40. ND = test not done

Abbreviations: *ELISA*, enzyme-linked immunosorbent assay; *IFA*, indirect immunofluorescence antibody test; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *L*, L segment; *M*, M segment; *MJNV*, Imjin virus; *PRNT*, plaque-reduction neutralization test; *RT-PCR*, reverse transcription polymerase chain reaction; *S*, S segment; *TPMV*, Thottapalayam virus; *WB*, western blot

for IgM and IgG antibodies against MJNV by ELISA and IFA. Confirmatory tests included WB and PRNT, and sera from some suspect cases were tested by RT-PCR for MJNV RNA (Table 9.7). The test results of 22 study subjects with suggestive evidence of MJNV infection are shown in Table 9.7. Three patients with HFRS-like diseases had detectable antibodies to MJNV, as determined by ELISA, IFA and WB, but confirmation by PRNT was lacking. Overall, no serological evidence of MJNV infection was found.

An important shortcoming of any serological survey in search of a rare infectious event is the failure to recruit individuals who are affected by that rare event. On the one hand, the inability to find individuals with antibodies against MJNV may indicate that MJNV does not cause infection in humans. On the other hand, this same (negative)

result could mean that the study population simply failed to enroll subjects with MJNV infection. In other words, if MJNV infection is associated with a rare or uncommon disease, we would be unable to show infectivity in humans. In this regard, even at the height of the 1993 HCPS outbreak in the Four Corners region, no serological evidence of SNV 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 SNV infection. Thus, even with the most lethal of infectious agents, one would erroneously conclude that the microbe is nonpathogenic or noninfectious, if the "right" patients are not tested.

6 Concluding Remarks

With the expanded host diversity and geographic distribution of hantaviruses has come a reexamination of previously long-held dogma about the host range, evolutionary origins and phylogeography of hantaviruses. Many more hantaviruses, possibly some in hosts belonging to other taxonomic orders and in unanticipated geographic regions, await discovery. Textbook chapters on hantaviruses will also need to be rewritten, as more information becomes known about the emergence and pathogenic potential of newfound hantaviruses. In this regard, some of the uncertainties and conundrums in hantavirus research is a direct consequence of the dearth of full-length genomes and hantavirus isolates. In particular, nearly all of the newly identified hantaviruses in shrews, moles, and bats have yet to be isolated. In fact, to date, there are only two non-rodent-borne hantavirus isolates in cell culture. One is TPMV, the prototype shrew-borne hantavirus, isolated from the Asian house shrew [73, 74], and the other is MJNV, isolated from the Ussuri white-toothed shrew [25]. There are no hantavirus isolates from moles or bats (or other shrews). Virus isolates would dramatically accelerate the acquisition of whole genome sequences of recently discovered hantaviruses.

The isolation of hantaviruses, however, is fraught with difficulty, with numerous failed attempts. Recently, the isolation of HOKV was achieved only after establishing a cell line from the rodent reservoir, the gray red-backed vole [188]. Whether such strategies will prove helpful or become necessary for other hantaviruses hosted by shrews, moles, and bats is worthy of serious consideration. In any case, until such time that multiple non-rodent-borne hantaviruses are isolated in cell culture, the biology, taxonomy and pathogenicity of these newly identified hantaviruses will remain speculative at best. Thus, the road ahead, at the dawn of a new era in hantavirology, is laden with challenges, but also innumerable opportunities and unlimited possibilities. Many discoveries and giant leaps in newfound knowledge can be anticipated. Above all, strong partnerships between health-care providers, public health workers, veterinarians, mammalogists, ecologists, and pathologists will be vital for the identification and rapid diagnosis of previously unrecognized infectious diseases, caused by newfound hantaviruses and other vector-borne and zoonotic microbial agents [189].

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