# CHAPTER 16

# Hantavirus Coevolution with Their Rodent Hosts

**Vincent Herbreteau,[1,2] Heikki Henttonen,[3] Kumiko Yoshimatsu,[4] Jean-Paul Gonzalez,[2] Yupin Suputtamongkol,[5] and Jean-Pierre Hugot[6]**

[1]*Laboratoire Espace, Santé, Territoire; Université Paris X- Nanterre, 200 avenue de la république, 92000 Nanterre, France*

[2]*IRD, UT 178, Bangkok, Thailand*

[3]*Finnish Forest Research Institute, Vantaa Research Centre, POB18 FIN-01301 Vantaa, Finland*

[4]*Institute for Animal Experimentation, Hokkaido University, School of Medicine, Sapporo, Japan*

[5]*Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

[6]*Muséum National d'Histoire Naturelle, Département Systématique et Évolution, UMR Origine, Structure et Évolution de la Biodiversité, 75231 Paris Cedex 05, France*

"J'ai toujours pensé que le secret de la formation des espèces est dans leur morphologie, que les formes animales sont un langage hiéroglyphique dont on n'a pas la clef, et que l'explication du passé est tout entière dans des faits que nous avons sous les yeux, sans savoir les lire. Un jour viendra où la zoologie sera historique, c'est-à-dire où, au lieu de se borner à décrire la faune existante, elle cherchera à découvrir comment cette faune est arrivée à l'état où nous la voyons. Il se peut que les hypothèses de Darwin à ce sujet soient un jour jugées insuffisantes ou inexactes, mais sans contredit, elles sont dans la voie de la grande explication du monde et de la vraie philosophie."

*Ernest Renan (1863).*

"Since a long time, I believed that the secret explanation of the origin of species has to be found in their morphology. The animal forms are a hieroglyphic language remaining enigmatic and the whole explanation of the past stands in unreadable facts, which are before our very eyes. One day in the future, Zoology will become historical instead of being limited to the description of the existing fauna, and it will try to discover how this fauna happened to be as we can observe it now. Perhaps, Darwin's hypotheses on this subject may be considered inadequate or inaccurate in the future, however, they certainly are on the way of the main explanation of our world and of the true Philosophy."

*Ernest Renan (1863).*

## 16.1 INTRODUCTION

Genus hantavirus is one out of five genera within the Bunyaviridae family. The Bunyaviridae groups more than 350 species, most of which are arboviruses vectored by mosquitoes, ticks, sand flies, and so on. Within the family, only genus Tospovirus is a plant virus. Most of the other Bunyaviridae may cause human diseases. Bunyavirus is the agent of La Crosse encephalitis, and California encephalitis; Phlebovirus of Rift Valley fever (RVF), and sand fly fever; Nairovirus of Crimean-Congo hemorrhagic fever (CCHF); hantavirus of hemorrhagic fever with renal syndrome (HFRS), or hantavirus pulmonary syndrome (HPS).

Hantaviruses, which are usually hosted by wild mammals (rodents and shrews), are potentially pathogenic for humans. Several serologically distinct virus species, associated with

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different syndromes, have been recognized. In Asia, Hantaan, Dobrava, Seoul, and Puumala cause the clinical forms of HFRS [36]. In South America, Sin Nombre and Andes are responsible for HPS [5]. A last group, Tula, widely distributed in Russia and Eastern Europe has never been associated with a human disease. Muridae rodents are the primary reservoir and, because each virus group is associated with a particular rodent family, the hypothesis of coevolution with cophylogeny has been suggested [7,24,25,36].

Coevolution may be defined as: the mutual evolutionary influence between two species: each of the species exerts selective pressure on the other, so they evolve together. Coevolution is an extreme example of mutualism and may be described as a change in the genetic composition of one species (or group) in response to a genetic change in another. Coevolution may be considered among broad groups of taxa, and because all interacting organisms bring about changes, initially it might seem that everything is involved in coevolution. However, some particular situations allow more accurate observation of the phenomenon: this is when coevolution is going on between pairs of species from each group. Patterns of paired coevolution are particularly frequent in the evolution of hosts and parasites. If the term is usually attributed to Ehrlich and Raven's study of butterflies on plants [8], the idea was very apparent in the "Origin of Species." Since Darwin, many authors have suggested that the phylogenetic relationships of highly host specific parasites would provide valuable information about the evolutionary history of their hosts [3]. This is because, sometimes, the life histories of two different lineages are so intimately linked that a speciation in one group induces a parallel speciation event in the other. In such a case, comparison of host cladograms and parasites is crucial. If they are congruent, this certainly suggests coevolutionary phenomena and "association by descent." Nevertheless, cophylogeny does not mean reciprocal phenomena: speciation of the host may induce the speciation of the parasite without parasite-induced speciation of the host. One needs to know the evolutionary history before deciding which type of co-"evolution" is observed. This means that phylogenetic analysis is necessary and constitutes the first step in this type of study.

Viruses are the "achieved" parasites: they are completely dependent on the cell machinery of their host, hijacked for their own profit. Conversely, their action on the survival of the host may deeply influence its evolution. Thus, they present all the opportunities for reciprocal influences on evolution.

## 16.2 GENERALITIES ON HANTAVIRUSES

Hantaviruses are a relatively newly discovered genus of virus. First isolated between North and South Korea in 1976, they were named for the Hantaan River, which delineates the endemic area shared by the two countries. However, it is now thought that hantaviruses have been infecting rodent populations for thousands of years and possibly humans since the beginning of the twentieth century, in different regions of the world. hantaviruses (genus hantavirus, family Bunyaviridae) are a group of at least 25 antigenically distinct viruses carried in rodents. Some of these viruses can cause hemorrhagic fever with renal syndrome and HPS in humans. HFRS is a group of clinically similar diseases that occur throughout Eurasia. HFRS includes several diseases that formerly had other names, including Korean hemorrhagic fever, epidemic hemorrhagic fever, and nephropathia epidemica. hantaviruses that can cause HFRS include Hantaan virus, Puumala virus, Dobrava virus, and Seoul virus.

### 16.2.1 Hantavirus Taxonomy

In the Eight Report of the International Committee on Taxonomy of Viruses [26], the family Bunyaviridae is subdivided into five genera: Orthobunyavirus, hantavirus, Nairovirus, Phlebovirus, and Tospovirus. Within genus hantavirus, 22 different species are recognized. In each virus species different strains, from one to eight, may be identified and named. Also, abbreviations are given for certain strains. Different criterions are used to decide which strain may be considered a distinct species. One of them is whether the primary rodent reservoir is a particular species or subspecies. We agree with this, and we have used this criterion to choose the different virus strains included in this study. However, the list given in the Eighth Report [26] shows that all the strains corresponding to this criterion are not considered to be distinct virus species. For instance, Andes or Sin Nombre include several strains, each one having a different hosts species and sometimes a different geographic origin. Also, some of these strains are assigned a particular abbreviation and others are not. Thus, there is no exact correspondence between the given species statute, the attribution of a particular abbreviation, the specificity for a particular host, or a particular geographic range. This is probably because quantitative criterions are also applied and are considered predominant. For instance, the report assess that "Species exhibit at least 7% difference in amino acid identity on comparison of the complete glycoprotein precursor and nucleocapsid protein sequences." Thus, in the following paragraph and in the figures:

- Virus species listed in the Eighth Report [26] are in italic script.
- Strain names are in roman script, or are represented using their abbreviation in caps when an abbreviation has been proposed.
- When different strains of a same virus species are included, a number or an adjective (generally dealing with the geographic origin) is added.
- The correspondence between the virus species, strain names, and abbreviations is given in Table 16.1.
- The main clades are named using the dominant virus species name (in black italic script); when different virus species are included in a same clade, or when the cladistic analysis suggests that several strains or species may be grouped together, a species name is proposed (in black italic script).

Table 16.1 consists of a list of hantaviruses included in the present study. First two columns: name of virus species and/or

**TABLE 16.1.** List of Hantaviruses Included in Present Study.

| | Virus Species and Strain | Abbreviation | Host Species | Family | Accession no. | Nucl | Region | Distribution | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *Dobrava*/Estonia | DOBV-Estonia1 | *Apodemus agrarius* | Murinae | AJ009773 | 1671 | PAL | Estonia (Saaremaa) | J. Gen. Virol. 80 (Pt 2), 371-379 (1999) |
| 2 | *Dobrava*/Estonia | DOBV-Estonia2 | *Apodemus agrarius* | Murinae | AJ009775 | 1671 | PAL | Estonia (Saaremaa) | J. Gen. Virol. 80 (Pt 2), 371-379 (1999) |
| 3 | *Dobrava*/Slovakia | DOBV-Slovakia1 | *Apodemus agrarius* | Murinae | AJ269549 | 1704 | PAL | Slovakia (Kosice) | J. Med. Virol. 63 (2), 158-167 (2001) |
| 4 | *Dobrava*/Bosnia | DOBV-Bosnia | *Apodemus flavicollis* | Murinae | L41916 | 1670 | PAL | Bosnia | J. Gen. Virol. 76 (Pt 11), 2801-2808 (1995) |
| 5 | *Dobrava*/Greece | DOBV-Greece1 | *Apodemus flavicollis* | Murinae | AJ410615 | 1290 | PAL | Greece (Northeast) | J. Med. Virol. 69 (3), 408-416 (2003) |
| 6 | *Dobrava*/Greece | DOBV-Greece2 | *Apodemus flavicollis* | Murinae | AJ410619 | 1290 | PAL | Greece (Northeast) | J. Med. Virol. 69 (3), 408-416 (2003) |
| 7 | *Dobrava*/Russia | DOBV-Russia1 | *Apodemus flavicollis* | Murinae | AF442623 | 1637 | PAL | Russia (Krasnodar) | Dekonenko, A. 2001 |
| 8 | *Dobrava*/Russia | DOBV-Russia2 | *Apodemus sp.* | Murinae | AF442622 | 1196 | PAL | Russia (Goryachiy) | Dekonenko, A. 2002 |
| 9 | *Dobrava*/Slovakia | DOBV-Slovakia2 | *Apodemus sp.* | Murinae | AJ269550 | 1704 | PAL | Slovakia (Kosice) | J. Med. Virol. 63 (2), 158-167 (2001) |
| 10 | *Hantaan*/76118 | HTNV-76118 | *Apodemus sp.* | Murinae | M14626 | 1696 | PAL | South Korea | [39] |
| 11 | *Hantaan*/Maaji | HTNV-Maaji | *Apodemus agrarius* | Murinae | AF321094 | 1700 | PAL | Korea (Maaji) | Virus Genes 21 (3), 227-232 (2000) |
| 12 | *Hantaan*/Amur AP61 | AMRV.AP61 | *Apodemus peninsulae* | Murinae | AB071183 | 1290 | PAL | Russia FE (Solovey) | Emerging Infect. Dis. 8 (8), 768-776 (2002) |
| 13 | *Hantaan*/Amur AP63 | AMRV.AP63 | *Apodemus peninsulae* | Murinae | AB071184 | 1696 | PAL | Russia FE (Solovey) | Emerging Infect. Dis. 8 (8), 768-776 (2002) |
| 14 | *Hantaan*/Guizhou | HTNV-Guizhou | *Apodemus sp.* | Murinae | AB027097 | 1635 | PAL | China (Guizhou) | Virology 278 (2), 332-345 (2000) |
| 15 | *Hantaan*/Da Bie Shan | DBSV | *Niviventer confucianus* | Murinae | AB027523 | 1654 | PAL | China (Anhui) | Virology 278 (2), 332-345 (2000) |
| **16** | ***Hantaan*/Bat** | **HTNV-Bat** | ***Rhinolophus ferrumequinum*** | **Rinolophidae** | **U37768** | **1696** | **PAL** | **Korea** | **Kim, G.-R. and Jung,Y.-T. 1995** |
| 17 | *Seoul*/L99 | SEOV-L99 | *Rattus losea* | Murinae | AF288299 | 1764 | PAL | China (Jiangxi) | Zhihui,Y. et al. (2000) |
| 18 | *Seoul*/Sapporo | SEOV-Sapporo | *Rattus norvegicus* | Murinae | M34881 | 1769 | PAL | Japan (Sapporo) | Virology 176 (1), 114-125 (1990) |
| 19 | *Seoul*/Shanxi | SEOV-Shanxi | *Rattus rattus* | Murinae | AF288643 | 1772 | PAL | China (Shanxi) | Yao, Z. et al., 2000 |
| 20 | *Seoul*/Tchoupitoulas | SEOV-Tchoupi | *Rattus rattus* | Murinae | AF329389 | 1785 | NEA | USA (Louisiana) | Yao, Z. et al. 2000 |
| 21 | *Seoul*/Zhejiang | SEOV-lZhejiang1 | *Rattus rattus* | Murinae | AB027522 | 1692 | PAL | China (Zhejiang) | Virology 278 (2), 332-345 (2000) |
| 22 | *Seoul*/Zhejiang | SEOV-Zhejiang2 | *Rattus rattus* | Murinae | AF288653 | 1772 | PAL | China (Zhejiang) | Yao, Z. et al. 2000 |

*(Continued)*

**TABLE 16.1.** (*Continued*)

| | Virus Species and Strain | Abbreviation | Host Species | Family | Accession no. | Nucl | Region | Distribution | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 23 | *Sin Nombre* | SNV | *Peromyscus maniculatus* | Neotominae | L25784 | 2059 | NEA | USA (S-West & Central) | Virology 200 (2), 715-723 (1994) |
| 24 | *Sin Nombre*/Convict Creek | SNV-Conv.74 | *Peromyscus maniculatus* | Neotominae | L33683 | 1287 | NEA | USA (California) | Virology 206 (2), 963-972 (1995) |
| 25 | *Sin Nombre*/Convict Creek | SNV-Conv.107 | *Peromyscus maniculatus* | Neotominae | L33816 | 1287 | NEA | USA (California) | Virology 206 (2), 963-972 (1995) |
| 26 | *Sin Nombre*/ Monongahela | MGLV | *Peromyscus maniculatus* | Neotominae | U32591 | 2082 | NEA | USA (Appalachian) | J. Gen. Virol. 76 (Pt 12), 3195-3199 (1995) |
| 27 | *New York*/RI1 | NYV-RI1 | *Peromyscus leucopus* | Neotominae | U09488 | 2078 | NEA | USA (North East) | J. Med. Virol. 46 (1), 21-27 (1995) |
| 28 | Limestone Canyon | LimCanyon | *Peromyscus boylii* | Neotominae | AF307322 | 1209 | NEA | USA (Arizona) | Virology 286 (2), 345-353 (2001) |
| 29 | *El Moro Canyon* | ELMCV | *Reithrodontomys megalotis* | Neotominae | U11427 | 1896 | NEA | USA (New Mexico) | [15] |
| 30 | Rio Segundo | RioSegundo | *Reithrodontomys mexicanus* | Neotominae | U18100 | 1749 | NEO | Costa Rica | Virology 207 (2), 452-459 (1995) |
| 31 | *Andes*/AH1 | ANDV-AH1 | *Oligoryzomys longicaudatus* | Sigmodontinae | AF004660 | 1876 | NEO | Argentina | [21] |
| 32 | *Andes*/Bermejo | BMJV | *Oligoryzomys chacoensis* | Sigmodontinae | AF482713 | 1933 | NEO | Argentina (Oran) | J. Virol. 76 (8), 3765-3773 (2002) |
| 33 | *Andes*/Chile | ANDV-Chile1 | *Oligoryzomys longicaudatus* | Sigmodontinae | AF291702 | 1871 | NEO | Chile (Aysen) | J. Virol. 76 (8), 3765-3773 (2002) |
| 34 | *Andes*/Chile | ANDV-Chile2 | *Oligoryzomys longicaudatus* | Sigmodontinae | NC003466 | 1871 | NEO | Chile (Aysen) | J. Virol. 76 (8), 3765-3773 (2002) |
| 35 | *Andes*/Lechiguanas | LECV | *Oligoryzomys flavescens* | Sigmodontinae | AF482714 | 1938 | NEO | Argentina (Lechiguana) | [20] |
| 36 | *Andes*/Norte | ANDV-Norte | *Oligoryzomys chacoensis* | Sigmodontinae | AF325966 | 1921 | NEO | Argentina Norte | Am. J. Trop. Med. Hyg. 66 (6), 713-720 (2002) |
| 37 | *Andes*/Oran | ORNV | *Oligoryzomys longicaudatus* | Sigmodontinae | AF482715 | 1919 | NEO | Argentina (Oran) | J. Virol. 76 (8), 3765-3773 (2002) |
| 38 | *Andes*/Pergamino | PRGV | *Akodon azarae* | Sigmodontinae | AF482717 | 1860 | NEO | Argentina | J. Virol. 76 (8), 3765-3773 (2002) |
| 39 | Maciel | Maciel | *Bolomys benefactus* | Sigmodontinae | AF482716 | 1869 | NEO | Argentina (Maciel) | J. Virol. 76 (8), 3765-3773 (2002) |
| 40 | *Laguna Negra* | LANV | *Calomys laucha* | Sigmodontinae | AF005727 | 1904 | NEO | Paraguay, Bolivia | Virology 238 (1), 115-127 (1997) |
| 41 | Rio Mamore | RioMamore | *Oryzomys microtis* | Sigmodontinae | U52136 | 1975 | NEO | Bolivia | Am. J. Trop. Med. Hyg. 57 (3), 368-374 (1997) |
| 42 | *Bayou* | BAYV | *Oryzomys palustris* | Sigmodontinae | L36929 | 1958 | NEA | USA (Louisiana) | J. Virol. 69 (3), 1980-1983 (1995) |
| 43 | *Black Creek Canal* | BCCV | *Sigmodon hispidus* | Sigmodontinae | L39949 | 1989 | NEA | USA (Florida) | J. Virol. 69 (3), 1980-1983 (1995) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 44 | *Muleshoe* | MULV | *Sigmodon hispidus* | Sigmodontinae | U54575 | 1989 | NEA | USA (Texas) | Am. J. Trop. Med. Hyg. 55 (6), 672-679 (1996) |
| 45 | *Caño Delgadito* | CADV | *Sigmodon alstoni* | Sigmodontinae | AF000140 | 1130 | NEO | Venezuela (Portuguesa) | Fulhorst,C.F., et al. 1997 |
| 46 | *Isla Vista* | ISLAV-1 | *Microtus californicus* | Arvicolinae | U19302 | 1720 | NEA | USA (California) | J. Gen. Virol. 76, 3195-3199 (1995) |
| 47 | *Isla Vista* | ISLAV-2 | *Microtus californicus* | Arvicolinae | U31534 | 1720 | NEA | USA (California) | J. Gen. Virol. 76, 3195-3199 (1995) |
| 48 | *Isla Vista* | ISLAV-3 | *Microtus californicus* | Arvicolinae | U31535 | 1302 | NEA | USA (California) | J. Gen. Virol. 76, 3195-3199 (1995) |
| 49 | *Prospect Hill* | PHV-1 | *Microtus montanus* | Arvicolinae | M34011 | 1675 | NEA | USA | Virology 175 (1), 167-175 (1990) |
| 50 | *Prospect Hill* | PHV-2 | *Microtus montanus* | Arvicolinae | Z49098 | 1675 | NEA | USA | [30] |
| 51 | Prairie Vole | PrairieVole | *Microtus ochrogaster* | Arvicolinae | U19303 | 1722 | NEA | USA (?) | Song,W., et al. 1995 |
| 52 | *Topografov* | TOPV | *Lemmus sibiricus* | Arvicolinae | AJ011646 | 1951 | PAL | Russia FE (Taymyr) | J. Virol. 73 (7), 5586-5592 (1999) |
| 53 | *Khabarovsk* | KHAV | *Microtus fortis* | Arvicolinae | U35255 | 1845 | PAL | Russia FE (Khabarovsk) | [16] |
| 54 | Vladivostock | Vladivostock | *Microtus fortis* | Arvicolinae | AB011630 | 1228 | PAL | Russia FE (Vladivostok) | Kariwa,H., et al. 1998 |
| 55 | *Tula*/Germany1 | TULV-Germany1 | *Microtus arvalis* | Arvicolinae | AF164093 | 1832 | PAL | Germany | Scharninghausen,J.J., et al. 1999 |
| 56 | *Tula*/Germany2 | TULV-Germany2 | *Microtus arvalis* | Arvicolinae | AF289821 | 1828 | PAL | Germany | Leitmeyer,K.C., et al. 2000 |
| 57 | *Tula*/Lodz | TULV-Lodz1 | *Microtus arvalis* | Arvicolinae | AF063892 | 1852 | PAL | Poland | Song,J.-W., et al. 1995 |
| 58 | *Tula*/Lodz | TULV Lodz2 | *Microtus arvalis* | Arvicolinae | AF063897 | 1852 | PAL | Poland | Song,J.-W., et al., 1995 |
| 59 | *Tula*/Moravia | TULV-Moravia | *Microtus arvalis* | Arvicolinae | Z69991 | 1831 | PAL | Moravia | J. Gen. Virol. 77 (Pt 12), 3063-3067 (1996) |
| 60 | *Tula*/Slovakia | TULV-Slvk1 | *Microtus arvalis* | Arvicolinae | AJ223601 | 1831 | PAL | Slovakia (Koziky) | J. Virol. 73 (1), 667-675 (1999) |
| 61 | *Tula*/Slovakia | TULV-Slvk2 | *Microtus arvalis* | Arvicolinae | AJ223600 | 1831 | PAL | Slovakia (Koziky) | J. Virol. 73 (1), 667-675 (1999) |
| 62 | *Tula*/Slovakia | TULV-Slvk3 | *Microtus arvalis* | Arvicolinae | Z48235 | 1831 | PAL | Slovakia (Malacky) | Virus Genes 10 (3), 277-281 (1995) |
| 63 | *Tula*/Slovakia | TULV-Slvk4 | *Microtus arvalis* | Arvicolinae | Y13979 | 1833 | PAL | Slovakia (Kosice) | J. Virol. 73 (1), 667-675 (1999) |
| 64 | *Tula*/Slovakia | TULV-Slvk5 | *Microtus arvalis* | Arvicolinae | Y13980 | 1832 | PAL | Slovakia (Kosice) | J. Virol. 73 (1), 667-675 (1999) |
| 65 | *Tula*/Slovakia | TULV-Slvk6 | *Microtus arvalis* | Arvicolinae | Z68191 | 1831 | PAL | Slovakia (Malacky) | Virus Genes 10 (3), 277-281 (1995) |

*(Continued)*

**TABLE 16.1.** (*Continued*)

| | Virus Species and Strain | Abbreviation | Host Species | Family | Accession no. | Nucl | Region | Distribution | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 66 | *Tula*/Russia | TULV-Russia | *Microtus gregalis* | Arvicolinae | Z30941 | 1847 | PAL | Russia (Tula) | J. Virol. 68 (12), 7833-7839 (1994) |
| 67 | *Tula*/Serbia | TULV-Serbia | *Microtus subterraneus* | Arvicolinae | AF017659 | 1834 | PAL | Serbia (Cacac) | Song,J.-W., et al. 1997 |
| 68 | *Puumala*/Bashkortostan | PUUV-Bashkor | *Clethrionomys glareolus* | Arvicolinae | AF442613 | 1733 | PAL | Russia (Bashkortostan) | Dekonenko,A. and Khasanova,S. (2001) |
| 69 | *Puumala*/Belgium | PUUV-Belgium | *Clethrionomys glareolus* | Arvicolinae | AJ277030 | 1837 | PAL | Belgium (Thuin) | Escutenaire S. (2001) |
| 70 | *Puumala*/CG1820 | PUUV-CG1820 | *Clethrionomys glareolus* | Arvicolinae | M32750 | 1784 | PAL | ? | Virology 174 (1), 79-86 (1990) |
| 71 | *Puumala*/Denmark | PUUV-Denmark | *Clethrionomys glareolus* | Arvicolinae | AJ238791 | 1831 | PAL | Denmark | J. Gen. Virol. 81 (Pt 12), 2833-2841 (2000) |
| 72 | *Puumala*/Evo | PUUV-Evo | *Clethrionomys glareolus* | Arvicolinae | Z30703 | 1832 | PAL | Finland | Virus Res. 38 (1), 25-41 (1995) |
| 73 | *Puumala*/Kamiiso | HOKV-Kamiiso | *Clethrionomys rufocanus* | Arvicolinae | AB010730 | 1833 | PAL | Japan (Hokkaido) | Virus Res. 59 (2), 219-228 (1999) |
| 74 | *Puumala*/Japan | HOKV-Japan | *Clethrionomys rufocanus* | Arvicolinae | AB010731 | 1833 | PAL | Japan (Tobetsu) | Virus Res. 59 (2), 219-228 (1999) |
| 75 | *Puumala*/Karelia | PUUV-Karelia1 | *Clethrionomys glareolus* | Arvicolinae | AJ238790 | 1832 | PAL | Russia (Karelia, Gomselga) | J. Gen. Virol. 81 (Pt 12), 2833-2841 (2000) |
| 76 | *Puumala*/Karelia | PUUV-Karelia2 | *Clethrionomys glareolus* | Arvicolinae | AJ238788 | 1828 | PAL | Russia (Karelia, Karhumaki) | J. Gen. Virol. 81 (Pt 12), 2833-2841 (2000) |
| 77 | *Puumala*/Karelia | PUUV-Karelia3 | *Clethrionomys glareolus* | Arvicolinae | AJ238789 | 1830 | PAL | Russia (Karelia, Kolodozero) | J. Gen. Virol. 81 (Pt 12), 2833-2841 (2000) |
| 78 | *Puumala*/Kazan | PUUV-Kazan | *Clethrionomys glareolus* | Arvicolinae | Z84204 | 1826 | PAL | Sweden? | J. Virol. 71 (12), 9515-9523 (1997) |
| 79 | *Puumala*/Norway | PUUV-Norway1 | *Clethrionomys glareolus* | Arvicolinae | AJ223369 | 1849 | PAL | Norway (Eidsvoll) | J. Gen. Virol. 79 (Pt 11), 2603-2614 (1998) |
| 80 | *Puumala*/Norway | PUUV-Norway3 | *Clethrionomys glareolus* | Arvicolinae | AJ223374 | 1828 | PAL | Norway (Mellansel) | J. Gen. Virol. 79 (Pt 11), 2603-2614 (1998) |
| 81 | *Puumala*/Norway | PUUV-Norway4 | *Clethrionomys glareolus* | Arvicolinae | AJ223375 | 1829 | PAL | Norway (Mellansel) | J. Gen. Virol. 79 (Pt 11), 2603-2614 (1998) |
| 82 | *Puumala*/Norway | PUUV-Norway5 | *Clethrionomys glareolus* | Arvicolinae | AJ223376 | 1871 | PAL | Norway (Solleftea) | J. Gen. Virol. 79 (Pt 11), 2603-2614 (1998) |
| 83 | *Puumala*/Norway | PUUV-Norway6 | *Clethrionomys glareolus* | Arvicolinae | AJ223377 | 1882 | PAL | Norway (Solleftea) | J. Gen. Virol. 79 (Pt 11), 2603-2614 (1998) |
| 84 | *Puumala*/Norway | PUUV-Norway7 | *Clethrionomys glareolus* | Arvicolinae | AJ223380 | 1827 | PAL | Norway (Tavelsjo) | J. Gen. Virol. 79 (Pt 11), 2603-2614 (1998) |
| 85 | *Puumala*/Omsk | PUUV-Omsk1 | *Clethrionomys glareolus* | Arvicolinae | AF367067 | 1732 | PAL | Omsk-Russia (W Siberia) | Dekonenko,A., et al. 2001 |
| 86 | *Puumala*/Omsk | PUUV-Omsk2 | *Clethrionomys glareolus* | Arvicolinae | AF367068 | 1732 | PAL | Omsk-Russia (W Siberia) | Dekonenko,A., et al. 2001 |

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|---|---|---|---|---|---|---|---|---|---|
| 87 | *Puumala*/Omsk | PUUV-Omsk3 | *Clethrionomys glareolus* | Arvicolinae | AF367069 | 1732 | PAL | Omsk-Russia (W Siberia) | Dekonenko,A., et al. 2001 |
| 88 | *Puumala*/Omsk | PUUV-Omsk4 | *Clethrionomys glareolus* | Arvicolinae | AF367070 | 1732 | PAL | Omsk-Russia (W Siberia) | Dekonenko,A., et al. 2001 |
| 89 | *Puumala*/Slovakia | PUUV-Slovakia | *Clethrionomys glareolus* | Arvicolinae | AF294652 | 1809 | PAL | Slovakia | Leitmeyer,K.C., et al. 2000 |
| 90 | *Puumala*/Sotkamo | PUUV-Sotkamo | *Clethrionomys glareolus* | Arvicolinae | X61035 | 1830 | PAL | Finland (Sotkamo) | J. Gen. Virol. 73 (Pt 4), 829-838 (1992) |
| 91 | *Puumala*/Udmurtia | PUUV-Udmurtia | *Clethrionomys glareolus* | Arvicolinae | Z21497 | 1827 | PAL | Finland (Udmurtia) | J. Gen. Virol. 75 (Pt 2), 405-409 (1994) |
| 92 | *Puumala*/Vranica | PUUV-Vranica | *Clethrionomys glareolus* | Arvicolinae | U14137 | 1828 | PAL | Bosnia (Vranica) | Arch. Virol. 140 (11), 2011-2026 (1995) |
| 93 | ***Thottapalayam*** | **Thottalayam** | ***Suncus murinus*** | **Soricidae** | **AY526097** | **1530** | **ORIENT** | **India (Thottalayam)** | **Schmaljohn,C.S. and Toney,A. (2004)** |

strain and abbreviation used in text and figures. Columns 3 and 4: scientific and Family names of principal host. Column 5 and 6: accession number of GenBank sequence, number of nucleotides given. Column 7: biogeographic areas, Palearctic (PAL), Nearctic (NEA), Neotropical (NEO), and Oriental (ORIENT). Column 8: country, and when possible province or locality, where virus strain has been collected. Column 9: reference of original publication; name of authors and year in case of direct submission.

### 16.2.2 Geographic Distribution

Hantaviruses have a large geographic distribution. Most of the recorded species were collected in the Holarctic and the Neotropics (Northern Asia, Europe, North America, and South America). Two species were isolated from South Asia [4]: Thottapalayam from a shrew (*Suncus murinus*) in India, and Thailand from a murine rodent of Thailand, *Bandicota indica* [10,45]. Recently, new hantaviruses have been isolated from different Rattus spp., during a study conducted in agricultural and urban areas in Cambodia [33]. A phylogenetic analysis of the partial S sequences of these viruses showed that viruses isolated either from *Rattus rattus* or *Rattus norvegicus* could be grouped into two different clades. During this last study, 75 specimens of *Bandicota* sp. were also analyzed and were found to be negative. All these results suggest that different types of hantaviruses are present in South Asia. Thus, extended investigations have to be completed to check if *B. indica* is the specific (and perhaps the single) natural host of Thailand virus; the biodiversity of closely related viruses present in other rodents living in the same geographic area; the phylogenetic relationships of these newly discovered viruses; their respective geographic distribution and if they may be considered a danger for humans living in the same area.

### 16.2.3 Morphology

The Bunyaviridae family to which genus hantavirus belongs are enveloped viruses with a genome that consists of three negative-sensed single-stranded RNA segments [1,9,37,38,39]:

- A small genomic segment S (1.8 kb) encoding the nucleocapsid N protein.
- A medium genomic segment M (3.7 kb) encoding a polyprotein that is cleaved to yield the envelope glycoproteins G1 and G2.
- A large genomic segment L (6.5 kb) encoding the L protein, which functions as the viral transcriptase replicase.

They include three structural proteins: two glycoproteins G1 and G2, and a nucleoprotein N. Several serologically distinct groups, associated with different syndromes, have been recognized: in the "Old World," Hantaan, Dobrava, Seoul, and Puumala cause the clinical forms of HFRS, whereas, in the "New World," Sin Nombre and Andes are responsible for HPS [15,38]. Another group, Tula, widely distributed in Russia and Eastern Europe, to central Asia and Siberia, has never been associated with any human disease [30].

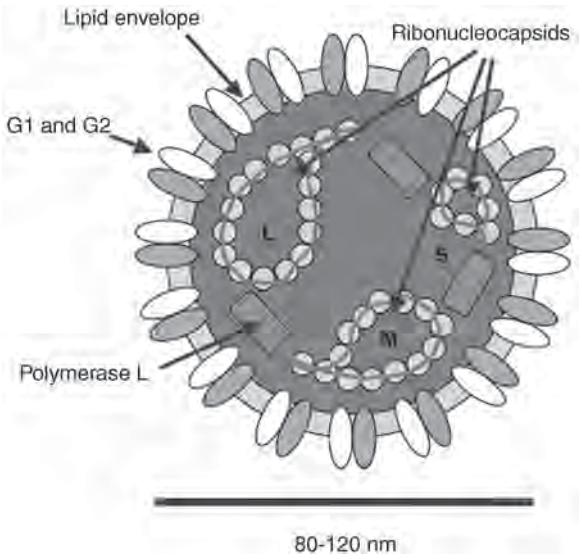


***Fig. 16.1.*** Bunyaviridae virion structure. The viral genome is composed of three ssRNA segments: one large (L) segment, one medium (M) segment, and one small (S) segment. All three segments have the same complementary sequences at the 5′ or 3′ termini.

### 16.2.4 Transmission

Unlike other members of the Bunyaviridae family hosted by mosquitoes, ticks or flies, specific wild rodent hosts, from the family Muridae, usually carry hantaviruses. These rodents shed the virus in their urine, feces, and saliva. Tiny droplets containing the virus get into the air: "aerosolization." Potentially pathogenic for humans, hantavirus infection occurs through inhalation of virus-contaminated aerosols of rodent excreta. Rodents are therefore the reservoir host for hantaviruses; infections can be spread among the natural hosts by aerosols and bites. As the virus is found in rodent saliva, feces, and urine, humans can become incidental hosts when they come into contact with infected rodents or their excretions. Often, rodent urine, droppings, or nests are disturbed in enclosed areas; the viruses are then inhaled in aerosolized dust. Hantaviruses can also be transmitted through broken skin, the conjunctiva, and other mucous membranes, by rodent bites and possibly by ingestion of contaminated food. Arthropod vectors do not seem to exist. Vertical transmission also appears to be negligible or nonexistent. Person-to-person spread has not been seen in HPS cases in North America or HFRS in Eurasia but may occur with the Andes virus in Argentina. Hantaviruses are sensitive to drying but have been found in neutral solutions for several hours at 37 °C and for several days in colder temperatures. Infectious viruses have also been detected in dried cell cultures for up to 2 days. Hantavirus spp. responsible for HFRS are closely associated with Murinae and Arvicolinae rodents. Sigmodontinae and Neotominae rodents transmit those responsible for HPS in the New World. They cause persistent asymptomatic infections in their natural hosts.

### 16.2.5 Diagnosis and Symptoms

Although hantaviral infection has been recorded worldwide, cases are not well reported. The incubation period varies from 14 to 17 days; most often, the symptoms appear after 14–30 days. Initial onset is marked by nonspecific flu-like symptoms, leading to diagnostic confusions with other common fevers, especially in the tropics: fever, chills, myaglia (muscle aches), headache, malaise, abdominal pain, nausea, vomiting dry, cough, or tachypnea (increased respiratory rate). In severe HFRS cases, symptoms include hypotension, shock, respiratory failure, and renal impairment or failure. In severe HPS cases, complications can cause cardiorespiratory failure. Most of the patients infected with Sin Nombre virus were reported to die after a few days. Hantavirus outbreaks are often associated with increased rodent populations or environmental factors that lead to increased human exposure to rodents. Worldwide, approximately 150,000 to 200,000 (excluding China) patients are hospitalized with HFRS each year. Different hantaviruses tend to cause mild, moderate, or severe cases of HFRS; the mortality rate can vary from 0.1% to 3% for Puumala virus infections, to approximately 5% to 15% for Hantaan and Dobrava virus infections. Seoul virus tends to cause moderate disease with mortality rates of approximately 1%. Sin Nombre and New York virus infections are often fatal; the mortality rate is estimated to be 40–50%. The renal variant form of HPS caused by the Andes, Bayou, and Black Creek viruses also has a high mortality rate. Convalescence from either HFRS or HPS can take weeks or months, but patients usually recover full lung function.

## 16.3 SEROLOGICAL PRESENCE WITHOUT CASES IN THAILAND

Rodents are a highly successful group of mammals occurring throughout the world in a wide variety of ecosystems. Although most rodent species live in the wild with little human interaction, some have adapted to human presence and activities, using agriculture and waste as food resources and nesting in buildings. They are considerable agricultural pests destroying crops or food stocks. In Asia, rodents cause 5–10% production loss of rice, which would feed 200 million Asians for a year (CSIRO). Rodents are also important reservoirs and vectors of organisms, which can spread in fields or habitations and cause more than 60 known diseases in humans and livestock. The close proximity between rodents and humans or animals favors the transmission dynamics of these diseases.

Considering the public health importance of rodents with the emergence of leptospirosis in 1996, the Ministry of Public Health and different research institutes has conducted trapping expeditions over the country. Most investigations have focused on serological surveys of leptospirosis or rickettsial diseases. Since 1998, the French Institute of Research Development (IRD) has sampled rodents in different biotopes representative of the rich biodiversity, focusing on their diversity and ecology, between January 1998 and December 2004. One thousand seven hundred and eighteen murine rodents, belonging to 30 different species, were trapped. A new identification field key for the Thai murine rodents was realized. Field campaigns were conducted closely with local farmers to exchange knowledge on rodent ecology and set up the trapping. Throughout the country, some people hunting and eating rodents regularly, showed a real knowledge of the different species. Representing a great part in the biomass, rodents are considered as a valuable source of meat. Hunters can recognize their burrows, noise and attract them with proper baits, chosen for their attractiveness in each place.

Rodents are trapped live and identified by species. Live trapping allows simultaneous monitoring of sympatric populations (species co-occurring in a same ecosystem). Methods can

***Fig. 16.2***. *Bandicota savilei*, a vector of Hantaviruses in Southeast Asia.

***Fig. 16.3***. Farmer demonstrating a traditional trap in Phrae province, northern Thailand.

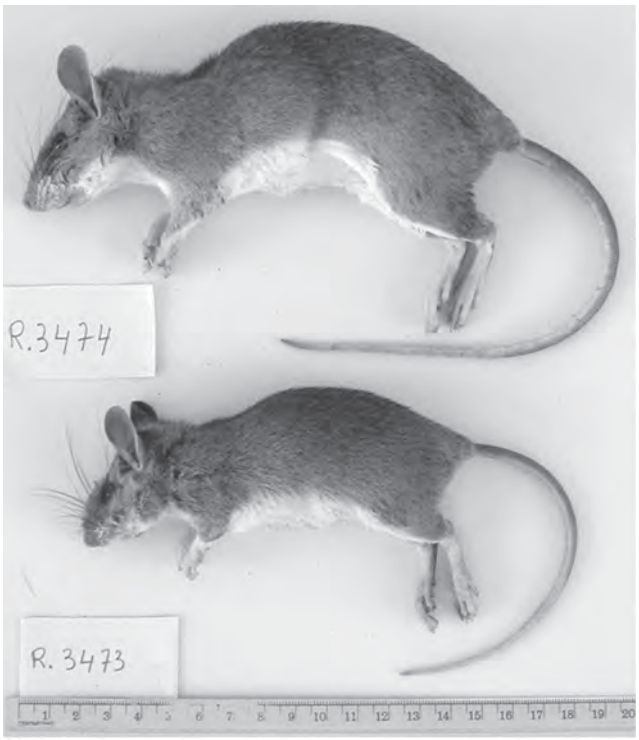


***Fig. 16.4***. Dealing with the difficulties of morphological identification: two subspecies of *Maxomys surifer* from Loei province, northeastern Thailand.

vary according to logistic and other priorities. Information is recorded on the sex and morphology: head–body length, tail length, skull length, ear length, feet length, and weight. Each place of capture is geographically referenced and described regarding the ecological characteristics. Blood samples are obtained from cardiac puncture immediately after the animal has been euphonized under strong ether anesthesia. Tissue specimens (lung, liver, spleen, and kidney) are collected and transferred immediately into liquid nitrogen. After processing, each animal voucher specimen is placed into 80% ethanol and labeled. Tubes are transported in liquid nitrogen to laboratories in Bangkok for later analysis of viral antibodies.

***Fig. 16.5***. Dissection in a laboratory at the Ministry of Public Health, in Sakhon Nakhon province, northeastern Thailand (Dr. Vincent Herbreteau).

### 16.3.1 Serological Investigations in Rodents

First serological investigations of hantaviruses in rodents were conducted between 1981 and 1983, in the frame of a worldwide survey of hantaan-related viruses. A global 7% (21/311) seropositivity was recorded in Thailand, with the highest prevalence, 15% (10/65), for *B. indica*, for the first time recognized as a major vector in Southeast Asia. Neutralization tests, which detected antibody in Rattus specific for hantaan-related viruses, failed to establish the specificity of antibody in *B. indica*, suggesting the occurrence of another hantaan-like virus in Thailand. High prevalence for *B. indica* was reported again in Kanchanaburi province in 1985 with 28.6% positive by IFA [10]. Then, in 1989, serological surveys in northern Thailand reported 4% seropositivity for *R. norvegicus* and 13% for *R. rattus* [35]. In 1990, another investigation in two Bangkok slum areas found one-third of *R. norvegicus* (19/61) and 6% of *Rattus exulans* (1/17) had hantavirus reacting sera [42]. In 1992, 110 rodents from Chiang Rai (northern Thailand) were tested by IFA (Leitmeyer, personal communication) for evidence of antibodies or antigens to four hantaviruses. Antigen-positive specimens were tested by RT-PCR for viral nucleic acids but first attempts of virus isolation failed. *B. indica* appeared as a main vector in rural areas with a high seropositivity 23.5% (8/34). Surprisingly, one *Mus cervicolor*, an endemic rare mouse of rice fields, tested positive to Hantaan virus [42]. Between 1998 and 2000, from 862 murine rodents collected throughout the country, 2.9% tested positive by immunofluorescent assay (IFA). In 1998, investigations on 692 rodents from Nakhon Pathom and Nakhon Ratchasima revealed lower prevalence to hantavirus reacting antibodies when tested by ELISA, which is a more specific method than IFA: 4.9% (16/325) of *R. exulans*, 4.6% (8/175) of *B. indica*, and 4.1% (2/49) of *R. norvegicus* tested positive [27]. In 2002, similar antibody prevalence for *B. indica* (4.3%) but lower for *R. exulans* (2.1%), *R. rattus* (0.9%), and *R. losea* (1.6%) were obtained by ELISA while surveying rodents from five provinces in northeastern Thailand [27].

During these surveys, positive samples could be found in the different regions, North, Northeast, Central Plain, and South, suggesting a wide distribution of hantaviruses in Thailand [27]. Serological surveys could identify hantavirus reacting antibodies in the most common species, also the easiest to catch: *B. indica*, *B. savilei*, *R. rattus*, *R. norvegicus*, *R. losea*, *R. exulans*, and *M. cervicolor* (Table 16.2). Species, which tested negative, *Berylmys berdmorei*, *Mus caroli*, and *Mus castaneus*, were not collected in sufficient number for statistical significance. Only *R. argentiventer*, with 77 specimens tested negative, seems not to be a host of hantavirus. Other murine rodents can be potential hosts or vectors of hantavirus. No significant differences in hantavirus antibody prevalence were found between males and females [27]. Knowledge of prevalence of hantavirus in rodents is limited by the difficulties of field sampling

**TABLE 16.2.** Serological Investigations of Murine Rodents in Thailand, Tested for Hantavirus Reacting Antibodies

| Species | Location | Seropositivity[a] | Test | Reference |
|---|---|---|---|---|
| *Rattus norvegicus* | Bangkok (C, 15) | 19/61 (31.1)<br>7/458 (1.53) | IFA 32-128 | [42]<br>Kantakamalakul et al., 2003 |
| | Nakhon Pathom (C, 14) | 2/49 (4.1) | ELISA | Gonzalez et al., 1998, unpub. |
| | Chonburi (E, 16) | 0/25 | PA 1:80 | Imvithaya et al., 2001 |
| | Khon Kaen (NE, 6) | 0/35 | ELISA | Nitatpattana et al., 2002 |
| *Rattus exulans* | Bangkok (C, 15) | 1/17 (5.9) | IFA 32-128 | [42] |
| | Nakhon Pathom (C, 14) | 1/45 (2.2) | ELISA | [27] |
| | Nakhon Ratchasima (NE, 9) | 9/257 (3.5) | ELISA | [27] |
| | Trang (S, 19) | 1/26 (3.8) | PA 1:80 | Imvithaya et al., 2001 |
| | Udon Thani (NE, 3) | 0/25 | PA 1:80 | Imvithaya et al., 2001 |
| | Surin (NE, 11) | 1/49 (2.0) | ELISA | Nitatpattana et al., 2002 |
| | Nakhon Phanom (NE, 5) | 1/31 (3.2) | ELISA | Nitatpattana et al., 2002 |
| | Kanchanaburi (C, 12) | 0/102 | ELISA | Herbreteau et al., 2003, unpub. |
| | Sakhon Nakhon (NE, 4) | 0/19 | PCR | Herbreteau et al., 2003, unpub. |
| *Rattus rattus* | Chiang Rai (N, 1) | 3/50 (6) | IFA 32-2048 | Leitmeyer, 1996, pers. comm. |
| | Nakhon Pathom (C, 14) | 1/68 (1.5) | ELISA | [27] |
| | Nakhon Ratchasima (NE, 9) | 0/36 | ELISA | [27] |
| | Surat Thani (S, 18) | 2/40 (5.0) | PA 1:80 | Imvithaya et al., 2001 |
| | Phra Nakhon Sri Ayuthaya (C, 13) | 1/67 (1.5) | PA 1:80 | Imvithaya et al., 2001 |
| | Chonburi (E, 16) | 3/30 (10.0) | PA 1:80 | Imvithaya et al., 2001 |
| | Phitsanulok (N, 2) | 3/88 (3.4) | PA 1:80 | Imvithaya et al., 2001 |
| | Chantaburi (E, 17) | 0/83 | PA 1:80 | Imvithaya et al., 2001 |
| | Trang (S, 19) | 1/51 (2.0) | PA 1:80 | Imvithaya et al., 2001 |
| | Nakhon Phanom (NE, 5) | 1/37 (2.7) | ELISA | Nitatpattana et al., 2002 |
| | Kanchanaburi (C, 12) | 1/43 (2.3) | PCR | Herbreteau et al., 2003, unpub. |
| *Rattus losea* | Chiang Rai (N, 1) | 6/25 (24.0) | IFA 32-2048 | Leitmeyer, 1996, pers. comm. |
| | Buriram (NE, 10 ) | 0/26 | ELISA | Nitatpattana et al., 2002 |
| *Bandicota indica* | throughout country | 10/65 (15) | IFA 32 | LeDuc et al., 1986 |
| | Chiang Rai (N, 1) | 8/34 (23.5) | IFA 32-2048 | Leitmeyer, 1996, pers. comm. |
| | Nakhon Pathom (C, 14) | 4/151 (2.6) | ELISA | Gonzalez et al., 1998, unpub. |
| | Nakhon Ratchasima (NE, 9) | 4/24 (16.7) | ELISA | Gonzalez et al., 1998, unpub. |
| | Petchabun (C, 6) | 3/49 (6.1) | PA 1:80 | Imvithaya et al., 2001 |
| | Phitsanulok (N, 2) | 2/52 (3.8) | PA 1:80 | Imvithaya et al., 2001 |
| | Nakhon Ratchasima (NE, 9) | 2/53 (3.8) | PA 1:80 | Imvithaya et al., 2001 |
| | Nakhon Phanom (NE, 5) | 0/59 | ELISA | Nitatpattana et al., 2002 |
| | Khon Kaen (NE, 7) | 6/49 (12.2) | ELISA | Nitatpattana et al., 2002 |
| | Buriram (NE, 10) | 2/37 (5.4) | ELISA | Nitatpattana et al., 2002 |
| | Surin (NE, 11) | 1/25 (4.0) | ELISA | Nitatpattana et al., 2002 |
| | Kalasin (NE, 8) | 0/38 | ELISA | Nitatpattana et al., 2002 |
| | Kanchanaburi (C, 12) | 0/16 | PCR | Herbreteau et al., 2003, unpub. |
| *Bandicota savilei* | Nakhon Pathom (C, 14) | 0/13 | ELISA | Gonzalez et al., 1998, unpub. |
| | Nakhon Ratchasima (NE, 9) | 0/10 | ELISA | Gonzalez et al., 1998, unpub. |
| | Phra Nakhon Sri Ayuthaya (C, 13) | 2/25 (8.0) | PA 1:80 | Imvithaya et al., 2001 |
| | Chonburi (E, 16) | 0/22 | PA 1:80 | Imvithaya et al., 2001 |
| | Phitsanulok (N, 2) | 0/36 | PA 1:80 | Imvithaya et al., 2001 |
| *Berylmys berdmorei* | Kanchanaburi (C, 12) | 0/11 | PCR | Herbreteau et al., 2003, unpub. |

[a]Number positive/total tested (percentage positive). N, north; NE, northeast; C, central; E, east; S, south. 1 to 19: Province number on Thailand map. PA, particle agglutination test; Unpub., unpublished; pers. comm., personal communication.

to catch rare species, and get knowledge about each species density, but also by the dated taxonomy of murine rodents in Thailand, actually under revision.

Serological investigations of murine rodents in Thailand, tested for hantavirus reacting antibodies.

A recent study was conducted in agricultural and urban areas in Cambodia to assess the presence of hantaviruses in rodent populations [33]. In 1998, rodents were trapped in two villages and in Phnom Penh city near market places and a rubbish dump. IgG antibodies to Hantaan virus were detected in

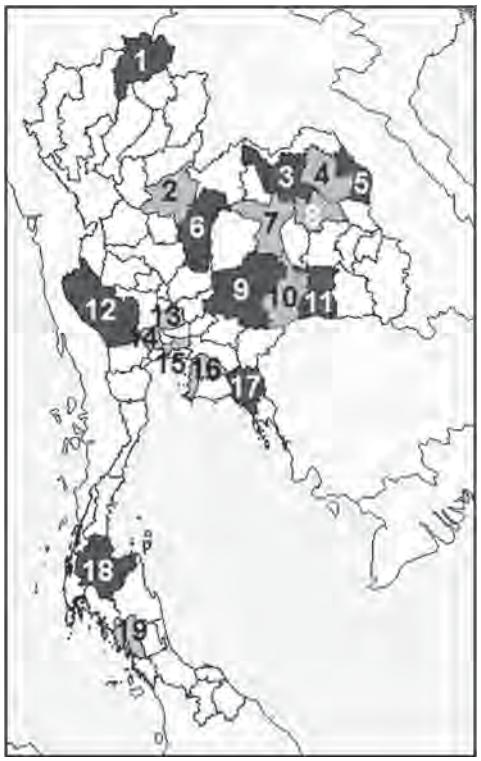


***Fig. 16.6.*** Location of Thai provinces where murine rodents were tested for Hantavirus-reacting antibodies.

54 (8.2%) rodents among 660 tested: 6.4% (13/203) among *R. rattus*, 20.9% (39/187) among *R. norvegicus*, 16.7% (2/12) among unidentified Rattus species, and none in 183 *R. exulans* or in 75 Bandicota spp. The presence of the viral genome was detected by a reverse transcription PCR amplifying part of the sequence coding for the nucleoprotein in the S segment, in 87% of the seropositive rodents. Thirty-one representative cDNAs were sequenced. Phylogenetic studies of the sequences indicated a close relationship with Seoul virus. However, the Cambodian-Seoul virus strain sequences clustered within two different phylogenetic lineages, one associated with *R. rattus* and the other with *R. norvegicus*.

### 16.3.2 Serological Investigations in Humans

Serological surveys carried out to detect evidence of hantavirus infection in human populations revealed that in Thailand, in different provinces and/or in different environments, 1.2–31.4% of individuals tested had hantavirus antibody [27,35]; the recent publication of the first human case in Thailand confirms the presence of hantavirus in Southeast Asia [40].

All this suggests that rodents are probably the primary reservoir, and that other mammals may be involved in the cycle of hantaviruses; new viruses, different hosts and different human syndromes may be expected to be discovered in the future. Additional work is needed in the traditional areas where hantaviruses have been recorded or suspected, mainly in Southeastern Asia where murine rodents are present, highly diversified and certainly reservoirs for hantaviruses.

## 16.4 PHYLOGENY OF HANTAVIRUSES

Different analyses, based on alignment of M or S sequences [7,13,16,18,19,20,21,25] have been performed and used to discuss the distribution of the hantaviruses, in relation to the biogeography and evolutionary history of their hosts. Generally, these studies were based on mixed data sets including sequences issued from wild mammals (collected in their natural range), and sequences exclusively known from human patients. Also, most often they were based on neighbor-joining analyses and incomplete data sets (including only a part of the known diversity of the viruses among their natural hosts), or data sets limited to particular geographic areas. The strong growth of phylogenetic biology during last two decades has been aided by recognition of the importance of a correct phylogenetic analysis as a necessary step, before interpreting evolution. Thus, in the following we redo an analysis of the S sequences and use the resulting cladogram to discuss the origin and distribution of rodent-borne hantaviruses.

### 16.4.1 Material and Methods

***16.4.1.1 Sequences alignment*** Only S sequences found in GenBank of virus isolated from precisely identified wild mammals, including complete CDS, were held. The data set includes 93 taxa (Table 16.1): 91 isolated from different rodent hosts; one isolated in Korea from a bat (Kim, direct submission 1995); Thottapalayam detected in India from a shrew (*Suncus murinus*) by Carey et al. [4], identified by Xiao et al. [45], complete S sequence recently introduced in GenBank by Schmaljohn and Toney (direct submission, 2004) used as outgroup. Retained sequences ranged between 1130 and 2082 nucleotides from which first 42 (primer) and nucleotides 1342–2082 (codon stop and noncoding region) were eliminated; nucleotides 43–1341 (coding part) were used for cladistic analyses. Alignment performed at amino acid level and analyzed at nucleotide level, using CLUSTAL-X [44] and SE-AL v2.0a11 [32].

***16.4.1.2 Aligning and coding indels*** During sequence alignment, it became necessary to include several gaps between nucleotides 766 and 813 (Fig. 16.7). Therefore, more than one equally optimal alignment might be proposed for this region. Comparative secondary structure alignment, currently considered a powerful method [14,28], could not be used here because no model is available for these organisms. We applied Barriel's method [2] of successive parsimony analysis using PAUP* 4.0b10 [41] to test different alignments, produced manually using SE-AL. In order to define the most parsimonious, we used the following criteria: (1) minimize the number of inferred mutations (number of steps), (2) test number of weighed mutations (one transition [Ts], preferred to one transversion [Tv]), and (3) minimize the number of variable sites.

Standard procedures for coding gaps suffer from several weaknesses: either the different sites are analyzed independently (gap = new state) and each gap is artificially weighed in relation

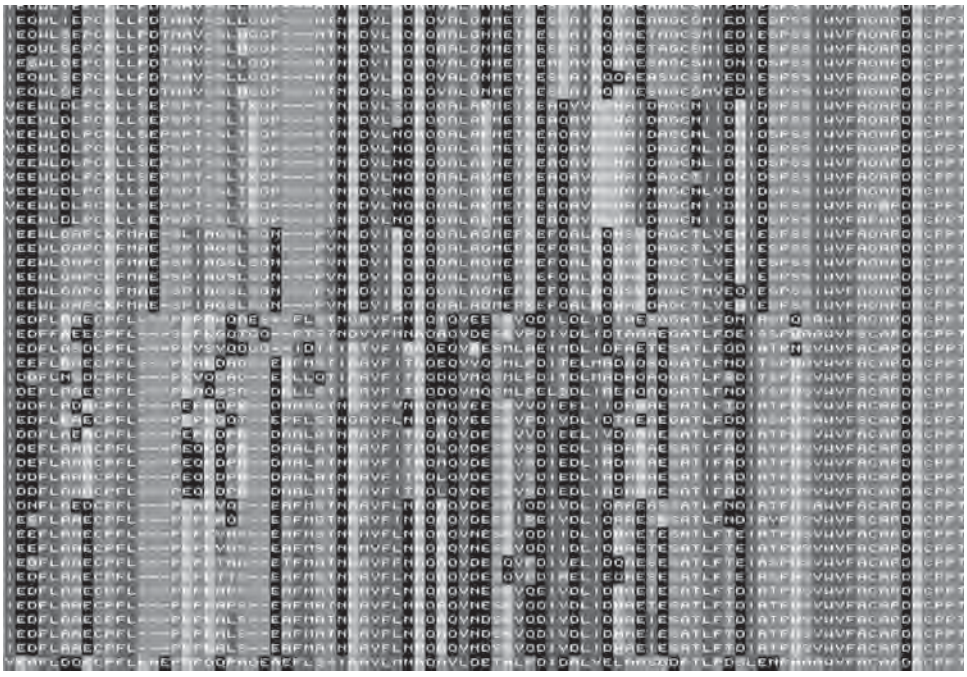

*Fig. 16.7*. Alignment of the S sequences in the hypervariable (HV) region. The alignment at the amino acid level makes necessary to introduce several indels. The HV region is flanked by two conserved cysteine.

to the number of sites, or each site is coded "?" (gap = missing data) and optimization procedure makes the whole zone devoid of phylogenetic information. To express potential phylogenetic information contained in zones with inter-nested insertions/deletions and substitutions, nine characters coding the presence/absence of deletions between nucleotides 766 and 813 were added. Finally, the matrix includes 1323 RNA characters and nine presence/absence characters.

***16.4.1.3 Sequence analyses*** Two methods likely to give results interpretable in an evolutionary context were used: maximum parsimony analysis (MP) and Bayesian analysis (MB). MacClade 4.0 [23] and Treeview 1.3 [29] were used for data and tree handling and for computation of statistics. MP analysis was computed using PAUP. Robustness of nodes was assessed using bootstrap method [11], computed after 10,000 replicates of heuristic search with closest stepwise addition of taxa. Modeltest 3.0 [31] was used to determine the best fitting settings: the general time reversible model [47] with among-site substitution rate heterogeneity described by a gamma distribution with eight categories [46] and a fraction of sites (INV) constrained to be invariable (GTR+I+G, selected by AIC). MB analysis using these settings was performed using MrBayes v3.0B4 [17]. This approach evaluates the posterior probability of a tree given the character matrix, that is, the probability that the tree is correct. Posterior probability is obtained after combining the prior probabilities of a tree and of the data with the likelihood of the data given that tree. Bayesian approach allows defining an explicit probability model of character evolution and obtaining a rapid approximation of posterior probabilities of trees, through the use of the Markov Chain Monte Carlo (MCMC) approach. MrBayes also allows performing phylogenetic analyses of data sets combining information from different subsets, evolving under different stochastic evolutionary models. Two partitions were distinguished in our original data set: partition 1 = nucleotide (characters 1–1299) for which the likelihood model chosen was the GTR+I+G; partition 2 = indels (characters 1300–1308) treated as presence/absence. Analysis was conducted with four independent Markov chains, run for 500,000 metropolis-coupled MCMC generations, with tree sampling every 10 generations and burn-in after 3300 trees. Consensus tree was computed using the "halfcompat" option, equivalent of 50% majority rule. Proportion values of posterior probability of bipartition, considered equivalent to bootstrap values [6] were used for evaluation of robustness of the nodes.

## 16.4.2 Results

MP or MB analyses yield consistent results. All bipartitions found by MP analysis with a bootstrap value superior or equal to 95% were also found by MB analysis with a posterior probability equal or superior to 95%. In addition, MB analysis gave a resolution and a support superior or equal to 50% for several nodes, which were unresolved, or resolved with a bootstrap inferior to 50%, in the MP analysis. Even if MB analysis is likely to favor higher values when compared to bootstrap analysis [6,17,48], the results are fully congruent and are presented in Figure 16.8. Figures 16.9 and 16.10 detail the composition of

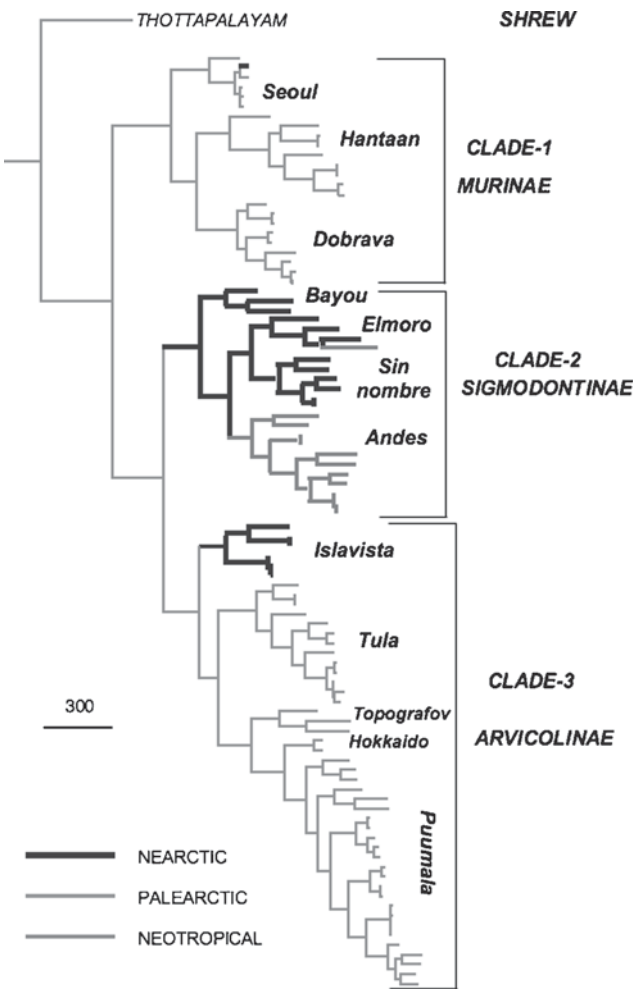


***Fig. 16.8.*** Phylogram resulting from Bayesian analysis using GTR + I + G model. Different color patterns are attributed to different biogeographical areas. Three main clades may be recognized. CLADE-1 and CLADE-2 are detailed in Figure 16.9. CLADE-3 is detailed in Figure 16.10. See color plates.

the three main identified clades. Figure 16.11 summarizes the relation between the virus phylogeny and the host taxonomy.

The cladogram is rooted between a basal branch corresponding with Thottapalayam and a monophyletic group including all the rodent-borne parasites, distributed following three main clades: CLADE-1 includes "Seoul, Hantaan, Dobrava"; CLADE-2 and CLADE-3 are sister clades including "Bayou, Sinnombre, Andes," and "Islavista, Tula, Puumala," respectively. Each clade and the sister grouping of CLADE-2 and CLADE-3 have a support superior or equal to 78%. CLADE-1 groups 22 taxa: all the viruses hosted by Murinae rodents, and the single strain found on a bat; CLADE-2 groups 23 taxa: all the viruses hosted by Sigmodontinae rodents; CLADE-3, groups 48 taxa: all the viruses hosted by Arvicolinae rodents. Regarding the biogeographical distribution, CLADE-1 is exclusively Palearctic, except Tchoupitoulas collected in the Nearctic (Louisiana); CLADE-2 is found exclusively in the "New World" and associates strains from the Nearctic and Neotropics; CLADE-3 may be divided into one Nearctic subclade (Islavista) and the sister grouping of two Palearctic subclades (Tula + Puumala).

***16.4.2.1 CLADE-1: "Seoul, Hantaan, Dobrava" (Fig. 16.9)*** Viruses hosted by Rattus spp. are distinguished from those hosted by *Niviventer confucianus* and Apodemus spp. With the exception of the parasite of Niviventer (considered by taxonomists closer to Rattus), this distribution matches the taxonomy of the rodents at genus level. However, different virus strains hosted by the same rodent species are not grouped together. The bat virus is included in Hantaan; its closest relative is HTNV-76118. Regarding the geographic distribution: Seoul is found in eastern China, with the exception of SEOV-Sapporo (Japan) and SEOV-Tchoupitoulas (Louisiana), which are sister taxa. Hantaan also is restricted to the eastern part of the Palearctic region, but with a wider distribution including several provinces in

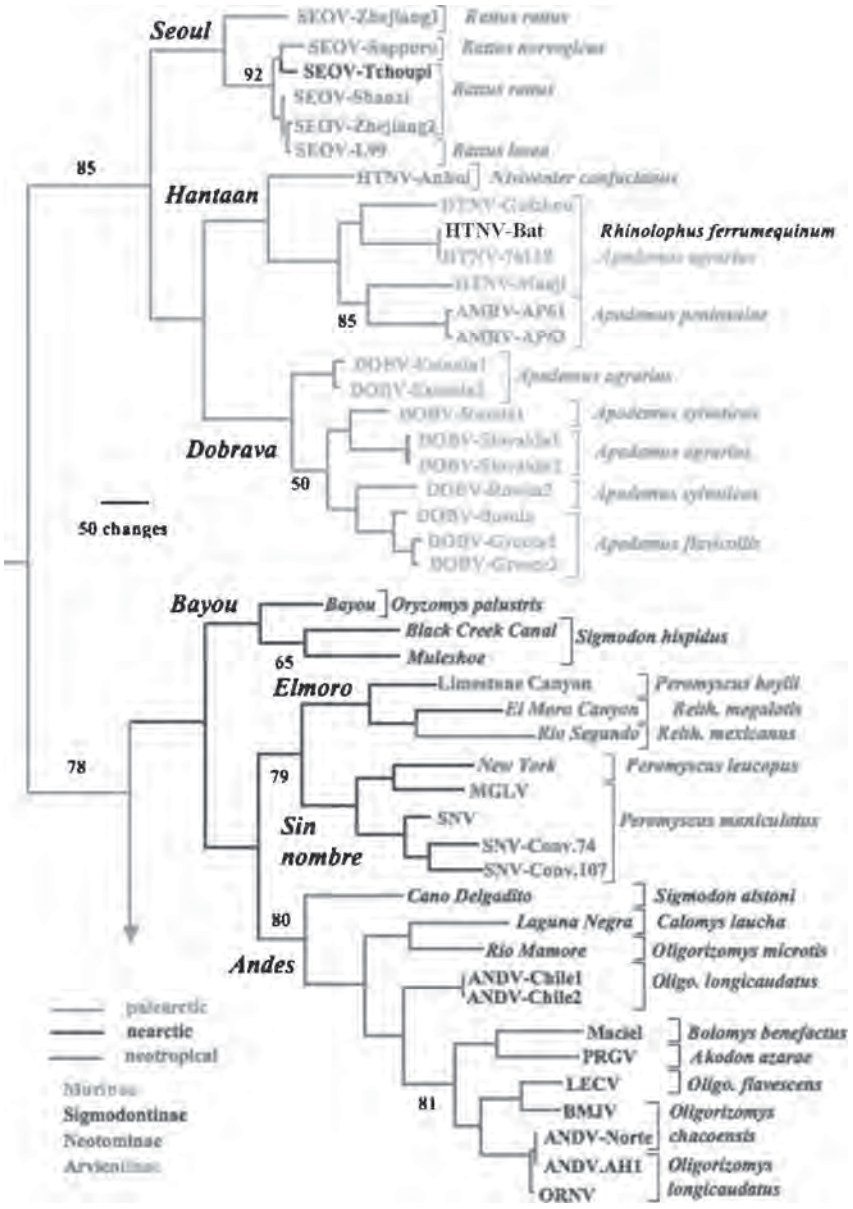


***Fig. 16.9.*** Detail of CLADE-1 and CLADE-2 of Figure 16.8. Posterior probability numbered when inferior to 95% (probability of no numbered nodes between 95 and 100). The scientific name of host for each virus strain is given; different color patterns are attributed to different host groups and to different biogeographical areas. Reith., Reithrodontomys; Oligo., Oligorizomys. See color plates.

China, Korea, and the Amur area (northeastern Siberia). Dobrava has a European distribution extending from Estonia towards Greece, through Western Russia, Slovakia, and Bosnia. The arrangement of Dobrava viruses on the cladogram generally fit with a north to south distribution.

***16.4.2.2 CLADE-2: Bayou, SinNombre, Andes (Fig. 16.9)*** From the three subclades, two are hosted by Sigmondontini rodents (Bayou, Andes), whereas Sinnombre is hosted by Neotomini rodents. Bayou, found in three states of Southeastern North America (Florida, Louisiana, and Texas) is hosted by two different genera, Oryzomys and Sigmodon. Sinnombre is subdivided into a group of three taxa found in Arizona, New Mexico, and Costa Rica, and is hosted by Peromyscus sp. and Reithrodontomys spp.; *a group* hosted by Peromyscus spp. ranging from Northeastern to Southwestern and Central United States. Andes, is exclusively found in the Neotropics and hosted by Sigmodontini rodents: Oligoryzomys is the most frequently, together with several other genera (Akodon, Bolomys, Calomys, Sigmodon). The most divergent species in this group is Caño Delgadito from Venezuela; the other species are arranged following their geographical origin: Laguna Negra and Rio Marmore (Bolivia and Paraguay); ANDV-Chile 1 and 2,

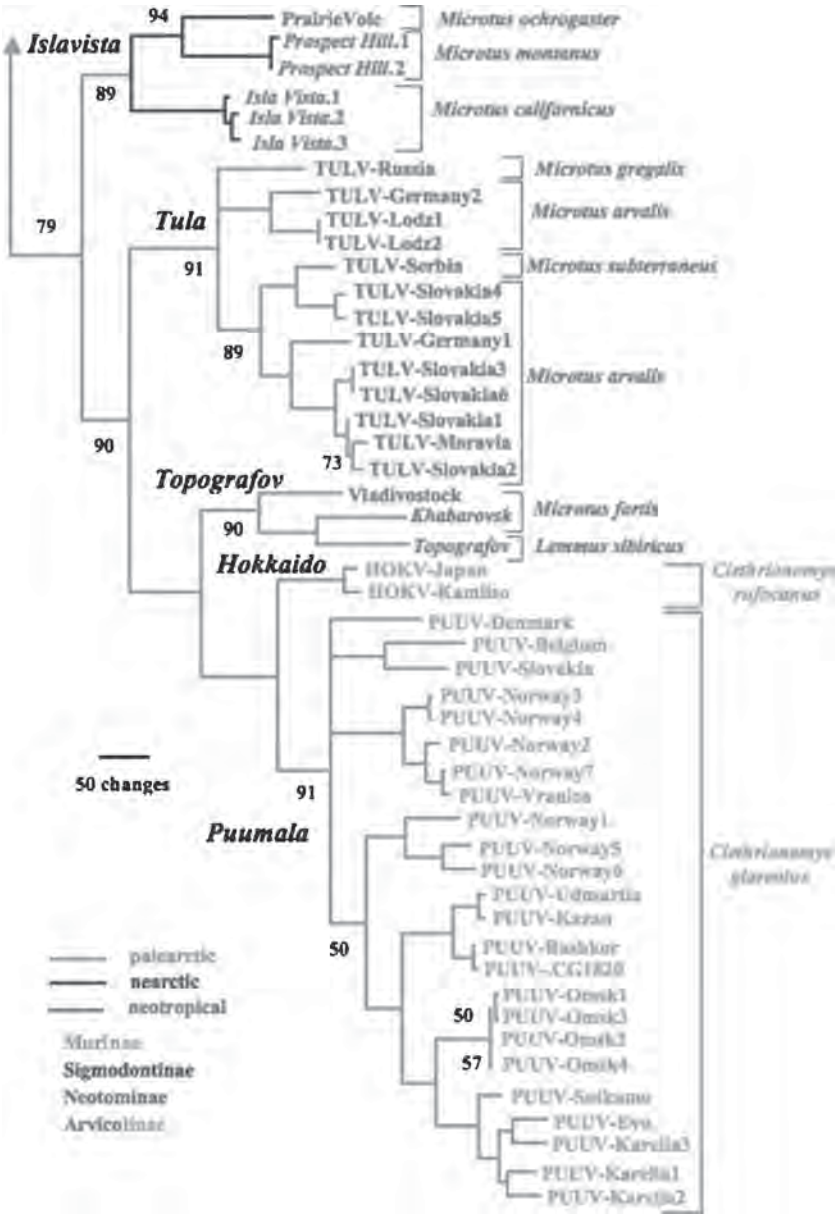


***Fig. 16.10.*** Detail of CLADE-3 given in Figure 16.8. Posterior probability numbered when inferior to 95% (probability of no numbered nodes between 95 and 100). For each virus strain, the scientific name of host is given; different color patterns are attributed to different host groups and to different biogeographical areas. See color plates.

(Chile); the last seven are from Northern Argentina. Distribution of virus taxa within CLADE-2 generally fits with the taxonomy of rodents at host tribe level and a dominant genus may be recognized for each of the main subgroups. However, the Sigmodontini parasites are not monophyletic; as in CLADE-1, no congruence is observed at host species level (closely related viruses hosted by different host species, viruses hosted by a same host species not closely related on the cladogram).

***16.4.2.3 CLADE-1: Prairie, Tula, Puumala (Fig. 16.10)*** CLADE-3 is the sister group of CLADE-2 and is hosted by Arvicolinae rodents. Tula and Puumala are strictly Palearctic, Islavista is strictly Nearctic. Microtus spp. is the dominant host for Islavista and Tula. Islavista may be subdivided into two groups: Islavista 1, 2, 3 are Californian, Prairie Vole and Prospect Hill 1 and 2 are from South Central United States. Tula has a European distribution extending north to south, from Poland, Germany, Moravia, Western Russia, and Slovakia. In Puumala: Microtus, associated with Lemnus, is present in a small basal group including three virus species found in the extreme east of Russian Siberia (Vladivostok, Khabarovsk, and Topografov); the other species are hosted by *Clethrionomys rufocanus* or *C. glareolus*. The parasites of *C. rufocanus* are Japanese strains (Hokkaido). The parasites of *C. glareolus* have a distribution extending from

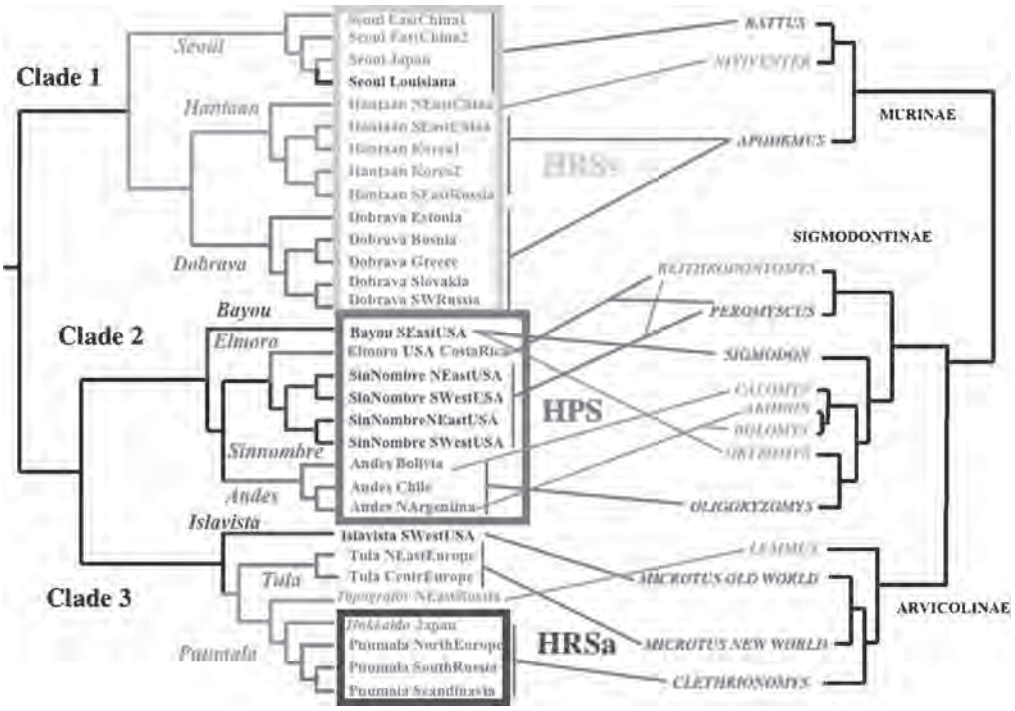


***Fig. 16.11.*** Correspondence between the phylogeny of genus Hantavirus, the classification of its hosts, and the type of human syndrome. See color plates.

Northwestern Europe (Denmark, Belgium) to Scandinavia, Finland, and South Central Russia. Among Puumala, a dominant host species may be recognized for each of the main subgroups. But, in Islavista and Tula, there is no general congruence between virus and host classifications at species level: closely related viruses hosted by different host species; viruses hosted by a same host species, not closely related on the cladogram.

***Fig. 16.12.*** *Maxomys Surifer* kept in a cage, before being sold in a rural market in Phrae province, northern Thailand.

## 16.5 DISCUSSION

### 16.5.1 Clades, Groups, Robustness of Nodes, and Molecular Data

Our analysis confirms the three main clades previously described within the hantaviruses [18,25] and supports the subdivision of each clade into three subclades. "Seoul," "Hantaan," "Dobrava," "Andes," "Tula," "Puumala," already have been named. We propose new names for several new groups:

- "Bayou," including Bayou, Black Creek, Muleshoe.
- "Sinnombre," including Sin Nombre, Convict Creek, Monongahela, and New York.

***Fig. 16.13.*** Painting in Wat Wang Luang, in Phrae province, northern Thailand.

- "Elmoro," including El Moro Canyon, Rio Segundo, and Limestone.
- "Islavista," including Prairie Vole, Prospect Hill, and Isla Vista.
- "Topografov," including Topografov, Khabarovsk, and Vladivostock.
- "Hokkaido," including Hokkaido and Kamiiso-8cr-95.

The support for corresponding nodes of the cladogram is generally between 80 and 100. The alignment shows that main clades and subclades are supported by amino acid changes caused by synonymous or non-synonymous nucleotide differences. Most changes occur in the HV region (Fig. 16.7) identified by several previous studies [22,30]. Hughes and Friedman [18] defined the HV region as residues 242–281. In our joint alignment, HV region corresponds to amino acid residues 249–317 and includes 92% of informative sites (for whole matrix, the percentage is 62%). This region also includes several regular indels corresponding with the main subdivisions of the cladogram.

## 16.5.2 Biogeography of Hantaviruses and Their Hosts

***16.5.2.1 Host specificity and correspondence with host taxonomy*** Lundkvist et al. [22], observed that "···evidence that at least in some hantaviruses the HV region is a target for host antibodies and · · · known importance of charged residues in determining antibody epitopes · · · suggest that changes in the HV region may represent adaptation to host-specific characteristics of the immune response." The strong correspondence between the indels and variations in the HV region and the distribution of the hantavirus in identifiable rodent groups support this hypothesis (Fig. 16.7).

The topology of the three main clades matches the phylogeny of the three host subfamilies to which they are respectively devolved. Within CLADE-1 and CLADE-3 different subclades have a dominant host genus easily recognizable. Within CLADE-2, a particular host tribe hosts each subclade, but it is less easy to identify a dominant genus (Fig. 16.8). The good correspondence of the phylogenies at their highest level is consistent with the hypothesis of coevolution: the hantavirus and the Muridae may have evolved and dispersed in parallel. But, whatever the clade considered, there is a mismatch of the host and parasite distributions at species level. It appears as if the host specificity disappeared somewhere between the species and/or genus level. Depending on the clade considered, this limit is variable: host switching at genus level appears difficult and unlikely within CLADE-1 and CLADE-3, and easier in CLADE-2; within CLADE-2, the highest diversity, thus weakest specificity at genus level, is observed in Andes.

***16.5.2.2 Biogeography of rodent-borne hantaviruses*** CLADE-1 is Palearctic except Tchoupitoulas, reported from a wild *R. norvegicus* in New Orleans. *R. norvegicus* is a cosmopolitan species, whose dependence on human living areas is well known and the presence of this hantavirus in the "New World" can be, interpreted as a case of dispersion by humans. CLADE-2 is exclusively found in the "New World": Figure 16.2 shows that unexpectedly following the hypothesis of coevolution, the parasites of the Nearctic Sigmodontini (Bayou) are not closely related to the parasites of Neotropical Sigmodontini (Andes). Most of the Sigmodontini biodiversity is found in the Neotropics, whereas their sister group, the Neotomini, is dominant in North America. Bayou seems limited to Southeastern United States, and may perhaps be interpreted as resulting from an ancient isolation of its hosts in a remote part of their range. CLADE-3 has a mixed distribution with one small Nearctic subclade (Islavista) and four Palearctic subclades (Tula, Topografov, Hokkaido, and Puumala). Islavista, Tula, and Topografov are hosted by different species of genus Microtus, Puumala, and Hokkaido are hosted by Clethrionomys spp. This distribution is consistent with a Palearctic origin, a passage into the "New World" probably transported by the Arvicolinae (most probably Microtus), a later dispersion in North and South America following the migrations of the Sigmodontinae. The usual hypothesis generally accepted for the radiation of Muridae is that of starting from their South Asian center of origin and having a parallel evolution. Within the subclades a different pattern is suggested, because transmission between different rodent species in a same genus (and between different genera in the Neotropics) looks possible.

Finally, two different patterns of dispersion explain the evolution of hantaviruses: the first one, characterized by a strong specificity for a particular group of hosts, explains the ancient history of this group and its coevolution with Muridae; the second one, characterized by a slack specificity, is corresponding with the recent and current history of viruses and their opportunistic circulation by using contacts between closely related rodent genera, species, and/or populations. This second pattern explains why from the point when host and parasite distribution was well documented (Dobrava, Tula, Puumala, and Andes), a geographic gradient become visible. Different pattern, following different specificity is in agreement with what is known about hantavirus survival outside their hosts. Sauvage et al. [34], considering the role of indirect transmission on virus persistence, suggest that viruses remain active outside the host, which could permit transmission without physical contact of infectious rodents. This explains how hantaviruses may switch when the specific barrier is low and when different hosts have overlapping territories.

***16.5.2.3 Comparison with previous studies*** The subdivisions of our cladogram in recognizable clades and subclades are generally fitting with groups already defined by previously published papers using different genes (S or M), different methods, and different data sets. However, some differences appear within clade arrangement (Fig. 16.11).

Within CLADE-1, following the authors, Dobrava is associated either with Hantaan or Seoul. Within CLADE-2, Limestone, El Moro, Rio Segundo constitute a particular clade, neither included in SINNOMBRE nor associated with another subgroup; Sinnombre and Andes sometimes are sister groups, but sometimes are associated differently. Within CLADE-3, in most phylogenic studies published previously, Tula is the sister group of Islavista.

In our results, the sister grouping of Dobrava with Hantaan is strongly supported (posterior probability superior to 80%) and several characters common to all parasites of Apodemus spp. may be observed in the alignment: a common deletion between nucleotides 784 and 796; several sequences of nucleotides, particularly in the HV region. Thus, our results support the hypothesis of a close relationship between the two main groups parasitizing Apodemus spp. There is a strong case for grouping the triplet Limestone, El Moro, Rio Segundo within a particular clade associated with Sinnombre. This topology associates all the parasites of Peromyscus spp. (in Sinnombre + Elmoro), grouping together taxa which has a particular geographic distribution and suggests that the "New World" hantavirus were first established in the Nearctic and secondarily emigrated to the Neotropics. Finally, within CLADE-3, the opposition of a Nearctic group (Islavista) and a Palearctic group (Tula + Topografov + Hokkaido + Puumala) is also well supported by data (posterior probability ranging between 80 and 90). If we compare our topology with the grouping of Islavista and Tula, both topologies support Microtus spp. as primary hosts, but our topology supposes an earlier separation between the Nearctic and the Palearctic species of this genus. Thus, generally our results support hypotheses in agreement with the most parsimonious interpretation of a parallel evolution of genus hantavirus and the Murinae.

#### *16.5.2.4 What are the limits of the hantavirus range?*

Although most Bunyaviridae are hosted by arthropods, genus hantavirus has rodents as principal hosts. However, two strains have been isolated from non-rodent mammals: Thottapalayam, isolated from a shrew; the Hantaan virus isolated from a bat. Thottapalayam sequence possess a common deletion with the members of CLADE-1 between nucleotides 805 and 813, but makes necessary the addition of several deletions when introduced in the alignment and lacks several conservative parts of the rodent-borne sequences. Thus, if Thottapalayam can be considered a hantavirus, it is highly divergent from other members of the genus. This is confirmed by its position in the cladogram and by values of total-character distances calculated using PAUP within the rodent-borne group, distances vary from 2 to 516; between Thottapalayam and others, distances range between 765 and 859. This suggests that Thottapalayam probably does not result from a recent host switching between rodent and shrew. Further investigations are needed to decide if this adaptation to a different group of mammals is incidental, or may represent the emerging tip of a different lineage.

The bat virus is included in Hantaan; its closer relative is HNVT.7611. No significant difference of branch length is observed between the two strains and their total-character distance equals 4, suggesting that the two sequences are almost identical; thus, the presence of a different virus species in *R. ferrumequinum* cannot be considered strongly established.

Most of hantavirus spp. found in wild animals were collected in the Holarctic, or the Neotropics (Northern Asia, Europe, North America, and South America). But, Thottapalayam comes from South Asia, and Thailand virus comes from Southeastern Asia where it is hosted by *B. indica*, a Muridae rodent. Also, serological surveys carried out to detect evidence of hantavirus infection in human populations revealed that in Thailand, in different provinces and/or in different environments, 1.2% to 31.4% of individuals tested had hantavirus antibody [26,35,42,43]; similar screenings, performed in West and Central Africa where human hantavirosis has not yet been reported, show that humans may have been infected by Hantaan-related virus [12]. All this suggests that if rodents are probably the primary reservoir, other mammals may be involved in the cycle of hantaviruses; new viruses, different hosts and different human syndromes may be discovered in the future. Additional work is needed in the traditional areas where hantaviruses have been recorded, mainly in Southeastern Asia and in Africa where Muridae rodents are present and highly diversified.

## 16.6 CONCLUSION

### 16.6.1 Presence Without Cases Versus Cases Without Notification?

With proof of hantaviruses presence in different rodent species and proof of regular transmission of rodent-borne diseases to humans for years, questions subsist as for the few notified cases and a unique confirmed one.

The presence of a virus and its vector in the environment does not necessarily imply human cases. The possibility of infection depends on a combination of factors conditioning the vulnerability and exposure of people. First of all, the transmission to humans occurs if people are exposed to the infections, requiring being in close proximity to rodents. These conditions exist in Southeast Asia where rodents are regularly hunted and eaten in the countryside. Even inside habitations all over the country, rats and especially the Polynesian rat, *R. exulans*, is common. In some villages, well-known hunters act as meat seller, keeping animals in cages at home or selling them in fresh markets.

Although culture and regionalism may show different situations of exposure, a global high exposure is expected for rural populations.

Lastly, the absence of cases could reflect a public health system not able to detect them. Even if Thailand is globally covered with public health infrastructures providing low-cost health care, strong inequalities subsist between social classes and regions. In rural areas, recourse to health services occurs

in case of severe fevers, a spontaneous behavior being to take paracetamol. Some cases may not be recorded. Another difficulty remains in the clinical diagnosis and possible confusion with other recurrent fevers in Thailand: leptospirosis, scrub typhus, or even dengue, some cases being also classified as "fever of unknown origin."

## ABBREVIATIONS

| | |
|---|---|
| cDNA: | Copy deoxyribonucleic acid |
| ELISA: | Enzyme-linked immunosorbent assay |
| HFRS: | Hemorrhagic fever with renal syndrome |
| HPS: | Hantavirus pulmonary syndrome |
| IFA: | Iimmunofluorescence antibody detection test |
| RNA: | Ribonucleic acid |
| RT-PCR: | Reverse transcriptase polymerase chain reaction |

## GLOSSARY

*Aerosolization*: Conversion into an aerosol. Aerosolization is the process of creating very small droplets of moisture that may carry microorganisms. The aerosolized droplets can be light enough to remain suspended in the air for short periods of time and facilitate inhalation of microorganisms.

*Arvicolinae*: A subfamily of the family Muridae, comprising at least 143 species. Voles and lemmings are Holarctic. Thus, within the three subfamilies of the Muridae, which are known to host some hantavirus, only the Arvicolinae are present on both sides of the Bering Strait. The Arvicolinae seem to be more comfortable in cold countries, and they are abundant and well adapted to the cold climate of Scandinavia, Siberia, and the most northern part of North America. However, some species are known in the southern part of their range, in Pakistan and India, as well as in Mexico and Guatemala.

*Bayesian analysis*: Bayesian inference is a statistical inference in which probabilities are interpreted not as frequencies or scale, but rather by their degree of credibility. The name comes from Bayes' theorem, which is frequently employed in this type of analysis.

*Clade*: (Greek: klados = branch). A clade is a monophyletic group of organisms. The members of a clade are all the organisms sharing one unique common ancestor, and this ancestor itself.

*Cladistics*: A method of classifying organisms, which requires all taxa to be clades. Recognition of the taxa to be included in a clade is based on the existence of at least one derived similarity, or "shared derived properties," or synapomorphies. Cladistics is opposed to "Phenetics," in which organisms are grouped based on their overall similarity.

*Cladogram*: Tree-like relationship diagram in which all organisms lie at the leaves, and each inner node represents the common ancestor of the dependent leaves. Ideally, a cladogram is binary. On either side of a split, the two taxa are called sister taxa or sister groups. Each sub-tree is a clade. Each clade is set off by at least one synapomorphy (one shared, derived character).

*Hantavirus*: (derived from the Hantaan River, where the etiologic agent of Korean hemorrhagic fever, the Hantaan virus, was first isolated) One of the five genera of the family Bunyaviridae, hantaviruses are spread by rodents, transmitted by aerosolization and target the kidneys, lungs or pulmonary system, and heart.

*Muridae*: The largest family within the mammalians contains over 1300 species, 281 genera, and 17 subfamilies. The origins of the Muridae are believed to be in Southeast Asia. Within this family, three subfamilies are known reservoirs for Hantavirus: Arvicolinae, Murinae, and Sigmodontinae.

*Murinae*: A subfamily of the family Muridae, comprising at least 423 species in 129 genera. The Murinae are the most successful group within the Rodentia. They have an extended natural range, but are limited to the "Old World": from Africa to Australia, from Europe and Eurasia to Asia. This group includes mice, rats, and their relatives. These species live commensally with humans and have reached a worldwide distribution.

*Phylogenetics*: (from Greek: phylon = tribe, race; genetikos = relative to birth) The study of evolutionary relatedness among various groups of organisms (e.g., species, populations).

*Phylogeny*: The evolutionary relationships between different species of organisms as represented in a phylogenetic tree. In molecular phylogeny, these relationships are determined by analysis of the similarities and differences in the sequences of genes common to various species.

*Reservoir or carrier*: A person or an animal, in which an infectious agent lives, which may not itself have any visible signs of disease caused by carrying the agent. The carrier can transmit the disease to humans or animals. Host may also be used.

*Sigmodontinae*: They are the second-largest subfamily of Muridae rodents, with at least 423 species and seven genera in eight tribes. Members of this group, the "New World" rats and mice, display a vast array of habits and physical characteristics. Sigmodontinae range from Tierra del Fuego northward through South America, Central America, Mexico, and into the United States. They are also found on the Galapagos Islands. Two subgroups are currently distinguished: Neotomini and Sigmodontini. Several recent works question the monophyletic origin of Sigmodontinae.

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