Virus Genes 30:2 157–180, 2005

New Ecological Aspects of Hantavirus Infection: A Change of A Paradigm and a Challenge of Prevention – A Review

MARTIN ZEIER,[1] MICHAELA HANDERMANN,[2] UDO BAHR,[1] BALDUR RENSCH,[2] SANDRA MÜLLER,[1] ROLAND KEHM,[2] WALTER MURANYI[2] & GHOLAMREZA DARAI[2,*]

[1]*Klinikum der Universität Heidelberg, Sektion Nephrologie, Bergheimerstr. 56a, D-69115 Heidelberg, Federal Republic of Germany*

[2]*Hygiene-Institut der Universität Heidelberg, Abteilung Virologie, Im Neuenheimer Feld 324, D-69120 Heidelberg, Federal Republic of Germany*

Received August 15, 2004; Accepted August 26, 2004

Abstract. In the last decades a significant number of so far unknown or underestimated pathogens have emerged as fundamental health hazards of the human population despite intensive research and exceptional efforts of modern medicine to embank and eradicate infectious diseases. Almost all incidents caused by such emerging pathogens could be ascribed to agents that are zoonotic or expanded their host range and crossed species barriers. Many different factors influence the status of a pathogen to remain unnoticed or evolve into a worldwide threat. The ability of an infectious agent to adapt to changing environmental conditions and variations in human behavior, population development, nutrition, education, social, and health status are relevant factors affecting the correlation between pathogen and host. Hantaviruses belong to the emerging pathogens having gained more and more attention in the last decades. These viruses are members of the family *Bunyaviridae* and are grouped into a separate genus known as *Hantavirus*. The serotypes Hantaan (HTN), Seoul (SEO), Puumala (PUU), and Dobrava (DOB) virus predominantly cause hemorrhagic fever with renal syndrome (HFRS), a disease characterized by renal failure, hemorrhages, and shock. In the recent past, many hantavirus isolates have been identified and classified in hitherto unaffected geographic regions in the New World (North, Middle, and South America) with characteristic features affecting the lungs of infected individuals and causing an acute pulmonary syndrome. Hantavirus outbreaks in the United States of America at the beginning of the 10th decade of the last century fundamentally changed our knowledge about the appearance of the hantavirus specific clinical picture, mortality, origin, and transmission route in human beings. The hantavirus pulmonary syndrome (HPS) was first recognized in 1993 in the Four Corners Region of the United States and had a lethality of more than 50%. Although the causative virus was first termed in connection with the geographic name of its outbreak region the analysis of the individual viruses indicate that the causing virus of HPS was a genetically distinct hantavirus and consequently termed as Sin Nombre virus. Hantaviruses are distributed worldwide and are assumed to share a long time period of co-evolution with specific rodent species as their natural reservoir. The degree of relatedness between virus serotypes normally coincides with the relatedness between their respective hosts. There are no known diseases that are associated with hantavirus infections in rodents underlining the amicable relationship between virus and host developed by mutual interaction in hundreds of thousands of years. Although rodents are the major reservoir, antibodies against hantaviruses are also present in domestic and wild animals like cats, dogs, pigs, cattle, and deer. Domestic animals and rodents live jointly in a similar habitat. Therefore the transmission of hantaviruses from rodents to domestic animals seems to

*Author for correspondence:
E-mail: g.darai@urz.uni-heidelberg.de

be possible, if the target organs, tissues, and cell parenchyma of the co-habitat domestic animals possess adequate virus receptors and are suitable for hantavirus entry and replication. The most likely incidental infection of species other than rodents as for example humans turns hantaviruses from harmless to life-threatening pathogenic agents focusing the attention on this virus group, their ecology and evolution in order to prevent the human population from a serious health risk. Much more studies on the influence of non-natural hosts on the ecology of hantaviruses are needed to understand the directions that the hantavirus evolution could pursue. At least, domestic animals that share their environmental habitat with rodents and humans particularly in areas known as high endemic hantavirus regions have to be copiously screened. Each transfer of hantaviruses from their original natural hosts to other often incidental hosts is accompanied by a change of ecology, a change of environment, a modulation of numerous factors probably influencing the pathogenicity and virulence of the virus. The new environment exerts a modified evolutionary pressure on the virus forcing it to adapt and probably to adopt a form that is much more dangerous for other host species compared to the original one.

Key words: bovine aortic endothelial cell, *Bunyaviridae*, ecology, Hantaan virus, hantavirus, Hemorrhagic fever with renal syndrome, Puumala virus

History

In the last decades a significant number of so far unknown or underestimated pathogens have emerged as fundamental hazards to health of the human population despite intensive research and exceptional efforts of the modern medicine to eradicate and embank infectious diseases. Almost all incidents caused by such emerging pathogens could be ascribed to agents that are zoonotic or expanded their host range and crossed species barriers. Many different factors influence the status of a pathogen concerning the question to remain unnoticed or evolve into a worldwide threat. The ability of an infectious agent to adapt to changing environmental conditions and variations in human behavior, population development, nutrition, education, social, and health status are relevant factors affecting the correlation between pathogen and host and represent the fertile ground for infectious agents to emerge from seeming insignificance.

Hantaviruses belong to the emerging pathogens gaining more and more attention in the last decades. These viruses are members of the family *Bunyaviridae* and were grouped in a separate genus known as *Hantavirus* [1–3]. Hantaviruses are enveloped, cytoplasmic viruses with a single-stranded, negative-sensed RNA genome that consists of three segments termed S (small), M (medium), and L (large) coding for the viral nucleocapsid protein (N), two envelope glycoproteins (G1, G2), and the viral RNA dependent RNA polymerase, respectively [2, 3].

Although the diseases caused by hantaviruses have been described since at least 80 years, the first Hantavirus has been isolated in 1978 [4]. The history of hantaviruses initiated from the outbreak of Korean hemorrhagic fever (KHF) that occurred during the Korean War in 1951–1953 on the bank of a small river called Hantaan near the village of Songnaeri in Korea. The causative agent of KHF was found to be very mysterious and its final identification engrossed a long time of intensive investigation. A quarter century after the Korean War Ho Wang Lee succeeded in 1978 to isolate a virus from lung tissue of the striped field mouse *Apodemus agrarius* that was experimentally infected with the agent of KHF [4]. The new virus was consequently termed Hantaan virus (HTN) where the KHF outbreak occurred [4]. HTN was serologically unrelated to any of the other known agents investigated so far. This virus predominantly causes hemorrhagic fever with renal syndrome (HFRS). HFRS is a disease characterized by renal failure, hemorrhages and shock, is caused by the HTN, Seoul (SEO), Puumala (PUU), and Dobrava (DOB) virus and affects more than 200,000 people each year in Europe and Asia. The lethality of HTN was found to be 3 to 10% [4, 5] dependent on the infrastructure of the regional public health service of the respective countries. Nephropathia epidemica (NE), a milder variant of

HFRS with a lethality of 0.1 to 0.2% [6–10] is caused by the serotype Puumala virus (PUU) which is responsible for diseases in north and middle Europe [11–18] as well as the European part of Russia [19–20]. The geographic distribution of the Old World hantaviruses is illustrated in Fig. 1a.

In the last decade, many hantavirus isolates have been identified and classified in hitherto unaffected geographic regions of the New World (North, Middle, and South America) with characteristic features affecting the lungs of infected individuals and causing an acute pulmonary syndrome. Hantavirus outbreaks in the United States of America at the beginning of the 10th decade of the last century fundamentally changed our knowledge about the appearance of the hantavirus specific clinical picture, mortality, origin, and transmission route in human beings. The hantavirus pulmonary syndrome (HPS) was first recognized in 1993 in the Four Corners Region of the United States with a lethality of more than 50%. The causative virus was first termed in connection with the particular geographic region that HPS occurred in, e.g. Black Creek Canal virus, Bayou virus and New York virus, etc. [21–27]. Molecular biological data obtained from individual viruses indicate that the causing virus of HPS is a genetically distinct hantavirus and finally it was termed Sin Nombre virus [28,29]. As expected, since 1995 HPS cases have been reported from the Central and South American continent as well [24,30–51]. Furthermore, other hantavirus subtypes have been identified e.g. Laguna Negra in Paraguay [35,40,45,51], Rio Mamore virus in Bolivia [33], Uran virus, Lechiquanas virus, and Pergamino virus in Argentina [46–48]. All these viruses are now known as Andes hantavirus [47,48] due to their collective identification characteristics. Infections with Andes virus in Argentina have severe novel clinical features. The geographic distribution of the New World hantaviruses is shown in Fig. 1b. According to the Pan American Health Organization the number of HPS cases and deaths registered in North and South America between 1993 and April 26, 2004 was found to be 1910 and 384, respectively. In addition to the high lethality caused by this virus, a person-to-person transmission has been reported [40,41,48] that normally does not occur in the course of hantavirus infections of humans. Although these data have not been confirmed in detail it raises considerable concern and merit to arrest the attention of the public health authority on the particular endemic geographic region.

Ecology and Transmission

Regarding hantavirus ecology and transmission it is known that each hantavirus serotype has a

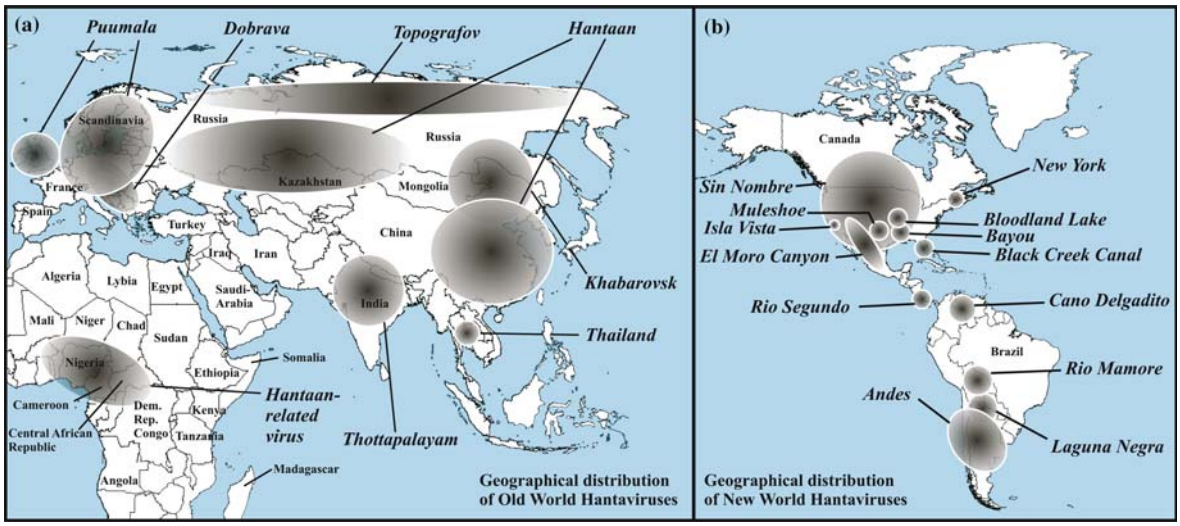

Fig. 1. Distribution of Old and New World hantaviruses.

special rodent species as natural host and can be spread to humans via dried and/or aerosolized virus containing urine, faeces, and saliva by inhalation or even by bites [52]. The dominant rodent hosts in Asia, Northern Europe and Western Europe are *Apodemus agrarius, Clethrionomys glareolus,* and *Apodemus flavicollis,* respectively. The geographic distribution of these species is shown in Fig. 2. However, the role of other species in transmission of viruses is also of considerable importance. It is known that *Lemmus sibiricus, Microtus arvalis, Microtus fortis, Bandicota indica,* and *Suncus murinus* are the main reservoir for the Topografov virus, the Tula virus, the Khabarovsk

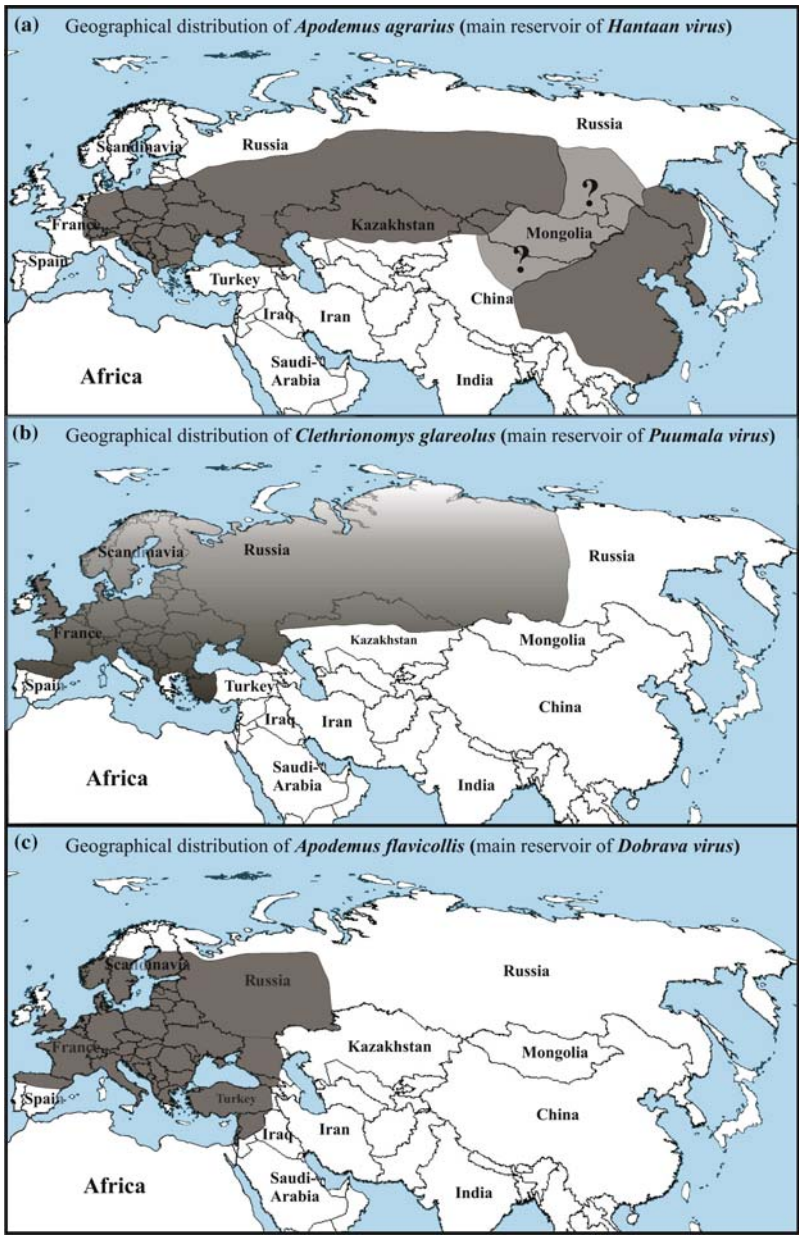

Fig. 2. Distribution of *Apodemus agrarius*, *Clethrionomys glareolus*, and *Apodemus flavicollis* known to be reservoirs for Old World hantaviruses.

virus, the Thailand virus, and the Thottapalayam virus, respectively. The geographic distribution of their specific hosts is illustrated in Fig. 3.

Field studies in rodent populations have revealed that seroprevalence for hantaviruses could be up to 50% depending on the population density [52]. Infections in rodent hosts may persist despite the presence of neutralizing antibodies. Bite wounds inflicted during fighting appear to be a major mode of virus transmission among rodents [52,53]. Although rodents are the major reservoir for hantaviruses, antibodies against hantavirus are also found in domestic and wild-life animals [39,54]. In a recent study in New Mexico in sera of domestic cats (2.8%) and dogs (3.5%) IgG antibody reactivity to nucleocapsid proteins was found [39,55]. Antibodies against hantaviruses were found in hares (3.5%) and in deer species (14.1%) [54,56,57]. Among 145 specimens of *Bos taurus* antibodies were present in two including one against the strain Hantaan [58]. The geographic distribution of animals known to serve as vectors for transmission of hantaviruses to men are summarized in Table 1. This finding is of particular interest, since it focuses attention on virus transmission from rodents to domestic animals. Despite the presence of IgG antibodies against various hantavirus subtypes in domestic animals it is unknown whether asymptomatic, persistent hantavirus infections exist in domestic animals. The cellular entry for the hantavirus is mediated by a specific integrin receptor, the $\alpha_V\beta_3$-integrin [97]. The $\alpha_V\beta_3$-integrin receptor is an abundant surface receptor on various endothelial cells and platelets [98,99]. An increased expression of the endothelial adhesion molecules ICAM-1, VCAM, and PECAM has been reported for hantavirus infected cells [100]. An overview on the animal species known to be infected by hantavirus serotypes and the natural reservoirs known for

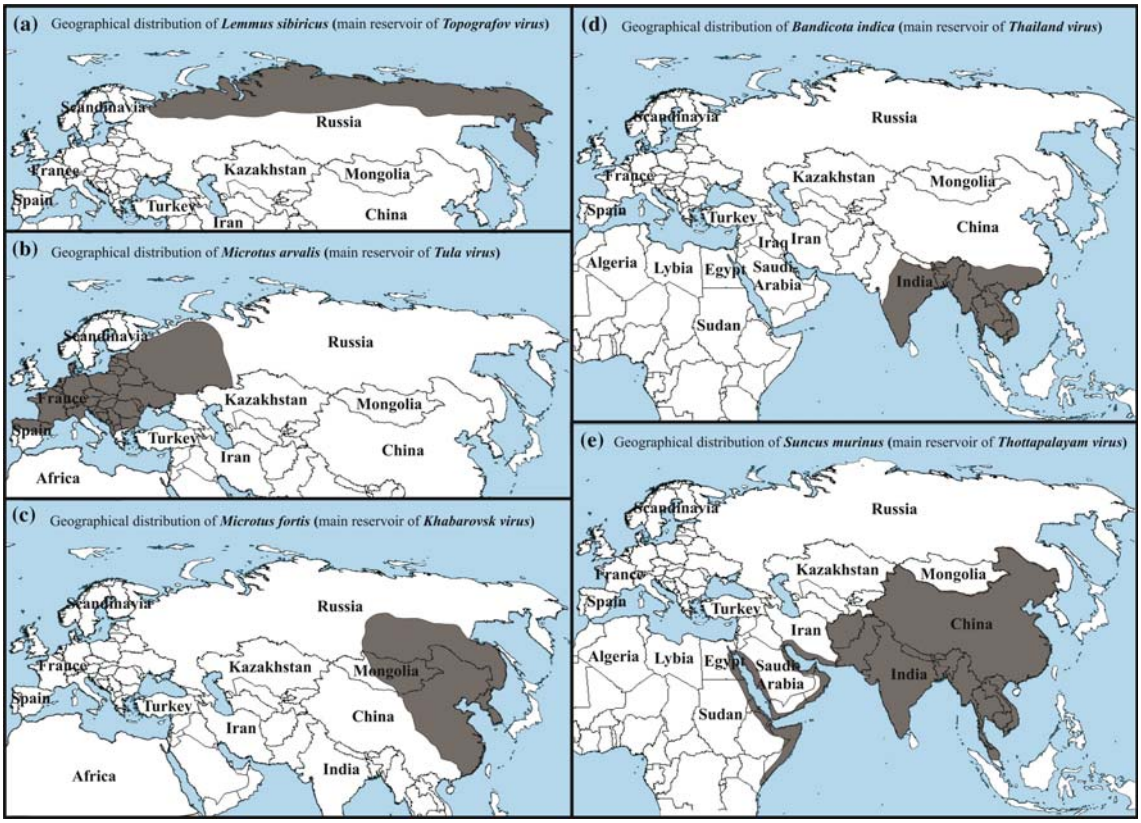

Fig. 3. Distribution of *Lemmus sibiricus*, *Microtus arvalis*, *Microtus fortis*, *Bandicota indica*, and *Suncus murinus* known to be reservoirs for the Topografov virus, the Tula virus, the Khabarovsk virus, the Thailand virus, and the Thottapalayam virus, respectively.

Table 1. Geographical distribution of animals known to serve as vector for transmision of hantaviruses to man

Geographic area	Vector	Disease	Virus	Accession No. (RNA-segment)	Ref.
Asia	*Lemmus sibiricus* (Siberian lemming)	?[a]	Topografov virus (TOP)	AJ011646 (S) AJ011647 (M) AJ011649 (L)	59
	Apodemus agrarius (striped field mouse)	HFRS	Hantaan (HTN)	L08753 (M) X55901 (L) U37768 (S)	60,61
	Rattus norvegicus (Norway rat and brown rat) *Rattus rattus* (black rat)	HFRS	Seoul (SEO)	AY006465 (S) X56492 (L) S47716 (M)	62–64
	Microtus fortis (reed vole)	?[a]	Khabarovsk virus (KBR)	U35255 (S) AJ011648 (M) AJ011650 (L)	65
	Bandicota indica (bandicoot rat)	?[a]	Thailand (THAI)	L08756 (M)	66
	Suncus murinus (shrew species)	?[a]	Thottapalayam (TPM)	AY526097 (S)	66
Europe	*Clethrionomys glareolus* (bank vole)	HFRS	Puumala (PUU)	M63194 (L) M29979 (M) M32750	18, 67–69
	Apodemus flavicollis (yellow-necked mouse) *Apodemus agrarius* (striped field mouse)	HFRS	Dobrava (DOB)	L41916 (S) L33685 (M)	18, 70–72, 150
	Apodemus agrarius (striped field mouse)	HFRS	Dobrava (DOB)	AJ269550 (S) AY168578 (M)	73 74
			Saaremaa	AJ616854 (S) AJ616855 (M) AJ410618 (L)	18,75,76
	Microtus arvalis (European common vole)	?[a]	Tula (TUL)	Z49915 (S) Z69993 (M)	77,78
North America	*Peromyscus maniculatus* (deer mouse)	HPS	Sin Nombre virus (SNV)	L25782 (L)[b] L37901 (L) L25783 (M) L25784 (S)	28
	Sigmodon hispidus (cotton rat)	HPS	Black Creek Canal virus (BCC)	L39951 (L)[b] L39950 (M)	79,80
	Microtus pennsylvanicus (meadow vole)	?[a]	Prospect Hill virus (PH)	M34011 (S) X55129 (M)[b]	81,82
	Microtus californicus (California vole)	?[a]	Isla Vista virus (ILV)	U31529 (S)[b] U19302 (S)	83
	Peromyscus leucopus (white footed mouse)	HPS	New York virus (NY)	U09488 (S)[b] U36801 (M)	25, 26
	Oryzomys palustris (rice rats)	HPS	Bayou virus(BAY)	U37534 (M)[b] L36930 (M) L36929 (S)	84,85
	Reithrodontomys megalotis (American harvest mouse)	?[a]	El Moro Canyon (ELMC)	U11425 (S)[b] U11427 (S) U26828 (M)	23,86
	Reithrodontomys mexicanus (harvest mouse)	?[a]	Rio Segundo (RIOS)	U18100 (S)	24
	Oligoryzomys fulvescens (Pygmy rice rat)	HPS	Choclo	AF395442 (S)[b] AF402330 (M)p[b]	44
	Peromyscus leucopus (white-footed mouse)	HPS	Monongahela	U32591 (S) [b] U32649 (M)	87

Table 1. continued

Geographic area	Vector	Disease	Virus	Accession No. (RNA-segment)	Ref.
	Sigmodon hispidus (cotton rat)	HPS	Muleshoe virus (MULEV)	U54575 (S)	88
	Reithrodontomys megalotis, R. mexicanus(harvest mice)	?[a]	Limestone Canyon virus (LSC)	AF307322 (S)[b] AF307323 (M)[b]	89
South America	*Oligoryzomys flavescens* (Yellow pygmy rice rats)	HPS	Lechiguanas	AF028022 (M) AF482714 (S)	36, 42, 46
	Oligoryzomys longicaudatus (long-tailed pygmy rice rat)	HPS	Andes (AND)	AF004659 (M)[b] AF004660 (S) AF291704 (L)	42,90,91
	Oligoryzomys longicaudatus (long-tailed pygmy rice rat)	HPS	Oran	AF482715 (S) AF028024 (M)	36, 46
	Oligoryzomys flavescens (Yellow pygmy rice rats)	HPS	Central Plata hantavirus	-	49
	Sigmodon alstoni (cotton rat)	HPS	Cano Delgadito	AF000140 (S)[b]	92
	Calomys laucha (vesper mouse)	HPS	Laguna Negra (LN)	AF005727 (S) AF005728 (M) AF005729 (L)[b]	35
	Oligoryzomys microtis (pygmy rice rat)	?[a]	Rio Mamore (RM)	U52136 (S) U73687 (M)[b]	33
	Oligoryzomys fulvescens (Pygmy rice rat)	HPS	Choclo	AF395442 (S)[b] AF402330 (M)[b]	44
	Bolomys obscurus (dark field mouse)	?[a]	Maciel virus	AF028027 (M)[b] AF482716 (S)	36, 46
	Akodon azarae (Azara's grass mouse)	?[a]	Pergamino	AF028028 (M)[b] AF482717	36, 46
	ND	HPS	Juquitiba	-	93
	Zygodontomys brevicauda (short-tailed cane mouse)	HPS	Calabazo virus	AF395443 (S)[b] AF402331 (M)[b]	44
	Bolomys lasiurus (hairy-tailed bolo mouse)	HPS	Araraquara	AF307325 (S)[bb] AF307327 (M)	43
Africa	*Mastomys sp.* (Multimammate mouse)	HF	Hantaan-related virus	ND	94
	ND	HFRS	Hantaan	ND	95,96,187
Australia	?	?	?		

[a]Pathogenicity for humans unknown.
[b]Partial.
ND: Not documented.
HF: Haemorrhagic fever.
Ref.: Reference.
HPS: Hantavirus pulmonary syndrome.
HFRS: Haemorrhagic fever with renal syndrome.

transmission of hantavirus species are given in Table 2 and 3, respectively.

These serological analyses from the late 1980s and early 1990s document that the transmission of hantaviruses is not only possible between rodents and humans by aerosols, but also by domestic animals living in close vicinity to rodents [110,117]. Recently the susceptibility of bovine aortic endothelial cells to hantavirus infections has been documented [118,119]. This endothelial cell line expresses the $\alpha_V\beta_3$-integrin receptor which is known to be the entrance pathway for the hantavirus infection. It is therefore possible that all endothelial cells, expressing this receptor, are susceptible to hantavirus infections.

In a retrospective and prospective study of HFRS in rural China it was shown that the risk factors for an infection were rat-contaminated

food, direct rodent contact, camping in grain fields, inter-village travelling and housing, and keeping cats [120]. In addition, observational and experimental studies in China have shown that the epidemic hemorrhagic fever virus replicates within domestic pigs and that the viral antigen is excreted via urine and faeces. According to this study the domestic pigs may be considered as reservoir hosts for transmission of epidemic hemorrhagic fever [113]. In an earlier study it was reported that neutralizing antibodies and antibodies against the nucleocapsid protein of the Puumala virus were detected in 5 out of 260 wild moose by neutralization test, ELISA, and immunofluorescent assay, respectively [117]. These animals all originated from endemic regions in the northern part of Sweden. This documents the possibility of interspecies infection due to close living in the same habitat. Furthermore, a Puumala virus infection was not only found in *Clethrionomys glareolus*, but also in *Microtus arvalis* and *Apodemus sylvaticus* [121]. A recently published review focuses on the burgeoning human population that causes disruption to natural habitats as more and more land is cleared for commercial and residential purposes [122]. Many rodents readily adapt to a life in human settlements, where they generally benefit from reduced predation and where they sometimes proliferate to high numbers. In a recent report on vector- and rodent-borne infectious diseases, the impact of climate variability and change on vector and rodent borne diseases is highlighted [183]. Rainfall, temperature and other weather variables affect in many ways the vectors and the pathogens they transmit. For example, high temperatures can increase or reduce the survival rate, depending on the vector, its behaviour, ecology, and many other factors. The tremendous growth in international travel increases the risk of importation of vector-borne diseases. These facts increase the likelihood of a possible hantavirus transmission from a rodent population to domestic animals as well as to humans. Not only domestic animals and rodents are infected by hantaviruses, but also non-human primates are obviously susceptible to hantavirus infections. The infection of Cynomolgus macaques with a wild type Puumula virus resulted in typical signs of HFRS including lethargy, anorexia, proteinuria, hematuria, plasma cytokine increase, C-reactive protein increase and temporary acute renal failure [109].

The clinical picture of HFRS has been described since at least eighty years and occurs from Southeast Asia throughout Eurasia to North and South Europe [4,5,18,79,123]. Those diseases caused or suspected to be caused by hantavirus species are listed in Table 4 and their history is given in Table 5.

HPS was first documented in the early nineties of the last century and is characterized by acute pulmonary edema [114] associated with an exceptionally high lethality. HPS seems to be restricted to North, Central and South America in company with a great number of causative hantavirus serotypes such as Sin Nombre, Black Creek Canal, Bayou, New York, Laguna Negra, Rio Mamore, and Andes [21,25,26,31,35,50,79,84,90,114,134–140]. It is known that every hantavirus serotype is connected to a special rodent species e.g. the subfamilies *Sigmodontinae*, *Murinae*, and *Arvicolinae* which serve as natural hosts without causing an apparent disease within the persistently infected animals. Viruses can be spread incidentally to humans via aerosolized, virus-containing rodent urine, faeces, and saliva by inhalation, through broken skin, the conjunctiva and other mucous membranes, or even by bites [104]. Figure 4 shows the geographic distribution of individual specific hosts for New World hantaviruses like *Reithrodontomys megalotis* (panel A), *Peromyscus maniculatus* (panel B), *Microtus pennsylvanicus* (panel C), *Microtus californicus* (panel D), *Peromyscus leucopus* (panel E), and *Sigmodon hispidus* (panel F) which are known to be the main reservoir for the El Moro Canyon virus, the Sin Nombre virus, the Prospect Hill virus, the Isla Vista virus, the New York virus, the Black Creek Canal virus, and the Muleshoe virus, respectively. As far as the hantavirus infections in Central and South America are concerned, the geographic distribution of the individual specific rodents is illustrated in Fig. 5 including *Oryzomys palustris* (panel A), *Reitrodontomys mexicanus* (panel B), *Sigmodon alstoni* (panel C), *Oligoryzomys microtis* (panel D), *Oligoryzomys longicaudatus* (panel E), and *Calomys laucha* (panel F) which are known to be the main reservoir for Bayou virus, Rio Segundo virus, Cano Delgadito virus, Rio Mamore virus, Andes virus, and Laguna Negra virus, respectively.

Table 2. Animal species known to be infected by hantaviruses in alphabetical order

Animal species/Order	Virus	Percentage of seroprevalence/Geographical region (Ref)
Alstońs cotton rat *Sigmodon alstoni*/*Rodentia*	Cano Delgadito	?/see Table 3
Asian house shrew *Suncus murinus*/ *Insectivora*	Thottapalayam	?/see Table 3
	Hantaan	?/Suburban Shanghai (101)
Bandicoot rat *Bandicota indica*/*Rodentia*	Thailand	?/see Table 3
Bank vole *Clethrionomys glareolus*/*Rodentia*	Puumala	?/see Table 3 4.7% / Saint Petersburg (102)
Black-faced Bunting *Emberiza spodocephala*/ *Passseriformes*	Hantavirus[a]	?/former USSR (103)
Black rat *Rattus rattus*/*Rodentia*	Seoul	?/see Table 3
Brush mouse *Peromyscus boylii*/*Rodentia*	Limestone Canyon	?/California, Western Oklahoma, USA, South to Queretaro and West Hidalgo, Mexico
California vole *Microtus californicus*/*Rodentia*	Isla Vista	?/see Table 3
Cat *Felis catus*/*Carnivora*	Sin Nombre	2.9% / Southwestern Canada (104)
	Puumala	2.8% / New Mexico, North East Arizona (39) 9.6–23% / United Kingdom (105) 5% / Austria (106,107)
Cattle *Bos taurus*/*Artiodactyla, Bovidae*	Puumala	0.7% / Czech Republic (58)
	Hantaan	0.7% / Czech Republic (58)
Chacoan pygmy rice rat *Oligoryzomys chacoensis*/*Rodentia*	Bermejo	?/West Paraguay, Southeast Bolivia, Westcentral Brazil, and North Argentina
Chevrieŕs field mouse *Apodemus chevrieri*/*Rodentia*	Hantavirus[a]	?/former USSR (103)
Chipmunk *Tamias minimus*/*Rodentia*	Sin Nombre	3% / East and Central USA (108)
Coal tit *Parus ater*/*Passeriformes*	Hantavirus[a]	?/former USSR (103)
Common pheasant *Phasianus colchicus*/*Galliformes*	Hantavirus[a]	?/former USSR (103)
Common shrew *Sorex araneus*/*Insectivora*	Hantavirus[a]	1.4% / Saint Petersburg (102)
Cynomolgus macaques *Macaca fascicularis*/ *Primates*	Puumala	Experimental infection (109)
Dark Bolo mouse *Bolomys obscurus*/*Rodentia*	Maciel	?/South Uruguay and Eeastcentral Argentina
Daurian redstart *Phoenicurus auroreus*/ *Passeriformes*	Hantavirus[a]	?/former USSR (103)
Deer *Capreolus capreolus*/Artiodactyla, Cervidae	Puumala	14.1% / Czech Republic (58)
Deer mouse *Peromyscus maniculatus*/*Rodentia*	Sin Nombre	?/see Table 3 7% / East and Central USA (108)
	New York	?/see Table 3
	Monongahela	?/see Table 3
Dog *Canis lupus forma domestica*/*Carnivora*	Sin Nombre	3.5% / New Mexico, Northeast Arizona (39)
Dove *Streptopelia orientalis*/*Columbiformes*	Hantavirus[a]	?/former USSR (103)
Eurasian pygmy shrew *Sorex minutus*/*Insectivora*	Hantavirus[a]	0.4% / Saint Petersburg (102)
European hare *Lepus sapensis*/*Lagomorpha*	Hantavirus[a]	?/former USSR (103)
European Nuthatch *Sitta europaea*/*Passeriformes*	Hantavirus[a]	?/former USSR (103)
Field vole, European common vole *Microtus arvalis*/*Rodentia*	Tula	?/see Table 3
	Hantavirus[a]	0.8% / Saint Petersburg (102)
Golden hamster *Mesocricetus auratus*/*Rodentia*	Hantavirus[a]	?/former USSR (103)
Grass field mouse *Akodon azarae*/*Rodentia*	Pergamino	?/Northeast Argentina, southern Bolivia, Paraguay, Uruguay, and South Brazil
Grey heron *Ardea cinerea*/*Ciconiiformes*	Hantavirus[a]	?/former USSR (103)
Grey red-backed vole *Clethrionomys rufocanus*/*Rodentia*	Hantavirus[a]	?/former USSR (103)
Greater White-toothed shrew *Crocidurarussula*/ *Insectivora*	Hantavirus[a]	?/former USSR (103)
Hairy-tailed Bolo Mouse *Bolomys lasiurus*/ *Rodentia*	Ararquara	?/East Bolivia, Paraguay, North Argentina, and Brazil south of the Amazon River
Hare *Lepus europaeus*/*Lagomorpha*	Puumala	3.5% / Czech Republic (58)
Harvest mouse *Micromys minutus*/*Rodentia*	Hantavirus[a]	0.6% / Saint Petersburg (102)

Table 2. continued

Animal species/Order	Virus	Percentage of seroprevalence/Geographical region (Ref)
Hispid cotton rat *Sigmodon hispidus*/*Rodentia*	Black Creek Canal	?/see Table 3
	Muleshoe	?/see Table
	Sin Nombre	3% / East and Central USA (108)
House mouse *Mus musculus*/*Rodentia*	Hantavirus[a]	?/former USSR (103)
Korean field mouse *Apodemus peninsulae*/*Rodentia*	Amur	?/Southeast Siberia from Northeast China (Xinjiang) and Altai Mountains to Ussuri, south through Northeast China and Korea, and East Mongolia to Southwest China; also on North Japanese islands
	Hantavirus[a]	?/former USSR (103)
Lesser rice-field rat *Rattus losea*/*Rodentia*	Hantavirus[a]	?/former USSR (103)
Long-tailed pygmy rice rat *Oligoryzomys longicaudatus*/*Rodentia*	Andes	?/see Table 3
	Oran	10.4% / Southcentral Chile (51)
		?/see Table 3
Marsh rice rat *Orizomys palustris*/*Rodentia*	Bayou	?/see Table 3
	Sin Nombre	17% / East and Central USA (108)
Marsh Tit *Parus palustris*/*Passeriformes*	Hantavirus[a]	?/former USSR (103)
Meadow vole *Microtus pennsylavanicus*/*Rodentia*	Prospect Hill	?/see Table 3
Mexican harvest mouse *Reithrodontomys mexicanus*/*Rodentia*	Rio Segundo	?/see Table 3
Montane vole *Microtus montanus*/*Rodentia*	Sin Nombre	3% / East and Central USA (108)
Moose *Alces alces*/*Artiodactyla, Cervidae*	Puumala	1.9% / Northern Sweden (110)
Multimammate mouse *Mastomys sp.*/*Rodentia*	Hantavirus[a]	1.8% / Central Africa (Central African Republic, Gabon); West Africa (Benin, Bourkina Fasso) (94)
Muskrat *Ondatra zibethicus*/*Rodentia*	Puumala	8% / Germany (111)
Musk shrew *Suncus murinus*/*Insectivora*	Thottapalayam	?/see Table 3
Northern red-backed vole *Clethrionomys rutilus*/*Rodentia*	Hantavirus[a]	?/former USSR (103)
Norway (brown) rat *Rattus norvegicus*/*Rodentia*	Seoul	?/see Table 3
		73.4% / Hokkaido, Japan (>6 months)
		15.2% / Hokkaido, Japan (<6 months) (112)
Fulvous Pygmy Rice Rat *Oligoryzomys fulvescens*/*Rodentia*	Choclo	?/West and East versants of South Mexico, through Mesoamerica, to Ecuador, northernmost Brazil, and Guianas in South America
Pig *Sus scrofa (forma domestica)*/*Artiodactyla, Suidae*	Hantavirus[a]	?/China (113)
Prairie vole *Microtus ochrogaster*/*Rodentia*	Bloodland Lake	?/Northern and Central Great Plains: East-central Alberta to South Manitoba, Canada, south to North Oklahoma and Arkansas, Central Tennessee and West Virginia, USA; relictual populations in Colorado, New Mexico, Louisiana, and Texas, USA
Pygmy rice rat *Oligoryzomys fulvescens*/*Rodentia*	Choclo	?/West and East versants of South Mexico, through Mesoamerica, to Ecuador, North Brazil, and Guianas in South America
Rat *Rattus flavipectus*/*Rodentia*	Hantavirus[a]	?/former USSR (103)
Reed vole *Microtus fortis*/*Rodentia*	Khabarovsk	?/see Table 3
Siberian lemming *Lemmus sibiricus*/*Rodentia*	Topografov	?/see Table 3
Small-eared pygmy rice rat *Oligoryzomys microtis*/*Rodentia*	Rio Mamore	?/see Table 3
Southern red-backed vole *Clethrionomys gapperi*/*Rodentia*	Sin Nombre	3.5% / East and Central USA (108)
Striped field mouse *Apodemus agrarius*/*Rodentia*	Hantaan	?/see Table 3
	Dobrava	?/see Table 3
	Saaremaa	?/see Table 3
	Hantavirus[a]	2.2% / Saint Petersburg (102)

Table 2. continued

Animal species/Order	Virus	Percentage of seroprevalence/Geographical region (Ref)
Sugar-cane mouse *Zygodontomys brevicauda*/*Rodentia*	Calabazo	?/Savannas from SE Costa Rica through Panama, Colombia, Venezuela, and the Guianas, to Brazil north of the Amazon River; including Trinidad and Tobago and smaller continental-shelf islands adjacent Panama and Venezuela.
Ural owl *Strix uralensis*/*Strigiformes*	Hantavirus[a]	?/former USSR (103)
Vesper mouse *Calomys laucha*/*Rodentia*	Laguna Negra	?/see Table 3
Western harvest mouse *Reithrodontomys megaloti*/*Rodentia*	El Moro Canyon	?/see Table 3
	Sin Nombre	33% / East and Central USA (108)
White-footed mouse *Peromyscus leucopus*/*Rodentia*	New York	?/see Table 3
	Blue River	?/see Table 3
	Sin Nombre	2% / East and Central USA (108)
Yellow-necked field mouse *Apodemus flavicollis*/*Rodentia*	Dobrava	?/see Table 3
Yellow pygmy rice rat *Oligoryzomys flavescens*/*Rodentia*	Lechiguanas	?/Southeast Brazil, Uruguay, and Argentina (south to Chubut Prov.)
Yellow-throated bunting *Emberiza elegans*/*Passeriformes*	Hantavirus[a]	?/former USSR (103)

[a]Serotype not determined.

The general opinion that rodents are the only infection source for humans cannot be sustained anymore. This postulate is based on a number of serological studies in the last years documenting that antibodies against hantaviruses were also present in a number of non-rodent wild and domestic animals. Evidence for hantavirus infections was found in cats and dogs in the United States and western Canada [39,104]. One European study reported on the presence of hantavirus antibodies in 9.6% of healthy cats and 23% of cats with chronic diseases in the United Kingdom, a possible transmission route of viruses from rodents to cats and from cats to man [105]. A similar study in Austria demonstrated that over 5% of cats have been exposed to hantaviruses [106,107]. Tokarevich et al. [102] reported on 1.4% seropositive common shrews in Saint Petersburg. In the Czech Republic, 3.5% of hares, 14.1% of deers (*Capreolus capreolus*), and 1.4% of cattle were found to possess antibodies against hantaviruses [58]. A survey of peridomestic animals in suburban Shanghai disclosed Hantaan virus infections in the insectivore *Suncus murinus* [141]. The prementioned data underline the possibility that rodents and humans are not the only hosts for hantaviruses. There is much evidence for the assumption that we have to substantially extend our idea of the hantavirus ecology and we ought to focus our attention on determining new possible routes for hantavirus transmission and infection sources. This also includes an extensive investigation of the species and cell types that are susceptible to hantavirus infections in order to get a clear picture of the hantavirus ecology and evolution. These strategies open a new window in understanding the underlying mechanism controlling virus-host interactions and make it possible to predict infection risks for humans in the future.

Host Barrier and Range of Hantaviruses

The predominant target cells of a hantavirus infection are various endothelial cell types lining the vasculature [142]. Although HFRS and HPS are characterized by altered vascular permeability and acute thrombocytopenia infected cells do not show apparent pathological changes during infection [143]. In addition, it had been reported that delayed induction of antiviral MxA in endothelial cells after infection with HTN virus promotes viral dissemination and contributes to the pathogenesis, virulence, and manifestation of HFRS [144]. For

Table 3. Main natural reservoirs known for transmission of hantavirus species

Rodent species	Hantavirus species	Rodent Distribution[a]
Apodemus agrarius	Hantaan Dobrava	Amur River through Korea to East Xizang and East Yunnan, West Sichuan, Fujian, and Taiwan (PRC and Taiwan) Central and East Europe
Apodemus flavicollis	Dobrava	South Scandinavia through European Russia to Urals, France, South Italy, the Balkans, North-West Spain, England and Wales, Syria, Lebanon, and Israel
Bandicota indica	Thailand	Sri Lanka, peninsular India to Nepal, Burma, North-East India, South China, Laos, Thailand, Vietnam, Taiwan
Calomys laucha	Laguna Negra	West-Central Brazil, North Argentina, Uruguay, South-East Bolivia, West Paraguay
Clethrionomys glareolus	Puumala	West Palearctic from Scandinavia to Lake Baikal, France, South to North Spain, North Italy, Balkans, West Turkey, North Kazakhstan, Altai & Sayan Mountains; Britain and Southwest Ireland
Lemmus sibiricus	Topografov	Holarctic tundra landscapes: in Palearctic, from White Sea, west Russia, to Chukotski Peninsula, Northeast Siberia, and Kamchatka; including Nunivak and St. George islands in the Bering Sea; in Nearctic, from West Alaska east to Baffin Island and Hudson Bay, and south in the Rocky Mountains to Central British Columbia, Canada
Microtus arvalis	Tula	From Central and North Spain throughout Europe (including Denmark) to western margin of Black Sea in the south and northeast to Kirov region (west of the Urals) in Russia; also populations on the Orkney Islands, Guernsey (Channel Islands), and Yeu (France)
Microtus californicus	Isla Vista	Pacific coast from South-West Oregon through California, USA to North Baja California, Mexico
Microtus fortis	Khabarovsk	Transbaikalia and Amur region south through Nei Mongol and East China to lower Yangtse Valley and Fujian
Microtus pennsylvanicus	Prospect Hill	Central Alaska to Labrador, including Newfoundland and Prince Edward Island, Canada; Rocky Mountains to North New Mexico, in Great Plains to North Kansas and in Appalachians to North Georgia, USA
Oligoryzomys longicaudatus	Andes	North-Central to South Andes, to approximately 50 degrees southern latitude, of Chile and Argentina
Oligoryzomys microtis	Rio Mamore	Central Brazil south of Rios Solimoes-Amazon and contiguous low lands of Peru, Bolivia, Paraguay, and Argentina
Oryzomys palustris	Bayou	South-East Kansas to East Texas, eastward to South New Jersey and peninsular Florida
Peromyscus leucopus	New York	Central and East USA to South Alberta and South Ontario, Quebec & Nova Scotia, Canada; to North Durango and along Caribbean coast to Isthmus of Tehuantepec and Yucatan Peninsula, Mexico
Peromyscus maniculatus	Sin Nombre	Alaska Panhandle across North Mexico; Canada, south through most of continental USA, excluding South-East and East seaboard, to southernmost Baja California Sur and to North-Central Oaxaca, Mexico
Rattus norvegicus	Seoul	Worldwide
Rattus rattus	Seoul	Worldwide
Reithrodontomys megalotis	El Moro Canyon	British Columbia and South-East Alberta, Canada; West and North-Central USA, south to North Baja California & interior Mexico to Central Oaxaca
Reithrodontomys mexicanus	Rio Segundo	South Tamaulipas and West-Central Michoacan, Mexico, south through Middle American highlands to West Panama; Andes of West Colombia and North Ecuador
Sigmodon alstoni	Cano Delgadito	Savannas over Northeast Colombia, North and East Venezuela, Guyana, Surinam, and North Brazil

Table 3. continued

Rodent species	Hantavirus species	Rodent Distribution[a]
Sigmodon hispidus	Black Creek Canal	South-East USA; South Nebraska to Central Virginia, south to South-East Arizona and peninsular Florida;
	Muleshoe	interior and East Mexico through Middle America to Central Panama; in South America to North Colombia and North Venezuela
Suncus murinus	Thottapalayam	Afghanistan, Pakistan, India, Sri Lanka, Nepal, Bhutan, Burma, China, Taiwan, Japan, Indomalayan Region; introduced into Guam, the Maldive Islands, and probably many other islands; introduced into coastal Africa, Madagascar, the Comores, Mauritius, and Réunion, and into coastal Arabia

[a]For details, refer to references 45, 114–116.

human umbilical vein endothelial cells as well as human dendritic and Vero E6 cells the cellular entry of hantaviruses is known to be mediated by $\alpha_V\beta_3$-integrin [144,145], an abundant surface receptor on various endothelial cells and thrombocytes [143,146]. It is accepted that $\alpha_V\beta_3$-integrin is the entry mediator for pathogenic hantaviruses [118,119,144–146] and expression was also found on epithelium cells of pig, dog and cattle [147,148]. Furthermore, the susceptibility of bovine aortic endothelial cells to a hantavirus infection has been clearly demonstrated *in vitro* [118,119]. Taken together, this data supports the fact that other species than rodents, primates, and *Homo sapiens sapiens* have to be susceptible to hantavirus infections.

Different species of rodents were identified and considered to serve as a natural host of the pathogens causing HFRS and NE in human beings e.g. *Apodemus agrarius*, *Clethrionomys glareolus* and *Apodemus flavicollis*, which are classical vectors for the transmission of Old World hantaviruses. Attempts to find a laboratory host or cell system for the replication of a presumptive virus were initially unfruitful. More than 25 years after the initial description of KHF in 1978 Lee succeeded in propagating this virus and detecting antibodies in sera of patients [4]. LeDuc and colleagues subsequently confirmed the clinical diagnosis of KHF in 94% of 245 military patients screened during 1951–1954 [149]. Although the Vero E6 cell line still provides the best cell system for culturing, replication, and propagation of hantaviruses it is obvious that a number of other mammal cells can also be susceptible to these viruses and assist as a suitable *in vitro* and *in vivo* system for replication and progeny of hantaviruses in general.

The hantavirus outbreak in the United States of America at the beginning of the 10th decade of the last century fundamentally changed our knowledge about the occurrence of the hantavirus specific clinical picture, mortality, origin and transmission route in man. Genetic analyses revealed that the new virus is most closely related to the Prospect Hill and the Puumala virus [21,22]. HPS is found all over the United States of America, as well as in the Chaco region of Argentina and Paraguay and the Andes region. Analysis of phylogenetic relationships among hantaviruses suggests that hantaviruses have had a longstanding co-evolutionary history with their predominant rodent carriers [185,186]. Closely related hantaviruses are generally isolated from rodents that are themselves evolutionary related. Specific hantavirus strains are linked to specific rodents inducing a variety of different clinical entities.

In addition to the New World hantaviruses several new ones have been documented since 1993 including the Thottapalayam virus recovered from shrews (*Suncus murinus*) [141], a hantavirus from rats (*Bandicota indica*) in Thailand, and the Dobrava virus from mice (*Apodemus flavicollis*) in Yugoslavia [70,71]. Due to the fact that domestic animals and rodents live jointly in a similar habitat, the transmission of hantaviruses from rodents to domestic animals seems to be possible if the target organs, tissues, and cell parenchyma of the co-habitat domestic animals possess adequate virus receptors and are suitable for hantavirus entry and replication. The detection of neutralizing

Table 4. Diseases caused or suspected to be caused by hantavirus species

Hantavirus species	Disease	Acute phase symptoms[a]
Dobrava Hantaan Seoul	HFRS Lethality: 1–15%	severe hemorrhage mild azotemia very severe proteinuria mild to moderate pulmonary capillary leakage mild to severe myositis moderate to very severe conjunctival injection moderate to very severe eye pain and myopia
Puumala	HFRS (mild)NE (Nephropathia epidemica) Lethality: < 1%	mild hemorrhage mild azotemia mild to very severe proteinuria rarely reported mild pulmonary capillary leakage mild myositis mild conjunctival injection moderate to very severe eye pain and myopia
New York Muleshoe Sin Nombre	HPS HCPS Lethality: > 40%	mild hemorrhage mild azotemia mild proteinuria Cardiogenic hypotension (HCPS) very severe pulmonary capillary leakage with non-cardiogenic pulmonary edema rarely reported myositis rarely reported mild conjunctival injection rarely reported eye pain and myopia
Andes Bayou Black Creek Canal Laguna Negra Rio Mamore	HPS HCPS (renal variant) Lethality: > 40%	mild hemorrhage mild azotemia moderate to severe proteinuria severe to very severe pulmonary capillary leakage moderate to very severe myositis rare to moderate conjunctival injection rarely reported eye pain and myopia
Cano Delgadito El Moro Canyon Isla Vista Khabarovsk Prospect Hill Rio Segundo Thailand Thottapalayam Topografov Tula	none recognized	none recognized

[a]For details, refer to references 114, 124, and 125.
HFRS: Hemorrhagic fever with renal syndrome.
HPS: Hantavirus pulmonary syndrome.
HCPS: Hantavirus cardiopulmonary syndrome.

antibodies in cats, dogs, pigs, and cattle revealed a prevalence of approximately 5% of specific antibodies against various serotypes of hantaviruses [39,55,58,113].

The susceptibility of bovine aortic endothelial cells to hantaviruses [118,119] is of considerable interest, since it focuses attention on a possible transmission to ungulate animals as non-rodent hosts. This discovery opens a new window on the host range of hantaviruses that comprise more than only humans and rodent species. The identification of seroprevalences for different hanta-

Table 5. History of diseases caused and/or suspected to be caused by hantaviruses

Year	Disease	Virus/Country	Incidence/No of cases	Ref./Remarks
~960	a hemorrhagic fever associated with renal syndrome	nd[a]/China	nd[a] /nd[a]	60
1485	'The English sweating disease' (HPS?)	nd[a]/England	nd[a] /nd[a]	126 / between the ages of 15 and 45 years
1508, 1517, 1528, 1551				
1913,1932	HFRS ?	nd[a]/Russia	nd[a] /nd[a]	114 / Japanese troops
1918,1936	HPS?	nd[a]/USA,Four Corners	nd[a] /nd[a]	127
1934	hantavirus disease, nephropathia epidemica (NE)(renal involvement)	nd[a]/Sweden	nd[a] /nd[a]	13
1942	mild hemorrhagic fever-like illness	nd[a]/Stalla, Finnland	population fluctations and mass migrations of lemmings (Lemmus lemmus)/ 1000	59, 128, 129 / Finnish and German troops
1950–1953	HFRS; Korean hemorrhagic fever (KHF)	nd[a]/Korea	Korean War/ >3000	60 / American Soldiers
1977	HFRS	Puumala /Puumala, Finnland	bank vole (Clethri-onomysglareolus)	123 / Isolation of the virus from the rodent
1978	HFRS	Hantaan/Korea	rodent reservoir (Apodemus agrarius	4 / Isolation of the virus
1981	HFRS	Hantaan/?	rodent reservoir (Apodemus agrarius	130 / cell culture
early 1980s	HFRS	Seoul/Europe	laboratory outbreaks	13
1986	HFRS	Hantaan/Korea	training exercise /14	131 / U.S. Marines
1987	HRFS	Hantaan/Central African Republic	nd[a] /nd[a]	115 / First documented case in Africa
1993	hantavirus pulmonary syndrome (HPS)/	Sin Nombre/USA, Four Corners	nd[a]/55	127, 132 / Initial name: "Four Corners Disease",Retrospective analyses indicate that HPS has been present in North America since as early as 1959.
1993	hantavirus pulmonary syndrome	Brazil	deforestation job/3	34
1993	Puumala	Germany, France, Belgium, and the Netherlands		127
1994	HPS	Sin Nombre/USA, Four Corners		133

[a]nd: not documented.
Ref.: Reference.
HPS: Hantavirus pulmonary syndrome.
HFRS: Haemorrhagic fever with renal syndrome.

virus serotypes in game and domestic oxen [58] is in agreement with this approaches and strongly supports this new aspect on the ecology of these important human pathogens. One can suppose

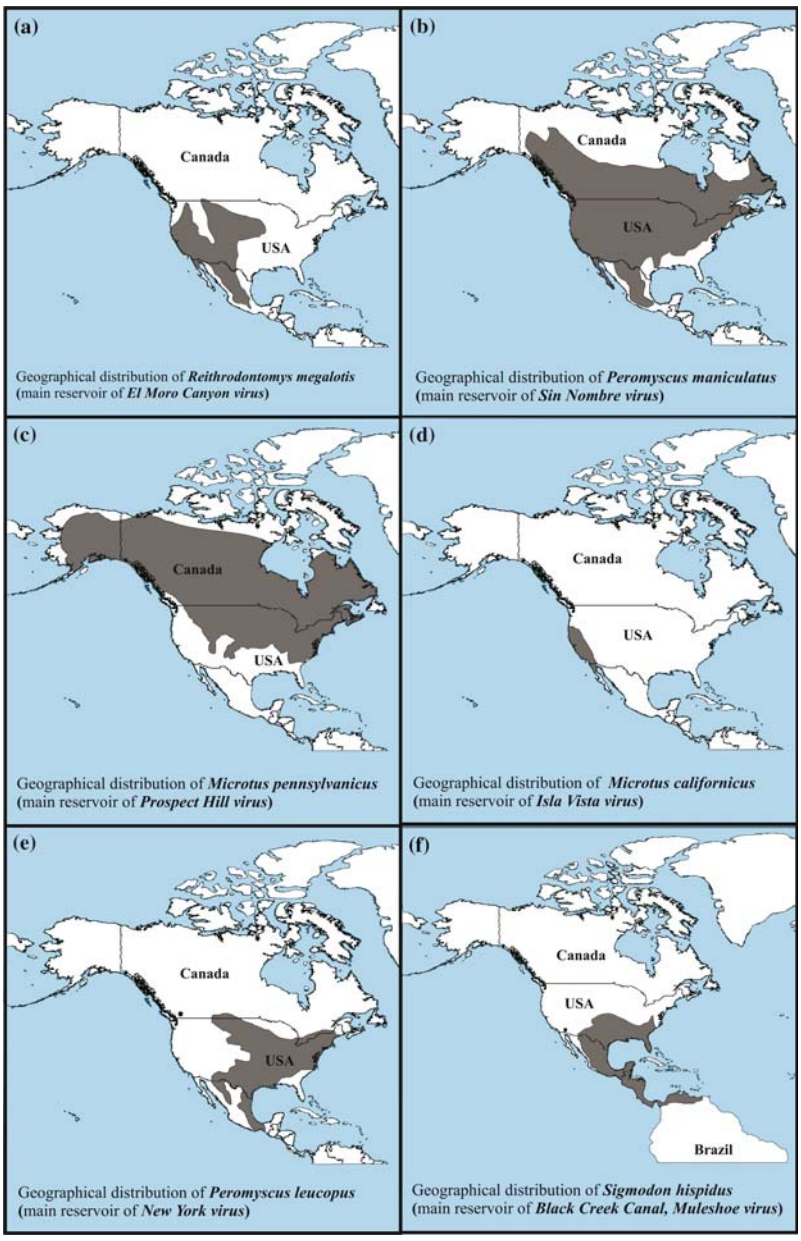

Fig. 4. Distribution of *Reithrodontomys megalotis*, *Peromyscus maniculatus*, *Microtus pennsylvanicus*, *Microtus californicus*, *Sigmodon hispidus* and *Peromyscus leucopus* in North America known to be reservoirs for New World hantavirus infections.

that the ecology of hantaviruses in domestic animals is different from that known for rodents. Advanced research on this subject should focus attention on the experimentally infection of domestic animals *in vivo*. Such studies should include the screening of domestic animals particularly in those endemic regions that are known to be platforms for the occurrence of hantavirus infections. The results of these investigations make it possible to assess the infection risk for humans that emanates from species that are until now not suspected to be a reservoir for hantaviruses.

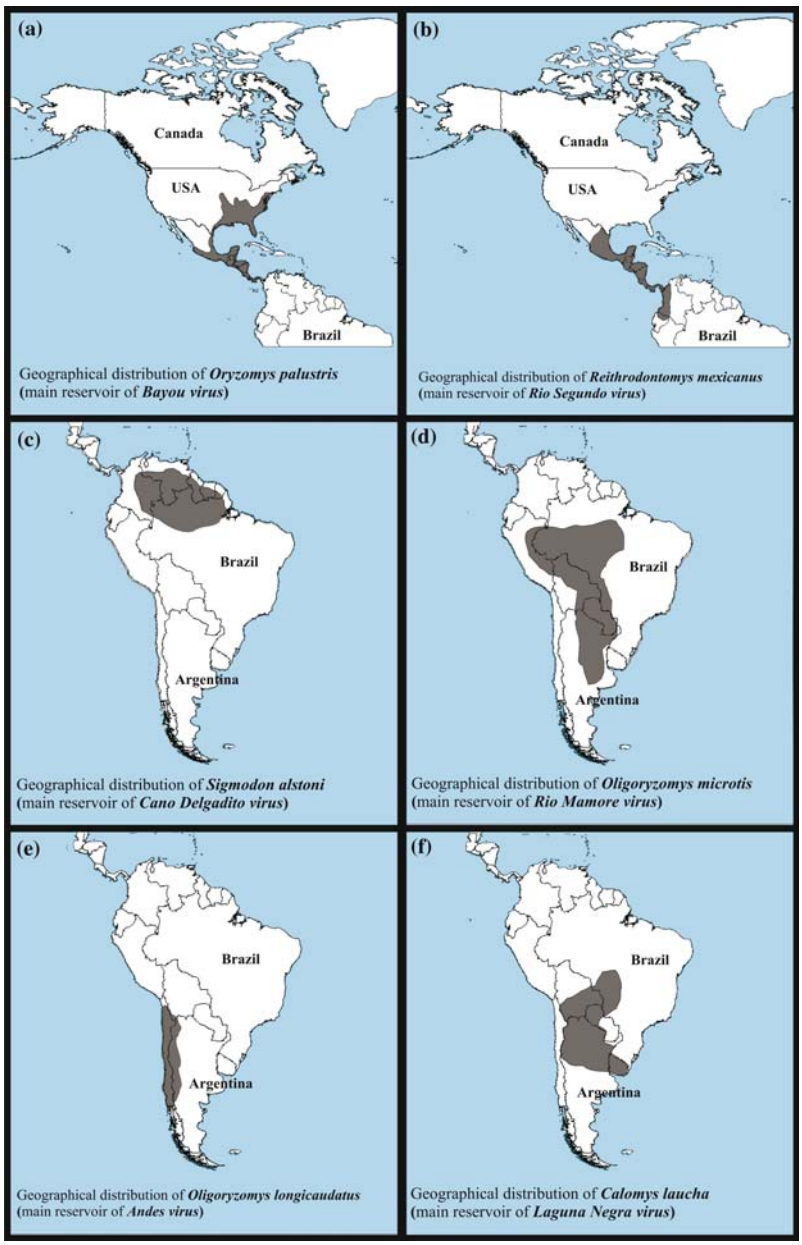

Fig. 5. Distribution of *Oryzomys palustris*, *Reithrodontomys mexicanus*, *Sigmodon alstoni*, *Oligoryzomys microtis*, *Oligoryzomys longicaudatus*, and *Calomys laucha* in Central and South America known to be reservoirs for New World hantavirus infections.

New Aspects on Reservoir, Transmission, and Distribution of Hantaviruses

The outbreak of the hantavirus infection in North America and the subsequent occurrence of HPS-like diseases in the South American continent was the first challenge after the discovery of HFRS caused by Old World hantaviruses. It should be committed that this event significantly improved our knowledge on the hantavirus reservoir, transmission, distribution, and ecology in the last decade. The recent reports on the detection of hantavirus specific antibodies in domestic animals, small mammals, and in wildlife [39,51,53,57,102] together with the

replication of hantaviruses in bovine aortic endothelial cells [118,119] are further evidence that *Rodentia*, *Insectivora*, *Lagomorpha*, and C*arnivora* cannot be considered anymore as the only reservoir and/or transmission source for hantaviruses. The detection of hantavirus antigens in the lung suspension of different bird species captured in the far east region of Russia by ELISA [151] is of particular importance in view of hantavirus transmission and ecology. The birds identified to be infected with hantaviruses belonged to the orders *Columbiformes, Passeriformes, Galliformes, Strigiformes,* and *Ciconiformes*. Although over one decade had passed the confirmation of this discovery is still open. The assessment that the hantavirus infection can be transmitted through bird species enforces the reevaluation of the interrogation concerning the hantavirus reservoirs, transmission, and ecology in more detail.

New Aspects on Geographic Distribution of Hantaviruses

The distribution and the identification of hantavirus infections on the African continent engrossed our idea on the reservoir, transmission, distribution, and ecology of these viruses that are endemic in this geographic area. The isolation and partial characterization of a new virus causing hemorrhagic fever in Zaire [152], the detection of antibodies against hantaviruses in man found in India, Iran, Central Africa, Alaska, and Bolivia by Gajdusek in 1982 [94], and supplying serological evidence for a Hantaan-related virus in Africa by Gonzalez and coworkers in 1984 [95] are earlier reports that hantaviruses are also endemic on this continent. The state of hantavirus infections in Africa was investigated by Gonzalez and co-workers in 1988 [96]. Furthermore, they reported a global prevalence of positive sera (6.15%) for the Hantaan virus in six central African countries (Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, and Gabon) [153]. In addition, the prevalence of hantavirus antibodies in human populations living in the Nile river delta of Egypt [154–156] and Djibouti [157] was reported. Nakounne and colleagues succeeded in the identification of antibodies against hantaviruses in the Central African Republic [158]. These investigators screened sera of 1762 individuals in two population groups (Pygmy and Bantu) by hantavirus specific enzyme immunoassay. They found a prevalence of IgG antibodies of 2% for the Hantaan virus [158]. No antibodies were detected against Seoul, Puumala, and Thottapalayam viruses [158] indicating that Hantaan or Dobrava-like viruses and their corresponding hosts are endemic in this area as well. Summarizing these facts a lot of effort for the prevention of the related diseases by the arrangement and by the administration of the specific public health policy has to be made.

Although the Australian continent is periodically attacked by an enormous increment of rodent population, there is still no significant and confirmed evidence for diseases caused by hantaviruses or hantavirus-like viruses. It is hard to believe that this continent is free from these human pathogens. Detailed serological and molecular epidemiological investigations are required for final clarification of the incident of hantavirus infections in Australia.

Conceptional Strategies for the Prevention of the Hantavirus Threat

The classical strategy for the prevention of diseases caused by microorganisms e.g. viruses is based on vaccination of individuals by passive, inactivated, attenuated, and subunit vaccines produced from the complete microbial organisms or its components. Although more than a quarter century has passed from the discovery of hantaviruses an effective and reliable vaccine suitable for protection of human beings against these emerging diseases is not available. Many efforts have been made to establish a hantavirus specific vaccine using passive immunization [159] and inactivated hantaviruses [160,161]. However, none of these approaches comply with the efficiency and safety conditions known for the use of vaccines in modern industrialized countries. The development of molecular biology and genetic engineering and their application for the vaccine production opened a new platform for the deployment and application of new generation vaccines. In this context extensive experimental approaches were performed for the investigation of hantavirus

specific DNA-vaccines [162–168], recombinant hantaviral glycoproteins [169–170], recombinant hantaviral nucleocapsid proteins [171–176], expression of viral nucleocapsid proteins in transgenic plants [177,178], and generation of human recombinant neutralizing antibodies against Hantaan viral glycoproteins by phage display technology [179,180]. Although all these technologies seem to be strategically rational and promising, it is still too early to predict one of these to be the frontier or a pioneer as a most suitable candidate for a new generation vaccine able to prevent a hantavirus infection in man.

In addition to this dilemma further environmental factors like genomic instability of hantaviruses, possibility of an eventual RNA intra- and/or intermolecular recombination, and shift and drift that is known for viruses with segmented RNA genomes, can lead to an alteration of virus-host interactions and generate an unexpected branch of the viral evolutionary tree. Reassortment processes between different lineages of Dobrava virus (DOBV-Af, DOBV-Aa) have been recently reported [73]. Such events can play an essential role in the hantavirus ecology inducing fundamental aftereffects e.g. changes of the genotype and phenotype of these human pathogens not only leading to unexpected incidents but also resulting in an enormous hazard to human beings and mammals in general. Therefore the establishment and existence of a control network mechanism is of immense prominence for providing the most suitable possibility for rapid detection, identification, prevention, and treatment of such emerging pathogens. This is the obligation of public health authorities throughout the world and particularly a task assignment of corresponding state organs in modern industrialized countries.

Although over half a century had passed since the first documented hantavirus outbreak during the Korean War a specific treatment and cure for hantavirus infections is still not available. A detailed discussion on the problems and impediments connected to the issue of hantavirus infection therapy and drug design and development against these infectious diseases is far from the objective of this review. However, the drug 1-ß-D-Ribafuranosyl- 1,2,4-triazol-3-carboxamid known as *Ribavirin* has shown to be effective as a viral inhibitory factor for hantaviruses [73,181,182]. As far as the effect of this drug on HPS infections is concerned several clinical trials are not yet completed. The advancement in molecular biology and pharmaceutical research in combination with new facilities for the detection of specific mechanisms determining virus-cell interactions on a molecular level are promising and can lead to the detection of a specific treatment against hantavirus infections in the near future.

Conclusions and Outlook

Hantaviruses are distributed worldwide and are assumed to share a long time period of co-evolution with specific rodent species as their natural reservoir. The degree of relatedness between virus serotypes normally coincides with the relatedness between their respective hosts [185,186]. There are no known diseases that are associated with hantavirus infections in rodents underlining the amicable relationship between virus and host which developed in years of mutual interaction. The most likely incidental infection of species other than rodents as for example humans turns hantaviruses from harmless to life-threatening pathogenic agents focusing the attention on this virus group, their ecology and evolution in order to assess their potential to represent a serious health risk for the human population [184]. It is of particular interest to understand the underlying mechanisms of pathology and evolution of hantaviruses in order to evaluate the future role of this emerging virus group on the stages of this world. A better understanding of hantavirus ecology would allow better controlling of the infection risk for humans and would probably allow predictions of future developments that mankind will be confronted with.

It is alarming that a virus that is originally harmless in its natural host turns out to be a pathological agent in another host e.g. humans with immense lethality. Up to now it seems that humans are only infected via virus-containing rodent excretions and that a person-to-person transmission normally does not take place. These facts allow for the hope that hantavirus infections would not result in worldwide catastrophic pandemics. However, in one case, the hantavirus serotype Andes, a transmission from infected to

healthy persons has been reported [41,48] uncovering the intrinsic potential of hantaviruses to probably turn out to be a more severe health risk than has been assumed so far. Another presumably underestimated source of infection for humans apart from rodents are other wild and domestic animal species. As already stated before serological evidence for susceptibility to hantavirus infections were found in many different non-rodent species. These data were corroborated by the findings concerning the susceptibility of bovine aortic endothelial cells to hantavirus infections posing the question whether other animals than rodents could represent so far unknown reservoirs for hantaviruses. In contrast to humans hantavirus-associated diseases have not been reported for animals so far. For that reason thorough and systematic screenings of wild and domestic animals for the presence of hantaviruses were not made except for rodent species. Domestic animals that live jointly in a similar habitat with rodents and humans especially those living in high endemic hantavirus regions have to be copiously screened for the presence of hantaviruses. Recent studies including the ones presented here back up the possibility of transmission of hantaviruses from rodents to other wild and domestic animals. It is of great importance to complete our picture of the hantavirus host range in order to get a reliable basis for investigations targeting the underlying mechanisms defining the species that are susceptible to hantavirus infections. Each transfer of hantaviruses from their original natural hosts to other incidental hosts is often accompanied by a change of ecology, a change of environment, and a modulation of numerous factors probably influencing the pathology of the virus. The new environment exerts a modified evolutionary pressure on the virus forcing it to adapt and probably to adopt a form that is much more dangerous for other host species compared to the original one. Even minimal changes in the primary structure of viral proteins influence the virulence of the respective hantavirus serotype without knowing the consequences that such changes would have on the relationship between hantaviruses and humans. Much more studies on the influence of non-natural hosts on the ecology of hantaviruses are needed in order to get a clear idea of the directions that the hantavirus evolution could pursue. An exhaustive knowledge about the influence of the host ecology on the ecology of viruses enables us to predict and avert future threats of emerging pathogens.

Acknowledgments

The authors are gratefully to Professor Konrad Andrassy, University of Heidelberg for his generous support. The authors thank Professor Ekkehard K.F. Bautz, University of Heidelberg and Professor Detlev Krüger, Humboldt University of Berlin for very helpful critical comments. The technical help of Gudrun Pohle is acknowledged.

References

1. Schmaljohn C.S. and Dalrymple J.M., Virology *131*, 482–491, 1983.
2. van Regenmortel M.H.V., Fauquet C.M., Bishop D.H.L., Carstens E.B., Estes M.K., Lemon S.M., Maniloff J., Mayo M.A., McGeoch D.J., Pringle C.R., and Wickner R.B., *Virus Taxonomy. Seventh Report of the International Committee on Taxonomy of Viruses*. Academic Press, San Diego, San Francisco, New York, Boston, London, Sydney, Tokyo, 2000.
3. Tidona C.A. and Darai G., *The Springer Index of Viruses*. Springer-Verlag, Berlin, Heidelberg, New York, 2002.
4. Lee H.W., Lee P.W., and Johnson K.M., J Infect Dis *137*, 298–308, 1978.
5. Lee H.W., Lee P.W., Baek L.J., and Chu Y.K., Arch Virol *1* Suppl., 5–18, 1990.
6. Myhrman G., Acta Med Scand *140*, 52–56, 1951.
7. Fjellstrom K.E., Acta Med Scand *167*, 111–120, 1960.
8. Niklasson B.S., Pediatr Nephrol *6*, 201–204, 1992.
9. Vanhille P., Binaut R., Kyndt X., Launay D., Thomas C., and Fleury D., Nephrologie *22*, 301–305, 2001.
10. Olsson G.E., Dalerum F., Hornfeldt B., Elgh F., Palo T.R., Juto P., and Ahlm C., Emerg Infect Dis *9*, 1395–1401, 2003.
11. van Yperselede Strihou C., van der Groen G., and Desmyter J., Adv Nephrol Necker Hosop *15*, 143–172, 1986.
12. Zeier M., Andrassy K., Waldherr R., and Ritz E., Dtsch Med Wochenschr *111*, 207–210, 1986.
13. Clement J., Heyman P., McKenna P., Colson P., and Avsic-Zupanc T., Emerg Infect Dis *3*, 205–211, 1997.
14. Settergren B., Rev Infect Dis *13*, 736–744, 1991.
15. Zeier M., Zoller L., Weinreich T., Padberg-Wolf E., Andrassy K., and Ritz E., Clin Nephrol *38*, 190–192, 1992.

16. Papa A., and Antoniadis A., Eur J Epidemiol *17*, 189–194, 2001.
17. Linderholm M. and Elgh F., Curr Top Microbiol Immunol *256*, 135–151, 2001.
18. Vapalahti O., Mustonen J., Lundkvist A., Henttonen H., Plyusnin A., and Vaheri A., Lancet Infect Dis *3*, 653–661, 2003.
19. Slonova R.A., Astakhova T.I., and Kompanets G.G., Zh Mikrobiol Epidemiol Immunobiol *5*, 97–101, 1997.
20. Miyamoto H., Kariwa H., Araki K., Lokugamage K., Hayasaka D., Cui B.Z., Lokugamage N., Ivanov L.I., Mizutani T., Iwasa M.A., Yoshimatsu K., Arikawa J., and Takashima I., Arch Virol *148*, 1543–1556, 2003.
21. Nichol S.T., Spiropoulou C.F., Morzunov S., Rollin P.E., Ksiazek T.G., Feldmann H., Sanchez A., Childs J., Zaki S., and Peters C.J., Science *262*, 914–917, 1993.
22. Feldmann H., Sanchez A., Morzunov S., Spiropoulou C.F., Rollin P.E., Ksiazek T.G., Peters C.J., and Nichol S.T., Virus Res *30*, 351–367, 1993.
23. Hjelle B., Chavez-Giles F., Torrez-Martinez N., Yates T., Sarisky J., Webb J., and Ascher M., J Virol *68*, 6751–6754, 1994.
24. Hjelle B., Anderson B., Torrez-Martinez N., Song W., Gannon W.L., and Yates T.L., Virology *207*, 452–459, 1995.
25. Hjelle B., Krolikowski J., Torrez-Martinez N., Chavez-Giles F., Vanner C., and Laposata E., J Med Virol *46*, 21–27, 1995.
26. Hjelle B., Lee S.W., Song W., Torrez-Martinez N., Song J.W., Yanagihara R., Gavrilovskaya I., and Mackow E.R., J Virol *69*, 8137–8141, 1995.
27. Khan A.S., Khabbaz R.F., Armstrong L.R., Holman R.C., Bauer S.P., Graber J., Strine T., Miller G., Reef S., Tappero J., Rollin P.E., Nichol S.T., Zaki S.R., Bryan R.T., Chapman L.E., Peters C.J., and Ksiazek T.G., J Infect Dis *173*, 1297–1331, 1996.
28. Chizhikov V.E., Spiropoulou C.F., Morzunov S.P., Monroe M.C., Peters C.J,. and Nichol S.T., J Virol *69*, 8132–8136, 1995.
29. Gavrilovskaya I., La Monica R., Fay M.E., Hjelle B., Schmaljohn C., Shaw R., and Mackow E.R., J Clin Microbiol *37*, 122–126, 1999.
30. Iversson L.B., da Rosa A.P., Rosa M.D., Lomar A.V., Sasaki Mda. G., and LeDuc J.W., Rev Assoc Med Bras *40*, 85–92, 1994.
31. Hjelle B., Torrez-Martinez N., and Koster F.T., Lancet *347*, 57, 1996.
32. Weissenbacher M., Cura E., Segura E.L., Hortal M., Baek L.J., Chu Y.K., and Lee H.W., Medicina *56*, 17–22, 1996.
33. Bharadwaj M., Botten J., Torrez-Martinez N., and Hjelle B., Am J Trop Med Hyg *57*, 368–374, 1997.
34. da Silva M.V., Vasconcelos M.J., Hidalgo N.T., Veiga A.P., Canzian M., Marotto P.C., and de Lima V.C., Rev Inst Med Trop Sao Paulo *39*, 231–234, 1997.
35. Johnson A.M., Bowen M.D., Ksiazek T.G., Williams R.J., Bryan R.T., Mills J.N., Peters C.J., and Nichol S.T., Virology *238*, 115–127, 1997.
36. Levis S., Morzunov S.P., Rowe J.E., Enria D., Pini N., Calderon G., Sabattini M., and St Jeor S., J Infect Dis *177*, 529–538, 1998.
37. Ferrer J.F., Jonsson C.B., Esteban E., Galligan D., Basombrio M.A., Peralta-Ramos M., Bharadwaj M., Torrez-Martinez N., Callahan J., Segovia A., and Hjelle B., Am J Trop Med Hyg *59*, 438–444, 1998.
38. Levis S., Rowe J.E., Morzunov S., Enria D.A., and St Jeor S., Lancet *349*, 998–999, 1997.
39. Malecki T.M., Jillson G.P., Thilsted J.P., Elrod J., Torres-Martinez N., and Hjelle B., J Am Vet Med Assoc *212*, 970–973, 1998.
40. Espinoza R., Vial P., Noriega L.M., Johnson A., Nichol S.T., Rollin P.E., Wells R., Zaki S., Reynolds E., and Ksiazek T.G., Emerg Infect Dis *4*, 93–95, 1998.
41. Padula P.J., Edelstein A., Miguel S.D., Lopez N.M., Rossi C.M., and Rabinovich R.D., Virology *241*, 323–330, 1998.
42. Calderon G., Pini N., Bolpe J., Levis S., Mills J., Segura E., Guthmann N., Cantoni G., Becker J., Fonollat A., Ripoll C., Bortman M., and Benedetti R., Emerg Infect Dis *5*, 792–797, 1999.
43. Johnson A.M., de Souza L.T., and Ferreira I.B., J Med Virol *59*, 527–535, 1999.
44. Vincent M.J., Quiroz E., Gracia F., Sanchez A.J., Ksiazek T.G., Kitsutani P.T., Ruedas L.A., Tinnin D.S., Caceres L., Garcia A., Rollin P.E., Mills J.N., Peters C.J., and Nichol S.T., Virology *277*, 14–19, 2000.
45. Yahnke C.J., Meserve P.L., Ksiazek T.G., and Mills J.N., Am J Trop Med Hyg *65*, 768–776, 2001.
46. Bohlman M.C., Morzunov S.P., Meissner J., Taylor M.B., Ishibashi K., Rowe J., Levis S., Enria D., and St Jeor S.C., J Virol *76*, 3765–3773, 2002.
47. Gonzalez Della Valle M., Edelstein A., Miguel S., Martinez V., Cortez J., Cacace M.L., Jurgelenas G., Estani S.S., and Padula P., Am J Trop Med Hyg *66*, 713–720, 2002.
48. Galeno H., Mora J., Villagra E., Fernandez J., Hernandez J., Mertz G.J., and Ramirez E., Emerg Infect Dis *8*, 657–661, 2002.
49. Delfraro A., Clara M., Tome L., Achaval F., Levis S., Calderon G., Enria D., Lozano M., Russi J., and Arbiza J., Emerg Infect Dis *9*, 846–852, 2003.
50. Chu Y.K., Owen R.D., Gonzalez L.M., and Jonsson C.B., Am J Trop Med Hyg *69*, 263–268, 2003.
51. Torres-Perez F., Navarrete-Droguett J., Aldunate R., Yates T.L., Mertz G.J., Vial P.A., Ferres M., Marquet P.A., and Palma R.E., Am J Trop Med Hyg *70*, 305–309, 2004.
52. Williams E.C. and Barker I.K. (eds), *Infectious Diseases of Wild Mammals*. 3rd edn, Iowa State University Press, Ames, 2001, pp. 254–270.
53. Mills J.N., Ksiazek T.G., Ellis B.A., Rollin P.E., Nichol S.T., Yates T.L., Gannon W.L., Levy C.E., Engelthaler D.M., Davis T., Tanda D.T., Frampton J.W., Nichols C.R., Peters C.J., and Childs J.E., Am J Trop Med Hyg *56*, 273–284, 1997.
54. Williams E.S., Yuill T., Artois M., Fischer J., and Haigh S.A., Rev Sci Tech *21*, 139–157, 2002.

55. Nowotny N., Weissenboeck H., Aberle S., and Hinterdorfer F., JAMA *272*, 1100–1101, 1994.
56. Stallknecht D.E., Blue J.L., Rollor E.A. III, Nettles V.F., Davidson W.R., and Pearson J.E., J Wildl Dis *27*, 238–247, 1991.
57. Pejcoch M., Danes L., Zahradkova S., and Pekna E., Cesk Epidemiol Mikrobiol Immunol *41*, 92–100, 1992.
58. Danes L., Pejcoch M., Bukovjan K., Veleba J., and Halackova M., Cesk Epidemiol Mikrobiol Immunol *41*, 15–18, 1992.
59. Vapalahti O., Lundkvist A., Fedorov V., Conroy C.J., Hirvonen S., Plyusnina A., Nemirov K., Fredga K., Cook J.A., Niemimaa J., Kaikusalo A., Henttonen H., Vaheri A., and Plyusnin A., J Virol *73*, 5586–5592, 1999.
60. McCaughey C., and Hart C.A., J Med Microbiol *49*, 587–589, 2000.
61. Xiao S.Y., Liang M., and Schmaljohn C.S., J Gen Virol *74*, 1657–1659, 1993.
62. Kariwa H., Isegawa Y., Arikawa J., Takashima I., Ueda S., Yamanishi K., and Hashimoto N., Virus Res *33*, 27–38, 1994.
63. Antic D., Lim B.U., and Kang C.Y., Virus Res *19*, 59–65, 1991.
64. Antic D., Lim B.U., and Kang C.Y., Virus Res *19*, 47–58, 1991.
65. Horling J., Chizhikov V., Lundkvist A., Jonsson M., Ivanov L., Dekonenko A., Niklasson B., Dzagurova T., Peters C.J., Tkachenko E., and Nichol S., J Gen Virol *77*, 687–694, 1996.
66. Xiao S.Y., Leduc J.W., Chu Y.K., and Schmaljohn C.S., Virology *198*, 205–217, 1994.
67. Stohwasser R., Giebel L.B., Zoller L., Bautz E.K., and Darai G., Virology *174*, 79–86, 1990.
68. Giebel L.B., Stohwasser R., Zoller L., Bautz E.K., and Darai G., Virology *172*, 498–505, 1989.
69. Stohwasser R., Raab K., Darai G., and Bautz E.K., Virology *183*, 386–391, 1991.
70. Hjelle B., and Glass G.E., J Infect Dis *181*, 1569–1573, 2000.
71. Avsic-Zupanc T., Xiao S.Y., Stojanovic R., Gligic A., van der Groen G., and LeDuc J.W., J Med Virol *38*, 132–137, 1992.
72. Scharninghausen J.J., Meyer H., Pfeffer M., and Davis D.S., Emerg Infect Dis *5*, 468–470, 1999.
73. Klempa B., Schmidt H.A., Ulrich R., Kaluz S., Labuda M., Meisel H., Hjelle B., and Krüger D.H., J Virol *77*, 804–809, 2003.
74. Sibold C., Ulrich R., Labuda M., Lundkvist A., Martens H., Schütt M., Gerke P., Leitmeyer K., Meisel H., and Krüger D.H., J Med Virol *63*, 158–167, 2001.
75. Nemirov K., Vapalahti O., Papa A., Plyusnina A., Lundkvist A., Antoniadis A., Vaheri A. and Plyusnin A., J Med Virol *69*, 408–416, 2003.
76. Nemirov K., Andersen H.K., Leirs H., Henttonen H., Vaheri A., Lundkvist A. and Plyusnin A., J Clin Virol *30*, 254–257, 2004.
77. Plyusnin A., Cheng Y., Vapalahti O., Pejcoch M., Unar J., Jelinkova Z., Lehvaslaiho H., Lundkvist A., and Vaheri A., Virus Res *39*, 237–250, 1995.
78. Vapalahti O., Lundkvist A., Kukkonen S., Cheng Y., Gilljam M., Kanerva M., Manni T., Pejcoch M., Niemimaa J., Kaikusalo A., Henttonen H., Vaheri A., and Plyusnin A, J Gen Virol *77*, 3063–3067, 1996.
79. Ravkov E.V., Rollin P.E., Ksiazek T.G., Peters C.J., and Nichol S.T., Virology *210*, 482–489, 1995.
80. Rodriguez L.L., Owens J.H., Peters C.J., and Nichol S.T., Virology *242*, 99–106, 1998.
81. Parrington M.A. and Kang C.Y., Virology *175*, 167–175, 1990.
82. Parrington M.A., Lee P.W., and Kang C.Y., J Gen Virol *72*, 1845–1854, 1991.
83. Song W., Torrez-Martinez N., Irwin W., Harrison F.J., Davis R., Ascher M., Jay M., and Hjelle B., J Gen Virol *76*, 3195–3199, 1995.
84. Morzunov S., Feldmann H., Spiropoulou C.F., Semenova V.A., Rollin P.E., Ksiazek T.G., Peters C.J., and Nichol S.T., J Virol *69*, 1980–1983, 1995.
85. Torrez-Martinez N. and Hjelle B., Lancet *346*, 780–781, 1983.
86. Torrez-Martinez N., Song W., and Hjelle B., Virology *211*, 336–338, 1995.
87. Song J.W., Baek L.J., Nagle J.W., Schlitter D., and Yanagihara R., Arch Virol *141*, 959–967, 1996.
88. Rawlings J.A., Torrez-Martinez N., Neill S.U., Moore G.M., Hicks B.N., Pichuantes S., Nguyen A., Bharadwaj M., and Hjelle B., Am J Trop Med Hyg *55*, 672–679, 1996.
89. Sanchez A.J., Abbott K.D., and Nichol S.T., Virology *286*, 345–353, 2001.
90. López N., Padula P., Rossi C., Miguel S., Edelstein A., Ramírez E., and Franze-Fernández M.T., Virus Res *50*, 77–84, 1997.
91. Meissner J.D., Rowe J.E., Borucki M.K., and St. Jeor S.C., Virus Res *89*, 131–143, 2002.
92. Fulhorst C.F., Monroe M.C., Salas R.A., Duno G., Utrera A., Ksiazek T.G., Nichol S.T., de Manzione N.M., Tovar D., and Tesh R.B., Virus Res *51*, 159–171, 1997.
93. Caramello P., Canta F., Bonino L., Moiraghi C., Navone F., Lipani F., Balbiano R., Caputo A.M., and Gai V., J Travel Med *9*, 326–329, 2002.
94. Gajdusek D.C., Scand J Infect Dis Suppl *36*, 96–108, 1982.
95. Gonzalez J.P., McCormick J.B., Baudon D., Gautun J.P., Meunier D.Y., Dournon E., and Georges A.J., Lancet *2*, 1036–1037, 1984.
96. Gonzalez J.P., Mathiot C.C., Bouquety J.C., Diemer J.M., Guerre L., Lesborder J.L., Madelon M.C., and Georges A.J., Ann Inst Pasteur Virol *139*, 301–304, 1988.
97. Gavrilovskaya I.N., Brown E.J., Ginsberg M.H., and Mackow E.R., J Virol *73*, 3951–3959, 1999.
98. Cheresh D. A., Proc Natl Acad Sci *84*, 6471–6475, 1987.
99. Hynes R.O., Cell *69*, 11–25, 1992.
100. Temonen M., Mustonen J., Helin H., Pasternack A., Vaheri A., and Holthofer H., Clin Immunol Immunopathol *78*, 47–55, 1996.
101. Xu Z.Y., Tang Y.W., Kann L.Y., and Tsai T.F., Am J Epidemiol *126*, 942–948, 1987.
102. Tokarevich N., Stoyanova N., Kozhukhova E., Makarova G., Volkova G., and Khnykin A., Epi North *2*, 1, 2001.

103. Tkachenko E.A. and Lee H.W., Kidney Int Suppl *35*, 54–61, 1991.
104. Leighton F.A., Artsob H.A., Chu M.C., and Olson J.G., Can J Public Health *92*, 67–71, 2001.
105. Bennett M., Lloyd G., Jones N., Brown A., Trees A.J., McCracken C., Smyth N.R., Gaskell C.J., and Gaskell R.M., Vet Rec *127*, 548–549, 1990.
106. Nowotny N., Lancet *343*, 921, 1994.
107. Nowotny N., Zentralbl Hyg Umweltmed *198*, 452–461, 1996.
108. Mills J.N., Johnson J.M., Ksiazek T.G., Ellis B.A., Rollin P.E., Yates T.L., Mann M.O., Johnson M.R., Campbell M.L., Miyashiro J., Patrick M., Zyzak M., Lavender D., Novak M.G., Schmidt K., Peters C.J., and Childs J.E., Am J Trop Med Hyg *58*, 525–532, 1998.
109. Klingstrom J., Plyusnin A., Vaheri A., and Lundkvist A., J Virol *76*, 444–449, 2002.
110. Ahlm C., Wallin K., Lundkvist A., Elgh F., Juto P., Merza M., and Tarnvik A., Am J Trop Med Hyg *62*, 106–111, 2000.
111. Vahlenkamp M., Muller T., Tackmann K., Loschner U., Schmitz H., and Schreiber M., Virus Res *57*, 139–150, 1998.
112. Arikawa J., Ito M., Yao J.S., Kariwa H., Takashima I., and Hashimoto N., J Vet Med Sci *56*, 27–32, 1994.
113. Zhang Y., Li X., and Tang J., Zhonghua Yu Fang Yi Xue Za Zhi *29*, 344–347, 1995.
114. Schmaljohn C., and Hjelle B., Emerg Infect Dis *3*, 95–104, 1997.
115. Center for Food Security and Public Health. Home page. <http://www.vetmed.iastate.edu/services/institutes/cfsph/default.html>. Accessed 2004 July 9.
116. NMNH Department of Systematic Biology, Division of Mammals–Mammal Species of the World Home Page. Home page. <http://www.nmnh.si.edu/msw/>. Accessed 2004 July 9.
117. Nuzum E.O., Rossi C.A., Stephenson E.H., and LeDuc J.W., Am J Trop Hyg *38*, 636–640, 1988.
118. Muranyi W., Kehm R., Bahr U., Müller S., Handermann M., Darai G., and Zeier M., Virology *318*, 112–122, 2004.
119. Bahr U., Muranyi W., Müller S., Kehm R., Handermann M., Darai G., and Zeier M., Virology *321*, 1–7, 2004.
120. Ruo S.L., Li Y.L., Tong Z., Ma Q.R., Liu Z.L., Tang Y.W., Ye K.L., McCormick J.B., Fisher-Hoch S.P., and Xu Z.Y., J Infect Dis *170*, 527–534, 1994.
121. Klingstrom J., Heyman P., Escutenaire S., Sjolander K.B., De Jeagere F., Henttonen H., and Lundkvist A., J Med Virol *68*, 581–588, 2002.
122. Lednicky J.A., Arch Pathol Lab Med *127*, 30–35, 2003.
123. Brummer-Korvenkontio M., Vaheri A., Hovi T., von Bonsdorff C.-H., Vuorimies J., Manni T., Penttinen K., Oker-Blom N., and Lähdevirta J., J Infect Dis *141*, 131–134, 1980.
124. Klempa B., Meisel H., Rath S., Bartel J., Ulrich R., and Kruger D.H., J. Clin. Microbiol *41* 4894–4897, 2003.
125. Hjelle B., Emerging Viruses Research Center. Home page. <http://hsc.unm.edu/pathology/HjelleLab/>. Accessed 2004 July 9.
126. Bridson E., Br J Biomed Sci *58*, 1–6, 2001.
127. Harper T.K. Hantavirus: Description, Vector, Mechanisms, Symptoms, etc. Website. <http://www.tarakharper.com/v_hanta.htm>. Accessed 2004 July 9.
128. Hentonnen H., and Kaikusalo A., in Stenseth N.C., and Inns R.A. (eds), *The Biology of Lemmings*, AcademicPress Inc., New York (NY), 1993, pp. 157–186.
129. Stuhlfault K., Dtsch Med Wochenschr *69*, 439–443, 474–477, 1943.
130. French G.R., Foulke R.S., Brand O.A., Eddy G.A., Lee H.W., and Lee P.W., Science *211*, 1046–1048, 1981.
131. Pon E., McKee K.T. Jr., Diniega B.M., Merrell B., Corwin A., and Ksiazek T.G., Am J Trop Med Hyg *42*, 612–619, 1990.
132. Hawes S., and Seabolt J.P., Clin Lab Sci *16*, 39–42, 2003.
133. Elliott L.H., Ksiazek T.G., Rollin P.E., Spiropoulou C.F., Morzunov S., Monroe M., Goldsmith C.S., Humphrey C.D., Zaki S.R., and Krebs J.W. Am J Trop Med Hyg *51*, 102–108, 1994.
134. Williams R.J., Bryan R.T., Mills J.N., Palma R.E., Vera I., De Velasquez F., Baez E., Schmidt W.E., Figueroa R.E., Peters C.J., Zaki S.R., Khan A.S., and Ksiazek T.G., Am J Trop Med Hyg *57*, 274–282, 1997.
135. Toro J., Vega J.D., Khan A.S., Mills J.N., Padula P., Terry W., Yadon Z., Valderrama R., Ellis B.A., Pavletic C., Cerda R., Zaki S., Shieh W.J., Meyer R., Tapia M., Mansilla C., Baro M., Vergara J.A., Concha M., Calderon G., Enria D., Peters C.J., and Ksiazek T.G., Emerg Infect Dis *4*, 687–694, 1997.
136. Mills J.N., and Childs J.E., in Williams E.C. and Barker I.K. (eds), *Infectious Diseases of Wild Mammals*, 3rd edn. Iowa State University Press, Ames, 2001, pp. 254–270.
137. Padula P.J., Sanchez A.J., Edelstein A., and Nichol S.T., J Gen Virol *83*, 2117–2122, 2002.
138. Suarez O.V., Cueto G.R., Cavia R., Gomez Villafane I.E., Bilenca D.N., Edelstein A., Martinez P., Miguel S., Bellomo C., Hodara K., Padula P.J., and Busch M., Mem Inst Oswaldo Cruz *98*, 727–732, 2003.
139. Pini N., Levis S., Calderon G., Ramirez J., Bravo D., Lozano E., Ripoll C., St Jeor S., Ksiazek T.G., Barquez R.M., and Enria D., Emerg Infect Dis *9*, 1070–1076, 2003.
140. Ferrer J.F., Galligan D., Esteban E., Rey V., Murua A., Gutierrez S., Gonzalez L., Thakuri M., Feldman L., Poiesz B., and Jonsson C., Ann Trop Med Parasitol *97*, 269–280, 2003.
141. Tang Y.W., Xu Z.Y., Zhu Z.Y., and Tsai T.F., Lancet *1*, 513–514, 1985.
142. Pensiero M.N., Sharefkin J.B., and Hay J., J Virol *66*, 5929–5936, 1992.
143. Davidovich I.M., Ter Arkh *62*, 68–71, 1990.
144. Kraus A.A., Raftery, M.J., Giese T., Ulrich R., Zawatzky R., Hippenstiel S., Suttorp N., Krüger D.H., and Schönrich G., J Virol *78*, 6143–6150, 2004.
145. Mackow E.R., and Gavrilovskaya I.N., Curr Top Microbiol Immunol *256*, 91–115, 2001.
146. Raftery M.J., Kraus A.A., Ulrich R., Krüger D.H., and Schönrich G., J Virol *76*, 10724–10733, 2002.
147. Mackow E.R., Ginsberg M.H., and Gavrilovskaya I.N., in Saluzzo J.F., and Dodet B. (eds), *Factors in the Emergence and Control of Rodent-borne Viral Diseases*

(Hantaviral and Renal disease). Elsevier, Paris, 1999, pp. 113–123.
148. Singh B., Rawlings N., and Kaur A., Histol Histopathol *16*, 1037–1046, 2001.
149. LeDuc J.W., Ksiazek T.G., Rossi C.A., and Dalrymple J.M., J Infect Dis *162*, 1182–1184, 1990.
150. Avsic-Zupanc T., Toney A., Anderson K., Chu Y.K., and Schmaljohn C., J Gen Virol *76*, 2801–2808, 1995.
151. Slonova R.A., Tkachenko E.A., Kushnarev E.L., Dzagurova T.K., and Astakova T.I., Acta Virol *36*, 493, 1992.
152. Johnson K.M., Lange J.V., Webb P.A., and Murphy F.A., Lancet *1*, 569–571, 1977.
153. Gonzalez J.P., Josse R., Johnson E.D., Merlin M., Georges A.J. Abandja J., Danyod M., Delaporte E., Dupont A., and Ghogomu A, Res Virol *140*, 319–331, 1989.
154. Corwin A., Habib M., Olson J., Scott D., Ksiazek T., and Watts D.M., Trans R Soc Trop Med Hyg *86*, 677–679, 1992.
155. Botros B.A., Sobh M., Wierzba T., Arthur R.R., Mohareb E.W., Frenck R., El Refaie A., Mahmoud I., Chapman G.D., and Graham R.R., Trans R Soc Trop Hyg *98*, 331–336, 2004.
156. Corwin A., Habib M., Watts D., Darwish M., Olson J., Botros B., Hibbs R., Kleinosky M., Lee H.W., Shope R., and Kilpatrick M., Am J Trop Med Hyg *48*, 776–783, 1993.
157. Rodier G., Soliman A.K., Bouloumie J., and Kremer D., Trans R Soc Trop Med Hyg 87, 160–161, 1993.
158. Nakounne E., Selekon B., and Morvan J., Bull Soc Pathol Exot *93*, 340–347, 2000.
159. Xu Z., Wei L., Wang H., and Jiang S., Biochem Biophys Res commun *298*, 552–558, 2002.
160. Cho H.W., Howard C.R., and Lee H.W., Intervirology *45*, 328–333, 2002.
161. Choi Y., Ahn C.J., Seong K.M., Jung M.Y., and Ahn B.Y., Vaccine *21*, 1867–1873, 2003.
162. Bharadwaj M., Lyons C.R., Wortman I.A., and Hjelle B., Vaccine *17*, 2836–2843, 1999.
163. Kamrud K.I., Hooper J.W., Elgh F., and Schmaljohn C.S., Virology *263*, 209–219, 1999.
164. Koletzki D., Schirmbeck R., Lundkvist A., Meisel H., Kruger D.H., and Ulrich R., J Biotechnol *84*, 73–78, 2001.
165. Hooper J.W., Custer D.M., Thompson E., and Schmaljohn C.S., J Virol *75*, 8469–8477, 2001.
166. Johansson P., Lindgren T., Lundstrom M., Holmstrom A., Elgh F., and Bucht G., Vaccine *20*, 3379–3388, 2002.
167. Bharadwaj M., Mirowsky K., Ye C., Botten J., Masten B., Yee J., Lyons C.R., and Hjelle B., J Gen Virol *83*, 1745–1751, 2002.
168. Custer D.M., Thompson E., Schmaljohn C.S., Ksiazek T.G., and Hooper J.W., J Virol *77*, 9894–9905, 2003.
169. Schmaljohn C.S., Chu Y.K., Schmaljohn A.L., and Dalrymple J.M., J Virol *64*, 3162–3170, 1990.
170. Schmaljohn C.S., Hasty S.E., and Dalrymple J.M., Vaccine *10*, 10–13, 1992.
171. Lundkvist A., Kalli-Kokko H., Sjolander K.B., Lankinen H., Niklasson B., Vaheri A., and Vapalahti O., Virology *216*, 397–406, 1996.
172. Ulrich R., Lundkvist A., Meisel H., Koletzki D., Brus K., Sjölander H.R., Gelderblom H.R., Borisova G., Schnitzler P., Darai G., and Krüger D.H., Vaccine *16*, 272–280, 1998.
173. Welzel T.M., Kehm R., Tidona C.A., Muranyi W., and Darai G., Virus Genes *17*, 185–198, 1998.
174. De Carvalho Nicacio C., Gonzalez Della Valle M., Padula P., Bjorling E., Plyusnin A., and Lundkvist A., J Virol *76*, 6669–6677, 2002.
175. Zanskiene A., Schmidt J., Geldmacher A., Ritzi A., Niedrig M., Lundkvist A., Kruger D.H., Meisel H., Sasnauskas K., and Ulrich R., J Biotechnol *111*, 319–333, 2004.
176. Gedvilaite A., Zvirbliene A., Staniulis J., Sasnauskas K., Kruger D.H., and Ulrich R., Viral Immunol *17*, 51–68, 2004.
177. Kehm R., Jakob N.J., Welzel T.M., Tobiasch E., Viczian O., Jock S., Geider K., Sule S., and Darai G., Virus Genes *22*, 73–83, 2001.
178. Khattak S., Darai G., and Rösen-Wolff A., Virus Genes *29*, 109–116, 2004.
179. Koch J., Liang M., Queitsch I., Kraus A.A., and Bautz E.K., Virology *308*, 64–73, 2003.
180. Liang M., Mahler M., Koch J., Ji Y., Li D., Schmaljohn C., and Bautz E.K., J Med Virol *69*, 99–107, 2003.
181. Huggins J.W., Kim G.R., Brand O.M., and McKee K.T. Jr., J Infect Dis *153*, 489–497, 1986.
182. Severson W.E., Schmaljohn C.S., Javadian A., and Jonsson C.B., J Virol *77*, 481–488, 2003.
183. Gubler D.J., Reiter P., Ebi K.L., Yap W., Nasci R., and Path J.A., Environ Health Perspect *109*, 223–233, 2001.
184. Mustonen J., Partanen J., Kanerva M., Pietilä K., Vapalahti O., Pasternack A., and Vaheri A., Kidney Int *49*, 217–221, 1996.
185. Plyusnin A., Vapalahti O., and Vaheri A., J Gen Virol *77*, 2677–2687, 1996.
186. Zhao X. and Hay J., Immunol Invest *26*, 191–197, 1997.
187. Coulaud X., Chouaib E., Georges A.J., Rollin P., and Gonzales J.P., Trans R Soc Trop Med Hyg *81*, 686, 1987.