CLINICAL MICROBIOLOGY REVIEWS, Apr. 2010, p. 412–441 Vol. 23, No. 2
0893-8512/10/$12.00 doi:10.1128/CMR.00062-09

A Global Perspective on Hantavirus Ecology, Epidemiology, and Disease

Colleen B. Jonsson,[1,2]* Luiz Tadeu Moraes Figueiredo,[3] and Olli Vapalahti[4]

Department of Microbiology and Immunology,[1] and the Center for Predictive Medicine for Biodefense and Emerging Infectious Diseases,[2] University of Louisville, Louisville, Kentucky; Virology Research Center, School of Medicine of the University of São Paulo, Ribeirão Preto City, São Paulo, Brazil[3]; and Department of Virology, Haartman Institute, and Department of Basic Veterinary Sciences, University of Helsinki, HUSLAB, Helsinki, Finland[4]

INTRODUCTION

In the past century, two major outbreaks of disease led to the discovery of hantaviruses in the Old and New Worlds. The first outbreak occurred during the Korean War (1950 to 1953), wherein more than 3,000 United Nations troops fell ill with Korean hemorrhagic fever, which is commonly referred to as hemorrhagic fever with renal syndrome (HFRS). The second outbreak of disease occurred in the Four Corners region of the United States in 1993 and was initially referred to as Four Corners disease, which is now called hantavirus pulmonary syndrome (HPS) or hantavirus cardiopulmonary syndrome (HCPS). These viruses can cause serious diseases in humans and have reached mortality rates of 12% (HFRS) and 60% (HPS) in some outbreaks. In 1978, nearly 25 years after the recognition of HFRS, the etiological agent for this disease, Hantaan virus (HTNV), and its reservoir, the striped field mouse (*Apodemus agrarius*), were reported by Lee et al. (239). This landmark study launched the recognition of additional HFRS-related viruses in Asia, Europe, and the United States (Table 1). Surveillance efforts showed the presence of HTNV and HTNV-like viruses in *Apodemus agrarius* and *A. peninsulae* rodents in Far East Russia, China, and South Korea and a distinct virus, Dobrava virus (DOBV), and Dobrava-like viruses harbored by *Apodemus flavicollis*, *A. agrarius*, and *A. ponticus* in Europe (18, 21, 125, 173, 211–213, 324). In the 1980s, it was discovered that urban cases of HFRS were caused by the rat-borne Seoul virus (SEOV) in Asia (57, 203), and in Europe, nephropathia epidemica (NE), which is a milder form of HFRS described in the 1930s (304, 465), was discovered to be caused by another hantavirus, Puumala virus (PUUV), harbored by the bank vole, *Myodes glareolus* (previously known as *Clethrionomys glareolus*) (76). The discovery of these hantaviruses has led to the appreciation that worldwide, there may be as many as 150,000 cases of HFRS each year, with more than half occurring in China (231, 403).

In contrast to these early pioneering efforts that led to the discovery of HTNV, the etiological agent of HPS, Sin Nombre virus (SNV) was identified within weeks of the Four Corners outbreak (148, 308). Technological advancements in molecular biology contributed largely to the ability of investigators to rapidly isolate and characterize this newly discovered virus. However, it was the weak cross-reactivity of human sera with the antigen from an Old World hantavirus that provided the first clue to the possible causative agent of HPS. Since the Four Corners outbreak, more than 2,000 cases of HPS have oc-

* Corresponding author. Mailing address: Center for Predictive Medicine for Biodefense and Emerging Infectious Diseases, University of Louisville, 950 N. Hurstbourne Parkway, Louisville, KY 40222. Phone: (502) 852-1339. Fax: (502) 852-5468. E-mail: cbjons01@louisville.edu.

TABLE 1. Geographic distribution of and disease associated with Old World and New World strains of hantavirus

Group and subfamily	Virus isolate or strain	Abbreviation[a]	Geographic distribution	Rodent host	Associated disease
Old World					
Murinae	Hantaan virus	HTNV	China, South Korea, Russia	*Apodemus agrarius*	HFRS
	Dobrava-Belgrade virus	DOBV	Balkans	*Apodemus flavicollis*	HFRS
	Seoul virus	SEOV	Worldwide	*Rattus*	HFRS
	Saaremaa virus	SAAV	Europe	*Apodemus agrarius*	HFRS
	Amur virus	AMRV	Far East Russia	*Apodemus peninsulae*	HFRS
	Soochong virus	—	South Korea	*Apodemus peninsulae*	Unknown
Arvicolinae	Puumala virus	PUUV	Europe, Asia, and Americas	*Clethrionomys glareolus*	HFRS/NE
	Khabarovsk virus	KHAV	Far East Russia	*Microtus fortis*	Unknown
	Muju virus	MUJV	South Korea	*Myodes regulus*	Unknown
	Prospect Hill virus	PHV	Maryland	*Microtus pennsylvanicus*	Unknown
	Tula virus	TULV	Russia/Europe	*Microtus arvalis*	Unknown
	Isla Vista virus	ISLAV	North America	*Microtus californicus*	Unknown
	Topografov virus	TOPV	Siberia	*Lemmus sibericus*	Unknown
New World					
Sigmodontinae	Sin Nombre virus	SNV	North America	*Peromyscus maniculatus*	HPS
	Monongahela virus	MGLV	North America	*Peromyscus leucopus*	HPS
	New York virus	NYV	North America	*Peromyscus leucopus*	HPS
	Black Creek Canal virus	BCCV	North America	*Sigmodon hispidus*	HPS
	Bayou virus	BAYV	North America	*Oryzomys palustris*	HPS
	Limestone Canyon virus	—	North America	*Peromyscus boylii*	Unknown
	Playa de Oro virus	—	Mexico	*Oryzomys couesi*	Unknown
	Catacamas virus	—	Honduras	*Oryzomys couesi*	Unknown
	Choclo virus	—	Panama	*Oligoryzomys fulvescens*	HPS
	Calabazo virus	—	Panama	*Zygodontomys brevicauda*	Unknown
	Rio Segundo virus	RIOSV	Cost Rica	*Reithrodontomys mexicanus*	Unknown
	Cano Delgadito virus	CADV	Venezuela	*Sigmodon alstoni*	Unknown
	Andes virus	ANDV	Argentina, Chile	*Oligoryzomys longicaudatus*	HPS
	Bermejo virus	BMJV	Argentina	*Oligoryzomys chocoensis*	HPS
	Pergamino virus	PRGV	Argentina	*Akodon azarae*	Unknown
	Lechiguanas virus	LECV	Argentina	*Oligoryzomys flavescens*	HPS
	Maciel virus	MCLV	Argentina	*Bolomys obscurus*	HPS
	Oran virus	ORNV	Argentina	*Oligoryzomys longicaudatus*	HPS
	Laguna Negra virus	LANV	Paraguay, Bolivia, Argentina	*Calomys laucha*	HPS
	Alto Paraguay virus	—	Paraguayan Chaco	*Holochilus chacoensis*	Unknown
	Ape Aime virus	—	Eastern Paraguay	*Akodon montensis*	Unknown
	Itapúa virus	—	Eastern Paraguay	*Oligoryzomys nigripes*	Unknown
	Rio Mamore virus	—	Bolivia, Peru	*Oligoryzomys microtis*	Unknown
	Araraquara virus	—	Brazil	*Bolomys lasiurus*	HPS
	Juquitiba virus	—	Brazil	*Oligoryzomys nigripes*	HPS
	Jaborá virus	—	Brazil, Paraguay	*Akodon montensis*	

[a] —, an abbreviation has not yet been designated by the ICTVdb Index of Viruses.

curred in sporadic clusters throughout the Americas and have led to the discovery of many different strains of these viruses and their rodent reservoirs (26, 28, 37, 70, 107, 110, 151, 179, 180, 441, 450).

At present, over 21 hantaviruses that cause illness in humans ranging from proteinuria to pulmonary edema and frank hemorrhage illnesses when transmitted from their rodent reservoirs to humans have been identified across the globe (Table 1). Additional hantaviruses may remain undiscovered, since in many countries, hantaviral infections are likely to go undetected and not reported, especially in Africa, the Middle East, and the Indian subcontinent. This is especially evident with the recent discovery of shrew-borne hantaviruses around the globe (192). Until these seminal discoveries, Thottapalayam virus (TPMV), a long-unclassified virus isolated from the Asian house shrew (*Suncus murinus*), was the only known shrew-borne hantavirus (406). Clearly, these and other hantaviruses deserve the attention of research scientists and public health officials with respect to their impact on public health and the quest for treatments and to promote public awareness of those hantaviruses that cause illness in humans (383). Here, we present a review of these fascinating viruses, with our major focus being on the ecology of and disease caused by these serious human pathogens. Finally, in our future prospects, we address new approaches to the study of hantaviruses that seek to integrate the ecology and evolution of these and other host-virus ecosystems through modeling. First, however, we introduce the basic biology of the virus.

HANTAVIRUS LIFE CYCLE

The genus *Hantavirus* resides in the family *Bunyaviridae*, a large family of over 300 viruses that infect animals, plants, humans, and arthropods (36, 100, 388). In general, hantavi-

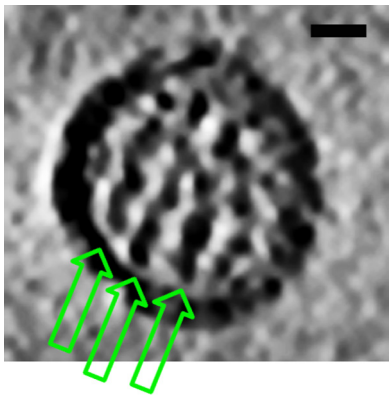

FIG. 1. Tomography of an HTNV virion particle. Shown is a near-tangential section through a tomographic reconstruction of a virion. A set of parallel rod-like densities (indicated by green arrows) can be seen beneath the membrane. Anisotropy is in the direction perpendicular to the page. The section is 5.1 nm thick, and the scale bar represents 25 nm. The tomogram was denoised by using nonlinear anisotropic diffusion as implemented in BSOFT (142a). (Photograph courtesy of Anthony J. Battisti and Paul R. Chipman, Purdue University; reproduced with permission.)

ruses are commonly referred to as Old World and New World hantaviruses due to the geographic distribution of their rodent reservoirs and the type of illness (HFRS or HPS) that manifests upon transmission to humans (382). Despite the differences in geographic locations and illnesses, the Old World and New World hantaviruses share high homology in the organizations of their nucleic sequences and exhibit similar aspects of their life cycles.

Genome Organization and Virion Structure

The first molecular analyses of HTNV showed that the genome comprises three negative-sense, single-stranded RNAs that share a 3′ terminal sequence of the three genome segments (385). The three segments, S (small), M (medium), and L (large), encode the nucleoprotein (N), envelope glycoproteins (Gn, formerly G1, and Gc, formerly G2), and the L protein or viral RNA (vRNA)-dependent RNA polymerase (RdRp), respectively (389). The total size of the RNA genome ranges from 11,845 nucleotides (nt) for HTNV to 12,317 nt for SNV. The treatment of HTNV with nonionic detergents releases three ribonucleoproteins (RNPs) that sediment to densities of 1.18 and 1.25 g/cm^3 in sucrose and CsCl, respectively, by using rate-zonal centrifugation methods (387). The RNP structures within the virion each consist of one viral RNA segment complexed with the N protein (82, 311). It is widely held for all of the viruses in the family *Bunyaviridae* that each genomic RNA forms a circular molecule that forms by base pairing between inverted complementary sequences at the 3′ and 5′ ends of linear viral RNA (140). The RNP complexes may contribute to the virion's internal filamentous appearance (86). The tomographic reconstruction of an HTNV virion shows a set of parallel rod-like densities (Fig. 1) that can be seen beneath the membrane, which presumably represent the three RNPs (A. J. Battisti and P. R. Chipman, Purdue University, unpublished data). Hantaviruses of the HTNV/SEOV lineage do not have a nonstructural (NSs) protein, which occurs in other genera within the *Bunyaviridae* (389). However, the New World hantaviruses and vole-borne PUUV-Tula virus (TULV) branch of hantaviruses contain an evolutionarily conserved NSs open reading frame (ORF) in an overlapping reading frame similar to that of the orthobunyaviruses. The expression of this ORF in PUUV-infected cells has been demonstrated and was suggested to influence the interferon response (171, 172). Hantaviruses lack a matrix protein, and therefore, the N protein may provide this function to facilitate physical interactions with the glycoprotein projections on the inner leaf of the lipid membrane and the RNPs.

Hantavirus virions are generally spherical in nature, with an average diameter of approximately 80 to 120 nm (168, 236, 268, 271, 390, 449). Ultrastructural studies of HTNV suggest that the virion has a surface structure composed of a grid-like pattern distinct from that of other genera of the family *Bunyaviridae* (168, 268, 449). The grid-like pattern of the outer surface reflects the glycoprotein projections, which extend ~12 nm from the lipid bilayer. Biochemical studies confirmed that these projections are composed of heterodimers of Gn and Gc (11).

Replication of Hantaviruses

Hantaviruses infect endothelial, epithelial, macrophage, follicular dendritic, and lymphocyte cells via the attachment of the viral glycoprotein to the host's cell surface receptor(s) (262, 266, 353, 409, 461), as illustrated in Fig. 2. Several studies suggested that the receptors that interact with the larger viral glycoprotein (Gn) for entry are integrins: β1 integrin for *Microtus*-borne hantaviruses considered to be apathogenic and β3 integrin for pathogenic hantaviruses causing HFRS and HPS (116, 118, 227). However, these may not be the sole receptors, since cells without β3 integrin proteins permit infection (299, 407). The pretreatment of cells with antibodies to decay-accelerating factor (DAF)/CD55 blocks infection by Old World hantaviruses, suggesting that DAF is a critical cofactor for infection (221). DAF is a glycosylphosphatidylinositol (GPI)-anchored protein of the complement regulatory system. Hantaviruses can enter polarized target cells from the apical and basolateral membrane surfaces (359, 370). HTNV enters via clathrin-coated pits, followed by movement to early endosomes and subsequent delivery to late endosomes or lysosomes (178). Within the endolysosomal compartments, the virus is uncoated to liberate the three RNPs into the cytoplasm. Viral RdRp initiates primary transcription to give rise to the S, M, and L mRNAs. The translation of the S and L mRNA transcripts occurs on free ribosomes, and the M-segment transcript occurs on membrane-bound ribosomes, which is cotranslated on rough endoplasmic reticulum (ER) (RER). For hantaviruses, the N protein is the most abundant viral protein and is synthesized early in infection (388). N plays key roles in several important steps in the virus life cycle, including translation, trafficking, and assembly (31, 182, 291, 323, 354, 355, 397, 398). Furthermore, recent evidence suggests that the N protein interacts with and can modulate the host immune response to infection (419, 420). The glycoprotein precursor is proteolytically processed into Gn and Gc during import into the ER (374, 409). For most hantaviruses, a conserved amino acid motif, WAASA, located at the end of Gn is presumed to be the proteolytic cleavage site (254). The Gn and Gc proteins

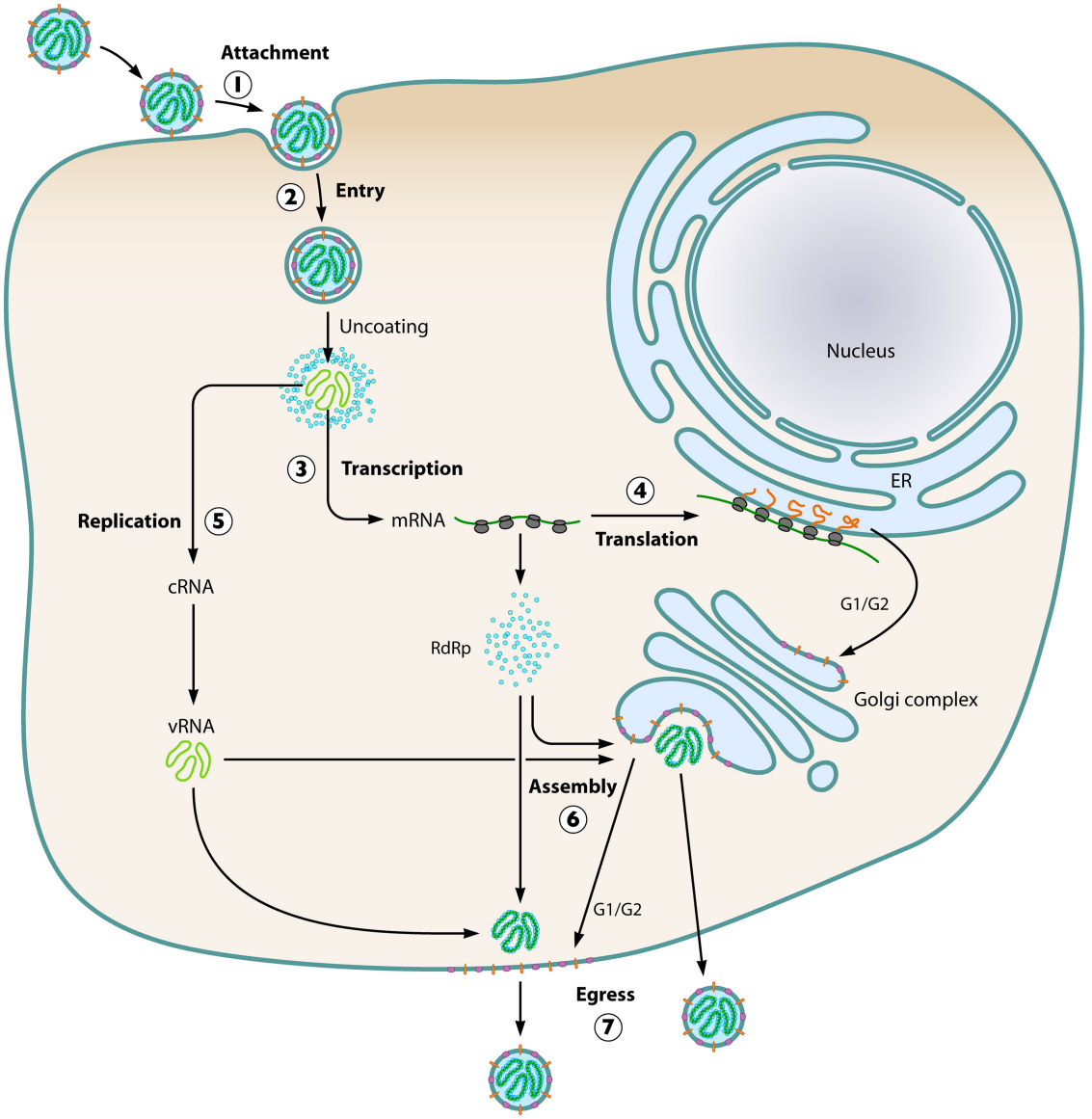

FIG. 2. The hantavirus life cycle. The basic steps include the attachment of the virion particle to the cell's surface through interactions between the host's cell surface receptors and the viral glycoprotein (1); entry through the use of receptor-mediated endocytosis and the uncoating and release of the viral genomes immediately thereafter (2); transcription of complementary RNA (cRNA) from the viral RNA (vRNA) genome using host-derived primers (3); translation of L, M, and S mRNAs into viral proteins using host machinery (4); replication and amplification of vRNA, assembly with the N protein, and transport to the Golgi apparatus (5); assembly of all components at the Golgi apparatus or, possibly for New World viruses, at the plasma membrane (alternative assembly) (6); and viral egress via the fusion of the Golgi vesicle harboring the mature virion particles with the plasma membrane (7).

are glycosylated in the ER and subsequently transported to the Golgi complex (11, 360, 374, 382, 434).

Soon after the initial burst of transcription, the viral polymerase switches from transcription to the replication of the S, M, and L genomic RNAs (Fig. 2). The newly synthesized vRNAs are encapsidated by the N protein to form the RNPs (388). The HTNV N protein traffics via microtubule dynein to the ER-Golgi-intermediate compartment (ERGIC) but not the ER, Golgi complex, or endosomes in HTNV-infected Vero E6 cells (354). Viral proteins and virion particles of other members of the *Bunyaviridae*, such as Uukuniemi virus (UUKV) (111, 175, 223) and Bunyamwera virus (375), accumulate at the Golgi complex. The UUKV N protein associates with *cis*-Golgi elements and accumulates in peripheral elements that could also include the ERGIC (175). This suggests that the ERGIC and the Golgi complex may be important for some aspects of virus assembly. Fascinating questions remain as to where or how the assembly of the RNPs takes place, whether the RdRp is part of the RNP complex, how the RNPs traffic to the Golgi complex, and the mechanisms that drive budding into and out of the Golgi complex to produce the infectious virion. It was suggested that New World hantaviruses may assemble and mature at the plasma membrane (358). This is illustrated in Fig. 2; however, at present, there is

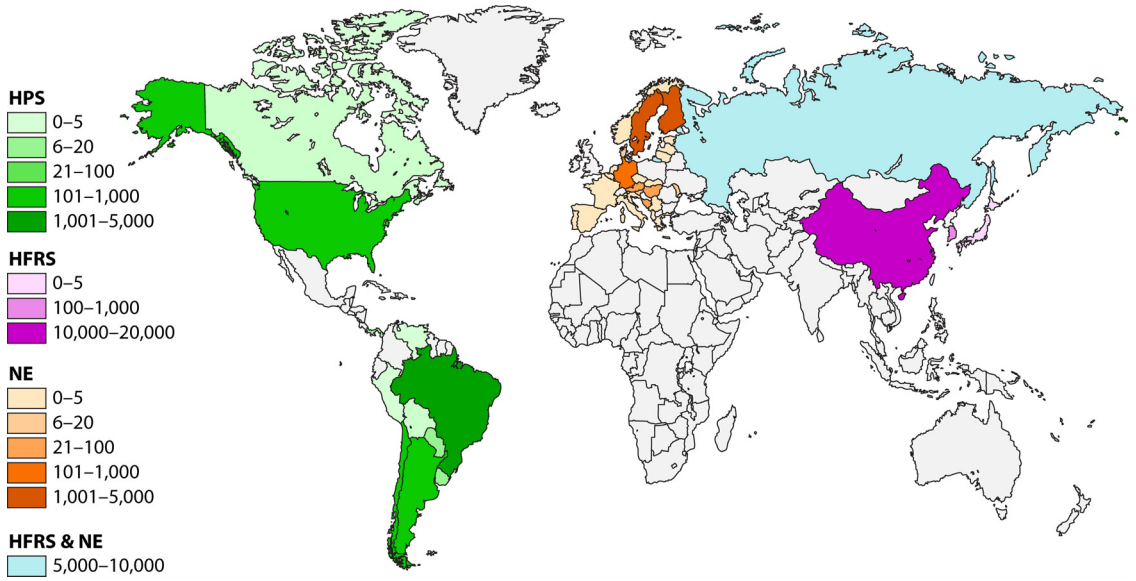

FIG. 3. Geographical representation of approximate hantaviral disease incidence by country per year. (Courtesy of Douglas Goodin, Kansas State University; reproduced with permission.)

no evidence for this pathway. This hypothesis rests on the observation that intracellular particles were not observed in cells infected with SNV or Black Creek Canal virus (BCCV). The localization of the N protein at the Golgi complex, presumably as an RNP complex, has been observed for both New World and Old World hantaviruses (334, 354, 355, 358, 410). In summary, Old and New World hantaviruses share common features of their life cycles; however, data from recent studies suggest that they may have evolved differently in specific interactions with host cell machinery (355). Future studies that address the molecular and mechanistic basis for these differences may provide insight into the underlying pathogenesis and illness of the two diseases.

ECOLOGY AND EVOLUTION OF HANTAVIRUS

The geographic distribution and epidemiology of human cases of diseases caused by hantaviruses have been considered a consequence of the distribution and natural history of their primary rodent (or insectivore) hosts (Fig. 3). The main known disease burden of hantaviruses in the Old World is HFRS, which caused by *Myodes*-, *Rattus*-, and *Apodemus*-borne hantaviruses, and that in the New World is HPS, which is caused by the sigmodontine-borne hantaviruses. In general, infection of these various rodent reservoirs by their respective hantaviruses does not produce an apparent disease. However, Childs et al. reported slower growth of *Rattus norvegicus* rodents infected with SEOV (65). Similarly, Douglass et al. reported that the body weights of *Peromyscus maniculatus* rodents newly infected with SNV grew slower than did those of uninfected mice (87). The infection of other animals is considered to be a spillover infection (196), although very little information on the natural history of these types of infections and the impact of acute infection is available. Field-oriented studies have focused on the ecology of these viruses to gain insight into (i) the maintenance of hantaviruses in their rodent reservoirs, (ii) factors that promote transmission, (iii) the prevalence and distribution of these viruses in nature, (iv) the prevalence of spillover in other animals with the rodent reservoir habitat, and (v) the evolution of these viruses in the context of their rodent hosts. Longitudinal studies have been conducted with several of the rodent reservoirs in areas in Europe, South Korea, and the Americas where the virus is endemic (52, 88, 273, 287, 288, 427). The unique associations of each viral genotype with a specific rodent host, the biosafety level (BSL) required for animal studies (BSL-3 and BSL-4), and the difficulty in the isolation of hantaviruses from rodent or human cases have limited laboratory studies of these viruses in their native reservoirs (1, 169, 170, 194, 206, 236, 457). Pioneering research efforts to study the New World hantaviruses in rodents in controlled outdoor habitats have been successful and should continue to provide critical insight into the biology of hantaviruses in their rodent hosts (43, 44, 317).

In the following section, we review the distribution of the Old and New World hantaviruses and briefly discuss factors that can lead to their emergence and spillover into human populations. The emergence and expansion of zoonotic diseases are particularly sensitive to ecological changes, population movements, and the intrusion of humans and domestic animals into sylvatic environments. Anthropogenic factors (e.g., deforestation, agricultural development, colonization, and urbanization) have increasingly placed human and domestic animal populations at risk of many vector-borne diseases. Mills classified regulators of zoonotic virus prevalence and transmission into five major classes: (i) environmental regulators (weather and food) that affect transmission rates through their effect on reproductive success and population densities; (ii) anthropogenic factors, such as disturbance, that impact the complexity of the ecosystem; (iii) genetic factors that could influence shedding; (iv) behavioral factors (e.g., fighting or communal); and (v) physiological factors control the host response to and length of infection (283). Hence, as with the

potential increase in arbovirus-transmitted diseases that can result from the global-warming scenarios of climate change, these five factors can differentially impact the biology and ecology of the host-virus ecosystem and, consequently, the risk of disease transmission to humans (29, 47, 77, 95, 208, 395, 423, 456). For example, disturbed rodent habitats, such as those caused by deforestation and extensive agriculture, may favor opportunistic or generalist species that may be reservoirs for hantaviruses (216). Environmental changes commonly decrease rodent diversity, which could enhance more host species interaction and, hence, more hantaviral transmission events (aggressive encounters) within a single species. As a consequence, this may activate a cascade with a greater transmission of the virus among rodents, leading to a greater the risk of spillover of rodents with virus into human activities (282).

Rodent Reservoirs of Old World Hantaviruses

In this section, we review the three classical rodent reservoirs that cause HRFS in the Old World. These reservoirs are (i) HTNV and related *Apodemus* mouse-borne viruses in Asia (Amur virus [AMRV] and Soochong virus [SOOV]) and Europe (DOBV and Saaremaa virus [SAAV]), (ii) SEOV and related rat-borne viruses in Asia (Gou virus [GOUV] and Serang virus [SERV]) and bandicoot rat (genus *Bandicota*)-borne viruses (Thailand virus [THAIV]), and (iii) *Myodes* vole-borne viruses, primarily PUUV in Europe (438). Although able to infect humans (394, 437), *Microtus*-borne viruses (TULV, Khabarovsk virus [KHAV], and Vladivostok virus) have not been clearly associated with human disease. The recent finding of a plethora of novel hantaviruses from various sorcid and talpid insectivores (14, 191, 408) will prompt studies of their ability to infect humans, but at the time of writing of this review, no published information was available regarding their possible significance to human health. Serological surveillance has shown the presence of antibodies to TPMV in a febrile patient in Thailand (312).

Apodemus mice, including *Apodemus flavicollis*, are widely present in most of Europe, excluding northern Scandinavia, the British Isles, and western Europe close to the Atlantic Ocean. In Europe, *A. flavicollis*, the yellow-necked forest mouse, harbors DOBV (22, 453), which is associated with severe HFRS with high rates of mortality in Europe. This virus, alternatively isolated from a human patient and called Belgrade virus, was identical genetically to the DOBV isolate (416). Later, a genetically related virus was isolated from *Apodemus agrarius* (same species but different subspecies than *A. agrarius koreae*) (307) and was named Saaremaa virus (SAAV) (alternatively, *A. agrarius*-derived strains have been called DOBV-Aa). *Apodemus agrarius* (the carrier of SAAV or DOBV-Aa lineages in Europe) resides in regions from the previous political "Iron Curtain" to the east. Although the viruses carried by *A. apodemus* (SAAV, or DOBV-Aa) and *A. flavicollis* (DOBV, or DOBV-Af) can be separated phylogenetically, there seems to be currently several lineages in *A. apodemus*, and in addition, a novel pathogenic lineage or virus has recently been detected in *Apodemus ponticus* (212). In the Far East and China, *Apodemus agrarius koreae* (Korean field mouse) is the carrier of HTNV, as originally detected in 1976. *Apodemus peninsulae* harbors a related, genetic variant of HTNV, called AMRV or SOOV (25, 177, 255, 458). However, *Apodemus peninsulae* harbors additional variants of HTNV (468), and the division into distinct monophyletic lineages exclusively in these two viral species is not strict. HTNV, AMRV, and SOOV are similarly pathogenic to humans, with considerable associated mortality. Recent analyses of HTNV suggest that it may have radiated from Guizhou, China, where its shows its highest genetic diversity (472).

As for the rat-carried viruses, *Rattus norvegicus* harbors SEOV worldwide with little geographical variation (for examples, see references 57, 75, 218, 228, 235, 442, 458, and 467). A distinct lineage related to SEOV is GOUV, harbored by *R. rattus* in China. SERV is carried by the Asian house rat (*Rattus tanezumi*) (346) and is widely distributed in Southeast Asia. Note that *Rattus tanezumi* may be classified incorrectly as *R. rattus* in the literature. In addition to these viruses, the greater bandicoot rat (*Bandicota indica*) and lesser bandicoot rat (*Bandicota savilei*), which are distinct species as shown by cross-neutralization assays, harbor THAIV (166, 330). Antibodies in humans and some clinical cases of human infection with these rat-carried viruses have been found, but the recorded significant disease burden of SEOV or SEOV-like viruses has so far come from urban China.

The most widely distributed rodent reservoir for hantaviruses in Europe is the bank vole, *Myodes glareolus*, the carrier of PUUV. The bank vole is found throughout Europe, except for the Mediterranean region, and into the Ural mountains in the east (for specific examples, see references 19, 30, 75, 81, 125, 313, 315, 316, and 365). The bank vole lives in a wide variety of woodland habitats, such as temperate broad-leaved and mixed forests, and prefer areas with dense vegetation (219).

The ecology of Old World hantaviruses in their rodent reservoirs depends upon complex interactions among competing drivers, including climate and landscape/habitat. HFRS epidemics correlate with an increased abundance in the populations of rodent reservoirs. Increases in rodent populations occur in many countries in temperate Central Europe and the Balkans as well as in Scandinavia but are due to different underlying reasons. In temperate Europe, rodent peaks are due to mast years. A mast year is a year when abundant nuts of forest trees accumulate on the ground and therefore provide abundant nutrients for forest rodents. The high rodent density (and corresponding epidemics) correlates with and can be predicted by high summer temperatures 2 years previous (when the flower buds develop) and high autumn temperatures 1 year prior (when the actual seed develops) (395, 423). Without the masting phenomenon, the rodent population density has only modest seasonal variations in temperate Europe, which does not enable the efficient spreading of the virus.

The considerable biodiversity of predators does not provide periods when diminished predation would allow the rodent population to increase considerably in Central Europe. In contrast, northern Europe, typified with cold, snowy winters, has harsh conditions that favor the predation of rodents by few specialist species (e.g., weasel), and the time lag between alternating abundances of prey and predators produces regular cycles of bank vole population densities of 3 to 4 years. For example, in Finland, bank voles are abundant in two consecutive autumns and winters (increase and peak years), followed

by a population crash the next spring (141, 142). The same pattern occurs in northern Sweden, but in the more temperate southern Sweden, the bank vole is present, but the populations are stable and hantavirus infections are rare (309, 313).

In line with the dependence of rodent ecology on climate, satellite data on climate and elevation have recently been used to predict the occurrence of PUUV infections in Scandinavia (314). In both central and northern Europe, there has been a trend in increased numbers of HFRS cases, which is partially due to increased surveillance and partially due to climatic factors such as warmer summers leading to mast years (141, 395). Also, in northern Europe, climatic factors may be an important factor in the largest outbreak of PUUV ever recorded in the winter of 2006 to 2007 (incidence of 313 cases/100,000 individuals in 2007 in Västerbotten, Sweden) (333). In northern Sweden, during a period of normal snow cover and peak in rodent populations, a sudden warm spell melted the snow in January, and consequently, freezing temperatures together with the lack of normal snow cover pushed the bank voles close to human dwellings, putting them into contact with the human population (314). Similarly, studies in China have shown that good seed crops, low rainfall, or a lack of flooding as well as an abundance of field mice, a consequence of the first two factors, predicted a higher incidence of *Apodemus agrarius*-borne HFRS cases (34, 161). Evidently, greater climatic factors influence the first two factors as well (131). Ratborne outbreaks in urban areas have different risk factors.

In addition to climate, other factors affecting the probability of transmission to humans are related to the structure of human settlements, occupation, and human activity. Hantaviruses are most likely aerosol transmitted, and infection occurs when closed, nonaerated, unused buildings (e.g., barns and cabins) to which rodents have had access are reopened and cleaned (79, 431, 463). PUUV remains infectious for at least 2 weeks in the excreta of bank voles at room temperature and colder temperatures, and a lack of UV radiation (indoors) apparently favors virus survival (184). In a recent study, the risk of human infection with PUUV in winter was most clearly associated with cigarette smoking and the condition of the house (whether rodents could enter). This suggests that the risk of transmission is greatest indoors, occurs by inhalation, and is affected by the condition of the respiratory tract (possibly the condition of the airways or presence of inflammation) (433). Rodent populations within the home may be controlled with poison instead of traps, but the approach leads to more exposure to potentially infectious excreta. Furthermore, this approach has the confounding issue of the movement of the toxin up the food chain, (e.g., owls). Typically, the risk for HFRS has been associated with farming, forestry, construction work, woodcutting, proximity to forests, and "seeing rodents" (2, 3, 5, 313, 431–433).

Recent research suggests that landscape composition as an important factor in the ecology of the rodent-hantavirus ecosystem. In China, geographic information systems and remote sensing techniques (e.g., elevation, normalized difference vegetation index [NDVI], precipitation, annual cumulative air temperature, land surface temperature, soil type, and land use) were used to ascertain which elements were associated with HFRS occurrences (456, 466). Increased HFRS incidence correlated with elevation, NDVI, precipitation, annual cumulative air temperature, semihydromorphic soils, timber forests, and orchards. Habitat structure can also influence the reservoir host population density by controlling the availability of cover, burrow space, and other elements of the habitat that would tend to favor (or inhibit) the presence of the host species. The large continuous forests of northern Europe may favor the efficient spreading of the virus in the reservoir population in comparison to the more fragmented forests of Central Europe. Recent research has shown positive relationships between anthropogenic land cover disturbance and the presence of hantavirus in a variety of ecosystems (127, 261, 376). These studies emphasized the role of pulse disturbances such as deforestation (413), agricultural land cover conversion (127), and recreational activities (261). In summary, the main factors correlating with human epidemics appear to be the density of rodent populations, which leads, after some thresholds, to the efficient spreading of the virus in the rodent population and, with some time lag, to increases in numbers human cases (e.g., the NE peak occurs 2 months after the rodent peak in Finland [185, 314]). However, it is clear that a simple increase in rodent population density does not necessarily translate into an increase in viral infection in a rodent population and that landscape, rodent population densities, and seroprevalence levels show a complex pattern of interactions.

In nature, the transmission of Old and New World hantaviruses between rodent reservoirs or to a nonreservoir rodent is thought to be primarily through aggressive behavior and exposure to saliva and excreta (121, 143, 369). Infection in the rodent has been thought to be subclinical. However, recently, it was shown that PUUV infection leads to impaired winter survival of the rodent, and evidently, the rodent needs to invest its limited resources to cope with the chronic infection (187). Chronically infected animals have high levels of neutralizing antibodies, although the animals are viremic for extended periods. Viral antigen and RNA can be readily detected in most, but not all, animals infected with hantaviruses, and the virus can be isolated in Vero E6 cells from tissues usually after passaging of the cells (429). Typically, during a period of high animal density, 30 to 70% of animals may be virus RNA and antigen positive (185). However, as noted above, not all animals positive for viral markers shed the virus actively (135).

In laboratory studies, the transmission of virus between rodents of the same species demonstrates that an infected rodent can transmit the virus horizontally to another rodent within the same cage or through infected bedding (170, 236, 238). The length of time that virus sheds in each type of excreta appears to be different for each hantavirus/rodent species. For example, the Old World hantavirus HTNV sheds infectious virus through saliva, urine, and feces from its *Apodemus* host but persists longest in the urine (241). For the New World hantaviruses, Black Creek Canal virus (BCCV) was shed through urine for 70 days to months after infection (169, 170). It is also noteworthy that although PUUV is present in tissues for the life span (maximum of about 2 years) of a bank vole, the virus is most efficiently spread in excreta during the first 2 months after infection. PUUV RNA levels peak within 11 to 28, 14 to 21, and 11 to 28 days, and PUUV RNA was detected up to 84, 44, and 44 days postinfection in saliva, urine, and feces, respectively (135). Significant differences in the seroprevalence levels for males and females have been reported (30, 67, 122, 205,

273, 284). Interestingly, mathematical modeling suggested that environmental spreading is required to obtain the current epidemiological patterns (380), even prior to the demonstration of the phenomenon in the laboratory (184). In summary, studies of Old and New World hantaviruses show that viral infection has at least two phases: (i) an acute phase, associated with high virus titers, and (ii) a chronic or persistent phase, associated with lower virus titers and the continued shedding of virus in excreta. Finally, unlike other rodent-borne viruses such as the arenaviruses, the virus is not transmitted vertically, and maternal antibodies can protect offspring from infection for some months (186). These observations further underscore the complexity of the structure of the susceptible rodent population.

Rodent Reservoirs of New World Hantaviruses

Since the first recognition of HPS in the southwestern United States in 1993 and the isolation of its causative agent, SNV, from deer mice (308), more than 30 new hantaviral strains or genetic lineages from various rodent species throughout the Americas have been identified (331, 383). HPS-causing hantaviruses in the United States and Canada include Monongahela virus (MNGV), harbored by *Peromyscus maniculatus* (405); New York virus (NYV), harbored by *Peromyscus leucopus* (149); Bayou virus (BAYV), harbored by *Oryzomys palustris* (199, 298); and BCCV (361), harbored by *Sigmodon hispidus*. In Latin America, the primary HPS-causing hantaviruses include Andes virus (ANDV), harbored by *Oligoryzomys longicaudatus* in Argentina (49, 245) and Chile (275, 317); Araraquara virus (ARAV), harbored by *Necromys lasiurus* in Brazil (107); Leguna Negra virus (LANV), harbored by *Calomys laucha* in Paraguay (70, 71, 318, 450); and Choclo virus, harbored by *Oligoryzomys fulvescens* in Panama (441). Sigmodontine-borne hantaviruses from the Americas that have not been associated with human disease include El Moro Canyon virus (ELMC) from *Reithrodontomys megalotis* (362); Rio Segundo virus (RIOSV), harbored by *Reithrodontomys mexicanus* (145); Limestone Canyon virus (LSCV), harbored by *Peromyscus boylii* (377); and Calabazo virus, harbored by *Zygodontomys brevicauda* in Panama (441). Rio Mamoré virus in the pygmy rice rat, *Oligoryzomys microtis*, from Bolívia has been described (32) and has not yet been linked to HPS. Recently, a fatal HPS case imported from Bolívia was reported in Canada (366). In Peru, HTN-007, isolated from the pygmy rice rat, is a variant of Rio Mamoré virus (349). Caño Delgadito virus, harbored by *Sigmodon alstoni* (110), in Venezuela and Catacamas virus (CATV), harbored by *Oryzomys couesi*, in the Honduras (281) have not yet been linked to any HPS cases. The ecology of what is known regarding these New World hantaviruses and additional reservoirs/genotypes are discussed below.

In Argentina, the primary rodent host for ANDV and Orán virus (ORNV) genotypes is *Oligoryzomys longicaudatus*, and that for Lechigunas virus (LECV) and Hu39694 virus genotypes is *Oligoryzomys flavescens*. *O. longicaudatus*, one of the most abundant rodent species, is also the reservoir of ANDV in Chile (317). Intriguingly, no other strains of hantaviruses in other rodents in Chile have been reported. In Argentina, surveillance studies have revealed a remarkable number of genotypes in several rodent species. Two additional genotypes recognized to cause HPS in Argentina are Maciel virus (MACV) and Bermejo virus (BMJV). MACV was identified from *Necromys benefactus* from central Argentina, while the BMJV genotype was originally recovered from a only single *Oligoryzomys chacoensis* rodent captured near Orán (318). Pergamino virus (PRGV), harbored by *Akodon azarae* from central Argentina, has not yet been linked to HPS (244). Nucleic acid sequences of a LANV-like virus were cloned from the blood of HPS patients from northwestern Argentina and from the lungs of *Calomys callosus* rodents (244). In Argentina, the spatiotemporal distribution of HPS cases from 1998 to 2001 in the Buenos Aires Province showed strong seasonality and correlation with ecological conditions (48).

Brazil, the largest country in Latin America, has a predominantly tropical climate and high biodiversity, supporting approximately 450 of the 540 known species of *Sigmodontinae* rodents (282). In Brazil, Juquitiba virus (JUQV) and Araucária virus are harbored by *Oligoryzomys nigripes*, a rodent that lives in the southern temperate Araucária pine forests and along the Atlantic rain forest. In the last few decades, both of these environments have been extensively deforested for lumber commerce and farming. *Necromys lasiurus*, which harbors ARAV, is a rodent that lives in cerrado regions (a savanna-like ecosystem) at the southeastern and central plateau. These regions have natural ecosystems that are largely degraded because of the intensive farming of sugar cane, cereals, and cattle. It is possible that *Necromys lasiurus* responds in an opportunistic and aggressive manner as its habitat experiences greater anthropogenic change, an important factor to consider in models of transmission of ARAV to humans (108, 282, 283, 414). Conversely, *Oligoryzomys nigripes* lives in natural habitats bordering cultivated areas (180, 282, 352). A LANV-like virus is harbored by *Calomys* species that live in the midwestern region in a landscape of cerrado and Amazon forest (426). This region has recently been undergoing deforestation for the farming of soybean and other cereals. *Oligoryzomys moojeni*, a rodent that lives in an extensively deforested part of the northern Amazon, is the probable reservoir for Castelo dos Sonhos virus. This region has been modified over the last decade for lumber commerce and cattle breeding (426). In the northeast, wherein HPS cases have occurred in a swamp region where the land is periodically flooded, *Oligoryzomys fornesi* is the probable reservoir of Anajatuba virus (426). Additional rodent reservoirs in the southeastern cerrado region of Brazil include *Necromys lasiurus*, *Akodon* species, and *Calomys tener*. *Akodon* rodents live in the pampas grasslands of Argentina, Uruguay, and southern Brazil as well as in Bolivia and Paraguay. These rodents are associated with PRGV hantavirus in Argentina (244) and Jabora viruses in Brazil and Paraguay (68).

In Paraguay, *Calomys laucha* was discovered to be the rodent reservoir for LANV responsible for the first noted outbreak of HPS in the western region (Chaco) of Paraguay (179). Serological surveys of rodents throughout Paraguay suggest additional hantavirus reservoirs in *Akodon azarae*, *A. montensis*, *Bibimys chacoensis*, *Graomys griseoflavus*, *Holochilus chacarius*, *Nectomys squamipes*, *Oligoryzomys chacoensis*, *O. fornesi*, *O. nigripes*, and an unidentified *Oryzomys* species (71). Hantaviral sequences from several of these rodents have been cloned and used in phylogenetic studies: *H. chacarius*, collected in the Chaco, and *A. montensis*, *O. chacoensis*, *O. ni-*

gripes, and *O. fornesi*, collected in eastern Paraguay (70). These analyses suggest that there are at least four additional hantaviruses endemic to Paraguay: Alto Paraguay virus (ALPAV), harbored by *Holochilus chacarius* (Chacoan marsh rat); Ape Aime virus (AAIV), harbored by *Akodon montensis* (montane akodont); an Itapúa37/JUQV-like virus, harbored by *Oligoryzomys nigripes* (black-footed colilargo); and BMJV-Ñeembucu (BMJV-ÑEBU), harbored by *Oligoryzomys chacoensis* (Chacoan colilargo). Recent studies of the Atlantic Forest show a sympatry of two additional strains of hantavirus, Jaborá and Itapúa37/JUQV-like viruses (68). In nearby Uruguay, the yellow pygmy rice rat (*O. flavescens*) may be the host for Andes Central Plata virus, a hantavirus associated with HPS in the southern region of Uruguay (83). Recently, JUQV-like hantaviruses have been shown to be carried by two different rodent species, *Oligoryzomys nigripes* and *Oxymycterus nasutus*, in Uruguay (84).

Despite the widespread occurrence of HPS cases north and south of Mexico, there have been no reported cases of HPS in Mexico. However, human populations with antibodies to hantaviral antigens have been detected in the general population in the Yucatan (428). Rodent species such as *Reithrodontomys megalotis*, *R. sumichrasti*, *Peromyscus maniculatus*, *P. melanotis*, and *P. hylocetes*, collected in the states of Oaxaca and Zacatecas, have been shown to have hantaviral antibodies or RNA (265). A unique genotype of hantavirus, Playa de Oro virus, was recently isolated from *Oryzomys couesi* (72) from Colimas, Mexico. In addition, *Oryzomys couesi* harbors Catacamas virus (CATV) in the Honduras (281). The phylogenetic relationships between the CATV and Playa de Oro virus show substantial divergence (72). No additional information on the ecology of these viruses is currently available. In Panama, rodent surveillance (376) and modeling efforts have revealed that rodent hosts of hantaviruses reside in small habitat fragmentations created by surrounding agricultural lands. An analyses of this ecosystem suggests that human activities (i.e., deforestation for cattle ranching) coupled with environmental factors (i.e., increased precipitation) may have synergistically coalesced for an increased risk of HPS in Panama (371).

In the United States, a number of longitudinal, ecological studies were established in the southwest shortly after the emergence of SNV (50–52, 87, 222, 289). Hence, what is presently known about the ecology of North American hantaviruses comes largely from studies of SNV infection of *Peromyscus maniculatus.* These landmark longitudinal studies reveal ecological and biological factors that contribute to virus maintenance in rodent reservoirs, such as correlations with decreases in species richness and the preponderance of males in the maintenance of SNV (50). As revealed for Panama (413) and the United States (74), longitudinal studies support the dilution effect hypothesis, which predicts that pathogen prevalence will be negatively correlated with increased species diversity. Only one longitudinal study (154, 273, 274) has focused on *Oryzomys palustris*, which harbors BAYV. The rodent genus *Oryzomys* is a large, diverse, and geographically widespread group distributed primarily in the neotropics (300), except for one species (*O. palustris*), which extends northward into the United States (134). These studies of BAYV infection of *O. palustris* showed a higher correlation of coastal prairie macrohabitat with virus presence and found that about 84% of seropositive animals were males and that the heaviest males were significantly more likely to be seropositive.

As discussed above for the Old World hantaviruses, the dramatic fluctuations in rodent reservoir populations and the prevalence of hantaviruses in these reservoir hosts give rise to localized, sporadic, and unpredictable HPS outbreaks. In the Americas and elsewhere, the ecology and emergence of hantavirus have been linked to precipitation climatology (95, 124). In North America, particularly in the southwest, outbreaks of HPS cases have been shown to correlate with weather and climatic events, especially precipitation (95, 132, 459). The little that is known about hantavirus ecology has come largely from studies of SNV conducted on coarse spatiotemporal scales (152, 293, 327, 412). These studies suggest that precipitation can increase reservoir species populations and, therefore, hantavirus prevalence by enhancing resource availability as an extension of the trophic-cascade hypothesis originally proposed to explain the incidence of plague (328). Remotely sensed indices of vegetation greenness, a surface property closely related to interannual climatic variation, have also been associated with occurrences of HPS, as have topography (elevation and aspect) and host macrohabitat (38, 120, 285). However, as discussed above for Old World hantaviruses, climate alone has not been sufficient to predict the spatiotemporal dynamics of the environment-reservoir-virus system. The ecology of hantaviruses depends largely on the microhabitat of its reservoir (52, 285, 287). Furthermore, the interactions of the rodent community have been shown to play an important factor in viral ecology (74). Clearly, the ecology and evolution of the virus are tightly associated with the ecological habitat of the rodent, and ecological models should incorporate landscape composition on finer spatial scales and consider microclimatic buffering inherent in the landscape.

Recent research suggests that habitat or landscape characteristics might also promote or constrain the prevalence of hantaviruses in their reservoirs (127, 128, 226, 273). As discussed above for the ecology of Old World hantaviruses, anthropogenic landscape disturbances in the United States and Panama have also been linked to the presence of hantavirus and/or HPS cases (261, 413). The dependent interaction of host rodent species and landscape led Goodin et al. to hypothesize that microhabitat might also influence the presence of hantavirus in the reservoir population in the context of climate in the neotropics in Paraguay (128). To test this hypothesis, Goodin et al. investigated the microhabitat characteristics of a reservoir/vector of hantavirus, *Akodon montensis*, at the Mbaracayú Biosphere Reserve, an Atlantic forest site in eastern Paraguay (128). Analysis of microhabitat preferences showed that the species preferred areas with little forest overstory and denser vegetation cover on and near the ground. Moreover, there was a significant difference in the microhabitats occupied by antibody-positive and antibody-negative rodents, indicating that microhabitats with greater overstory cover may be conducive to the promotion of the transmission and maintenance of hantavirus in *A. montensis*.

Evolution of Hantaviruses

Phylogenetic analyses of hantaviruses and their rodent hosts suggested that hantaviruses have a long-standing coevolution-

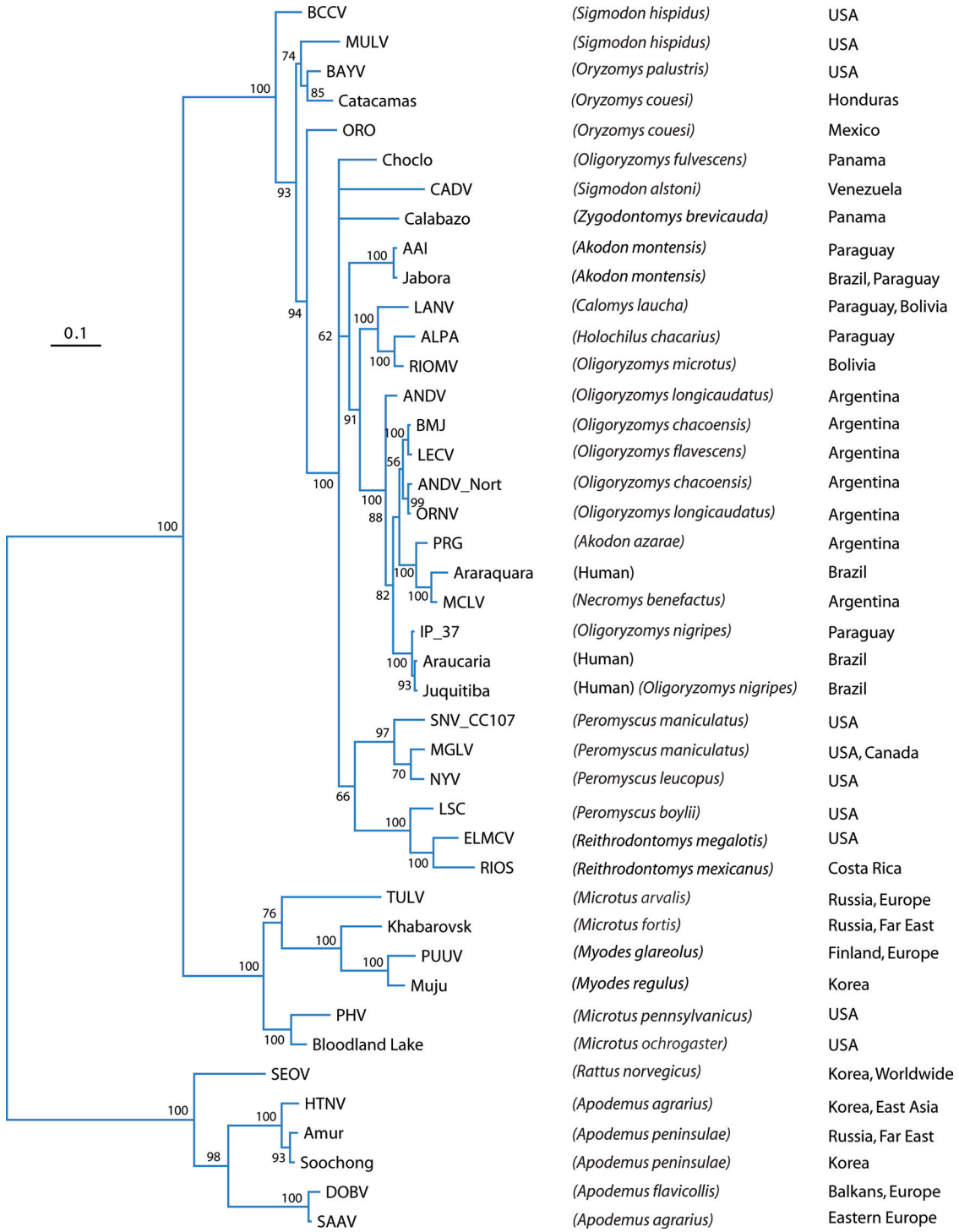

FIG. 4. Phylogenetic tree of representative hantaviruses from the Old and New Worlds. (Courtesy of Yong-kyu Chu, University of Louisville; reproduced with permission.)

ary history with their predominant rodent carriers (reviewed in references 336 and 339). A representative phylogenetic tree is shown in Fig. 4. However, exceptions have occurred, and these exceptions have provoked scientific debates and controversies (210, 342, 343, 356, 357). Recent work by Ramsden et al. suggests that concepts of the geographic distribution and epidemiology of hantaviruses based on the natural history of their primary rodent hosts must be rethought considering their findings that hantaviruses are approximately 900 years old and exhibit short-term evolutionary rates equivalent to those seen for rapidly evolving RNA viruses (356, 357). The deduced mutation frequency, approximately 10^{-3} to 10^{-4}, is similar to

the frequency for other RNA viruses in this respect (153). Although theoretical calculations of the rate of evolution could result in a faster evolution than previously appreciated, certain findings remain to be addressed in this context, such as the high degree of similarity of hantaviruses carried by *Microtus* rodents, which radiated 1 to 2 million years ago, on different continents. Furthermore, since data from experimental studies support the finding that hantaviruses form quasispecies populations both in nature (344, 345) and in cell culture (92, 93), how do these characteristics influence models of evolution and rodent ecology (85)? The underlying constraints of quasispecies in the evolution of hantaviruses have not been experimentally analyzed in animal models or wild-rodent hosts.

Clearly, species jumps (virus shifting to a new host) have occurred during the evolution of the *Hantavirus* genus (e.g., between the *Microtus* VLA and KHAV and *Lemmus*-carried Topografov virus [TOPV]) (348, 435) as well as during the evolution of the insectivore-borne hantaviruses (191, 192). The evolution of the *Apodemus*-borne viruses has also not strictly followed that of their rodent hosts and has included reassortment and recombination. In the Old World, reassortment of hantaviruses occurs in nature within lineages, between lineages, and even between different viruses (246, 337, 365, 471). Natural and laboratory genetic reassortment of genomic RNA segments within SNVs among *Peromyscus maniculatus* rodents (139, 246), in cell culture experiments (272), and within the DOBVs among two different rodent host species, *Apodemus flavicollis* and *A. agrarius* (210), have been reported. In addition, reassortments between the genetically more distantly related SNV and BCCV have been identified in nature (368). In an *in vitro* study with mixed infection using ANDV and SNV, a genetic reassortment was isolated with the large (L) and small (S) segments of SNV and the M segment of ANDV (272). In Paraguay, phylogenetic studies of hantavirus suggested prior natural reassortments in *Akodon montensis* (70). While the sequence of events of original donor and recipient species and viruses awaits future studies, the taxonomy and nomenclature of these viruses have become and will continue to be challenging.

PUUV shows extensive geographical variation. However, proximal to the PUUV phylogenetic clade is Muju virus, from the royal vole, *Myodes regulus*, in South Korea, which likely causes HFRS (408). This is followed by Hokkaido virus (or lineage) in *Myodes rufocamus*, which seems to carry a distinct virus in Japan, China, and Russian Siberia (348). In general, PUUVs are comprised of geographical variants where PUUV genotypes in each country or geographic area form genetic clusters (e.g., PUUV phylogeny in Europe to some extent follows postglacial recolonization routes of rodents). An especially demonstrative case is that of Sweden, where the strains in northern Sweden are separated from those of central Sweden. Recolonization after the last Ice Age occurred from separate directions in these regions. The demarcation line is only about 50 km wide and separates the bank vole populations harboring different mitochondrial species and PUUV lineages (17, 159). However, as sequence data accumulate, more recent data have shown that the both within and between PUUV lineages, mixing by reassortment occurs frequently (364, 365). Purifying selection takes place to maintain the integrity of the viral genome, and the quasispecies nature of PUUV within a rodent gives the possibility of a rapid selection of genetic variants, as shown experimentally by changing the transmission route (401). Altogether, the level of genetic variation (at the nucleotide level) was 0.2 to 1.2% within individual rodents, 1 to 2% within a population, 6 to 8% within a PUUV lineage, and up to 17% between lineages (344).

EPIDEMIOLOGY OF HANTAVIRUS INFECTIONS

The epidemiology of hantavirus infections in human populations is based largely on incidences of peridomestic exposure of humans to rodents in areas of endemicity. In the majority of these cases, humans acquire infection after direct contact with infected rodents or their excreta, which occurs mostly by inhaling virus-contaminated aerosol. In the Americas, person-to-person transmission has not been observed for the majority of hantaviruses (444); however, cases of person-to-person transmission of ANDV have been reported, although rarely, in Argentina and Chile (320, 443). Intriguingly, recent surveillance data showed PUUV RNA in saliva of patients; however, inhibitory substances in saliva may prevent the transmission of live virus (333). ANDV is less sensitive *in vitro* to the antiviral inhibitory substances in saliva than other hantaviruses (136). A geographical representation of the relative global distributions of HFRS and HPS cases by country is presented in Fig. 3.

Epidemiology of Old World Hantaviruses

Immediately following the initial discovery of HTNV (237, 239), epidemiological studies of HFRS significantly progressed in both human and rodent populations. Initially, studies showed that farmers, soldiers, and rural inhabitants were most likely to fall victim to HFRS. Initially, it was believed that HFRS occurred only in rural areas of Eurasia, specifically China, South Korea, eastern Russia, and northern Europe (234). Prudent surveillance demonstrated that HFRS caused by SEOV could also occur in urbanized cities and in many parts of the world (240). The ecological dynamics of the reservoirs of the virus and the reasons behind the epidemics are described above.

In Europe, PUUV causes most HFRS cases, with 35,424 cases reported by the end of 2006 (141, 142); 95% of the cases were reported after 1990. The diagnostics for the detection of PUUV became available in some countries in 1979; however, in many countries, the first cases were reported only during the last decade. In general, PUUV infections occur throughout the continent within the range of the *Myodes glareolus* habitat. DOBV (derived from *A. flavicollis*) infections have so far been identified only in the Balkan region (13, 20, 258, 325), although the host species is distributed in a much larger area. SAAV (and/or DOBV-Aa) carried by *A. agrarius* has been detected in field mice in central and eastern Europe (Estonia, Russia, Denmark, Slovenia, and Slovakia [for examples, see references 18, 173, 207, 338, 340, and 399]) and has been associated with human disease in outbreaks in Russia (114, 212, 257, 341) and individual cases in Germany (209) and Slovakia (399). The data accumulated so far have not associated SAAV/DOBV-Aa with high rates of mortality, in contrast to DOBV infections (from *A. flavicollis*) in the Balkan peninsula (20, 212, 325).

Most cases of PUUV infection diagnosed in Europe have

come from Finland (24,672 cases before 2007 [46, 141]). Other countries where more than a thousand cases have been recorded include northern Sweden, Belgium and France (which share a region of endemicity in northeastern France and Ardennes), Germany, and Norway (141). In northern Europe, the epidemics typically peak in November to December during high-rodent-density years (when the abundant, infected rodents come into more contact with humans in the countryside), with another peak in August (typically when urban dwellers have been exposed during their summer holidays) (46). In Finland and northern Sweden, the average seroprevalence is about 5%. In rural communities, for elderly males, seroprevalences over 50% have been detected (4, 46). Up to 2,195 and 3,200 cases per calendar year have been detected in 2007 and 2008 in Sweden and Finland, respectively (314; see also www.thl.fi). On average, the disease predominates in individuals 40 to 45 years of age, with a 2:1 male-to-female ratio (46).

Since the disease was first reported in Germany, an average of 400 cases have been documented per year, with a record-high peak of 1,687 cases in 2007. Most of the cases were PUUV infections occurring in Baden-Württemberg and were encountered during the spring and summer months (451). Surveys show seroprevalences of 1.7% (SAAV increasing toward the east [470]) and 6.7% (PUUV seroprevalence in another region in Lower Bavaria where the disease is endemic [277]). Another region of endemicity is northeastern France and the Ardennes region in Belgium. In both France and Belgium, 50 to 150 cases were seen in the beginning of this millennium; however, 2005 was a record-high epidemic year (e.g., 253 and 372 cases in France and Belgium, respectively). As in Germany, the rodent and HFRS peaks were highest during the summer, followed by good mast years of trees the previous year, and, therefore, were a consequence of climate factors (141, 423).

In the Balkans, cases of both PUUV and DOBV infections are common and, similar to Central Europe, show a higher incidence after mast years. A gradient of PUUV/DOBV cases is found, with DOBV dominating southwards toward Greece. A considerable antibody prevalence has been reported for different Balkan countries (e.g., 5% for Bosnia, 4% for Greece, and 1.7% for Slovenia, with 21 to 136, 2 to 8, and 5 to 27 cases in this millennium, respectively [142]), suggesting that only some—probably the most severe—cases are diagnosed. Outbreaks have occurred in the Balkans in 1995 during wartime (when 354 cases were diagnosed in an outbreak in Bosnia-Herzegovina) and later in 2002 and 2005, with the case numbers peaking in the summer. Note that SEOV is prevalent in rats in Europe, but very limited data on human infections or disease are available.

In Russia, 89,162 HFRS cases were detected from 1996 to 2006, and the mean incidence was 5.8 cases/100,000 individuals (1997 to 2007), peaking in the outbreak year of 1997, with 14.3 cases/100,000 individuals. The incidence of HFRS in Russia varies geographically. The areas where the disease is most endemic are the regions in the Volga Federal District, especially Tatarstan, Udmurtia, Samara, Orenburg, and Bashkirostan, the latter with the highest incidence (68 cases/100,000 individuals/year) in these regions where PUUV infection prevails (114). In Russia, *Apodemus agrarius*-derived SAAV (DOBV-Aa) outbreaks have occured within the Central Federal District in western Russia (e.g., in Lipetsk during 2001 to 2002, cases were associated with *A. agrarius* DOBV/SAAV lineages). Recently, in the southern region of Sochi, another DOBV lineage was identified in *A. ponticus*, which was associated with more-often-severe HFRS (27% and 55% severe cases in Lipetsk and Sochi, respectively) (212). In the Siberian region, HFRS is registered less often, whereas in the Far East region of Russia, there are similar rodents and HFRS cases as those found in South Korea and China, where the *A. peninsulae*-carried viruses (AMRV/SOOV) cause severe HFRS outbreaks (255).

In China during the last few years, 12,000 to 20,000 HFRS cases have been registered with the China Center for Disease Control, with a mortality rate of approximately 1% (http://www.chinacdc.net.cn/n272562/). These include cases caused by *Apodemus*-borne HTNV and HTNV-like viruses (Amur/Soochong virus) as well as rat-borne SEOV. Cases occur throughout the year, but the peak in incidence occurs in November and December. However, previously, much higher case numbers (as well as mortality) were reported (231, 403), which suggested 1,256,431 cases from 1950 to 1997 and 44,304 deaths (3.53%), with the highest annual peak in 1986, with 115,985 cases. The HFRS incidence data for 1994 to 1998 showed that the highest incidence was in the middle and eastern part of China, with top incidences of 20.3, 18.9, 8.2, 7.7, 5.0, and 4.6 cases/100,000 individuals in the Heilongjiang, Shandong, Zhejiang, Hunan, Hebei, and Hubei Provinces, respectively, covering 70% of all cases (456), and was correlated with low elevation, semihumid climate, and other abiotic factors (also see above for ecological factors related to outbreaks). Epidemiological studies in China suggested that camping or living in huts in fields, living in a house on the periphery of a village, and cat ownership are risk factors (372, 454, 455). Formalin-inactivated traditional vaccines have been widely used in China (reviewed in references 158 and 403). Inactivated vaccines have been reported to be well tolerated, induce good humoral immune responses, and have good efficacy (63, 253, 256).

In South Korea, most cases are caused by HTNV (AMRV/SOOV), and a small percentage of HFRS cases may be caused by Muju virus (MUJUV), harbored by *Myodes regulus* (408). Hundreds of HFRS cases were registered in the 1970s and 1980s, with a sharp increase in the number of cases in the early 1990s to up to 1,200 cases per year. From 2001 to 2008, 323 to 450 HFRS cases were registered annually in the Republic of Korea (408a). It has been debated to which extent the use of Hantavax (administered to millions) has influenced the decrease in case numbers in the late 1990s (326).

HFRS probably occurs in other countries in Asia, as antibodies to THAIV have been found in rodents and humans in Thailand (330, 411), Indonesia (130, 346, 347), and India (58, 59). Antibodies have been detected in serosurveys of humans conducted in Africa. However, the true disease burden of these human infections remains poorly defined; this is also true concerning the growing number of insectivore hantaviruses. The PUUV-like Hokkaido virus in *Myodes rufocanus* present in Japan has not been associated with human disease, nor has disease associated with SEOV—also present in local rodents—been found in Japan since 1984 (15).

Finally, we note that hantaviruses have not yet been detected in Great Britain. It has been suggested that a rapidly fatal viral infectious disease, the "English sweating disease," that ap-

peared in England in 1485, 1508, 1517, 1528, and, finally, 1551 was caused by an HPS virus (91, 418, 424). The illness attacked primarily males between the ages of 15 and 45 years, with a high fatality. A review of these epidemics suggested that HPS does not match the English sweating disease completely.

Epidemiology of New World Hantaviruses

Prior to May 1993, hantavirus-associated disease was not recognized in the United States. It was at this time that a cluster of previously healthy residents living in rural areas in the Four Corners region of the southwestern United States died of acute unexplained respiratory distress (61). As will be discussed in more detail later in this review, their illnesses progressed from a prodrome of fever and myalgias to a rapid respiratory decline with the sudden onset of noncardiogenic pulmonary edema and hypotensive shock. This initial outbreak of HPS was recognized by the New Mexico Office of the Medical Investigator and Indian Health Service, and approximately 2 weeks after receiving laboratory diagnostic specimens, Public Health Service scientists had identified a newly recognized hantavirus, SNV, and its reservoir, *Peromyscus maniculatus*. American Indian healers living in the affected areas were aware of similar deaths occurring over three cycles during the 20th century in association with identifiable ecological markers and had developed preventative measures. An emergency phone hotline was established by the Centers for Disease Control and Prevention (CDC) and was successful in rapidly identifying the widespread sporadic geographic distribution of HPS cases throughout the United States (417). Since the time of this outbreak though March 2007, 465 HPS cases in the United States have been reported to the CDC, and 35% of these resulted in death (64% male and 37% female), with a mean age of patients of 38 years (range, 10 to 83 years). The greatest numbers of cases have been reported for New Mexico (71), although over half of the confirmed cases have been reported from areas outside the Four Corners area. HPS cases have been reported in 30 U.S. states, with the majority in the western half of the country occurring in residents of rural areas. Risk of exposure to hantavirus has been correlated with occupational exposures in which an employee might encounter a rodent or rodent droppings (176, 243, 292, 464). The greatest risk is associated with entering closed buildings that are rodent infested (16). SNV does not appear to be transmitted to neonates after exposure to breast milk, show maternal transmission, or show any unique pathology in pregnant women (160, 322). Vertical transmission of HTNV has been reported (233).

The first cluster of HPS cases outside the United States occurred in Paraguay from July 1995 through January 1996 (450). In this outbreak, 17 cases of HPS caused by LANV were confirmed for persons living in the western part of Paraguay. Since the first outbreak of HPS in Paraguay in 1996 and 1997, there have been over 125 cases. In 2005, the first case was confirmed in the eastern Department of Itapúa (Norma Coluchi, Ministry of Health, personal communication). At present, HPS-causing hantaviruses have not been identified; however, rodent surveillance data suggest that ANDV-like viruses are endemic in this region (70). Most public health workers suspect that additional HPS cases in rural areas are undetected, as there have been no systematic efforts to survey for this illness. Interestingly, the cases that have been identified have a lower mortality rate (~15%) than those in Chile and Argentina that are caused by ANDV (~40%).

In Argentina, the first noted outbreak of HPS cases was reported from September through December of 1996 in the southern Andean city of El Bolson, a ski resort nestled in the Andes Mountains. During this outbreak, 18 cases occurred, and three of these cases were three doctors who treated patients with the disease and who became ill. The illnesses of the physicians strongly suggested person-to-person transmission. This was especially clear in the case of a physician in Buenos Aires (well outside the El Bolson area) who became ill 27 days after taking care of an HPS patient who had been transferred from the outbreak area to Buenos Aires (443, 444). Person-to-person transmission has never been observed before with any other type of hantavirus, either those causing HPS in the Americas or those causing HFRS in Europe and Asia. During the period of 1996 to 2001, the Argentine Health Ministry reported 324 cases of HPS. Of these, 138 came from provinces of the north (Salta and Jujuy), 124 were from the central region (Buenos Aires and Santa Fe), and 62 were from the south of the country (Chubut, Neuquén, and Rio Negro). The mortality rate reached 30% between 1996 and 2001. Pathogenic ANDV lineages that cause HPS circulate in three areas of endemicity: ANDV in the southwestern provinces of Rio Negro, Chubut, and Neuquén; LECV and Hu39694 viruses in the central Buenos Aires and Santa Fé Provinces; and ORNV in the northwestern Salta Province. In general, the risk of human disease comes from peridomestic exposure to virus-infected rodent reservoirs (49).

Shortly after the outbreak of HPS in Argentina, a cluster of 25 HPS cases that occurred between July 1997 and January 1998 with two family clusters was recognized in the Coyhaique Health District of the Aysen region of Chile (425). Unique to the outbreak in Aysen were three children with petechiae, one of whom died from hemorrhagic pulmonary secretions and bleeding from puncture sites (103). Overall, it is difficult to isolate hantaviruses from patients; however, the first human isolate of ANDV was isolated from the serum of an asymptomatic 10-year-old Chilean boy who died 6 days later (113). In Chile, the first case of HPS was described in 1995, although cases have been identified retrospectively as far back as 1975 (27). Through 2006, 485 cases have been reported, with a 37% mortality rate, in different zones of Chile, which confirms the prediction that the disease may appear throughout the geographic distribution of the rodent reservoir (306). A recent prospective study concluded that the risk of person-to-person transmission is greatest among close household contacts (sex partners and persons who sleep in the same bed or room) of index patients with ANDV infection. In this study of household contacts of index patients with HPS, the overall risk of secondary cases in the household was 3.4%. The risk was 17.6% among sex partners of index cases, versus 1.2% among household contacts who were not sexual partners (104).

The first outbreak of HPS in Panamá occurred in 1999 to 2000 in Los Santos, with 12 cases and a 25% case fatality rate (28, 441). However, the three fatal cases were not confirmed by serology. Sequence analysis of the virus genome showed this virus to be a novel hantavirus, Choclo virus. Serological and virus genetic analyses of rodents trapped in the area showed

Oligoryzomys fulvescens to be the likely reservoir of Choclo virus. In addition, *Zygodontomys brevicauda* rodents were shown to harbor another genetically unique hantavirus, Calabazo virus (441).

In Uruguay, the first three cases of HPS were reported in 2004 in the area bordering Brazil (Ministry of Health of Uruguay, 2004). Two closely related hantaviruses, LECV and Andes Central Plata virus, are associated with HPS (83). Both of these viruses are carried by *Oligoryzomys flavescens*. However, a JUQV-like hantavirus in Uruguay, carried by two rodent species, *Oligoryzomys nigripes* and *Oxymycterus nasutus*, was recently described (84).

In Brazil, the first reported HPS cases occurred in 1993 in the southeast, caused by JUQV, and in this small outbreak, 66% of the patients had a fatal outcome (439). Person-to-person transmission has not been observed (310). From 1993 through April 2009, 1,145 HPS cases were reported in Brazil, with a 39.5% case fatality rate, and were caused mostly by five lineages of hantavirus: Araucária strain, Araraquara, LANV-like, Castelo dos Sonhos, and Anajatuba viruses (44a, 180, 276). The case fatality rate for HPS in the Central Plateau and southeastern regions caused by ARAV (44.5%) was significantly higher than that in southern regions caused by JUQV (32.5%; 126 deaths out of 387 cases) ($P = 0.0051$ by Fisher exact test; χ^2, 4.8293; $P < 0.05$) (108). Although some geographic overlap of ARAV and JUQV occurs, these results suggest that ARAV strains may have higher virulence than JUQV or other hantaviruses in Brazil (108). Based on data collected from 70 Brazilian patients living in the cerrado region and having HPS caused by ARAV, the disease inflicted mostly males (75.7%), 35.8 years old, with a 54.3% case fatality. Agricultural activities are correlated with the risk of exposure (276). HPS cases and serological evidence of human hantavirus infection have been reported in other places in northwestern and northeastern Brazil and are likely to be caused by other novel genotypes of hantaviruses (107, 108, 414).

TABLE 2. Occurrence of different signs, symptoms, and laboratory findings for patients with serologically confirmed HFRS and HPS

Finding[a]	Occurrence (%) in patients with[b]:				
	HTNV	SEOV	PUUV	SNV	ARAV
Fever	100	100	99–100	100	100
Dyspnea					87
Tachycardia					81
Shock					33
Headache	86–87	89	85–100	71	47
Abdominal pain	85–92	68	64–67	24	NA
Backache	91–95	85	82	29	NA
Nausea	82–91	61	78–83	71	25
Dizziness	50	52	12–25	41	NA
Petechiae	32–94	48	12	0	NA
Minor bleeding	37	7–20	11	NA	9
Internal hemorrhages	34	13	NA	NA	NA
Cough	31	14	60	71	54
Hypotension	80	17	1–2	50	56
Myopia	57	NA	12–31	NA	NA
Arthralgia	NA	NA	0–15	29	NA
Oliguria	60–67	37	54–70		
Polyuria	92–95	63	97–100	40	NA
Leukocytosis	91	69	23–57	95–100	67
Thrombocytopenia	78	83	52–75	100	93
Hematocrit					70
Proteinuria	100	94	94–100	40	NA
Hematuria	85	73	58–85	57	NA
S-creatine	97	83	Yes	No	51
Mortality	5–10	<1	0	40	54

[a] Based on reported findings for HTNV (233), SEOV (203, 233), PUUV (301, 396), SNV (90), and ARAV (53) infections.
[b] NA, not applicable.

CLINCAL COURSE OF HANTAVIRAL ILLNESSES AND PATHOLOGY

Spectrum of HFRS Disease in Europe and Asia

The incubation period for HFRS is approximately 3 weeks, ranging from 10 days to 6 weeks (112, 220). HFRS is a generalized infection, and the severity of the disease as well as the clinical pattern vary, apart from the causative agent, individually from subclinical to lethal. In general, HFRS caused by HTNV, Amur virus, and DOBV are more severe, while SEOV is more moderate and PUUV is mild. As noted above, the disease associated with *Apodemus agrarius* in Europe (SAAV or DOBV-Aa) seems to be milder, although clearly, insufficient data exist on patients infected with *A. agrarius*-derived viruses. Classically, HFRS occurs in five distinct phases: febrile, hypotensive, oliguric, polyuric, and convalescent. Pulmonary involvement and neurological manifestations may occur early in the course of NE (6, 250, 251). Approximately 11 to 40% of persons with febrile illness develop hypotension, and approximately 40 to 60% develop oliguria. The clinical symptoms of the febrile stage are eventually augmented to the hypotensive stage, characterized by thirst, restlessness, nausea, and vomiting, each lasting hours or days (Table 2). Approximately one-third of all patients during the hypotensive stage of HFRS develop shock and mental confusion (232). Symptoms of vascular leakage, abdominal pain, and tachycardia are observed during this stage. Oliguria is urine output of less than 400 ml per day. The oliguric phase lasts from 1 to 16 days for HFRS, in contrast to 4 to 24 h for HPS. Conjunctival, cerebral, and gastrointestinal (GI) hemorrhages occur in about one-third of all patients (232). The oliguric stage accounts for approximately one-half of all hantavirus-related deaths. In this stage, patients are at risk for hypertension, pulmonary edema, and complications of renal insufficiency. Dialysis is required for approximately 40% of HTNV and 20% of SEOV patients. Death is usually due to complications from renal insufficiency, shock, or hemorrhage. These phases can be hard to distinguish, especially in less severe cases. Although the "virus gradient" of severity of symptoms is, in general, as described above, an individual PUUV case may be severe, an individual HTNV infection may be mild, or cases may present with subclinical seroconversion. Death occurs in less than 0.1% in patients infected with PUUV, whereas fatality rates as high as 15% have been observed for HFRS patients infected with HTNV. SEOV is associated with a mortality rate of less than 1%. In contrast to PUUV in Europe, with approximately 0.1% mortality, the mortality rate for hospitalized DOBV (*A. flavicollis*-borne) cases has been reported to be 9 to 12% in the Balkans (20, 325). However, considering the 4% seroprevalence in some areas of Greece, it may be that mild cases may remain undiagnosed.

For PUUV cases, the disease usually starts abruptly with fever, followed by headache and abdominal pains, sometimes with vomiting or diarrhea (225, 301, 396). Somnolence, dizziness, and other signs of central nervous system (CNS) involvement may occur. PUUV RNA has been found in cerebrospinal fluid, although encephalitis is rare (263). Visual disturbances include sudden myopia, which is pathognomonic for NE, which occurs in one-third of patients (sudden shortsightedness of −1 diopters [217]), and loss of vision and other ophthalmological manifestations may also occur. In severe cases, hypotension or shock may develop (301, 438). Oliguria, anuria, and other signs of renal involvement (elevated serum creatinine level and proteinuria) together with back pain begin on days 3 to 4 and may require dialysis treatment (for 5% of hospitalized PUUV patients). In the second week, polyuria develops (224, 301, 396). In PUUV infections, manifest hematuria (or other hemorrhagic manifestations, e.g., petechiae) is rare, but microscopic hematuria is usually seen in the laboratory. Other typical laboratory findings include proteinuria, high serum creatinine levels, low thrombocyte counts, and high C-reactive protein levels (resembling bacterial infections) (224, 301, 396). Pulmonary infiltrates or edema vaguely reminiscent of HPS may occur in hospitalized patients (190, 250). Additionally, cardiac manifestations and arthritis can occur. A recent study found that 57% of patients have electrocardiogram (ECG) changes in the acute phase (264). In rare cases, shock and severe pulmonary edema may occur. The mortality rate, according to recent data, is about 0.1%. Severe anuria and shock are associated with the HLA B8-DR3 haplotype (303). The disease is rare in children, but if they contract the disease, the clinical picture is similar but usually milder than that for adults, except for more common abdominal manifestations (301). Complications include hypophyseal hemorrhage and consequent hypopituitarism (137) and mesangiocapillary glomerulonephritis (302). In addition, an association of PUUV and other hantaviruses with hypertension has been suggested and debated (76, 123, 279, 438). A higher prevalence of tubular proteinuria and increased urinary protein excretion and higher systolic blood pressure are seen 6 years after acute NE, although at 10 years, most of the changes were not significant (279, 280).

The clinical picture for DOBV is similar to that described above for PUUV but more severe, with more hemorrhagic complications, shock (21 to 28%), oliguric renal failure (30 to 47%), and abdominal and pleural effusions being encountered more often. As for PUUV infections, GI symptoms and ECG changes are common (20, 267, 324). Severe neurological sequelae have also been described (56). DOBV resembles HTNV-like viruses. For HTNV, a severe course with shock, serious hemorrhages or electrolyte imbalance, renal failure, or pulmonary edema occurs in 20 to 30% of patients, whereas 30 to 40% of cases are considered mild (229, 233). Compared to PUUV infection, petechiae, rash, and mucosal injection are also more evident, and hypotension, later hypertension, and bleeding tendency are more common. The symptoms reported for SEOV infections are again milder (203). The treatment of severe HFRS requires maintaining the fluid balance and circulatory volume while avoiding dangerous overhydration (for patients that are anuric and with leaky capillaries), which is of critical importance. Patients with renal insufficiency may need dialysis treatment.

Spectrum of HPS Disease in the Americas

HPS is a severe acute disease associated with a rapid onset of respiratory failure and cardiogenic shock (198, 331, 335). HPS bears some resemblance to HFRS except that the lungs are targeted for capillary leakage instead of the kidneys (41, 278, 294, 295, 332, 440, 461). However, kidney involvement has been recognized in HPS cases (329). The clinical presentation of HPS disease and the case fatality rate have been noted to depend upon the strain of infecting hantavirus (89, 331, 367, 462). Cases of HPS have been reported for the following American countries: the United States, Canada, Argentina, Bolívia, Brazil, Chile, Panama, Paraguay, and Uruguay. Furthermore, benign hantaviral infections have been reported, without cardiopulmonary disease, which could explain the large number of individuals in South America with antibodies to hantavirus but who have never had recognizable HPS (54, 101, 102, 204).

The outcome of HPS is usually severe, because 1 to 3 days after the onset of respiratory symptoms, the disease produces a leaking syndrome in the lung capillaries, from which the patient evolves to respiratory failure followed by cardiogenic shock. Renal failure signs and myositis have also been reported for cases of HPS caused by ANDV and ARAV in South America (53, 319) and SNV, BAYV, and BCCV in North America (146, 197, 329). Generally, the onset of HPS symptoms occurs after an incubation period of 9 to 33 days (mean, 14 to 17 days). These estimates are based on cases where investigations of exposure to the rodent reservoir have been well determined (460). The clinical course of HPS disease in Brazil will be reviewed in depth below. Overall, the clinical course can be broken into five distinct phases, with clinical variation in the incidence and severity of symptoms among patients. Following the incubation period, patients develop a febrile prodrome with fever, myalgia, and progressively worsening thrombocytopenia, often accompanied by headache, back pain, abdominal pain, and diarrhea. Both IgM and IgG antibodies appear shortly after the onset of the prodrome.

Based on data collected from 70 Brazilian HPS cases, illness starts with fever (for 79% of the cases), myalgia (60%), and weakness (21%) (53). Twenty-five percent of the patients also show gastrointestinal symptoms, including nausea, vomiting, and diarrhea. These prodrome symptoms usually last no more than 5 days. After the second day of disease, patients start to have dyspnea (87%) and cough (44%), followed by tachycardia (81%) and low arterial blood pressure levels (56%). Cyanosis reflecting respiratory failure was found for 21% of the cases 5 to 6 days after the onset of symptoms. Four to seven days after the onset of illness, a decreased blood pressure occurred for 44% of the patients, and shock occurred for 33% of patients. Renal failure based on increased levels of creatinine occurred in 51% of the patients. In addition, two patients had transient anuria. Mild hemorrhagic disturbances such as hematuria, hematemesis, intestinal bleeding, and metrorrhagia were observed for 50% of the patients between days 3 and 5 after the onset of illness. Fewer than 150,000 platelets/mm^3 of blood were observed for 92% of the patients, metabolic acidosis was found in 57% of patients, blood O_2 saturation was <90% in 50% of patients, the hemoconcentration was >45% in 70% of patients, and leukocytosis was found for 67% of patients. In-

creased blood levels of aspartate transaminase (AST) and alanine aminotransferase (ALT) were found for 73% and 83% of the patients, respectively (53). Bilateral and diffuse lung interstitial rales in chest radiographies evolving to alveolar rales were observed for the majority of the cases (53). Most of the HPS patients were admitted to the hospital between days 3 and 6 after the onset of symptoms. Fatal outcome occurred 1.3 ± 0.5 days after admission to the hospital, and on the contrary, survivors stayed in the hospital for 8.9 ± 4.5 days (53). Other studies describing the clinical presentations of HPS from other regions within the American Continent corroborate most of the clinical data presented here (27, 90, 295, 366, 400).

Pathogenesis

HPS has a complex pathogenesis associated with the presence of the infecting hantavirus and an intense immune activation that results in changes in vascular permeability. Most patients develop pulmonary edema followed by respiratory failure, hypotension, and cardiogenic shock (97). Hantaviral infection in the lungs begins with an interaction of Gn and Gc surface glycoproteins with target endothelial cells, macrophages, and platelets that have β3 integrin receptors at the cell membrane (116, 117). These cells allow virus replication, which induces immune activation (115). Immune activation, especially by macrophages and CD8 T cells, may be involved in the pathogenesis that leads to respiratory failure and to severe HPS (96, 201). Activated macrophages secrete proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6. An excess of cytokines produced by macrophages and activated hantavirus-specific T cells upon antigen recognition on infected pulmonary endothelial cells is probably critical for HPS pathogenesis (201). CD4 T cells, after antigen recognition, differentiate at least two subsets of helper cells, T helper 1 (Th1) and Th2 cells. Th1 cells produce gamma interferon (IFN-γ) and TNF-β (or lymphotoxin-α), responsible for cell-mediated immunity, and this differentiation is regulated by IL-12. Th2 cells produce IL-4 and IL-5 and promote humoral and allergic responses (196). On the other hand, inducible regulatory T cells that produce IL-10 and transforming growth factor β (TGF-β), two immunosuppressive cytokines, have an important role in regulating the immune response and infection-induced pathology (40). Pro- and anti-inflammatory Th1 and Th2 cytokine profiles associated with the sera of 21 HPS patients infected with ARAV showed very high levels of IL-6 for fatal HPS cases (39). The depressive effects of IL-6 on myocardial function have been documented *in vitro*, in animal models, and in other human diseases (109, 174). A positive correlation between IL-6 and nitric oxide (NO) serum concentrations suggests a direct negative inotropic effect through NO induction by IL-6 (109). Furthermore, IL-6 levels were correlated negatively with arterial blood pressure in patients, suggesting that IL-6 has an important role in inhibiting cardiac function and inducing hypotension in HPS, and the magnitude of IL-6 expression could be decisive for the outcome of HPS patients. Cytokines of the Th1 pattern, IL-12, TNF-β, and IFN-γ, were detected in some HPS patients, and their significantly different levels were probably related to serum sample collections at distinct phases of the disease. IFN-γ levels in a group of patients with fewer than 7 days of disease were significantly increased, suggesting early Th1 activation in HPS. The involvement of Th1 cells in HPS is suggested by the high levels of IL-12 and TNF-β found for some patients. Furthermore, positive correlations between IL-12 and IFN-γ and between IFN-γ and TNF-α were observed. Th1 immune responses play key roles in antiviral immunity, favoring viral clearance; however, they also produce immunopathogenic effects that may aggravate HPS (133). High levels of TNF-β were correlated with hypotension and hemocentration, and a positive correlation was found between IL-12 and hemocentration. Thus, these results indicate that Th1 immune response effector cytokines correlate with the severity of HPS. IL-4, the major cytokine associated with the Th2 pattern, was absent in the sera of HPS patients, but the level of IL-5, another important cytokine associated with Th2 cells, was significantly increased in these patients. High levels of IL-6 present in HPS patients, along with IL-5, suggest that there is some Th2 immune response activation in HPS, in accordance with the strong humoral response observed for HPS patients with SNV (33), which includes Th2 antibody classes such as IgA, IgG1, and IgG3 (42). These results suggest that a mixed pattern of Th1 and Th2 responses could occur in HPS. A mixture of Th1 and Th2 T-cell patterns, shown by IFN-γ and IL-4 intracellular staining of peripheral blood mononuclear cells (PBMC), was also demonstrated for patients with HFRS although with preferential Th1 differentiation (415). The soluble IL-2 receptor (sIL-2R) is released from the surface of T cells upon activation, when systemic inflammation is present, serving as cytokines; are secreted by distinct subtypes of regulatory T cells; and play a crucial role in the control of the immune response and immunopathology (290). Interestingly, TGF-β levels were low in HPS patients in the first 7 days of disease. TGF-β regulates inflammatory responses with a critical and nonredundant function as an antagonist of Th1 development (249). It is possible that the inhibition of TGF-β production could occur during hantavirus infection. The downregulation of T-cell function by the inhibition of their proliferation is thought to be important for TGF-β-mediated immunosuppression (305). Large amounts of hantavirus-specific CD8 T cells are present in the blood of HPS patients compared to numbers of these cells in other viral infections (201). Low levels of TGF-β could explain the intense immune response present in HPS patients and suggest a decreased regulatory effect on the production of Th1 cytokines in the first week of illness. Chen and Yang showed that in the early stages of HFRS, the level of suppressor T-cell activity was decreased, and a negative correlation between the suppression level and the proportion of CD8 cells was observed (64). It is tempting to speculate that the hantavirus-induced inhibition of TGF-β production affects regulatory T-cell generation in the early stage of HPS, but the underlying mechanism of this phenomenon is unknown. The protective effect of TGF-β in HPS patients was suggested by the positive correlation between TGF-β serum levels and blood arterial pressure. In addition, the hypothesis that TGF-β1-expressing regulatory T cells may play an important role in limiting immunopathology in the natural reservoir host was suggested by a study of the immune response in deer mice (*Peromyscus maniculatus*) that were experimentally infected with SNV (393). Despite the contingent deficiency of TGF-β-mediated regulatory function in HPS patients, the

downregulation of the immune response to hantavirus seems to be mediated by IL-10. High levels of IL-10 were detected in the sera of HPS patients. Supporting this, a high number of IL-10-producing cells was observed in the myocardium of fatal HPS cases during the acute phase of the illness (133). In addition, IL-10 serum concentrations correlate with those of IL-12. Indeed, IL-10 production is enhanced in human T cells by IL-12 by a mechanism of negative-feedback regulation of the immune response. However, the regulatory mechanism mediated by IL-10 seems to be inefficient because IL-10 levels correlated with hypotension and hemoconcentration in HPS patients (39). The potential role of immunoregulation abnormalities in HPS remains an open question.

The basic mechanisms behind HFRS pathogenesis also relate to increased vascular permeability, and as noted above, the causative agents infect endothelial cells without cytopathic effects (78, 422, 438). There has not been a proper animal model for HFRS, and the Syrian hamster model for ANDV and HPS (157) is not applicable for HFRS. However, cynomolgus monkeys infected with wild-type PUUV strains (not cell culture adapted) produce NE-like disease symptoms and clinical pathology, including elevations of nitric oxide, various cytokine (IL-10, IL-6, and TNF-α), and C-reactive protein (214) levels. In histological studies of animals, viral antigen and RNA detected by *in situ* hybridization and nucleocapsid protein detected by immunohistochemical staining were observed in kidney, spleen, and liver tissues. In the kidneys, the virus-infected cells colocalized with inflammatory cell infiltrations and tubular damage, and these infiltrations contained mainly CD8-type T cells (402). These findings are similar to those reported for human kidney tissues of NE patients (421), suggesting that viral replication together with the immune response are involved in tissue injury (422). Importantly, there is a genetic predisposition toward severe HFRS disease related to HLA type (303).

LABORATORY DIAGNOSIS

Serological Tests

Upon the onset of symptoms, virtually all acute HFRS and HPS cases have IgM and IgG antibodies to the N protein. Hence, serological tests that detect IgM and/or IgG antibodies to hantaviral antigens in serum are the most common approaches for the laboratory diagnosis of suspected cases of HPS and HFRS. One of the first serological tests used for diagnoses of HFRS in Europe and Asia was the indirect immunofluorescence assay (IFA) using hantavirus-infected cells fixed as an antigen on microscope slides. The use of virus-infected cells for serological tests is not widely used because cell culture infections require BSL-3 laboratories. Thus, most hantavirus antigens currently used in serological tests are those derived by using recombinant DNA methods. These antigens are mostly N proteins, but Gn and Gc proteins have also been produced. The N protein has been expressed and purified from a number of recombinant expression systems, including bacterial (183, 189), baculovirus (189, 391), insect (436), *Saccharomyces* spp. (363, 392), plant (195, 200), and mammalian (35) cells. All three structural proteins (Gn, Gc, and N) can induce a high level of IgM detectable at the onset of symptoms (45, 94, 106, 259, 434), but the IgG response to the glycoproteins may be delayed, and in the acute phase, the diagnostic IgG IFA pattern is granular (188). The N protein, the most abundant viral protein, induces a strong humoral immune response in humans and rodents and shows three major epitopes of cross-reactive antigens for hantaviruses. Numerous studies have demonstrated that these antigenic sites are located in the amino-proximal region of the N protein (252, 260, 350).

The N protein is suitable for use as an antigen in immunoenzymatic assays (EIAs) for the diagnosis of hantavirus infection (106, 147) as well as strip immunoblot tests (147). However, the most common serological tests for hantaviruses are indirect IgG and IgM enzyme-linked immunosorbent assays (ELISAs) as well as IgM capture ELISAs. The rapid IgM capture ELISA developed by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Centers for Diseases Control and Prevention (CDC) is effective for the diagnosis of HFRS and HPS (99). These tests take about 4 to 6 h when performed by trained personnel. Virus-infected lysates or purified N protein can be used as an antigen in ELISAs. ELISAs have been developed for the South American hantaviruses as well (321). Recently, the recombinant N protein (rN) of ARAV was purified from *Escherichia coli* cells. To test ARAV rN as an antigen for antibody detection, sera from 30 patients from Argentina previously known to be seropositive for hantavirus were tested, and all were found to be positive for IgG and IgM by ELISA by using either ARAV or ANDV rN antigens. Six out of 60 serum samples from Brazilian patients with suspected HPS (10%) were positive by IgM ELISA using the ARAV rN antigen, and seven were positive using the ANDV rN antigen. Considering the results obtained with these 90 sera, in terms of hantavirus antibody detection, the sensitivity of the IgM ELISA using the ARAV rN antigen was 97.2%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 98.1%. The results show that ARAV rN is a suitable antigen for the diagnosis of hantavirus infection in Brazil and Argentina (105, 106). An immunochromatographic test for the fast diagnosis of HFRS (167) and HPS (Nanocore) using the rN protein of ARAV as an antigen has been tested (106).

Immunoblot and neutralization tests have also been used for the serological diagnosis and typing of suspected hantaviral infections (33, 102, 126, 252, 350). Valdivieso et al. performed a neutralization test to detect ANDV and SNV in plasma samples from 20 HPS patients from Chile and the United States by a focus reduction neutralization assay with Vero E6 cells and found high titers of neutralizing antibodies to these viruses (430). This type of neutralization test could be used as a routine test for the serological diagnosis of hantaviral infections. It is widely recognized that a plaque reduction neutralization test (PRNT) is the most definitive method to facilitate the identification and differentiation of hantaviruses (73, 386). It is a specific test that can detect and measure neutralizing antibodies. Cross-PRNT permits the serotypic classification of hantavirus infection in rodents and humans (69, 73, 242). Although the assay is highly specific and is capable of distinguishing hantaviruses with serum from experimentally infected animals, it was shown to be less specific when human acute-phase sera from HFRS and HPS patients were used (69). Neutralization tests are laborious and require BSL-3 laboratories.

However, these tests remain the methods of choice for distinguishing between related hantavirus infections serologically, although early sera may show more broad cross-reactivity than convalescent-phase sera.

Molecular Diagnostics

As reviewed above, HPS is a fast-evolving disease with a high case fatality rate, and thus, there is a clear need for rapid diagnostic tests. In 12 to 24 h, a patient can evolve from acute febrile illness to severe pneumonia with respiratory failure and cardiogenic shock. Thus, rapid diagnosis is essential for these patients. Highly sensitive diagnostic tests have been developed based on the detection of the virus genome. The hantavirus genome can be rapidly detected by reverse transcription-PCR (RT-PCR) with clinical samples, such as blood, serum, or organ fragments, from the first day after the onset of illness. The detection of viral genomes in patients before the first day of symptoms has been reported (104, 318). In general, primary amplification of hantaviral RNA from cell culture can be performed by using RT-PCR (119, 144). However, the low levels of viral RNA present in human and rodent tissue samples can require nested-RT-PCR techniques using primers selected for regions with high homology. Nested-RT-PCR tests have been developed, for example, for HTNV (247), SNV (150), PUUV (98), and ARAV (296, 351).

TREATMENT AND PREVENTION

At present, we know of no antivirals, vaccines, or immunotherapeutics approved by the U.S. Food and Drug Administration (FDA) for any of the hemorrhagic fever viruses, including HFRS and NE. Ribavirin has *in vitro* and *in vivo* antiviral activity against members of the *Bunyaviridae* and the *Arenaviridae*. Ribavirin reduces mortality and was proven effective for the treatment of lethal encephalitic suckling mice (202) infected with HTNV (165). Studies performed in China with HFRS patients suggest that the drug ribavirin provides an improved prognosis when given early in the course of disease. In that study, it was found that if ribavirin therapy was initiated before the end of the first week of illness, there was a 7-fold reduction in the risk of dying (163, 164). Ribavirin has been examined for the treatment of HPS, but the results were inconclusive (60, 62, 278). In those studies, intravenous ribavirin was well tolerated; 71% of recipients became anemic, and 19% underwent transfusion. Based on these limited trials, ribavirin had no apparent clinical benefit for HPS patients. These results suggest that the efficacy of ribavirin as a treatment for hantavirus disease may depend on the phase of infection and the severity of disease at the time of first administration of the drug. A recent report by Rusnak et al. confirms that the early treatment of HFRS with intravenous ribavirin reduces the occurrence of oliguria and the severity of renal insufficiency (373).

Analyses of blood collected from HFRS patients show that patients remain viremic during the acute phase of disease (12). These results suggest that the administration of human neutralizing antibodies during this phase might prove effective for the treatment and/or prophylaxis of hantaviral infections. At present, there have been no published reports of controlled clinical trials of immunotherapy for HFRS or HPS. However, studies of hamsters and rats indicated that the passive transfer of neutralizing monoclonal antibodies (MAbs) or polyclonal sera to HTNV can passively protect animals from challenge with hantaviruses (193, 384). Furthermore, an HTNV Gc-specific neutralizing MAb administered up to 4 days after challenge with virus cured hamsters of infection (248). The passive immunization of primates with neutralizing MAbs to PUUV protects them from subsequent PUUV challenge (215). Studies have shown that the passive transfer of sera from rhesus macaques vaccinated with the M segment of ANDV can protect against lethal challenge with ANDV in hamsters (80). These data suggest that a posthantavirus prophylaxis treatment regimen may be effective, as shown for other viral diseases such as rabies, hepatitis A and B, and varicella viruses (381). In spite of the potential promise of passive immunotherapy for the treatment of hantavirus infection, sufficient concentrations of antibodies must be present and effective for an adequate duration and at the relevant site of pathogen challenge. Current protocols for the systemic administration of Ig may not achieve these criteria for pathogen challenge of the lung in HPS cases.

The abrupt onset of respiratory failure and shock in HPS disease calls for treatments that are rapid and targeted to the site of infection. However, as with HFRS, there are no FDA-approved antivirals, vaccines, or immunotherapeutics available for the treatment of HPS disease; thus, treatment is primarily supportive. It is recommended that patients be moved to a unit with intensive cardiopulmonary care. With the rapid onset of pulmonary edema, focus on blood pressure and maintenance of oxygenation is key. Intubation and mechanical ventilation (usually required for 5 to 7 days) are provided as required. The quick deterioration of the condition of the patient also warrants the use of a flow-directed continuous-cardiac-output-measuring pulmonary artery catheter as soon as it is needed. Indicators of poor outcome include pulmonary edema and cardiac arrhythmias that are aggressively treated. Interestingly, in Chile, 81% of the patients in one study had hemorrhage in the cardiovascular stage of the disease (55). This has not been described for other American cases.

The prevention of diseases caused by hantaviruses is based on principles of rodent control such as reducing rodent shelter and food sources in and around the home, eliminating rodents inside the home and preventing them from entering the home, using standard precautions for preventing hantavirus infection while rodent-contaminated areas are being cleaned up (16), prevention measures for persons who have occupational exposure to wild rodents (2), and precautions for campers and hikers (10, 66). In addition to minimizing the risk of hantavirus exposure, the prevention of hantaviral disease could be augmented by effective vaccines and strategic vaccination of at-risk populations. Vaccination of individuals in areas of endemicity or those who could be exposed to the virus in military, clinical, and research settings may offer a strategy for reducing the risk and incidence of disease. In Chile and Argentina, medical personnel treating HPS patients would be considered an at-risk population because of the possibility of the person-to-person transmission of ANDV. The basic strategy of vaccine efforts has focused on glycoproteins, which elicit a protective neutralization response (80, 155–157, 230, 269). The first clin-

ical trials for a DNA-based vaccine for HTNV are under way at the USAMRIID.

FUTURE PROSPECTS AND CONCLUDING REMARKS

The emergence of zoonotic pathogens remains one of the great unsolved mysteries in biology. In the past century, numerous pathogens have emerged and reemerged, with an estimated frequency of one new pathogen every 18 months. Of these new pathogens, the majority have zoonotic origins in wildlife, and many have been RNA viruses such as the hantaviruses, severe acute respiratory syndrome coronavirus (SARS CoV), Ebola virus, Nipah virus, Hendra virus, West Nile virus, and, most recently, the 2009 H1N1 swine flu that initially emerged in Mexico (181, 297). These and many other viruses harbored in vertebrates and invertebrates will continue to provide potential sources of new infections of humans and domestic or wild animals. There are many principles that have been learned from past epidemics and pandemics. Fundamentally, however, there remain gaps in our understanding of the ecology and natural history of zoonotic viruses; how they are maintained in their reservoirs; the processes and mechanisms that lead to transmission, host switching, recombination, and reassortment; and molecular events that lead to the transfer and adaptation to a new host and posttransfer adaptation.

One approach to answering these and other questions has been to formulate and analyze mathematical models for virus-host models of the SIR (susceptible, infectious, and recovered) type. These types of models have been applied to a variety of viral zoonoses (see, e.g., references 24, 129, and 162) and have led to some new and interesting questions and hypotheses. These types of approaches have led to several new mathematical models that describe the dynamics of the rodent-hantavirus interaction (7–9, 270, 448). These models incorporate the important features of hantaviral infection in wild rodent populations and of rodent population dynamics: differences in male and female seroprevalence, density-dependent survival with little or no disease-related deaths, lack of vertical transmission, and random mating. As reported by Allen et al., deterministic and stochastic models have been formulated for male and female rodents identified as either susceptible (S), latent (E), infectious (I) (viral shedding), or recovered (R) (no viral shedding) (SEIR model) (7). Some important questions have arisen from the model formulations. Are infected (RNA-positive) rodents infectious for their entire life? Should models include only the states S, E, and I, or should they include R? Should additional infectious stages be included, I_1 and I_2, where newly infected and chronically infected rodents are distinguished (378, 379, 446, 452)? As discussed above, field data on landscape, rodent densities, and seroprevalence levels show a complex pattern of interactions. To gain insight into the relationship among rodent densities, hantaviral infection, and the environment, models can include environmental stochasticity. In these models, carrying capacity is assumed to vary randomly and seasonally, independently from the population dynamics. The variation in carrying capacity directly affects the population dynamics and indirectly affects the infection process. The stochastic simulations show that hantaviral outbreaks can be triggered by a large increase in rodent population densities, but due to stochastic variability, this is not always the case. These investigations and others have led to new mathematical findings for seasonally varying populations that enable estimations of the basic reproduction number, the threshold for disease outbreaks (23, 442a, 446, 447).

Analysis of multispecies SIR-type models suggests possible consequences of spillover infections (6, 168). The spillover species can potentially contribute to the maintenance of the pathogen in the wild, especially during times of low prevalence, provided that there is spillback infection. In addition, the spillover species may be instrumental in the evolution of new hantaviruses. The role that developmental stages, juvenile (nonreproductive) or adult (reproductive), play in the persistence of infection was investigated in a discrete-time SI model (C. Wesley, L. Allen, C. Jonsson, Y. K. Chu, and R. Owen, presented at the International Conference on Difference Equations and Applications, Kyoto, Japan, 2007). The level of infection is reduced in nonreproductive stages because of their short duration and the assumption of maternal antibody protection. Thus, our models show that the inclusion of the nonreproductive stages leads to lower overall seroprevalence levels and underscore the differences that can arise in vertically versus horizontally transmitted viruses.

Models can be translated across zoonotic diseases and, in conjunction with data analysis, provide insight into ecological trends, an understanding of the underlying causes of outbreaks, and guidelines for their control and prevention. The integration of basic and applied research with modeling will be instrumental in gaining a comprehensive understanding of how zoonotic viruses are maintained and transmitted within their natural ecosystems and the mechanisms that lead to their emergence or "outbreaks." Furthermore, these types of efforts can lead to the discovery of new ecological paradigms and a true understanding of the nature of episodic zoonotic epidemics such as those caused by Ebola virus, SARS CoV, Nipah virus, and Machupo virus as well as many new viruses, including hantaviruses, that remain to be discovered.

ACKNOWLEDGMENTS

We thank Yong-kyu Chu, Douglas Goodin, Anthony J. Battisti, and Paul R. Chipman for figures included in this review. We thank Ki-Joon Song for information on HFRS cases in South Korea and Linda J. Allen for discussions on mathematical modeling.

We thank the NIH (grants 1 R01 TW006986-01 and R03TW007813) for supporting part of the work (C.B.J.) referenced in this review.

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Colleen B. Jonsson received her Ph.D. from Purdue University in 1990 from the Department of Biochemistry. She has held positions as an Assistant and Associate Professor at New Mexico State University (1993 to 2003), Adjunct Faculty at the University of Alabama—Birmingham (2003 to 2009), and Senior Scientist and Program Leader at Southern Research Institute (SR). Currently, she is a Professor at the University of Louisville (UofL) in the Department of Microbiology and Immunology, Director for the UofL Center for Biodefense and Emerging Infectious Diseases and Regional Biocontainment Laboratory, and Program Director of the SR Specialized Biocontainment Screening Center. Her interest in hantaviruses was sparked when she moved to New Mexico in 1993 and an outbreak of hantavirus illness in humans emerged in this region. Shortly thereafter, a hantavirus outbreak occurred in Paraguay, where she has conducted the majority of her field work.

Luiz Tadeu Moraes Figueiredo graduated in medicine from the University of Uberlandia, MG, Brazil, in 1976. His doctorate thesis was presented to the School of Medicine of the University of São Paulo in Ribeirão Preto City, SP, Brazil, in 1985. He was a postdoctoral fellow at the Yale Arbovirus Research Unit, Yale University, New Haven, CT, 1985 to 1987. Presently, Dr. Figueiredo is a Full Professor of Infectious and Tropical Diseases and the Director of the Virology Research Center of the School of Medicine of the University of São Paulo in Ribeirão Preto City, SP, Brazil.

Olli Vapalahti is an M.D. with a specialty in clinical microbiology and is a Professor of Zoonotic Virology. He studied medicine at the University of Helsinki, Helsinki, Finland, where he also completed his thesis on genetic and antigenic properties of Puumala and Tula viruses in 1996. His research group focuses on various aspects (e.g., ecology, epidemiology, diagnostics, and disease associations) of zoonotic viruses and arboviruses, including hantaviruses. He is also responsible for a diagnostic laboratory unit for viral zoonoses at the Helsinki University Central Hospital.