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ECOLOGY OF RODENT-ASSOCIATED HANTAVIRUSES IN THE SOUTHERN CONE OF SOUTH AMERICA: ARGENTINA, CHILE, PARAGUAY, AND URUGUAY

R. Eduardo Palma,[1,7] **Jaime J. Polop,**[2] **Robert D. Owen,**[3,5] **and James N. Mills**[4,6]
[1] Departamento de Ecología and Centro de Estudios Avanzados en Ecología y Biodiversidad, CASEB, Pontificia Universidad Católica de Chile, Alameda 340, Santiago 6513677, Chile
[2] Departamento de Ciencias Naturales, Universidad Nacional de Río Cuarto, Agencia Postal No. 3, 5800 Río Cuarto, Córdoba, Argentina
[3] Department of Biological Sciences, Texas Tech University, Lubbock, Texas 79409, USA
[4] Viral Special Pathogens Branch, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, Georgia 30333, USA
[5] Current address: Martín Barrios 2230 c/ Pizarro, Barrio Republicano, Asunción, Paraguay
[6] Current address: 1335 Springdale Road, Atlanta, Georgia 30306, USA
[7] Corresponding author (email: epalma@bio.puc.cl)

ABSTRACT: Thirteen hantavirus genotypes, associated with at least 12 sigmodontine reservoir rodents, have been recognized in the four countries that represent the Southern Cone of South America. Host–virus relationships are not as well defined as in North America; several Southern Cone hantaviruses appear to share a common host and some viruses do not occur throughout the range of their host. Although hantavirus–host relationships in the Southern Cone are less strictly concordant with the single-host–single-virus pattern reported elsewhere, recent studies suggest that much of the ambiguity may result from an incomplete understanding of host and hantavirus systematics. Although some Southern Cone host species are habitat generalists, some sympatric species are habitat specialists, helping to explain how some strict host–virus pairings may be maintained. In some cases, host population densities were higher in peridomestic habitats and prevalence of hantavirus infection was higher in host populations in peridomestic habitats. Seasonal and multiyear patterns in climate and human disturbance affect host population densities, prevalence of infection, and disease risk to humans. Unusually high hantavirus antibody prevalence in indigenous human populations may be associated with frequent and close contact with host rodents. Ongoing studies are improving our understanding of hantavirus–host ecology and providing tools that may predict human risk.

Key words: Argentina, Chile, ecology, hantavirus, host, Paraguay, rodents, Uruguay.

INTRODUCTION

Hantavirus infection in rodents and humans in the Southern Cone of South America (Paraguay, Uruguay, Argentina, and Chile) has been recognized since 1982, when antibodies to a Seoul-like virus were detected in 10 of 101 *Rattus norvegicus* and *Rattus rattus* trapped in port areas of Buenos Aires and Mar del Plata (Maiztegui et al., 1983; LeDuc et al., 1986). The discovery of Sin Nombre virus (SNV) and associated hantavirus pulmonary syndrome (HPS) in North America in 1993 prompted prospective and retrospective studies in South America to determine whether hantaviruses circulated in native South American rodent populations and whether hantaviruses might be associated with respiratory distress of unknown etiology in the Southern Cone. The first prospectively diagnosed cases of HPS in the Southern Cone were reported in 1994 and 1995 (Williams et al., 1997; Baró et al., 1999; Enría and Pinheiro, 2000); HPS was retrospectively confirmed in Chile and Argentina from as early as 1975 (Baró et al., 1999; Parisi et al., 1996), indicating that HPS is not a new phenomenon in the Southern Cone. The earliest host studies demonstrated that mice of the rodent family Cricetidae, subfamily Sigmodontinae, especially the genus *Oligoryzomys*, was the major reservoir of hantaviruses transmitted to humans in the Southern Cone (Williams et al., 1997; Levis et al., 1998). Hantavirus pulmonary syndrome in the Southern Cone is unique in that a contiguous area in Argentina and Chile is the only place where human hantavirus infection (by Andes virus [ANDV]) has been shown to be transmitted person to person (Enría et al., 1996; Padula et al., 1998; Ferres et al., 2007). Since the first recognized cases of HPS in the Southern Cone in 1994, the region has been the focus of intensive studies of hantavirus ecology. Recent reviews of the ecology of hantavirus–host relationships in Europe and North America have been published (Olsson et al., 2010; Mills et al., 2010). Nevertheless, there has been no comprehensive review of hantavirus ecology in the Southern Cone. We describe the recognized hantavirus–host associations in the Southern Cone, discuss their distribution and ecology, relate lessons learned from serosurveys and ecologic studies, and suggest directions for future research.

Host–virus associations

Thirteen named genotypes of New World hantaviruses are currently recognized from the Southern Cone in association with at least 12 species of sigmodontine rodent hosts (Table 1, Fig. 1). Only two of these genotypes (Andes and Laguna Negra) are recognized as viral species according to the International Committee on the Taxonomy of Viruses (ICTV, 2009). In addition, as mentioned above, the Old World Seoul virus occurs in association with its cosmopolitan host, the Norway rat (*R. norvegicus*) at least in eastern Argentina (Maiztegui et al., 1983). Sigmodontine rodents and associated hantaviruses exhibit a pattern suggestive of cospeciation throughout the Americas (Morzunov et al., 1998; Plyusnin and Morzunov, 2001; Yates et al., 2002; Chu et al., 2006, although see Ramsden et al., 2009), including the Southern Cone. The phylogenetic and taxonomic relationships among the Southern Cone hantaviruses have not been fully resolved by taxonomists. Although in general, each hantavirus is associated with a single primary host species, several apparent exceptions to this pattern in the Southern Cone may relate to our imperfect knowledge of the taxonomy of the host species. Recent work on the phylogenetics of *Oligoryzomys* (Rivera et al., 2007; Gonzalez-Ittig et al., 2010; Palma et al., 2010) has contributed to our understanding of the complexity of the relationships between species of *Oligoryzomys* and several hantaviruses. We now know, for example, that the host for Oran virus is *Oligoryzomys chacoensis*, not *Oligoryzomys longicaudatus* (host for ANDV), as originally described (Rivera et al., 2007). *Oligoryzomys flavescens* is now described as a species complex and the host for Lechiguanas and Central Plata genotypes in eastern Argentina and Uruguay appears to be a separate nominal species (*O. flavescens*-east) than the host of Bermejo virus (*O. flavescens*-west; Gonzalez-Ittig et al., 2010; Table 1). Still some relationships are yet to be defined; the host of the HU39694 genotype was also described as *O. flavescens* (Levis et al., 1997), but the virus and host are from northern Buenos Aires province, an area about halfway between the samples that were described as O. *flavescens*-east and *O. flavescens*-west and these mice were not studied.

Although the sample sizes on which associations have been based are generally small, several Southern Cone hantaviruses have been associated with more than one species of potential host (Table 1). Laguna Negra virus (LANV) appears to be associated with two related host species, *Calomys laucha* in the Paraguayan Chaco (Williams et al., 1997) and *Calomys callosus* in northern Argentina (Levis et al., 2004) and Bolivia (Carroll et al., 2005). Juquitiba virus, which is associated with *Oligoryzomys nigripes*, was recently identified in three *Oxymycterus nasutus*, as well as one *Oligoryzomys nigripes* in southern Uruguay (Delfraro et al., 2008). The identification of host–virus associations in the Southern Cone is based on highly variable evidence, ranging from a few antibody-positive individuals (Delfraro et al., 2008) to broad cross-sectional and longitudinal studies, virus isolation and sequencing, and laboratory transmission studies (ANDV;

Levis et al., 1998; Lopez et al., 1997; Padula et al., 2004). The reliable establishment of natural host–virus associations is helping to clearly define true host–virus relationships (Rivera et al., 2007), but additional work is needed to clearly understand the roles of host specificity, spillover, host-jumping, and cospeciation in hantavirus–host associations.

Geographic distributions of hosts and viruses

The recognized geographic distributions, biomes, and habitat associations of hantavirus hosts in the Southern Cone also are summarized in Table 1. Accurate descriptions of host ranges and habitat preferences facilitate the identification of potential disease-endemic areas and more accurate geographic assignment of risk to human populations. Nevertheless, the complex and still relatively poorly understood systematics of many sigmodontine rodents in South America, combined with the scant sampling records for some taxa, complicate the documentation of accurate distributional data. Although several species once believed to be distributed across large geographic areas (e.g., *O. longicaudatus* and *O. flavescens*) are being recognized as complexes of species or subspecies (Rivera et al., 2007; Palma et al., 2010; Gonzalez-Ittig et al., 2010), other widespread species (e.g., *C. laucha*) are still in need of careful taxonomic study.

Not all hantaviruses are distributed throughout the recognized range of the host species. This lack of correspondence may be due to one or a combination of factors including a requirement for threshold population densities to sustain infection in the reservoir (Madhav et al., 2007), or the existence of unrecognized cryptic host species that might not support infection by a specific virus (Mills and Childs, 1998). Although most hantavirus–host species in the Southern Cone have not been sampled throughout their range, sampling of *O. longicaudatus* in Chile has been extensive (Medina et al., 2009). The major focal area for ANDV is the Valdivian temperate forests of south-central Chile, southward from the Bío-Bío River, near Concepción, to the Aisén region, near Cohaique (Table 1, Fig. 1). Nevertheless, ANDV has been reported in *O. longicaudatus* populations as far north as the Coquimbo region (30°S, Fray Jorge National Park [Torres-Perez et al., 2004]), and southward to Patagonia, near Punta Arenas (52°S, Fuerte Bulnes [Belmar-Lucero et al., 2009]). Thus ANDV has been documented throughout most of the distribution of *O. longicaudatus* in Chile, with a structured geographic pattern according to major ecogeographic zones: Mediterranean, Temperate and Patagonian Forests (Torres-Pérez et al., 2010). In Argentina, ANDV in *O. longicaudatus* is recognized only from the Valdivian temperate forests (Rio Negro, Neuquén, and Chubut provinces [Levis et al., 1998; Enría and Pinheiro, 2000; Cantoni et al., 2001; Piudo et al., 2005]).

Laguna Negra virus does not occur throughout the currently recognized range of its host. Although LANV has been documented in association with *C. laucha* (and *C. callosus*) populations in the Paraguayan Chaco and adjacent Bolivia and northern Argentina (Williams et al., 1997; Yahnke et al., 2001; Levis et al., 2004; Carroll et al., 2005), it is conspicuously absent from the southern part of the range of the host in central Argentina, where antibody testing of more than 1,000 *C. laucha* from 20 localities in Santa Fe and Buenos Aires provinces failed to yield evidence of infection with LANV (Mills and Childs, 1998). This suggests that the southern population of *C. laucha* may be a genetically distinct species or subspecies (Mills and Childs, 1998). In central Argentina, there is striking sympatry of hantavirus genotypes, particularly in northern Buenos Aires and southern Santa Fe provinces, where Lechiguanas, HU39694, Pergamino, and Maciel viruses occur together (Fig. 1 [Levis et al., 1998]). Of these, only Lechiguanas and HU39694 appear to share a host (*O. flavescens*). In Uruguay, despite the widespread distribution of its host (also

TABLE 1. Recognized hantaviruses in the Southern Cone of South America, their primary hosts, known countries of virus presence, distribution and habitat of reservoir host, and associated disease.

Virus	Host	Known virus range	Distribution and biome[a] of host	Host habitat	Disease[b]	References
Andes (ANDV)	*Oligoryzomys longicaudatus*	S Argentina Chile	Argentina: Valdivian temperate forest & steppe. Chile: Mediterranean (matorral) ecoregion (27°S) S to Valdivian temperate & Magellanic subpolar forest & Tierra del Fuego (55°S)	Shrub, forest edge, forests with bamboo (e.g., *Chusquea quila*), brushy peridomestic habitat	HPS	Levis et al., 1998; Enría and Pinheiro, 2000; Lozada et al., 2000; Torres-Pérez et al., 2004; Palma et al., 2007; Polop et al., 2010
Orán (ORNV)	*Oligoryzomys chacoensis*	N Argentina	Argentine & Paraguayan Chaco		HPS	Levis et al., 1998; Pini et al., 2003; Rivera et al., 2007
Juquitiba[c] (JUQV)	*Oligoryzomys nigripes*, *Oxymycterus nasutus*	N Argentina S Brazil E. Paraguay Uruguay	Ol.n: Atlantic forest of Paraguay & NE Argentina; marshes & wet grasslands of C and SE Brazil; Ox. n: Areas of human disturbance, SE Brazil & Uruguay	Ol.n: marshes and wet grassland, rain forest Ox.n: disturbed areas, roadsides, shrublands, *Acacia* and *Eucalyptus* plantations	HPS	Chu et al., 2006; Padula et al., 2007; Rivera et al., 2007; Delfraro et al., 2008
Lechiguanas (LECV)	*Oligoryzomys flavescens*-east[d]	C Argentina SW Uruguay	Argentina: Pampas, Parana flooded savanna, Yungas, 22–40°S; Uruguay: Savanna	Cultivated fields, roadsides, railroad rights-of-way, grasslands, forest, marshes, rivers	HPS	Massoia and Fornes, 1965; Mills et al., 1991; Polop and Sabattini, 1993; Levis et al., 1997; Porcasi et al., 2005; Rivera et al., 2007
HU39694	*Oligoryzomys flavescens*,	C Argentina	See Lechiguanas	See Lechiguanas	HPS	Levis et al., 1998
Maciel (MACV)	*Necromys benefactus*	C Argentina	Arid Chaco, Espinal & Pampas of Argentina	Relatively stable areas in disturbed habitats (roadsides, railroad rights-of-way)	NR	Mills et al., 1991; Levis et al., 1998; Pardiñas et al., 2004
Bermejo (BMJV)	*Oligoryzomys flavescens*-west[d], *O. chacoensis*	N Argentina E Paraguay	NW Argentina, especially Yungas		HPS	Levis et al., 1998; Padula et al., 2002; Chu et al., 2006; Rivera et al., 2007
Pergamino (PRGV)	*Akodon azarae*	C Argentina	Chaco, Espinal and Pampas of C Argentina;	Crop fields, railroads, crop field borders	NR	Mills et al., 1991; Levis et al., 1997; Levis et al., 1998; Pardiñas et al., 2004

TABLE 1. Continued.

Virus	Host	Known virus range	Distribution and biome[a] of host	Host habitat	Disease[b]	References
Laguna Negra (LANV)	*Calomys laucha, C. callosus*	NW Paraguay N Argentina	Cl: Chaco of N Argentina & Paraguay, Argentine Pampa to Uruguay; Cc: Savanna, Chaco, Bolivia, Argentina, Paraguay	Cl: crop fields and its borders Cc: grasslands, forest edges, brush, crop fields, weeds, roadsides, orchards	HPS	Kravetz and Polop, 1983; de Villafañe et al., 1988; Pearson, 1993; Williams et al., 1997; Levis et al., 2004; Carroll et al., 2005; Pardiñas and Teta, 2005; Polop et al., 2010
Alto Paraguay (ALPV)	*Holochilus chacarius*	Paraguay	Mesic Parana Atlantic forests, Paraguay, NE Argentina		NR	Chu et al., 2006
Ape Aime[e] (AAIV)	*Akodon montensis*	Paraguay	Parana Atlantic forests of E Paraguay, NE Argentina & SE Brazil	Areas of intermediate disturbance, dense understory with sparse overstory, old fields	NR	Chu et al., 2006; Ghimire, 2006; Goodin et al., 2009; Chu et al., 2011
Jaborá (JABV)	*Akodon montensis*	S Brazil, Paraguay	See Ape Aime	See Ape Aime	NR	Raboni et al., 2009; Chu et al., 2011
Central Plata (no abbreviation)	*Oligoryzomys flavescens*[b]	Uruguay	See Lechiguanas	See Lechiguanas	HPS	Delfraro et al., 2003

[a] Biome identifications follow Figure 1.

[b] HPS = hantavirus pulmonary syndrome; NR = none recorded.

[c] Includes Juquitiba IP37 and IP38 from *O. nigripes* in Paraguay.

[d] Recognized as a distinct nominal species by Gonzales-Ittig et al. (2010).

[e] AAIV is a reasortment with S segment of JABV and M segment of PRGV (Chu et al., 2011).

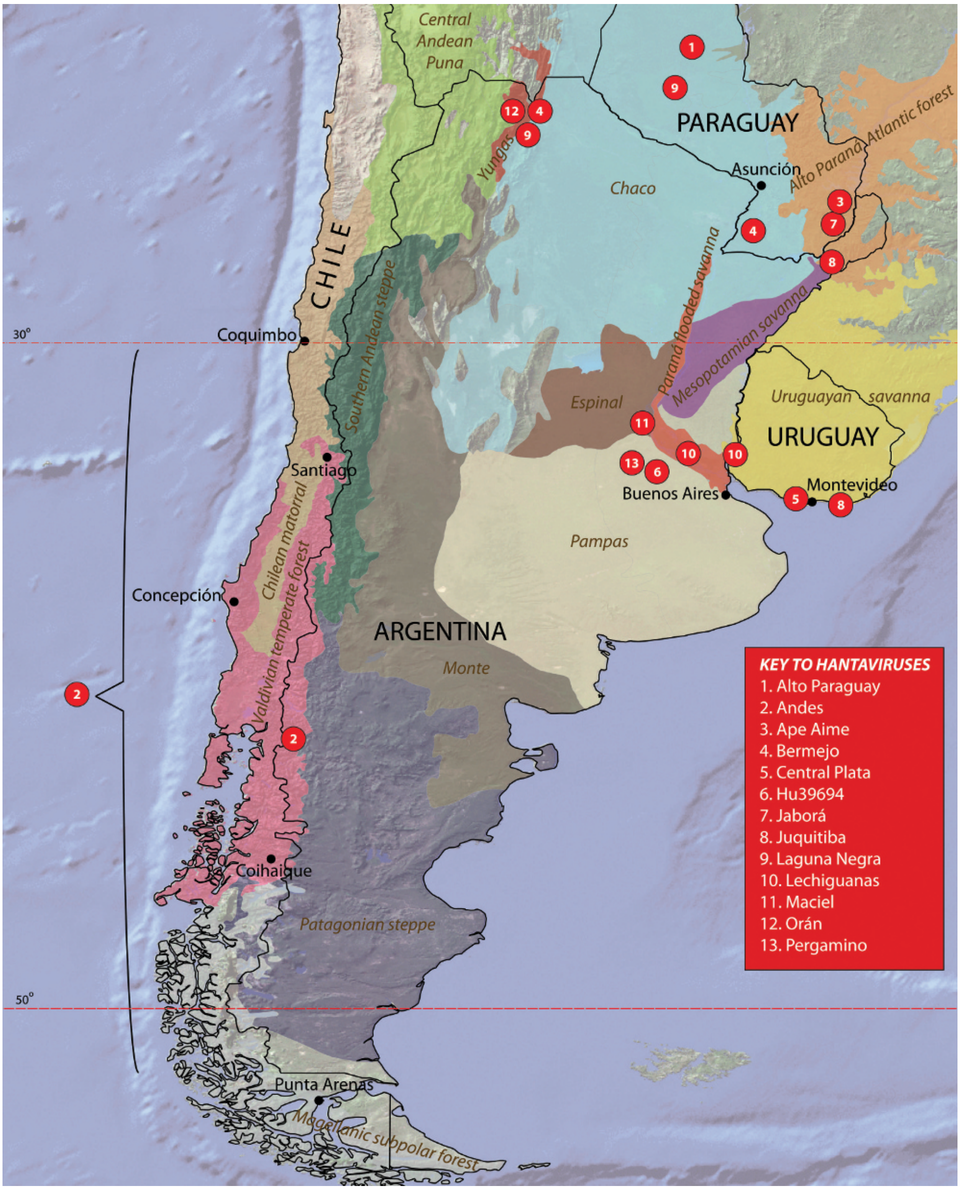

FIGURE 1. New World hantaviruses in the Southern Cone and their associated biomes. Numbered circles identify the approximate locations of the first description in each Southern Cone country for each of the 13 recognized hantaviruses (see table for host associations). The large bracket represents the currently recognized geographic extent of Andes virus in *Oligoryzomys longicaudatus* host populations in Chile. Ape Aime (3), Jabora (7), and Juquitiba IP37 (8) viruses were described from the same locality. Bermejo (4) and Orán (12) viruses were both described from near the town of Orán in Argentina. Biome identifications and boundaries based on World Wildlife Fund ecoregions accessible through the United Nations Environmental Programme GEO Data Portal: http://geodata.grid.unep.ch/.

reported to be *O. flavescens*), Central Plata virus has been detected only in the southern half of the country, particularly in rural Montevideo, Canelones, Florida, and San José; human HPS cases are also restricted to these areas (Delfraro et al., 2003). The reasons for apparent restriction of virus activity to portions of the host range are unclear. Continued taxonomic studies of host species and serosurveys throughout host ranges are needed.

Field studies: Habitat-specific findings

In addition to the large-scale patterns, host and pathogen populations may vary among habitat types on a local scale (Table 1). It has been suggested that hosts for zoonotic viruses are more likely to be opportunistic, generalist species that frequently inhabit anthropogenically disturbed habitats (Mills, 2006). Indeed, the majority of host species listed in Table 1 are at least partly associated with anthropogenically disturbed habitats. It is possible that some of the specific life-history traits of these opportunistic species (e.g., high motility, high fecundity, and capacity to reach very high population densities) predispose them to evolve and maintain associations with zoonotic pathogens. It is also possible, however, that this pattern is sampling error: We are more likely to recognize zoonotic pathogens associated with opportunistic species because those are species with which we come into contact and share our environment (Mills, 2006).

Among the species associated with anthropogenically disturbed habitats, there seems to be a gradient in tolerance to disturbance. Three syntopic species on the Argentine Pampa offer an example. *Necromys benefactus* frequents only the most stable areas of its disturbed agricultural habitat (e.g., roadsides and railroad rights-of-way; Table 1); *Akodon azarae* may inhabit these stable areas as well as intermediate-disturbance, weedy crop field habitats; *C. laucha* seems to occur only in the most disturbed crop-field habitat (Table 1). This habitat partitioning may be the outcome of competitive interactions. It also seems to prevent frequent spillover of distinct viruses hosted by these species (e.g., Maciel virus in *N. benefactus* and Pergamino virus in *A. azarae*; as mentioned above, *C. laucha* hosts LANV, but apparently not on the Pampa).

Akodon montensis was more abundant in habitats of intermediate levels of anthropogenic disturbance (Ghimire, 2006). In the Interior Atlantic Forest of eastern Paraguay, *A. montensis* was most frequently trapped in areas with little forest overstory and denser vegetation near the ground (Goodin et al., 2009). Moreover, there was a significant difference in the habitat occupied by antibody-positive vs. antibody-negative rodents, indicating that habitats with greater overstory cover may promote transmission and maintenance of Ape Aime virus in *A. montensis*.

Prevalence of infection in other host species may vary among habitats. Rodents trapped from 15 sites throughout Paraguay were more likely to have hantavirus antibodies in anthropogenically disturbed habitats (Goodin et al., 2006). Similarly, antibody prevalence in *O. flavescens* in Uruguay was higher in environments modified by humans (agroecosystems, roadsides, shrub lands, artificial woods, and peridomestic areas) than in undisturbed habitats (Delfraro et al., 2003). The mechanism(s) leading to higher infection prevalence in disturbed habitats is not clear, but the apparent correlation between anthropogenic disturbance and prevalence of infection in some hosts suggests that such disturbance may increase risk of HPS for some human populations.

Chu et al. (2009) found Jaborá and Juquitiba IP37 viruses in *A. montensis* and *Oligoryzomys* sp., respectively, captured 20 m apart in the Interior Atlantic Forest of eastern Paraguay. Moreover, Chu et al. (2011) reported RNA-segment reassortment of these same hantaviruses in *A. montensis*, indicating close and interactive associations enabling host switching between *A. montensis* and *Oligoryzomys* sp., and thus at least partially shared microhabitat utilization.

Temporal patterns

Human HPS cases in the Southern Cone occur throughout the year, with peak incidence generally in spring. In general, sigmodontine populations in the Southern Cone show an annual cycle of population density with a minimum in spring and a peak in the autumn (Mills et al., 1991; Guthmann et al., 1997; Polop et al., 2010). The highest hantavirus antibody prevalence in host populations generally occurs during the spring period of low population densities (Cantoni et al., 2001; Piudo et al., 2005; Mills et al., 2007). Nevertheless, the highest absolute numbers of antibody-positive animals were associated with the highest population densities. Thus the relatively higher risk to humans in spring may be associated with the higher prevalence of recent infections and, therefore, greater viral shedding by hosts.

Studies have documented striking demographic variation in *O. longicaudatus* (Lima and Jaksic, 1998; Pearson, 2002; Murúa and Briones, 2005; Sage et al., 2007), one of the sigmodontine rodents most strongly affected by climatic events. Mast seeding events of grasses such as the bamboo, *Chusquea quila*, may trigger population irruptions ("ratadas"), with population densities as high as 100 mice/ha (Fuentes and Campusano, 1985; Jimenez et al., 1992; Gallardo and Mercado, 1999). During the 2001 ratada in southern Chile, hantavirus antibody prevalence was >11%, almost twice that normally found in the southern Andes (Murúa et al., 2003). Experiments with discrete-time models populated with data from Paraguayan field studies indicated that periods of high antibody prevalence may result from stochastic variation as well as favorable environmental conditions (Wesley et al., 2009).

Mechanisms of transmission

Hantaviruses are thought to be transmitted to humans predominantly via airborne particles of saliva, urine, or feces from infected rodents. Studies comparing sexes and age classes for Southern Cone host species corroborate the hypotheses that older animals are more frequently infected than younger animals, and males more frequently than females (Mills et al., 1997; Torres-Perez et al., 2004), suggesting that hantaviruses are maintained in reservoir populations by horizontal virus transmission primarily among male mice. Nevertheless, in small sample sizes of antibody-positive *O. flavescens* in central Argentina, higher hantavirus prevalence was not observed in males or older animals (Mills et al., 2007), leading those authors to speculate that transmission in *O. flavescens* might follow a different mechanism. Experimental transmission between rodents has been demonstrated only with ANDV in *O. longicaudatus* (Padula et al., 2004). These results suggested that saliva was the principal medium of transmission but did not rule out a role for feces or urine.

Association of scars or wounds with the presence of hantavirus antibody has been used to suggest intraspecific agonistic encounters as a mechanism of hantavirus transmission within host populations (Mills et al., 1999). Nevertheless, the low evidence of aggression in some *Oligoryzomys* species suggests that fighting and biting would not be a common mechanism of virus transmission among some host species, and that viral transmission may occur during communal nesting in winter (Suárez et al., 2003; Mills et al., 2007; Polop et al., 2010).

Spillover to other rodent species

Transient or spillover infections from the primary host may occur where species are syntopic. *Abrothrix longipilis*, *Abrothrix olivaceus*, and the phyllotine *Loxodontomys micropus* with antibodies to a hantavirus (presumably ANDV) in Chile and Argentina were considered spillover infections (e.g., Piudo et al., 2005; Lázaro et al., 2007; Polop et al., 2010). The detection of Pergamino virus (hosted by *A. azarae*) genetic material in one *O. flavescens* individual was considered spillover infection and an example of two hantavirus lineages occurring in the same species at the same location (Suárez et al., 2003).

In Paraguay, eight species (*A. azarae, Bibimys chacoensis, Graomys griseoflavus, Nectomys squamipes, Oxymycterus delator, Oligoryzomys chacoensis, O. fornesi,* and an unidentified species of *Oligoryzomys*) had antibody to one or more unidentified hantaviruses and were considered possible spillover hosts (Chu et al., 2003; Delfraro et al., 2008). The role of secondary hosts in the transmission of hantaviruses is controversial. Although it has been hypothesized that increased diversity of the potential host assemblage may lead to lower rates of pathogen transmission (including hantaviruses [Mills, 2005]), susceptible, infected, susceptible and susceptible, infected, recovered multihost models indicate that under certain circumstances, persistence of infection in rodent populations can be enhanced by the presence of secondary or spillover species (McCormack and Allen, 2007a). Additional modeling using Paraguayan data indicated that environmental changes that result in greater habitat overlap can result in more interspecific encounters that may lead to outbreaks or even pathogen establishment in a new host (Allen et al., 2009).

Spillover to human populations

Unlike in North America, infection in human populations in the Southern Cone can be common, especially among indigenous populations. In the central Chaco of Paraguay, 78 (40%) of 193 indigenous people were antibody positive. There was no difference in prevalence between sexes, and antibody prevalence increased with age (67% in those over 53 years of age [Ferrer et al., 1998]). In Canindeyú, eastern Paraguay, 7 (25%) of 28 indigenous Ache had antibody (Chu et al., 2003). Although the infecting hantavirus cannot be accurately determined by serology, with few exceptions antibody-positive sera had more intense reactivity with Río Mamoré and SNV antigens (New World hantaviruses) than with Old World Seoul virus antigen (Ferrer et al., 1998; Chu et al., 2003). Infection in nonindigenous populations may be much rarer, perhaps reflecting differential living or working environments that result in decreased exposure to infected rodents (Ferrer et al., 1998). However, the HPS outbreaks of 1995–1996, 2008, and 2011 in the Paraguayan Chaco involved primarily nonindigenous residents (Williams et al., 1997; Owen, unpubl.).

One study of the relationship between HPS cases and environmental, demographic, and rodent distribution variables supports the frequency-of-exposure concept. Using generalized linear models, Busch et al. (2004) suggested that the seasonal pattern of HPS cases in Buenos Aires province, Argentina was due to an increase in the probability of interaction between humans and rodents. The increased interaction may be caused by an increase either in rodent population density, increased use of the same habitat by rodents and humans, or seasonal variation in the proportion of hantavirus-infected rodents.

Spatial and temporal patterns

In a large area of northern Buenos Aires and southern Santa Fe provinces in Argentina, antibody-positive *O. flavescens* were captured in only two of six study sites monitored for 3 years, although the species was captured at all sites (Mills et al., 2007). These results suggest that the presence of the virus in host populations is temporally sporadic and spatially focal in these host populations, as has been reported in other hantavirus–host systems (Glass et al., 1998). On the other hand, deterministic and stochastic models incorporating multiple hosts or multiple patches have demonstrated that under certain conditions, hantavirus persistence may be enhanced by "refugia" both within alternate (spillover) species and loosely connected patches (such as would be more commonly encountered in fragmented landscapes; [McCormack and Allen, 2007a, b; Allen et al., 2009]). Owen et al. (2010) found a complex pattern of spatial and temporal variation in both population abundance and antibody prevalence in *A. montensis* in the Interior Atlantic Forest of eastern Paraguay. They found highest antibody prevalences in habitats of intermediate disturbance (i.e., no recent disturbance, but selective logging evidenced by older tree stumps; Goodin et al., 2009) and the greatest variation in prevalences in the most disturbed habitat (recent selective logging and road construction).

Environmental factors associated with prevalence of infection in host populations

Simplification of ecosystems through deforestation and other anthropogenic disturbances may result in increased viral transmission in rodent hosts, and increased risk to humans (Mills, 2005). Anthropogenically disturbed habitats usually support few predators, and although rodent species assemblages are depauperate, high population densities of a few opportunistic host species may contribute to increased transmission, dramatically increasing the prevalence of infection in host populations. In Argentina, population densities for hantavirus host species in peridomestic rural sites were similar to or higher than those in open fields represented by other rural sites, suggesting a higher risk in peridomestic settings (Calderón et al., 1999). Nevertheless, some studies in Argentina demonstrated a higher trap success and higher numbers of infected animals in natural, relatively undisturbed areas than in urban and periurban areas (Cantoni et al., 2001). It is likely that relative risk among habitats and levels of disturbance will vary according to the preferences and habits of individual host species.

Factors of a more regional or even global scale may have equal or greater influence on host populations and prevalence of infection. Studies in central Chile showed a close association between El Niño Southern Oscillation events and abundance of sigmodontine rodent populations (Meserve et al., 1995; Jaksic et al., 1997). Increased numbers of host rodents were followed by increased antibody prevalence in host populations after 1 or 2 months, suggesting delayed-density-dependent effects on antibody prevalence. Delayed-density-dependent prevalence may also occur on a seasonal scale, related to seasonal reproduction in temperate climates. Populations of *A. azarae*, *Necromys benefactus*, and *O. flavescens* in central and southern Argentina had low antibody prevalence in autumn when populations were at peak density but consisted of primarily young mice. Antibody prevalence was highest in the spring, when overwintered populations were smaller but consisted of older mice. High antibody prevalences during times of low population density, with lower prevalences in months with high population densities, suggested delayed-density-dependent effects on antibody prevalence in those populations (Mills et al., 2007).

Perspectives, future studies

The diversity of sigmodontine rodents in South America is very high; the number and diversity of hantavirus relationships with sigmodontine hosts is unknown but potentially great. The natural host relationships, host and virus distribution, systematics and biogeography, and the biology of Southern Cone hantaviruses in their primary and any secondary hosts needs to be better defined. Although major advances have been made for some taxa (e.g., some *Oligoryzomys* spp.), studies are needed of the life history characteristics and ecologic and evolutionary relationships of *O. chacoensis, O. nigripes, N. benefactus, A. montensis, C. callosus*, and others.

Important questions regarding hantavirus–host systems remain unanswered, including: Can rodents other than the primary reservoirs (e.g., transiently infected hosts) contribute to the long-term maintenance of hantaviruses in nature?

What are the mechanisms for the maintenance and spread of hantaviruses in natural populations? Is a minimum threshold host density necessary to sustain long-term infection? What environmental factors (biotic, abiotic, and structural) affect population density? What is the role of rodent community diversity in hantavirus maintenance and transmission? What are the distributions of specific host–virus associations and the variation in host and virus genetics throughout the Southern Cone? Are there different mechanisms of viral transmission in different hosts? What are the effects of hantavirus infection on growth, behavior, or survivorship in host populations?

A comprehensive review (Klein and Calisher, 2007) suggests that there is generally a single hantavirus–single rodent host association. Although a body of evidence supports this conclusion (Yates et al., 2002), recent authors discard host–hantavirus coevolution (Ramsden et al., 2009). Studies in Paraguay reported hantavirus antibody in 10 species, four of which (from three genera) carried detectable hantavirus RNA, suggesting either that several hantaviruses are cocirculating in Paraguay, or that some hantavirus strains are capable of infecting multiple hosts (Chu et al., 2006). In Chile, studies are underway to evaluate whether ANDV is responsible for antibody found in other sigmodontine species besides the primary ANDV host (*O. longicaudatus*), such as *A. longipilis* and *A. olivaceus*.

For hantaviruses in the Southern Cone, we still know very little about environmental factors that influence host populations, virus transmission, or virus shedding. Field and laboratory studies of effects of environmental factors are needed. The integration of results from these studies with remote sensing and spatial analysis of satellite images can provide models that may help predict specific times and places of increased risk to human populations. Long-term ecology–epidemiology studies underway in Chile and Argentina will develop predictive models using satellite imagery, as well as integrate biotic and abiotic data, to better predict the risk of human disease. Researchers in Paraguay are synthesizing data from rodent and hantavirus studies, satellite imagery, ground-based vegetation data, and mathematical modeling toward production of predictive models of host abundance, prevalence of hantavirus infection, and human risk.

Laboratory studies of hosts and pathogens are needed in parallel with field studies. Some critical information regarding virus biology within the host, virus maintenance within individuals and populations, and intra- and interspecific transmission will best (perhaps only) be gained by simulating natural conditions in outdoor, seminatural captive colonies. Such data are particularly needed for parameterization of mathematical models. Successful transmission studies have been conducted in such an environment (Padula et al., 2004) and we anticipate that critically important data will be generated by investigative teams using similar outdoor colonies.

We have summarized what is known about hantavirus–host relationships in the Southern Cone and identified some of the gaps in our knowledge. We have not covered the expanding literature on these topics in the northern Neotropics, or in Central America. Reviews from these areas are needed. Nor have we attempted (except briefly) to compare and contrast Southern Cone patterns with those seen in North America, Europe, and Asia. We hope that our review and the recent reviews from North America and Europe will stimulate such comparative studies.

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