

ECOLOGICAL FACTORS OF RODENT ASSEMBLAGE STRUCTURE AFFECTING
HANTAVIRUS PREVALENCE AT VARYING SPATIAL SCALES

by

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DEDICATION

To all the wonderful rodents sharing our world . . .

ACKNOWLEDGEMENTS

My deepest Love and Grattitude to Megan, Noah, Posey, Pebbledisco, and LooLoo.

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LIST OF ABBREVIATIONS

Abbreviation	Description
ACE	Abundance Coverage-Based Estimate of Richness
AIC_c	Akaike Information Criterion
BP	Berger-Parker Dominance Index
CDC	Centers for Disease Control
EID	Emerging Infectious Disease
ELISA	Enzyme-Linked Immunosorbant Assay
ENSO	El Niño Southern Oscillation
<i>H'</i>	Shannon Diversity Index
H(C)PS	Hantavirus (Cardio) Pulmonary Syndrome
HCR	Hispid Cotton Rat (<i>Sigmodon hispidus</i>)
HFRS	Hemorrhagic Fever with Renal Syndrome
ICTV	International Committee on Taxonomy of Viruses
IUCN	International Union for Conservation of Nature
LSCV	Limestone Canyon Virus
MDHS	Most Dominant Host Seroprevalence
MNTD	Mean Nearest Taxon Distance
MPD	Mean Pairwise Distance
NAO	North Atlantic Oscillation
NE	Nephropathia Epidemica
PCA	Principal Component Analysis
PD	Faith's Phylogenetic Distance
PDO	Pacific Decadal Oscillation
PIE	Hurlbert's Probability of Interspecific Species Encounters; Index of Evenness
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SNV	Sin Nombre Virus
TAS	Total Assemblage Seroprevalence
WMA	Wildlife Management Area
WMDHS	Weighted Most Dominant Host Seroprevalence
WTAS	Weighted Total Assemblage Seroprevalence

ABSTRACT

Zoonotic pathogens are the dominant cause of novel and reemerging infectious diseases. Hantaviruses (family Bunyaviridae) and their associated human diseases occur globally and differ according to their geographic distribution and type of illness exhibited in humans. Prevention of these diseases requires surveillance of seroprevalence in animal populations. Small mammal assemblage structure and species richness are suggested as strong drivers for the maintenance and spread of hantavirus infections. Climatic factors, such as precipitation, can influence reservoir density and abundance by increasing available food resources. These fluctuations in rodent assemblage structure can contribute to the maintenance or reduction of hantavirus seroprevalence. My research objectives were to: 1) determine the ecological correlates of hantavirus prevalence in small mammal assemblages at the site, region, continent, and global levels; 2) to compare differences in prevalence found in sylvan and disturbed habitats; 3) investigate the relationship between phylogenetic diversity and prevalence; 4) develop predictive models for hantavirus prevalence in rodent assemblages using defined ecological correlates; and 5) to quantify transmission events and seroconversions between naïve and infected rodents. I found that of the currently recognized 681 Cricetid, 730 Murid, 61 Nesomyid, and 278 Sciurid species, approximately 11.3%, 2.1%, 1.6%, and 1.1% respectively, have known associations with hantaviruses. The diversity of hantaviruses hosted by rodents and their distribution among host species supports a reassessment of the paradigm that each virus is associated with a single host species. By considering reservoir host diversity and

distribution patterns I holistically evaluate the symbiotic and pathogen-host associations between rodents and hantaviruses. I examine this association on a global taxonomic and geographical scale, model these associations, compare habitats (i.e. sylvan vs. peridomestic) across a latitudinal gradient from Texas through México with emphasis placed on the rodent host diversity and distribution, and quantify infection seroconversion rates of naïve, wild rodents from interactions with naturally infected conspecifics.

I. INTRODUCTION

In this dissertation, I explore the complexities of the hantavirus disease system as it occurs in the natural world. This document is meant to be read as four separate manuscripts examining ecological correlates of hantavirus prevalence in small mammal (particularly rodent) assemblages at varying spatial scales.

In Chapter 1, I provide a comprehensive examination into our current understanding of global mammalian host distributions and the hantaviruses they carry. Additionally, this chapter challenges the current dogma of a one-virus-one-host paradigm, provides insight pertaining to shared interspecies distributions, how this factor addresses the need for a new perspective on hantavirus maintenance and co-circulation, and highlights areas throughout the world where surveillance of these viruses can better facilitate our understanding and enhance our ability to prevent disease outbreaks in humans.

Chapter 2 utilizes this information, and translates our current knowledge of hantavirus-host distributions to provide predictive models at the global and continental scale. These models utilize data provided from research across the globe to aid in predicting what biological and ecological characteristics of small mammal assemblages predict hantavirus prevalence. These models may prove useful in the prediction of hantavirus outbreaks based from environmental and biotic factors obtained through surveillance of small mammal (i.e. rodent) species diversity.

Habitat and anthropogenic disturbance play a key role in the persistence of zoonotic diseases. In Chapter 3, I address the role habitat disturbance plays in the prevalence of hantaviruses in small mammal assemblages from sites across southern

México through northeast Texas. At each site, I compare differences in assemblage prevalence based on habitat type, where concurrent rodent sampling was conducted at disturbed (e.g. peridomestic) versus sylvan habitats at each site across the region. Additionally, species diversity and dominance characteristics were compared from both habitat types. The results of this study greatly challenge the current focus of species diversity playing a dominant role in disease maintenance (i.e. “the dilution effect”) Instead, I address a species identity effect, where hantavirus prevalence is not necessarily decreased with increased species richness, but rather infection persistence is driven in part by the distinctiveness of species comprising the assemblage.

Finally, Chapter 4 addresses the mechanisms behind hantavirus transmission. Here, I examine seroconversion rates of naïve (e.g. uninfected) hispid cotton rats (*Sigmodon hispidus*) through exposure to an infected cohort at controlled varying densities. I constructed large, outdoor experimental enclosures (20 x 20 meters; 4 total). Within each enclosure, 12 game-cameras were positioned for maximum area coverage and were used to collect still and video images of individual rodent interactions. Wild cotton rats were caught, infection status (i.e. naturally hantavirus infected or naïve) determined through enzyme-linked immunosorbent assay (ELISA), marked with a unique pelage identifier and placed in enclosures (e.g. experimental arenas) at varying densities: low = 1 infected, 1 naïve; medium = 1 infected, 5 naïve; and high = 1 infected, 10 naïve. During each five-night trial, cameras recorded activity patterns and potential infection transmission events quantified as contact rates.

This research has also provided avenues for policy changes within the department of Biology. I have contributed to the development of protocols regarding the holding and

receiving of vertebrate mammals (i.e. rodents) for research purposes. Furthermore, this work has paved the way for future studies regarding hantaviruses at the molecular level. I developed protocols for safe, effective ELISA techniques which have contributed to many additional projects regarding hantavirus research and international collaboration. Additionally, the enclosures constructed are a valuable contribution to the Department of Biology, and encourage interdisciplinary collaborative research.

II. GLOBAL DIVERSITY AND DISTRIBUTION OF HANTAVIRUSES AND THEIR HOSTS

Background

Emerging infectious diseases (EIDs) are on the rise worldwide, and are mostly zoonotic (Taylor et al. 2001; Klempa et al. 2006; Jones et al. 2008; Halliday et al. 2012; Karesh et al. 2012). Many pathogens are endemic and typically occur naturally in wild animal populations (Wobeser 2007; Karesh et al. 2012). Considering the history of outbreaks, it is likely that we will see continued emergence and resurgence of zoonotic pathogens (Jones et al. 2008). Hence, to assure human health we must know the patterns of pathogen diversity hosted by wildlife species (Anthony et al. 2013; Ezenwa et al. 2015).

The discovery of an exceptionally virulent pathogen during the pre-emergence phase could lead to the prevention of widespread outbreaks (Dearing and Disney 2010) and requires SMART (strategic, measurable, adaptive, responsive and targeted) surveillance of reservoir hosts (Mills et al. 2010; Aguirre et al. 2012; Halliday et al. 2012). The undiscovered richness of viruses in mammals is estimated to exceed 320,000 viruses, where each mammalian species hosts on average around 50 viruses, some of which are pathogenic (Anthony et al. 2013). Because of shared recent ancestry, viruses hosted by other mammals have a higher likelihood of affecting humans (Longdon et al. 2011) making mammals the most relevant reservoirs of zoonotic pathogens in contrast to other taxonomic groups (i.e., amphibians, reptiles, etc.). The ecology and life histories of wild mammals that harbor pathogens require our attention to understand how pathogens that

are responsible for widespread mortality and morbidity in humans are maintained in nature (Tatem et al. 2006).

Within class Mammalia, the order Rodentia is the most numerous, encompassing around 2,277 species of the 5,400 described mammalian species translating to 42% of the world's mammalian biodiversity (Wilson and Reeder 2005). Rodents populate every continent (except Antarctica) and are reservoir hosts for a wide variety of zoonotic pathogens (Meerburg et al. 2009). Therefore, knowing the diversity, distribution, and pathogen associations in these species is essential to understanding the ecology of zoonotic diseases.

Addressing the myriad of pathogens carried by rodents is beyond the scope of this study as there have been reviews in this regard (Morand et al. 2015). Instead, I chose to focus on tallying and describing known hantavirus-host associations and the global distribution of rodent hosts. Since hantaviruses negatively affect human health by producing hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) which are diseases of global concern (WHO 2016, www.who.int), a worldwide focus on rodent hosts is clearly needed to understand these pathogens. Herein, I review the diversity and distribution of rodent host species that are known to harbor hantaviruses (family *Bunyaviridae*: genus *Hantavirus*), paying special attention to rodent species serving as reservoir hosts of those hantaviruses that cause disease in humans. I define a host species as a species in which hantaviruses replicate and are actively transmitted to other individuals or are naturally shed into the environment. Reservoirs, are also defined here as host species associated with hantaviruses known to cause hantavirus disease in humans.

Thorough and extensive reviews of hantaviruses and their associated diseases have greatly contributed to our understanding of these viruses on a global scale (Zeier et al. 2005; Jonsson et al. 2010; Vaheri et al. 2013). However, previous reviewers have devoted their greatest attention to the viruses rather than the hosts. Emphasis on the mammals harboring these viruses remains limited and research is often driven toward certain species (e.g., *Peromyscus maniculatus*, the host of Sin Nombre virus in North America), with no systematic review aimed to cover all known hosts. Though I present a comprehensive list of all known or suspected hosts of hantaviruses, I focus attention on rodents (specifically, the family Cricetidae), and seek to provide a different context that may aid the understanding of the relationships between rodents and the hantaviruses they harbor. Assessment of the current state of knowledge of these associations will be useful to mammalogists, veterinarians, virologists, public health officials, ecologists, and other researchers interested in the study of zoonotic diseases.

Hantaviruses and Associated Diseases

Hantaviruses are among the most widely distributed emerging pathogens (Chandy et al. 2008; Knust and Rollin 2013). There are over 90 hantavirus genotypes described worldwide with at least 22 of these known to be pathogenic to humans (Bi et al. 2008; Krüger et al. 2011; King et al. 2012; Vaheri et al. 2013). Humans are a spillover host of these viruses that acquire the infection when particles of infected rodent excreta are inhaled (Jonsson et al. 2010). Human diseases associated with hantaviruses are most frequently categorized as hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS; sometimes referred to as hantavirus cardiopulmonary

syndrome [HCPS]). Our knowledge regarding the global presence of HFRS and HPS is limited to clinically confirmed human case reports. In many regions of the world, numerous deaths potentially associated with these viruses are likely not confirmed or are misdiagnosed, thus the exact global burden of hantavirus disease remains unknown (Jonsson et al. 2010).

The genus *Hantavirus* is broadly segregated into two major groups, “Old World” and “New World” hantaviruses, where pathogenic Old World strains are associated with HFRS while pathogenic New World strains with HPS (Muranyi et al. 2005). Human disease is typically restricted to the area of distribution of rodent reservoirs of the families Cricetidae and Muridae associated with New World and Old World illnesses, respectively (Vaheri et al. 2013). This generalization assigns HFRS to the Old World and HPS to the Americas. However, a non-endemic host species (i.e. *Rattus norvegicus*) and its associated hantavirus (Seoul virus) and disease have also been confirmed in the Americas and the United Kingdom (Lundkvist et al. 2013). Hence, globalization may provide an avenue for the further introduction of infected exotic reservoirs into naïve environments expanding the reach of these diseases.

Systematic review of rodent hosts of hantaviruses

I conducted a search of peer-reviewed literature by using a combination of terms such as “hantavirus, rodents, HPS, HFRS, nephropathia epidemica, hosts, and reservoirs” for articles published from 1971-2015 using Google, Google Scholar, Web of Science (www.webofknowledge.com), and the Centers for Disease Control and Prevention (CDC) homepage (www.cdc.gov). The CDC website provided relevant articles and related links

including PubMed (www.pubmed.gov) and the U.S. National Library of Medicine (www.nlm.nih.gov). References listed in journal articles were also used to source the original reports in primary literature of hantavirus hosts, their associated viruses, and any related human disease. My objective was to gather a globally comprehensive list of wild mammals in which specific hantavirus genetic material (RNA) has been identified. Therefore, my list only includes host-virus associations confirmed by genetic techniques (PCR). Thus, my criteria exclude records of serologic results in which a specific hantavirus cannot be identified. When necessary, corrections for rodent host taxonomy were noted (I used Wilson and Reeder (2005) as taxonomic reference) and included in the final dataset. Furthermore, my list includes hantavirus genotypes initially described in the literature as unique, though further analysis of hantavirus phylogenetics classify some viruses as likely variants of existing named viruses (Chu et al. 2006; Firth et al. 2012; Klempa et al. 2013). The hantavirus taxonomy remains as initially described by the reporting authors or accepted by the International Committee on Taxonomy of Viruses (ICTV; 24 hantaviruses) though some genotypes may hold names associated with specific geographic regions (Krüger et al. 2011; King et al. 2012; Vaheri et al. 2013).

Results from my search are summarized in tables arranged alphabetically by host family and species name. Table 1 lists only rodent hosts and Table 2 summarizes information regarding non-rodent hosts. In these tables I also provide a description of the host's distribution (Wilson and Reeder 2005), an approximate distribution area (km²) derived from IUCN distribution maps (www.iucnredlist.org), taxonomic classification (*sensu* Wilson and Reeder 2005), hantavirus genotypes identified in each host, and any associated human disease. Finally, I compared the geographic range size (km²) of known

hantavirus rodent hosts with the range sizes of species of the same genus whose relationships with hantaviruses remain unknown, and describe hantavirus pathogen-host associations co-circulating in both the nearctic and neotropics.

Rodent host diversity and their distributions

My review of the peer-reviewed literature identified 141 small mammal species genetically found to host hantaviruses (Tables 1 and 2). Approximately 69% (97/141) are rodents representing four families: Cricetidae, Muridae, Nesomyidae, and Sciuridae. Of the 681 Cricetid, 730 Murid, 61 Nesomyid, and 278 Sciurid currently recognized rodent species (Wilson and Reeder 2005), approximately 11% (77/681), 2% (15/730), 2% (1/61), and 1.1% (3/278) respectively, are known to have associations with hantaviruses (Figure 1). Over 29% (42/141) of the small mammals with known associations to hantaviruses are reservoirs for hantaviruses related to human disease (Table 1). From these, 42% (33/78) were cricetids, and 60% (9/15) were murids.

To holistically evaluate the pathogen-host associations between rodents and hantaviruses we must consider the current knowledge regarding host diversity and distribution patterns. A relevant issue to stress is that the list I generated of known associations between mammals and hantaviruses (Table 1 and 2) do not imply that each hantavirus is present throughout the range of the host. The factors that affect the prevalence of a hantavirus throughout the range of a host represent a whole set of questions not addressed by my review. But a first step in this direction is ascertaining the potential maximum geographical extent of a hantavirus determined by its host(s). Clearly, co-circulation of one or more hantaviruses can occur within rodent assemblages

composed of multiple known hosts and can, in many instances, allow for these species to harbor different hantaviruses due to their wide geographical ranges (Tables 1 and 3; Rollin et al. 1995; Khan et al. 1996; Rawlings et al. 1996; Wang et al. 2014). Sympatric ranges can facilitate the sharing (or apparent sharing) of a regional hantavirus by multiple hosts (Tables 1 and 4). For example, the ubiquitous deer mice, genus *Peromyscus*, are prolific and diverse rodents distributed throughout North America. Of the 56 species within this genus (Wilson and Reeder 2005), only 15 (<27%) are known to be hosts for 13 hantaviruses where six of these viruses are known to be responsible for HPS (Table 1). Two of these *Peromyscus* species (*P. maniculatus* and *P. leucopus*) occupy extremely large geographic ranges and are associated with multiple hantavirus lineages while a phylogenetically similar host species (*P. mexicanus*; Bradley et al. 2007) inhabits a smaller geographic range and hosts one hantavirus with no known connection to human disease (Table 1). The distributions of these three *Peromyscus* species overlap in Central México, providing an opportunity to study the sharing of hantaviruses among these phylogenetically similar but distinct rodent hosts in terms of their known associations with hantaviruses. However, studies focused on these kinds of contrasts have not been conducted. I hope that this review can serve as an initial guide for further inquiries which can close the gaps in our knowledge of rodent-hantavirus associations.

Peromyscus maniculatus is arguably the most studied species of its genus regarding North American hantaviruses. However, while not directly recognized as specific, co-diverging hosts for hantaviruses, individuals of other *Peromyscus* species have also been reported as having cross-reactive antibodies to the Sin Nombre virus associated with *P. maniculatus* (Childs et al. 1994; Schmaljohn et al. 1995; Hjelle et al. 1996; Song et al.

1996; Kuenzi et al. 2000; Calisher et al. 2001 & 2002; Drebot et al. 2001; Madhav et al. 2007; Sinclair et al. 2007; Lonner et al. 2008; Waltee et al. 2009; Amman et al. 2013; among others). The geographic coverage for these other *Peromyscus* species is wide ranging in North America from *P. gossypinus* in Oklahoma (Nisbett et al. 2001) to *P. levipes* in Tamaulipas (Castro-Arellano et al. 2009) and *P. megalops* in Guerrero (Milazzo et al. 2012). There may be little or no direct overlap in the distributions of sister species, yet host-specific hantaviruses have been identified in related species that are currently geographically isolated (Wilson and Reeder 2005; Milazzo et al. 2012). This supports that the overlapping distributions of related host species have allowed for intermediary viral transmission between host species (Bennett et al. 2014). For example, Limestone Canyon virus (LSCV) is usually regarded to be specifically associated with *P. boylii* whose distribution occurs throughout much of the western US and parts of central México (Figure 2; Table 1; Sanchez et al. 2001). However, viral strains closely related to LSCV have also been found in *P. melanotis* and in two restricted-range *Peromyscus* species endemic to Mexico, *P. ochraventer* and *P. hylocetes* (see Table 1), which are allopatric to each other and to *P. boylii* (Figure 2). *Peromyscus hylocetes* is limited to the Cordillera Transvolcanica, from west-central Jalisco eastwards to the Distrito Federal and northern Morelos whereas *P. ochraventer* is restricted to moist forests of southern Tamaulipas and adjacent San Luis Potosí, México (Wilson and Reeder 2005). In this case, although the distributions of *P. boylii*, *P. ochraventer*, and *P. hylocetes* are disjunct, LSCV transmission may have been facilitated through interactions between *P. boylii* and *P. melanotis*. This last species may have served as a bridge for interspecies LSCV transmission given that the collective distributions of these three related species (*P.*

hylocetes, *P. melanotis*, and *P. ochraventer*) overlays the distribution of *P. boylii*. This insight gives support to the claim of Milazzo et al. (2012) that these species are likely carriers of LSCV or LSCV-like viruses. The closely related viral strains in these four species of *Peromyscus* could be due to cross species transmission but an alternative explanation is that radiation and coevolution of host and virus has occurred. It is evident that a closer look is needed into the distributions of *Peromyscus* hosts harboring hantaviruses and the phylogenetic patterns within assemblages as they very likely influence the distribution of hantaviruses (Bennett et al. 2014; Luis et al. 2015).

Further examples of interspecies sharing of hantaviruses can be seen in voles, which are represented by several genera, including 62 recognized species in the genus *Microtus* (family Cricetidae, subfamily Arvicolinae, Wilson and Reeder 2005), of which 12 species (~19%) are genetically identified as hosts of 11 hantaviruses (Figure 1; Tables 1 and 3). *Microtus* spp. are unique hantavirus hosts in that they are distributed in both the Nearctic and Palearctic ecoregions (Wallace 1894). In the Palearctic (hereafter, Old World), the collective distributions of several *Microtus* species (*M. agrestis*, *M. arvalis*, *M. levis*, and *M. subterraneus*) span most of Great Britain and mainland Europe, into the Middle East, China, and portions of eastern Russia (Figure 3; Table 1). These Old World *Microtus* species are hosts of Tula virus (TULV), suggesting their large, sympatric distributions may contribute to hantavirus-sharing dynamics between these closely related species, further blurring the virus-host species specificity paradigm (Plyusinin et al. 1994; Scharninghausen et al. 2002). Additionally, Vladivostok and Yuanjiang viruses are currently only associated with *M. fortis* (Kariwa et al. 1999; Zou et al. 2008) and seem to be limited to this host's distribution in the lowlands of the Transbaikalia and Amur

regions, south through east and central China and the Korean Peninsula (Wilson and Reeder 2005) (Tables 1 and 4). The fragmented distribution of *M. fortis* in eastern Asia may limit the potential interaction with other *Microtus* hosts. However, research conducted north of the Korean Peninsula, where the easternmost fragments of the *M. fortis* distribution overlay that of *M. maximowiczii* (Figure 3), determined both species are hosts for Khabrovsk virus (KHAV). The evidence suggests that the presence of this virus cannot support the single-host hypothesis (Tables 1 and 4) (Zou et al. 2008).

Half of the 18 currently recognized species of *Oligoryzomys* are associated with 17 different hantaviruses (Tables 1 and 3). All but one species (*O. fulvescens*) of this genus are restricted to South America. The distribution of *O. fulvescens* (Figure 4) spans a wide range encompassing two biogeographic zones, from northern México to northern South America (Wilson and Reeder 2005). Within this distribution, it has been implicated as a reservoir for Choclo, Lechiguanas, and Maripa viruses causing HPS, and Maporal virus, whose association with human disease is inconclusive (Table 1) (Levis et al. 1997; Vincent et al. 2000; Enria et al. 2001; Delfraro et al. 2003; Fulhorst et al. 2004; Hanson et al. 2011; de Thoisy et al. 2014; González-Ittig et al. 2014). *Oligoryzomys fulvescens* may act as a co-reservoir for Maripa virus together with a non-oryzomine species, *Zygodontomys brevicauda* (de Thoisy et al. 2014). Their distributions are shared along the Central American isthmus and across a large area of northern South America (Figure 4; Table 1), yet Maripa is the only hantavirus known to infect both genera (Table 3). Additionally, *O. fornesi* and *O. nigripes* are also co-reservoirs with a non-oryzomine rodent (*Akodon cursor*) hosting Juquitiba virus (Tables 1 and 3) (Padula et al. 2007; Guterres et al. 2014). Also, *O. nigripes* has been shown to be a co-reservoir with

Oxymycterus nasutus for a Juititaba-like hantavirus (Tables 1 and 3), with the distributions of *A. cursor*, *O. nigripes*, and *O. nasutus* having considerable overlap (Figure 4) (Wilson and Reeder 2005; Delfraro et al. 2008). This suggests these different species are all likely capable of transmission of viruses among different reservoir species across their geographic ranges, thus contributing to the spread, maintenance, and likely to the evolution of these closely related pathogens. Presumably the high rodent species diversity in this region contributes to the large number of rodent-hantavirus associations in South America (Tables 1 and 4) (Jones et al. 2008). Moreover, if 50% of studied *Oligoryzomys* species have been either tied to specific hantaviruses, or in some instances found to share hantaviruses with other species and taxa (Tables 1, 3, and 4), then it stands to reason that novel hantaviruses await discovery in this genus.

The need to-re-evaluate the one virus – one host paradigm

Though not without contest (Ramsden et al. 2009; Schlegel et al. 2014), the conventional host-hantavirus paradigm suggests, with some exceptions, that the recognized hantavirus-host pairings resulted from the co-divergence of a unique relationship between one host and one hantavirus (Scharninghausen et al. 2002; Hepojoki et al. 2012; Plyusnin and Sironen 2014). If this is correct, then the maximum potential number of hantaviruses would be one hantavirus for each recognized species of the recognized hantavirus host families. This estimate suggests >90% of the potential rodent-hantavirus associations remain unknown. Non-rodent small mammals (32 soricomorph, 9 chiropteran, and 3 didelphid species) also serve as hosts for hantaviruses, however, the viruses from these groups of mammals have not been linked to disease in humans (Table

2). Soricomorph hosts (families Soricidae and Talpidae) occur in all global regions except much of South America and all of Antarctica. Additionally, confirmed chiropteran hosts (families Hipposideridae, Nycteridae, Phyllostomidae, Rhinolophidae, and Vespertilionidae) of specific hantaviruses are found in Africa, Asia, and South America. Genetic evidence of hantaviruses in some Phyllostomid bats of México has recently been found, but host-virus specificity remains unknown (Rico-Chávez et al. 2015). Although some hantaviruses are known to occur only in close association with a single host genus (Tables 1, 2, and 3), many (e.g., Dobrava-Belgrade and Sin Nombre) are associated with multiple host species thus enabling them to cover very wide distributions (Tables 1 and 3) and allow for regional differences in genetic specificity (Herbreteau et al. 2006; Holmes and Zhang 2015).

Current knowledge of rodents as hosts of hantavirus is likely very incomplete. My review shows that species that are known to host hantaviruses are more widely distributed than species with unknown associations with hantavirus ($Z = 8.03$, $P < 0.0001$). This is supported by a binomial generalized mixed model (Likelihood Ratio = 132.1, $df = 1$, $P < 0.0001$; $N = 551$), on the relationship between the likelihood that a species hosts a known hantavirus (dependent variable) and its geographical range (fixed effect), accounting for genus as a random factor (see Supplemental Material, SM1). Apparently, the current knowledge of hantavirus host species is likely biased toward those species with comparatively larger distributions. A comprehensive examination of potential host species should emphasize those species with restricted ranges, particularly when addressing the potential for human hantavirus disease in areas where these rodent species are endemic.

Another interesting result of my binomial model is that 63% of the variance is explained by the random factor, genus. This suggests that certain genera are more likely to host known hantaviruses, while an association with hantaviruses is unknown in other genera. To examine this bias, I estimated the phylogenetic distance between taxa on a dated supertree of mammals (Bininda-Emonds et al. 2007) and repeated my binomial model considering phylogenetic distance as a random factor (Figure 5; Supplemental material SM2). Adding this evidence to the fact that hantaviruses can be found in taxa other than rodents, I can suggest that these unknown associations represent a gap in our knowledge rather than a nonexistent association. Thus, for a better understanding of the diversity of hantaviruses, studies must also consider lineages of rodents with unknown associations with hantaviruses.

Although advances in our understanding of hantaviruses and their distributions continue, a large percentage of potential host taxa remain unexplored. For example, México is among the top countries in the world for mammalian diversity (Safi et al. 2011; Ceballos 2014). Though rodent hosts of hantaviruses have been confirmed, many have yet to be thoroughly studied and the significance of these species for human disease is unknown (Castro-Arellano et al. 2009; Milazzo et al. 2012; Milholland, unpublished data). For example, ~37 species of *Peromyscus* are endemic to México and, to our knowledge, 28 of these remain untested for hantaviruses. To fully understand hantavirus-host dynamics, it is critical to explore the distributions of all potential hosts and investigate the interactions of these species with conspecifics and other susceptible host taxa.

There are challenges in gathering information on hantaviruses due to the remote, limited distributions and rarity of some rodents. Tropical regions with high diversity remain understudied. The most common means of identifying new host-hantavirus associations has been follow-up studies of human illness, yet in many regions where hosts are distributed, cases of hantavirus disease go unreported or are misdiagnosed (Schlegel et al. 2014). Thus, entire rodent faunas likely have not been explored as they are mistakenly dismissed as unassociated with hantaviruses. Augmenting our knowledge about the presence of unrecognized hantaviruses will aid in the reduction of misdiagnoses and potentially curtail hantavirus-related illness.

Shifting focus to a community-interaction approach for investigating potential hosts of hantaviruses can greatly enhance our understanding of the diversity and distributions of these pathogens, their hosts, and implications for human disease (Johnson et al. 2015; Luis et al. 2015). Local communities are bridged biogeographically at regional scales by the dispersal, colonization, and/or invasion of species that may serve as pathogen hosts and reservoirs (Leibold et al. 2004). Consequently, metacommunity structure can facilitate spillover and, perhaps, ultimate establishment of hantaviruses in phylogenetically related species. For a pathogen it may be easier to colonize and establish in species phylogenetically related to the original host (Wiens and Graham 2005; Woolhouse et al. 2005; Streicker et al. 2010). These and other ecological interactions provide opportunities for viral exchanges with novel species that are potential hosts (Suzán et al. 2015). Also, the introduction of a host species and its associated hantavirus into a new and phylogenetically diverse host assemblage can allow for host-switching across taxa (Yanagihara et al. 2014). It is contested whether the Heteromyidae harbor

hantaviruses, and the contemporary paradigm contends that antibody-positive individuals are likely the consequence of a spillover infection from an infected cricetid reservoir and dismissed without genetic characterization of the virus (Salazar-Bravo et al. 2004; Arellano et al. 2012). Nevertheless, examples of heteromyid individuals having hantavirus antibodies are everpresent in the literature (Mills et al. 1997; Mantooth et al. 2001; Alemán et al. 2006; Arellano et al. 2012; Milholland, unpublished data). Therefore, inquiry regarding the distribution of hantavirus hosts, the regional influence of metacommunity dynamics between host species, and species interactions producing genetic exchanges must be addressed across multiple scales.

Global environmental change and anthropogenic landscape alterations have been associated with an increase in EID incidence worldwide (Klempa 2009; Semenza and Menne 2009; Wilson 2009; Calisher et al. 2011). Together, these factors are disrupting natural host dynamics (Steffen et al. 2011) causing higher incidence of EIDs (Mills et al. 2010; Reusken and Heyman 2013). Worldwide, incidence of hantavirus-related disease seems to fluctuate with cyclical patterns in ecologic systems, particularly in host abundance variations (Olsson et al. 2003, 2010; Cvetko et al. 2005; Madhav et al. 2007; Pettersson et al. 2008). As rodents respond to changes in climate and human population densities continue to increase, surveillance will require focus on hantavirus hosts, their distributions, and the inter/intra-specific interactions across regions (Johnson et al. 2015). Thus, having a comprehensive picture of the host-virus associations is a goal requiring attention.

APPENDIX SECTION

Table 1. A comprehensive list of known rodent hosts for hantaviruses worldwide. Data is gathered from peer-reviewed literature through 2015. Extant rodent taxonomy and descriptive distributions are derived from Wilson & Reeder 2005. Rodent range sizes (km²) are taken from distribution maps from the International Union for Conservation of Nature Red List (www.iucnredlist.org). List is organized by family and species are arranged alphabetically.

Family	Host/Reservoir	Distribution of Host/Reservoir	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Human Disease	Reference(s)
Cricetidae	<i>Akodon azarae</i>	Argentina, Paraguay, Uruguay & extreme S Brazil.	1.23E+06	Pergamino	Argentina	unknown	Levis et al. 1998
Cricetidae	<i>Akodon cursor</i>	Atlantic Forest formations in SE Brazil & perhaps NE Argentina; range limits uncertain.	8.24E+05	Juquitiba	Paraguay	HPS	Bohman et al. 2002 Padula et al. 2007
Cricetidae	<i>Akodon montensis</i>	Paraguay, Argentina, & Brazil.	1.05E+06	Ape Aime-itapúa, Araucária, Jaborá, Jaborá-like, Juquitiba & Juquitiba-like	Brazil & Paraguay	HPS	Chu et al. 2006 Goodin et al. 2009 Raboni et al. 2009, 2012 de Araujo et al. 2012 de Oliveira et al. 2011 Guterres et al. 2014
Cricetidae	<i>Akodon paranaensis</i>	NE Argentina; SE Brazil.	3.23E+05	Araucária, Jaborá & Juquitiba	Brazil	unknown	de Oliveira et al. 2012 Raboni et al. 2012 Guterres et al. 2014
Cricetidae	<i>Akodon serrensis</i>	SE Brazil; distributional limits uncertain.	2.76E+05	Jaborá	Brazil	unknown	Roboni et al. 2012
Cricetidae	<i>Akodon simulador</i>	E lower Andean slopes, 650-2400 m, from SC Bolivia to NW Argentina.	1.57E+05	Laguna Negra	Argentina	HPS	Levis et al. 2004
Cricetidae	<i>Calomys calidus</i>	EC Argentina & E Paraguay; parts of Brazil.	5.59E+04	Laguna Negra	Brazil	HPS	Travassos da Rosa et al. 2012
Cricetidae	<i>Calomys callosus</i>	Dry & subhumid Bolivia, Argentina, & Paraguay; portions of Brazil.	3.15E+06	Laguna Negra & Rio Mamoré	Argentina & Bolivia	HPS	Levis et al. 2004 Carrol et al. 2005
Cricetidae	<i>Calomys laucha</i>	Dry biotopes in Bolivia, Argentina, & Paraguay; extreme S Brazil Uruguay.	1.44E+06	Laguna Negra	Bolivia & Paraguay	HPS	Johnson et al. 1997
Cricetidae	<i>Calomys tener</i>	Atlantic Forest region and habitats bordering the Cerrado, SE Brazil, NE Argentina, and E Bolivia; range limits need refinement.	1.71E+06	Andes	Brazil	HPS	Figueiredo et al. 2010
Cricetidae	<i>Cricetulus barabensis</i>	Steppes of S Siberia from Irtysh River to Ussuri region, S through Transbaikalia to Mongolia), NE China, and Korean Peninsula.	3.69E+06	Seoul & Seoul-like	China	unknown	Wang et al. 2000 Li et al. 2007
Cricetidae	<i>Ethenomys miletus</i>	Mtns of Sichuan & E of the Salween River Valley; S China.	4.03E+05	Luxi	China	unknown	Zhang et al. 2011
Cricetidae	<i>Holochilus chararius</i>	Paraguay & Argentina.	7.67E+05	Alto Paraguay	Paraguay	unknown	Chu et al. 2003, 2006
Cricetidae	<i>Holochilus sciureus</i>	Orinoco & Amazon River basins; Venezuela, NW of the Andes, Guianas, Brazil, & Amazonian regions of Colombia, Ecuador, Perú & Bolivia.	9.32E+06	Rio Mearim	Brazil	HPS	Rosa et al. 2005
Cricetidae	<i>Julliamys sp.</i>	Species to be identified. Limits unknown.	unknown	Andes	Brazil	HPS	Araujo et al. 2011
Cricetidae	<i>Lagurus lagurus</i>	Steppes, mountains, and northern deserts from Ukraine through Kazakhstan; S Russia, adjacent W Mongolia, and NW China.	4.71E+06	Tula	Kazakhstan	unknown	Plyushina et al. 2008
Cricetidae	<i>Lemmus sibiricus</i>	Paleartic tundra landscapes; E White Sea, Russia, to W border of the Lena River.	2.17E+06	Topografov	Siberia	unknown	Vapalahti et al. 1999
Cricetidae	<i>Loxodontomys micropus</i>	S Andes of Chile and Argentina, from about 38°S latitude to Straits of Magellan.	4.48E+05	Andes	Chile	HPS	Medina et al. 2009
Cricetidae	<i>Microtus agrestis</i>	Britain; Scandinavia & Baltics through Siberia to the Lena River; mainland Europe; Ukraine & Kazakhstan; Urals; Altai Mtns, China & Lake Balk region.	1.08E+07	Tula	Croatia & Germany	unknown	Scharninghausen et al. 2002 Schmidt-Chanasit et al. 2010

Family	Host/Reservoir	Distribution of Host/Reservoir	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Human Disease	Reference(s)
Cricetidae	<i>Microtus arvalis</i>	Throughout mainland Europe & much of Scandinavia; Russia; China; the Altai Mtns & Kazakhstan; the Caucasus, Turkey & Iran.	6.89E+06	Tula & Tula-Malacky	Austria, Belgium, Croatia, Czech Republic, Germany, Netherlands, Poland, Russia & Slovakia	HFRS	Plyusnin et al. 1994, 1995 Sibold et al. 1995 Heyman et al. 2002 Klempa et al. 2003a Scharninghausen et al. 2002 Song et al. 2004 Plyusnina et al. 2008a Reusken et al. 2008 Schmidt et al. 2014
Cricetidae	<i>Microtus californicus</i>	Oak woodlands and grasslands of Pacific coast; Oregon through California (USA), Baja California Norte (México).	2.88E+05	Convict Creek & Isla Vista	United States	HPS	Song et al. 1995 Turell et al. 1995
Cricetidae	<i>Microtus fortis</i>	Lowlands of Transbaikalia & Amur, China, Sakhalin Isl & the Korean Peninsula. Discontinuous distribution in four regions. Largest range is in forests or steppes from Volga River eastward through Kazakhstan, across the Pamirs, Tien Shan and Altai Mtns. NW China, N Mongolia, and Transbaikalia to Amur; NE China: N Lena River Basin; N Siberian tundra, from the Kolyma River W to Taymyr Peninsula; mouth of the Ob River to the White Sea. Finland & Baltics; Urals & Siberia; Iran, Ukraine & Turkey; Slovakia, Romania, Bulgaria, Greece, Macedonia, Serbia, Montenegro & Albania.	1.97E+06	Khabarovsk, Vladivostok & Yuanjiang	China & Russia	unknown	Hörling et al. 1996 Kariwa et al. 1999 Zou et al. 2008
Cricetidae	<i>Microtus gregalis</i>		4.54E+06	Tula	Kazakhstan	unknown	Plyusnina et al. 2008a
Cricetidae	<i>Microtus levis</i> ¹		3.86E+06	Tula	Russia	unknown	Plyusnin et al. 1994
Cricetidae	<i>Microtus maximowiczii</i>	E shore of Lake Baikal to upper Amur region, Mongolia & China.	1.64E+06	Khabarovsk	China	unknown	Zou et al. 2008
Cricetidae	<i>Microtus montanus</i>	Cascade, Sierra Nevada, & Rocky Mountain ranges: SC British Columbia, Canada, south to EC California, S Utah, & NC New Mexico, USA; disjunct populations in S Nevada, EC Arizona, & WC New Mexico. N & C Great Plains; Texas (USA); Canada.	1.45E+06	El Moro Canyon ² & Prospect Hill	United States	unknown	Rowe et al. 1995
Cricetidae	<i>Microtus ochrogaster</i>		3.21E+06	Bloodland Lake	United States & Canada	unknown	Hjelle et al. 1995b
Cricetidae	<i>Microtus oeconomus</i>	Holarctic in tundra, northern taiga, and grassy meadows. In Palearctic, Fennoscandia to N European Russia, Kamchatka Peninsula, and borderlands of Bering Sea; S through Baltic region to NE Germany, through Europe NE Asia; relic populations in Netherlands; absent from the British Isles but present on St. Lawrence Isl in Bering Sea. In Nearctic, from Alaska through Yukon Territory, E to W Northwest Territories, and S to extreme NW British Columbia and Alexander Archipelago, Alaska.	1.86E+07	Khabarovsk	Russia	unknown	Plyusnina et al. 2008b
Cricetidae	<i>Microtus pennsylvanicus</i>	Meadowlands, boreal & mixed coniferous-deciduous biomes of North America; Alaska to Canada; Rocky Mountains to New Mexico, Kansas, & Appalachians; Georgia, South Carolina, Florida; Chihuahua (México).	1.20E+07	Prospect Hill	United States & Canada	unknown	Lee et al. 1985

Family	Host/Reservoir	Distribution of Host/Reservoir	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Human Disease	Reference(s)
Cricetidae	<i>Microtus</i> ³ <i>subterraneus</i>	Atlantic coasts of N and C France through S Netherlands, across C Europe; Switzerland; Slovakia; Czech Republic; Italy to Ukraine and the Don River, S through Romania and Balkan region into N and SE Greece, and Turkey; E to S of Trabzon; isolated populations in Russia and Estonia.	2.88E+06	Tula	Serbia & (former) Yugoslavia	unknown	Song et al. 2002
Cricetidae	<i>Myodes</i> ⁴ <i>glareolus</i>	W Palaearctic forests; France & Scandinavia to Lake Baikal; Spain, N Italy, the Balkans, Turkey, Kazakhstan & Altai, Sayan Mtns; Britain & Ireland.	8.68E+06	Puumala	Austria, Finland, Germany, Hungary, Norway & Sweden	HFRS/NE	Brummer-Korvenkontio et al. 1980 Lundkvist et al. 1998 Aberle et al. 1999 Schilling et al. 2007 Plyusnina et al. 2009a Razzauti et al. 2009
Cricetidae	<i>Myodes</i> ⁴ <i>regulus</i>	Korean Peninsula.	1.49E+05	Muju	Korea	unknown	Song et al. 2007
Cricetidae	<i>Myodes</i> ⁴ <i>rufocanus</i>	N Palearctic; Scandinavia through Siberia (Russia); S Ural & Altai Mtns, Transbaikai, China, Korea & Japan.	1.31E+07	Puumala-like & Hokkaido	China, Finland, Japan & Siberia	unknown	Kariwa et al. 1995 Zhang et al. 2007 Dekonenko et al. 2003
Cricetidae	<i>Neacomys spinosus</i>	WC Brazil to Andean foothills and lowlands of SE Colombia, E Ecuador, E Peru, N and C Bolivia.	3.10E+06	Andes-like	Peru	unknown	Razuri et al. 2014
Cricetidae	<i>Necomys</i> ⁵ <i>benefactus</i>	Atlantic coast in Uruguay & Argentina.	3.87E+05	Maciel	Argentina	HPS	Levis et al. 1998 Bohman et al. 2002
Cricetidae	<i>Necomys</i> ⁵ <i>lasiurus</i>	Brazil S of the Amazon River; extreme SE Peru & NE Argentina; range limits uncertain.	5.63E+06	Araraquara & Juquitiba	Brazil	HPS	Johnson et al. 1999 Suzuki et al. 2004 Figueiredo et al. 2009
Cricetidae	<i>Neotoma lepida</i>	SE Oregon to C Utah and WC Colorado, S through Nevada, NW Arizona, and S California (USA); to S Baja California Sur (México).	9.84E+05	Sin Nombre	United States	HPS	Dearing et al. 1998
Cricetidae	<i>Neotoma mexicana</i>	SE Utah & C Colorado, USA, S through W & interior México, to highlands of Guatemala, El Salvador, & W Honduras.	1.78E+06	El Moro Canyon	United States	unknown	Hjelle et al. 1994
Cricetidae	<i>Oligoryzomys chacoensis</i>	Dryer habitats of Bolivia, Paraguay, Brazil & Argentina.	7.61E+05	Andes, Bermejo & Ñeembucú	Argentina & Paraguay	HPS	Levis et al. 1997, 1998, 2004 Gonzalez Della Valle et al. 2002 Chu et al. 2003
Cricetidae	<i>Oligoryzomys ellurus</i> ⁶	Brazil; range limits uncertain.	2.26E+06	Castelo dos Sonhos	Brazil	HPS	Johnson et al. 1999 Firth et al. 2012
Cricetidae	<i>Oligoryzomys flavescens</i>	E Paraguay, SE Brazil, Uruguay & N to SC Argentina; range limits uncertain.	3.15E+06	Andes, Central Plata & Lechiguanas	Argentina, Chile & Uruguay	HPS	Levis et al. 1998 Gonzalez Della Valle et al. 2002 Delfraro et al. 2003
Cricetidae	<i>Oligoryzomys fornesi</i>	Argentina, Paraguay, & Brazil; parts of Uruguay.	1.74E+06	Anajutuba & Juquitiba	Argentina, Brazil, Paraguay & Uruguay	HPS	Rosa et al. 2005 Chu et al. 2009 Guterres et al. 2014

Family	Host/Reservoir	Distribution of Host/Reservoir	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Human Disease	Reference(s)
Cricetidae	<i>Oligoryzomys fulvescens</i> ⁷	S México, through C America, Ecuador, Venezuela, Guianas & N Brazil.	2.90E+06	Calabazo, Choclo, Lechiguana, Maporal & Maripa	Argentina, French Guiana, Panamá, Uruguay & Venezuela	HPS	Levis et al. 1997 Vincent et al. 2000 Enria et al. 2001 Delfraro et al. 2003 Fulhorst et al. 2004 Salazar-Bravo et al. 2004 Armien et al. 2009 Hanson et al. 2011 de Thoisy et al. 2014 González-Iltig et al. 2014
Cricetidae	<i>Oligoryzomys longicaudatus</i>	Chile & Argentina; S along Andes; Argentina; range limits uncertain.	6.29E+05	Andes ⁸	Argentina & Chile	HPS	López et al. 1996 Levis et al. 1998 Bohman et al. 2002 Meissner et al. 2002
Cricetidae	<i>Oligoryzomys micratis</i>	Amazon Basin of Brazil & lowlands of Perú, Bolivia & Paraguay.	2.72E+06	Rio Mamoré	Bolivia & Peru	HPS	Bharadwaj et al. 1997 Powers et al. 1999 Carroll et al. 2005
Cricetidae	<i>Oligoryzomys nigripes</i>	Paraguay, Argentina, Atlantic Forest region & Brazil.	3.21E+06	Araucaria, Itapúa, Juquitiba, Juquitiba-like & Lechiguana	Argentina, Brazil, Paraguay & Uruguay	HPS	Vasconcelos et al. 1997 Chu et al. 2003 Suzuki et al. 2004 Raboni et al. 2005, 2009 Padula et al. 2007 Delfraro et al. 2008 Vadell et al. 2011 de Araujo et al. 2012
Cricetidae	<i>Oligoryzomys stramineus</i>	Cerrado & Caatinga formations of NE & C Brazil.	5.30E+05	Juquitiba	Brazil	unknown	Figueiredo et al. 2009
Cricetidae	<i>Oligoryzomys sp.</i>	Species to be identified. Limits unknown. (See Rocha et al. 2011)	unknown	Rio Mamoré	Brazil	unknown	Rocha et al. 2011 Firth et al. 2012
Cricetidae	<i>Ondatra zibethicus</i>	North America, including Newfoundland; S to the Gulf of México, Rio Grande & lower Colorado River valleys. Introduced & widespread in the Palearctic, including C & N Europe, Ukraine, Russia, & Siberia; parts of Mongolia & China, NE Korea, and Honshu Isl, Japan.	1.47E+07	Puumala-like	Germany	unknown	Vahlenkamp et al. 1998
Cricetidae	<i>Oryzomys couesi</i>	S Texas; México; S through C America (Belize), to NW Colombia; Jamaica, Isla Cozumel, Baja California Sur & Sonora.	1.48E+06	Catacamas & Playa de Oro	Honduras & México	unknown	Milazzo et al. 2006 Chu et al. 2008
Cricetidae	<i>Oryzomys palustris</i>	SE USA, coastal Texas, the Gulf coast & throughout Florida.	1.51E+06	Bayou	United States	HPS	Khan et al. 1995 Morzunov et al. 1995 Torres-Martinez et al. 1998
Cricetidae	<i>Oxymycterus nosutis</i>	Uruguay & adjacent SE Brazil.	5.59E+05	Juquitiba-like	Uruguay	HPS	Delfraro et al. 2008
Cricetidae	<i>Oxymycterus quaeator</i> ⁹	NE Argentina, SE Brazil, and perhaps extreme E Paraguay.	7.84E+05	Araucaria & Juquitiba	Brazil	HPS	Raboni et al. 2012 Guterres et al. 2014
Cricetidae	<i>Peromyscus aztecus</i>	Humid montane and cloud forests, 800-3140 m, from C Veracruz & C Guerrero, through Oaxaca & E Chiapas, México, to Guatemala, Honduras, & El Salvador.	2.19E+05	Montano	México	unknown	Saasa et al. 2012
Cricetidae	<i>Peromyscus beatae</i>	Veracruz & Guerrero to Oaxaca, Chiapas (México); Guatemala, El Salvador & Honduras.	1.46E+05	Huitzilac & Montano	México	unknown	Kariwa et al. 2012 Saasa et al. 2012

Family	Host/Reservoir	Distribution of Host/Reservoir	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Human Disease	Reference(s)
Cricetidae	<i>Peromyscus boylii</i>	Much of SW USA; California to W Oklahoma; S to Baja California Norte & Trans-Pecos Texas; Sierra Madre Occidental & Central Plateau to Queretaro & Hidalgo (México).	2.53E+06	Limestone Canyon, Prospect Hill & Sin Nombre	United States	unknown	Childs et al. 1994 Sanchez et al. 2001
Cricetidae	<i>Peromyscus californicus</i>	C & S California, USA, excluding San Joaquin Valley, to NW Baja California Norte, México.	1.33E+05	Isla Vista & Sin Nombre	United States	HPS	Song et al. 1995 Luis et al. 2013
Cricetidae	<i>Peromyscus eremicus</i>	California, Nevada, & Utah to Trans-Pecos Texas; coastal to Sinaloa, Zacatecas & San Luis Potosí.	1.22E+06	Sin Nombre	México	HPS	Milazzo et al. 2012
Cricetidae	<i>Peromyscus hylacetes</i>	Endemic to the Cordillera Transvolcanica, from WC Jalisco E to Distrito Federal and N Morelos, México.	3.74E+04	Limestone Canyon	México	unknown	Milazzo et al. 2012
Cricetidae	<i>Peromyscus leucopus</i>	Canada; C & E USA, excluding Florida; S to Durango and along Caribbean coast to Yucatán Peninsula (México).	5.83E+06	Blue River, Monongahela, New York & Sin Nombre	United States & México	HPS	Hjelle et al. 1995c Morzunov et al. 1998 Rohdes III et al. 2000 Kariwa et al. 2007 Milazzo et al. 2012
Cricetidae	<i>Peromyscus levipes</i>	C Nuevo León and W Tamaulipas, in and along the Sierra Madre Oriental, to C Veracruz, Tlaxcala, Distrito Federal, and Morelos, México.	1.61E+05	Limestone Canyon	México	unknown	Milazzo et al. 2012
Cricetidae	<i>Peromyscus maniculatus</i>	Alaskan panhandle across Canada; through continental USA; Baja California Sur & Oaxaca (México).	1.30E+07	Convict Creek, El Moro Canyon, Monongahela, Prospect Hill & Sin Nombre	United States & Canada	HPS	Childs et al. 1994 Schmaljohn et al. 1995 Rawlings et al. 1996 Song et al. 1996 Drebot et al. 2001 Sinclair et al. 2007
Cricetidae	<i>Peromyscus megalops</i>	Humid forests in mountains of C Guerrero, S & NC Oaxaca, México.	4.42E+04	Carrizal	México	unknown	Saasa et al. 2012
Cricetidae	<i>Peromyscus melanotis</i>	Cordillera Transvolcanica in C México, N along Sierra Madre Oriental to S Nuevo León and along Sierra Madre Occidental to W Chihuahua; isolated populations in SE Arizona, USA.	4.95E+05	Limestone Canyon	México	unknown	Milazzo et al. 2012
Cricetidae	<i>Peromyscus mexicanus</i>	Atlantic coast; San Luis Potosí to Tehuantepec, (México); Pacific coast, from Guerrero-Oaxaca to Chiapas; Guatemala, El Salvador, Honduras, & Nicaragua; Costa Rica & Panamá.	3.67E+05	Rio Segundo	Panamá	unknown	Salazar-Bravo et al. 2004
Cricetidae	<i>Peromyscus ochraventer</i>	Moist forests of S Tamaulipas and adjacent San Luis Potosí, México.	3.90E+03	Limestone Canyon	México	unknown	Milazzo et al. 2012
Cricetidae	<i>Peromyscus spicilegus</i>	Low to middle elevations, 15-1980 m, along the W flanks of the Sierra Madre Occidental, México; from SE Sonora and extreme SW Chihuahua to NE Colima and WC Michoacán.	1.26E+05	Limestone Canyon	México	unknown	Milazzo et al. 2012
Cricetidae	<i>Peromyscus truei</i>	USA, SW & C Oregon to W & SE Colorado; S to N Baja California Norte (México), Arizona, & New Mexico; isolated populations in N Texas & S Baja California Sur.	1.45E+06	Prospect Hill & Sin Nombre	United States	unknown	Childs et al. 1994 Hjelle et al. 1996
Cricetidae	<i>Reithrodontomys creper</i>	Upper elevations, Cordilleras Tilarán, Costa Rica, to Chiriquí region, W Panamá.	1.23E+04	Rio Segundo	Panamá	unknown	Salazar-Bravo et al. 2004
Cricetidae	<i>Reithrodontomys megalotis</i>	W Canada; through W USA; S Baja California Norte through interior México to C Oaxaca.	5.12E+06	El Moro Canyon, Huizilac & Sin Nombre	United States & México	unknown	Hjelle et al. 1994, 1995a Kariwa et al. 2012
Cricetidae	<i>Reithrodontomys mexicanus</i>	Tamaulipas & Michoacán (México); Mid-American highlands to Panamá; Andes of Colombia & Ecuador.	5.40E+05	Rio Segundo	Costa Rica & Panamá	unknown	Hjelle et al. 1995a Salazar-Bravo et al. 2004

Family	Host/Reservoir	Distribution of Host/Reservoir	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Human Disease	Reference(s)
Cricetidae	<i>Reithrodontomys sumichrasti</i>	Mid-American highlands; Jalisco & San Luis Potosí to Guerrero & Oaxaca, Chiapas, Veracruz & Mirador (México) to Nicaragua; Costa Rica to Panamá.	3.29E+05	Carrizal & Rio Segundo	México & Panamá	unknown	Salazar-Bravo et al. 2004 Kariwa et al. 2012
Cricetidae	<i>Sigmodon alstoni</i>	Savannas over Colombia & Venezuela, Guyana, Surinam & Brazil.	8.40E+05	Caño Delgadito & Maporal	Venezuela	unknown	Fulhorst et al. 1997 Milazzo et al. 2010
Cricetidae	<i>Sigmodon hispidus</i>	Nicaragua to C Panamá, C America; in S America to N Colombia and N Venezuela; northern limits uncertain.	7.61E+05	S. hirsutus-associated hantavirus	Panamá	unknown	Armién et al. 2009
Cricetidae	<i>Sigmodon hispidus</i>	SE USA; Nebraska to Virginia; Arizona to peninsular Florida; NW Chihuahua to N Tamaulipas (México) to Zacatecas & San Luis Potos.	2.62E+06	Bayou, Black Creek Canal & Muleshoe	United States	HPS	Ravkov et al. 1995 Rollin et al. 1995 Rawlings et al. 1996 Torrez-Martínez et al. 1998
Cricetidae	<i>Sigmodon mascotensis</i>	W México to extreme SW Chiapas; arid basins of Hidalgo, Puebla & Oaxaca.	2.53E+05	Playa de Oro	México	unknown	Chu et al. 2008
Cricetidae	<i>Thomomys nigrata</i>	SE Brazil, E Paraguay, and NE Argentina.	1.06E+06	Araquara-like & Andes	Brazil	unknown	Araujo et al. 2011, 2012
Cricetidae	<i>Zygodontomys brevicauda</i>	Savannas from SE Costa Rica through Panamá, Colombia, Venezuela, & the Guianas; Brazil N of Amazon River; Trinidad & Tobago; shelf islands adjacent Panamá & Venezuela.	1.69E+06	Calabazo, Choclo, Maripá & Necolí	Colombia, French Guiana & Panamá	HPS	Vincent et al. 2000 Salazar-Bravo et al. 2004 Armién et al. 2009 Londoño et al. 2011 ¹⁰ de Thoisy et al. 2014
Muridae	<i>Apodemus agrarius</i>	Paleartic and Oriental regions; C Europe; Amur River region in E Russia through Korea and China; Senkaku Isl group of Japan; Taiwan.	1.15E+07	Dobrava-Belgrade, Hantaan, Kurkino Saaremaa & Seoul	China, Estonia, Finland, Germany, Hungary & Korea	HFRS & NE	Lee et al. 1978, 1982 Plyusnin et al. 1997, 2003 Nemirov et al. 1999 Kiempa et al. 2003b Sironen et al. 2005 Plyusnin et al. 2006 Jakab et al. 2007 Li et al. 2007 Schlegel et al. 2009 Liu et al. 2012 Kiempa et al. 2013
Muridae	<i>Apodemus flavicollis</i>	England & Wales; Spain through Europe to Finland & Sweden; Italy, Balkans & Greece; Belarus & Ukraine to Urals; Turkey, Armenia & Iran; Syria, Lebanon & Israel; Aegean & Adriatic Mediterranean Isls.	6.07E+06	Dobrava-Belgrade	Austria, Germany, Hungary & Slovenia	HFRS	Avsic-Zupanc et al. 1992 Kiempa et al. 2003b Jakab et al. 2007 Schlegel et al. 2009 Schmidt et al. 2014
Muridae	<i>Apodemus peninsulae</i>	Siberia to Ussuri (Russia); Japanese island of Hokkaido; E Mongolia, China & Tibet.	8.90E+06	Amur & Soochong	Russia	HFRS	Yashina et al. 2000, 2001 Baek et al. 2006 Jiang et al. 2007
Muridae	<i>Apodemus ponticus</i>	Endemic to the Caucasus, from shore of Azov Sea to the Caucasus (S Russia, Georgia & Azerbaijan). European & N African: Europe N to Scandinavia; S to NW Turkey; E to C Belarus, E Ukraine, & adjacent W Russia. Range in N Africa extends from Atlas Mtns in Morocco E across Algeria to Tunisia; Iceland, Britain & Ireland; Aegean, Tuscan & Mediterranean Isls.	3.48E+05	Dobrava-Belgrade & Sochi	Russia	HFRS	Kiempa et al. 2008 Dzagurova et al. 2012
Muridae	<i>Apodemus sylvaticus</i>	India, Sri Lanka, Bangladesh, Nepal, Myanmar & China; Taiwan, Thailand, Laos, Cambodia & Vietnam.	5.00E+06	Dobrava-Belgrade	Czech Republic	unknown	Weidmann et al. 2005
Muridae	<i>Bandicota indica</i>		5.38E+06	Thailand	Thailand	unknown	Elwell et al. 1985 Xiao et al. 1994

Family	Host/Reservoir	Distribution of Host/Reservoir	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Human Disease	Reference(s)
Muridae	<i>Hylomyscus allenii</i> ¹²	Equatorial Guinea & W Africa from Guinea to Gabon & Cameroon; range limits unknown.	1.51E+06	Sangassou	Guinea	HFRS	Klempa et al. 2006, 2012
Muridae	<i>Mus musculus</i>	Spread over world continents and islands (except Antarctica) through close human associations humans; in some areas restricted to human dwellings and habitats maintained by human activity; sometimes feral where introduced; and maintaining natural, wild populations in other regions.	5.21E+07 ¹²	Dobrava-Belgrade, Leakey/Hantaan), Prospect Hill, Seoul & Sin Nombre	China, Czech Republic, & United States	unknown	Baek et al. 1988 Arthur et al. 1992 Childs et al. 1994 Weidmann et al. 2005 Jiang et al. 2008
Muridae	<i>Niviventer confucianus</i>	Myanmar & China; mtns of NW Thailand & extreme NW Vietnam; mtns in N Laos.	3.97E+06	Da Bie Shan & Hantaan	China	unknown	Wang et al. 2000
Muridae	<i>Rattus argentiventer</i>	Indochina: Thailand & Koh Samui off the E coast of peninsular Thailand, Cambodia, C Laos, & Vietnam in Indochina; Philippines, Sulawesi & New Guinea.	1.71E+06	Seoul	Vietnam	HFRS	Huong et al. 2010 Cuong et al. 2015
Muridae	<i>Rattus losea</i>	Taiwan, China, Hong Kong, Vietnam, Laos & Thailand.	2.04E+06	Seoul	China & Korea	HFRS	Elwell et al. 1985 Zhang et al. 2010
Muridae	<i>Rattus norvegicus</i>	Siberia, China & Japan; introduced worldwide.	1.92E+07 ¹²	Andes, Seoul & Tchoupitoulas	Belgium, Cambodia, Chile, China, France, Indonesia, Japan, Korea, Netherlands, United Kingdom, United States & Vietnam	HFRS/HPS	Lee et al. 1982 Tsai et al. 1985 Reynes et al. 2003 Heyman et al. 2004, 2009 Pyusina et al. 2004 Fernández et al. 2008 Luan et al. 2012 Jameson et al. 2013 Cross et al. 2014 Dupinay et al. 2014 Verner-Carlsson et al. 2015
Muridae	<i>Rattus rattus</i>	Native to Indian Peninsula & introduced worldwide in the temperate zone & parts of the tropical & subantarctic zones. Southern limit is subantarctic Macquarie Isl.	7.90E+06 ¹²	Andes, Anjozorobe, Guo, Seoul & Thailand	Cambodia, Chile, China, Korea & Madagascar	HFRS/HPS	Elwell et al. 1985 Wang et al. 2000 Reynes et al. 2003, 2014 Medina et al. 2009 Johansson et al. 2010 Zhang et al. 2007, 2010
Muridae	<i>Rattus tanezumii</i>	SE Asia: Afghanistan to Nepal, Bhutan, India & Bangladesh; China, Korea & Indochina; Taiwan & Japan, Philippines, to Isils of New Guinea & Fiji.	7.48E+06	Hantaan, Jurong, Serang & Seoul	Indonesia & Singapore	unknown	Chin et al. 2000 ¹³ Pyusina et al. 2009b Johansson et al. 2010
Muridae	<i>Stenocephalemys albipes</i>	Ethiopia; endemic to Ethiopian Plateau between 800-3300 m.	3.61E+05	Tigray	Ethiopia	unknown	Blasdel et al. 2011 Meheretu et al. 2012
Nesomyidae	<i>Elurus majori</i>	Montane forests, 1000-2000 m, E Madagascar; Montagne d'Anbre to Anosyenne Mnts.	7.33E+04	Anjozorobe	Madagascar	unknown	Reynes et al. 2014
Sciuridae	<i>Tamias dorsalis</i>	E Nevada, S Idaho, Utah, SW Wyoming, & NW Colorado S through Arizona and W New Mexico (USA) to NW Durango, W Coahuila, and coastal Sonora (Mexico).	6.32E+05	Prospect Hill & Sin Nombre	United States	unknown	Childs et al. 1994
Sciuridae	<i>Tamias¹⁴ minimus</i>	C Yukon (Canada) S through Sierra Nevada and S New Mexico, E to Michigan (USA) & W Quebec (Canada).	5.24E+06	Convict Creek	United States	unknown	Turell et al. 1995
Sciuridae	<i>Tamias quadrivittatus</i>	Mnts of Colorado & Utah S; NE Arizona & S New Mexico (USA).	2.97E+05	Prospect Hill	United States	unknown	Childs et al. 1994

(N, S, E, and W) refer to cardinal compass directions; (C) central; (Mnts) mountains; (HPS) hantavirus (cardio)pulmonary syndrome; (HFRS) hemorrhagic fever with renal syndrome; (NE) nephropathia epidemica; (1) *M. rassi/meridionalis* reported; (2) n=1; (3) formerly *Pitymys*; (4) formerly *Clethrionomys*; (5) formerly *Bolomy*; (6) *O. uzbekensis* reported as subspecies (see, Hanson et al. 2011 & González-titig et al. 2014); (8) and possibly Orán virus; (9) *O. judex* synonym; (10) *Zygodontomys cherriei* reported; (11) *H. simus* reported; (12) range size reported by the IUCN Red List does not include naturalized areas; (13) *R. flavipictus* synonym; (14) formerly *Eutamias*.

Table 2. Comprehensive list of known non-rodent hosts genetically associated with specific hantaviruses. Data is gathered from peer-reviewed literature through 2014. Extant host taxonomy and descriptive distributions are derived from Wilson and Reeder 2005. Range size (km²) is taken from distribution maps from the International Union for Conservation of Nature Red List (www.iucnredlist.org). List is organized taxonomically by order and family. Host species are arranged alphabetically.

Order	Family	Host	Distribution of Host	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Reference(s)
Chiroptera	Hipposideridae	<i>Hipposideros pomona</i>	S Asia, through S China, & SE Asia; India & Nepal; Myanmar, Thailand, Lao PDR, Cambodia, Viet Nam & N Peninsular Malaysia.	2.84E+06	Xuan Son	Vietnam	Arai et al. 2013
Chiroptera	Nycteridae	<i>Nycteris hispida</i>	Senegal, Gambia, & S Mauritania; Somalia & S to Angola, Mozambique, Botswana, & Malawi; Zanzibar & Equatorial Guinea.	1.15E+07	Magboi	Sierra Leone	Weiss et al. 2012
Chiroptera	Phyllostomidae	<i>Anoura caudifer</i>	Colombia, Venezuela, Guianas, Surinam, Brazil, Ecuador, Peru, Bolivia, NW Argentina.	8.86E+06	Araquara-like	Brazil	de Araujo et al. 2012
Chiroptera	Phyllostomidae	<i>Diphylla ecaudata</i>	N, C, & S America; S Tamaulipas (Mexico) to Venezuela, Peru, Bolivia, & C, E & S Brazil.	8.09E+06	Araquara-like	Brazil	de Araujo et al. 2012
Chiroptera	Rhinolophidae	<i>Rhinolophus affinis</i>	Widespread throughout much of S Asia, S & C China & SE Asia; from Bangladesh, Bhutan, India & Nepal; Myanmar, through Thailand, Lao PDR & Viet Nam, into Peninsular Malaysia, Indonesia, to S of Borneo.	5.51E+06	Longquan	China	Guo et al. 2013
Chiroptera	Rhinolophidae	<i>Rhinolophus pusillus</i>	Wide range from S Asia, E to Japan; S & SW China, including Taiwan, S through mainland SE Asia to Indonesia & Borneo.	3.93E+06	Longquan	China	Guo et al. 2013
Chiroptera	Rhinolophidae	<i>Rhinolophus sinicus</i>	Throughout S Asia, and much of C, S & SW China; India & Nepal, Myanmar & Viet Nam.	2.17E+06	Longquan	China	Guo et al. 2013
Chiroptera	Vespertilionidae	<i>Pipistrellus abramus</i>	S Ussuri region (Russia and China), the W half of China including Taiwan, Japan, the Korean Peninsula, Viet Nam, Myanmar, & India.	3.84E+06	Huangpi	China	Guo et al. 2013
Chiroptera	Vespertilionidae	<i>Neoromicia nanus</i>	South Africa to Ethiopia, Eritrea, Sudan, Niger, Mali, & Senegal; Madagascar; Pemba & Zanzibar	n/a	Mouyassué	Côte d'Ivoire	Sumbicay et al. 2012
Didelphomorphia	Didelphidae	<i>Micoureus paraguayanus</i>	Atlantic forest region of Brazil up to the N border of Espírito Santo state, S to Rio Grande do Sul, and E to Misiones, Argentina, and eastern Paraguay.	9.63E+05	Araquara-like	Brazil	de Araujo et al. 2012
Didelphomorphia	Didelphidae	<i>Monodelphis theringi</i>	Endemic to SE Brazil; found in Rio Grande do Sul, São Paulo, Santa Catarina and Espírito Santo.	6.78E+05	Araquara-like	Brazil	de Araujo et al. 2012
Didelphomorphia	Didelphidae	<i>Didelphis aurita</i>	Coastal Brazil from Bahia to Rio Grande do Sul, W of the lower Rio Paraguay, to E Paraguay & NE Argentina.	1.41E+06	Araquara-like	Brazil	de Araujo et al. 2012

Order	Family	Host	Distribution of Host	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Reference(s)
Sorticomorpha	Soricidae	<i>Anurosorex squamipes</i>	Shaanxi, Hubei, Sichuan & Yunnan (China); Myanmar (Burma); India; N Vietnam; Thailand.	1.19E+06	Cao Bang & Lianghe	China & Vietnam	Guo et al. 2013 Song et al. 2007b
Sorticomorpha	Soricidae	<i>Anurosorex yamashinai</i>	Endemic to Taiwan, Province of China; occupies elevations ranging from 300-3,000 m asl.	3.42E+04	Xinyi	Taiwan	Yanagihara et al. 2014
Sorticomorpha	Soricidae	<i>Blarina brevicauda</i>	Canada; S to Nebraska & Virginia (USA).	4.11E+06	Camp Ripley	United States	Arai et al. 2007
Sorticomorpha	Soricidae	<i>Blarina carolinensis</i>	Illinois E to Virginia; through E Texas and N Florida (USA).	8.66E+05	Iamonia	United States	Aria et al. 2007 Ruesken & Heyman 2013
Sorticomorpha	Soricidae	<i>Crocidura douceti</i>	Forest-savanna border of Guinea, Côte d'Ivoire & Nigeria.	1.58E+05	Bowé	Guinea	Gu et al. 2013b
Sorticomorpha	Soricidae	<i>Crocidura lasiura</i>	Ussuri Region (Russia) and China to Korea.	1.57E+06	Imjin	China & Korea	Song et al. 2009 Lin et al. 2014
Sorticomorpha	Soricidae	<i>Crocidura obscurior</i>	Sierra Leone to Côte d'Ivoire; possibly Nigeria.	3.73E+05	Azagny	Côte d'Ivoire	Kang et al. 2011b
Sorticomorpha	Soricidae	<i>Crocidura shantungensis</i>	SE Siberia, E China & Korea including Taiwan, Cheju, Tsushima and Kamishima Isl. (Japan).	3.04E+06	Jeju	Korea	Arai et al. 2012
Sorticomorpha	Soricidae	<i>Crocidura theresae</i>	Guinea savanna from Ghana to Guinea.	3.36E+05	Tanganya	Guinea	Klempa et al. 2007
Sorticomorpha	Soricidae	<i>Myosorex geata</i>	Only known from the type collection from the Uluguru Mountains of Tanzania. It occurs at elevations between 1,500-2,000 m asl and possibly higher.	4.63E+02	Tanzania	Uluguru	Yanagihara et al. 2014
Sorticomorpha	Soricidae	<i>Myosorex zinki</i>	Endemic to Mount Kilimanjaro, Tanzania; thought to occur at elevations between 2,470 - 4,000 m asl	1.17E+03	Tanzania	Kilimanjaro	Yanagihara et al. 2014
Sorticomorpha	Soricidae	<i>Neomys fodiens</i>	Most of Europe; British Isles to Lake Balkal, Russia, China, & Mongolia; Siberia and N Korea.	1.31E+07	Boginia & Laihia	Finland	Heyman et al. 2011b Gu et al. 2013a
Sorticomorpha	Soricidae	<i>Sorex araneus</i>	C, E, & N Europe including the British Isles; France, Italy & Spain to Siberia.	1.32E+07	Altai & Seewis	Czech Republic, Finland, Germany, Hungary, Russia, Slovakia, & Switzerland	Song et al. 2007a Kang et al. 2009 Yashina et al. 2010 Schlegel et al. 2012 Weiss et al. 2012 Gu et al. 2013a
Sorticomorpha	Soricidae	<i>Sorex caecutiens</i>	Taiga & tundra zones from E Europe to E Siberia; Ukraine, N Kazakhstan, Altai Mtns, Mongolia, & China; Korea, Sakhalin, & Japan.	1.77E+07	Anga, Artybashi & Lena River	Russia	Weiss et al. 2012 Yanagihara et al. 2014
Sorticomorpha	Soricidae	<i>Sorex cinereus</i>	North America throughout Alaska & Canada; along the Rocky & Appalachian Mtns.	1.16E+07	Ash River	United States	Aria et al. 2008a

Order	Family	Host	Distribution of Host	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Reference(s)
Soricomorpha	Soricidae	<i>Sorex cylindricauda</i>	China, Sichuan, and Moupin.	3.29E+05	Quiandao Lake & Qian Hu Shan	China	Yanagihara et al. 2014 Zuo et al. 2014
Soricomorpha	Soricidae	<i>Sorex daphaenodon</i>	Ural Mountains to Siberia; Kamchatka Peninsula; China.	8.19E+06	Seewis	Siberia	Yashina et al. 2010
Soricomorpha	Soricidae	<i>Sorex isodon</i>	From Fennoscandia in W, through N & C Russia, N Mongolia, N China, and N Kazakhstan, to the Pacific coast; in Europe, from Finland to N Russia and N Belarus; isolated populations in Norway & Sweden.	1.22E+07	Yakeshi	China	Guo et al. 2013
Soricomorpha	Soricidae	<i>Sorex minutus</i>	Europe to Yenesei River & Lake Balkal, S to Altai & Tien Shan Mtns.	1.43E+07	Asikkala & Seewis	Czech Republic, Finland, Germany & Slovakia	Heyman et al. 2011a Schlegel et al. 2012 Gu et al. 2013a Radosa et al. 2013
Soricomorpha	Soricidae	<i>Sorex monticolus</i>	Montane boreal & coastal coniferous forest; Alaska to California & New Mexico; Montana, Wyoming, & Colorado (USA); Manitoba (Canada); Chihuahua, Durango (Mexico).	4.49E+06	Jemez Springs	United States	Arai et al. 2008a
Soricomorpha	Soricidae	<i>Sorex palustris</i>	Montane & boreal areas of N America; Alaska to the Sierra Nevada, Rocky & Appalachian Mtns.	6.21E+06	Fox Creek	United States	Arai et al. 2007 Kang et al. 2009b
Soricomorpha	Soricidae	<i>Sorex roboratus</i>	Russia; S to Altai Mtns, N Mongolia, and Primorsk Krai.	9.30E+06	Kenkeme	Siberia	Kang et al. 2010
Soricomorpha	Soricidae	<i>Sorex trowbridgii</i>	Coastal ranges Washington to California; SW British Columbia.	3.78E+05	Tualatin	United States	Kang et al. 2009a
Soricomorpha	Soricidae	<i>Sorex tundrensis</i>	Siberia, S to the Altai Mtns; Mongolia & China; Alaska (USA); Yukon, (Canada).	1.60E+07	Seewis	Siberia	Yashina et al. 2010
Soricomorpha	Soricidae	<i>Sorex unguiculatus</i>	Pacific coast of Russian Far East from Vladivostok to the Amur, S into NE China Korea; Is of Sakhalin (Russia) and Hokkaido (Japan), and the Japanese islands of Rebun, Rishiri, Teuri, Moyuyuri, Yagishiri, and Daikoku.	1.19E+06	Sarufutsu	Japan	Yanagihara et al. 2014
Soricomorpha	Soricidae	<i>Sorex vagrans</i>	Riparian & montane areas Great Basin & Columbia Plateau; Canada; Montana, Wyoming, and Utah (USA); Nevada to Sierra Nevada (California).	9.60E+05	Powel Butte	United States	Kang et al. 2009b
Soricomorpha	Soricidae	<i>Suncus murinus</i>	Middle East, India, Sri Lanka, Nepal, Bhutan, Myanmar, China, Taiwan, Japan, & Indonesian Region; Indonesia, Guam, Maldives Is, Philippines, coastal Africa & Arabia.	8.44E+06	Thottapalayam	China, India, Nepal & Vietnam	Carey et al. 1971 Guo et al. 2011 Kang et al. 2011c Luan et al. 2012
Soricomorpha	Talpidae	<i>Neurotrichus gibbsii</i>	SW Canada to WC California (USA).	2.21E+05	Oxbow	United States	Kang et al. 2009a
Soricomorpha	Talpidae	<i>Scalopus aquaticus</i>	E USA	3.46E+06	Rockport	United States	Kang et al. 2011a
Soricomorpha	Talpidae	<i>Scaptomyx fuscicaudus</i>	C & S China to N Myanmar & N Viet Nam.	8.92E+05	Dahonggou Creek	China	Yanagihara et al. 2014

Order	Family	Host	Distribution of Host	Distribution Range Size (km ²)	Hantavirus(es)	Country of First Detection(s)	Reference(s)
Soricomorpha	Talpidae	<i>Talpa europaea</i>	Temperate Europe including Britain to the Ob and Irtysh Rivers (Russia).	6.46E+06	Nova	Hungary	Kang et al. 2009b
Soricomorpha	Talpidae	<i>Urotrichus talpoides</i>	Japan; Kyushu & Nagasaki.	2.87E+05	Asama	Japan	Arai et al. 2008b

(N, S, E, and W) refer to cardinal compass directions; (C) = central; (Mnts) = mountains; (Isis) = islands; (†) = *R. monaceros* reported

Table 3. A list of known rodent host/reservoir taxonomy and genetically associated hantaviruses. Values in parentheses indicate the number of species within each taxonomic level; Rodent taxonomy adapted from Wilson and Reeder (2005) and arranged alphabetically in descending hierarchy. Ratio of currently identified host/reservoir rodent species per genus is derived from peer-reviewed literature through 2015.

Family	Subfamily	Genus	Number of Known Host/Reservoir Species	Number of Hantaviruses	Ratio of Known Host Species Within the Genus (%)	Hantavirus(es)
Cricetidae (681)	Arvicolinae (151)	<i>Eothenomys</i> (8)	1	1	12.5	Luxi
		<i>Lagurus</i> (1)	1	1	100.0	Tula
		<i>Lemmus</i> (5)	1	1	20.0	Topografov
		<i>Microtus</i> (62)	12	11	19.4	Bloodland Lake; Convict Creek; El Moro Canyon; Isla Vista; Khabarovsk; Prospect Hill; Tula; Tula-Malacky; Vladivostok; Yuanjiang
		<i>Myodes</i> (12)	3	4	25.0	Hokkaido; Muju; Puumala; Puumala-like
		<i>Ondatra</i> (1)	1	1	100.0	Puumala-like
		<i>Cricetulus</i> (6)	1	2	16.7	Seoul ; Seoul-like
		<i>Neotoma</i> (22)	2	2	9.1	El Moro Canyon; Sin Nombre
		<i>Peromyscus</i> (56)	15	13	26.8	Blue River; Carrizal; Convict Creek; El Moro Canyon; Huitzilac; Isla Vista
						Limestone Canyon; Monogahela; Montano; New York; Prospect Hill; Sin Nombre; Rio Segundo
	Sigmodontinae (370)	<i>Reithrodontomys</i> (20)	4	5	20.0	Carrizal; El Moro Canyon; Huitzilac; Rio Segundo; Sin Nombre
		<i>Akodon</i> (41)	6	7	14.6	Ape Aime-Itapú; Araucária; Jaborá; Jaborá-like; Juquitiba; Juquitiba-like; Pergamino
		<i>Calomys</i> (12)	4	3	33.0	Andes; Laguna Negra; Rio Mamoré
		<i>Juliomys</i> (2)	1	1	50.0	Andes
		<i>Holochilus</i> (3)	2	3	66.7	Alto Paraguay; Rio Mamoré; Rio Mearim
		<i>Loxodontomys</i> (2)	1	1	50.0	Andes
		<i>Neacomys</i> (8)	1	1	12.5	Andes-like
		<i>Necomys</i> (9)	2	3	22.2	Araraquara; Juquitiba; Maciel
		<i>Oligoryzomys</i> (18)	9	17	50.0	Anajatuba; Andes; Araucária; Bermejo; Calabazo; Castelo dos Sanhos; Central Plata; Choclo; Itapúa; Juquitiba; Juquitiba-like; Lechiguana; Maporal; Maripa; Ñembucú; Orán; Rio Mamoré
		<i>Oryzomys</i> (41)	2	3	4.9	Bayou; Catacamas; Playa de Oro
		<i>Oxymycterus</i> (16)	2	3	12.5	Araucária; Juquitiba; Juquitiba-like
		<i>Sigmodon</i> (14)	4	7	28.6	Bayou; Black Creek Canal; Caño Delgadito; Maporal; Muleshoe; Playa de Oro; <i>S. hirsutus</i> - Associated Hantavirus
		<i>Thaptomys</i> (1)	1	1	100.0	Araquara-like
	Murinae (547)	<i>Zygodontomys</i> (2)	1	4	50.0	Calabazo; Choclo; Maripa; Necoclí
		<i>Apodemus</i> (20)	5	7	25.0	Amur/Soochong; Dobrava-Belgrade; Hantaan; Kurkino; Saaremaa; Seoul
		<i>Bandicota</i> (3)	1	1	33.3	Thailand
		<i>Hylomyscus</i> (8)	1	1	12.5	Sangassou
		<i>Mus</i> (38)	1	5	2.6	Dobrava-Belgrade; Leaky (Hantaan); Prospect Hill; Seoul; Sin Nombre
		<i>Niviventer</i> (17)	1	2	5.9	Da Bie Shan; Hantaan
		<i>Rattus</i> (64)	5	9	7.8	Andes; Anjozorbe; Guo; Hantaan; Jurong; Serang; Seoul; Tchoupitoulas; Thailand
		<i>Stenocephalemys</i> (4)	1	1	25.0	Tigray
		<i>Eliurus</i> (10)	1	1	10.0	Anjozorobe
		<i>Tamias</i> (25)	3	3	12	Convict Creek; Prospect Hill; Sin Nombre
Nesomyidae (61)	Nesomyinae (23)					
Sciuridae (278)	Xerinae (128)					

Table 4. A list of hantaviruses circulating in multiple, extant rodents which are described as co-divergent reservoir/host species in the peer-reviewed literature; Hantaviruses are listed alphabetically; Parentheses indicate human disease; HPS = hantavirus (cardiopulmonary) syndrome; HFRS = hemorrhagic fever with renal syndrome; NE = nephropathia epidemica; Rodent taxonomy from Wilson and Reeder (2005); Data through 2015.

Hantavirus	Family	Subfamily	Host/Reservoir Species
Andes & Andes-like (HPS)	Cricetidae	Sigmodontinae	<i>Akodon azarae</i>
	Cricetidae	Sigmodontinae	<i>Akodon montensis</i>
	Cricetidae	Sigmodontinae	<i>Caomys tener</i>
	Cricetidae	Sigmodontinae	<i>Juliomys sp.</i>
	Cricetidae	Sigmodontinae	<i>Loxodontomys micropus</i>
	Cricetidae	Sigmodontinae	<i>Neacomys spinosus</i>
	Cricetidae	Sigmodontinae	<i>Necomys lasiurus</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys chacoensis</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys flavescens</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys longicaudatus</i>
	Cricetidae	Sigmodontinae	<i>Thaptomys nigrita</i>
	Muridae	Murinae	<i>Rattus norvegicus</i>
	Muridae	Murinae	<i>Rattus rattus</i>
Araucária & Araucária-like (unknown)	Cricetidae	Sigmodontinae	<i>Akodon montensis</i>
	Cricetidae	Sigmodontinae	<i>Akodon paranensis</i>
	Cricetidae	Sigmodontinae	<i>Necomys lasiurus</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys nigripes</i>
	Cricetidae	Sigmodontinae	<i>Oxymycterus quaestor</i>
	Cricetidae	Sigmodontinae	<i>Thaptomys nigrita</i>
Dobrava-Belgrade (HFRS)	Muridae	Murinae	<i>Apodemus agrarius</i>
	Muridae	Murinae	<i>Apodemus flavicollis</i>
	Muridae	Murinae	<i>Apodemus ponticus</i>
	Muridae	Murinae	<i>Apodemus sylvaticus</i>
	Muridae	Murinae	<i>Mus musculus</i>
El Moro Canyon (unknown)	Cricetidae	Arvicolinae	<i>Microtus montanus</i>
	Cricetidae	Neotominae	<i>Neotoma mexicana</i>
	Cricetidae	Neotominae	<i>Peromyscus maniculatus</i>
	Cricetidae	Neotominae	<i>Reithrodontomys megalotis</i>
Isla Vista (HPS)	Cricetidae	Arvicolinae	<i>Microtus californicus</i>
	Cricetidae	Neotominae	<i>Peromyscus californicus</i>
Jaborá (unknown)	Cricetidae	Sigmodontinae	<i>Akodon montensis</i>
	Cricetidae	Sigmodontinae	<i>Akodon paranensis</i>
	Cricetidae	Sigmodontinae	<i>Akodon serrensis</i>
Juquitiba & Juquitiba-like (HPS)	Cricetidae	Sigmodontinae	<i>Akodon cursor</i>
	Cricetidae	Sigmodontinae	<i>Akodon montensis</i>
	Cricetidae	Sigmodontinae	<i>Akodon paranensis</i>

Hantavirus	Family	Subfamily	Host/Reservoir Species
	Cricetidae	Sigmodontinae	<i>Necomys lasiurus</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys fornesi</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys nigripes</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys stramineus</i>
	Cricetidae	Sigmodontinae	<i>Oxymycterus nasutus</i>
	Cricetidae	Sigmodontinae	<i>Oxymycterus quaestor</i>
Khabarovsk (unknown)	Cricetidae	Arvicolinae	<i>Microtus fortis</i>
	Cricetidae	Arvicolinae	<i>Microtus maximowiczii</i>
	Cricetidae	Arvicolinae	<i>Microtus oeconomus</i>
Laguna Negra (HPS)	Cricetidae	Sigmodontinae	<i>Akodon simulator</i>
	Cricetidae	Sigmodontinae	<i>Calomys callidus</i>
	Cricetidae	Sigmodontinae	<i>Calomys callosus</i>
	Cricetidae	Sigmodontinae	<i>Calomys laucha</i>
Limestone Canyon (unknown)	Cricetidae	Neotominae	<i>Peromyscus boylii</i>
	Cricetidae	Neotominae	<i>Peromyscus hylocytes</i>
	Cricetidae	Neotominae	<i>Peromyscus levipes</i>
	Cricetidae	Neotominae	<i>Peromyscus melanotis</i>
	Cricetidae	Neotominae	<i>Peromyscus ochraventer</i>
	Cricetidae	Neotominae	<i>Peromyscus spicilegus</i>
Maripa (HPS)	Cricetidae	Sigmodontinae	<i>Oligoryzomys fulvescens</i>
	Cricetidae	Sigmodontinae	<i>Zygodontomys brevicauda</i>
Monongahela (HPS)	Cricetidae	Neotominae	<i>Peromyscus leucops</i>
	Cricetidae	Neotominae	<i>P. maniculatus nubiterrae</i>
Playa de Oro (unknown)	Cricetidae	Sigmodontinae	<i>Oryzomys couesi</i>
	Cricetidae	Sigmodontinae	<i>Sigmodon mascotensis</i>
Prospect Hill (HPS)	Cricetidae	Arvicolinae	<i>Microtus montanus</i>
	Cricetidae	Arvicolinae	<i>Microtus pennsylvanicus</i>
	Cricetidae	Neotominae	<i>Peromyscus boylii</i>
	Cricetidae	Neotominae	<i>Peromyscus maniculatus</i>
	Cricetidae	Neotominae	<i>Peromyscus truei</i>
	Muridae	Murinae	<i>Mus musculus</i>
	Sciuridae	Xerinae	<i>Tamias dorsalis</i>
	Sciuridae	Xerinae	<i>Tamias quadrivittatus</i>
Puumala & Puumala-like (HFRS/NE)	Cricetidae	Arvicolinae	<i>Myodes glareolus</i>
	Cricetidae	Arvicolinae	<i>Myodes regulus</i> ¹
	Cricetidae	Arvicolinae	<i>Myodes rufocanus</i>
	Cricetidae	Arvicolinae	<i>Ondatra zibethicus</i>

Hantavirus	Family	Subfamily	Host/Reservoir Species
Rio Mamoré (HPS)	Cricetidae	Sigmodontinae	<i>Calomys callosus</i>
	Cricetidae	Sigmodontinae	<i>Holochilus sciureus</i> ²
	Cricetidae	Sigmodontinae	<i>Oligoryzomys fornesi</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys microtus</i>
	Cricetidae	Sigmodontinae	<i>Oligoryzomys sp.</i> ³
Rio Segundo (unknown)	Cricetidae	Neotominae	<i>Peromyscus mexicanus</i>
	Cricetidae	Neotominae	<i>Reithrodontomys creper</i>
	Cricetidae	Neotominae	<i>Reithrodontomys mexicanus</i>
	Cricetidae	Neotominae	<i>Reithrodontomys sumichrasti</i>
Seoul (HFRS)	Cricetidae	Cricetinae	<i>Cricetulus barabensis</i>
	Muridae	Murinae	<i>Apodemus agrarius</i>
	Muridae	Murinae	<i>Mus musculus</i>
	Muridae	Murinae	<i>Rattus argentiventer</i>
	Muridae	Murinae	<i>Rattus losea</i>
	Muridae	Murinae	<i>Rattus norvegicus</i>
	Muridae	Murinae	<i>Rattus rattus</i>
	Muridae	Murinae	<i>Rattus tanezumi</i>
Sin Nombre (HPS)	Cricetidae	Neotominae	<i>Neotoma lepida</i>
	Cricetidae	Neotominae	<i>Peromyscus boylii</i>
	Cricetidae	Neotominae	<i>Peromyscus californicus</i>
	Cricetidae	Neotominae	<i>Peromyscus eremicus</i>
	Cricetidae	Neotominae	<i>Peromyscus leucops</i>
	Cricetidae	Neotominae	<i>Peromyscus maniculatus</i>
	Cricetidae	Neotominae	<i>Peromyscus truei</i>
	Cricetidae	Neotominae	<i>Reithrodontomys megalotis</i>
	Muridae	Murinae	<i>Mus musculus</i>
	Sciuridae	Xerinae	<i>Tamias dorsalis</i>
Tula (unknown)	Cricetidae	Arvicolinae	<i>Lagurus lagurus</i>
	Cricetidae	Arvicolinae	<i>Microtus agrestis</i>
	Cricetidae	Arvicolinae	<i>Microtus arvalis</i>
	Cricetidae	Arvicolinae	<i>Microtus gregalis</i>
	Cricetidae	Arvicolinae	<i>Microtus levis</i>
	Cricetidae	Arvicolinae	<i>Microtus subterraneus</i>

(1) see, Luis et al. 2013; (2) see, Rosa et al. 2005; (3) see, Rocha et al. 2011

Figure 1. Global contrast between total number of rodent species recognized and number serving as Hantavirus hosts per genus in which Hantaviruses have been reported. Rodents are grouped by family and arranged alphabetically by genus. Blue and orange bar sections represent the number of known and unknown (respectively) rodent host species for hantaviruses. The percentage of total species these hosts represent is shown in purple font at the end of bars. Numbers in white font indicate the number of hantaviruses associated within each genus. Rodent taxonomy from Wilson and Reeder (2005). Data through 2015.

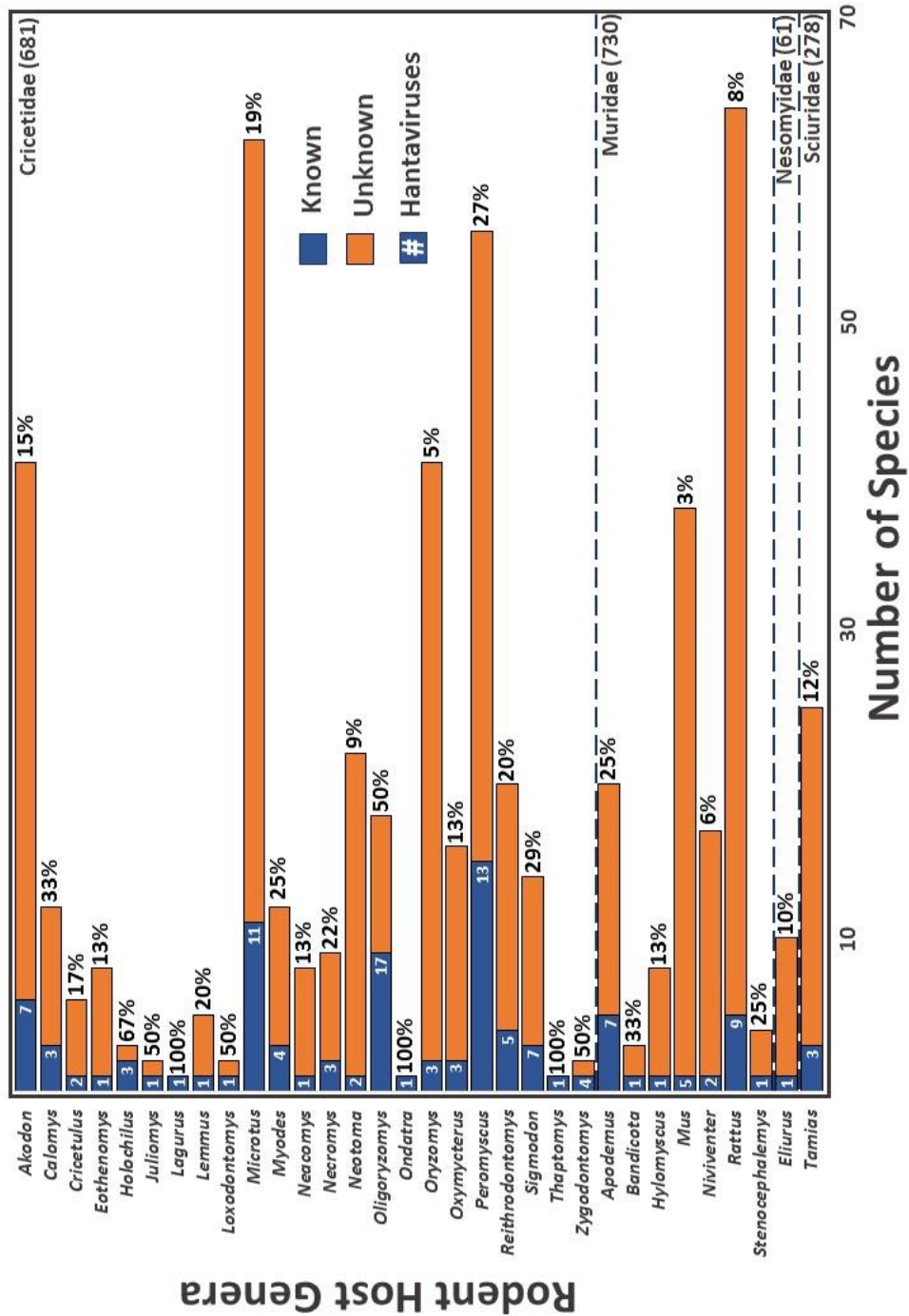
Figure 2. Distribution of selected *Peromyscus* species in Mexico and the Southwestern USA, and the distribution of Limestone Canyon virus (LSCV). All *Peromyscus* species included here have been reported as hosts to LSCV. The overlapping distributions of *P. boylii* and *P. melanotis* suggests *P. melanotis* (dotted line) serves as a transition host for the LSCV found in geographically isolated *Peromyscus* species (*P. ochraventer* and *P. hylocetes*). Background and distributions are taken from IUCN (iucnredlist.org).

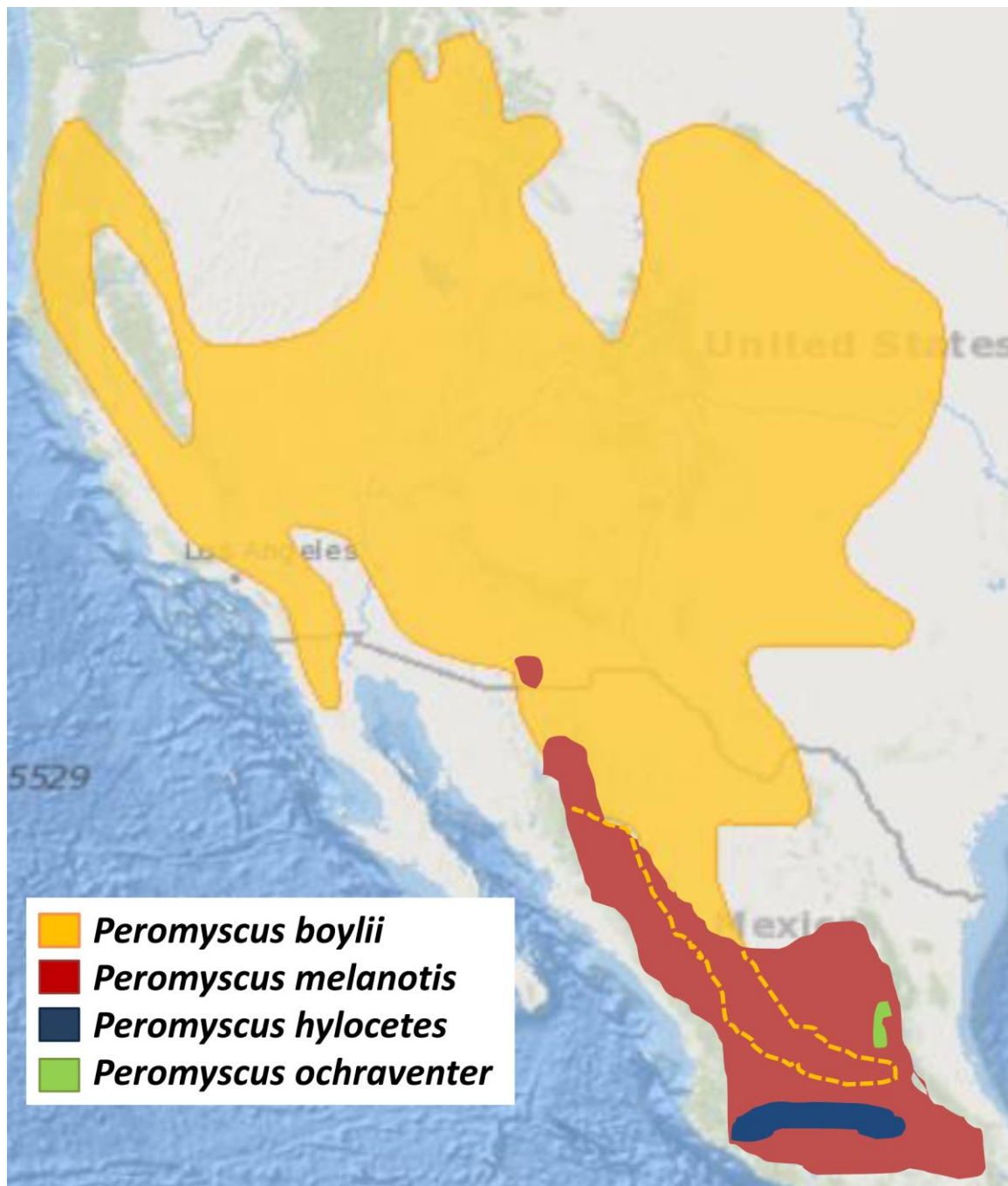
Figure 3. The distributions of selected Old World *Microtus* species. The coinciding distributions may facilitate regional transmission of hantaviruses between and among *Microtus* hosts throughout fragmented populations. The distribution of Tula virus (TULV) is widespread throughout Europe and Asia by the shared distributions of its hosts (e.g. *M. agrestis*, *M. arvalis*, and *M. levis*). The overlapping distributions of *M. fortis* and *M. maximowiczii* suggest dispersal of the regional Khabarovsk virus (KHAV) eastward. Background and distributions are taken from IUCN (iucnredlist.org).

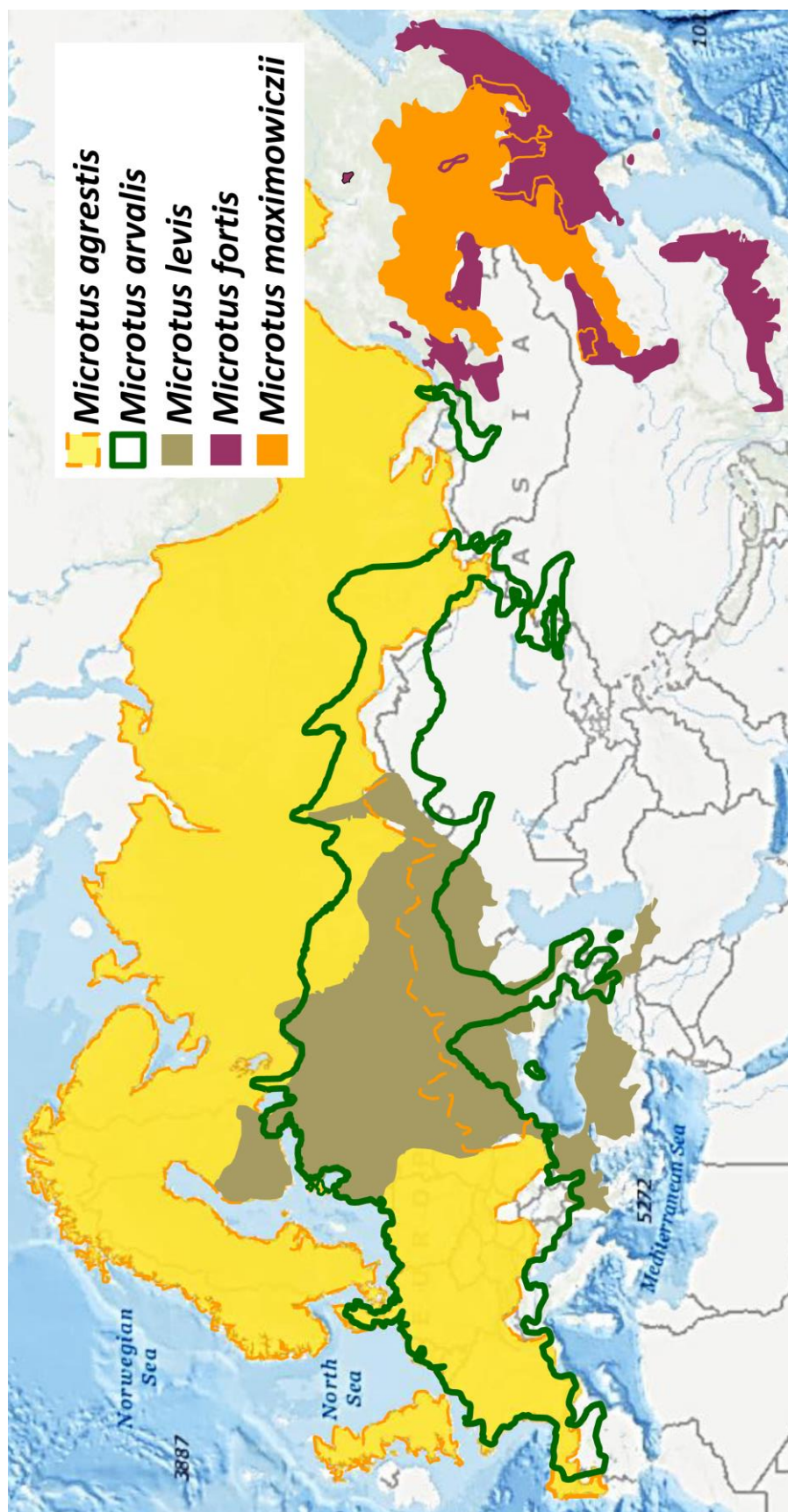
Figure 4. The distributions of overlapping cricetid rodent species of varying genera serving as hosts and reservoirs for hantaviruses in South America. Hantaviruses

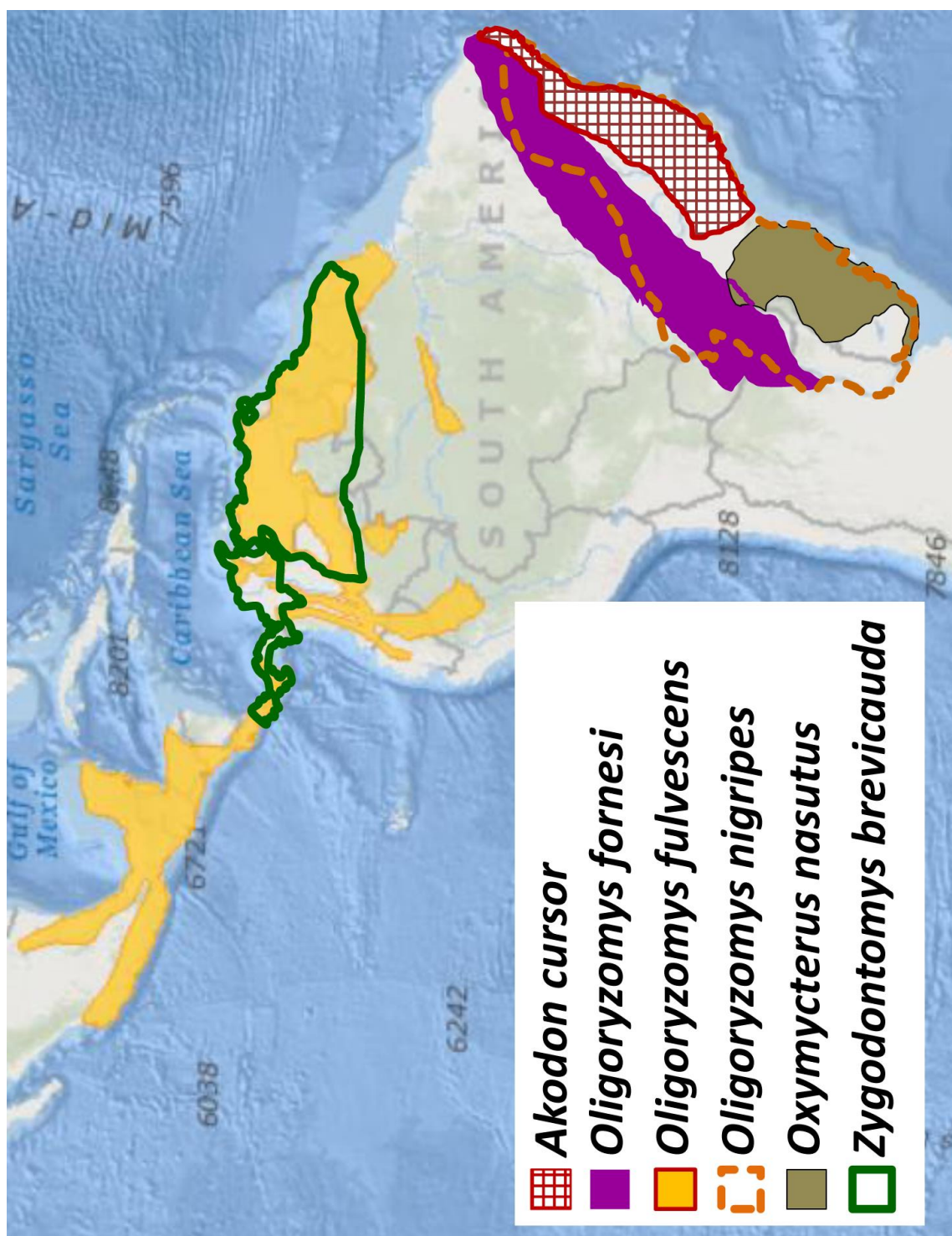
associated with all species shown (except *O. fulvescens* and *Z. brevicauda*) are limited to South America. The distributions of *O. fulvescens* and *Z. brevicauda* suggest South American hantaviruses are present in Central America. Background and distributions are taken from IUCN (iucnredlist.org).

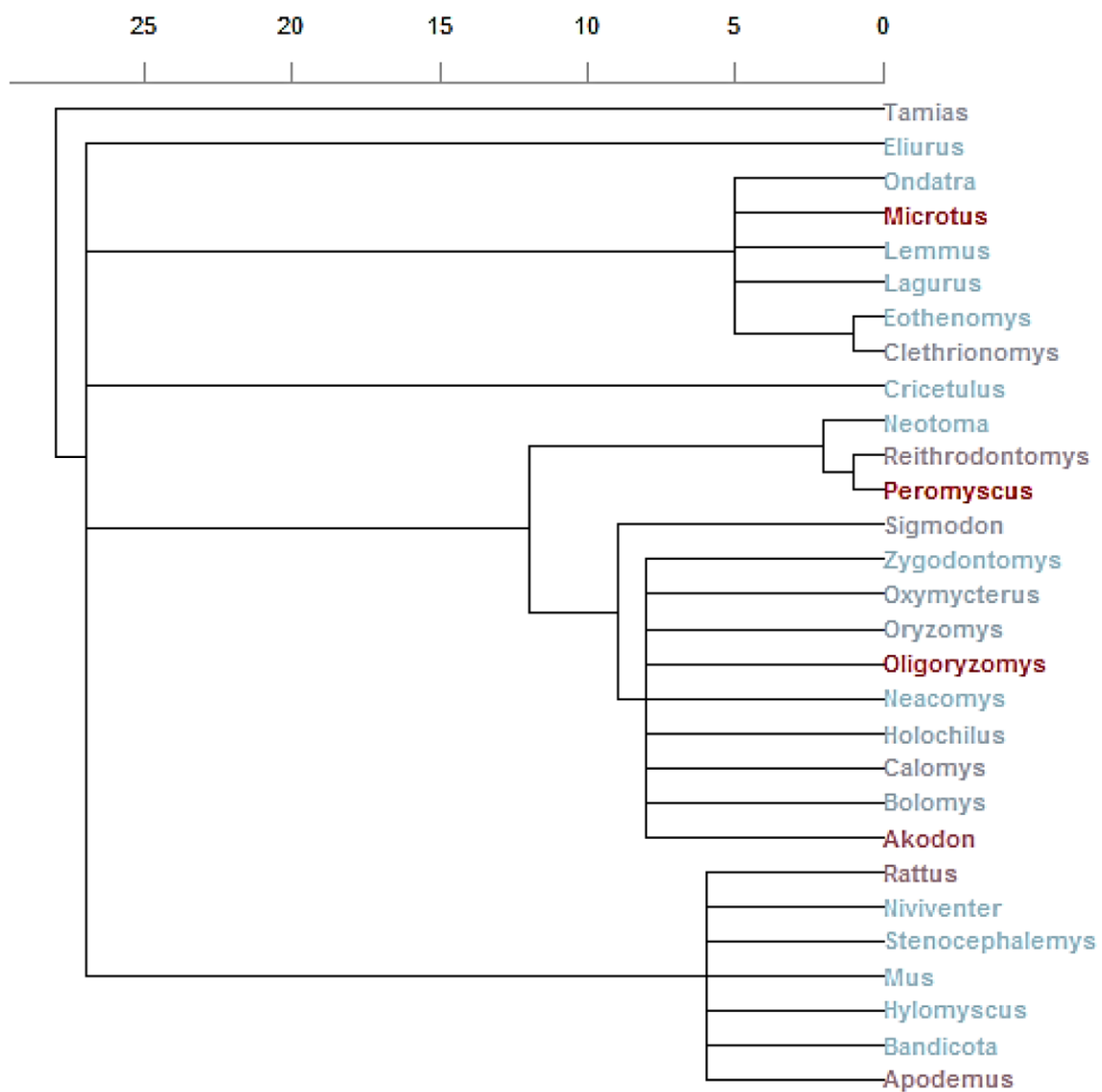
Figure 5. Rodent phylogeny in millions of years before present. Genera with species hosting hantaviruses are presented in a gradient from blue (1 host) to red (15 hosts). I estimated the phylogenetic distance between taxa on a dated supertree of mammals (Bininda-Emonds et al. 2007) and repeated my binomial model considering phylogenetic distance as a random factor (for details on the analysis see Supplementary Material SM2). Phylogenetic relationships between taxa explain 29% (range: 8-47) of variance; thus, rodent species hosting known hantaviruses are from specific lineages.











Supplementary Material

SM1. To investigate whether species hosting known hantaviruses were more widely distributed than species with unknown associations, I performed a binomial, Generalized Linear Mixed Model (GLMM). The GLMM was fitted at the maximum likelihood that a hantavirus-host association is known for a taxon, as a linear function of the geographic range of the taxon. Statistical significance of the model was corroborated with a Likelihood Ratio test (LR), comparing the likelihood of the model with the likelihood of a null model, (i.e. the same model but without the fixed effect, “geographic range”; Burnham and Anderson 2002). The P value was estimated at degrees of freedom equal to the difference of parameters (Δ) between the two models, (i.e. $df = 1$). The variable “geographic distribution” was standardized to the mean ($\bar{x}$): $x_{std} = (\ln x) - (\ln \bar{x})$, and statistical significance, rejecting that $\beta = 0$, was corroborated with a Z test. GLMM was performed with the R package lme4 (Bates et al. 2015).

Geographic range: $\beta = 0.8 \pm 0.099$; $Z = 8.03$, $P > 0.0001$)

Genus (random effect): variance = 0.63

Log Likelihood = -169.1

Log Likelihood of null model = -235.2

LR test = 132.15, $df = 1$, $P < 0.0001$

SM2. I assessed the phylogenetic bias in our knowledge of the hantavirus-rodent associations by repeating the binomial model in SM1 and accounting for the phylogenetic distances between taxa. Phylogenetic distances were estimated from the supertree of mammals (Bininda-Emonds et al. 2007), and used as a random factor in a Binomial Generalized Mixed Model (Figure SM1). Posterior probabilities of the model were estimated by fitting the model to the data in a Markov Chain of 1 000 000 iterations, sampling every 1000 and discarding 10 000 iterations as burn in period. This Bayesian test was performed in the R package MCMCglmm (Hadfield 2010, Bates et al. 2015), assuming prior values from a X^2 distribution at 1 degree of freedom (de-Villemereuil 2002). Phylogenetic effect was estimated as the inheritance of the model given by: the variance explained by the phylogenetic relationships between taxa / (total variance + 1). Upper and lower values (range) were estimated at the 95% of confidence of the posterior distribution.

Variable	Posterior mean	Lower limit at 95% CI	Upper limit at 95% CI	Effective Sample Size
Intercept	-0.77	-1.90	0.30	1154
geographic range (fixed effect)	0.64	0.48	0.78	990
phylogeny (random effect)	0.92	0.20	1.95	990

Dependent binary variable: (1) known or (0) unknown association with hantavirus.

Heritability (at 0.95 probability) = 0.29, range at 0.95 CI = 0.10 - 0.50.

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III. ECOLOGICAL CORRELATES OF HANTAVIRUS SEROPREVALENCE IN WORLDWIDE RODENT ASSEMBLAGES

Background

The recent increase in the emergence and proliferation of pathogens is being driven by the impacts of anthropogenic habitat degradation (Langlois et al. 2001; Foley et al. 2005; Voutilainen et al. 2012), climate change (Alitzer et al. 2013), and increases in human populations (Keesing et al. 2010). Collectively, these factors can contribute to decreased biodiversity and increased impacts at the human-wildlife interface thus disrupting ecosystem function and likely changing disease transmission dynamics (Keesing et al. 2010; Dirzo et al. 2014; Suzán et al. 2015; Tian et al. 2017). Zoonotic pathogens transmit from animals to humans and are the dominant cause of these novel and emerging infectious diseases (EIDs) (Taylor et al. 2001; Klempa et al. 2006; Halliday et al. 2012; Karesh et al. 2012). Many such pathogens are enzootic within animal populations and typically occur in wild animal populations (Wobeser 2007; Karesh et al. 2012). Currently, the expansion of human populations and densities are encroaching on limited wildlife habitat, thus increasing the potential for human-wildlife interactions (Daszak et al. 2000). Wildlife hosts of EIDs comprise a complex network of host species and individuals where infections persistence depends on interactions at varying scales between, and within, species assemblages (Suzán et al. 2015). Many of these highly pathogenic EIDs affecting humans worldwide are associated with rodent reservoirs (Khaiboullina et al. 2005; Meerburg et al. 2009; Morse et al. 2012; Vaheri et al. 2013; Lee et al. 2014) and existing patterns of transmission, ecological factors driving disease

persistence, and mammalian assemblage characteristics maintaining prevalence remain poorly understood (Murray et al. 2015; Han et al. 2016).

Hantaviruses (family *Bunyaviridae*) are among the most widely distributed emerging pathogens (Chandy et al. 2008) to date and are found on every continent, *sans* Antarctica (Knust and Rollin 2013). Currently, there are over ninety hantavirus serotypes described worldwide, where 24 are officially recognized by the International Committee on Taxonomy of Viruses (Krüger et al. 2011; King et al. 2012; Vaheri et al. 2013; Milholland, in review). At least 22 of these viruses are known to be pathogenic to humans (Bi et al. 2008). Small mammals serve as hantavirus hosts as they maintain and amplify these pathogens in nature with no apparent sign of disease (Jonsson et al. 2010); thus, becoming the source of infection that spread these viruses to spillover hosts (Mills and Childs 1998; Lee et al. 2014). The worldwide distributions of hantaviruses are dependent upon the natural history and presence of these hantavirus associated host species (Schmaljohn and Hjelle 1997; Plyusnina et al. 2004; Schlegel et al. 2014; Milholland et al., in review).

Human hantaviral disease manifests as a hemorrhagic fever with renal syndrome (HFRS) or nephropathia epidemica (NE) in Eurasia, India, and Africa (Old World hantaviruses), and hantavirus (cardio) pulmonary syndrome (HPS), in the Americas (New World hantaviruses) (Mertz et al. 2006; Ettinger et al. 2012; Knust and Rollin 2013; Montoya-Ruiz et al. 2014; Witkowski et al. 2014). While NE is less severe, HFRS and HPS are acute viral febrile diseases (Khaiboullina et al. 2005) and can be responsible for human mortality rates as high as 70% (Jay et al. 1997; Calisher et al. 2002). Humans become infected by breathing aerosolized virus particles shed in rodent saliva, urine, and

feces where it can persist for extended periods in the environment (Nuzum et al. 1988; Mills et al. 1997; Kallio et al. 2006; Vaheri et al. 2013). The national average of HPS-related mortality in the US is approximately 40% (Krüger et al. 2011) being higher (>50%) in South America (Firth et al. 2012). While mortality is higher for HPS than HFRS, only a few thousand HPS cases have been reported in the past decades, where ~50,000 HFRS cases are reported annually (Schlegel et al. 2014).

Rodents of the families *Cricetidae* and *Muridae* are the principal known hosts of hantaviruses (Jonsson 2010; Araujo et al. 2012). To date, hantaviruses carried in these rodents are the only known serotypes causing disease in humans, with some of these species the reservoirs of these pathogens (Guo et al. 2013). Hantavirus seropositive individuals from species in the *Heteromyidae*, *Nesomyidae*, and *Sciuridae* have also been documented suggesting these families might serve as hosts for hantaviruses (Mills et al. 1998; Torres-Pérez et al. 2010; Arellano et al. 2012; Milholland et al., in review). Some hantaviruses are shown to have close associations with shrews (family *Soricidae*) (Carey et al. 1971; Song et al. 2007c; Aria et al. 2008a,b; Kang et al. 2011b), moles (family *Talpidae*) (Jonsson et al. 2010; Kang et al. 2011a), and bats (families *Rhinolophidae*, *Nycteridae*, and *Vespertilionidae*) (Aria et al. 2013; Sumbicay et al. 2012; Vaheri et al. 2013).

Within-species transmission typically occurs horizontally via aggressive behavior, often associated with territory defense among adult males (Glass et al. 1988; Escutenaire et al. 2002; Hinson et al. 2004; McIntyre et al. 2005). Rodents become chronically infected and show relatively no clinical signs despite the presence of antibodies (McCaughey and Hart 2000; Khaiboullina et al. 2005; Kariwa et al. 2012; Schlegel et al.

2014). Vertical transmission is thought to be altogether absent or negligible in both wild and experimental environments (Mills et al. 1997; Schmaljohn and Hjelle 1997), however, it has been documented in cotton rats (*Sigmodon hispidus*) (Hutchinson et al. 2000; Schountz and Prescott 2014). Spillover hantaviral infections are accidental infections in secondary, dead-end hosts which may constitute a major source of EIDs in humans, other primates (Chen et al. 2010), domestic and sylvan animals (Schlegel et al. 2009; Jonsson et al. 2010; Featherstone et al. 2013; Jameson et al. 2013; Lunkvist et al. 2013; Taori et al. 2013) like lagomorphs (Childs et al. 1994) and marsupials (Araujo et al. 2012). However, ecological factors facilitating spillover events, particularly at the human-wildlife interface, lack empirically driven predictive models (Lloyd-Smith et al. 2009; Tian et al. 2017). Prevention of these disease outbreaks requires surveillance of seroprevalence in animal populations (Mills et al. 2010; Halliday et al. 2012) and the development of accurate predictive models (Polop et al. 2010).

Small mammal assemblage structure and species richness have been suggested as strong drivers for the maintenance and spread of hantavirus infections in rodent populations (Glass et al 1998; Calisher et al. 2002; Allen et al. 2006). Prevalence of hantavirus infection is suggested to be negatively correlated with increased assemblage species diversity whereby the increase in species richness causes a decrease in pathogen transmission (Clay et al. 2009a; Brooks and Zhang 2010; Ostfeld 2011). This “dilution effect” (Ostfeld and Keesing 2000) can be attributed to the relationship between the dominance of reservoirs in the assemblage and the reduced abundance of species comprising the rest of the assemblage (Abbott et al. 1999; Douglass et al. 2001; Clay et al. 2009a; Kariwa et al. 2012). This phenomenon results when increased assemblage

diversity suppresses, or dilutes, disease prevalence and transmission events (Ostfeld and Keesing 2000; Zargar et al. 2015). The dilution effect can also operate when inadequate hosts for the propagation of pathogens (i.e., non-competent hosts) become infected and are unable to infect other individuals (McGill et al. 2006; Keesing et al. 2010). These non-competent, dead-end hosts tend to be phylogenetically distant from the principle host species (Herbreteau et al. 2006). Though the general assumption for the decrease in disease prevalence is often attributed to species richness alone, this misconception often disregards the zoonotic potential of the rest of rodent species comprising an assemblage beyond the main reservoir species (Han et al. 2016). Thus, an apparent phylogenetic dilution effect may better explain hantavirus transmission dynamics (Huang et al. 2016b; Milholland, unpublished data) where species identities more accurately affect probabilities of localized infections (Gagic et al. 2015). Anthropogenic changes to habitat often favor population increases of generalist rodent species, many of which are hantavirus reservoir species (Schmaljohn and Hjelle 1997; Langlois et al. 2001; Mackelprang et al. 2001) while decreasing species diversity (Yates et al. 2002; Suzán et al. 2009). These environmental alterations can increase the risk of human interaction with infected rodents (Kuenzi et al. 2001; Root et al. 2003; Lonner et al. 2008; Hjelle and Torres-Pérez 2010; Torres-Pérez et al. 2010; Calisher et al. 2011). It may be possible to predict hantavirus-related disease risk by using abundance estimates of specific host species (Keesing et al. 2006) and species identity indices as predictors (Calisher et al. 2002; Mills et al. 2010, Gagic et al. 2015). These relationships have been studied in some zoonotic systems (Glass et al. 2002; Allen et al. 2006), including specific hantavirus related human infections (Zeimes et al. 2012; Murray et al. 2015; Bordes et al. 2016), and particular host species

(Sauvage et al. 2003; Adler et al. 2008), yet the general form of a predictive model for hantaviruses has not been thoroughly addressed (Schlegel et al. 2014).

Here, I aim to identify assemblage descriptors and phylogenetic indices as predictor variables that are correlates of hantavirus prevalence within small mammal assemblages. I define hantavirus prevalence as the percentage of infected individuals per total assemblage abundance. My hypotheses include: 1) small mammal assemblages with higher species richness and/or more phylogenetically diverse species will have fewer seroprevalent individuals, where this relationship may be mediated by the differences in rodent host species abundance between low and high species richness assemblages; 2) known reservoir species will be the dominant component in less diverse assemblages having high prevalence; and 3) higher phylogenetic lineage divergence of species in the assemblage will contribute to a decrease in seroprevalence via the dilution effect as interspecific transmission is less probable.

My research objectives were to: 1) determine the dominance and relatedness correlate(s) of hantavirus prevalence in small mammal assemblages in a global and continental scale; 2) determine any quantitative associations of diversity, dominance, and phylogenetic diversity indices with seroprevalence; and 3) develop and compare predictive models for hantavirus prevalence in small mammal assemblages using defined ecological correlates.

Methods

Species abundance distributions for rodent assemblages worldwide were gathered from peer-reviewed publications, using a combination of terms such as “Hantavirus,

rodents, HCPS, HFRS, nephropathia epidemica, hosts, and reservoirs” for articles published from 1971-2014 using Google, Google Scholar, Web of Science, and the Centers for Disease Control and Prevention (CDC) homepage (www.cdc.gov). The CDC website provided relevant articles and related links including PubMed (www.pubmed.gov) and the U.S. National Library of Medicine (www.nlm.nih.gov). References listed in journal articles were also utilized to source the initial reports of hantavirus hosts, their related serotypes, and any human disease associations. Site data were categorically grouped by continent (i.e. Asia, Europe, North America, and South America), as reports of hantavirus surveys are often followed by human disease outbreaks and are monitored differently according to geographic and political regions (Schlegel et al. 2014). For inclusion in my study, all individuals within the assemblage must have been trapped in Sherman live traps or snap traps and tested for hantavirus antibodies where at least one seropositive individual was reported at each site. Additionally, I included only sites included in those articles reporting a raw abundance equal to, or greater than, 20 individuals ($n \geq 20$) in the sampling effort.

For each site, I gathered the following data: 1) the geographic identity (e.g. political location, latitude and longitude); 2) the year and month of trapping or collection; and 3) the abundance and identity of each species trapped or collected, including the number and identity of seropositive individuals. The specific geographic identity (i.e., site) was constrained, where sites were limited to trapping transects within an area no greater than 5 km² and trapping effort occurred within a 12-month period. Additionally, type-specific hantavirus infection was recorded if the genetic identity of the hantavirus is

confirmed by reverse transcription polymerase chain reaction (RT-PCR). Hantavirus identity information was used for reference only.

Seroprevalence was calculated as four, separate response variables for multiple regression analysis. Assemblage prevalence was calculated as a percent of seroprevalent individuals with the total number of individuals in an assemblage (Total Assemblage Seroprevalence, TAS) at each site. This TAS value was also weighted (Weighted Total Assemblage Seroprevalence, WTAS), by using the number of seroprevalent individuals in each assemblage as a percentage of the sum of all individuals reported for the continent and worldwide levels. Weighting the reported relative abundance of each site and the respective site seroprevalence aids in accounting for the variability in survey efforts between sites within each spatial level (i.e. continent and worldwide).

Additionally, the seroprevalence of the most dominant host within each assemblage served as a response variable (Most Dominant Host Seroprevalence, MDHS). The MDHS was determined as the most abundant known hantavirus host (sensu the list by Jonsson et al. 2010) testing seropositive in the reported assemblage. This MDHS value was also weighted (Weighted Most Dominant Host Seroprevalence, WMDHS). WMDHS was calculated by the number of seroprevalent dominant host individuals at the site level divided by the sum of that species reported in all assemblages at each spatial level (continent and worldwide).

A total of eleven diversity (e.g. assemblage) descriptors were gathered or calculated for all sites. These assemblage characteristics served as predictor variables against the response variables for seroprevalence: TAS, WTAS, MDHS, and WMDHS. These predictor variables included: 1) *Raw total abundance (n)*, or, the number of

individuals for all species reported for the assemblage; 2) *Raw species richness* (s), the total number of species recorded at each site; 3) *Estimated species richness* (s_{est}), was also used because sampling effort can limit or bias the reported number of species. To compensate for this potential bias, the Chao estimate and the abundance coverage-based estimate of species richness (ACE) was calculated using EstimateS programs (Chao 1984; Chao and Lee 1992; Colwell 2005). These estimated values were compared to the raw species richness with a student's t-test to determine if any difference exists for use in the analysis; 4) *Shannon diversity index* (H') was calculated using EcoSim 700 (Gotelli and Entsminger 2001). A benefit of using the Shannon diversity index (hereafter, shd) is that collectively among sites, (shd) generally follows a normal distribution (Shannon 1948; Magurran 2004); 5) *Hurlbert's PIE index* is the probability of an interspecific encounter (PIE) is the probability that two randomly sampled individuals from an assemblage pertain to two distinct species (Hurlbert 1971). This evenness index, or measure of heterogeneity (Adler et al. 2008), was used to combine species richness and dominance characteristics of the assemblage (Gómez 2007). I used EcoSim 700 to calculate (PIE) (Gotelli and Entsminger 2001); 6) *Mean nearest taxon distance and mean pairwise distance* was a phylogenetic hypothesis created in R using a cytochrome-b (Cyt-b) phylogeny created with data obtained from GenBank (<http://www.ncbi.nlm.nih.gov/genbank/>) comprising all species included in the generated dataset. This phylogeny was used to generate predictor variables (Mean Nearest Taxon Distance, MNTD; Mean Pairwise Distance, MPD) from the relatedness of each species within an assemblage using the "bladj" algorithm of phylocom (<http://phylodiversity.net/phylocom/>) (Webb et al. 2002, 2008; Ives and Helmus 2010).

The MNTD and 7) *MPD* values were compared with a student's t-test to determine if any differences exist for use in the analysis; 8) *Phylogenetic diversity totals* (PD) relates to the minimum total length of all phylogenetic branches required to span a given set of taxa on the phylogenetic tree (Clarke and Warwick 1998). The bifurcating phylogeny branch lengths were calibrated to million years before present divergence and PD totals estimated as Faith's PD (Barker 2002). This phylogenetic species variability index was also based on cladistic information, and this index quantifies the variability among species composing an assemblage (Helmus et al. 2007). PD was summarized using a matrix of the pairwise distances between taxa using Picante (<http://artax.karlin.mff.cuni.cz/r-help/library/spacodiR/html/00Index.html>) for R (Barker 2002; Binninda-Emonds et al. 2007); 9) an ordinate *Rank* (*rk*) was used where each species was given a discrete rank variable (from 1 to *s*) in decreasing values of the reported (*n*) within each assemblage. The rank variable for the assemblage was representative of the rank of the most dominant host within that assemblage. Rodents carrying hantaviruses which are known to directly cause disease in humans were listed as "reservoirs;" 10) *Rarity Threshold* (*R_t*) was a classification of how common a species is from the sum of all species collected in each assemblage. With this categorical predictor variable, "rare" species are determined as having a relative abundance below the rarity threshold, (*R_t*) calculated as (*n/s*). Species whose relative abundance is greater than this ratio were categorically listed as "abundant;" 11) *The Berger-Parker dominance index* (*BP*) was determined by the inverse of the proportional abundance of the most abundant species: $[d = 1 / (n_{\max} / N)]$, where, (*n_{max}*) = the number of individuals in the most abundant species, and (*N*) is the total number of individuals in the assemblage (Berger

and Parker 1970; Magurran 2004). This index was used to describe the dominance component of the most abundant seroprevalent host or reservoir in the assemblage. In the instance where multiple host/reservoir species were seropositive in an assemblage, the (n)-value and the site-specific attributes were used as context to determine the dominant species component.

Statistical analysis

The relationship(s) between the response variable (seroprevalence calculated as TAS, WTAS, MDRS, or WMDRS) of the assemblage to the predictor variable(s) mentioned above were analyzed through multiple regression models in R version 3.3.0, and the “leaps” package (Lumley 2017). These response variables were also compared using a log-transformation as means of standardizing and as an attempt to compensate for variability between reports. Because of the nature in which the predictor variables are derived, correlations between predictor variables were analyzed using the Pearson product-moment correlation (Pearson r). Where correlations were present, principal component analysis (PCA) (e.g. dimensionality reduction) was used to unify, or compress, correlated variables into a single index (i.e. eigenvectors), thus reducing statistical issues of multicollinearity (Miller 2014; Huang 2016a). Additionally, all response and predictor variables were scrutinized, where violations in homoscedasticity were determined and corrected to fit a normal distribution. Models were compared using the Akaike Information Criterion (AIC_c) (Akaike 1973).

Results

My literature search produced 72 papers reporting data within my constraints. Data from a total of 187 unique sites in Asia, Europe, North America, and South America (13, 10, 23, and 26, respectively) were used for analysis. Assemblage characteristics for each continent are summarized in Table 1. A significant difference exists between MPD and MNTD ($t_{185} = -7.02$; $p < 0.001$), therefore both measures of phylogenetic relatedness were used in the analysis. However, the Chao estimate (ACE) of species richness based on relative abundance was no different ($t_{186} = -7.22$; $p < 0.001$) in comparison to raw species richness (s) within the reports. Thus, the species richness value reported in the literature was used in the dataset. Model selection (Table 2) indicates the top model accounting for TAS ($R^2_{\text{adj}} = 0.20$; $p < 0.001$) includes the total abundance (n) of the assemblage, the ordinate rank of the most dominant host, and the mean nearest taxon distance (MNTD) of species comprising the assemblage. Additionally, two compressed assemblage descriptors (diversity1 and phylo1) were notable predictors of hantavirus prevalence. Results of PCA compressions used in the model selection are shown in Figure 1.

Cricetid rodent species (76%; 32/42 total species) accounted for the most dominant hantavirus hosts (140 sites), followed by murid hosts (29%; 12/42) at 44 sites (Table 3). In total, three soricomorph species, *Sorex araneus* (n = 1), *Suncus murinus* (n = 13) (Family Soricidae), and *Urotrichus talpoides* (n = 3) (Family Talpidae) were found to have antibodies to hantaviruses, with serotypes confirmed through PCR. Two of these soricid species, *S. murinus* and *U. talpoides*, were found to be the only species with seropositive individuals (1/20 and 3/6, respectively) in rodent dominated assemblages.

Globally, 66% (124/187) of sites occurred in disturbed, or peridomestic, habitats with 36% (68/187) sampled following a human-hantavirus disease outbreak. Differences in assemblage prevalence regarding habitat type (sylvan vs. disturbed) approached significance ($t_{185} = -1.35$; $p = 0.09$). All recorded sites in Asia occurred in disturbed or peridomestic settings, while 88%, 94%, and 39% were reported in Europe, South America, and North America, respectively. At the time of my inquiry, we could find no reports from the continent of Africa meeting my criteria.

Discussion

It is clear, the phylogenetic relatedness of potential host species comprising assemblages plays a role in the prediction of hantavirus prevalence (Table 2). As expected, larger PD, MPD, and MNTD values correspond to greater assemblage diversity (Faith 1992; Magurran 2004), and show a general trend in the reduction of seroprevalence (Figure 2). While this trend is also present with higher species richness (Figure 3), species richness alone does not efficiently explain predictions of prevalence. This supports a cautious use of describing dilution effects directly associated with total species number, while requiring consideration that prevalence trends may be driven by the phylogenetic relatedness of species comprising the assemblage (Johnson et al. 2015; Suzán et al. 2015; Milholland, unpublished data). Each of the top six models contain multiple predictor variables associated with phylogenetic diversity, where a majority (5/6) include the ordinate rank of the most dominant host in the assemblage (Table 2). These data support my first and third hypotheses where, on average, the more phylogenetically diverse assemblages tend to have lower hantavirus prevalence, while

higher species richness can influence a decrease in prevalence in some cases (Figures 2 and 3).

It is interesting to note, the second-best model explaining the variation in the dataset carries an AIC_c weight 0.87 units below the top model, with an AIC_Δ of 6.05 (Table 2). This suggests that the data supporting the model (tas~n+rk+diversity1+phylo1+mntd) best explains the variation in total assemblage hantavirus prevalence at the global scale. Although the R^2_{adj} (0.20) value is low, I feel this number is reflective of the lack of systematic reporting in the literature and the high variability in trapping expertise and efforts.

The presence of dominant host and reservoir species also strengthens the probability of increased prevalence (Table 3). The highest assemblage prevalence in my dataset (TAS=48%) was from an Arizona home in North America where rodents were sampled following an outbreak of HPS (Hjelle et al. 1996). The dominant component of this assemblage, *Peromyscus maniculatus* (n = 23/33; 70% seropositive), was the only species shown to have hantavirus antibodies, while other assemblage species tested (*Peromyscus truei*, n = 11; *Reithrodontomys megalotis*, n = 4) only had naïve individuals. In Bosnia, the highest prevalence recorded (45.7%) was at a site where all species (*Apodemus flavicollis*, n=12/28, 43%; *Apodemus sylvaticus*, n=3/6, 50% seroprevalence; and *Mus musculus*, n=1/1, 100% seroprevalence) were closely related (Subfamily Murinae) and all species had individuals testing positive for hantavirus antibodies of an unknown serotype (Glicic et al. 1992). Yet, if we look at an assemblage in Germany with moderately unrelated species (*Myodes glareolus*, n=23/35, 65.7% seroprevalence; *Apodemus flavicollis*, n=0/17; and *Apodemus sylvaticus*, n=0/1), as is the case in Essbauer

et al. (2007), we find a relatively high seroprevalence (43.4%), where regionally, the Puumala virus is attributed to *M. glareolus* (Milholland, in review). Additionally, it is important to note that high prevalence, can also be associated with high species diversity. For example, in São Paulo, Brazil, an assemblage composed of 14 distinct species was shown to have 15.7% prevalence (Araujo et al. 2012). Though it may be unusual to find such a high prevalence in such a diverse assemblage, it is important to consider species interactions and spillover maintenance of hantavirus presence at the community scale. This assemblage was composed of eight genera of cricetid rodents (*Oligoryzomys* n=4/23, 17% seropositive; *Oryzomys* n=1/7, 14% seropositive; *Akodon* n=3/26, 12% seropositive; *Thaptomys* n=1/2, 50% seropositive; *Juliomys* n=1/2, 50% seropositive; *Nectomys* n=0/3; and *Delomys* n=0/1) and three genera of didelphid marsupials (*Monodelphis* n=1/7, 14% seropositive; *Micoureus* n=1/3, 33% seropositive; and *Marmosops* n=0/4) where all seropositive individuals were found to carry the Ararquara-like virus (Araujo et al. 2012; Milholland, in review). Thus, predictions of hantavirus prevalence may not be entirely reliant upon the dominance of specific known host species (e.g. rodents) as these viruses can be maintained within small mammal communities with high diversity.

Two soricomorph species, (*Suncus murinus* and *Urotrichus talpoides*) were found as the only seropositive species within rodent dominated assemblages in Vietnam (Luan et al. 2012) and Japan (Arai et al. 2008b), respectively. In the case of *S. araneus*, this was the first report for the Seewis Virus (Song et al. 2007b), and Arai et al. (2008b) report the Asama virus as the first mole-born hantavirus, and carried by *U. talpoides*. The highest hantavirus diversity was found in *S. murinus*. This shrew species was found to carry the Hantaan (Xu et al. 1987), Seoul (Chin et al. 2000), and Thottapalayam viruses (Luan et

al. 2012) suggesting that viral host-switching can be a fundamental driver of hantavirus maintenance.

I encourage continued surveillance of, not only hantaviruses, but other zoonotic pathogens which may be present in small mammal assemblages. I feel sampling for these data should become standard practice when conducting field research. I have shown that understanding small mammal assemblage structure is fundamental in predicting hantavirus prevalence. Knowledge of zoonotic pathogen dynamics, such as hantavirus-system ecology, can assist surveillance and aid strategy development to counter EID threats to humans (Daszak et al. 2000; Murray et al. 2015).

Climate change is affecting seasonal weather patterns and anthropogenic landscape alterations are promoting the increase in human-wildlife interactions (Klempa 2009; Calisher et al. 2011). Stochastic weather patterns (e.g. increased frequency of heavy rainfall) can create unpredictable, often chaotic, patterns of resource availability affecting mammalian-host populations and densities (Tian et al. 2017). Worldwide, incidence of hantavirus-related disease seems to fluctuate with cyclical patterns in ecological systems (Olsson et al. 2003, 2010; Cvetko et al. 2005; Madhav et al. 2007; Pettersson et al. 2008). Together, these factors are disrupting natural ecosystem dynamics (Steffen et al. 2011) and escalating incidence of EIDs (Mills et al. 2010; Reusken and Heyman 2013). My models describe the general relationship between host assemblage ecology, host assemblage characteristics (which may be characteristic of habitat disturbance), and the importance of species phylogenetic relatedness within a given assemblage. These factors, concerted with species abundance and dominance

characteristics, can provide valuable insight into the hantavirus-system and may contribute to the prevention of hantaviral human diseases.

APPENDIX SECTION

Table 1. The table describes ranges of small mammal assemblage diversity characteristics at the continent level. Hantavirus seroprevalance ranges are listed as the ratio (%) of infected individuals divided by the total number of individuals within the assemblage. Numbers in parentheses indicates the number of sites included for each continent in the dataset.

Continent	Range									
	n	s	tas (%)	mdrs (%)	rank	shd	pie	BP	pd	mntd
Asia (40)	21-677	2-12	1-40	1-59	1-3	0.5-1.7	0.28-0.80	1-7	164-608	11-123
Europe (17)	21-158	2-9	1-46	2-66	1-3	0.1-1.8	0.05-0.82	1-5	181-477	3-67
North America (96)	21-600	2-17	1-48	2-100	1-11	0.1-2.5	0.04-0.90	1-28	162-763	4-100
South America (34)	22-327	2-13	2-27	2-50	1-4	0.1-2.1	0.03-0.83	1-13	186-568	2-122

(n) = relative abundance; (s) = species richness; (tas) = % total assemblage prevalence; (mdrs) = % prevalence of the most dominant host within the assemblage; (rank) = the ordinate rank of the most dominant host in the assemblage based on relative abundance (n); (shd) = Shannon diversity index; (pie) = Hurlbert's Probability of Interspecies Encounter index of evenness; (BP) = Berger-Parker dominance index; (pd) = phylogenetic diversity index; (mntd) = mean pairwise distance; (mntd) = mean nearest taxon distance.

Table 2. The table presents models accounting for hantavirus prevalence in small mammal assemblages at the global scale. Sites (n=187) are from reports in peer-reviewed literature published between 1973-2014. Models are compared using Akaike Information Criterion (AIC_c). Response variable (tas) is the % total hantavirus prevalence at the global scale. Response variables include diversity and phylogenetic indices describing assemblage characteristics. Principal Component Analysis (PCA) was used to collapse assemblage descriptor covariates.

Models	<i>k</i>	<i>logLik</i>	<i>AIC_c</i>	Δ	<i>wt</i>	R^2_{adj}	<i>p</i>
tas ~ n + rk + diversity1 + phylo1 + mntd + ϵ	7	-226.265	467.2	0.00	0.915	0.20	<0.001
tas ~ rk + diversity2 + bp + pd + mpd + mntd + ϵ	8	-228.201	473.2	6.05	0.044	0.18	<0.001
tas ~ rk + diversity2 + bp + phylo1 + mntd + ϵ	7	-229.971	474.6	7.41	0.022	0.17	<0.001
tas ~ rk + diversity3 + phylo2 + ϵ	5	-232.952	476.2	9.08	0.010	0.15	<0.001
tas ~ rk + diversity2 + bp + phylo2 + ϵ	6	-232.676	477.8	10.66	0.004	0.15	<0.001
tas ~ diversity3 + phylo2 + ϵ	4	-235.018	478.3	11.10	0.004	0.14	<0.001

(n) = relative abundance; (rk) = ordinate rank of most dominant host; (mntd) = mean nearest taxon distance; (BP) = Berger-Parker dominance index; (pd) = phylogenetic diversity index

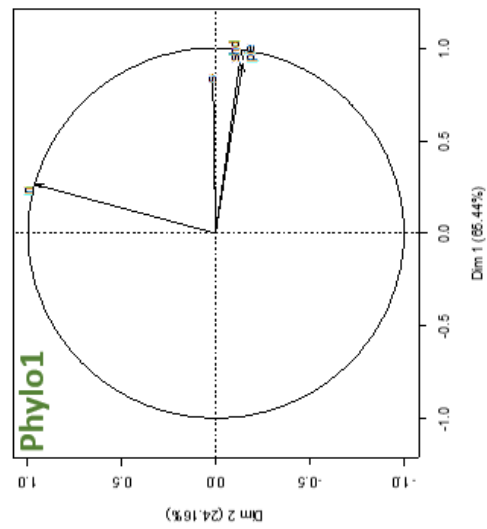
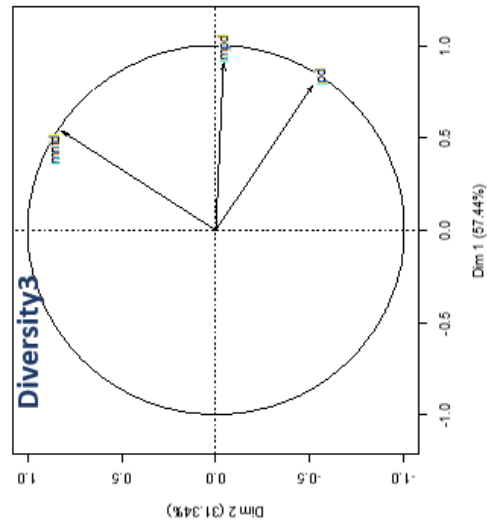
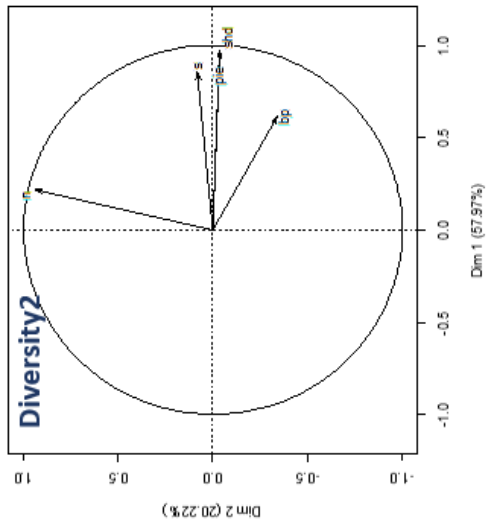
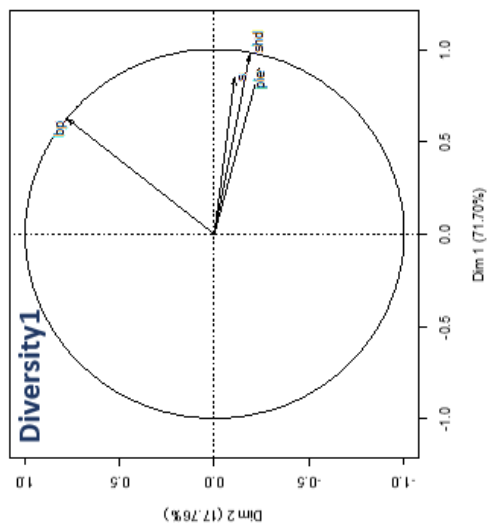
Table 3. A list of small mammal hantavirus host and reservoir (indicated by *; carrying hantaviruses known to cause disease in humans; see Chapter 1) species. Each listed species was found to be the most dominant component comprising an assemblage and was seropositive for antibodies against hantaviruses. Species are listed alphabetically by taxonomic order, family, subfamily, and species. (# of sites) indicates the number of sites where the species was found to be the dominant component; (N_{total}) indicates the number of each species sampled globally; and (Mean Intraspecies Prevalence) is the average seroprevalence for all individuals within a species combined; small mammal taxonomy follows (Wilson and Reeder 2005).

Order	Family	Subfamily	Most Dominant Host Species	# of Sites	N_{total}	Mean Intraspecies Prevalence (%)
Soricomorpha	Soricidae	Crocidae	<i>Suncus murinus</i>	1	20	5.0
	Talpidae	Talpinae	<i>Urotrichus talpoides</i>	1	6	50.0
Rodentia	Cricetidae	Arvicolinae	<i>Eothenomys miletus</i>	1	129	17.8
			<i>Microtus arvalis</i> *	2	109	13.0
			<i>Microtus pennsylvanicus</i>	1	209	28.7
			<i>Myodes glareolus</i> *	6	368	16.4
			<i>Myodes rufocanus</i>	3	134	25.4
		Neotominae	<i>Neotoma albigula</i>	1	27	3.7
			<i>Peromyscus attwateri</i>	1	116	6.0
			<i>Peromyscus beatae</i>	1	50	34.0
			<i>Peromyscus boylii</i>	10	304	21.3
			<i>Peromyscus leucopus</i> *	4	116	11.2
			<i>Peromyscus levipes</i>	3	69	14.1
			<i>Peromyscus maniculatus</i> *	42	1627	15.9
			<i>Peromyscus melanotis</i>	1	34	2.9
			<i>Peromyscus spicilegus</i>	1	9	22.2
			<i>Peromyscus truei</i>	1	8	12.5
			<i>Reithrodontomys megalotis</i>	6	68	20.8
			<i>Reithrodontomys sumichrasti</i>	2	20	58.3
		Sigmodontinae	<i>Abrothrix longipilis</i>	1	37	8.1
			<i>Akodon azarae</i>	5	291	11.1
			<i>Akodon cursor</i> *	2	33	6.1
			<i>Calomys callosus</i> *	2	174	6.6
			<i>Calomys laucha</i> *	1	13	30.8
			<i>Holochilus sciureus</i> *	1	51	29.4
			<i>Necomys lasiurus</i> *	3	244	6.7
			<i>Oligoryzomys longicaudatus</i> *	2	119	21.1
			<i>Oligoryzomys microtus</i> *	2	69	14.6
			<i>Oligoryzomys nigripes</i> *	3	65	14.1
			<i>Oryzomys couesi</i>	3	412	13.5
			<i>Oryzomys palustris</i> *	13	794	20.6
			<i>Oxymycterus nasutus</i> *	1	89	4.5
			<i>Sigmodon alstoni</i>	8	313	19.5
			<i>Sigmodon hispidus</i> *	7	294	14.0
Rodentia	Echimyidae	Eumysopinae	<i>Proechimys canicollis</i>	1	2	50.0
Rodentia	Muridae	Murinae	<i>Apodemus agrarius</i> *	3	192	5.8
			<i>Apodemus flavicollis</i> *	5	183	30.1
			<i>Apodemus peninsulae</i> *	1	70	5.7
			<i>Apodemus sylvaticus</i>	2	124	3.7
			<i>Bandicota indica</i>	3	298	5.6
			<i>Bandicota savilei</i>	1	83	4.8
			<i>Mus musculus</i>	2	27	22.6
			<i>Niviventer confucianus</i>	2	66	11.7
			<i>Rattus exulans</i>	3	309	4.0
			<i>Rattus norvegicus</i> *	19	2286	24.9
			<i>Rattus rattus</i> *	1	57	22.8
			<i>Rattus tanezumi</i>	2	146	12.1

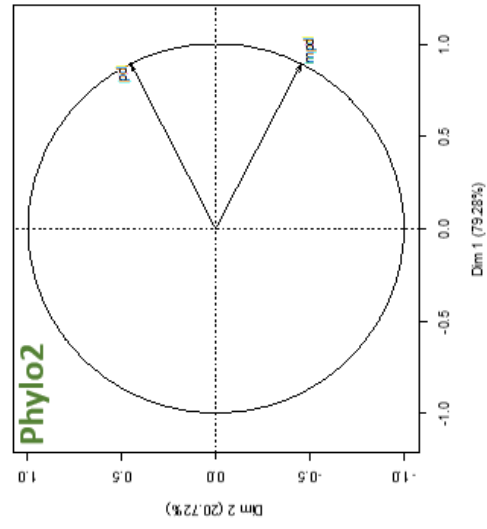
Figure 1. The results of covariate collapsing using Principal Component Analysis (PCA) to derive eigenvectors describing small mammal assemblage characteristics (in blue) and phylogenetic relatedness indices (in green). These five descriptors were used as predictor variables in the global model selection to account for variation in predicting total assemblage hantavirus seroprevalence (TAS%).

Figure 2. The scatterplots show the relationship of total assemblage seroprevalence (TAS) against three phylogenetic indices: phylogenetic diversity (PD), mean pairwise distance (MPD), and mean nearest taxon distance (MNTD) as calculated using Picante for R. Data are shown at the global scale.

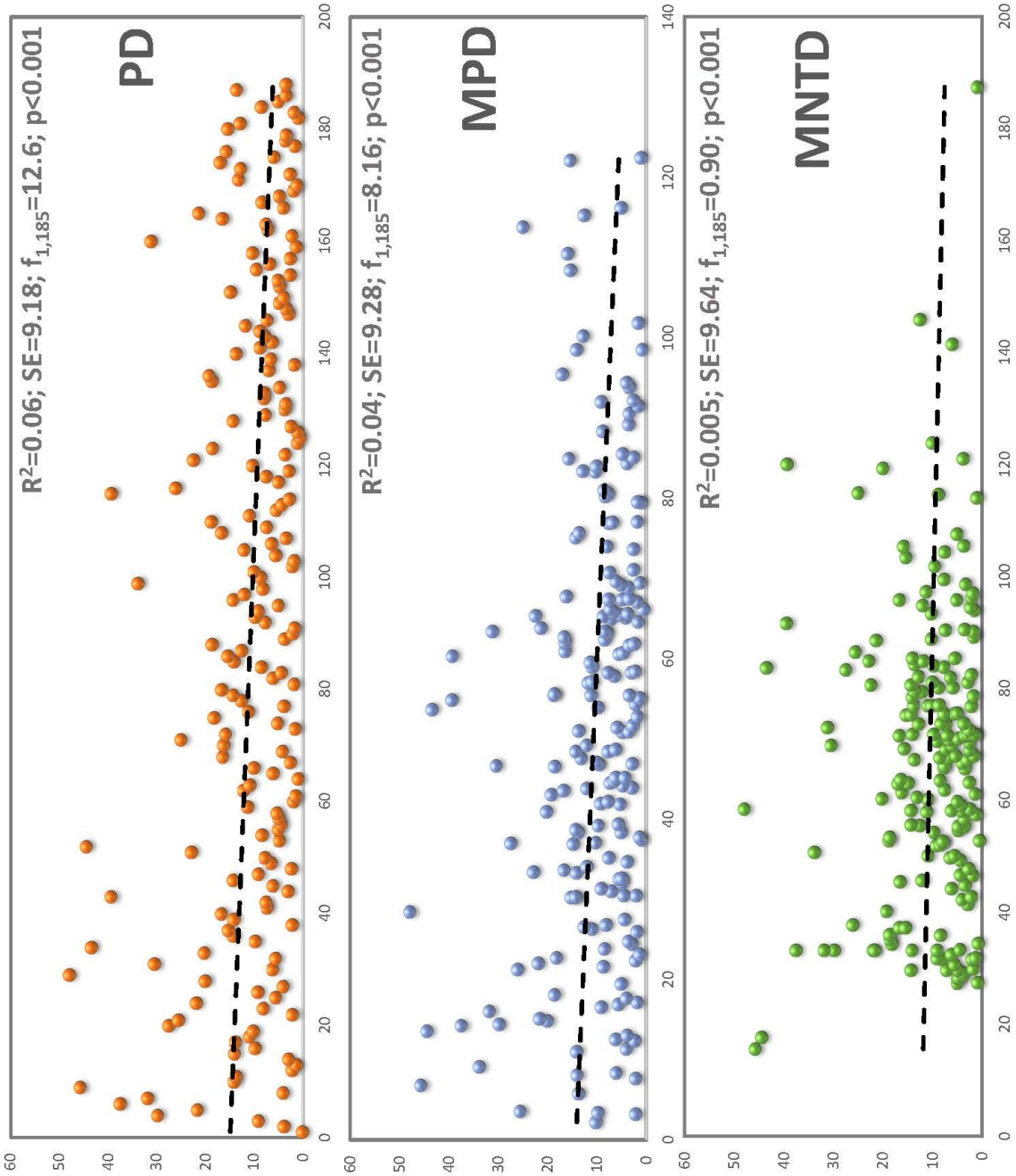
Figure 3. The regression analysis shows the general decrease in overall hantavirus seroprevalence from small mammal assemblages worldwide and species richness increases.

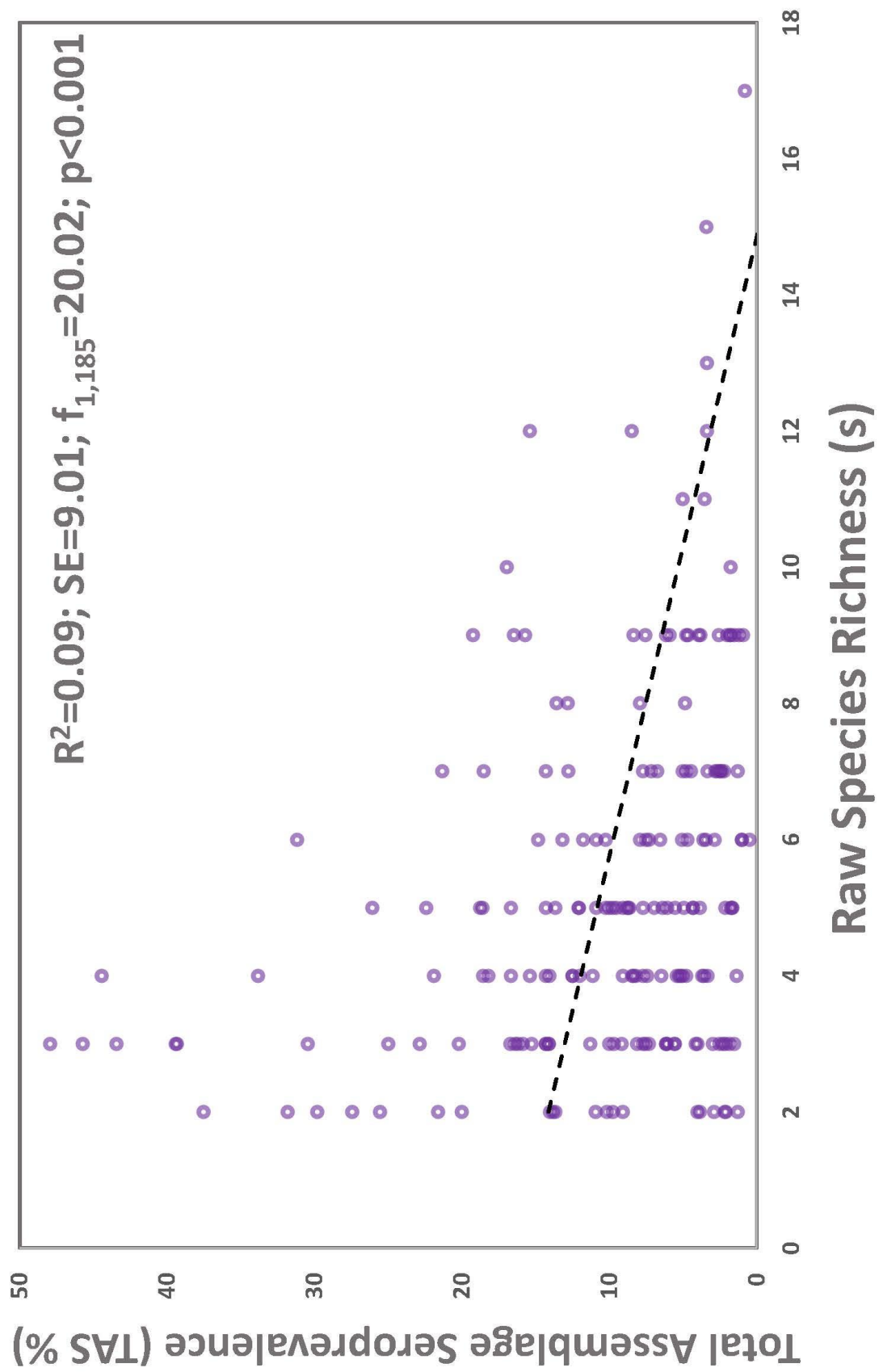


bp = Berger- Parker Dominance
n = raw abundance
pie = Hurlbert's evenness
s = raw species richness
shd = Shannon's diversity
mntd = mean nearest taxon distance
mpd = mean pairwise distance
pd = phylogenetic diversity



Total Assemblage Seroprevalence (TAS %)





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IV. PREVALENCE OF HANTAVIRUSES IN RODENT ASSEMBLAGES FROM SYLVAN AND DISTURBED HABITATS ACROSS TEXAS AND MÉXICO

Background

Anthropogenic habitat disturbance continues to increase worldwide, leaving very few areas unchanged by human alterations (Burney and Flannery 2005; Johnson et al. 2013). These changes can have severe impacts on biological diversity by altering ecological relationships (Foley et al. 2005) and modifying natural host-pathogen dynamics (Keesing et al. 2006) potentially leading to the emergence of infectious diseases in humans and wildlife (Mills et al. 2010; Hjelle and Torres-Pérez 2010; Gottdenker et al. 2014).

Although the study of emerging infectious disease (EID) dynamics from zoonotic origins is challenging, recent advances promise great strides in this area in this area of research. One of the current trends is to consider whole ecological communities where zoonotic pathogens occur, and the potential factors facilitating pathogen persistence within them, and how these factors contribute to outbreaks of human disease (Johnson et al. 2015, Suzán et al. 2015). Species richness, the abundance of each species, and host species interactions (both intra/interspecies) within assemblages likely have strong roles in modulating pathogen levels within local assemblages (Zargar et al. 2015).

Recent theories indicate that a relationship exists between community diversity and pathogen prevalence with most of the inferences referred to assemblages (i.e. groups of species of the same taxa). Two contrasting outcomes of this relationship have been proposed, being labeled as the “dilution effect” and the “amplification effect” (Ostfeld and Keesing 2000; Keesing et al. 2006; Pagán et al. 2012; Zargar et al. 2015). In the case

of a dilution effect, species diversity in an assemblage presumably suppresses disease prevalence and transmission events (Ostfeld and Keesing 2000; Zargar et al. 2015), often occurring when inadequate hosts for the propagation of pathogens (i.e. non-competent hosts) become infected and are unable to infect other individuals (McGill et al. 2006; Keesing et al. 2010; Cohen et al. 2016). However, while this general assumption for the decrease in disease prevalence is often attributed to species richness alone, assemblages comprised of many phylogenetically similar species, or species with high pathogen competency, can increase infection transmission, persistence, and prevalence, thus creating an amplification effect due to species diversity (Rubio et al. 2014; Han et al. 2016; Huang et al. 2016; Milholland, unpublished data). These models of disease presence have both been supported with experimental and observational evidence, particularly in the case of vector-borne diseases (e.g. Lyme disease) (LoGiudice et al. 2003; Dizney and Ruedas 2009; Ostfeld and Keesing 2012) with no consensus on the generality of each one because the mechanisms that govern the relationship between diversity and pathogen prevalence are still not fully understood. For example, in the case of hantaviruses, the phylogenetic relationship of each species comprising the assemblage plays a crucial role in hantavirus transmission and maintenance, as host-switching between related species and pathogen persistence are intimately entwined (Levis et al. 1998; Morzunov et al. 1998; Monroe et al. 1999; Bohlman et al. 2002; Nemirov et al. 2010; Ramsden et al. 2008; Milholland, in review).

The degree of EID prevalence is often associated with the condition of the habitat (Jones et al. 2008; Daszak et al. 2001; Patz et al. 2004; Gottdenker et al. 2014). Regionally distinct communities of a given taxa (hereafter, assemblages; sensu, Fauth et

al. 1996) can also be influenced by metacommunity dynamics (Holyoak et al. 2005) which, in turn, shape EID persistence and transmission dynamics at landscape scales (Dearing and Dizney 2010; Keesing et al. 2010; Suzán et al. 2015). Small mammal assemblage structure in disturbed habitats often differs from assemblages in sylvan environments (Murphy and Romanuk 2014; Rubio et al. 2014). Hantavirus prevalence is often negatively correlated with habitats containing high species diversity via dilution effect dynamics (Clay et al. 2009; Suzán et al. 2009) and as species richness increases, prevalence of infection often is decreased (Calisher et al. 2002; Reusken and Heyman 2013). Anthropogenic changes to sylvan landscapes have been shown to decrease species richness and/or increase phylogenetic similarities of assemblages across spatial scales (Olden and Rooney 2006). This homogenization of species composition can produce a replacement of specialist species with more adaptive, generalist species, where these potential changes can have very relevant ecological consequences (Olden et al. 2004; McKinney 2006), including the spread and maintenance of EIDs (Previtali et al. 2010).

Often, anthropogenic habitat disturbance decreases assemblage diversity by extirpating dietary or microhabitat specialists (Mills et al. 2010) while increasing abundance of generalist species, many of which are reservoirs of hantaviruses (Mills 2007; Calisher et al. 2007; Lehmer et al. 2008; Dearing and Dizney 2010). However, highly disturbed sites can also impede the survival of wild, native, and specialist rodent species, including infected hosts (Lehmer et al. 2008). These anthropogenically dominated sites pose risks (e.g. poison, traps, domestic predators) and competition with human commensal rodent species, with only a few species being able to thrive in these environs (Meerberg et al. 2009; Dizney et al. 2010; Morand et al. 2015). A reduction in

rodent diversity comprising disturbed areas may then increase the abundance of resilient, opportunistic hantavirus rodent reservoir species inhabiting species-poor areas, resulting in a greater potential for human-host interactions (Calisher et al. 2002; Clay et al. 2009; Rubio et al. 2014).

Sylvan, or markedly less disturbed, habitats presumably can maintain a lower assemblage seroprevalence associated to higher species richness via the dilution effect (Ostfeld and Keesing 2000; Blasdell et al. 2011). Comparing these natural sites to those anthropogenically modified habitats can provide a measure of the relationship of hantavirus prevalence with species diversity in the same area. The relationship between rodent assemblage structure of sylvan and disturbed sites, and differences in hantavirus seroprevalence between them, will allow inference into correlations between habitat alteration, species diversity, and hantavirus infection (Kuenzi et al. 2005; Dizney et al. 2010).

Purpose and Objectives

My research question is centered in ascertaining if rodent assemblage structure differs between sylvan and disturbed sites at a given locality, and if so, do disturbed habitats support greater assemblage-wide hantavirus seroprevalence as well as greater relative abundance and numerical dominance of hantavirus reservoir rodent species at these sites? Moreover, if species richness differs between sylvan and disturbed habitats, are differences in hantavirus seroprevalence consistent with the dilution or the amplification effects? The objectives of this research were to: 1) determine the rodent assemblage structure in sylvan and disturbed habitats from the same locality in selected

sites across Mexico and Texas; 2) determine hantavirus seroprevalence in rodents and other small mammals from each habitat type in each locality; and 3) compare seroprevalence in sylvan and disturbed habitats, considering the small mammal assemblage structure at each habitat. I hypothesized sylvan habitats will have higher species diversity and lower dominance of reservoir species compared to disturbed habitats and that hantavirus prevalence would be higher in disturbed habitats.

Methods

Ethics Statement

Texas fieldwork was conducted with prior approval from Texas State University (IACUC#'s 1206-0113-02 and 201598223), Texas Parks and Wildlife (#TPWD-SPR-1112-1052), and United States Department of the Interior (#BITH-2015-SCI-0016). Rodent sampling in Mexico was approved by Secretaría de Medio Ambiente y Recursos Naturales (permit SGPA/DGVS/00622/11).

Study Sites

Twenty sites were chosen across Texas (United States) and the Mexican states of Chihuahua, Hidalgo, Morelos, Tamaulipas, and Veracruz (see, Figure 1 and Table 1). Study sites (listed below) follow a north-to-south latitudinal gradient, encompassing a vast region beginning in northeast Texas, and concluding in the southern portion of Morelos in central México thus covering both Neartic and Neotropical sites. Texas sites included: Gus Engeling Wildlife Management Area (WMA); Big Thicket National Preserve; Mason Mountain WMA; areas within and around the city of San Marcos; Tejas

Ranch; Chaparral WMA; and Las Palomas WMA. Sites in México included: Janos, Chihuahua; Alta Cima, Gómez Farías, and San Jose in the state of Tamaulipas; Chilcuatla, Hidalgo; Coatepec, Veracruz; and Yautepec, Zacualpan, Tepalcingo, Miacatlán, Puente de Ixtla, Tepoztlán, and Tetela del Volcan in the state of Morelos. Unique sylvan and disturbed transects were selected and sampled concurrently at each site between January 2012 and January 2016. Habitats with the most historically natural conditions were described as sylvan and habitats exhibiting visible recent anthropogenic modifications or with existing structures (e.g. buildings, roads, and barns) were considered disturbed.

Rodent Trapping

Small mammals were trapped with Sherman live-traps (H. B. Sherman Traps, Tallahassee, FL, USA) using curvilinear transects and spaced approximately five meters apart and baited with rolled oats, peanut butter, and imitation vanilla. Concurrent trapping effort for both habitats occurred for three consecutive nights as weather and logistics allowed. All captured rodents were humanely euthanized with sedation via isoflurane, followed by cervical dislocation and processed in the field according to appropriate use and safety protocols (Mills et al. 1995; Kelt et al. 2007, 2010; Sikes et al. 2011; Leary et al. 2013). From each individual, tissues (i.e. blood, heart, lung, liver, kidney, spleen, and articulating joint) were flash frozen in liquid nitrogen then stored at -80°C or placed in 95% ethanol (i.e. articulating joint and spleen) for future analysis. Skull and pelt voucher specimens were also collected and are currently held at Texas State University, San Marcos, or Texas A&M University, College Station, TX.

Rodent Species Identification

Trapped rodents were identified in the field. However, juvenile and subadult *Peromyscus* species are notoriously difficult to differentiate (McDaniel et al. 1983). I used skull vouchers to identify suspect *Peromyscus* using skull measurements and occlusal surface characteristics (Hall 1981). If rodent species identification remained equivocal I resorted to genetic identification of specimens. DNA was extracted from frozen tissue samples following manufacturer protocol from the Qiagen DNeasy Blood and Tissue Kit (Qiagen Inc., Valencia California) and stored at -30° C. The mitochondrial Cytb gene was amplified and sequenced for each specimen using two sets of overlapping primers: 1) MVZ05 forward (5'- CGA AGC TTG ATA TGA AAA ACC ATC GTT G - 3') (Smith and Patton, 1993) and P3' reverse (5'- TCT CTC CGG TTT ACA AGA CCA AAG T -3'), 2) LGL 765 forward (5' - GAA AAA CCA YCG TTG TWA TTC AAC T - 3') (Bickham et al. 2004) and 752 reverse (5'- GCA GGA GTG TAA TTA TCG GGG TCT -3'). These primer sets were used for mtDNA amplification via polymerase chain reaction (PCR) and as sequencing primers. PCR amplification reactions totaled 25 µL consisting of the following: 12.5 µL GoTaq ® Green Master Mix, that contain 3mM MgCl₂, and 400µM of dNTPs(Promega Corporation, Madison, WI), 0.5 µL forward primer, 0.5 µL reverse primer, 1 µL DNA template, and 10.5 µL nuclease free water (Promega Corporation, Madison, WI). Amplifications were performed in a Peltier Thermo Cycler-200 (Bio-Rad Laboratories Inc., Hercules, CA) with parameters modified from C. W. Edwards and R. D. Bradley (2002): denaturation at 94°C for 1 min, followed by 35 cycles of 30 sec at 94°C, 1 min at 50°C, and 70 sec at 72°C. A final extension

period of 4 min at 72°C followed to complete the amplifications. PCR products were purified by ExoSAP protocol (Affymetrix Inc., Santa Clara, CA). Purified PCR products were then sequenced using a BigDye terminator cycle sequencing kit (Life Technologies, Carlsbad, CA). Included in this CSR reaction, which totaled 10 µL. Amplifications were performed in a PTC-200 with the following steps: denaturation at 96°C for 2 min, followed by 35 cycles of 20 sec at 96°C, 20 sec at 50°C, 4 min at 60°C. CSR products were then cleaned following Sephadex protocol (Signal-Aldrich, St. Louis, MO), suspended in 10 µL of HiDi™ formamide (Life Technologies, Carlsbad, CA) and sequenced on an Applied Biosystems Genetic Analyzer 3500xL (Life Technologies, Carlsbad, CA). Sequences were aligned in Geneious 8.1.7 (Biomatters Ltd, Auckland, New Zealand) and a consensus sequence generated from the alignment of each primer set for every specimen was compared to the National Center of Biotechnology Information GenBank database.

Enzyme-Linked Immunosorbant Assays (ELISA) to Determine Seroprevalence

Blood samples were collected using Nobuto strips (Advantec Inc.®, Pleasanton, California, USA) and used for enzyme-linked immunosorbant assay (ELISA) techniques in the laboratory. Blood samples on Nobuto strips were dried in sunlight to kill any active virus before performing the ELISAs. Initial ELISA testing occurred at the Arthropod-Borne Infectious Diseases Laboratory (AIDL), Colorado State University, and completed at Texas State University, Department of Biology. Because the Sin Nombre Virus (SNV) antigen is cross-reactive with several hantaviruses (Schountz et al. 2014), specific viral types were not determined. Under BSL-2 conditions, with BSL-3 precautions (CDC

1994), dried Nobuto strips were placed in separate microfuge tubes and rehydrated into 1:5 dilutions overnight at 4 °C in 500 µL elution buffer comprised of sterile filtered Dulbecco's phosphate buffered saline (DPBS), 0.5% bovine serum albumin (BSA), and 1.0% penicillin/streptomycin mix. Recombinant SNV nucleocapsid antigen was diluted to 1 µg/mL in DPBS, and 100 µL dispensed into wells of a 96-well polyvinylchloride plate (Schountz et al. 2014). Plates were incubated overnight at 4 °C, washed (3x) with DPBS-Tween 20, and blocked with 150 µL/well of 0.25% porcine skin gelatin (Sigma-Aldrich Corp. St. Louis, MO) in DPBS (pH 7.4) for at least one hour. Dilutions in microfuge tubes were heat inactivated at 60 °C for 30 minutes as a precaution to further inactivate any hantaviruses without damaging IgG antibodies. Samples were further diluted (1:100) in microfuge tubes by adding 475 µL to 25 µL of sample. Plates were washed (3x) with DPBS-Tween 20 and 100 µL of each sample, a positive control, and a negative control were added and incubated at ambient temperature for one hour. Plates were washed (4x) with DPBS-Tween 20 and 100 µL of 1:5,000 purified Recomb® (Thermo Scientific Rockford, IL) protein A/G horseradish peroxidase (HRP) dilute in DPBS added to wells and incubated at ambient temperature for 45 minutes. Plates were again washed (4x) with DPBS-Tween 20 and 100 µL of activated 2,2' -azinobis(3-ethylbenzthiazolinesulfonic acid (ABTS) added to wells for 15 minutes. Absorbance in each well was recorded at 405 nm (BioTek PowerWave XS, BioTek Instruments, Inc.) where positive samples were determined as 0.20 optical density (OD) units greater than the negative control.

Assemblage Structure and Dominance Components

I used capture data and ELISA results to compare the seroprevalence and assemblage structures between the two habitat types at each site and collectively across Texas and Mexico. Assemblage dominance descriptors included the following: (SRPV)= the percent prevalence of hantavirus antibody-positive individuals captured in each habitat per site; (N)= the number of individuals of each species captured in each habitat per site (i.e., species abundance); (S)= species richness included the number of different species captured in each habitat per site; and (PIE), Hurlbert's probability of interspecies encounters (Hurlbert 1971) as a measure of assemblage evenness. Estimates of PIE provide a numerical description of the proportions of species distributed throughout each assemblage. Seroprevalence and assemblage dominance descriptors were compared using Student's t-tests. At sites where hantavirus antibodies were detected, the ordinate rank of the most abundant host, the number of infected dominant host individuals, and the relative proportion of the dominant host species within the assemblage (DR) was calculated.

Regression Analysis

I conducted regression analysis and model selection using R studio version 3.3.0, using only sites with seropositive individuals. Step-wise linear regression analysis using the "leaps" package (Lumley 2017) was performed with (SRPV) as the dependent (response) variable and (N) and (S) as discrete variables, and the most dominant host species and habitat type (i.e. sylvan or disturbed) as categorical predictors. Models were

compared using the Akaike Information Criterion (AIC_c) with the “MuMin” package for model selection (Akaike 1973; Bartón 2016).

Results

Sampling and Capture Totals

Total sampling effort included 16,875 trapnights from January 2012 - January 2016 across 13 different ecoregions (Table 1) resulting in the capture of 2,406 individual small mammals. In Texas, 1,009 rodents and 62 soricomorphs were collected with an additional 1,335 rodents collected in Mexico. In total, 40 species of small mammals were identified comprising 2 taxonomic orders (Rodentia and Soricomorpha) including 4 and 1 families and 8 and 1 subfamilies, respectively (Table2). In all, 313 small mammals tested positive for antibodies against hantaviruses thus evincing an overall prevalence of 13% throughout all sites. However, distribution of prevalences was highly heterogenous going from sites with zero infected individuals like Alta Cima (Tamaulipas, MX) and Yautepec (Morelos, MX) to the site with the highest prevalence occurring at Chilcuatla (Hidalgo, MX) with a 34% prevalence and in which both habitat types were dominated by *Peromyscus maniculatus* (Tables 2 and 3). Janos, Chihuahua had the highest species richness (S=13) in sylvan habitats dominated by *Dipodomys merrriami* where 22% of these rodents (56/255) were had antibodies for hantaviruses.

Statistical Results

Student’s t-tests revealed no statistical differences in seroprevalence (TAS; $t_{17}=-1.15$; $p=0.27$), capture abundance (N; $t_{17}=0.46$; $p=0.33$), species richness (S; $t_{17}=-1.26$;

$p=0.11$), or evenness distributions of species (PIE; $t_{17}=-0.84$; $p=0.20$) within assemblages between habitat types across sites (Figure 2). Regression analysis and AIC_c model selection suggests species identity to be the strongest factor in accounting for hantavirus prevalence across sites ($R^2=0.91$; $f_{12,11}=8.9$; $p>0.001$) (Table 4).

Discussion

To my knowledge, this study represents the most extensive hantavirus serosurvey using standardized methods, to compare prevalence between sylvan and disturbed habitat types at large scale. I accomplished my objective to identify factors in rodent assemblage structure correlated with hantavirus prevalence between two sylvan and disturbed habitat types. Though my hypothesis was not supported, my data suggests that the characteristics of assemblage structure (e.g. high species diversity = lower disease prevalence) do not adhere to current conceptions of species richness negatively influencing prevalence via a dilution effect (Clay et al. 2009; Calisher et al. 2002; Reusken and Heyman 2013).

Most rodents testing positive for hantaviruses were cricetid rodents of the subfamily Neotominae. However, 6 sites were dominated by heteromyid species (Table 2) representing 3 subfamilies (Dipodomyinae, Heteromyinae, and Perognathinae) with 84, 6, and 18 testing positive for hantaviruses, respectively. Detections of hantavirus seropositive heteromyids are often dismissed as spillover occurrences, when researchers focus on specific host species. Here, and elsewhere, we find cases in which heteromyids appear to be associated to hantavirus prevalence (Table 2) (Mills et al. 1997; Torres-Pérez et al. 2010; Arellano et al. 2012; Milholland, in review). For example, *Liomys irroratus* appears to significantly influence the presence of hantaviruses in Las Palomas

WMA and Zacualpan (Tables 2, 3, and 4) though given the capture abundance, this species is not necessarily the dominant component of the assemblage. Moreover, *L. irroratus* (2/15) were found to be hantavirus positive in Hidalgo, México where this species was fourth in ordinate rank. Furthermore, within the same assemblage, 1 of 3 *Perognathus flavus* had hantavirus antibodies while ranking 7th in the assemblage. This supports the notion that hantaviruses can be maintained in phylogenetically diverse assemblages with high species richness.

This leads to questions regarding community assembly, hantavirus maintenance, and spatial scale. The ecological structure of species assemblages at certain localities may vary across seasons or conditions, especially if the species comprising the assemblages share similar habitats, utilize resources in similar ways, or are in competition for these resources (McKinney and Lockwood 1999). The persistence and transmission dynamics of hantaviruses across Texas and México may rely on interactions between infected and naïve individuals at various spatial scales and from interactions between adjacent assemblages, or meta-communities (Suzán et al. 2015) and be dependent upon host species distributions and their infection competency and potential (Johnson et al. 2015; Han et al. 2016; Milholland, in review).

Biotic homogenization, or a process by which adjacent communities become similar over time (Baeten et al. 2012) is often driven by habitats influenced (e.g. disturbed) by anthropogenic manipulations (Foley et al. 2005; McKinney 2005; Trentanovi et al. 2013). This disturbance alters available environmental resources favoring generalist host species with large home ranges, or highly adaptable exotic species (McKinney and Lockwood 1999; Trentanovi et al. 2013). It has been shown that

habitat preservation and conservation decrease the expansion of invasive host species and increase species diversity (Jones et al. 2008; Abadie et al. 2011).

As human densities increase, natural habitats are becoming increasingly sparse with little sylvan areas remaining (Foley et al. 2005). Though urban disturbance can create artificial microhabitats increasing localized species richness (McKinney 2006), immigrating species are often generalist species with high competency of spreading EIDs (Han et al. 2016). At what spatial scale do we find differences in species richness, phylogenetic composition, and dominance components of rodent host assemblages? Understanding the spatial scale at which differences in assemblage species composition become apparent is critical (Suzán et al. 2015) to effective surveillance and prevention of zoonotic disease.

APPENDIX SECTION

Table 1. List of sites following a north-south latitudinal gradient through Texas and México where small mammals were sampled for hantavirus prevalence. At each site, equal trapping efforts compared sylvan and disturbed (e.g. peridomestic) habitats; WMA = wildlife management area.

Country	State	Site	Geographic Location	Ecoregion
United States	Texas	Gus Engeling WMA	31°57'32"N 95°53'28"W	East Central Texas Plains – Post Oak Savannah
		Big Thicket National Preserve	30°32'22"N 94°20'25"W	Piney Woods
		Mason Mountain WMA	30°50'12"N 99°13'23"W	Edwards Plateau
		San Marcos	29°53'18"N 97°56'47"W	Edwards Plateau-Blackland Praries Interface
		Tejas Ranch	29°46'30"N 97°22'53"W	East Central Texas Plains – Floodplains and Low Terraces
		Chaparral WMA	28°19'53"N 99°25'13"W	Southern Texas Plains
		Las Palomas WMA	26°18'48"N 97°30'27"W	Western Gulf Coastal Plain
		Janos	30°54'7"N 108°25'17"W	Sierra Madre Occidental
México	Tamaulipas	Alta Cima	23°3'38"N 99°12'14"W	Great North American Plains
		Gómez Farías	23°3'56"N 99°10'8"W	North GulfCoast Plains
		San Jose	23°2'47"N 99°13'53"W	Sierra Madre Oriental
	Hidalgo	Chilcuatla	20°19'29.892"N 99°13'39"W	Central Volcanic Belt
	Veracruz	Coatepec	19°27'54"N 96°59'56"W	South Gulf Coastal Plain
	Moerlos	Yautepec	18°47'57"N 99°3'51"W	Sierra Madre del Sur
		Zacualpan	18°49'22"N 98°45'59"W	Sierra Madre del Sur
		Tepalcingo	18°35'28"N 98°58'57"W	Sierra Madre del Sur
		Miacatlán	18°46'10"N 99°23'16"W	Sierra Madre del Sur
		Puente de Ixtla	18°27'51"N 99°15'25"W	Sierra Madre del Sur
		Tepoztlán	18°47'59"N 99°4'6"W	Sierra Madre del Sur
		Tetela del Volcan	18°54'53"N 98°41'35"W	Sierra Madre del Sur

Table 2. List of small mammals captured and tested for hantavirus antibodies across sites in Texas and México between January 2012 - January 2016. Mammals are arranged alphabetically according to taxonomic identification (Wilson and Reeder 2005). (N) = number of individuals collected and tested for hantavirus antibodies; (TSI) = total number of seropositive individuals.

Order/Family	Subfamily	Species	N	TSI
Rodentia/Cricetidae	Neotominae	<i>Baiomys musculus</i>	24	0
Rodentia/Cricetidae	Neotominae	<i>Baiomys taylori</i>	60	6
Rodentia/Cricetidae	Neotominae	<i>Hodomys alleni</i>	1	0
Rodentia/Cricetidae	Neotominae	<i>Neotoma albigula</i>	8	4
Rodentia/Cricetidae	Neotominae	<i>Neotoma floridana</i>	26	19
Rodentia/Cricetidae	Neotominae	<i>Neotoma mexicana</i>	4	0
Rodentia/Cricetidae	Neotominae	<i>Neotoma micropus</i>	14	5
Rodentia/Cricetidae	Neotominae	<i>Ochrotomys nuttali</i>	41	2
Rodentia/Cricetidae	Neotominae	<i>Onychomys arenicola</i>	87	19
Rodentia/Cricetidae	Neotominae	<i>Onychomys leucogaster</i>	15	2
Rodentia/Cricetidae	Neotominae	<i>Peromyscus attwateri</i>	23	2
Rodentia/Cricetidae	Neotominae	<i>Peromyscus boylii</i>	7	1
Rodentia/Cricetidae	Neotominae	<i>Peromyscus difficilis</i>	41	11
Rodentia/Cricetidae	Neotominae	<i>Peromyscus furvus</i>	7	0
Rodentia/Cricetidae	Neotominae	<i>Peromyscus gossypinus</i>	95	9
Rodentia/Cricetidae	Neotominae	<i>Peromyscus leucopus</i>	380	16
Rodentia/Cricetidae	Neotominae	<i>Peromyscus levipes</i>	136	4
Rodentia/Cricetidae	Neotominae	<i>Peromyscus maniculatus</i>	117	41
Rodentia/Cricetidae	Neotominae	<i>Peromyscus melanophrys</i>	66	16
Rodentia/Cricetidae	Neotominae	<i>Peromyscus mexicanus</i>	15	0
Rodentia/Cricetidae	Neotominae	<i>Peromyscus ochraventer</i>	56	2
Rodentia/Cricetidae	Neotominae	<i>Peromyscus pectoralis</i>	35	2
Rodentia/Cricetidae	Neotominae	<i>Peromyscus species</i>	25	0
Rodentia/Cricetidae	Neotominae	<i>Reithrodontomys fulvescens</i>	50	1
Rodentia/Cricetidae	Sigmodontinae	<i>Oryzomys couesi</i>	3	0
Rodentia/Cricetidae	Sigmodontinae	<i>Oryzomys paulustris</i>	3	0
Rodentia/Cricetidae	Sigmodontinae	<i>Oryzomys species</i>	3	0
Rodentia/Cricetidae	Sigmodontinae	<i>Sigmodon hispidus</i>	200	23
Rodentia/Cricetidae	Sigmodontinae	<i>Sigmodon toltecus</i>	25	0
Rodentia/Heteromyidae	Perognathinae	<i>Chaetodipus hispidus</i>	55	1
Rodentia/Heteromyidae	Perognathinae	<i>Chaetodipus penicillatus</i>	83	11
Rodentia/Heteromyidae	Dipodomysinae	<i>Dipodomys merriami</i>	255	56
Rodentia/Heteromyidae	Dipodomysinae	<i>Dipodomys ordii</i>	9	0
Rodentia/Heteromyidae	Dipodomysinae	<i>Dipodomys spectabilis</i>	110	28
Rodentia/Heteromyidae	Heteromyinae	<i>Liomys irroratus</i>	109	6
Rodentia/Heteromyidae	Perognathinae	<i>Perognathus flavus</i>	45	6
Rodentia/Heteromyidae	Perognathinae	<i>Perognathus merriami</i>	8	0
Rodentia/Muridae	Murinae	<i>Mus musculus</i>	75	8
Rodentia/Muridae	Murinae	<i>Rattus rattus</i>	19	6
Rodentia/Sciuridae	Sciurinae	<i>Glaucomys volans</i>	6	0
Rodentia/Sciuridae	Xerinae	<i>Spermophilus variegatus</i>	3	1
Soricomorpha/Soricidae	Soricinae	<i>Cryptotis parva</i>	62	5

Table 3. Total number of small mammals collected and tested for hantavirus antibodies from sites across Texas and México. Mammals were concurrently trapped in disturbed and sylvan habitats at each site; Trapping occurred from January 2012-January 2016; Sites are listed in a north-south latitudinal gradient; (N) = relative abundance; (PIE) = Hurlbert's index of evenness; (SRPV(%)) = percent hantavirus seroprevalence; (TSI) = total number of seroprevalent individuals; (DR) = dominance index of most abundant host in the assemblage; (Rank) = ordinate abundance rank of dominant host in the assemblage; (#Positive) = number of seropositive dominant host species; ((%Infection_{exp}))= expected hantavirus prevalence based on total regional prevalence; (Infection_{obs})= whether estimated prediction of prevalence was higher/lower than, or equivalent to, observed sampling; (blue arrows)= observed prevalence was lower than expected; (red arrows)= observed prevalence was higher than expected; (green ≈)= observed prevalence was approximately as expected.

Country	State	Site	N	S	PIE	TSI	SRPV(%)	DR	Rank	#Positive	(%)Infection _{exp}	Infection _{obs}	Dominant Host Species
United States	Texas	Gus Engling WMA-Disturbed	71	10	0.81	3	4.23	0.38	1	1	6.78	→	<i>Sigmodon hispidus</i>
		Gus Engling WMA-Sylvan	80	8	0.84	10	12.50	0.26	1	3	7.64	→	<i>Peromyscus gossypinus</i>
		Big Thicket National Preserve-Disturbed	122	8	0.78	15	12.30	0.03	7	10	11.65	≈	<i>Neotoma floridana</i>
		Big Thicket National Preserve-Sylvan	81	7	0.78	13	16.05	0.35	1	5	7.74	→	<i>Peromyscus gossypinus</i>
		Mason Mountain WMA-Disturbed	60	5	0.54	1	1.67	0.03	4	1	5.73	→	<i>Neotoma micropus</i>
		Mason Mountain WMA-Sylvan	64	7	0.72	4	6.25	0.27	2	2	6.11	≈	<i>Peromyscus atwateri</i>
		San Marcos-Disturbed	135	9	0.79	22	16.30	0.36	1	13	12.89	→	<i>Sigmodon hispidus</i>
		San Marcos-Sylvan	72	6	0.39	0	0.00	N/A	N/A	N/A	6.88	→	N/A
		Tejas Ranch-Disturbed	41	6	0.42	0	0.00	N/A	N/A	N/A	3.92	→	N/A
		Tejas Ranch-Sylvan	36	4	0.30	2	5.56	0.83	1	2	3.44	→	<i>Peromyscus leucopus</i>
		Chaparral WMA-Disturbed	102	7	0.63	9	8.82	0.19	2	5	9.74	→	<i>Sigmodon hispidus</i>
		Chaparral WMA-Sylvan	30	5	0.76	2	6.67	0.40	1	1	2.87	→	<i>Peromyscus leucopus</i>
		Las Palomas WMA-Disturbed	136	8	0.68	3	2.21	0.20	2	2	12.99	→	<i>Liomys irroratus</i>
		Las Palomas WMA-Sylvan	41	4	0.62	1	2.44	0.07	3	1	3.92	→	<i>Neotoma micropus</i>
		Janos-Disturbed	26	6	0.74	11	42.31	0.46	1	6	2.48	→	<i>Onychomys arenicola</i>
		Janos-Sylvan	682	13	0.80	140	20.53	0.37	1	56	65.14	→	<i>Dipodomys merriami</i>
		Alta Cima-Disturbed	64	5	0.72	0	0.00	N/A	N/A	N/A	6.11	→	N/A
México	Tamaulipas	Alta Cima-Sylvan	49	3	0.55	0	0.00	N/A	N/A	N/A	4.68	→	N/A
		Gómez Farías-Disturbed	10	4	0.78	1	10.00	0.40	1	1	0.96	→	<i>Peromyscus pectoralis</i>
		Gómez Farías-Sylvan	13	1	N/A	1	7.69	1.00	1	1	1.24	→	<i>Peromyscus pectoralis</i>
		San Jose-Disturbed	73	3	0.27	1	1.37	0.85	1	1	6.97	→	<i>Peromyscus levipes</i>
		San Jose-Sylvan	28	3	0.64	4	14.29	0.43	1	2	2.67	→	<i>Peromyscus levipes</i>
		Hidalgo-Disturbed	93	9	0.84	37	39.78	0.24	1	14	8.88	→	<i>Peromyscus maniculatus</i>
		Hidalgo-Sylvan	99	5	0.72	28	28.28	0.39	1	14	9.46	→	<i>Peromyscus maniculatus</i>
		Veracruz-Disturbed	18	6	0.76	1	5.56	0.44	1	1	1.72	→	<i>Mus musculus</i>
		Veracruz-Sylvan	26	5	0.73	0	0.00	N/A	N/A	N/A	2.48	→	N/A
		Yauatepec-Disturbed	5	2	0.60	0	0.00	N/A	N/A	N/A	0.48	≈	N/A
México	Morelos	Yauatepec-Sylvan	16	5	0.81	0	0.00	N/A	N/A	N/A	1.53	→	N/A
		Zacualpan-Disturbed	13	3	0.72	1	7.69	0.31	2	1	1.24	→	<i>Liomys irroratus</i>
		Zacualpan-Sylvan	6	2	0.60	0	0.00	N/A	N/A	N/A	0.57	≈	N/A
		Tepalcingo-Disturbed	34	5	0.80	1	2.94	0.18	4	1	3.25	≈	<i>Peromyscus levipes</i>
		Tepalcingo-Sylvan	11	5	0.78	0	0.00	N/A	N/A	N/A	1.05	→	N/A
		Miacatlán-Disturbed	1	1	N/A	0	0.00	N/A	N/A	N/A	0.10	≈	N/A
		Miacatlán-Sylvan	1	1	N/A	1	100.00	N/A	N/A	1	0.10	→	<i>Liomys irroratus</i>
		Puente de Ixtla-Disturbed	23	3	0.63	0	0.00	N/A	N/A	N/A	2.20	→	N/A
		Puente de Ixtla-Sylvan	20	4	0.72	0	0.00	N/A	N/A	N/A	1.91	→	N/A
		Tepoztlán-Disturbed	15	6	0.86	1	6.67	0.27	1	1	1.43	→	<i>Mus musculus</i>
		Tepoztlán-Sylvan	4	2	0.67	0	0.00	N/A	N/A	N/A	0.38	≈	N/A
		Tetela Del Volcan-Disturbed	4	3	N/A	0	0.00	N/A	N/A	N/A	0.38	≈	N/A
		Tetela Del Volcan-Sylvan	1	1	N/A	0	0.00	N/A	N/A	N/A	0.10	≈	N/A

Table 4. Regression analysis with model selection. Top models are listed predicting hantavirus prevalence (srpv) at sites across Texas and México; both habitat types (sylvan and disturbed) combined, where at least one rodent tested positive for hantavirus antibodies; R^2_{adj} reported for bottom 3 models; Coefficients and descriptive statistics of top model shown below.

Model	df	loglik	AIC _c	Δ	wt	R ²	p
srpv ~ species + ϵ	14	-62.89	200.4	0	0.999	0.91	<0.001 ***
srpv ~ rank + species + ϵ	15	-62.08	214.2	13.72	0.001	0.8	0.001 **
srpv ~ rank + n + habitat + species + ϵ	16	-61.75	233.2	32.77	0	0.78	<.01 **
srpv ~ rank + n + species + ϵ	18	-61.49	295.8	98.34	0	0.72	0.02 *

srpv ~ species + ϵ ; ($f_{12,11}=8.9$)

Coefficients	Estimate	SE	t	p
(intercept)	20.53	4.91	4.18	0.00 **
<i>Liomys irroratus</i>	-15.58	6.01	-2.59	0.03 *
<i>Mus musculus</i>	-14.42	6.01	-2.40	0.04 *
<i>Neotoma floridana</i>	-8.23	6.95	-1.19	0.26
<i>Neotoma micropus</i>	-18.48	6.01	-3.07	0.01 **
<i>Onychomys arenicola</i>	21.78	6.95	3.14	0.01 **
<i>Peromyscus attwateri</i>	-14.33	6.95	-2.06	0.06
<i>Peromyscus gossypinus</i>	-6.25	6.10	-1.04	0.32
<i>Peromyscus leucopus</i>	-14.42	6.10	-2.40	0.04 *
<i>Peromyscus levipes</i>	-14.33	5.67	-2.53	0.03 *
<i>Peromyscus maniculatus</i>	13.51	6.10	2.25	0.05 *
<i>Peromyscus pectoralis</i>	-11.68	6.10	-1.94	0.08
<i>Sigmodon hispidus</i>	-10.75	5.67	-1.90	0.08

Figure 1. Sites samples across Texas and México where small mammals were trapped and tested for hantavirus antibodies. At each site, sylvan and disturbed habitats were sampled concurrently.

Figure 2. Boxplots showing results of small mammal assemblage characteristics across all sites comparing disturbed and sylvan habitats. Results suggest there are no differences in site abundance, species richness, or evenness of species occurrence between habitat types, nor was habitat type an artifact of hantavirus prevalence.

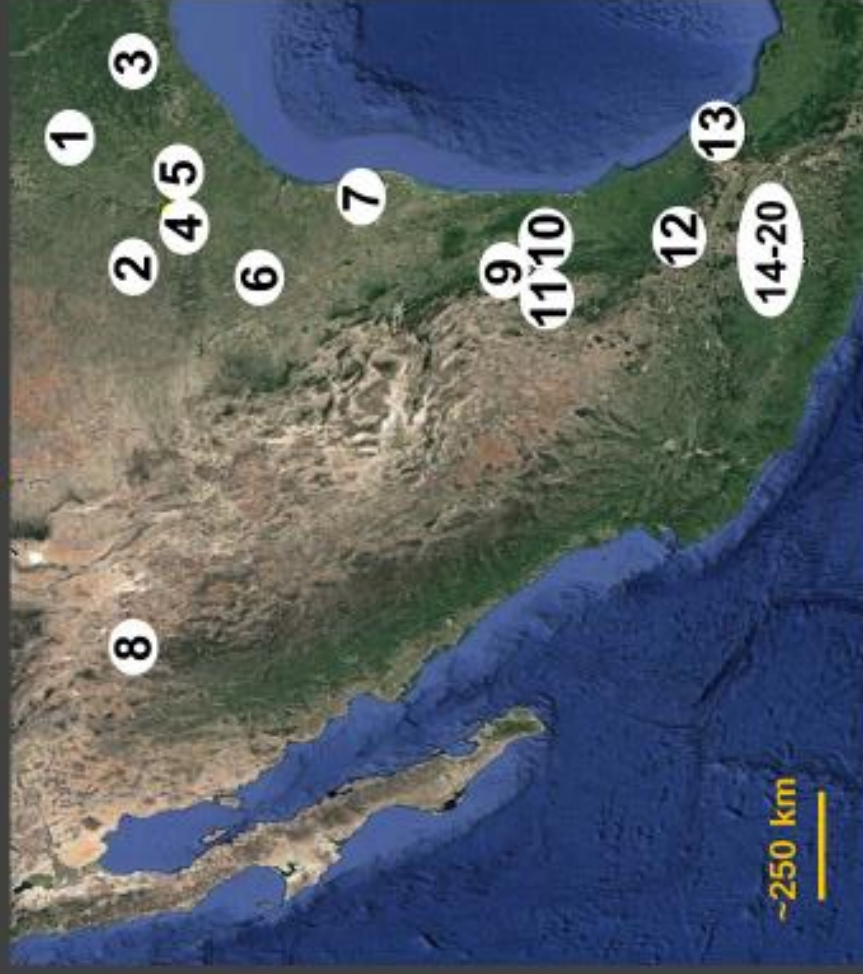
Texas

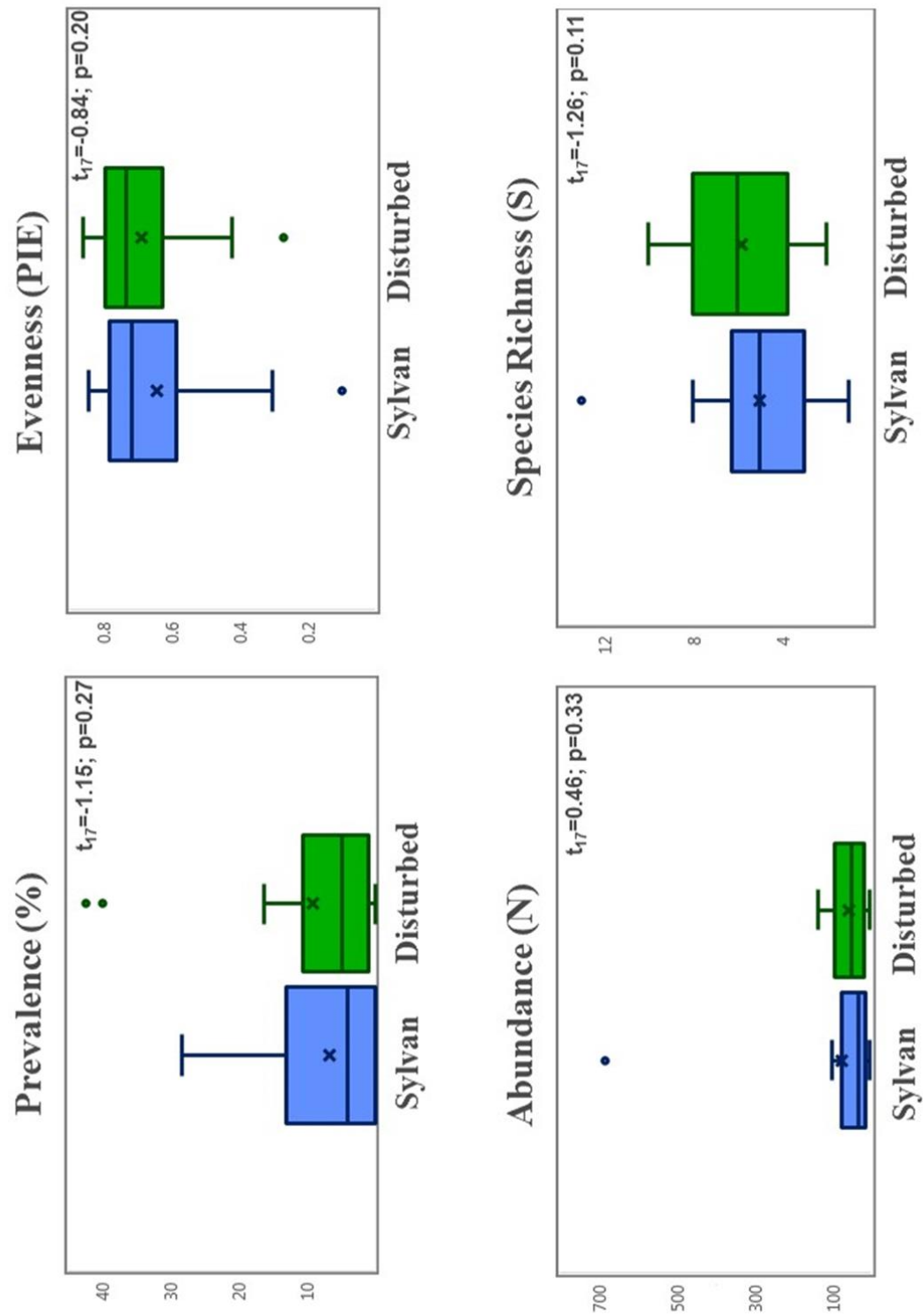
- 1) Gus Engeling WMA
- 2) Big Thicket NP
- 3) Mason Mountain WMA
- 4) San Marcos
- 5) Tejas Ranch
- 6) Chaparral WMA
- 7) Las Palomas WMA

México

- 8) Janos, Chihuahua
- 9) Alta Cima, Tamaulipas
- 10) Gomez Farias, Tamaulipas
- 11) San Jose, Tamaulipas
- 12) Chilcuatla, Hidalgo
- 13) Coatepec, Veracruz
- 14) Yautepec, Morelos
- 15) Zacualpan, Morelos
- 16) Tepalcingo, Morelos
- 17) Miacatlan, Morelos
- 18) Puente de Ixtla, Morelos
- 19) Tepoztlan, Morelos
- 20) Tetela del Volcan, Morelos

Study Sites





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V. SEROCONVERSIONS OF HANTAVIRUS INFECTION IN HISPID COTTON RATS (*SIGMODON HISPIDUS*) AT VARYING DENSITIES

Background

Global warming and climate change are affecting climatic patterns in ways associated with an increase in emerging infectious diseases (EIDs) incidence worldwide (Klempa 2009; Semenza and Menne 2009; Wilson 2009). Climatic events can influence disease dynamics (Altizer et al. 2013) but mechanisms responsible for the changes in pathogen-host interactions are not well known (Harvell et al. 2002). Zoonotic pathogen outbreaks have been described as ecological responses to cyclical weather patterns (Jonsson et al. 2010; Voutilainen et al. 2012). These cycles can drive strong fluctuations in plant and animal populations (Stenseth et al. 2002) and are increasing in frequency and intensity (Vecchi and Knuston 2007). Host-pathogen interactions are likely influenced by climate patterns such as: El Niño Southern Oscillation (ENSO); North Atlantic Oscillation (NAO); and Pacific Decadal Oscillation (PDO) (Dearing and Disney 2010). Yet, factors promoting outbreaks of zoonotic pathogens through the interactions of biotic and abiotic features are still poorly understood (Hjelle and Torres-Pérez 2010).

Abiotic environmental conditions (e.g. precipitation) can favor certain rodent species to proliferate (Brown and Heske 1990; Brown and Ernest 2002; Mills et al. 2010). For example, ENSO events have been associated with an increase of hantavirus seroprevalence in rodent populations and in the number of HPS cases in the southwestern United States (Engelthaler et al. 1999; Yates et al. 2002). This relationship suggests that an increase in host populations is a response to an increase in resource availability (Ostfeld et al. 2006) where hantavirus transmission and infection prevalence is

augmented by a rise in host densities (Calisher et al. 2002; Luis et al. 2010). However, individual influences of environmental factors (e.g. seasonality, precipitation, mast yields, etc.) have been studied (Brady and Slade 2004; Clement et al. 2009) also confound our understanding of this dynamic disease system (Bagamian et al. 2012a,b; Zeimes et al. 2012) while mechanisms of transmission remain poorly understood (Schlegel et al. 2014; Murray et al. 2015; Han et al. 2016).

In the US, population oscillations in several species of small mammals, including hantavirus host species, have been observed, yet the causality of such abundance fluctuations remains unclear (Myers et al. 2009; Schlegel et al. 2014). Hantavirus prevalence in rodents has been tied to the number of reported cases of human hantaviral-disease (Khan et al. 1996; Madhav et al. 2007; MacNeil et al. 2011) where trends in human-hantavirus disease reports often follow above average precipitations events, though at inconsistent lag intervals (Engelthaler et al. 1999; Yates et al. 2002; Mills et al. 2010). Also, increased incidence of human hantaviral diseases near urban population centers has been associated to increases in rodent abundance due to climatic events affecting regional ecology (Clement et al. 2009; Himsworth et al. 2013). Though insightful, these relationships are largely studied at local scales (Olsson et al. 2009) and investigations driven in response to specific outbreaks (Schlegel et al. 2014) neglecting and overall context of hantavirus persistence at regional scales (Suzán et al. 2015).

Hantaviruses are known to be transmitted through direct contact between infected and susceptible (hereafter, naïve) individuals perpetuating the virus in the local assemblage (Adler et al. 2007). A minimum number, or threshold level, of infected individuals in a population is needed to maintain virus persistence (Madhav et al. 2007).

Hantaviruses are horizontally transmitted pathogens and have been found to be density-independent in relatively natural, undisturbed habitats (Douglass et al. 2001; Pearce-Duvet et al. 2006). However, fragmented habitats influenced by human activity can artificially increase local rodent densities and prevalence of the Sin Nombre Virus (SNV), a zoonotic hantavirus (Langlois et al. 2001), suggesting higher densities of conspecifics may increase encounter potential and transmission events, hence seroprevalence (Hjelle and Torres-Pérez 2010; Bagamian et al. 2012a; Schlegel et al. 2014). This suggests the mechanisms of hantavirus ecology function on a delayed density-dependent prevalence (Madhav et al. 2007; Begon et al. 2009) where peaks in population seroprevalence are positively correlated with abundance dynamics from a previous season (Carver et al. 2011) or a near-distant point in time (Yahnke et al. 2001). Another possible mechanism of hantavirus transmission dynamics may be frequency-dependent (Bagamian et al. 2012a), where infection in the population subsists independent of density, but rather by seasonal and/or behavioral characteristics exhibited by a species (Bernshtein et al. 1999; Calisher et al. 1999; Pearce-Duvet 2006; Dearing and Disney 2010). As hantavirus transmission requires direct (Glass et al. 1988; Escutenaire et al. 2002; Bi et al. 2008; Schlegel et al. 2014) or indirect (Kariwa et al. 1998; Bernshtein et al. 1999; Kallio et al. 2006) contact with infected individuals or virus particles in the environment (Reusken and Heyman 2013) certainty of transmission mechanisms remains equivocal.

Hispid cotton rats (HCR), *Sigmodon hispidus*, occur throughout the south-central United States and are ubiquitous throughout Texas (Bradley et al. 2008). In Texas, male HCR exhibit site fidelity within their home ranges (Spencer et al. 1990), and the area of a

home range is negatively correlated with conspecific density (Cameron and Spencer 1985). Additionally, as densities increase, males display greater tolerance of intruding females suggesting a dominance hierarchy in this species and a polygynous mating system (Cameron and Spencer 1985). Furthermore, daily and multi-day space-use patterns observed in male *HCR* suggests systematic (e.g. clockwise) movements (Cameron 1995) during foraging where highly aggressive males (Cameron and Kruchek 2005) maintain an approximately 0.08 ha area (Spencer et al. 1990). *HCR* are natural reservoirs for two host-specific hantaviruses, the Black Creek Canal (Rollin et al. 1995; Khan et al. 1996) and Muleshoe (Rawlings et al. 1996) hantaviruses in the United States. To date, these are the only known viral types directly linked to *HCR*, though seropositive individuals have been identified through the presences of cross-reactive antibodies, and tested for specific strains of Playa de Oro (Chu et al. 2008), Bayou (Torrez-Martinez et al. 1998; McIntyre et al. 2005), and SNV (Mills et al. 1998).

The measure of contact rates between infected and naïve individuals has been deemed the “Holy Grail” (Clay et al. 2009) of hantavirus research, connecting the underlying mechanisms of transmission and infection, where direct contact through aggressive, agonistic behavior is suspected as a crucial driver of hantavirus transmission during wounding events (Escuintaire et al. 2002; Hinson et al. 2004), however, this mechanism has not been studied thoroughly in *HCR*. Indirect means of transmission have been shown where the Black Creek Canal virus has been isolated from *HCR* urine and feces at least 70 days post-infection in experimental settings (Glass et al. 1998; Hutchinson et al. 1998) causing infection in susceptible cohorts (Hutchinson et al. 2000). This suggests the potential for indirect transmission in species marking territorial

boundaries with urine and feces and among individuals engaging in olfactory exploration attempting to secure a breeding home range (Holsomback et al. 2009). Many pioneering laboratory (Lee et al. 1981; Yanagihara et al. 1985; Botten et al. 2000a, 2002; Padula et al. 2004) and field experiments (Botten et al. 2000b; Suzán et al. 2009; Bagamian et al. 2012a,b) have examined basic aspects of assemblage composition and hantavirus transmission yet remain equivocal in clarifying mechanisms (Shountz and Prescott 2014). To further investigate density-driven mechanisms of hantavirus persistence in local assemblages, I experimentally modified rodent densities, where wild caught HCR were selectively placed in outdoor enclosures and their activity patterns observed over time.

Here, I address an inferred relationship between contact rates (e.g. direct interaction between individuals) and density in adult, male HCR at varying densities. I hypothesized that the number of seroconversions would increase with increasing density. My objectives were to quantify density-dependent seroconversions of naïve individuals between adult, male HCR of known infection status, and to correlate seroconversions with observed agonistic behavior patterns (i.e. contact rates).

Methods

Disclaimer

Due to time constraints, lengthy IACUC approval discussions, and the extremely high volume of digital video data (~0.6 TB), contact rates are not reported. However, I, and two undergraduate research assistants are currently analyzing these data. This project has also contributed to several funded Undergraduate Research opportunities.

Rodent Trapping to estimate average densities

I surveyed rodent relative-abundance for density estimates using capture-mark-release efforts with multiple trapping grids of 0.5 ha (Calisher et al. 2007) at selected sites within and around the San Marcos, TX area with Sherman live-traps (H. B. Sherman Traps, Tallahassee, FL, USA) baited with rolled oats, peanut butter, and vanilla extract (permit #: TPWD SPR-1112-1052; IACUC201531106). Traps were placed at ~10-meter intervals, set one hour prior to sunset, and checked at twilight the following morning to avoid heat-induced stress to captured rodents. Sites were chosen based on previous trapping efforts (see Chapter 3) and from additional sites with habitat types preferred by HCR (Slade and Swihart 1983). These efforts were used to provide a range (i.e. minimum to maximum) reference of naturally occurring HCR densities in the San Marcos, TX area. The average maximum density observed served as the baseline for the approximate maximum experimental stocking densities. For use in experimental trials, HCR were trapped and collected following a similar protocol, however, I used curvilinear transects to optimize trap success and to increase spatial coverage.

Only adult, male HCR were used in this study. Their size allowed for individual identification to be noticeable in camera data, and their territorial behavior increased the likelihood of agonistic encounters (Slade and Swihart 1983; Cameron and Spencer 1985; Spencer et al. 1990; Cameron 1995). Additionally, I used only male HCR to decrease variability and nullify increases in experimental densities through reproduction recruitment. Age class of captured male HCR was determined by scrotal enlargement and body mass, i.e., (those weighing ≥ 70 grams were considered juveniles) (Layne 1974; Slade and Swihart 1983). Initial blood samples were collected via Nobuto strips

(Advantec, Inc.®) from tail-snips to test for natural hantavirus infection using enzyme-linked immunosorbent assay (ELISA, see details below) (Mills et al. 1995). Blood samples were also taken from trapped female HCR before being given a unique ear tag (National Band & Tag Co. Newport, Kentucky), and released on site. Juvenile males were also blood sampled by tail-snip, and released on site. Suitable HCRs were transported to an off-site holding facility and each placed in a separate cage. Due to the limited space capacity of the holding unit, HCR trapping occurred as needed throughout the experiment.

Quarantine holding

Rodents exhibit an initial post-infection, acute viremia lasting approximately 7-10 days followed by an ~14-35-day period where the rodent immune system is developing neutralizing immunoglobulin G (IgG), which can then be detected in the blood (Hutchinson et al. 2000). Currently, field assays for detecting rodent antibody responses to hantavirus (i.e. seroprevalence) utilize ELISA techniques (Schountz and Prescott 2014). While time is necessary for infected rodents to develop detectable IgG proteins, HCR with an initial negative ELISA result were housed in cages for at least 25 days before experimental inclusion. This allowed time for seroconversion/naïve status to be positively confirmed by periodic serologic (i.e. ELISA) testing.

All rodents were cared for following guidelines set forth by the *Guide for the Use of Laboratory Animals* and standard safety protocols for hantavirus research (Mills et al. 1995; Kelt et al. 2010; Sikes et al. 2011; Bagamian et al. 2012a,b). Captured adult, male HCRs were held in wire, mesh bottom polycarbonate rodent cages (model 1264C;

Tecniplast, West Chester, PA; The Guide), using one cage per individual. Because hantaviruses are shed in urine and feces, cages were placed on supports surrounded by a moat/pan sanitation system where the wire flooring allowed waste to fall through the flooring into trays of 10% bleach (sodium hypochlorite) solution where these viruses are destroyed and prevented from becoming airborne. Cages were thoroughly washed and disinfected with 10% bleach solution and allowed to dry in direct sunlight between each use.

Cages were housed on shelves in a climate-controlled, portable building (Keter Stronghold 3.05 x 2.44 m Resin Storage Shed, Model # 157479) constructed inside a large barn at the Texas State University Freeman Center (hereafter, Freeman) in San Marcos, TX. The holding unit allowed quarantined HCR to be protected from the environment and avoided extreme fluctuations of temperature, noise, and disturbance. Ambient temperature (20-26 °C) was maintained using an air conditioning unit (12,000 BTU 115-Volt Window Air Conditioner, Model # ESA412M) and an independent space heater when necessary. Additionally, natural photoperiod was simulated within the holding facility using a lamp (60 watt LED bulb) connected to a timer with settings adjusted according to natural diurnal/nocturnal cycles. The resin construction of the holding facility allowed for easy cleaning and disinfection (10% bleach solution).

Caged HCR were given fresh water and food *ad libitum* and the health of each rodent was monitored daily, where food amounts were regulated to avoid obesity. Water trays containing bleach solution and excrement were cleaned with bleach, sundried, and changed approximately every third day. After a 30-day quarantine, blood samples from each individual via tail-snip was retested using ELISA to determine infection status. The

pelage of each HCR to be used in experimental trials was first shaved using hair trimmers (Oster®, model #78960-100) to remove the hispid guard-hair layer revealing the downy coat, then bleached (Salon Care™ Quick White Powder and Professional 40 vol. Crème Developer) with a unique identifier pattern (e.g. stripes, spots, shapes, etc.), and ear tagged (Milholland et al. 2010).

Outdoor Experimental Enclosures

I constructed four outdoor experimental enclosures at Freeman (Figure 1). Each enclosure (20x20 m²) was fashioned using metal flashing (~1 m wide), partially buried (~0.3 m) to provide a barrier against digging rodents, and secured with rebar. The design allowed for each enclosure to share two sides forming a large 40 x 40 m complex. Vegetation surveys in each enclosure were conducted to gather an inventory baseline of native flora present. The enclosures were mechanically mowed pre-trial to maintain a vegetative height of approximately 0.05 m, where clippings (e.g. grasses, seeds, and forbs) were left as food sources. Canopies (Academy Sports Easy Shade Shelter; item#ZS1010AL; ~3x3 m²) were placed at the complex center, and at the center of each enclosure (Figure 1). Two artificial nest boxes (Figure 2) were buried in each enclosure with surface-to-nest PVC tubing serving as access burrows and affixed with a filled water bottle. Additionally, mesh cages (1x1x0.3 m³) were constructed and filled with native grasses from the area around the enclosure site as an additional food source, and means of cover.

Restrictive structures were constructed around and above the enclosure complex to reduce the potential for avian, mammalian, and reptilian predation events during

experimental trials. Enclosures were surrounded by an approximately 1.5 m high wire horse fence (McCoy's Stay Tuff Hi-Tens, #06049028) allowing for ~1m of space to access the enclosure perimeter. This outer fence was also electrified (Zareba®, #ESP10M-Z) and gated. Wildlife polypropylene hardware cloth (Sta-Green, #208513; cut to ~0.5 m in height) was affixed at ground level inside the outer fencing functioning as a solid barrier. The entire complex was then covered in mesh, heavy knotted netting (3T Products, #NKH2100-150) utilizing the internal canopies and fencing as a ceiling for accessing enclosures. Finally, the enclosure complex perimeter was dusted with snake repellent (Dr. T's Snake-A-Way Snake Repellent™, #DT364B). Maintenance and necessary up-keep of the enclosure complex, and predator-prevention integrity continued throughout the study. To monitor rodent activity, I used twelve game cameras (Bushnell® Trophy Cam HD, model #119676C, Overland Park, KS, USA) fastened to partially buried PVC tube sections selectively interspersed throughout each enclosure as to maximize the area covered in each camera field-of-view (Figure 3). Cameras were arranged to allow for maximum experimental arena coverage in each camera field-of-view (FOV) and flash FOV for nighttime still and video captures (Figure 4).

Recording transmission events

Each trial began with the release of uniquely marked HCR, with known serostatus (i.e. infected or naïve) at experimentally controlled densities. Six trials for each density category were performed, and determined as: low=1 infected, 1 naïve; medium=1 infected, 5 naïve; and high=1 infected, 10 naïve. Individuals were only used once in each enclosure, as to avoid statistical bias and repeated measures. HCR were selected at

random for each trial, accounting for space and time constraints related holding facility availability, quarantine time periods, and infection status. Seroconversion status of each individual was determined by ELISA after ~30-day, post-trial quarantine. Trials began around midday on day one, and rodents were left undisturbed in an assigned enclosure for five nights. Camera traps were active throughout the trial period, and recorded one motion triggered snapshot followed by 60 seconds of high definition video. Intervals between motion-triggered recording events were preset to 1 second, ensuring maximum activity capture. The infra-red camera function allowed for nocturnal activity to be recorded. Rodents were then gathered by hand on day six, weighed, and returned to clean cages for an additional (post-trial) ~30-day quarantine. Camera data was downloaded for future analysis.

Statistical Analysis

A single-factor ANOVA was performed in R studio (0.99.902) to reveal any existing differences in the number of seroconversions between the three densities. Additionally, Tukey's HSD multiple comparison analysis was performed to determine where any differences in density categories occurred. Video data was organized according to density category. Contact rates are not reported here due to time constraints. However, these data are currently being analyzed and are contributing to Undergraduate Research opportunities and will be included in the final manuscript for publication.

Results

Rodent Trapping

Natural HCR density estimates were consistent with published literature and found to range from ~50-100 rodents per ha (Clark et al. 2003; Sulock et al. 2004). Wild HCR were captured at the U.S. Fish and Wildlife Service Aquatic Resources Center (USFWL; 29°50'22.34"N, 97°58'32.25"W) and Blanco Vista (BV; 29°57'18.49"N, 97°53'51.95"W) near San Marcos, TX. between 25 August 2016 – 10 February 2017. Overall trap nights (757; BV=105, USFWL=652) yielded 129 HCR males (BV=7, USFWL=122) and 129 females (BV=10, USFWL=119) with an overall mean trap success of 30% (BV=16 %, USFWL=37%). Two individual, non-target rodent species were captured and collected (*Baiomys taylori*, n=1; *Mus musculus*, n=1). From these captures, 86 male adult HCR were held in the holding facility and either used, or considered, for experimental trials. A total of 3 individuals naturally seroconverted during the pre-trial quarantine after initially testing negative for hantavirus antibodies. HCRs were actively housed and attended to from 25 August 2016 – 05 May 2017 (253 days).

A total of 74 adult male HCRs (mean weight 116 g; SE=2.6) were used in the experimental trials. Twenty trials occurred between 06 October 2016 – 10 April 2017, however two trials, both high density, were repeated due to separate predation events (one feral cat and one Great-Horned Owl). Thus, 18 complete trials were used for final analysis representing 6 trials for each density category. Overall seroconversions were 23%, with the respective percentages for each category as follows: low density=17%

(n=1), medium density=27% (n=8), and high density=28% (n=17). ANOVA results ($f_{2,15}=4.35$; $p=0.03$) and Tukey's HSD are shown in Table 1 and Figure 5.

Discussion

The expectation that the number of seroconversions would increase with increasing density was shown to be true with a statistically significant difference between low and high densities. Preliminary video observations results indicate a higher frequency of multiple rodents interacting in the FOV as density increases. Interestingly, to date no images of direct contact or agonistic battling (e.g. fighting) behavior have been observed. Rodent chasing has been observed, yet with no direct physical contact.

Additionally, when HCR were gathered post-trial, shared nesting was observed despite the density category. This suggests transmission events may occur passively or through fomite transmission from environmental materials. Though, HCR have not been shown to actively use a latrine system in their burrows or nests, while caged individuals in these trials showed preference in location for which to release excrement. Though anecdotal, this information suggests excrement concentrated areas in natural nests both shared, or otherwise. With respect to bank voles (*Myodes glareolus*) and the Puumala virus (PUUV) in Sweden, contaminated bedding and environmental structures were found to experimentally infect rodents and remain infectious over the course of several days (Kallio et al. 2006).

It is also interesting to note that throughout the trial periods (October-April, or Fall-Spring) the number of seroconversions increased in each density category. Because HCR were chosen at random, and because serostatus was confirmed pre-trial, this

suggests that seasonality may play a role in disease transmission (Douglass et al. 2007; Bagamian et al. 2012a,b).

While a few studies suggest negative correlations between host density and hantavirus prevalence (Boone et al. 1998; Abbott et al. 1999; Douglass et al. 2001), many have shown evidence supporting density-driven hantavirus persistence (see review in Rubio et al. 2014) which are affirmed by my quantified conclusions. Human cases and risks of hantavirus disease have been shown to be directly correlated with increasing host densities (Yates et al. 2002; Keesing et al. 2010). This raises serious concerns for human health as stochastic climatic factors (e.g. increased temperatures and precipitation) increase in frequency and intensity (Epstein 1995) giving rise to increased environmental resources (i.e. food) facilitating explosions in hantavirus rodent host densities (Clark et al. 2003; Myers et al. 2009; Schlegel et al. 2014). This, combined with decreasing habitat availability due to anthropogenic disturbance, are directly influencing the increased risk of zoonotic potentials at the human-wildlife interface (see Chapter 2) (Keesing et al. 2010; Dirzo et al. 2014; Suzán et al. 2015; Tian et al. 2017).

My study has shown the infection potential exhibited by a single infected host at varying assemblage densities of conspecifics. It is very clear that at least 50% of naïve individuals can become infected in a period of 5 days when rodent densities are relatively high. This alarming rate (~1 infection/day) could be further intensified by highly-gregarious infected individuals, or super-spreaders (Schountz et al. 2012), present in an assemblage, a hypothesis that can be further explored with the data gathered in the present trials. As climate continues to change, often producing favorable conditions for extreme fluctuations in hantavirus-host populations, continued surveillance should

remain a high priority, as a means of zoonoses prevention and as a safeguard for public health.

APPENDIX SECTION

Table 1. Results of single-factor ANOVA comparing differences in seroconversions factored by density of naïve *Sigmodon hispidus* in outdoor enclosures; dark bar indicates mean differences in serconversions~density.

ANOVA	df	ss	ms	<i>f</i>	<i>p</i>
density	2	21.44	10.72	4.35	0.032*
Residual	15	30	2.46		

Tukey's HSD 95% family-wise confidence level (Grand Mean = 1.44)

Seroconversion~Density Means		
low	medium	high
0.17	1.33	2.83

* indicates significant difference

Figure 1. Aerial view of the outdoor enclosure complex, Texas State University – Freeman Center, San Marcos, TX.

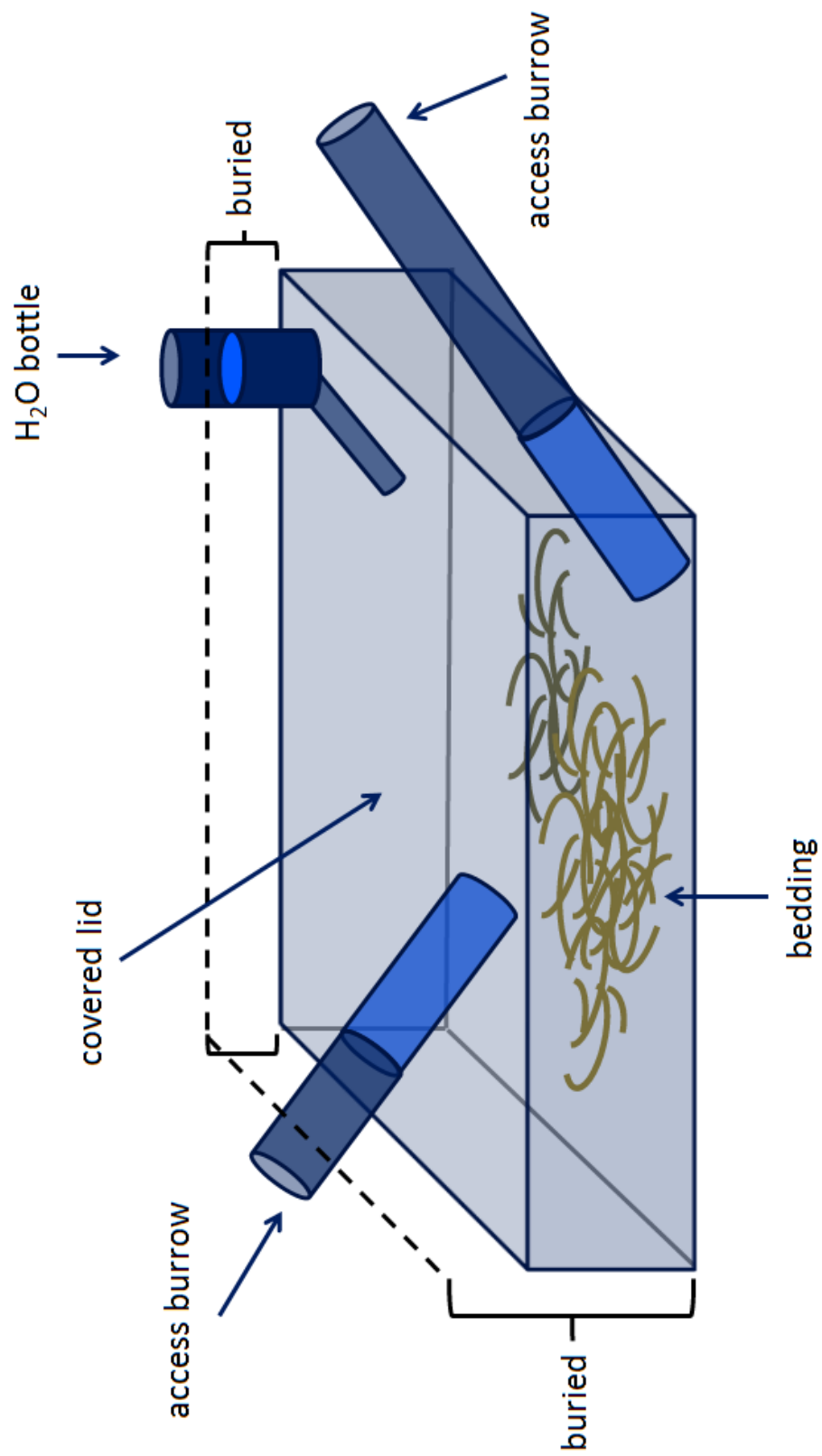
Figure 2. Nestbox schematic. *Sigmodon* were provided access to two nestboxes buried in each outdoor enclosure. Water was provided *ad libitum*. Clean bedding of natural grass material was provided and surface-to-nest PVC tubing served as burrows.

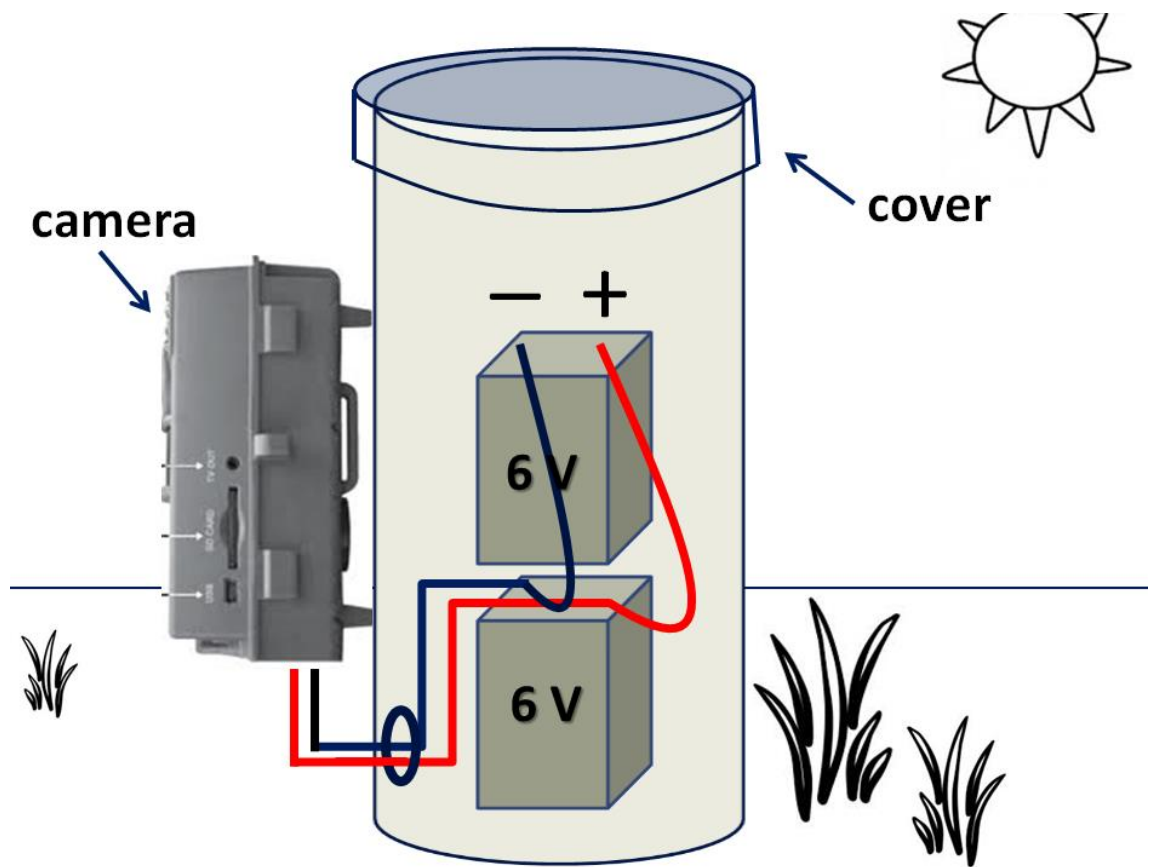
Figure 3. A schematic of the camera station apparatus. Each camera was attached to a partially buried PVC tube housing an external power supply composed of two 6 volt batteries (in series) and protected by a weatherproof covering.

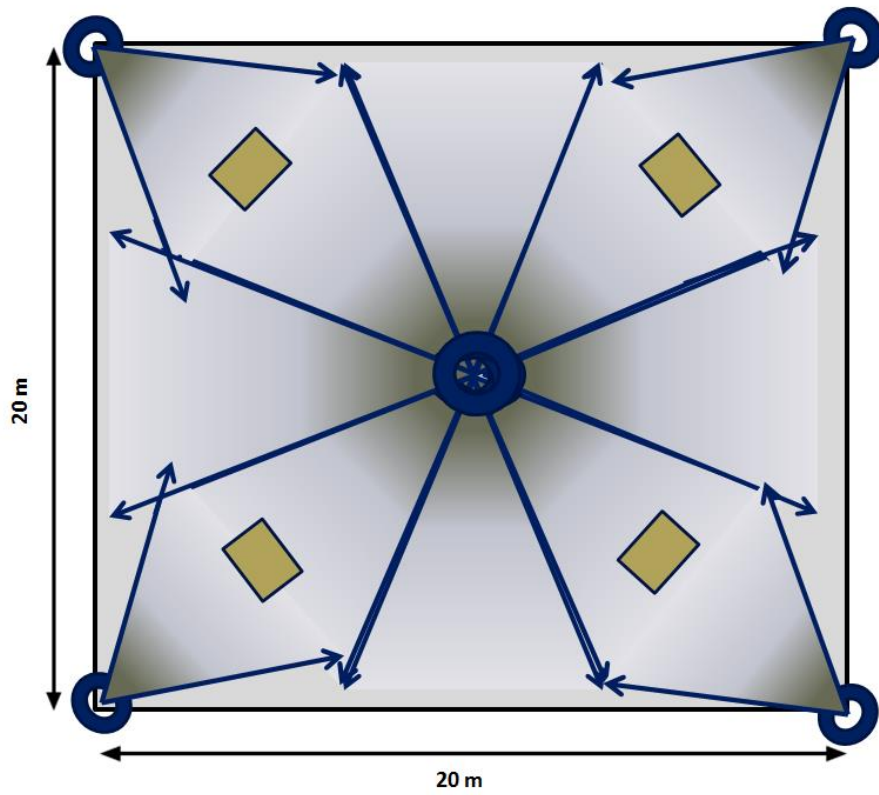
Figure 4. An approximation of camera placement and optimal camera field of view (FOV). Twelve cameras were arranged in each 20 m² enclosure where the angle of the FOV is approximately 45° with a maximum flash distance ~20 m. Manufacturer recommendations place optimal flash and picture quality between 3-20 m.

Figure 5. Histogram of overall seroconversions percentages between three density categories: low=1 infected, 1 naïve; medium=1 infected, 5 naïve; and high=1 infected, 10 naïve. The graph shows 23% infection in low density=17% (n=1), medium density=27% (n=8), and high density=28% (n=17). ANOVA results ($f_{2,15}=4.35$; $p=0.03$) show differences in density categories occurring between low and high densities (shown by Tukey's HSD relationships in orange).

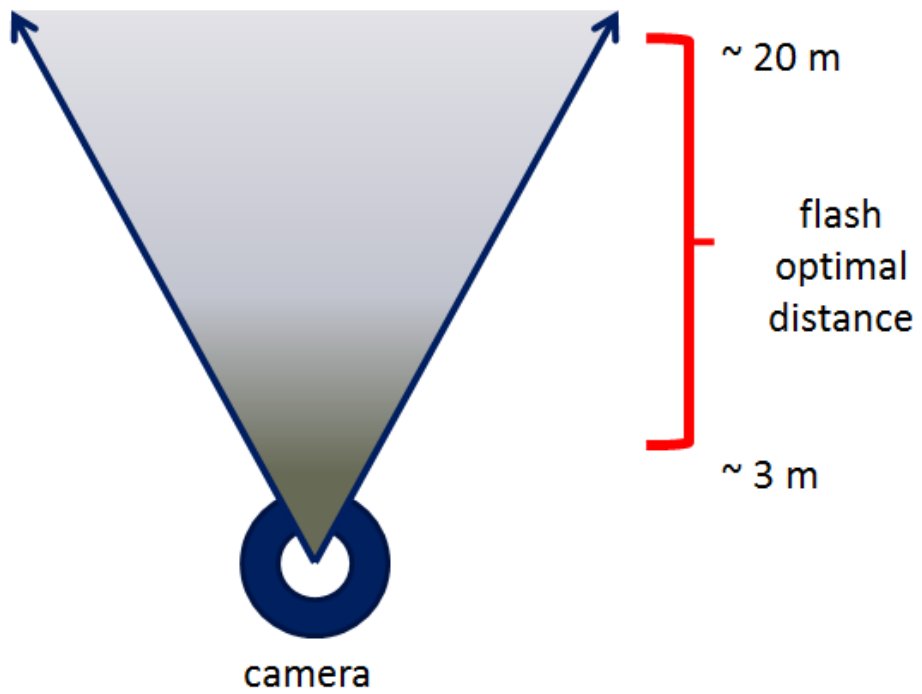


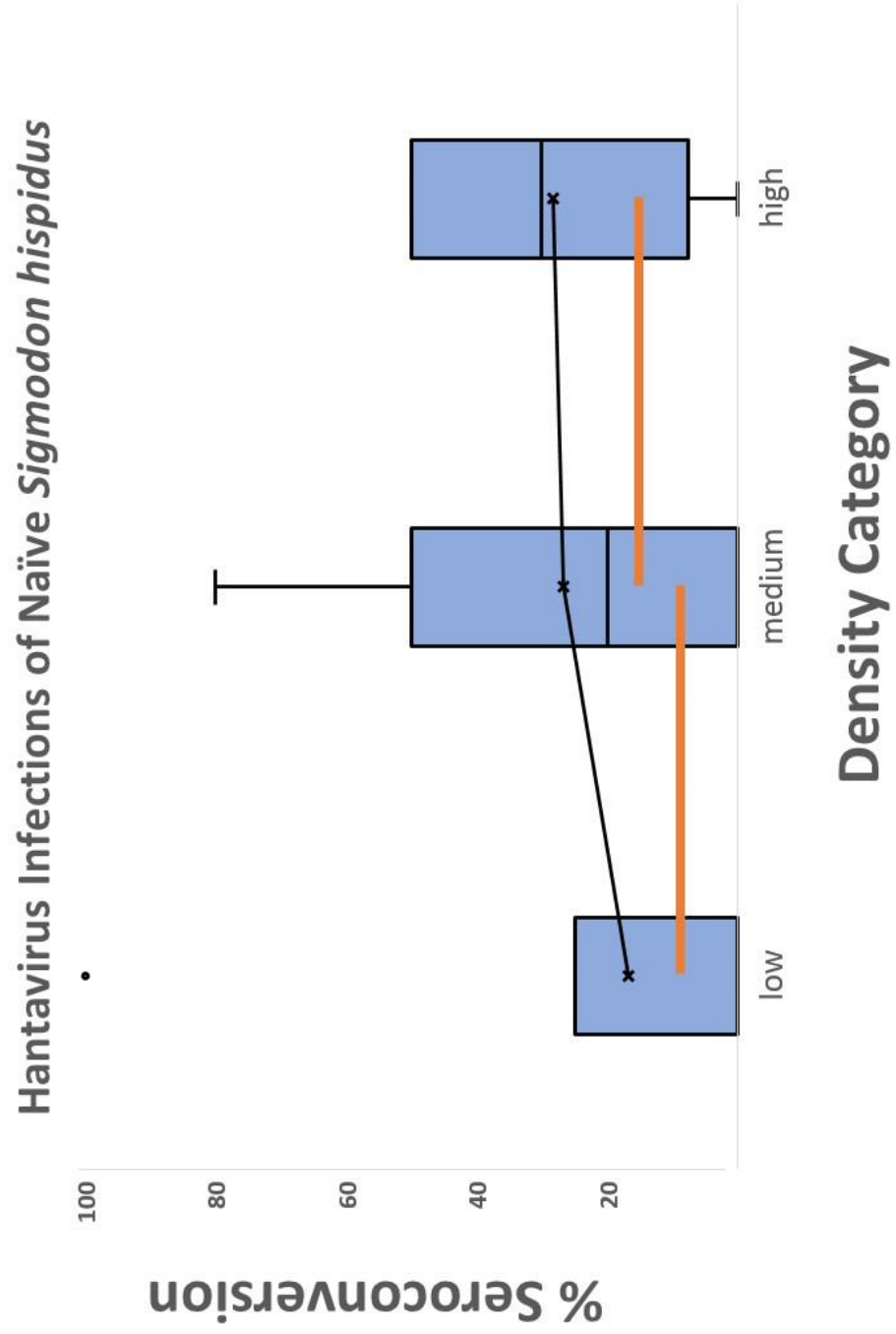






FOV





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