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Ecology of hantavirus in a changing world

M. Denise Dearing and Laurie Dizney

Department of Biology, University of Utah, Salt Lake City, Utah, USA

Address for correspondence: M. Denise Dearing, Department of Biology, University of Utah, Salt Lake City, Utah, USA. denise.dearing@utah.edu

Hantavirus **is a genus of virus represented by 45 different species and is hosted by small mammals, predominantly rats and mice. Roughly, half of all hantaviruses cause diseases in humans that vary in morbidity from mild to severe. The natural and anthropogenic changes occurring in the environment appear to be impacting the ecology of hantaviruses and their natural hosts as well as the incidence of hantaviral diseases in humans. Although such studies are limited at this time, there is evidence that natural climate cycles such as El Niño as well as anthropogenic climate change enhance hantavirus prevalence when host population dynamics are driven by food availability. Climate appears to have less of an effect on hantavirus when host populations are controlled by predators. Human alteration to the landscape also appears to enhance hantavirus prevalence when the disturbance regime enriches the environment for the host, for example, agriculture. More long-term studies on multiple species of hantavirus are needed to accurately predict the outcome of changing environmental conditions on prevalence in hosts as well as disease incidence in humans.**

Keywords: climate change; disturbance; hantavirus; landscape alteration; pathogen transmission; fragmentation; biodiversity; invasive species

Introduction

The rapid and extensive anthropogenic alterations to ecosystems are having profound effects on the distribution and ecology of organisms, including parasitic ones. The goal of this paper is to review how such changes affect or may affect the dynamics of *Hantavirus*, a genus of virus represented by at least 45 different species distributed worldwide.[1,2] After a brief introduction to the natural history of this system, we review how aspects of climate change and landscape alterations may influence hantavirus. We close with a section on recommendations for scientist and policy makers. Information on epidemiology, human pathology, treatments, and vaccines have recently been reviewed by others and will not be covered extensively here.[1,2]

Natural history of hantaviruses

Hantaviruses are negative-sense, single-stranded RNA viruses with a small (<11 kb), tripartite genome.[3] They are pathogens of small mammals, particularly rodents of the family Muridae. Different species (or genotypes) of hantavirus appear to be somewhat host specific.[4] Reassortment of genetic material between species of hantavirus appears to be rare. For example, in some locations, up to three species of hantavirus occur in their respective mammalian host, with no exchange of genetic material among hantavirus species.[5,6] Hantaviruses occur worldwide and are disproportionately represented in temperate regions,[2] although this distribution pattern may be more related to human disease surveillance efforts than actual distribution of the virus in its natural host. The diagnostic tools developed over the past 15 years have resulted in the explosive discovery of hantaviruses (at least 31 species since 1997) and in unexpected hosts such as shrews.[7] Thus, it is likely systematic surveys of hantavirus occurrence in small mammal communities will uncover many more species of hantavirus as well as host species other than Murid rodents.

Hantavirus infections in humans are incidental and are not part of the virus's natural ecology. Approximately one half of the currently described

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hantaviruses cause disease in humans.[2] Annually, hantavirus infections in humans result in more than 200,000 hospitalizations and hundreds of deaths.[1,2] The total number of hantavirus infections in humans is much greater than the number of hospitalizations and deaths because many infections are not severe enough to be reported. North Americans are likely most familiar with the species of hantavirus known as "Sin Nombre virus" (SNV) hosted by the deer mouse (*Peromyscus maniculatus*). Infection with Sin Nombre virus can lead to Hantavirus CardioPulmonary Syndrome (HCPS or HPS) in humans.[8] HCPS can result from infection with many of the hantavirus species in North and South America and has a mortality rate of up to 40%. Fortunately, the number of human cases in the Americas is low, with roughly 200 cases annually.[2] In contrast, numerous species of hantavirus in Europe and Asia lead to a disease known as Hemorrhagic Fever with Renal Syndrome (HFRS), which accounts for the vast majority of human infections.[1,2,4] HFRS has a lower mortality rate than HCPS, ranging from a mild disease with less than a 0.1% mortality rate for Puumala virus to a severe one with a 12% mortality rate for Haantan or Dobrava virus.[2] Hotspots for human cases of HFRS include China, Russia, Korea, and Finland.[1,2] The underlying mechanism responsible for the differences in pathology between the Euro-Asian and the American hantavirus species is unknown. Humans acquire hantavirus infections through inhalation of contaminated excreta from the small mammal host.[4] As is typically the case for most human pathogens, the diseases have been known for millennia, but the etiological agents have only recently been identified.[1,2,4,9]

All hantaviruses have a primary mammalian host with which they have had a long coevolutionary history.[10,11] Initially, the hosts of hantaviruses were thought to be restricted to rodents, primarily rats, mice, and voles in the family Muridae, subfamily Cricetinae. More recently, several species of insectivores in the shrew (Soricidae) and mole (Talpidae) families have been documented as hosts.[7,12–16] A recent list of the majority of currently known hantaviruses and their hosts can be found in Heyman *et al.*[1]

Transmission of hantaviruses is interesting from a number of aspects. *Hantavirus* is a unique genus within its family, the Bunyaviridae, as it is the only one that does have a documented arthropod vector(s). There are significant species-specific differences in transmission among hantaviruses within the hosts. Some such as SNV, appear to be transmitted only directly through the transfer of infected body fluids, particularly during aggressive behaviors of the host, but also potentially during allogrooming.[17–19] In contrast, many hantaviruses (e.g., Puumala, Seoul, Black Creek Canal, Haantan) are also indirectly transmitted among hosts through the inhalation of contaminated excreta.[20–24]

The majority of hantaviruses are named for the location in which they were discovered and lack the term "hantavirus" in their name, for example, Dobrava virus. An exception to this rule is Sin Nombre virus, which was discovered in the Four Corners region of the United States. The naming of this virus was particularly arduous.[9] The numerous suggestions for names related to different localities in the Four Corners region resulted in sequential objections from several different groups. Thus, Sin Nombre, "without name" in Spanish, was the final moniker agreed upon for this virus.

The ecology of hantaviruses will likely be altered by the various changes occurring on the planet. Small mammals, the primary hosts of hantaviruses, are vulnerable to the impacts of habitat disturbance and climate change. Persistence of the virus outside of the host is temperature and humidity dependent; thus, as temperature regimes change so will the environmental abundance of the virus.[25] Such changes in virus persistence and host distribution could clearly alter the natural host–pathogen dynamics. These changes could lead to modifications in the epidemiology of human hantavirus infections and such alterations are already being critically evaluated by various public health organizations.[26–28] In this synthesis, we review our understanding of how the changing environment could impact hantavirus prevalence in hosts and subsequently in humans. For many of the topics covered in this review, there were often a limited number of studies. The paucity of investigations is likely the result of the newness of hantavirus to the scientific community and the recent development of assays to test for hantaviruses in hosts. We anticipate many more studies in this area in the next decade that will improve our ability to predict how hantavirus will respond to differing conditions.

Effects of climate

Naturally occurring climate cycles

The El Niño Southern Oscillation (ENSO), the North Atlantic Oscillation (NAO), and the Pacific Decadal Oscillation (PDO) are three key climate cycles likely to have impacts on hantavirus–host interactions. These cycles influence plant productivity, small mammal cycles, and vertebrate predators.[29] The ENSO is the foremost annual climate cycle on Earth. The cycle begins in the tropical Pacific Ocean and results in either warmer (El Niño) or colder (La Niña) than normal sea surface temperatures on cycles of 2–7 years. El Niño events have profound effects on global rainfall patterns resulting in increased rainfall on the western coasts of South and North America, and decreased rainfall in Indonesia and the Pacific.[30] Strong El Niño events have worldwide consequences. For example, some El Niño events result in extremely cold winters in Europe. The low temperatures generated by these strong El Niño's are rare and recorded only a few times a century. Such severe lows can have long lasting effects on ecosystems.[31]

The NAO, although not as globally influential as the ENSO, has considerable effects, particularly on Europe and the coastal Atlantic region of the United States. NAO events originate in the Atlantic Ocean and result in changes in the strength of the westerly winds across the North Atlantic. Positive-phase NAO events result in increased precipitation and temperatures in northern Europe and the southeastern United States as well as increased aridity in the Mediterranean, whereas negative phase events have the opposite set of effects. NAOs alternate between positive and negative phases approximately every 2–5 years, with positive phases tending to last longer than negative phases.

The PDO has its primary impact on western North America. During positive phases, the PDO causes increased precipitation in the southwest and reduced precipitation in the northwest; the effects are reversed in the negative phase.[32] This effect is similar to but weaker than those produced by the ENSO.[32] Its cycles are longer than either the NAO or the ENSO. Over the past 1000 years, the PDO periodicity has been a 50- to 70-year cycle.[32]

The impact of climate cycles on hantaviruses are currently limited to two studies, one on the ENSO and another on the NAO. Later we summarize the findings of each study. It is not surprising that studies have not yet been published on hantavirus with respect to the PDO given the length of time between intervals.

El Niño events have been implicated as an important driver for SNV in both deer mice and humans in the southwestern United States.[33,34] El Niño events in the Southwest can result in elevated precipitation and warmer winter temperatures. These changes in abiotic conditions are thought to result in elevated food resources for rodents (seeds and arthropods), which in turn increase population densities of rodents 1–2 years after an El Niño event. Cases of SNV in humans increase 2–3 years after an ENSO event. The density of rodents infected with SNV (number of infected mice per hectare), caused by either increases in total deer mouse density, increases in prevalence (% of mice infected), or both, is proposed as the fundamental mechanism driving the increase in human cases of HCPS after an El Niño[34] and has been coined the "Trophic Cascade Hypothesis."[33,34] The effect of an ENSO on SNV in deer mice and humans suggests that global climate change could also significantly alter the dynamics of this host–pathogen interaction.

In contrast, a study in Sweden found no relationship between the NAO and the number of cases of HFRS in humans over two time series totaling 37 years.[35] HFRS in Scandanavia is caused by Puumala virus, which is hosted by the bank vole (*Myodes glareolus)*. The only factor predictive of HFRS in Sweden was the abundance of bank voles. Although the analysis included an impressive long-term data set on host abundance (25 years), the incidence of Puumala virus infections in the host was not measured. The authors acknowledge that the NAO may be too coarse a measurement and that temperature and precipitation individually may be better predictors of vole abundance and HFRS incidence.

The conflicting results of the two studies underscore the need for more studies in this area. One question that emerges from these studies is, how do top-down versus bottom-up forces on the host population mediate the role of natural climate cycles on hantavirus infection? The population dynamics of bank voles in the NAO study cited earlier are largely governed by top-down forces, particularly specialist predators, whereas the population dynamics of deer mice in the southwestern United States are driven by the bottom-up force of food

availability.[34–36] Puumala infections in bank voles are an excellent system for future comparative studies as the cyclic populations in northern Europe are governed by top-down forces, whereas acyclic populations in central and southern Europe, are driven more by food availability.[36–38]

Long-term studies on prevalence in animal hosts are critical to understanding the dynamics of zoonotic diseases in humans with respect to climate cycles. Several of the hantaviruses in Europe, Asia, and South America currently seem to lack such surveillance efforts. This observation is based on the absence of scientific papers in this area and may not reflect actual monitoring efforts. The new National Ecological Observatory Network underway in the United States includes monitoring Sin Nombre virus in deer mice at numerous stations across the country for a 30-year period. Such long-term data sets will greatly improve our understanding of hantavirus ecology in natural hosts as well as our ability to predict human infections.

Climate change

The idea that anthropogenic climate change will alter the dynamics of infectious agents in a manner that increases disease incidence in humans has become pervasive over the past decade. The propagation of this hypothesis is illustrated in the exponential number of scientific papers published on this topic since 1980. Recently, journals from such diverse fields as ecology, public health, and medicine have dedicated articles, special sections, and even entire issues, to this topic.[28,39–41] Moreover, the proposed impact of climate change on infectious diseases has been incorporated into governmental reports on climate change.[42,43] Despite the intense research being conducted in this area, our understanding of the way in which climate change will impact hantavirus infections in hosts and humans is still in its infancy.

Two aspects of the natural history of hantaviruses and their hosts suggest that climate change could alter their dynamics to favor increased incidence in hosts and humans. First, the population dynamics and distribution of their hosts, that is, small mammals, can be affected by climate, although there is considerable debate regarding the strength of such bottom-up factors initiated through climate versus that of top-down factors such as predation.[34,44–47] Food availability and harshness of winter, which are key factors governing population size and distributions of rodents, can be altered by climate.[48] An example of climate change influencing rodent distribution and abundance is seen in the northerly expansion of four rodent species in the Great Lakes region.[49] Second, climate change may have the greatest impact on pathogens with seasonal fluctuations because the correlation of season and infection patterns suggests that short-term (monthly) changes in weather influence pathogen dynamics. That many hantaviruses seem to have a seasonal cycle, with prevalence often being greater in the spring than in the fall, makes it a good candidate for susceptibility to climate change.[50–52]

Climate change has been implicated as the driving force behind the increasing number of human hantavirus infections in certain areas of Europe. Puumala virus is common in bank voles across Europe.[24] Transmission of Puumala virus between voles can occur either directly or indirectly.[20,24] Humans become infected with Puumala from contact with contaminated soil and can contract a mild form of HFRS known as nephropathia epidemica (NE).[24,53] This zoonosis is considered to be emerging in parts of Europe (*e.g.*, Belgium, France, Germany), where it was uncommon just a decade ago.[1,37,54–57] Independent studies on NE incidence in Belgium implicate warmer temperatures as the central factor responsible for increases in NE. These research groups found a strong relationship between warmer summer temperatures two years prior to an NE outbreak and warmer autumn temperatures 1 year prior to an NE outbreak.[37,54,55] They propose that the warmer summer temperatures promote mast seed production of broadleaf trees the following summer, thereby driving up food availability, which in turn leads to an increase in vole populations. The warmer autumn temperatures are predicted to increase over winter survival of voles. A similar scenario has been constructed to explain the increase of NE in Germany.[57] Long-term data on masting events of broadleaf trees are consistent with this hypothesis.[37,54,55] However, no long-term data sets (>2 years) are available on vole population or Puumala prevalence in voles across the same time span (1985–2007) to validate the host component of the hypothesis. Surprisingly, data from short-term studies (2004–2005) on Puumala prevalence in voles are at odds with the expectations from the longer-term research on the zoonosis in humans.[37,54,58,59]

In the short-term, Puumala virus prevalence and number of infected voles was negatively correlated with winter temperatures, such that during warmer winters, prevalence and number of infected voles declined. The proposed mechanism for this pattern was a decrease in survival of the virus in the environment under warmer conditions leading to reduced indirect transmission between voles.[55]

Although the studies are limited, the results suggest that climate change may have different consequences for host prevalence versus human disease. In this system, human disease does not appear to be a simple function of host prevalence. Changes in human behavior driven by warmer winter temperatures may have led to an increase in human exposure that more than compensated for a decline in infected host density and persistence of virus in nature. Understanding the way in which climate change will alter human behavior in conjunction with pathogen dynamics will be key in predicting human disease outcomes.

Finally, climate change is likely to dampen existing hot spots of hantavirus activity as well as generate new hot spots as the climatic conditions become less or more suitable for the host. For example, the American Southwest is known for high levels of Sin Nombre virus activity in both hosts and humans.[33,34] However, if this region becomes hotter and drier as predicted by climate change models,[42,43] the peromyscine hosts of Sin Nombre virus could be replaced by species more tolerant of these conditions such as Heteromyid rodents, which are not known to host hantaviruses. This shift in the rodent community could lead to lower host prevalence and reduced risk for humans.

Effects of landscape alteration

Background

Humans have greatly altered the landscape in the past century, converting land to farms, pastures, roads, and urban centers, as well as reconverting land in certain areas (*e.g.,* northeastern United States) to forest. Thirteen million hectares of forest are destroyed annually.[60] It is estimated that 14,000–40,000 species are lost annually in tropical forests alone.[61] These alterations not only transform the physical habitat but also alter the frequency of human contact with hantaviral hosts, which can either decrease exposure (urban centers) or promote exposure (parks, farms, and homes in close proximity to them). Large-scale human encroachments and the resulting intensity of human use have likely changed biotic interactions, including dynamics of infectious diseases transmission.

A priori, human disturbance of habitat is predicted to elevate the prevalence of hantavirus within an ecosystem. Disturbed habitats tend to favor more generalist species that can tolerate and adapt to ecological changes.[62] Many hantaviruses are hosted by generalist species leading to the hypothesis that disturbed habitats will harbor more potential hantavirus reservoirs or change the behaviors of hosts, which could increase prevalence, in turn increasing the threat of transmission to humans (Fig. 1).[63] Currently, the majority of research supports the hypothesis that increased disturbance increases prevalence in the hosts. However, landscape alteration may lead to decreased hantavirus prevalence if it makes the habitat unsuitable for host species, as some studies have found (Fig. 1). Later we discuss these conflicting results to attempt to reconcile the disparate outcomes.

Host dynamics

The dynamics and the ecology of the host play a key role in the outcome that disturbance will have on hantavirus prevalence. Human disturbance often increases fragmentation of the landscape, which has been shown to increase both densities and movement distances of host species.[64–68] These two consequences of fragmentation potentially increase contact rates, and therefore pathogen transmission, among hosts.

Several studies on North and South American hantaviruses report higher hantavirus prevalence in hosts living in fragmented landscapes (Table 1). In some of these studies, the fragmentation was caused by agriculture and forestry. However, in one study, the disturbance was created from all-terrain vehicles (ATVs), which denuded most of the vegetation less than 1 m high and compacted the soil, rendering much of the area unsuitable for the host.[69] In each of these studies, the authors hypothesized that increased densities along with behavioral changes, such as increased movement, are likely the underlying mechanisms.[69–72]

In contrast, other studies have found lower prevalence in hosts living in disturbed habitats when compared to less disturbed areas (Table 1). One of these

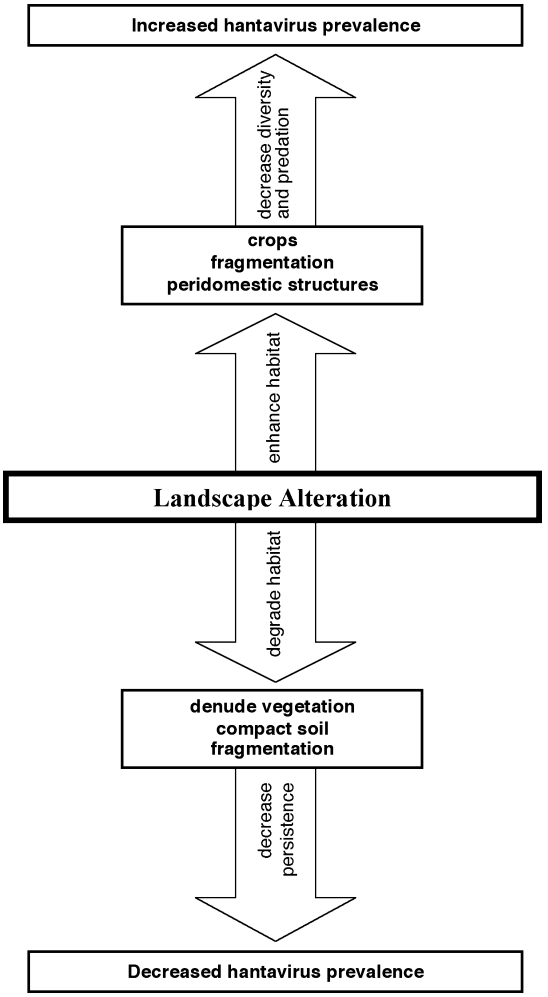

Figure 1. Alternative outcomes of differing disturbance regimes on hantavirus prevalence.

studies was a follow-up study to Mackelprang *et al.*'s initial work.[69] In some of the same ATV disturbed sites, plus less disturbed control sites which were not included in the preliminary study, Lehmer *et al.*[73] conducted a longer-term study with greater replication. Interestingly, the authors found a negative relationship between SNV prevalence and disturbance but no direct relationship between SNV prevalence and host density. They suggested that the disturbance created by ATV reduced long-term survival of deer mice, including SNV-positive deer mice, such that infection could not be maintained over time. Their results were consistent with a previous study, also on SNV in deer mice, which proposed the same mechanism for low prevalence.[74] Although the disturbances were different in these two studies, they both resulted in depauperate habitats with highly compacted soils.

Taken together, the contradictory results of these studies point to several issues that could be of importance to understanding the effects of disturbance on pathogen transmission. First, the resulting type of habitat caused by disturbance is likely paramount to hantavirus ecology. In some cases, disturbance results in preferred habitats for hosts, such as cropland where food and cover can be more plentiful than in undisturbed areas. In contrast, landscape alteration may sometimes make habitats less desirable for host use, as in the case of ATVs, where soil is compacted and denuded of vegetation. When disturbance results in preferred habitat for the host, prevalence appears to increase, whereas when disturbance results in less preferred habitat the opposite effect is seen (Table 1, Fig. 1). Second, shorter-term versus longer-term studies may reveal different results both of which may be relevant.[69,73–75] For example, short-term transmission may depend on density-dependent factors but over the long-term other factors, such as persistence, may be more important in sustaining hantavirus in a population. Third, it is essential to understand the ecology of the host species to understand the effects of human disturbance. For example, unlike most of the studies of hantavirus in the Americas, prevalence of Puumala virus in bank voles was highest in areas of Belgium where the proportion of remote forests was high.[55] This finding is likely a result of bank voles preferring forests and only dispersing into disturbed and less preferred habitat at extremely high densities, in addition to the density-dependent transmission of Puumala virus within bank vole populations.[53,58,76,77] Even within a particular host–pathogen system, host ecology may be different over its geographic range. For instance, the ecological differences between the cyclic bank vole populations in Scandinavia versus the acyclic bank vole populations in Belgium and France are hypothesized to account for the 10-fold higher incidence of human cases of NE in the north, as well as their periodicity, which follow the voles' cycles.[78]

Hosts as commensals

Human altered landscapes are often associated with homes, barns, and storage facilities

Table 1. The outcome of disturbance on different species of hantavirus

Hantavirus	Host	Type of disturbance	Result of disturbance	Citation
Haantan virus	Apodemus agrarius	Land conversion to agriculture	Increased human risk	112,113
Laguna Negra virus	Calomys laucha	Land conversion to agriculture	Increased host prevalence	91
Puumala virus	Myodes glareolus	Decreased species diversity	Increased host prevalence	59
Puumala virus	Myodes glareolus	Urbanization	Decreased host prevalence	58
Puumala virus	Myodes glareolus	Human habitations near forests	Increased human risk	56
Choclo virus	Oligoryzomys fulvescens	Fragmentation	Increased host prevalence	72
Choclo virus	Oligoryzomys fulvescens	Deforestation for cattle ranching	Increased host prevalence	111
Choclo virus	Oligoryzomys fulvescens	Decreased species diversity	Increased host prevalence	98
Choclo virus	Oligoryzomys fulvescens	Human habitations	Increased host prevalence	79
Four strains of hantaviruses	Paraguayan host species	Land conversion to agriculture	Increased host prevalence	70
Sin Nombre virus	Peromyscus maniculatus	Fragmentation	Increased host prevalence	69,71
Sin Nombre virus	Peromyscus maniculatus	Soil compaction, decreased vegetation	Decreased host prevalence	73,74
Sin Nombre virus	Peromyscus maniculatus	Decreased species diversity	Increased host prevalence	63,96,99,100
Sin Nombre virus	Peromyscus maniculatus	Human habitation	Increased host prevalence	51,71
Calabazo virus	Zygodontomys brevicauda	Fragmentation	Increased host prevalence	72
Calabazo virus	Zygodontomys brevicauda	Decreased species diversity	Increased host prevalence	98

(peridomestic buildings) that are frequented by humans. Domestic activities, such as sweeping and vacuuming, aerosolize rodent excreta in an enclosed space, vastly increasing the chance of transmission to humans if the excreta are infected. In addition, prevalence increases in hosts in peridomestic settings compared to natural habitats, inside buildings as opposed to outside buildings, and in residences and immediate surroundings compared to areas farther away from residences.[51,71,79] Several factors related to the indoor environment could enhance transmission not only among hosts but also to humans. Indoor settings typically have low UV, controlled temperature, and elevated humidity. All of these abiotic factors may enhance viral persistence in the environment, which would increase the probability of indirect transmission. The movements of hosts may be restricted within buildings leading to concentrated areas of urine and feces, which could also increase the probability of indirect transmission. The resources for rodents are often more consolidated and greater indoors, which could lead

to an increase in host density with an increase in contact rates. Currently, it is unknown which of these mechanisms increase the prevalence of hantavirus in mice living indoors. However, because many human hantavirus infections are acquired in peridomestic settings, an understanding of the ecology of hosts in this setting will be important in reducing risk to humans.[63,77]

Invasion capacity of hosts

Although many small mammal hosts of hantavirus are generalists, they are typically not known for their invasion capabilities; most host species come into contact with humans in wild or rural settings and seem unable to establish in large urban centers. However, two host species, the Norway rat (*Rattus norvegicus*) and the black rat (*R. rattus*) are quintessential invasive species with a cosmopolitan distribution and close associations with humans, particularly in large metropolitan areas. Black and Norway rats host Seoul virus, and Norway rats can also host Hantaan virus.[1] Both of these viruses cause HFRS in humans.[4] Individual Norway rats appear to have rather limited movement patterns within cities; nonetheless, their occurrence in port cities around the world creates conduits for transcontinental movement of hantaviruses via infected rats on ships.[80–83] Genomic diversity exists within strains and viral reassortment has been documented within but not between species of hantavirus.[84,85] Thus, Norway rats traveling transcontinentally on ships could acquire infections of diverse hantavirus genotypes of Seoul virus, resulting in the evolution of new genotypes through viral reassortment. Novel genotypes could result in enhanced mortality or morbidity in humans, as is often the case with the influenza virus.

A second area of concern with respect to these *Rattus* species is the potential spread of indigenous hantaviruses to new areas. Hantaviruses appear to be somewhat specific to a host species.[4] However, infections have been documented in mammalian species not typically classified as the host.[6,86] For example, Sin Nombre virus is hosted by deer mice,[87] but sympatric Desert woodrats (*Neotoma lepida*) also can have Sin Nombre virus infections.[86] Although the transmission capacities of woodrats infected with Sin Nombre virus have not been tested in the laboratory, the pattern of infection is similar to the deer mouse, that is, chronic and in the same tissues suggesting that woodrats may be able to transmit Sin Nombre virus.

The intensity and extent of interactions between Norway or black rats and other mammalian hosts of hantavirus is unknown. Recently, two Norway rats in Argentina and one black rat in Chile were documented with antibodies for Andes virus.[83,88] Because Andes virus is hosted by the long-tailed rice rat (*Oligoryzomys longicaudatus*), the results suggest intimate contact between *Rattus* species and native rodent species in South America. Further studies are required to determine whether these invasive *Rattus* species can transmit Andes virus to other individuals including humans. However, the results are notable given that Andes virus causes HCPS and is the only hantavirus with evidence for human to human transmission.[89,90] Thus, the spread of Andes virus outside of South America by *Rattus* species could have global consequences for human health. It would be useful to understand the frequency of long-distance migrations by invasive *Rattus* species, as well ecological conditions under which hantaviruses switch hosts, to be able to predict and circumvent such problems in the future.

Community dynamics

Beyond host dynamics, it is necessary to consider the effects of landscape alteration on other species within the community, which can influence numbers and behaviors of reservoirs in such a way as to impact pathogen transmission. For example, hantaviral hosts often appear to be the dominant rodent species in disturbed habitats.[72,91,111] Community dominance may be a factor in hantavirus ecology by increasing the probability that an encounter will be with another host, thus augmenting the chance of transmission.

Dilution effect

A major consequence of habitat alteration is loss of species. A decrease in biodiversity has been hypothesized to increase certain pathogens through the "dilution effect."[92–94] This phenomenon, whereby increasing species diversity decreases pathogen prevalence by diluting availability of competent hosts with increased numbers of less competent hosts, has been strongly supported in tick-transmitted Lyme disease and its hosts.[93,95] Although the mechanism would be different, a dilution effect is theoretically possible in directly

transmitted pathogens such as hantaviruses if (1) individuals of the host species remain as species diversity decreases, (2) the pathogen is spread within the host species horizontally, and/or (3) the presence of other species cause encounters among the host species to decrease.[96] Given the generalist nature of many hosts and the hypothesized transmission through biting, hantavirus prevalence should respond to changes in levels of biodiversity. Indeed, Peixoto and Abramson used a mathematical model to show how increased species diversity could dilute hantavirus prevalence in the host species,[97] suggesting decreased host density as the mechanism. However, it is also possible that increased species diversity decreases infection prevalence by altering the host's behavior.

The dilution effect has only recently been examined in hantaviruses. Five studies have found an increase in prevalence of host species with a decrease in small mammal diversity.[59,63,96,98,99] Three of these studies examined SNV dynamics in the United States, one examined Chaclo and Calabazo hantaviruses in Panama and one investigated Puumala virus in Belgium. In addition, four of these studies were comparisons of habitats with different levels of biodiversity, whereas one was a manipulative experiment within natural habitats. The effect of diversity on prevalence appears to be the result of more than simply a reduction in host-density as density alone was not predictive of prevalence in two of three studies that addressed this issue.[96,98,99] Overall, the results of these studies suggest that the dilution effect has broad applicability within the realm of hantavirus, reaching across types of ecosystems, host and pathogens, and modes of transmission.

Clay *et al.*[100] went one step further to try to uncover mechanisms behind the dilution effect by exploring the role of host persistence and contact rates. They found a negative relationship between species diversity and the number of deer mice that persisted to the next season, suggesting that deer mice more frequently die in, or disperse from, areas of higher diversity. They also found a negative relationship between SNV prevalence and the number of pinyon mice (*Peromyscus truei*) in a habitat. They speculated that the presence of pinyon mice might change the behavior, movement, or maturation of deer mice. Moreover, increasing levels of species diversity decreased intraspecific encounter rates but not duration of encounters.

Predation

Along with decreased biodiversity often comes reduction of predator populations. It might seem intuitive that predators can control rodent populations and therefore are important in controlling pathogen transmission, but this has been difficult to show empirically.[48] The specialist predator hypothesis predicts that specialist predators will drive prey cycles, but alternate predators are also needed to stabilize upper limits of prey.[101] Recent evidence shows strong support for this type of top-down control of prey cycles, at least in Greenland and Finland.[45,102–104] Alternatively, the mesopredator release hypothesis predicts that the loss of top carnivores, which rarely eat prey as small as rodents, results in increased numbers of smaller predators, which rely on rodents for much of their diet thereby reducing rodent numbers.[105] Landscape alteration often decreases or completely eliminates predators from human-influenced landscapes.[106–108] Many hantavirus vectors are generalist species that live and/or thrive in these landscapes.[62] It has been hypothesized that this release from predatory controls affects rodent behavior in such a way as to augment hantaviral transmission.[73,74,96] Although the effects of predation on hantavirus transmission has not yet been empirically tested, given that loss of predators can result in an increase in rodent numbers and change rodent behaviors, it seems likely that transmission of at least some hantaviruses will be augmented by the loss of predators due to landscape alteration.[109,110] The loss of predators may be particularly important at high latitudes where rodents appear to be largely controlled by top-down forces.

Human dynamics

Ultimately, the risk of hantavirus to humans depends on proximity of humans to hosts and their excreta, and therefore human behaviors are a necessary aspect of pathogen transmission. In southern Europe where hosts tend to stay in forested areas, forest workers, hunters, and people who live less than 100 m from forested areas have an increased risk of contracting NE from contact with contaminated excreta from bank voles.[55] In South America, where hosts tend to be generalist species, human exposure is often associated with agricultural practices.[70,79,91,111] In China, Hantaan virus, hosted by the striped field mouse (*Apodemus*

agrarius), causes HFRS and is significantly associated with agriculture, timber forests and soils associated with agriculture. Human behavior was not directly addressed in any of these studies,[112,113] so it is difficult to know whether the increase in human risk in the associated landscapes is due to either particular behaviors or increased prevalence in the host as seen in many of the studies or both. However, the behavioral aspect is vital to public health, particularly if certain occupations such as farming increase human risk. For example, in China alone, Hantaan virus causes 40,000–60,000 cases annually, which represents 70–90% of the world's cases of HFRS, and causes the most severe form of HFRS.[2]

Human behavior during warfare is not typically considered in ecological studies of host–pathogen dynamics. However, this component of landscape alteration appears to favor the transmission of hantaviruses and should be included, given that many armed conflicts have arisen recently in areas with documented hantavirues (e.g., Georgia region, Slovenia). In fact, hantaviruses were originally discovered on a global scale during the Korean conflict when thousands of troops from the United Nation forces contracted an unknown hemorrhagic fever.[4] Hantaviruses have been implicated as the cause of "trench nephritis" in conflicts extending back to the American Civil War as well as World War I and II.[1] During such conflicts, soldiers in makeshift camps can have increased exposure to rodents and rodent excreta. Furthermore, transmission of hantaviruses may be facilitated if soldiers are immunocompromised by the stresses of combat. This outcome of war with respect to hantavirus transmission is an area for concern for public and world health officials managing such conflicts.

Conclusions and recommendations for science and policy

Climate change and landscape alteration are affecting hantavirus transmission, but the outcomes can differ among different hantaviruses as well as within the same strain. The disparity appears to be a function of many factors including geographic area, type of alteration, host species, and the hantavirus species. Furthermore, the underlying mechanisms that mediate hantavirus transmission are largely unknown. Thus, predicting how transmission dynamics of all hantavirus species will change in the face of a large-scale or global human disturbance may be premature. Because the tools to definitively diagnose hantaviruses in the host and humans have only been available for the past 15 years, the multiyear ecological studies and replication needed to evaluate effects of long-term factors are limited. The continuation and establishment of long-term ecological efforts on hantaviruses should be valued and encouraged as these studies will be critical in predicting future human risk. Establishment of hantavirus surveillance in hosts occurring in areas with persistent or large numbers of human cases such as China may be essential in managing human risk on a global scale.

It is evident that much work remains to be done in the transmission dynamics of hantavirus. Undoubtedly, there are genetic, immunological, and physiological aspects that are important. Currently, there are no specific treatments or generally accepted vaccines.[114] Even if a vaccine can be developed, production and administration are costly and logistically difficult, particularly if everyone in the region could potentially become infected. This leaves prediction and prevention as the best measures to protect human health, which both require ecological knowledge of the host and virus. At the very least, information about host–pathogen ecology will allow predictions of times and areas of high risk.[34,77] Public education programs during such high-risk times could decrease human cases. Ideally, although, by minimizing landscape alteration and climate change, ecosystem level control can be used to proactively protect the public from the increasing threat of hantavirus.

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Conflicts of interest

The authors declare no conflicts of interest.

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