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Hantaviruses and a neglected environmental determinant

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ABSTRACT

Most human pathogenic hantaviruses cause severe hemorrhagic fevers with a high rate of fatalities, such as occurs due to the genotypes causing hantavirus cardiopulmonary syndrome carried by the New World Sigmodontinae and Neotominae rodents. An increasing number of outbreaks and the possibility of cases spreading over international borders have led to greater interest in these viruses and the environmental determinants that facilitate their transmission. Rodents, shrews, moles and bats act as reservoir hosts of hantaviruses, and within the hantavirus transmission flow, the prevalence and distribution of infection in reservoir hosts is influenced by a range of factors. Climate change and landscape alteration affect hantavirus transmission, but the outcomes can differ among different hantaviruses and for the same virus in differentbiomes. However, it is evident that the underlying mechanisms that mediate hantavirus transmission are largely unknown, so that much work remains to be done regarding the transmission dynamics of hantaviruses. Overall, our review highlights the importance of examining interactions over several trophic levels and the underlying mechanisms (density and trait-mediated indirect effects) linking predation risk and hantavirus transmission, to develop an ecological framework to understand disease in natural, preserved and degraded systems.

1. Introduction

Viruses of the family *Bunyaviridae* (the bunyaviruses) share several molecular characteristics. Based on their differences, they have been classified into five genera: *Orthobunyavirus*, *Hantavirus*, *Nairovirus*, *Phlebovirus* and *Tospovirus* [1]. Within the bunyaviruses, the genus *Hantavirus* contains the most important zoonotic pathogens of humans, attracting studies worldwide. These RNA viruses are associated with multiple species of rodents, shrews, moles and bats [2]. Hantaviruses are the etiologic agents of Hemorrhagic Fever with Renal Syndrome (HFRS) in Europe and Asia, and Hantavirus Pulmonary Syndrome (HPS)/Hantavirus Cardiopulmonary Syndrome (HCPS) in the Americas [3,4]. Hantaviruses are an emerging global threat to public health, affecting about 30,000 humans annually [4].

The first HFRS outbreak was reported among U.S. soldiers deployed to fight in the Korean War in the 1950s, and was blamed on the high level of contact between carrier rodents and soldiers residing outdoors [5,6]. More than 60 years after the first reported outbreak of human disease, hantavirus infections have been reported in many countries in Europe/Asia, with highly variable annual case numbers. In the period from 2000 to 2009, probably more than 300,000–400,000 human disease cases occurred in European and Asian countries [7–10]. The outbreak of the hantavirus infections in North America and the subsequent occurrence of HPS/HCPS in South America was a great challenge after the discovery of HFRS caused by Old World hantaviruses. In the Americas, the diversity and distribution of hantaviruses are highly complex, with more than 40 hantavirus genotypes described, nearly half of them pathogenic to humans [11]. More than 4000 HPS/HCPS cases had been reported in South America up to 2013, with high case-fatality ratios for the most common viral genotypes (between 30% and 40%) [12].

Unlike other members of the *Bunyaviridae*, hantaviruses are not vector-borne but are instead transmitted between their vertebrate hosts through aggressive interactions or the inhalation of excreta [3]. Rodents, shrews, moles and bats act as reservoir hosts of hantaviruses, and their infection is chronic and nearly asymptomatic [13–15]. However, hantavirus infection has been shown to impair the survival of some reservoir animals [16,17]. Therefore, it is not surprising that the ecology and geographical distribution of hantaviruses are related to the distribution of their natural reservoir species. An increasing number of outbreaks and the possibility of cases spreading over international borders has led to increased interest in these viruses and the environmental determinants that facilitate transmission. Ecological studies that evaluate the risk factors for human infection contribute significantly to understanding the dynamics of hantavirus transmission.

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2. Environmental determinants

Hantaviruses are transmitted horizontally within reservoir populations, either directly through aggressive interactions or indirectly through the environment [18–20]. In the latter situation, infection occurs when susceptible individuals inhale infectious particles released into the environment, resulting in spillover events or cross-species transmission [21–24]. Within the hantavirus transmission flow, the prevalence and distribution of infection in rodent hosts are influenced by a range of factors. The multifactorial landscape of the hantavirus infection system is complex due to factors that are both direct and indirect modifiers of prevalence in populations. Therefore, both the number of infected rodents, related to their density and virus prevalence, and abiotic properties determine the environmental viral load and thus human risk of acquiring infection [25]. Studies with local geographical scale are important, especially when environmental factors differ. For example, in some areas there are more cases of HCPS in the autumn/winter, but the seroprevalence in rodents is higher in the summer. The possible explanation for this is that despite the lower seroprevalence in winter, there is greater approximation of humans to rodents, due to lower supply of food, dry climate and grain harvest [26–28]. In other studies, the highest incidence of HCPS cases was found in November and December and was associated with the higher number of animals infected with hantavirus [29,30]. Understanding the interplay of landscape, climate and factors associated with hantavirus transmission is vital to resolve the determinants of HCPS cases at local and larger scales.

2.1. Landscape and climate

The ecology and factors driving hantavirus emergence will likely be altered by the various changes occurring on the planet. The El Niño Southern Oscillation (ENSO), the Pacific Decadal Oscillation (PDO) and the North Atlantic Oscillation (NAO) are three key climate cycles likely to have impacts on hantavirus-reservoir interactions. These cycles influence plant productivity, small mammal reproduction, and vertebrate predator activity [31]. Rodents, shrews, moles and bats, which act as reservoir hosts for hantaviruses, are vulnerable to the impacts of climate change and habitat disturbance. Therefore, the persistence of the virus outside of the reservoir depend on temperature and humidity, so as temperature regimes change, so will the environmental abundance of viruses [21,32].

The relation of landscape, climate and social factors associated with hantavirus transmission has been widely studied. The factor “precipitation” is the most studied climatic predictor of HCPS outbreaks, with several authors indicating a positive correlation with rodent densities and prevalence of hantavirus [33–38]. High rainfall increases vegetation growth, raising rodent densities and increasing the probability of human-rodent encounters and consequent hantavirus transmission [39,40]. For example, studies in semiarid environments of the southwestern United States have demonstrated relationships between increased precipitation and vegetation growth and subsequent deer mouse abundance, infection prevalence, and HCPS cases [37,41–43]. These effects are more evident following ENSO events in this particular region, lead to aggravation of unfavorable arid conditions, increase and expansion of local populations and the dispersal of hosts from nearby suitable habitat [41,43,44]. However, this positive relation may apply only in environments where water is a limiting factor of native flora growth. Therefore, while precipitation can positively affect HCPS, it can also have no or negative effects, depending on its magnitude and region [35,45]. Recently, Prist and collaborators highlighted there is a large gap in studies concerning the relations of HCPS and landscape configuration, temperature and the interaction between climate and landscape variables. Overall, despite many remaining questions, current evidence indicates that when the landscape remains above a certain structural threshold, which allows preserving the integrity of small mammal community, the prevalence and risk of HCPS are lower, but this still needs to be tested empirically [46].

In Europe, both the amplitude and the magnitude of outbreaks of HFRS have increased. The mechanisms that drive the incidences are complex and multi-factorial. Most articles have investigated associations between two dependent variables (rodent reservoir seroprevalence and HFRS incidence) and numerous factors, including food availability, habitat characteristics or climate factors, considering both direct and indirect (through virus survival outside the host) transmission pathways [25,44,47]. Monchatre and collaborators reviewed and compiled the current knowledge of the key environmental drivers of hantavirus infection in rodents and humans in Europe [47]. This review gave strong support that food availability and temperature of previous autumn/winter influence both HFRS incidence and host seroprevalence. HFRS incidence was positively associated with these two drivers, whereas reservoir seroprevalence was positively associated with food availability and negatively associated with temperature. More specifically, although not observed in all studies, the normalized difference vegetation index (NDVI), or NDVI-based food availability indices, appears to positively influence reservoir seroprevalence and HFRS at different spatial and temporal scales, regardless of the type of statistical analysis, highlighting the robustness of this result. In contrast, results of the relations between HFRS incidence and/or reservoir seroprevalence and other independent variables (e.g., precipitation) appear less robust [47].

These studies deal only with deciduous biomes, where weather-induced mast events drive bank vole fluctuations and consequently PUUV induced HFRS epidemiology. In temperate Europe, bank vole populations display seasonal fluctuations and occasional irregular eruptions, caused by masting, i.e., a heavy seed crop of oak and beech [48]. Masting has been linked to human nephropathy epidemics, likely brought about by growth of the local vole population [48–50]. However, a considerable proportion of HFRS in Europe occurs in northern Europe (northern Sweden, Finland, northern Russia) in the boreal coniferous taiga zone, where masting effects do not occur. In boreal forests of northern Europe, deciduous trees do not undergo masting events and vole population abundance cycles of 3 to 5 years are assumed to be driven by predators [51,52]. This dichotomy, whereby within one host-virus system (like the bank vole and PUUV) there are biome-specific epidemiologies, is well-established. Even if these vole fluctuations may superficially look similar in northern and central Europe, their underlying causes are totally different. Cycles in the north are a top-down process while fluctuations in the temperate zone are a bottom-up process [53,54].

2.2. Dilution effect

Human activities, land use change and habitat destruction contribute to reducing biodiversity and disruption of natural processes [55,56]. Biodiversity, including the number, abundance, and composition of genotypes, populations, species, functional types, communities, and landscape units, strongly influences the frequency and severity of pathogen infections in humans [57–61]. The dynamics of zoonotic pathogens can be affected by genetic diversity within host populations, species diversity within host communities, and diversity among communities. In principle, diversity can either increase or decrease pathogen transmission and disease risk. The dilution effect suggests that where species vary in susceptibility to infection by a pathogen, higher diversity often leads to reduced disease risk. The basic idea behind the dilution effect hypothesis is that biodiversity (typically measured by species richness, or the number of different species present in a particular spatially defined locality) protects against infection by zoonotic pathogens. That is, high host diversity “dilutes” disease risk [62–64].

Field studies have demonstrated that the does occur in many natural systems. A dilution effect is probable because: (a) reservoirs differ in

quality for pathogens or vectors; (b) higher quality reservoirs tend to occur in species-poor communities, whereas lower quality reservoirs tend to occur in more diverse communities; and (c) lower quality reservoirs regulate abundance of high-quality reservoirs or of vectors, or reduce encounter rates between these reservoir hosts and pathogens or vectors [65]. To test the dilution effect in hantaviruses, Dizney and Ruedas examined 17 ecological variables associated with prevalence of the directly transmitted Sin Nombre virus (SNV) in its wild host, the deer mice (*Peromyscus maniculatus*). The prevalence of Sin Nombre hantavirus increased from 2 to 14% as non-host species diversity decreased, showing that the transmission of an agent can significantly increase after loss of species [66]. Clay and collaborators investigated the mechanisms by which diversity influenced the prevalence of SNV. They monitored both intra and interspecific encounters of deer mice using foraging arenas at five different sites with disparate levels of species diversity to examine two probable mechanisms that may contribute to the dilution of SNV prevalence: (1) reduced frequency of encounters between deer mice, or (2) reduced duration of contacts between deer mice. They showed that species diversity influences the dynamics of SNV by reducing encounters between deer mice in a trade-off between intra and interspecific interactions [67]. However, Voutilainen and collaborators also paid attention the importance of reservoir population structure. They found true dilution in spring, when small mammals breed and are territorial, but no dilution in autumn, when populations are dominated by young non-territorial non-breeding subadults. It is noteworthy that population structure has not usually been taken into account in small mammal dilution studies, so the results of these studies may include a lot of noise [68].

Recently, Khalil and collaborators, in a well-studied system, investigated the dilution of the Puumala hantavirus (PUUV) in bank voles (*Myodes glareolus*) by two competitors and a predator. The field vole (*Microtus agrestis*) and the common shrew (*Sorex araneus*) are bank vole competitors and Tengmalm's owl (*Aegolius funereus*) is a main predator of bank voles. In this study, the infection likelihood in bank voles decreased when common shrew density increased, suggesting that common shrews reduced PUUV transmission. Field voles suppressed bank vole density in meadows and clear-cuts and indirectly diluted PUUV infection. Further, the decline in the population of Tengmalm's owl in 1980–2013 may have contributed to higher PUUV infection rates in bank voles in 2003–2013 compared to 1979–1986 [69]. Another study investigated whether voles (*Microtus* spp.), which occur intermittently, influenced estimated standing antibody prevalence to SNV among deer mice, whose populations are persistent. They found a reduction in deer mice antibody prevalence associated with the presence of voles, independent of vole abundance [70]. Blasdell and collaborators analyzed the relationship between hantavirus seroprevalence and rodent species diversity. They also found that hantavirus seroprevalence increased as rodent biodiversity decreased, to the risk of human disease may also potentially increase [71].

3. Predation as a neglected environmental determinant

Hantaviruses and others pathogens responsible for zoonotic diseases use the same basic pathways to spread within host populations as they use to infect humans. They exit a reservoir host, either in excreta (feces, urine or saliva) or via a bite, and enter a new host – rodent or human – through inhalation, swallowing or skin punctures [19,21,32,72,73]. It seems logical to assume that the greater the abundance of reservoirs, the higher the potential infection rate of pathogens, and therefore the higher the risk will be of people's contracting the disease [74]. If this is true, then any factor that influences reservoir density should help diminish or increase the incidence of zoonotic diseases such as those caused by hantaviruses (Fig. 1).

Wildlife populations participate in ecological interactions with various other populations that occupy the same habitat, thus building an ecological community. Commonly, the species in the community

Fig. 1. Analysis of environmental determinants, landscape, climate, dilution effect, among others, it has been a source of wide debate. However, looking at this scenario, what is the importance of predation in the dynamics of hantavirus transmission?

form a complex web of trophic interactions called the food web. Because food webs can represent a random sample of all species found in natural communities, theoretical studies of community ecology often concentrate on subunits of a web [75]. This is far from ideal because these data typically ignore parasites and diseases and restrict the findings to either parasitoid-host communities or predator-prey communities [76]. Many reservoir-pathogen interactions are embedded in a web of other interspecific interactions. In natural communities, pathogens and their reservoirs are typically embedded within a web of interactions with other species, which can indirectly affect the pathogen. Among these interactions, predation is a central process that contributes to the structure and function of ecological communities [77,78].

Predators have a diversity of direct and indirect effects within food webs and also influence infectious disease dynamics because pathogens rely on the biological networks in which they live. Predators can directly and indirectly influence reservoir-pathogen interactions by consuming infected individuals, by removing infectious pathogens stages and by changing reservoir traits. For example, predation can increase or decrease the prevalence of infectious diseases depending on how it affects the frequency of infected individuals or high-quality hosts in the population [79,80]. Predation intensity on reservoir populations can alter host–pathogen dynamics [81,82] and even affect pathogen persistence in the reservoir population [83,84]. In general, predation often has major impacts, directly influencing the prey by suppression of population [78,85–88].

Wild carnivores are part of food webs and “preserved” ecosystems and interact with both reservoir and non-reservoir species. As human activities continue to increase “degraded” ecosystems, interest about the role of species diversity in modifying zoonotic cycles is growing. Small mammals are an important part of ecosystems and their monitoring can indicate whether an ecosystem is preserved or degraded [89]. Understanding small mammals' response to disturbances and habitat modifications is fundamental to understanding infectious disease dynamics. Therefore, as “degraded” ecosystem intensity increases, host species gradually become the dominant species [90]. It seems logical to assume that the greater the abundance of rodent reservoirs, the higher the prevalence will be of infected rodents, and therefore the higher the risk of human contact with the virus. The argument that predators can protect human health through reduction of host densities or by selectively preying on infected individuals from the population is plausible. Within this context, rodents are the preferred prey of many taxa of predators, including mammals, birds and reptiles, and these predators can be strong limiting factors and regulators of reservoir

density and consequently the prevalence of hantavirus infection.

Carnivora is an order of mammals that includes canids (e.g., wolves and dogs); felids (cats); ursids (bears); mustelids (weasels); procyonids (raccoons); pinnipeds (seals); and others, making up 12 families and 270 species in all [91]. While some carnivores do eat only meat, some carnivores also supplement their diets with vegetation on occasion. For example, Felidae (cats) and Mustelidae (members include weasels, stoats, polecats, minks, martens, fishers, wolverines, otters, badgers and others), are unusual mammalian groups whose members are all obligate carnivores (hypercarnivores) [92].

Mustelids are primarily carnivorous, but some species may at times eat plant material. Many animal taxa are preyed upon by various members of this family. However, many mustelids are especially adept at capturing small mammalian prey. Weasels, for example, are capable of chasing and capturing rodents in their burrows [93–95]. The small mustelids, the least weasel (*Mustela nivalis nivalis*) and the stoat (*Mustela erminea*), are key predators in the boreal vole cycle, the principal host of PUUV (*Myodes glareolus*) in Europe [96]. They are small and highly adapted to preying on voles even in their nests and under snow cover, and can be the main cause of mortality in vole populations [97]. Predation by the small mustelids in the southwest and by the whole predator guild in the north is an essential contributor to the regular, high-amplitude vole cycle in northern Europe. The observed strengthening of delayed density dependence in vole populations coincides with strengthening small mustelid influence on the summer population growth rates of voles. A strong impact of these small mustelids during summers appears important to cyclic vole dynamics [51].

The crab-eating fox (*Cerdocyon thous*) is a small canid with twilight and nocturnal habits from savannas and forests of South America. This animal is essentially carnivorous, with more than 87% of prey composed of vertebrates. Small rodent species compose the most important food source of the crab-eating fox, with up to 52% relative frequency, including hantavirus reservoir genera (*Akodon* and *Oligoryzomys*) [98,99]. Among other animals, coatis (*Nasua nasua*) are omnivores whose diet consists of small vertebrates, invertebrates and fruit. Rodents are the most frequently ingested mammals (42%) among the total of small vertebrates consumed [100]. However, few studies have evaluated the importance of these animals, either regarding ecological factors or the dynamics of hantavirus infection. Escutenaire and collaborators investigated in Belgium the susceptibility of a predatory species of bank voles (*Clethrionomys glareolus*), the reservoir of Puumala hantavirus in Europe. Blood samples of 125 red foxes (*Vulpes voles*) were serologically tested and 20 presented serum reactivity (16%) [101].

Raptors, or “birds of prey”, are a group of predatory birds including hawks, owls, eagles and falcons. Some species of owl are widely distributed throughout the world. Owls feed primarily on small vertebrates, particularly rodents. In the Brazilian Cerrado biome, a study evaluated the diet of the barn owl (*Tyto alba*, family Tytonidae) based on regurgitated pellets. In total, small mammals corresponded to 86% of food items, and the second most preyed species was *N. lasiurus,* which is the reservoir of Araraquara hantavirus [102]. In Europe, rodents, especially voles (Arvicolinae), make up at least 70% of the biomass eaten by barn owls. A typical barn owl consumes one to five rodents per night, and a family of barn owls eats about 3000 rodents each year [103,104].

In Belgium, Heyman and collaborators evaluated data from the population of barn owls, the most widely distributed owl species in Europe. In the late seventies, the barn owl appeared on the Red List of endangered species in Belgium. For this study, they analyzed the data provided by surveillance of owl populations and the human hantavirus infection data provided by the national reference laboratory for hantavirus infections in Brussels, Belgium. Although the authors considered the time series relatively short (1982–2009), they reported a correlation was present between the number of hantavirus infections in a certain year and the breeding success of the barn owl. In closing, they recommended the monitoring barn owl populations since the species can be a sentinel marker for predicting the risk of hantavirus infection in the human population [103]. In Chile, in an attempt to reduce numbers of rice rats (*Oligoryomys longicaudatus*) and therefore reduce the risk of infection in humans, the Chilean Forest Service increased efforts to promote breeding of Chilean white owls and Magellanic horned owls in the Valparaíso region, a natural focus of hantavirus infection. Since 2002, they have been placing nest boxes in the area, providing habitat for these owls to reproduce and monthly censuses have revealed that up to 30 chicks are produced a year, which then disperse into neighboring regions [105].

Khalil and collaborators showed that Tengmalm's owl (*Aegolius funereus*) selectively preys on hantavirus-infected individuals of the bank vole (*Myodes glareolus*), which is the reservoir host of Puumala hantavirus. The authors suggested a complex relationship between zoonotic disease prevalence in hosts, their predators, and landscape structure [106]. In turn, Camelo-Neto and collaborators, through mathematical models, found the possibility of controlling the spread of hantavirus epidemics by introducing predators in areas of mice colonies in an appropriate way so that control does not kill all the mice, but allows lower spread of hantaviruses [107]. More recently, a study analyzed research investigating different aspects of avian predation on rodent populations in order to increase understanding of the impact and effectiveness of avian predation on rodent pests. The authors identified 28 studies where the success of avian predator attraction methods for the purpose of rodent control had been evaluated. The study highlighted three key issues: (i) the number of studies was small, indicating the need for more research concerning avian predation on agricultural rodent pests; (ii) the majority of studies lacked proper experimental designs (multiple time series design, control, replication) to allow for informative analysis; and (iii) the majority of studies relied on simple indexes to quantify rodent and avian predator abundance [108].

It is important to highlight interactions over several trophic levels linked to predation and pathogen transmission to understand hantavirus dynamics in “degraded” systems. Domestic dogs and cats are the species most closely related to humans, and consequently are the most abundant and widespread carnivorous mammals in the world. Domestic dogs and cats are present in altered environments and disturbed ecosystems (agricultural and rural areas) that have suffered loss of biodiversity and where the composition of rodent communities is restricted to generalist species. These generalist species are frequently reservoirs of hantavirus. For example, *Necromys lasiurus* and *Oligoryzomys nigripes* are the main reservoirs of hantavirus in the Atlantic Forest and Cerrado (savanna-like) biomes in South America [30,109–111]. The two species have wide geographic distribution, great abundance and generalist habit, and their dominance in agricultural and peridomestic areas increases the absolute risk of hantavirus infection [2].

Domestic dogs and cats may have an important role in reducing human disease risk (possible barriers) in agricultural and peridomestic areas. However, few data are available about hantavirus in domestic dogs and cats. In the 1990s in New Mexico and northeastern Arizona, serum samples of cats, dogs, horses, cattle and coyotes were analyzed for hantavirus antibodies by western immunoblot assays. All samples from horses, cattle and coyotes were nonreactive and sera from 4 of 145 (2.8%) cats and 4 of 85 (3.5%) dogs were reactive to full-length Sin Nombre virus-encoded nucleocapsid proteins [112]. In Austria, Nowotny evaluated 200 feline serum samples and found a seroprevalence of 5% [113]. A study conducted in Canada evaluated the infection by several agents, including hantavirus, in 240 dog and 242 cat samples. The overall serological prevalence of hantavirus antibodies in cats was 2.9%, but no dog was reactive [114]. In two regions of Belgium, hantavirus antibodies were found in both species, with significantly higher seroprevalence in cats than dogs (16.9% vs. 4.9%) [115].

4. Conclusion

Climate change and landscape alteration are affecting hantavirus transmission, but the outcomes can differ among different hantaviruses. However, it is evident that the underlying mechanisms that mediate hantavirus transmission are largely unknown so that much work remains to be done to investigate the transmission dynamics of hantaviruses. The establishment of long-term ecological studies of hantaviruses should be encouraged, since these studies will be critical in predicting future human risk, mainly the effect of predation. Unfortunately, studies of predators are scarce, making it impossible so far to know their true impact on hantaviruses. Overall, our review highlights the importance of examining interactions over several trophic levels and the underlying mechanisms (density and trait-mediated indirect effects) linking predation risk and hantavirus transmission, to enable developing an ecological framework for understanding disease in natural systems. The argument is that predators limit rodent numbers, rodent numbers limit pathogen numbers, and pathogen numbers in rodents then determine disease incidence in people. Because such interactions can affect infection positively or negatively, understanding the net effects of predation on hantavirus transmission under natural conditions is important.

Conflicts of interest

The authors declare no conflict of interest.

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