

# Effects of Anthropogenic Events and Viral Persistence on Rodent Reservoirs of Hantavirus Infection: Understanding Host-Pathogen Interactions Facilitates Novel Approaches to Intervention Strategies

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**Abstract** Hantaviruses are primarily rodent-borne pathogens which have received considerable attention recently due to their high mortality rates in humans. In order to find the causes of rapid transmission and emergence of hantavirus-associated diseases anthropogenic changes are a priority. These include deforestation, urbanization, noise pollution, light pollution and electromagnetic fields, all of which have been shown to profoundly affect rodent physiology and immunology. Moreover, anthropogenic events promote human-rodent co-habitation and thereby provide a driver to increase rates of transmission and, by extrapolation, levels of infection in humans. Such environmental disruption acts as a chronic stressor to rodents and causes elevated concentrations of glucocorticoids, which are a major class of immunosuppressive hormone. Glucocorticoids are responsible for altering the immune tolerance of rodents, thereby rendering them susceptible to infection. Glucocorticoids induce regulatory T lymphocytes to reduce inflammatory and antiviral responses and to activate regulatory responses, principally through production of the cytokines interleukin-10 and transforming growth factor- $\beta$  to support viral persistence. In order to develop a low-cost intervention strategy for hantavirus infection consideration should be given to a systemic approach to therapy. This would both aim to achieve a reduction of anthropogenic stressors and to gain a greater understanding of host-pathogen interactions.

**Keywords:** *hantavirus, rodent, reservoir, viral persistence, anthropogenic event, glucocorticoid, regulatory T lymphocyte, anti-viral*

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## 1. Introduction

Developing strategies to counter the emergence and reemergence of infectious diseases has been the subject of an appreciable research effort over recent decades [1]. Currently, three-quarters of emerging human infectious diseases are caused by zoonotic pathogens, i.e. those that are transmitted naturally between vertebrate animals and humans, often through the agency of a vector or fomite [2,3]. At present, rodents are known to be a reservoir to more than 60 human-infecting viruses, including hantaviruses, the subject of this review, but also lymphocytic choriomeningitis virus, plague and leptospirosis [4,5]. Hence, control of rodents in situations of co-habitation with humans is a public health priority. Whereas rodents, the normal host of hantaviruses, show no signs of disease, infection in humans is severe and may be fatal [6,7].

Although anthropogenic stresses, caused by humans, are recognized as a major driving force to facilitate the recent repeated breakout of infectious diseases from wildlife reservoirs [8,9], neither the impact of such stressors nor their mechanism of action has been studied [10]. The emergence of hantaviruses could also be attributed to anthropogenic stressful events [8]. Several anthropogenic factors, for example deforestation, urbanization, noise and light pollution, and electromagnetic fields, contribute to the alteration of endocrine balance in rodents. These stressors are also responsible for immune, nervous and physiological alterations [11]. Rodents that are exposed to chronic anthropogenic stress are reported to have elevated levels of glucocorticoids (GCs) [12], a major class of immunosuppressive steroid hormone released from the adrenal gland [13]. Interactions between endocrine, nervous and immune systems play a major role in determining the outcome of host-pathogen interactions

[14]. GCs are responsible for reducing the resistance of wild animals to viruses and increase their tolerance to harbouring the virus in a minimal range without causing any disease [15]. The possibility has been suggested that by activating organ-specific regulatory mechanisms GCs also influence the host-pathogen interaction [16,17].

In this review, hantavirus-associated disease symptoms and their epidemiology, current treatment, prevention and vaccine development are discussed. We describe the mechanism of viral persistence in rodents driven by glucocorticoid hormone and also shed light on different types of anthropogenic events thought to play a role in facilitating the emergence and transmission of hantavirus-associated diseases in urban areas. An understanding of the chronicity of hantavirus infection in rodents, and its transmission to humans, would prove valuable to control

programs for treating newly emerging and reemerging infectious diseases.

## 2. Transmission and Epidemiology

Hantaviruses are negative-sensed, enveloped, single stranded RNA viruses that belong to the genus *Hantavirus* and family *Bunyaviridae*. This family includes four other genera (*Nairovirus*, *Orthobunyavirus*, *Phlebovirus* and *Tospovirus*) with about 330 species currently recognized [18]. The precise number of hantavirus species to be identified is a matter of debate, but over 20 distinct viral species exist in nature; at least 11 are associated with human disease.

**Table 1. Geographical Distribution of Pathogenic Hantaviruses with their Natural Reservoirs**

Hantavirus Serotype	Associated Clinical Syndrome	Natural Reservoir	Geographical Distribution
Amur	HFRS	<i>Apodemus peninsulae</i> (Korean field mouse)	Far east Russia, Southeast Siberia, Northeast China, South Korea
Dobrava-Af	HFRS	<i>Apodemus flavicollis</i> (Yellow-necked field mouse)	Central Europe, European Russia
Dobrava-Aa	HFRS	<i>Apodemus agrarius</i> (Striped field mouse)	Central and Eastern Europe
Puumala	NE, a type of HFRS	<i>Clethrionomys glareolus</i> (Red bank vole)	Europe-wide
Seoul	HFRS	<i>Rattus norvegicus</i> , <i>Rattus rattus</i> (Brown rat, black rat)	Worldwide
Tula	HFRS	<i>Microtus arvalis</i> (Common vole)	Northern and Eastern Europe
Hantaan	HFRS	<i>Apodemus agrarius</i> (Striped field mouse)	Central Europe, Korea, China, Taiwan
Andes Oran	HPS	<i>Oligoryzomys longicaudatus</i> (Long-tailed pygmy rice rat)	Argentina, Chile, Uruguay
Araraquara	HPS	<i>Bolomys lasiurus</i> (Hairy-tailed bolo mouse)	Brazil
Bermejo	HPS	<i>Oligoryzomys chacoensis</i> (Chacoan pygmy rice rat)	Northwest Argentina
Black Creek Canal	HPS	<i>Sigmodon hispidus</i> (Hispid cotton rat)	USA (Florida)
Castelo dos Sonhos	HPS	–	Brazil
Choclo	HPS	<i>Oligoryzomys fulvescens</i> (Fulvous pygmy rice rat)	Panama
Hu39694	HPS	–	Argentina
Juquitiba	HPS	<i>Oligoryzomys nigripes</i> (Black-footed pygmy rice rat)	Brazil
Laguna Negra	HPS	<i>Calomys laucha</i> (Vesper mouse)	Bolivia, Paraguay
Lechiguanas	HPS	<i>Oligoryzomys flavescens</i> (Yellow pygmy rice rat)	Argentina
Maciel	HPS	<i>Necromys benefactus</i> (Dark field mouse)	Argentina
Sin Nombre	HPS	<i>Peromyscus maniculatus</i> (Deer mouse)	USA, Canada
New York	HPS	<i>Peromyscus leucopus</i> (White-footed mouse)	USA
Rio Mamore	HPS	<i>Neacomys spinosus</i> (Common bristly mouse)	Bolivia
Oran	HPS	<i>Oligoryzomys longicaudatus</i> (Long-tailed pygmy rice rat)	Northern Argentina
Monongahela	HPS	<i>Peromyscus maniculatus</i> (Deer mouse)	Eastern USA

The transmission of hantaviruses involves the transfer of virus to humans from a typically disease-free hantavirus-associated rodent host. The geographical distribution of each species is dependent upon the regional location of its reservoir host, that which serves as a source of infection and potential reinfection of humans and as a means of sustaining the pathogen long-term (Table 1) [19]. Humans may become infected after coming into contact

with hantavirus-infected rodent egestion, excretions and secretions, or soiled nesting material. This is most commonly through airborne transmission via inhalation of aerosols containing the virus [20,21]. Persons dwelling in confined spaces that contain fresh droppings, urine or saliva from infected rodents place themselves at risk of becoming infected [22]. Interpersonal transmission is very uncommon with the noted exception of Andes virus [23].

Similar negative-stranded RNA viruses, such as Ebola and Marburg, can be transmitted by contact with infected human blood and body fluids, and are known to spread to patient care workers in African hospitals [24]. These viruses, however, do not transfer readily in a modern hospital setting implementing universal precautions. In general, droplet and/or fomite transfer has not been demonstrated for hantaviruses in either the haemorrhagic or pulmonary forms.

Recognized risk factors for transmission include the presence of rodents and rodent excreta in the proximity of domestic and work place buildings. In endemic areas particular problems are associated with summer cottages that have poor ventilation and with farmhouses on land with abundant rodent populations [19,25,26,27]. Long-term residential stay for work or military service in forests with a high prevalence of hantavirus-infected rodents also poses a significant risk of transmission [26,28,29]. In Europe and Asia the most reported cases of hantavirus infection come from Russia and China, respectively [30,31]. Ecological disturbances play a crucial role in hantavirus transmission. Reduction of the natural habitat of a reservoir host combined with loss of biodiversity promotes migration of infected rodents into areas of human habitation. This has the effect of further increasing the rate of pathogen transmission [19,32].

### 3. Evolution of Hantaviruses

It was long since thought that hantaviruses have co-evolved with their rodent host [33,34], but the concept of co-divergence is supported by recent evidence of host switching, i.e. cross-species transmission, followed by local host adaptation [35]. Increasing evidence suggests that in addition to rodents, shrews and moles also serve as hosts for hantaviruses [35,36,37,38].

Phylogenetic analysis suggests that ancestral soricomorphs, consisting of five families –*Soricidae* (shrews), *Talpidae* (moles), *Solenodontidae* (solenodons), *Erinaceidae* (hedgehogs and gymnures) and *Nesophontidae* (now extinct West Indies shrews) – may be the original mammalian hosts for hantaviruses [39]. Hantaviruses are unique in being the only known genus of *Bunyaviridae* which maintain rodent hosts, with all other viruses in this family carried by insects or arthropods. This lends credibility to the view that present day hantaviruses may have arisen from invertebrate-borne vectors as for other members of the *Bunyaviridae* [38]. Another recent study showed that hantaviruses share a mixed evolutionary history of infection of both shrews and rodents instead of being monophyletic with rodents, which is of direct relevance to the host switching event [37]. Care should be taken to distinguish shrews and moles from rodents as they differ in many characteristics, such as evolution, taxonomic order and lifespan, while at the same time sharing the common trait of inhabiting the same environmental communities, which sheds light on our understanding of host switching. This could occur following inter- or intra-species wounding or by virus shedding in respiratory secretions or excretions within the same ecological niche [35,40]. Immunologically-based mechanisms of persistence of hantaviruses in shrews and

moles appear similar to those which are thought to have occurred in rodents throughout evolutionary history [41].

### 4. Hantavirus-Associated Major Clinical Syndromes

Hantaviruses show no clinical symptoms in rodents while humans, considered an unnatural dead-end host for infection, are susceptible to two distinct manifestations of hantavirus-associated clinical disease, haemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). The name hantavirus comes from the Hantan River region of South Korea, for which Hantaan virus, the cause of Korean haemorrhagic fever that was first isolated in the late 1970s, is named [4]. During the Korean War (1950-1953) more than 3,000 United Nations soldiers were infected with Korean haemorrhagic fever, now referred to as HFRS. Another notable outbreak during 1993 in the 'Four Corners' region of the Southwestern United States was associated with HPS [42].

HFRS and HPS share some common clinical signs. These include increased vascular permeability with hypotension, haemoconcentration, overexpression of CD8<sup>+</sup> T lymphocytes and sometimes elevated leukocyte levels in peripheral blood [43]. While the name HFRS indicates a renal involvement with haemorrhagic fever, its clinical development is divided into five distinct stages: febrile; hypotensive; oliguric; diuretic and convalescent. A usual fatality rate due to HFRS in humans of 5-20% is widely recognized [44]. In some cases, it has been known to cause permanent renal failure. Facial flushing and conjunctival injection are initial signs of HFRS, followed by high fever, backache, abdominal pain, photophobia and pharyngeal enanthem. Febrile stage symptoms arise usually 2-3 weeks after exposure and typically occur for 3-7 days. The hypotensive stage follows onset of fever and involves a drop in blood pressure due to vascular leakage. Reduced kidney function causes abnormal urinary sediment. The onset of renal failure and proteinuria, together with severe abdominal or back pain, is observed in the oliguric phase. The diuretic phase, characterized by the passing of 3-6 litres of urine per day, begins from day 11 and can last for a couple of days to weeks. Symptoms improve as recovery occurs during the convalescent phase, which lasts from weeks to several months [43,44].

HPS is noted for influenza-like symptoms including high fever, headache, myalgia and shortness of breath [45]. Hypotension and acute non-cardiac pulmonary oedema may develop within 2-15 days. Neutrophilic leukocytosis and haemoconcentration are also observed. HPS can deteriorate rapidly into acute respiratory failure and, despite mechanical ventilation and intervention with potent diuretics, is characterized by a high mortality rate of approximately 50% [44,46].

### 5. Anthropogenic Stresses in Urban Areas and their Effects on Rodents

A man-made disturbance of the natural environment is known as an anthropogenic event, which results in stress to wild animals. This has been identified as a key factor in

the advent of emerging infectious diseases (EIDs) in wildlife but has not been studied in detail [10]. Although hantaviruses have persisted in rodents for thousands of years, the advent of civilization has increasingly brought about chronic anthropogenic events which are thought to promote more efficient transmission of the virus and thereby the emergence of hantavirus-associated diseases [47]. Here, we discuss several classes of anthropogenic events most common in urban areas, including deforestation, urbanization, noise pollution, light pollution and electromagnetic fields, and evaluate how each affects rodent physiology and immunity. These effects probably facilitate the rapid transmission of hantaviruses in urban areas.

### **5.1. Effects of Deforestation and Urbanization**

The rate of urbanization by human populations is escalating rapidly which favours direct human dominance over nature in environments in which deforestation is a common event. Since urbanization is correlated positively with loss of biodiversity, this influences shift and migration of host, vector, food competition and, most importantly, host-pathogen ecology [48,49]. A high level of biodiversity is responsible for a reduction of pathogen transmission while anthropogenic factors are found to decrease diversity and to increase pathogen transmission risk [32]. Landscape fragmentation increases rodent population density in areas of high food competition, which consequently brings rodents into close contact with humans. This supports inter- or intra-species transmission and a high prevalence of viruses [50,51]. Effects of urbanization, such as habitat fragmentation, deforestation and food scarcity leading to increased feeding competition, act as chronic stressors for rodents. This results in rapid physiological changes and lower immunity to viruses, which is mediated by GCs [52,53].

### **5.2. Effects of Noise**

Noise pollution is identified as a source of anthropogenic stressors to urban animals. Significant levels of physiological changes occur in those rodents that are exposed to noise, while no such changes are observed in rodents in fields with little outside sound [54,55]. Changes in physiological and behavioral responses in rodents due to noise effects may be characterized by an elevated level of corticosterone, immune alteration, a decrease in reproductive function, reduced body weight and reduced gastric secretion. Noise pollution also has profound effects on the rodent nervous system. This may be demonstrated by subjecting rodents to conditions of either noise or quiet. When rats were subjected to an electronically generated noise stimulus of 10 Hz to 10 kHz at a specific time every morning for 3 weeks, they developed an attenuation of their parasympathetic nervous system while their sympathetic nervous system remained unchanged [54]. Intestinal mucosa of rats exposed to high levels of noise developed significant inflammation compared to the gut of rats kept in quiet conditions. Furthermore, rats subjected to loud noise were found to have a reduced humoral immune response and phagocytic activity and also showed a decreased number of T lymphocytes [56].

### **5.3. Effects of Artificial Lighting**

Humans first started to interfere with the natural day-night cycle following the discovery of fire. This increased over the last century with the invention of artificial lighting, which escalated to the extent of now causing what we recognize as 'light pollution'. Rapid urbanization is further intensifying levels of artificial light at night in metropolitan areas where the night sky is always lit as if by a full moon [57,58]. Exposure to continuous artificial light at night can suppress the rhythmicity of circadian activity, body temperature and initiate sleep deprivation in rodents, which has the potential to modulate the immune system [59,60,61]. Sleep deprivation further activates the hypothalamic-pituitary-adrenal (HPA) axis and may alter the consequent stress response [62]. The balance of several hormones, including GCs, prolactin, adrenocorticotropic-releasing hormone, corticotrophin-releasing hormone, serotonin and melatonin, is altered by the constant light or light-light cycle. Continuous low level artificial light at night is identified as reducing melatonin production in rodents and this phenomenon could suppress immunostimulation [60,63]. Increased concentrations of plasma corticosterone are observed in male mice under conditions of prolonged artificial lighting, which is an indicator of stress [64,65]. Artificial lighting is also responsible for suppression of cell-mediated and humoral immune responses in rodents [61]. These findings collectively suggest potential harmful effects of disrupting natural lighting by introducing artificial light. In contrast, environmentally-attached species, those which are not exposed to artificial lighting, do not show any sign of these physiological or immunological changes [65].

### **5.4. Effects of Electromagnetic Fields**

The absolute dependence on electricity in the daily lives of people resident in developed nations and, increasingly, in developing nations means that globally humans discharge a significant level of electromagnetism into the environment. In this age of widespread electrification we are surrounded by transformers, power lines, mobile telephone signal transmitters, radio waves, microwaves and electronic devices, the activities of which generate electromagnetic fields (EMFs). The correlative evidence that extremely low frequency (ELF) EMFs are a health hazard has become a matter of great concern in recent decades [66,67]. City dwellers have considerable exposure to ELF magnetic flux on a daily basis. Leakage of stray current is the most common source of magnetic flux in urban environments [68]. In most countries, electrical power is generated at an ELF-EMF frequency of 50/60 Hz. The flow of alternating current generates a low level EMF. Several reports have suggested that long-term exposure to ELF-EMF induces elevated levels of plasma corticosterone and depressive-like behaviours in rodents [69,69,71]. Continuous exposure of rodents to ELF-EMF promotes a state of chronic stress and triggers activation of the HPA axis [71]. Another recent report provided evidence that rats exposed to EMF have significantly higher levels of corticosterone than do control animals [72]. Chronic low power density microwaves have also been shown to increase corticosterone concentrations in rats [73]. EMF-mediated chronic stress and an elevated persistence of GCs are causally linked to a significant

reduction of mononuclear cells, especially CD8<sup>+</sup>T lymphocytes. Production of interleukin (IL)-2 is also decreased. All these events result in suppression of cellular immunity in rats [74,75].

## 6. Anthropogenic Events Promote Human-Rodent Co-Habitation to Increase Prevalence of Infection

From the above discussion it is apparent that anthropogenic events are responsible directly or indirectly for infectious disease outbreaks like hantaviruses. These may be considered as provoking rodent migration into areas of human dwelling while simultaneously causing suppression of rodent immunity to viruses to render them more suitable reservoir hosts. It is noteworthy that anthropogenic events not only play an important role in disease occurrences but, conversely, are thus a consideration for approaches to disease prevention. By restricting anthropogenic events it may be possible to reduce human-rodent co-habitation and thereby contribute to more effective disease control management.

GCs are secreted by an animal when it detects a stressor and are responsible for initiation of a stress response. Acute stress, commonly known as the 'flight-or-flight' response, is characterized by induction of the catecholamine hormones epinephrine (adrenaline) and norepinephrine (noradrenaline), whereas chronic stress is distinguished by release of the GC hormones cortisol and corticosterone. Of the two, corticosterone is found more abundantly among rodents although some species appear to express both [76,77]. The mammalian immune system has two unique properties termed 'resistance' and 'tolerance' whereby resistance mechanisms are directed specifically towards a pathogen to limit its burden while tolerance mechanisms are concerned with reducing the indirect impact of a given infection by neutralizing the effects of toxins and metabolic byproducts produced by the associated pathogen [78]. GCs are responsible for reducing resistance and elevating tolerance, thereby supporting viral persistence [14]. It is well known that the endocrine, nervous and immune systems all interact to regulate the fate of host-pathogen interactions [79,80]. Most hantavirus outbreaks occur in those areas where the environment is extensively disturbed due to anthropogenic changes and rodents experience chronic anthropogenic stresses [8]. Since chronic stress is responsible for increasing an animal's susceptibility to infection [81], this is a likely reason why viral infections are more prevalent in urban animals than in their rural counterparts [52].

We suggest that due to the immunosuppressive activity of GCs it is possible that urban rodents, exposed to considerable and varied stresses, have a greater prevalence of hantavirus infection than do rodents resident in a less stressful rural environment. Hence, the heightened susceptibility of urban rodents to virus transmission due to enforce dgreater contact with humans may be causally linked to increased hantavirus outbreaks in populated areas. A comparison of the microbial burden of rodents from wild and urban dwellings is justified. A recent study of urban-dwelling Norway rats identified the presence of novel viruses besides hantaviruses [82]. This is a possible

indication of a difference in wild and urban rodents' viral loads.

## 7. Mechanism of Hantavirus Persistence in Rodents

The mechanism by which rodents support hantavirus infection without showing any signs of disease is just starting to be revealed. The study of host-pathogen interactions is a recently established field of virology research with the potential to provide insight into how a host maintains viruses without clinical signs, which may inform future antiviral therapies. Generally, viruses are considered to follow one of two strategies for survival: 'hit and run'; 'hit and stay'. Regarding infection of rodents, hantaviruses follow the hit and stay strategy. In order to establish persistent infection a hantavirus must not show any cytopathic effect towards its host and must escape from host immune defence. Although naturally hosts do not benefit from harbouring viral infection, depending on the environment a commensal state may be established [83].

The enzyme matrix metalloproteinase 9 (MMP-9), known to disrupt the endothelial membrane and extracellular matrix in normal physiological processes, is elevated by hantavirus infection of monocytes and macrophages. This enables hantaviruses to gain the access required to disseminate into tissue. This is necessary only to achieve a high viral load in rodent lungs and not for viral persistence; expression of MMP-9 is reduced when infection is established [84]. Expression of pattern recognition receptors in lungs [85] and antigen-presenting molecules, e.g. MHC class II, is reduced following hantavirus infection in rats, indicating their contribution to persistence of infection [86,87]. Clinical manifestations in hantavirus-infected humans are thought to be due to excessive pro-inflammatory and CD8<sup>+</sup> T lymphocyte responses while rodents demonstrate reduced pro-inflammatory and antiviral responses and increased regulatory responses in persistent hantavirus infection [44,88]. During chronic infection, expression of antiviral interferon (IFN)- $\beta$ , IFN- $\gamma$  and pro-inflammatory cytokines is reduced [85,88]. Expression *in vitro* of the Hantaan virus (HTNV) resistance protein Mx2 is also suppressed during Seoul virus (SEOV) infection [89,90]. Increased hantaviral load and mortality are both observed in CD8<sup>+</sup> T lymphocyte-deficient rats, indicating that these immune cells play a crucial role in suppressing hantavirus replication and host infection; therefore, to establish a persistent infection hantaviruses must evade CD8<sup>+</sup> T lymphocyte-mediate immunity [43,91,92].

Regulatory T (T<sub>reg</sub>) CD4<sup>+</sup>CD25<sup>+</sup> lymphocytes act to suppress pro-inflammatory and CD8<sup>+</sup> T cell activity to maintain host homeostasis and thereby enable hantaviral persistence (Figure 1) [93]. Inactivation of T<sub>reg</sub> lymphocytes reduced expression of SEOV RNA in rat lungs, which is a clear indication of T<sub>reg</sub> involvement in virus persistence [16,94]. During chronic infection T<sub>reg</sub> lymphocytes suppress synthesis of tumour necrosis factor (TNF)- $\alpha$  and inflammatory responses and promote expression of transforming growth factor (TGF)- $\beta$ , IL-10 and FoxP3 [16,95]. T helper (Th) 1 CD4<sup>+</sup> lymphocytes express IFN- $\gamma$ , IL-2 and TNF- $\alpha$  and facilitate the cell-

mediated immune activity of CD8<sup>+</sup> T lymphocytes, natural killer (NK) cells and macrophages [96], while Th2 lymphocytes express IL-4, IL-5, IL-10 and IL-13, and promote antibody-mediated immunity [97]. T<sub>reg</sub> lymphocytes, mediated by FoxP3, may initiate Th1-Th2 lymphocyte pathway polarization [98] and could also suppress the activity of antigen-presenting cells, such as macrophages and dendritic cells (DC), and B lymphocytes [99,100]. DC, which secrete TNF- $\alpha$  and IFN- $\alpha$ , are also susceptible to hantavirus infection. However, immature or tolerogenic DC may activate T<sub>reg</sub> lymphocytes through the mediation of TGF- $\beta$  to exert suppressive activity [7,100,101]. Antibodies specific for hantaviruses are not able to eliminate the virus, but after infection they remain detectable throughout life [84,102]. Infants acquire maternally-derived antibodies for the first two months following birth, which provide some protection [103,104].

GCs are capable of reducing host resistance to viruses and facilitate viral persistence by increasing tolerance to infection. When challenged by chronic anthropogenic stressors, immunologically suppressed rodents express elevated levels of GCs which mediate an organ-specific regulation that supports tolerance while removing resistance to hantavirus infection [15]. GCs block inflammatory pathways and induce apoptosis mediated by T<sub>reg</sub> lymphocytes [17,105,106,107]. GCs not only suppress

differentiation of DC but also induce production of tolerogenic DC which express elevated IL-10 and TGF- $\beta$ . Such tolerogenic DC are responsible for generation and activation of T<sub>reg</sub> lymphocytes to exert a regulatory control over CD8<sup>+</sup> lymphocyte-mediated antiviral responses (Figure 1) [108,109,110,111]. GCs cause a polarization of CD4<sup>+</sup> lymphocyte subsets from Th1 to Th2 and increase production of Th2 cytokines which further stimulate alternatively activated M2 macrophages [109,111,112,113]. M2 macrophages are characterized by excessive synthesis of IL-10 and TGF- $\beta$ , which is triggered mainly by elevated levels of GCs which suppress activity of classically activated M1 macrophages [80,111,114,115]. High mortality rates attributable to an exaggerated pro-inflammatory response and efficient virus clearance are both observed in the absence of GCs, as demonstrated experimentally for other viral infections [116,117]. This clearly indicates the critical function of GCs to viral persistence and in establishing an equitable balance in the host-pathogen interaction. This suggests that such GC-operated mechanisms as discussed above provide a regulatory feedback loop to protect the host against excessive immune response-associated pathology. Accordingly, we propose that GCs may play a pivotal regulatory role to support hantavirus persistence in rodents.

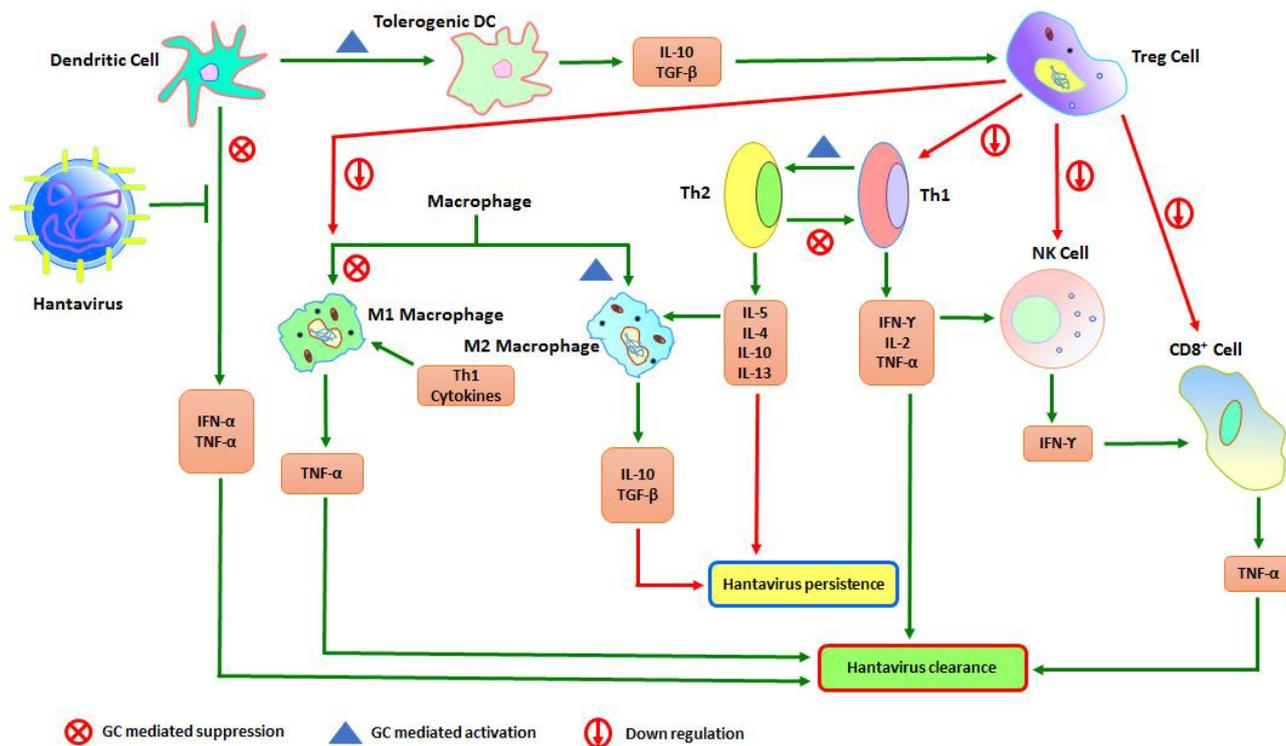


Figure 1. Cellular Immune Responses during Hantavirus Persistence in Rodents

## 8. Approaches to Treatment and Prevention

There is currently no drug that is approved by the US Food and Drug Administration for treatment of hantavirus infection. Ribavirin (1- $\beta$ -D-ribofuranosyl-1,2,4-triazole-3-carboxamide) has shown anti-hantaviral activity both *in vitro* and, to a lesser extent, *in vivo*. In murine models,

ribavirin-treated animals exhibited higher survival rates [118,119,120]. However, clinical trials on ribavirin do not corroborate sufficiently such promising results to justify commercial development as an anti-hantaviral drug [121,122].

The lack of specific treatment places an increased emphasis on preventative strategies aimed at minimizing rates of infection. Obviously, avoidance of contact with rodents and their excretions is the best way to prevent infection. Foodstuffs that are attractive to rodents should be kept in sealed containers and stored in small quantities

in a domestic setting. Farmers who work on land with abundant rodent populations are recommended to wear a face mask in order to avoid inhalation of infectious material and thereby to minimize the risk of infection [19]. Seasonal residences should be well ventilated with fresh air before occupancy [44,123].

## 9. Current Developments in Vaccine Research

Although considerable effort has been applied to vaccine development against hantaviruses at present there is no efficacious vaccine therapy available for humans. Traditional vaccine approaches have been followed in Asia, including rodent brain- and cell culture-derived inactivated vaccines [124]. In particular, a mouse brain-derived vaccine, Hantavax<sup>®</sup>, was marketed commercially in Korea [125]. However, none of these vaccines has gained approval in the US for therapeutical use [126]. Studies with animal models show that these conventional inactivated vaccines derived from HTNV or SEOV would not protect against Puumala virus (PUUV) that is prevalent in Europe [127,128].

Current strategies are focused on developing a DNA vaccine to elicit neutralizing antibodies against hantavirus glycoproteins [129]. One approach is to prepare a single vaccine that would protect against multiple pathogenic hantavirus species. A recent study shows that a combination of plasmids from four pathogenic hantavirus species, HTNV, PUUV, Andes virus (ANDV) and Sin Nombre virus (SNV), could elicit comparable levels of neutralizing antibody against each species [130]. A combination of either HTNV and PUUV or ANDV and SNV provided only partial success. These preliminary findings indicate that a quadravalent vaccine could be a promising option for future anti-hantaviral vaccine research.

## 10. Call for a Multidisciplinary Systemic Approach

The emergence and reemergence of infectious diseases highlight the urgent need for effective public health surveillance and management systems. Rodents have developed an organ-specific tolerance mechanism mediated by GCs to promote their own survival. However, unplanned and unorganized urbanization is continuously increasing the fragmentation of habitats and the unwanted interactions of humans with infected wild species, which is attributable for the increasing appearance of EIDs. Research continues with the aim of elucidating fully the mechanism of viral persistence and the role of GCs in its regulation in rodents. Humans develop up-regulated pro-inflammatory responses against hantaviruses which, in rodents at least, are postulated to come under the control of GCs. There is some evidence to suggest that programmed cell death may be slow or absent from excessive immune responses in cases of human infection [7,131]. An in-depth understanding of hantavirus persistence may provide insights to inform the ongoing fight against hantavirus-associated diseases. It may be reasonably assumed that some features of immune evasion mechanisms are shared

by all viruses. Therefore, an effective management system against infection with one virus species may provide a model for wider implementation as well as to direct strategic development of low cost therapies for future use.

## 11. Conclusion

For hantavirus infections, understanding and alleviating pathogenesis in humans affords only a partial view of a complex biological system that involves the pathogen and, potentially, both human and rodent hosts. In recent years, the suppressive effect of a stress response in humans has been clearly established but the effect(s) of stressors on other animals is far less known. In this respect, it can be argued that human negligence and poor management are major factors in the increased incidence of most EIDs. Humans, animals and their shared environment are all interlinked in a complex networked system. Therefore, future research should focus simultaneously on systemic and holistic approaches that consider molecular pathogenesis, virulence, endocrine and immune activities, host-pathogen interactions, vaccine targets, ecology and biodiversity. Without recognition of the interdependence of contributing factors, partial and fragmented insights gained from conventional approaches to research will not achieve consistent success in the fight against EIDs. In such circumstances, further hantavirus species may emerge, possibly involving different geographical areas and novel animal hosts.

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## Conflict of Interest

The authors declare no actual or potential conflicts of interest in relation to this article.

## Abbreviations

GC glucocorticoid, HFRS haemorrhagic fever with renal syndrome, HPS hantavirus pulmonary syndrome, EID emerging infectious disease, HPA hypothalamic-pituitary-adrenal, EMF electromagnetic fields, ELF extremely low frequency, MMP-9 matrix metalloproteinase 9, IFN interferon, HTNV Hantaan virus, SEOV Seoul virus, T<sub>reg</sub> regulatory T, TNF tumour necrosis factor, TGF transforming growth factor, IL interleukin, Th T helper, NK natural killer, DC dendritic cell, PUUV Puumala virus, ANDV Andes virus, SNV Sin Nombre virus, NE nephropathia epidemica (also known as epidemic nephropathy).

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