

Hantaviruses as priority zoonotic diseases: A comprehensive review

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Abstract

Hantaviruses are zoonotic agents that play a significant role in global public health, primarily due to their ability to cause two highly severe clinical syndromes: Hemorrhagic Fever with Renal Syndrome (HFRS), which is predominant in Eurasia, and Hantavirus Cardiopulmonary Syndrome (HCPS/HPS), which is primarily found in the Americas. Although long recognized, the complex interactions between the virus, its rodent reservoir, and environmental factors make hantaviruses still a relevant epidemiological threat today. This review aims to provide a comprehensive overview of their virological characteristics, epidemiological patterns, pathogenesis mechanisms, risk factors, diagnostic methods, therapeutic options, prevention strategies, and the latest developments in hantavirus vaccines. Several studies have shown that the diversity of hantavirus species is strongly influenced by the ecology of their natural reservoirs, resulting in geographically specific virus distribution patterns. Pathogenesis mechanisms are primarily related to impaired immune response regulation and increased vascular permeability, which underlie the emergence of severe clinical manifestations in the kidneys and respiratory system. Key risk factors include exposure to environments contaminated with rodent excretions, agricultural activities, housing conditions with rodent infestations, and environmental changes that influence reservoir population dynamics. Diagnosis requires a combination of serological testing and molecular detection methods, while clinical management remains supportive due to the lack of specific and effective antiviral therapy. Although vaccine development has shown progress, its implementation remains limited to specific regions. These findings emphasize the importance of implementing a One Health approach that integrates ecological surveillance, clinical preparedness, and rodent control-based prevention strategies to sustainably reduce the risk of hantavirus zoonosis.

Keywords: disease, hantavirus, HCPS, HFRS, zoonosis

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Introduction

Hantaviruses are a group of single-stranded, negative-sense RNA viruses belonging to the Hantaviridae family (Afzal *et al.*, 2023). The viral genome is composed of three main segments: Small (S), Medium (M), and Large (L), which sequentially encode the nucleocapsid protein, envelope glycoproteins (Gn and Gc), and the RNA-dependent RNA polymerase enzyme (Meier *et al.*, 2021). The main characteristic of hantaviruses is the highly specific ecological relationship between each virus species and the rodent species that serve as their natural reservoir, so that their geographic distribution patterns and epidemiological dynamics are largely determined by the ecological conditions of wildlife in a region (Gorris *et al.*, 2025). Currently, hantaviruses are recognized as significant zoonotic pathogens due to their role in causing two major, highly severe clinical syndromes in humans: Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Cardiopulmonary Syndrome / Hantavirus Pulmonary Syndrome (HCPS/HPS) (Tariq and Kim, 2022; Chen *et al.*, 2023).

HFRS is primarily reported in Asia and Europe, with Hantaan virus (HTNV), Seoul virus (SEOV), Puumala virus (PUUV), and Dobrava-Belgrade virus (DOBV) as the primary causes (Sehgal *et al.*, 2023). Clinically, HFRS is characterized by systemic vascular dysfunction accompanied by hemoconcentration, hemorrhagic manifestations, and impaired renal function that can progress to acute renal failure (Jiang *et al.*, 2016). Conversely, in the Americas, hantavirus infection is generally associated with Hantavirus Cardiopulmonary Syndrome (HCPS), a severe condition characterized by extensive pulmonary edema, acute respiratory failure, and a high mortality rate (Safronetz *et al.*, 2014). Sin Nombre virus (SNV) and Andes virus (ANDV) are the most predominant etiologic agents, with ANDV being the only hantavirus species to date proven capable of human-to-human transmission through close contact (Jacob *et al.*, 2023).

The history of modern hantavirus research began with an outbreak of an unknown etiology among thousands of military personnel during the Korean War in the 1950s (Kuhn and Schmaljohn, 2023). The condition, characterized by fever, bleeding, and impaired kidney function—then known as Korean hemorrhagic fever—was only explained after the successful isolation of HTNV in 1978 from the rodent *Apodemus agrarius* (Mir, 2010). This discovery marked a significant milestone, spurring the rapid development of hantavirus virology, epidemiology, and ecology (Noh *et al.*, 2019). Since then, numerous hantavirus species have been identified, each showing a close association with specific rodent reservoirs, such as *Myodes glareolus*, *Peromyscus maniculatus*, and *Rattus norvegicus* (Shehata *et al.*, 2025).

Human hantavirus infection generally occurs through inhalation of aerosol particles containing infected rodent excretions (Avšič-Županc *et al.*, 2019). The risk of exposure increases during various activities that generate dust, such as cleaning long-unused buildings or warehouses, agricultural harvesting, construction work, and outdoor activities in areas with high rodent populations (Watson *et al.*, 2014).

Transmission through rodent bites is relatively rare, while human-to-human transmission has only been demonstrated for ANDV (Toledo *et al.*, 2022). This transmission pattern underscores the importance of human-environmental interactions as a key factor in the dynamics of hantavirus epidemiology (Jonsson *et al.*, 2010).

In many endemic areas, hantavirus infection remains a significant public health problem, primarily due to high morbidity and mortality rates, as well as limited diagnostic methods in the early stages of the disease, which often exhibit nonspecific symptoms (Afzal *et al.*, 2023). Furthermore, changes in land use and the environment—including deforestation, habitat fragmentation, agricultural expansion, and urbanization—contribute to increased interactions between humans and commensal rodents (Tian *et al.*, 2024). Global climate factors, such as the El Niño phenomenon, have also been reported to play a role in driving rodent population surges by increasing the availability of food sources, ultimately increasing the risk of hantavirus transmission (Douglas *et al.*, 2021).

The complexity of the interactions between viruses, animal reservoirs, humans, and the environment makes hantaviruses a vivid illustration of the urgency of implementing a One Health approach (Adnyana *et al.*, 2023). A thorough understanding of reservoir ecology, viral molecular properties, epidemiological dynamics, and exposure risk factors is crucial for strengthening surveillance systems, designing prevention strategies, and reducing the potential for outbreaks (Xiong *et al.*, 2026). Therefore, a comprehensive scientific review of hantaviruses remains highly relevant in supporting zoonotic disease control efforts globally (Jonsson *et al.*, 2010). This review aims to present a comprehensive analysis covering aspects of virology, epidemiology, pathogenesis mechanisms, risk factors, diagnostic methods, and prevention strategies for hantaviruses, to deepen scientific understanding and support effective zoonotic control efforts.

Etiology

Hantaviruses belong to the Hantaviridae family, within the Bunyavirales order, a large group of segmented RNA viruses that commonly infect vertebrates (Laenen *et al.*, 2019). In terms of genome structure, hantaviruses have single-stranded, negative-sense RNA composed of three segments: Small (S), Medium (M), and Large (L) (Muyangwa *et al.*, 2015). Each segment encodes major structural and non-structural proteins, namely the nucleoprotein (N), the envelope glycoproteins Glycoprotein n (Gn) and Glycoprotein c (Gc), and the enzyme RNA-dependent RNA polymerase (RdRp) (Hussein *et al.*, 2011). These three genome components play crucial roles in the viral replication process, determining tissue tropism, and evading host immune responses (Muyangwa *et al.*, 2015).

The genus of greatest clinical significance is Orthohantavirus, a group of hantaviruses that naturally circulate in various species of rodents, talpids, members of the family Soricidae, and bats (Romeo *et al.*, 2025). Although most hantaviruses maintain an infectious

cycle within their natural reservoirs without causing disease, a number of species are known to cause severe infections in humans, primarily through exposure to aerosols containing the urine, feces, or saliva of the reservoir animal (Afzal *et al.*, 2023). Based on geographic differences, evolutionary pathways, and clinical presentations in humans, Orthohantaviruses are generally divided into two main groups: Old World hantaviruses and New World hantaviruses (Noack *et al.*, 2020).

Old World hantaviruses are widespread in Asia and Europe and are generally associated with the clinical manifestation of HFRS (Tariq and Kim, 2022). This group includes several main species, including HTNV, SEOV, PUUV, and DOBV (Mir, 2010). Each species exhibits a specific affinity for its natural reservoir, such as *Apodemus agrarius* for HTNV, *Rattus norvegicus* for SEOV, and *Myodes glareolus* for PUUV (Mittler *et al.*, 2019). The stability of the evolutionary relationship between hantaviruses and their reservoirs supports the concept of coevolution, although reports of genetic recombination and host switching indicate that hantavirus evolution is dynamic and complex (D'Souza and Patel, 2020).

In contrast, New World hantaviruses, which are distributed from North America to South America, are the primary cause of HCPS/HPS, a highly fatal form of acute respiratory disease (Jonsson *et al.*, 2008). This group includes several important viruses, including SNV, ANDV, Laguna Negra virus, and Araraquara virus (Jacob *et al.*, 2023). Among all hantaviruses, Andes virus is unique in that it is the only species proven to be capable of human-to-human transmission, particularly through close contact during the infectious phase (Alonso *et al.*, 2020).

The hantavirus classification system continues to evolve with the discovery of homologous viruses in various non-rodent species, such as bats and shrews, which were previously not considered primary reservoirs (Zhang, 2014). Although the zoonotic potential of most of these newly identified viruses remains uncertain, these findings indicate that hantavirus diversity is much broader than previously thought and raise the possibility of the existence of other, as yet undetected, species (Yanagihara *et al.*, 2014).

Epidemiology

The epidemiology of hantaviruses is strongly influenced by the ecology of their natural reservoirs, resulting in marked variations in human disease manifestations across geographic regions (Douglas *et al.*, 2021). Globally, hantaviruses are grouped into two main categories: Old World hantaviruses, which are dominant in Asia and Europe, and New World hantaviruses, which are distributed in the Americas (Hussein *et al.*, 2011). These differences correlate with the clinical spectrum they cause, with infections in Eurasia typically causing HFRS, while in the Americas they more frequently result in HCPS/HPS (Hjelle and Torres-Pérez, 2010). Table 1 presents a summary of the global epidemiology of hantaviruses based on geographic distribution, emphasizing the interrelationship between virus distribution, its natural

reservoir, and the clinical syndromes that appear in humans.

In East Asia, particularly in China, South Korea, and Eastern Russia, HFRS is the most frequently reported form of hantavirus infection and accounts for more than half of all hantavirus cases globally (Zhang *et al.*, 2010; Kariwa *et al.*, 2012; Klein *et al.*, 2025). HTNV and SEOV are the primary etiologic agents, with the highest incidence rates found in rural areas and population groups with high levels of contact with rodents (Kariwa, 2017). Seasonal patterns of disease incidence are often associated with population fluctuations of *Apodemus agrarius* and *Rattus norvegicus*, as well as agricultural activities such as harvest seasons that increase the frequency of human interaction with rodent habitats (Shehata *et al.*, 2025).

In Europe, hantavirus distribution patterns vary widely and are strongly influenced by the characteristics of temperate forest ecosystems (Koehler *et al.*, 2022). PUUV is the primary causative agent of nephropathia epidemica, a milder form of HFRS that is endemic in Scandinavia, Finland, and Central Europe (Evander and Ahlm, 2009; Klempa *et al.*, 2013; Mustonen *et al.*, 2024). Increased cases are often reported during periods of *Myodes glareolus* population surges, which are closely associated with masting years (Fabbri *et al.*, 2025). In contrast, DOBV is more common in the Balkans and is associated with more severe HFRS manifestations (Županc *et al.*, 2014).

In North America, hantavirus infection commonly manifests as HCPS, with SNV as the predominant etiologic agent (Hjelle and Torres-Pérez, 2010; Warner *et al.*, 2020). HCPS was first recognized in 1993 in the southwestern United States and has since become a significant public health issue due to its high fatality rate, reportedly around 30–40% (Khan *et al.*, 1996). Case distribution patterns show a strong association with the presence of the primary reservoir, *Peromyscus maniculatus*, and are influenced by climatic factors, such as increased rainfall, which enriches rodent food sources and ultimately drives rodent populations (Gorris *et al.*, 2025).

In South America, hantavirus diversity is relatively high and includes various strains, including ANDV, Laguna Negra virus, and Araraquara virus (Firth *et al.*, 2012). Andes virus is important in an epidemiological context because it is the only hantavirus proven to be capable of human-to-human transmission, particularly through close contact in household settings (Toledo *et al.*, 2022). HCPS outbreaks in countries such as Argentina and Chile are often associated with agricultural activities, hunting, and rural settlements, which increase the risk of exposure to aerosols contaminated with rodent excretions (Ferro *et al.*, 2024; Torres-Pérez *et al.*, 2025).

Globally, the dynamics of hantavirus epidemiology are influenced by environmental changes, the expansion of human settlements, and climate variability, which directly impact rodent population fluctuations (Tian *et al.*, 2024). Climate phenomena such as El Niño are known to increase rainfall and food availability, thus driving the growth of reservoir animal populations and increasing the risk of hantavirus transmission (Anyamba *et al.*, 2019). Furthermore, rapid urbanization in developing countries increases the intensity of human

interaction with commensal rodents, such as *Rattus* spp., potentially expanding the distribution of Seoul virus to previously non-endemic areas. Figure 1

illustrates the global distribution of Old World and New World hantavirus strains and their associated rodent reservoirs.

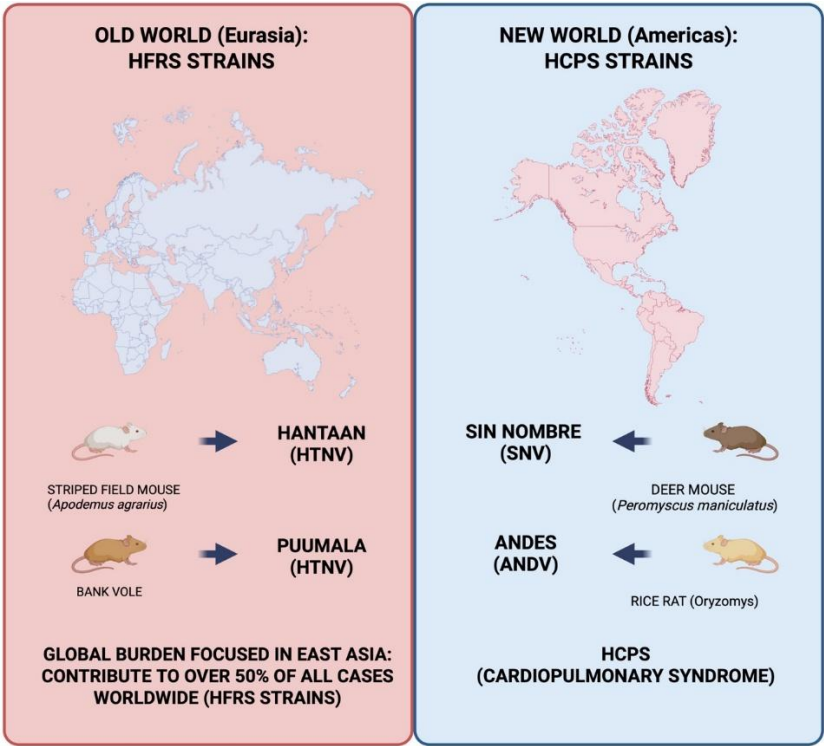


Figure 1 Global distribution of old world and new world hantavirus strains and their rodent reservoirs associated with HFRS and HCPS.

Table 1 Global epidemiology of hantaviruses.

Region	Dominant Hantavirus Strains	Main Clinical Syndrome	Primary Reservoir Species	Key Epidemiological Characteristics	References
East Asia (China, South Korea, and Eastern Russia)	HTNV and SEOV	HFRS	<i>Apodemus agrarius</i> , <i>Rattus norvegicus</i>	Contributes >50% of global cases; strong seasonality; high incidence in rural populations with rodent exposure; influenced by agricultural cycles.	(Zhang <i>et al.</i> , 2010; Kariwa <i>et al.</i> , 2012; Klein <i>et al.</i> , 2025)
Europe (Scandinavia, Finland, Central and Balkan regions)	PUUV and DOBV	HFRS (mild for PUUV; severe for DOBV)	<i>Myodes glareolus</i> , various <i>Apodemus</i> spp.	Transmission associated with forest ecosystems; outbreaks linked to mast years; heterogeneous distribution across regions.	(Evander and Ahlm, 2009; Klempa <i>et al.</i> , 2013; Mustonen <i>et al.</i> , 2024)
North America (USA and Canada)	SNV	HCPS/HPS	<i>Peromyscus maniculatus</i>	High-case fatality rate (30–40%); first identified in 1993; incidence increases with rainfall and rodent population surges.	(Hjelle and Torres-Pérez, 2010; Warner <i>et al.</i> , 2020)
South America (Argentina, Chile, Brazil, and Paraguay)	ANDV, Laguna Negra virus, and Araraquara virus	HCPS/HPS	Various <i>Oligoryzomys</i> spp. and other sigmodontine rodents	High viral diversity; human-to-human transmission confirmed for ANDV; outbreaks linked to agriculture, hunting, and rural settlements.	(Ferro <i>et al.</i> , 2024; Torres-Pérez <i>et al.</i> , 2025)

Although hantavirus infections have been reported in various countries, the actual number of cases is estimated to be higher than officially recorded figures due to limitations in surveillance systems and low diagnostic capacity in some endemic areas (Ferro *et al.*, 2020). Therefore, strengthening surveillance through genomics-based approaches, combined with integrated ecological and epidemiological analyses, is crucial to gain a more accurate understanding of virus circulation patterns and to anticipate the emergence of new variants that could potentially increase the risk of zoonotic transmission (Hill *et al.*, 2026).

Pathogenesis

The pathogenesis of hantavirus infection in humans is influenced by a complex relationship between the virus, vascular endothelial cells, and the host immune response (Schönrich *et al.*, 2015). Transmission generally occurs through inhalation of aerosol particles originating from the excretions of infected rodents (Afzal *et al.*, 2023). Afterward, the virus enters the respiratory tract and infects vascular endothelial cells, which serve as the primary site of replication (Hägele *et al.*, 2021). The process of viral entry into cells is mediated by the interaction between viral envelope glycoproteins (Gn and Gc) with $\beta 3$ or $\beta 1$ integrin receptors, depending on the hantavirus species (Ermonval *et al.*, 2016). This receptor interaction not only allows virus entry but also disrupts the physiological function of integrins in maintaining endothelial stability and integrity, ultimately contributing to increased vascular permeability (Gavrilovskaya *et al.*, 2012).

During replication, hantaviruses do not cause direct cytopathic effects, unlike most other viruses (Scholz *et al.*, 2017). Tissue damage is primarily caused by impaired regulation of the host immune response (Borges *et al.*, 2006). Excessive activation of both the innate and adaptive immune systems trigger the production and release of proinflammatory cytokines, such as Tumor Necrosis Factor-alpha (TNF- α), Interleukin-6 (IL-6), and Interferon-gamma (IFN- γ) (Kombe *et al.*, 2024). This massive increase in cytokines contributes to widespread capillary permeability, which is the primary pathophysiological mechanism in both HFRS and HCPS (Taylor *et al.*, 2025). In HFRS, vascular leakage primarily occurs in the kidney tissue, leading to hematuria, proteinuria, and acute renal failure (Mir, 2022). Meanwhile, in HCPS, endothelial dysfunction is more predominant in the lungs, leading to severe pulmonary edema and cardiopulmonary dysfunction that can potentially lead to acute heart failure (Meza-Fuentes *et al.*, 2023).

In addition to these mechanisms, cytotoxic T cell activation significantly contributes to worsening tissue damage (Outinen *et al.*, 2021). Histopathological findings indicate high lymphocyte infiltration in target tissues, with the degree of Cluster of Differentiation 8 positive (CD8⁺) T cell activation reportedly closely related to the severity of clinical manifestations (Liu *et al.*, 2021). Nevertheless, this immune response remains crucial for virus elimination, placing the host in a complex and paradoxical immunopathogenesis situation (Saavedra *et al.*, 2021). ANDV, uniquely transmissible between humans, is thought to induce a

stronger immune response and exacerbate the pathogenic effects in the lungs through a similar mechanism, but with greater intensity (Sundström *et al.*, 2016).

Endothelial dysfunction and increased capillary leakage are further exacerbated by activation of the coagulation and fibrinolytic systems (Connolly-Andersen *et al.*, 2014). In HFRS, increased vascular permeability, coupled with impaired hemostasis, contributes to the development of bleeding manifestations (Perkins and Mackman, 2026). Tissue factor activation, decreased platelet count due to excessive consumption, and impaired platelet adhesion collectively exacerbate the hypervascular condition and increase the risk of bleeding (Laine *et al.*, 2015).

Immune Response

The immune response to hantavirus infection is a major determinant of the clinical course and severity of disease in humans (Saavedra *et al.*, 2021). Although hantaviruses do not cause direct cytopathic damage to infected cells, excessive immune system activation plays a dominant role in the development of severe clinical syndromes, such as HFRS and HCPS (Koehler *et al.*, 2022). The complex dynamics between viral tropism, activation of various immune cell compartments, and an imbalance of inflammatory mediators are the primary basis for the immunopathogenesis of these diseases (Hjelle and Torres-Pérez, 2010).

In the early stages of infection, the innate immune system is activated through the recognition of viral molecules by pattern recognition receptors (PRRs), such as Toll-Like Receptor 3 (TLR3), Toll-Like Receptor 7 (TLR7), and Retinoic acid-Inducible Gene I (RIG-I) type receptors (Ermonval *et al.*, 2016). Activation of this pathway triggers the synthesis of Interferon-alpha/Interferon-beta (IFN- α/β) and various proinflammatory cytokines, including Interleukin-1 beta (IL-1 β), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF- α) (Wang *et al.*, 2023a). However, some pathogenic hantaviruses, such as HTNV and ANDV, have been reported to suppress the interferon signaling pathway by modulating host proteins, thereby reducing the effectiveness of the antiviral state and allowing continued viral replication in endothelial cells (Mackow *et al.*, 2014).

The adaptive immune response develops in the later stages of infection through the activation of CD4⁺ T cells and CD8⁺ T cells (Liu *et al.*, 2021). Cytotoxic CD8⁺ T cells play a crucial role in viral clearance, but excessive activation has been shown to be associated with more severe tissue damage (Iglesias *et al.*, 2022). Increased lymphocyte infiltration in kidney tissue in HFRS and in the lungs of HCPS indicates that cytotoxic T cell-mediated injury contributes to increased vascular permeability (Saavedra *et al.*, 2021). This excessive T cell activation leads to the release of effector molecules such as granzymes and perforin and increased IFN- γ production, further exacerbating endothelial dysfunction (Braun *et al.*, 2014).

In addition to T cell involvement, B cells play a role in producing neutralizing antibodies, which are detectable from the first week of infection (Jonsson *et al.*, 2010). Immunoglobulin M (IgM) and Immunoglobulin

G (IgG) antibody levels often correlate with clinical improvement, although humoral responses alone are not always sufficient to prevent the progression of severe disease if cellular immune regulation is impaired (Elgh *et al.*, 1997). Under certain conditions, elevated antibody levels can also contribute to other immunopathological mechanisms, such as immune complex formation, particularly in the acute phase of HFRS (Jiang *et al.*, 2016).

Dysregulation of cytokine production, known as the cytokine storm, is one of the most prominent immunological characteristics of hantavirus infection (Khaiboullina *et al.*, 2017). Elevated concentrations of cytokines such as TNF- α , IL-6, Interleukin-8 (IL-8), and Vascular Endothelial Growth Factor (VEGF) have been reported to be closely associated with increased capillary permeability, a key pathophysiological mechanism in both hantavirus clinical syndromes (Spiropoulou and Srikiatkachorn, 2013). Abnormally elevated VEGF levels contribute to further endothelial dysfunction through disruption of tight junctions and stimulation of vascular leakage (Schönrich *et al.*, 2015). In HCPS, this cytokine surge triggers severe pulmonary edema, while in HFRS, it leads to impaired renal function and the appearance of hemorrhagic manifestations (Garanina *et al.*, 2019).

Pathology

Hantavirus infection causes characteristic pathological changes and varies according to the resulting clinical syndrome, namely Hantavirus Pulmonary Syndrome (HPS) in the Americas and HFRS in the Eurasian region (Bi *et al.*, 2008). Although the two syndromes display different clinical presentations, both are based on similar pathogenetic mechanisms, namely the involvement of vascular endothelial cells as targets of infection without direct cytolysis, which is then followed by an excessive immune response and leads to systemic capillary dysfunction (Mackow *et al.*, 2013).

In HPS, pathological changes are primarily localized to the lung tissue (Safronetz *et al.*, 2014). Endothelial cell infection triggers widespread increased capillary permeability, resulting in interstitial and alveolar edema, clinically manifested as acute respiratory failure (Llah *et al.*, 2018). Mononuclear cell infiltration, particularly CD8⁺ lymphocytes, is frequently observed around blood vessels, reflecting an overactivation of the cytotoxic immune response (Mocanu *et al.*, 2023). Histopathologically, the alveolar spaces are filled with fluid with a high protein content, hyaline membranes may form, and severe vascular congestion is evident (de Oliveira and Faccini-Martínez, 2020). Although alveolar epithelial damage is relatively minimal, severe endothelial dysfunction is a major factor in determining the severity of HPS (Spiropoulou and Srikiatkachorn, 2013).

In HFRS, pathological involvement primarily focuses on the kidneys. Initial changes are characterized by vascular congestion and interstitial edema, which then progress to acute tubular necrosis, particularly in the proximal tubule segments (Peters *et al.*, 1999). Renal blood vessels experience increased

permeability with focal hemorrhages, contributing to hematuria and proteinuria (Mir, 2022). In more severe cases, hemorrhagic diathesis involving multiple organs can occur, reflecting a systemic disruption of vascular homeostasis (Wang *et al.*, 2023b). At the molecular level, increased expression of proinflammatory cytokines, such as TNF- α , IL-6, and IFN- γ , plays a role in exacerbating tissue damage and increasing the risk of shock due to plasma leakage (Afzal *et al.*, 2023).

Clinical Manifestations

The clinical presentation of hantavirus infection varies widely, depending on the virus type and the geographic location of infection. In general, hantaviruses in humans cause two main syndromes: HFRS, which is primarily found in Asia and Europe, and HCPS/HPS, which is more frequently reported in the Americas. Although these two syndromes exhibit distinct clinical characteristics, they share a fundamental similarity: increased vascular permeability, which plays a central role in disease pathogenesis.

Clinical Features of HFRS

HFRS generally progresses through five clinical stages: the febrile phase, the hypotensive phase, the oliguric phase, the polyuric phase, and the convalescent phase (Zou *et al.*, 2016). In the initial stage, sufferers experience a sudden high fever accompanied by prodromal symptoms such as headache, back pain, myalgia, and gastrointestinal disturbances (Koehler *et al.*, 2022). Facial and conjunctival hyperemia are characteristic clinical findings, particularly in cases of infection caused by HTNV (Zhang *et al.*, 2022).

The hypotensive phase occurs as a consequence of increased vascular permeability and has the potential to progress to shock if not promptly treated (Afzal *et al.*, 2023). In the oliguric phase, impaired kidney function becomes apparent, characterized by reduced urine volume, heavy proteinuria, hematuria, and elevated serum creatinine levels (Mir, 2022). If the patient successfully survives this critical period, the polyuric phase follows as a sign of clinical improvement, with a significant increase in urine output as kidney function recovers (Koehler *et al.*, 2022). The convalescent phase can last from several weeks to several months (Afzal *et al.*, 2023). The HFRS fatality rate varies across virus species, ranging from less than 1% in PUUV infections to more than 10% in HTNV and DOBV (Bi *et al.*, 2008).

Clinical Features of HCPS

HCPS generally exhibits a more rapid onset and a more aggressive clinical course than HFRS (D'Souza and Patel, 2020). The disease begins with a prodromal phase resembling an influenza syndrome, including fever, malaise, myalgia, and gastrointestinal complaints (Matheus *et al.*, 2023). Within approximately 3–5 days, patients enter the cardiopulmonary phase, characterized by a nonproductive cough, tachypnea, worsening dyspnea, and severe hypoxemia (Arruda *et al.*, 2006).

Acute capillary leakage in the lung tissue triggers the formation of interstitial and alveolar pulmonary edema,

which rapidly progresses to acute respiratory failure (Singh *et al.*, 2014). In some patients, cardiac dysfunction, characterized by a decrease in left ventricular ejection fraction, may occur, thought to be related to the effects of systemic inflammation and compensatory hemodynamic responses to relative hypovolemia (López *et al.*, 2019). The fatality rate for HCPS is high, ranging from 30–40%, especially in cases that do not receive adequate ventilatory support and intensive care (Dheerasekara *et al.*, 2020).

Systemic Manifestations and Laboratory Findings

Both HFRS and HCPS are generally accompanied by changes in hematological and biochemical parameters reflecting impaired vascular homeostasis (Taylor *et al.*, 2025). Thrombocytopenia is the most consistent laboratory finding and can be detected early in the disease (Denecke *et al.*, 2010). Furthermore, an elevated hematocrit indicates hemoconcentration associated with systemic vascular leakage (Cheung *et al.*, 2021). Biomarker levels such as lactate dehydrogenase (LDH), C-reactive protein (CRP), and proinflammatory cytokines, including IL-6, often correlate with clinical disease severity (Outinen *et al.*, 2021).

In HFRS, the dominant laboratory findings include elevated serum creatinine and urea levels, accompanied by heavy proteinuria (Tkachenko *et al.*, 2025). In contrast, in HCPS, arterial blood gas analysis shows severe hypoxemia with an increased alveolar-arterial gradient, and the characteristic radiological finding of bilateral pulmonary edema (Hamid *et al.*, 2021).

Diagnosis

Establishing a diagnosis of hantavirus infection requires a multidisciplinary approach that combines clinical assessment, epidemiological history, laboratory test results, and virological detection methods (Mattar *et al.*, 2015). This is because the initial manifestations of the disease are nonspecific and often resemble other infections, such as leptospirosis, influenza, dengue, and atypical pneumonia (de Oliveira and Faccini-Martínez, 2020). Therefore, a correct diagnosis can only be achieved through the integration of a thorough clinical evaluation with specific laboratory confirmation (Mocanu *et al.*, 2023).

In the early stages of the disease, clinical suspicion of hantavirus infection is based on the presence of acute fever accompanied by myalgia, thrombocytopenia, and signs of capillary leak (Denecke *et al.*, 2010). In HFRS, clinical features include hematuria, proteinuria, elevated creatinine levels, and hypotension that progress through the stages of the disease: febrile, hypotensive, oliguria, diuresis, and recovery (Lu *et al.*, 2024). Conversely, in HPS/HCPS, rapid progression to noncardiogenic pulmonary edema and acute respiratory failure are crucial clinical indicators (Singh *et al.*, 2014). However, because these manifestations are nonspecific, virological confirmation is still necessary for a definitive diagnosis (Saavedra *et al.*, 2021).

Serological testing is the most widely used approach in clinical practice to diagnose hantavirus

infection (Yoshimatsu and Arikawa, 2014). Identification of IgM and IgG antibodies by Enzyme-Linked Immunosorbent Assay (ELISA), Indirect Immunofluorescence Assay (IFA), or Western blot allows detection of both ongoing infection and prior exposure (Vilibic-Cavlek *et al.*, 2021). IgM antibodies are generally detected in the early acute phase, while IgG levels increase during the convalescent phase (Clark *et al.*, 2026). However, differences in the timing of seroconversion between hantavirus species can affect test sensitivity, making the use of antigens that correspond to regional distribution—such as HTNV, PUUV, SNV, or ANDV—crucial to improve diagnostic accuracy (Lam *et al.*, 2001).

To improve diagnostic accuracy, particularly in the very early phase before an antibody response develops, the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) method is used to directly detect viral RNA (Seo *et al.*, 2021). This technique is extremely useful not only for confirming infection but also for determining viral genotypes, phylogenetic analysis, and case verification in the context of epidemiological investigations (Clement *et al.*, 2020). Hantavirus genotyping is most commonly performed by sequencing the small (S) segment of the viral genome, which encodes the nucleocapsid (N) protein, due to its conserved yet phylogenetically informative characteristics across hantavirus species (Filippone *et al.*, 2019). RT-PCR assays for hantavirus commonly target conserved regions of the S segment gene, which encodes the N protein, due to its high sequence conservation across hantavirus species and suitability for sensitive molecular detection (Mir and Panganiban, 2005). However, under certain conditions—particularly in rapidly progressing HPS infections—viremia levels can decrease while patients are receiving treatment, thus reducing the sensitivity of molecular detection (Hussein *et al.*, 2011).

In addition to serological and molecular approaches, additional methods such as immunohistochemistry (IHC) and in situ hybridization can be applied to tissue samples, particularly in fatal cases (Hama *et al.*, 2022). Detection of hantavirus antigen in lung or kidney tissue provides histopathological evidence of active infection, and these techniques are frequently used in outbreak investigations and postmortem studies (Madaei *et al.*, 2021).

Routine laboratory tests can provide early indications of hantavirus infection (Ekanayake *et al.*, 2025). In HFRS, common findings include thrombocytopenia, hemoconcentration, leukocytosis with a left shift, an elevated hematocrit, and impaired renal function (Lupuşoru *et al.*, 2021). Meanwhile, in HPS, typical laboratory findings include an elevated hematocrit due to plasma leakage, accompanied by severe hyponatremia and hypoxemia (Maleki *et al.*, 2019).

Epidemiological factors play a crucial role in strengthening diagnostic suspicion of hantavirus infection (Watson *et al.*, 2014). A history of contact with rodents, activities in rural or outdoor areas, occupations with high exposure risks—such as farming, warehouse work, or military personnel—and the geographic distribution of cases are helpful in

guiding the initial diagnostic assessment (Riccò *et al.*, 2021). Combining epidemiological information with serological and molecular test results has been shown to increase sensitivity and specificity in establishing a diagnosis (Whitmer *et al.*, 2024).

In public health, the development of genomic surveillance and innovative point-of-care methods based on isothermal amplification, such as loop-mediated isothermal amplification (LAMP), show significant potential for enhancing early detection, particularly in endemic areas with limited resources (Torres *et al.*, 2024). However, various challenges remain, including antigenic variation among hantavirus species, limited access to advanced diagnostic facilities, and the dependence of certain methods on patient seroconversion (Sanada *et al.*, 2012).

Differential Diagnosis

Differential diagnosis of hantavirus infections is a crucial component of clinical practice, given that early disease manifestations are often nonspecific and mimic a variety of other infections (Brorstad *et al.*, 2010). The clinical presentation of hantaviruses is strongly influenced by the viral genotype and the syndromes they cause: HFRS, which is predominant in Eurasia, and HCPS/HPS, which is primarily found in the Americas (de Oliveira *et al.*, 2014). Both syndromes have clinical stages that can overlap with various other disease conditions, therefore establishing a correct diagnosis requires the integration of clinical assessment, epidemiological data, and laboratory test results (Vial *et al.*, 2023). Table 2 summarizes the main differential diagnoses for the two hantavirus clinical syndromes, HFRS and HCPS/HPS, highlighting diseases that exhibit similar symptoms in both the early and late stages. Figure 2 compares the clinical manifestations of hantavirus infection, highlighting the distinct organ system involvement between HFRS and HCPS.

In HFRS, the initial manifestations of high fever, myalgia, headache, and gastrointestinal symptoms often resemble various other viral infections, including influenza, dengue, leptospirosis, and arenaviruses (Papa and Antoniadis, 2001). In later stages, the appearance of hematemesis, bleeding, and impaired renal function further complicate the diagnosis, as these clinical features can resemble severe leptospirosis (Weil's disease), bacterial sepsis, dengue hemorrhagic fever, or yellow fever (Sion *et al.*, 2002). Leptospirosis is the most frequently considered differential diagnosis, given that both diseases are characterized by fever, abdominal pain, thrombocytopenia, and acute renal failure (Khairullah *et al.*, 2024). Clinically, differentiation can be aided by the history of exposure—contact with rodents in hantaviruses versus exposure to contaminated water in leptospirosis—and differences in laboratory findings, such as hyperbilirubinemia, which is generally more prominent in leptospirosis (Bakelants *et al.*, 2020).

In HCPS/HPS, initial manifestations such as fever, malaise, mild cough, and myalgia often resemble influenza, COVID-19, or bacterial pneumonia (de Lemos *et al.*, 2022). Rapid progression to the cardiorespiratory phase, characterized by noncardiogenic pulmonary edema, severe hypoxemia, and circulatory shock, can produce a clinical picture resembling Acute Respiratory Distress Syndrome (ARDS) from various causes, including other hantavirus infections, avian influenza, severe adenovirus infections, and sepsis (Matthay *et al.*, 2019). Important differential diagnoses include Q fever, tularemia, and psittacosis, which can also present with atypical pneumonia (Cunha, 2006). COVID-19, particularly in the early phase of the pandemic, often presents a diagnostic challenge with HCPS because both conditions share the characteristics of fever, progressive dyspnea, and bilateral infiltrates on chest radiographs (Igi *et al.*, 2021).

Pathologically, hantavirus infection is characterized by systemic capillary leakage resulting from endothelial dysfunction, a characteristic that distinguishes it from many other viral infections (Outinen *et al.*, 2021). However, because similar characteristics can also be seen in severe dengue and sepsis, laboratory confirmation remains essential (Avšič-Županc *et al.*, 2019). Diagnostic techniques such as RT-PCR, IgM/IgG antibody detection using ELISA, and immunohistochemistry play a crucial role in distinguishing hantavirus from pathogens with similar manifestations (Ekanayake *et al.*, 2025). In endemic areas, the differential diagnosis should also include local zoonotic diseases, including scrub typhus, severe malaria, and various forms of hemorrhagic fever (Cleri *et al.*, 2006).

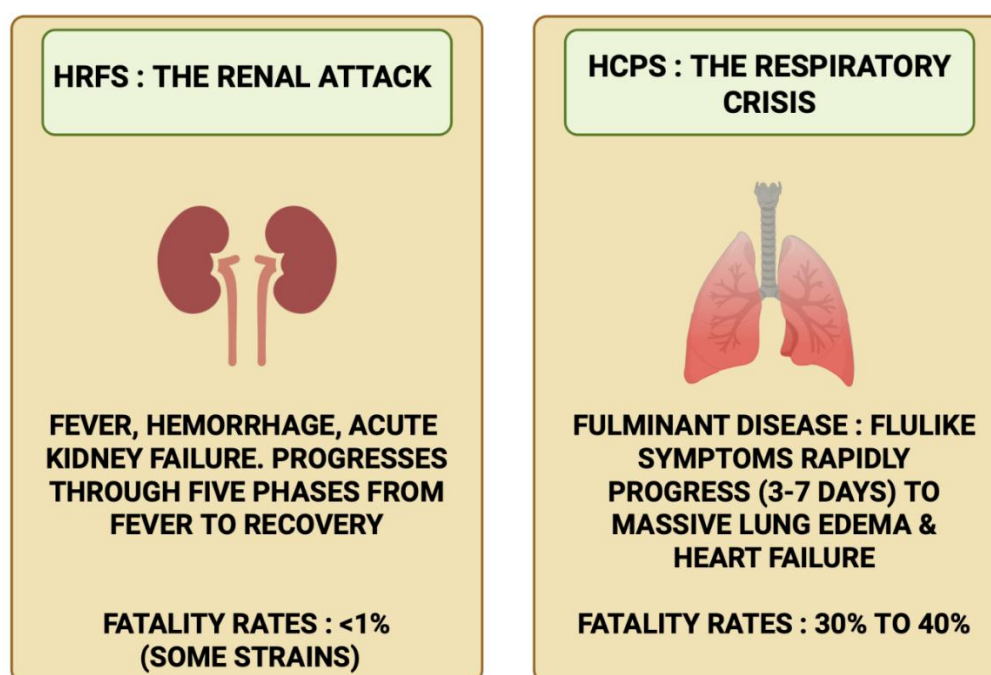


Figure 2 Comparative clinical manifestations of hantavirus infection: Renal-dominant HFRS versus respiratory-dominant HCPS. HCPS is characterized by rapid clinical deterioration, typically progressing to severe pulmonary edema and cardiopulmonary failure within approximately 3–7 days following the onset of the cardiopulmonary phase.

Transmission

The primary reservoir of hantaviruses consists of various rodent species, particularly those from the families Muridae and Cricetidae, which act as natural sources and sites for viral replication without causing clinical manifestations in their hosts (Yanagihara *et al.*, 2014). Each hantavirus is generally associated with a specific reservoir with which it has coevolved over a long period, resulting in a relatively stable relationship between the virus and its host (Kell, 2022). For example, Hantaan virus is closely associated with *Apodemus agrarius*, Seoul virus with *Rattus norvegicus* and *Rattus rattus*, Puumala virus with *Myodes glareolus*, and Sin Nombre virus with *Peromyscus maniculatus* (Schountz and Prescott, 2014). The strong association between viruses and their natural reservoirs reflects molecular adaptations that allow efficient viral replication without triggering an excessive inflammatory response in the host (Klimaj *et al.*, 2024).

Transmission of hantavirus from the reservoir to humans occurs primarily through inhalation of aerosols containing virus particles from the urine, feces, or saliva of infected rodents (Afzal *et al.*, 2023). The virus is known to persist in the environment, particularly in humid and low-temperature conditions, increasing the risk of human exposure, particularly in densely populated areas, storage facilities, agricultural areas, and rural environments (Riccò *et al.*, 2021). In addition to inhalation, transmission can also occur through direct contact with rodents or through contaminated open wounds, although these transmission routes are relatively rare (Ermonval *et al.*, 2016). In a small number of cases, such as Andes virus infections in South America, human-to-human transmission has been reported, although the exact mechanism remains incompletely understood.

Figure 3 illustrates the main transmission pathways and key risk factors of hantavirus infection.

The ecology of hantavirus transmission is strongly influenced by environmental conditions and the behavior of rodents as reservoirs (Guterres and de Lemos, 2018). Fluctuations in host animal populations can occur seasonally and are primarily influenced by food availability, climate factors, and habitat changes (Dearing and Dizney, 2010). Increased rainfall, climate phenomena such as the El Niño–Southern Oscillation (ENSO), and landscape modification due to urbanization have the potential to trigger rodent population surges, thereby increasing the risk of virus transmission to humans (Douglas *et al.*, 2021). Furthermore, changes in land use, including agricultural expansion and deforestation, increase the frequency of interactions between humans and rodent habitats, ultimately increasing the opportunities for zoonotic transmission (Rulli *et al.*, 2025).

The discovery of hantaviruses in shrews, moles, and bats in recent decades indicates that the hantavirus reservoir is likely much more diverse than previously understood (Bennett *et al.*, 2014). Although most of the hantaviruses identified in these non-rodent species have not been proven to be zoonotic, their presence reinforces the notion that hantaviruses have a long and complex evolutionary history and suggests the potential for new strains to emerge through spillover or host switching (Mir, 2010).

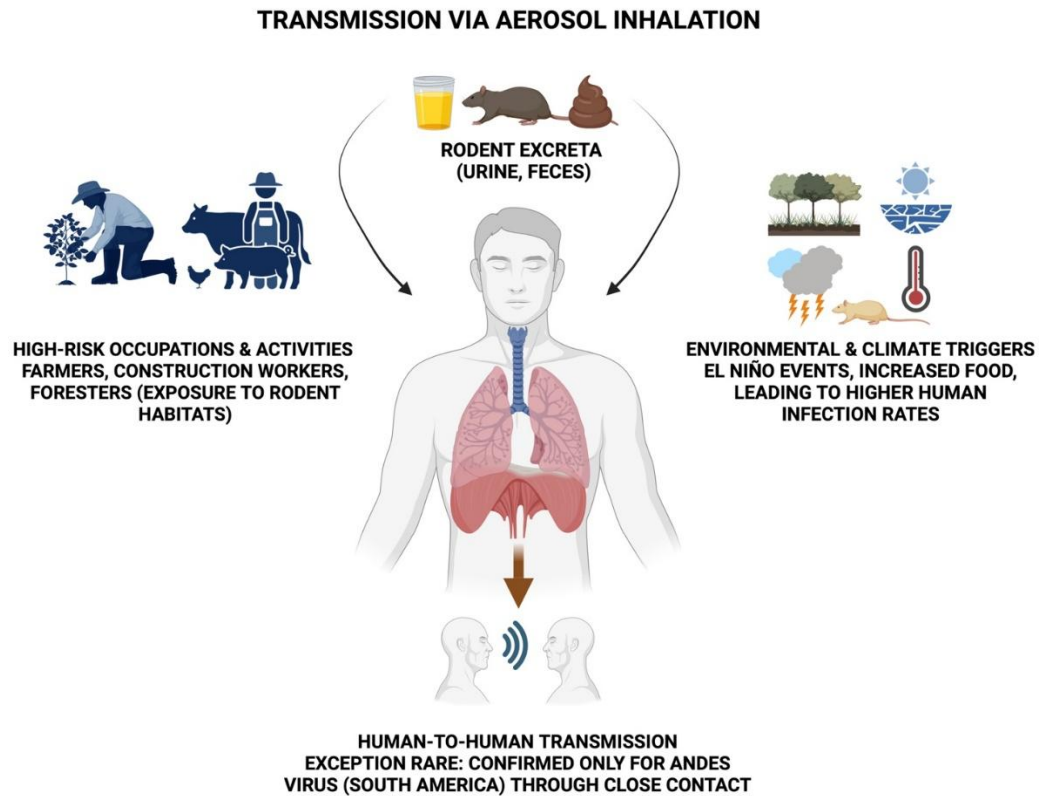


Figure 3 Transmission pathways and risk factors of hantavirus infection: aerosol exposure from rodent excreta and rare human-to-human spread.

Table 2 Clinical differential diagnosis of hantavirus based on HFRS and HCPS syndromes.

Syndrome	Differential diagnosis diseases	Main clinical similarities	Key clinical / Laboratory differences
Hemorrhagic Fever with Renal Syndrome (HFRS)	Influenza	Fever, myalgia, and malaise	No bleeding phase or renal failure; milder disease course
	Dengue / Dengue Hemorrhagic Fever	High fever, thrombocytopenia, and bleeding	Renal manifestations are more prominent in HFRS; dengue shows more pronounced leukopenia and hemoconcentration
	Leptospirosis (Weil's disease)	Fever, myalgia, renal failure, and bleeding	Severe hyperbilirubinemia in leptospirosis; history of exposure to contaminated water vs rodents
	Yellow fever	Fever, bleeding, and organ disorders	Jaundice is more prevalent in yellow fever; geographic distribution differs
	Bacterial sepsis	Fever, shock, and intravascular coagulation	Positive bacterial culture; no biphasic clinical phase like HFRS
	Arenavirus (e.g. Lassa fever)	Hemorrhagic fever and bleeding	Transmission via African rats; neurological symptoms more frequent
	Influenza	Fever, mild cough, and myalgia	Rapid progression to pulmonary edema is not seen in influenza
	COVID-19	Fever, dyspnea, and bilateral pulmonary infiltrates	COVID-19 has a slower progression phase; SARS-CoV-2 PCR is positive
	Bacterial pneumonia	Fever, cough, and difficulty breathing	Leukocytosis and response to antibiotics; lobar infiltrates are more typical
	Avian influenza	Severe pneumonia and ARDS	History of poultry exposure; positive influenza A/H5 or H7 PCR
Hantavirus Cardiopulmonary Syndrome (HCPS/HPS)	Severe adenovirus	Fever, ARDS, and respiratory failure	More common in children/immunocompromised; positive adenovirus PCR
	Q-fever	Atypical fever and pneumonia	The liver is often involved (hepatitis); <i>Coxiella burnetii</i> serology is positive.
	Tularemia	Pneumonia, fever, and ulcerative lesions	History of rabbit / arthropod exposure; <i>F. tularensis</i> culture
	Psittacosis	Atypical pneumonia	Bird exposure history; <i>Chlamydia psittaci</i> serology

Table 3 Major risk factors for hantavirus infection in humans

Risk factor category	Description	Examples / Key details
Environmental exposure	The most significant risk factor, related to contact with rodent excreta in their natural habitat	Activities in forests, agricultural fields, unmaintained houses, storage warehouses; inhalation of rodent urine/feces aerosols
High-risk occupations	Jobs that increase frequency of exposure to rodents or contaminated environments	Farmers, forestry workers, military personnel, construction workers, laboratory researchers, wilderness explorers
Recreational activities	Outdoor activities that place individuals in rodent habitats	Hiking, camping, cleaning cabins/warehouses, remote outdoor activities
Geographical and rodent ecology variation	Risk depends on local reservoir and distribution of rodent species carrying the virus	Asia/Europe: <i>Apodemus</i> , <i>Myodes</i> → HFRS; Americas: <i>Peromyscus</i> , <i>Oligoryzomys</i> → HCPS; Urban areas: <i>Rattus norvegicus</i> , <i>Rattus rattus</i> → SEOV
Seasonal fluctuations and climatic events	Rodent populations increase under certain conditions, raising exposure risk	Harvest season, rainy season, and El Niño events that boost rainfall and rodent population growth
Human-made environmental conditions	Rapid urbanization and poor sanitation increase human proximity to commensal rodents	Densely populated settlements, substandard housing, poor ventilation, low sanitation; global risk of Seoul virus spread
Risky behaviors	Human activities that trigger contact with rodent excreta without adequate protection	Cleaning old warehouses without PPE, storing food uncovered, handling contaminated feed or waste
Individual susceptibility (host factors)	Host factors influence clinical outcomes but do not always increase infection risk	Adult males more frequently exposed due to outdoor occupations; low immunity or comorbidities worsen clinical severity

Risk Factors

The risk of hantavirus infection is determined by the complex interactions between humans, environmental conditions, and the ecology of rodents, the primary reservoirs of the virus (Tian and Stenseth, 2019). Since hantaviruses are generally not transmitted through human-to-human contact—except in Andes virus infections—the level of exposure depends primarily on the intensity and frequency of an individual's contact with aerosols or excretions of infected rodents (Toledo *et al.*, 2022). Therefore, a comprehensive understanding of these risk factors is crucial for prevention efforts, identifying vulnerable population groups, and formulating effective public health strategies (Garcia *et al.*, 2025). Table 3 presents a summary of the major risk factors contributing to hantavirus infection as a rodent-based zoonosis.

Environmental exposure is the most dominant risk factor for hantavirus infection (Tian and Stenseth, 2019). Activities that increase contact with urine, feces, saliva, or rodent nests are directly correlated with an increased likelihood of infection (de Oliveira *et al.*, 2014). Individuals working in rural areas, forested areas, storage facilities, agricultural land, and poorly maintained dwellings have higher exposure rates (Garcia *et al.*, 2025). Furthermore, certain occupations—such as farmers, forestry workers, construction workers, explorers, military personnel, and laboratory workers—face a greater risk due to repeated exposure to rodent-infested areas (Ricco *et al.*, 2021). Recreational activities, including hiking, camping, and cleaning out sheds or cabins in remote areas, have also been reported as important triggers in various epidemiological studies (Gorris *et al.*, 2025).

Risk factors for hantavirus infection are also significantly influenced by geographic differences (Afzal *et al.*, 2023). In Asia and Europe, the presence and infestation of rodents from the genera *Apodemus* and *Myodes* are closely associated with increased incidence of HFRS, while in the Americas, *Peromyscus* and *Oligoryzomys* species serve as the primary

reservoirs of hantaviruses that cause HCPS (de Oliveira *et al.*, 2014). Seasonally fluctuating rodent population dynamics—particularly during harvest seasons or periods of high rainfall that increase food availability—are often accompanied by increased numbers of human cases (Clement *et al.*, 2009). Furthermore, global climate phenomena such as El Niño can accelerate rodent population growth through increased rainfall, indirectly increasing the potential for virus transmission to the human population (Ferro *et al.*, 2024).

The environment resulting from human activities also contributes as a significant risk factor for hantavirus transmission (Gorris *et al.*, 2025). Rapid and poorly planned urbanization in several developing countries has led to the expansion of commensal rodent habitats, such as *Rattus norvegicus* and *Rattus rattus*, into high-density residential areas (Guillebaud *et al.*, 2026). This situation increases the opportunity for the spread of Seoul virus (SEOV), which has the potential to infect humans even in previously non-endemic areas (Kang *et al.*, 2021). Furthermore, poor housing quality, inadequate ventilation systems, and poor environmental sanitation further increase the likelihood of virus exposure (Gorris *et al.*, 2025).

Human behavior is also a significant determinant of the risk of hantavirus infection (Guterres and de Lemos, 2018). Activities such as cleaning long-unused rooms or buildings without adequate protective equipment, handling contaminated feed or waste, and storing food in the open can increase the likelihood of exposure to rodent excretions (de St Maurice *et al.*, 2017). Several studies have shown that improperly stored food in homes, warehouses, or barns is a major predisposing factor to infection (de Oliveira *et al.*, 2014; Mocanu *et al.*, 2023).

In addition to environmental and behavioral factors, individual characteristics also contribute to risk levels (Gorris *et al.*, 2025). Although hantavirus infection can occur in all age groups, the highest incidence is generally found in adult males, thought to be related to occupational exposure and more intense

outdoor activities (Jonsson *et al.*, 2010). Host factors such as immune status, nutritional status, and the presence of certain comorbidities play a role in complicating the course and clinical outcome, although they have not been proven to directly increase susceptibility to infection (Vaheri *et al.*, 2023).

Treatment

To date, there are no specific antiviral agents consistently proven effective in the management of hantavirus infections in humans (Vial *et al.*, 2023). Therefore, clinical management still focuses on supportive therapy, which includes hemodynamic stabilization, management of respiratory and renal dysfunction, and prevention of complications related to systemic capillary leak (Koehler *et al.*, 2022). Nevertheless, various therapeutic candidates have been studied in both experimental and clinical trials, although the results have shown varying degrees of effectiveness (Taylor *et al.*, 2025).

In HPS, management primarily relies on intensive supportive care in a critical care unit (Ulloa-Morrison *et al.*, 2024). Patients typically enter an acute cardiopulmonary phase characterized by noncardiogenic pulmonary edema and rapidly progressing respiratory failure (Taylor *et al.*, 2025). Therefore, primary interventions include mechanical ventilation, positive end-expiratory pressure (PEEP) to maintain adequate oxygenation, and continuous hemodynamic monitoring (Bugedo *et al.*, 2016). In some referral centers, the use of extracorporeal membrane oxygenation (ECMO) has been reported to reduce mortality in severe HPS cases, particularly when performed in the early stages of respiratory failure refractory to conventional therapy (Crowley *et al.*, 1998).

In HFRS, management focuses on controlling hemodynamic and renal dysfunction resulting from capillary leakage and acute tubular necrosis (Mir, 2022). Controlled fluid administration, correction of electrolyte imbalances, monitoring of renal function parameters, and hemodialysis in cases of acute renal failure have been shown to contribute to improved clinical outcomes (Aker *et al.*, 2000). During the oliguric phase, fluid restriction is crucial to prevent complications such as pulmonary edema and fluid overload (Avšič-Županc *et al.*, 2019). Although the mortality rate in HFRS is relatively lower than in HPS, successful recovery remains highly dependent on the implementation of adequate and optimal supportive therapy (Dheerasekara *et al.*, 2020).

Pharmacologically, ribavirin—a nucleoside analog with broad-spectrum antiviral activity—is the most extensively studied agent (Beaucourt and Vignuzzi, 2014). Several clinical trials in HFRS cases caused by Hantavirus infection have reported that intravenous ribavirin can reduce disease severity and mortality, particularly when administered early in the viremic phase (Moreli *et al.*, 2014). Conversely, the benefits of ribavirin in HPS have been reported to be limited or inconsistent (Ogg *et al.*, 2013). Therefore, the use of ribavirin remains controversial, given the differences in virulence levels among hantavirus species, the heterogeneity of clinical study designs, and the

potential for serious side effects such as hemolytic anemia (Mayor *et al.*, 2021).

In addition to ribavirin, several innovative therapeutic candidates are still in development, including neutralizing monoclonal antibodies, inhibitors of viral entry into host cells, and immunomodulatory agents aimed at correcting endothelial dysfunction (Graci and Cameron, 2006). Preclinical studies in animal models have shown promising potential, particularly for neutralizing antibodies targeting the Gn and Gc envelope glycoproteins (Duehr *et al.*, 2020). However, to date, no immunological therapies have successfully reached advanced clinical trials. Efforts to develop vaccines and prophylactic strategies are ongoing, but they are not yet widely available for clinical application (Afzal *et al.*, 2023).

Vaccination

Hantavirus vaccine development has long been a major focus of global research, primarily due to the high mortality rate associated with HPS and the significant public health burden posed by HFRS (Chai *et al.*, 2025). However, no hantavirus vaccine has received widespread international recognition and use, and the effectiveness of those that have been developed remains limited to specific geographic contexts (Bae *et al.*, 2021).

Hantavirus vaccination initiatives were first developed in East Asia, particularly in South Korea and China, regions with high HFRS incidence (Yi *et al.*, 2018). Inactivated vaccines derived from the HTNV and SEOV strains have been used since the late 1980s (Clement *et al.*, 2019). These vaccines are inactivated whole-virus vaccines and are administered through multiple booster doses (Liu *et al.*, 2020). Epidemiological studies have shown that these vaccines significantly reduce the incidence of HFRS in high-risk groups, such as rural communities and military personnel (Yi *et al.*, 2018). However, their effectiveness is not uniform, and the resulting immune response tends to be transient, necessitating periodic boosters (Saavedra *et al.*, 2021).

From an immunological perspective, hantavirus vaccines are designed to induce the formation of neutralizing antibodies targeting the envelope glycoproteins Gn and Gc, which play a crucial role in the virus's entry into host cells (Serris *et al.*, 2020). The development of next-generation vaccines is now focused on platforms considered safer and more immunogenic, such as Deoxyribonucleic Acid (DNA) vaccines, subunit vaccines, viral vector-based vaccines, and Messenger Ribonucleic Acid (mRNA) vaccine technology, which has attracted widespread attention due to its success in other infectious diseases (Brisse *et al.*, 2020). DNA vaccines expressing hantavirus glycoproteins have been shown to stimulate antibody and T-cell responses in animal models, but early clinical trials have shown moderate immunogenicity, necessitating further optimization efforts (Hooper *et al.*, 2024).

In the Americas, particularly in areas where HPS is endemic, vaccine development strategies face additional challenges (Hjelle and Torres-Pérez, 2010).

Hantaviruses circulating in this region, such as SNV and ANDV, have significant genetic and antigenic differences compared to Eurasian hantaviruses, so vaccines developed and used in Asia do not provide effective protection against HPS (Manigold and Vial, 2014). Furthermore, the rapid clinical course of HPS demands a vaccine capable of eliciting robust and long-lasting protective immunity before exposure (Kwilas *et al.*, 2014). Current approaches in HPS vaccine research include the development of neutralizing monoclonal antibodies targeting the conserved Gn/Gc epitopes, as well as mRNA-based vaccine platforms that have been shown to induce robust immune responses in preclinical studies (Chai *et al.*, 2025).

One of the main obstacles to hantavirus vaccine development is the high diversity of viral species and reservoirs, coupled with wide geographic variation (Madrères *et al.*, 2019). Unlike viruses, which have a few dominant strains, hantaviruses consist of numerous species-specific variants, making a "universal" vaccine strategy difficult to implement (Wang *et al.*, 2023c). Furthermore, clinical trials are often hampered by the low number of annual cases in some regions, limiting evaluation of vaccine effectiveness on a population scale (Tscherne *et al.*, 2025).

Although several vaccine candidates have shown promising results in experimental research, no hantavirus vaccine has yet received global approval from the World Health Organization (WHO) or other international health authorities (Chai *et al.*, 2025). The success of future vaccine development will likely depend on the adoption of new technologies that address hantavirus antigenic diversity, stimulate long-term immunity, and provide cross-species protection (Aram *et al.*, 2025). The combination of genomic technologies, reverse vaccinology, and modern vaccine platforms presents an opportunity to accelerate the development of more effective and widely applicable hantavirus vaccines (Bae, 2019).

Control

Efforts to prevent and control hantavirus infections require a multidisciplinary strategy that combines environmental interventions, behavioral changes, and epidemiological surveillance systems (Shehata *et al.*, 2025). Because there are no specific antiviral therapies or vaccines widely accessible to humans, a preventative approach is crucial to reducing the risk of transmission (Avšič-Županc *et al.*, 2019). Given that hantaviruses are zoonotic and closely linked to the population dynamics of rodents as their natural reservoir, vector control and limiting human contact with these animals are a key focus of public health strategies (D'Souza and Patel, 2020).

Prevention strategies begin with environmental management aimed at reducing human contact with rodents (Childs *et al.*, 1993). These measures include controlling rodent populations through good sanitation practices, eliminating food sources, sealing gaps in buildings, and maintaining the cleanliness of food storage areas (Garcia *et al.*, 2025). In rural or endemic areas, educating the public about the risks of activities that increase exposure—such as cleaning

warehouses or barns without protection—is crucial (Watson *et al.*, 2014). Safe cleaning procedures for potentially contaminated areas should be implemented, for example, by pre-moistening surfaces to prevent aerosolization of infectious particles (Dheersekara *et al.*, 2020).

At the population level, rodent surveillance and environmental monitoring play a crucial role in detecting increased zoonotic risks (Carvalho *et al.*, 2025). Changes in the abundance of animal reservoirs, particularly during periods of food abundance or specific climatic conditions, can drive increased incidences of human infection (Guterres and de Lemos, 2018). Therefore, integrating ecological, climatic, and epidemiological data is a crucial strategy for predicting and preventing outbreaks (Jonsson *et al.*, 2010). Furthermore, genomics-based surveillance programs are increasingly important for identifying new hantavirus variants and understanding their transmission patterns (Kim *et al.*, 2021).

Individual-level prevention focuses on personal protection through the use of personal protective equipment (PPE), such as particulate masks, gloves, and protective clothing, especially for groups of workers at high risk of exposure, such as farmers, warehouse staff, and laboratory personnel (Artika and Ma'roef, 2017). Implementing biosafety practices in Biosafety Level 2 (BSL-2) and Biosafety Level 3 (BSL-3) laboratories is also crucial to preventing nosocomial infections, given that hantavirus can be transmitted through accidentally generated aerosols (Tang *et al.*, 2024).

Although there is currently no widely available hantavirus vaccine for humans, research on DNA-based vaccine candidates, inactivated virus vaccines, and recombinant platforms is ongoing (Chai *et al.*, 2025). In China and South Korea, several inactivated vaccines have been implemented on a limited basis for Hantaan virus and Seoul virus, respectively, but their long-term efficacy and potential for global use require further evaluation (Liu *et al.*, 2020). In addition to vaccine development, research into molecules that target endothelial stability or inhibit virus-receptor interactions is also an important direction for future prevention strategies (Mittler *et al.*, 2019).

From a policy perspective, a One Health approach is a crucial foundation for long-term control efforts (Ghosal *et al.*, 2024). Because hantaviruses are closely linked to interactions between humans, animals, and the environment, intersectoral collaboration—including public health, agriculture, ecology, and meteorology—is essential to support early detection, risk mitigation, and rapid response to potential outbreaks (Gorris *et al.*, 2025).

Challenges and Future Directions

Hantavirus research faces numerous challenges that limit a comprehensive understanding of transmission dynamics, pathogenesis, and disease control strategies (Mittler *et al.*, 2019). One major obstacle is the complexity of reservoir ecology (Tian and Stenseth, 2019). Each hantavirus species is typically associated with specific rodents, but environmental changes, urbanization, and ecosystem

shifts due to climate change can alter reservoir distribution and open up opportunities for new spillovers (Shehata *et al.*, 2025). Therefore, future research should focus on ecological modeling and genomics-based surveillance to predict reservoir movement and the potential emergence of new variants (Glass, 2023).

From a virological perspective, understanding of the molecular mechanisms of hantavirus pathogenesis remains limited, particularly regarding how the interaction between the virus and endothelial cells and the excessive immune response leads to capillary leakage (Hepojoki *et al.*, 2014). Further research is needed to identify potential molecular targets as a basis for developing effective antiviral therapies, given that current treatment remains supportive (Afzal *et al.*, 2023). Structural biology approaches, such as cryo-electron microscopy and analysis of protein-virus interactions, are expected to provide deeper insights into the virus's strategies for evading the immune response (Meier *et al.*, 2021).

In the diagnostic field, the biggest challenge is detecting infection at an early stage when symptoms are still non-specific and mimic other diseases (Krüger *et al.*, 2001). Therefore, the development of biomarker-based rapid diagnostic methods or point-of-care platforms is a priority to ensure optimal clinical management (Ekanayake *et al.*, 2025). Furthermore, integrated molecular surveillance in endemic areas remains crucial to monitor viral genetic changes, particularly in strains with the potential for human-to-human transmission, such as Andes virus (Toledo *et al.*, 2022).

Hantavirus vaccine development remains hampered by several factors, including antigenic differences between species, limited data from clinical trials, and limited vaccine use outside East Asia (Krüger *et al.*, 2011). Future research should focus on evaluating newer generations of vaccines, such as those based on recombinant viral vectors or mRNA platforms, which have the potential to provide broader protection against multiple hantavirus strains (Aram *et al.*, 2025).

In conclusion, Hantaviruses are RNA zoonotic pathogens with a highly specific ecological relationship to rodent reservoirs. Their geographic distribution and epidemiological patterns are therefore strongly influenced by the interactions between the virus, the host, humans, and the environment. Human infection can lead to two serious clinical syndromes, HFRS and HCPS, with high morbidity and mortality and marked regional variations. Transmission occurs primarily through inhalation of aerosols from rodent excretions, and the risk of infection increases with changing environmental and climatic conditions. Limitations in early detection and the complexity of risk factors make hantaviruses a continuing public health challenge. Therefore, an integrated One Health approach—encompassing an understanding of virology, reservoir ecology, epidemiological dynamics, and environmental factors—is essential to strengthen global hantavirus surveillance, prevention, and control.

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