



Hantavirus Infection as an Emerging Global Zoonotic Threat: From Molecular Basis to Clinical Management and Public Health Perspectives

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Abstract

Hantavirus infection is a rodent-associated zoonosis caused predominantly by members of the genus Orthohantavirus and characterized by substantial geographic, ecological, and clinical heterogeneity. Human disease ranges from nonspecific febrile illness to two severe syndromic presentations: hemorrhagic fever with renal syndrome (HFRS), reported mainly in Europe and Asia, and hantavirus pulmonary or cardiopulmonary syndrome (HPS/HCPS), reported mainly in the Americas. Disease severity is driven by the interaction of viral factors, endothelial dysfunction, altered vascular permeability, platelet abnormalities, and coordinated innate and adaptive immune responses rather than by extensive direct cytolysis alone. This review integrates current knowledge of hantavirus taxonomy, genome organization, reservoir ecology, transmission, global epidemiology, molecular pathogenesis, clinical progression, laboratory diagnosis, supportive and antiviral management, prevention, vaccine development, and emerging surveillance approaches. Particular attention is given to the 2026 Andes hantavirus cluster associated with the MV Hondius expedition cruise, which demonstrated limited secondary person-to-person transmission and the importance of international contact tracing. Advances in molecular surveillance, genomics, rapid diagnostics, immunotherapeutic strategies, and One Health preparedness are discussed alongside persistent barriers, including restricted therapeutic options, limited cross-protective vaccines, diagnostic delays, and ecological unpredictability. An integrated prevention and response framework that connects rodent ecology, clinical recognition, laboratory capacity, intensive care, and public-health surveillance remains essential for reducing hantavirus-associated morbidity and mortality.

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1. Introduction

Hantavirus infection is a zoonotic disease associated primarily with small mammals and remains an important cause of severe acute febrile illness in regions where pathogenic orthohantaviruses circulate. Human infection is usually acquired through contact with an infected reservoir host or through inhalation of virus-containing material generated from rodent urine, feces, saliva, or nesting material. The epidemiology is highly focal because individual viral lineages are often maintained within particular reservoir species, and human risk therefore changes with habitat, rodent density, occupational exposure, seasonality, land use, and human behavior. The two major clinical syndromes are hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary or cardiopulmonary syndrome (HPS/HPCPS), which differ in the dominant organs involved but share important pathophysiological features centered on vascular permeability and dysregulated host responses [1].

The modern understanding of hantavirus disease has evolved from outbreak recognition to molecular epidemiology and systems-level surveillance. The discovery of Hantaan virus in the late twentieth century established the rodent reservoir connection, while the 1993 outbreak in the southwestern United States and identification of Sin Nombre virus established HPS as a distinct severe clinical entity in the Americas. Subsequent studies demonstrated extensive viral and ecological diversity, including the ability of Andes virus to undergo limited person-to-person transmission under conditions of close and prolonged exposure. Current taxonomy places the mammalian human-pathogenic viruses within the family Hantaviridae, subfamily Mammantavirinae, and genus Orthohantavirus, reflecting a broader understanding of hantavirid diversity than the older classification systems used in many clinical reviews [2].

Despite improved laboratory diagnostics and supportive critical care, hantavirus infection remains difficult to manage because the clinical deterioration of severe disease can be rapid and no globally licensed curative antiviral therapy is available. This review therefore examines the disease as an integrated ecological, virological, clinical, and public-health problem. Particular emphasis is placed on mechanisms that connect viral entry and replication with endothelial dysfunction, organ-specific syndromes, diagnostic decision-making, treatment limitations, vaccine development, and the growing importance of genomic and One Health surveillance [3].

2. Historical Background and Discovery

2.1 Early Recognition and the Korean Hemorrhagic Fever Era

The clinical syndrome now recognized as HFRS drew major international attention during the Korean War, when thousands of United Nations soldiers developed an acute febrile illness accompanied by renal dysfunction, hemorrhagic manifestations, hypotension, and shock [4]. The disease was initially described as Korean hemorrhagic fever, and the geographic association with the Hantaan River became an important clue to its natural history. Although the outbreak produced a strong epidemiological signal, the etiological agent remained elusive for decades because the disease was associated with an environmentally acquired infection that did not fit the conventional models of human-to-human viral transmission [5].

A decisive breakthrough came in 1978 when Ho-Wang Lee and colleagues isolated the etiological virus from the striped field mouse, *Apodemus agrarius*, in the region of the Hantaan River. This finding established a durable link between pathogenic hantaviruses and persistent infection in rodent hosts and created the basis for ecological surveillance. The discovery also clarified why human disease was geographically patterned and why rodent abundance, habitat disturbance, and occupational exposure could alter risk without requiring sustained transmission between people [6].

2.2 Expansion of Hantavirus Discovery and Classification

Following the identification of Hantaan virus, related viruses were recognized in multiple regions and linked to distinct reservoir hosts. Seoul virus was associated with commensal rats and demonstrated a distribution compatible with urban exposure, whereas Puumala virus became closely associated with nephropathia epidemica, a comparatively milder form of HFRS in northern and central Europe. Dobrava-associated disease was recognized as another severe HFRS phenotype in parts of southeastern Europe. The expanding catalogue showed that hantavirus ecology is structured by host-virus relationships rather than by geography alone [7].

The current taxonomic framework further reflects this diversity. ICTV classifies Hantaviridae within the class Bunyaviricetes and order Elliovirales; mammalian hantaviruses are distributed across several genera, while human disease is associated with Orthohantavirus. The genome architecture is conserved across the family, but viral sequence

variation, glycoprotein properties, reservoir adaptation, and host-response differences contribute to species-specific ecological and clinical phenotypes. This modern classification is important because older descriptions based only on a few rodent-borne viruses can underestimate the breadth of hantavirid diversity [8].

2.3 Emergence of Hantavirus Pulmonary Syndrome

In 1993, an outbreak in the Four Corners region of the United States was characterized by rapidly progressive respiratory failure in previously healthy individuals. Investigation identified a previously unrecognized hantavirus that was subsequently named Sin Nombre virus and traced to the deer mouse, *Peromyscus maniculatus*. The event established HPS as a severe pulmonary syndrome distinct from the renal-predominant disease recognized in Eurasia. It also demonstrated the value of integrating clinical observation, epidemiology, molecular virology, and wildlife investigation during an unexplained outbreak [9].

The discovery of Andes virus and subsequent South American outbreaks provided additional insight into hantavirus transmission. Unlike most pathogenic hantaviruses, Andes virus has repeatedly been associated with limited human-to-human transmission among close contacts. This phenotype does not represent sustained community transmission; rather, it highlights a specific transmission capability that becomes epidemiologically relevant when close contact occurs during the period of high clinical infectivity [10].

2.4 Hantavirus in the Twenty-First Century

Twenty-first-century hantavirus surveillance increasingly recognizes that emergence is shaped by interactions among ecological change, host population dynamics, climate variability, land-use change, mobility, and diagnostic capacity. Urbanization may increase contact with commensal rodents, while deforestation and agricultural expansion can alter wildlife interfaces. Climate-related changes can influence rodent population abundance and movement in some ecosystems, but the relationship is nonlinear and depends on local precipitation, food availability, predator dynamics, and habitat structure. Consequently, environmental change should be viewed as a set of modifiers of transmission opportunity rather than as a single causal driver [11].

A particularly instructive recent event occurred in 2026 in association with the MV Hondius expedition cruise. The outbreak was identified after severe respiratory illness among passengers and crew and

was attributed to Andes virus. By 2 July 2026, WHO reported 13 linked cases, including 12 laboratory-confirmed cases and one probable case, with three deaths. All identified cases were among people who had travelled on the vessel. The investigation supported a point-source introduction followed by limited secondary person-to-person transmission, and WHO reported that the outbreak was contained with no further related transmission expected. The event illustrates how a pathogen that ordinarily depends on zoonotic exposure can create a short-lived international public-health challenge when infected individuals enter a confined travel setting [12].

3. Virology and Molecular Characteristics

3.1 Taxonomy and Virion Architecture

Hantaviridae is a diverse family of enveloped negative-sense RNA viruses. The current ICTV framework places the family in the realm Riboviria, kingdom Orthornavirae, phylum Negarnaviricota, class Bunyaviricetes, and order Elliovirales. Mammalian hantavirids occur in several genera, but the human pathogenic viruses currently recognized belong to Orthohantavirus. The virion is generally pleomorphic and approximately 80–160 nm in diameter, with an envelope containing the Gn and Gc glycoproteins arranged as surface spikes. These glycoproteins mediate attachment, entry, and important antigenic interactions with the host immune system [13].

The association of specific orthohantaviruses with particular rodent or other small-mammal reservoirs is a defining ecological feature. Reservoir infection is generally persistent and clinically inapparent, suggesting long-term host adaptation. In humans, however, the outcome can range from mild or nonspecific illness to rapidly progressive HFRS or HCPS. The disconnect between apparently benign reservoir infection and severe human disease emphasizes that pathogenicity depends on both viral properties and the context of spillover into an immunologically different host [14].

3.2 Genome Organization and Viral Proteins

Orthohantaviruses possess a tripartite, negative-sense RNA genome comprising small (S), medium (M), and large (L) segments. The S segment encodes the nucleocapsid protein, which binds genomic RNA and participates in ribonucleoprotein organization and replication. The M segment encodes a glycoprotein precursor that is processed into Gn and Gc, the principal envelope proteins. The L segment encodes the viral RNA-dependent RNA polymerase, which carries out transcription and replication of the segmented genome. Viral mRNAs are capped but not polyadenylated, and cap-snatching from host cellular mRNAs contributes to efficient transcription [15].

The tripartite architecture is biologically consequential because replication depends on coordinated packaging and synthesis of three distinct RNA segments. Segment reassortment and sequence variation can alter viral phenotype and complicate molecular surveillance. At the same time, conserved structural and enzymatic functions provide targets for diagnostic assay design, antibody development, antiviral screening, and vaccine engineering. Understanding the relationships among N, Gn/Gc, and polymerase functions therefore remains central to translating virological knowledge into clinical and public-health applications [16].

3.3 Viral Entry, Replication, and Cellular Tropism

Hantavirus attachment and entry involve interactions between viral glycoproteins and host-cell receptors, with beta-3 integrins representing an important component of the receptor biology described for pathogenic hantaviruses. Endothelial cells are a major cellular target, yet infection of these cells does not typically produce the extensive direct cytolysis that characterizes some other viral diseases. Instead, hantavirus replication occurs in the setting of altered endothelial signaling, cytoskeletal regulation, junctional integrity, platelet interactions, and inflammatory mediator release. This helps explain why dramatic vascular leakage can coexist with relatively limited structural destruction of the endothelial monolayer [17].

After entry, the negative-sense RNA genome must be transcribed by the viral polymerase before viral proteins can be produced. Newly synthesized ribonucleoprotein complexes and glycoproteins are assembled through coordinated intracellular trafficking, followed by budding and release of progeny virions. The precise contribution of individual host pathways to severe disease continues to be investigated, but current models emphasize that pathogenicity emerges from the combination of viral replication, host-cell signaling, complement and coagulation pathways, platelet-endothelial interactions, and innate and adaptive immune responses [18].

4. Reservoirs and Transmission

4.1 Reservoir Ecology

Rodents constitute the principal reservoir hosts for the orthohantaviruses that cause human disease, with many viral lineages showing a close association with particular host species. Examples include *Apodemus* species for Hantaan virus, *Rattus* species for Seoul virus, bank voles for Puumala virus, and *Peromyscus maniculatus* for Sin Nombre virus. Andes virus is associated with sigmodontine rodents in South

America. Reservoir specificity helps shape geographic distribution and also means that changes in host abundance or habitat can alter human exposure even when the virus itself has not changed [19].

Reservoir surveillance is therefore more informative when it integrates virological detection with ecological measurements such as rodent density, reproductive cycles, vegetation, food availability, habitat fragmentation, and human land use. From a One Health perspective, spillover should be understood as the outcome of a connected system involving reservoir competence, environmental contamination, human behavior, and access to health services [20].

4.2 Routes of Transmission to Humans

Most human infections result from exposure to infectious rodent excreta or contaminated environmental material. Aerosolization is particularly relevant when dried urine, feces, or nesting material is disturbed during sweeping, cleaning, construction, farming, or entry into enclosed spaces. Transmission may also occur when contaminated material contacts mucous membranes or broken skin. Rodent bites and scratches are possible but are less common routes. Ingestion of contaminated food or water is biologically plausible but is less clearly established than inhalational or direct mucosal exposure [21].

The incubation period is variable and generally spans approximately one to eight weeks, depending on the virus and exposure context. Because the early clinical syndrome is nonspecific, a history of rodent exposure often provides the epidemiological clue that makes targeted laboratory testing appropriate. Exposure assessment should therefore include home and workplace conditions, cleaning activities, agricultural or forestry work, travel to endemic regions, and direct contact with rodents or rodent-contaminated materials [22].

4.3 Human-to-Human Transmission

Person-to-person transmission is not a general feature of hantavirus infection. The best-established example is Andes virus, for which limited transmission has been documented among household members, intimate contacts, and healthcare-associated close contacts. Available observations indicate that prolonged, close contact during the early clinical phase is particularly relevant. Other pathogenic hantaviruses have not demonstrated comparable sustained human-to-human transmission, and routine community spread is not characteristic of HFRS in Europe and Asia [23].

The distinction between zoonotic transmission and limited secondary transmission has direct infection-

control implications. Most cases should be approached through standard infection-prevention principles and exposure assessment, whereas suspected Andes virus infections during an outbreak warrant enhanced attention to close contacts, appropriate precautions, and public-health notification. The 2026 MV Hondius event illustrates that a confined environment can facilitate a short chain of secondary transmission without implying that Andes virus behaves like a continuously circulating respiratory pathogen [24].

5. Global Epidemiology

5.1 Geographic Distribution and Burden

Hantavirus infections occur across multiple continents, but their burden is uneven. HFRS is concentrated in Europe and Asia and is particularly important in China, the Republic of Korea, Russia, and parts of northern and central Europe, where Puumala virus contributes substantially to disease. HCPS is mainly reported in North, Central, and South America and is less common in absolute case numbers than HFRS but has a comparatively high case-fatality proportion. WHO currently estimates that approximately 10,000 to more than 100,000 hantavirus infections occur worldwide each year, with the largest burden in Asia and Europe [25].

National surveillance intensity differs considerably, so reported incidence should not be interpreted as a direct measure of true transmission. Underdiagnosis

can occur where access to serology, molecular testing, or intensive care is limited, while enhanced surveillance may increase case detection without representing a true increase in transmission. Epidemiological interpretation therefore requires attention to testing capacity, case definitions, reporting practices, and ecological context [26].

5.2 Major Human-Pathogenic Viruses and Clinical Associations

The relationship between individual viruses, reservoirs, and syndromes is summarized in Table 1. This comparison demonstrates that geographic distribution and disease phenotype are linked through specific virus-reservoir systems rather than through a single globally uniform hantavirus entity. It also illustrates why diagnostic and preventive strategies are more effective when they incorporate regional epidemiology and exposure history [27].

Hantaan and Dobrava-associated infections are generally associated with more severe HFRS than Puumala infection, whereas Sin Nombre and Andes viruses are prominent causes of HCPS. Seoul virus has a worldwide distribution because of its association with commensal rats and can produce HFRS. The table should therefore be viewed as a clinical-ecological framework rather than an exhaustive taxonomy of hantaviruses [28].

Table 1: Representative human-pathogenic orthohantaviruses, reservoir associations, geographic distribution, and clinical phenotype.

S. No.	Virus / clinical type	Principal reservoir association	Geographic pattern	Predominant human syndrome	Relative clinical pattern	References
1.	Hantaan virus	Apodemus agrarius	East Asia, especially China and Korea	HFRS	Often severe renal and vascular disease	[29]
2.	Seoul virus	Rattus norvegicus / Rattus rattus	Broad global distribution with urban associations	HFRS	Usually milder than Hantaan but clinically variable	[30]
3.	Puumala virus	Myodes glareolus and related bank voles	Northern and central Europe, parts of Eurasia	HFRS / nephropathia epidemica	Generally milder HFRS with substantial renal involvement	[31]
4.	Dobrava virus	Apodemus flavicollis and related mice	Southeastern / central Europe	HFRS	Potentially severe renal and systemic disease	[32]
5.	Sin Nombre virus	Peromyscus maniculatus	North America	HPS/HCPS	Rapid pulmonary edema and cardiopulmonary instability	[33]
6.	Andes	Sigmodontine	South	HPS/HCPS	Severe pulmonary	[34]

	virus	rodents, including Oligoryzomys species	America, especially Argentina and Chile		disease; limited person-to-person transmission documented	
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Table 1 highlights the ecological specificity that underlies the geographic and clinical heterogeneity of hantavirus disease. The same broad virus family therefore generates distinct risk profiles according to the reservoir host and region, reinforcing the need for location-specific exposure histories and diagnostic strategies [35].

5.3 Ecological and Anthropogenic Drivers

Hantavirus epidemiology is highly sensitive to ecological conditions that influence reservoir populations and human contact. Increased rodent abundance can follow favorable food conditions or climatic patterns, while changes in land use can bring humans into closer contact with reservoir habitats. Agricultural expansion, forestry, construction, and disturbance of previously enclosed or abandoned structures are recurring exposure contexts. Urbanization creates a parallel pathway through commensal rodents, particularly for Seoul virus [36].

Climate variability may intensify risk in some ecosystems by altering rodent reproduction, food availability, and population density, but these effects are spatially heterogeneous. Consequently, predictive models are most useful when they integrate meteorological variables with ecological and socioeconomic information rather than relying on temperature or rainfall alone. This is also where genomic surveillance can add value by detecting changes in viral lineage distribution while ecological surveillance identifies where exposure opportunity is increasing [37].

5.4 The 2026 MV Hondius Outbreak as a Public-Health Case Study

The 2026 MV Hondius event provides a contemporary example of how hantavirus infection can become an international surveillance challenge through travel and limited human-to-human transmission. WHO reported that the outbreak was first notified on 2 May 2026 and, by 2 July 2026, included 13 linked cases, 12 laboratory-confirmed for Andes virus and one probable case, with three deaths. More than 650 contacts were followed in 33 countries and territories. The outbreak was declared over after completion of the follow-up period without additional linked transmission [38].

The most informative lesson from this event is not that hantavirus has become a broadly transmissible respiratory pathogen, but that rare secondary

transmission can create complex cross-border operational demands when cases occur in a mobile, densely connected environment. The response required rapid laboratory confirmation, clinical isolation, contact tracing, risk communication, repatriation planning, and coordinated monitoring. It therefore reinforces the need for diagnostic readiness and international information exchange even for pathogens whose baseline community transmissibility remains low [39].

6. Pathogenesis and Molecular Mechanisms

6.1 Endothelial Dysfunction and Vascular Leakage

A defining feature of severe hantavirus disease is altered vascular permeability. Pathogenic orthohantaviruses can infect endothelial cells without necessarily causing widespread cell death, yet signaling changes within the endothelial compartment can disrupt barrier regulation and fluid homeostasis. Interactions involving integrins, cytoskeletal pathways, cell-cell junctions, complement, coagulation-related mediators, and inflammatory signals collectively increase endothelial permeability. In HFRS, these changes are particularly evident in the renal microvasculature and are associated with capillary leakage, thrombocytopenia, hypotension, and acute kidney injury. In HCPS, extensive pulmonary vascular leak contributes to noncardiogenic pulmonary edema, hypoxemia, and rapid cardiopulmonary deterioration [40].

The pathophysiological importance of vascular leakage explains why apparently modest viral loads can coexist with severe clinical illness. Disease severity reflects not only replication but also the magnitude and timing of host responses. Platelet consumption, endothelial-platelet interactions, and altered coagulation can further disturb microvascular integrity. The resulting physiology differs by virus and host but can converge on a common endpoint of tissue edema, impaired organ perfusion, and hemodynamic instability [41].

6.2 Innate and Adaptive Immune Responses

The immune response to hantavirus is complex and cannot be reduced to a simple cytokine storm model. Early innate responses involve pattern-recognition pathways and the production of interferons and inflammatory mediators that influence endothelial behavior and leukocyte recruitment. Monocytes, macrophages, dendritic cells, and natural killer cells may shape the inflammatory environment, while

adaptive responses involving virus-specific antibodies and T cells contribute to both viral control and immunopathology. The balance between protective immunity and inflammatory injury is likely to influence disease severity [42].

Humoral immunity develops rapidly in many symptomatic patients, making antibody detection clinically useful. Neutralizing antibodies directed against the viral glycoproteins are considered important components of protection, although the correlates of durable and cross-protective immunity remain incompletely defined. Cellular responses can be robust and may contribute to disease through effects on infected endothelial tissue and inflammatory signaling. These features explain why vaccine development has focused on inducing protective neutralizing antibodies while avoiding formulations that fail to cover antigenic diversity across clinically relevant viruses [43].

6.3 Organ-Specific Pathobiology in HFRS and HPS/HCPs

The clinical distinction between HFRS and HPS/HCPs reflects differences in vascular beds, viral lineage, host

response, and organ susceptibility rather than completely separate pathogenic mechanisms. HFRS typically features fever followed by hypotension, thrombocytopenia, vascular leakage, and acute kidney injury, with oliguria and subsequent polyuria during recovery in severe cases. Renal dysfunction reflects altered glomerular and tubular physiology, endothelial permeability, inflammatory signaling, and changes in renal perfusion. HPS/HCPs is dominated by rapidly increasing pulmonary capillary permeability that produces pulmonary interstitial and alveolar edema, impaired gas exchange, hypoxemia, reduced cardiac output, and shock [44].

Figure 1 integrates the major biological steps from reservoir exposure to organ-specific disease. Its central message is that clinical deterioration occurs through the interaction of viral entry, endothelial dysfunction, immune signaling, and vascular leakage rather than through a single lesion or pathway. This integrated model is important for interpreting why early supportive care is effective when it anticipates the physiological consequences of vascular leak and why late presentation can lead to abrupt multi-organ deterioration [45].

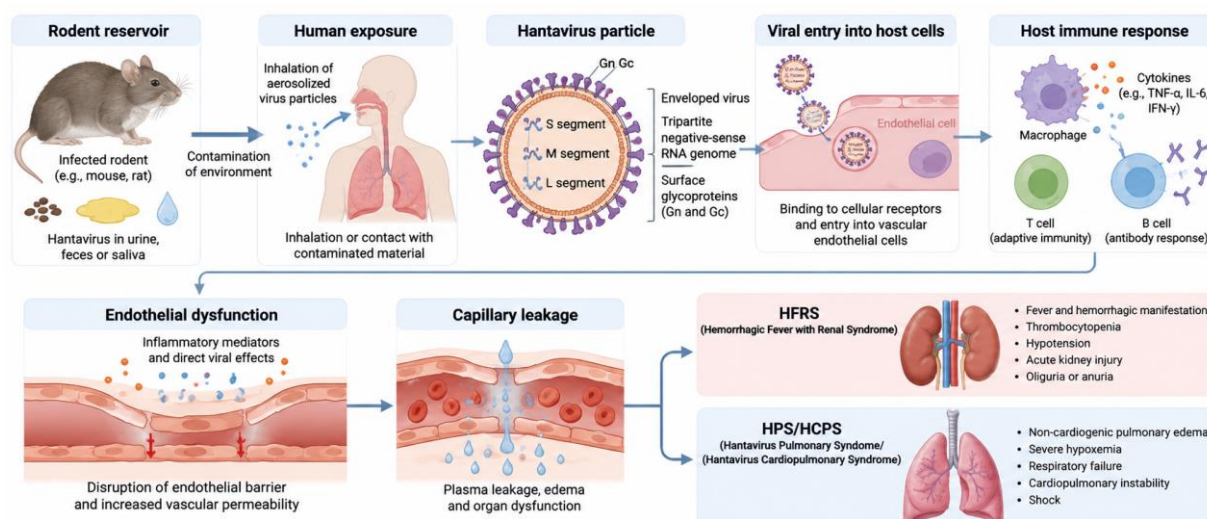


Figure 1: Hantavirus transmission and pathogenesis from reservoir exposure to endothelial dysfunction, vascular leakage, and organ-specific clinical syndromes.

Figure 1 provides a mechanistic overview of how zoonotic exposure can progress to severe disease. The figure emphasizes the transition from rodent-associated exposure to viral entry and host immune activation, followed by disruption of endothelial barrier function and the divergent renal and cardiopulmonary phenotypes of HFRS and HPS/HCPs.

7. Clinical Manifestations and Disease Progression

7.1 Early Clinical Phase

The initial illness is usually nonspecific, which is a major barrier to recognition. Fever, chills, headache, myalgia, marked fatigue, nausea, vomiting, abdominal or back pain, and malaise can resemble influenza, COVID-19, leptospirosis, dengue, bacterial sepsis, or other acute febrile illnesses. A careful exposure history becomes particularly valuable when a patient has recently cleaned a rodent-infested structure, worked in agricultural or forest environments, handled rodents, or travelled in an endemic area [46].

The early phase should not be interpreted as evidence of mild disease. Some patients deteriorate rapidly after a short prodrome, particularly with HCPS. Early examination should therefore include careful assessment of hemodynamics, oxygen saturation, respiratory effort, urine output, and laboratory markers of thrombocytopenia or hemoconcentration. Early recognition permits timely transfer to a facility capable of intensive monitoring before the onset of irreversible cardiopulmonary or renal failure [47].

7.2 Hemorrhagic Fever with Renal Syndrome

HFRS typically evolves through phases of fever, hypotension, oliguric renal dysfunction, polyuric recovery, and convalescence, although the sequence and severity vary by virus. Thrombocytopenia, hemoconcentration, proteinuria, hematuria, and rising creatinine are clinically useful clues. Severe disease may involve hypotension, bleeding manifestations, acute kidney injury, fluid overload, electrolyte disturbances, and shock. Puumala virus generally produces a milder syndrome than Hantaan or Dobrava viruses, but significant renal and systemic complications can still occur [48].

The renal phase is clinically challenging because fluid therapy must be individualized. Overaggressive fluid administration during a period of capillary leak can worsen pulmonary edema, whereas inadequate volume replacement can aggravate hypotension and renal hypoperfusion. Careful assessment of intravascular volume, urine output, electrolyte status, and pulmonary findings is therefore more appropriate than fixed-volume fluid protocols [49].

7.3 Hantavirus Pulmonary or Cardiopulmonary Syndrome

HPS/HCPS may progress within hours from a nonspecific febrile prodrome to cough, dyspnea, pulmonary edema, hypoxemia, hypotension, and shock. Pulmonary edema is typically noncardiogenic and results from increased pulmonary capillary permeability. Severe illness may be accompanied by

myocardial depression and reduced cardiac output, creating a combined respiratory and circulatory emergency. Mortality is highest during the cardiopulmonary phase, which is why immediate escalation of care is critical when oxygenation or hemodynamic status deteriorates [50].

The clinical distinction from primary bacterial pneumonia, influenza, COVID-19, or cardiogenic pulmonary edema requires integration of imaging, laboratory results, exposure history, and the speed of physiological deterioration. In endemic settings, unexplained rapidly progressive pulmonary edema with thrombocytopenia and a compatible exposure history should prompt specific hantavirus testing and early intensive care consultation [51].

7.4 Severe Disease, Complications, and Prognosis

The principal complications of severe hantavirus infection are acute respiratory distress, shock, acute kidney injury, fluid and electrolyte disturbances, hemorrhagic manifestations, and multi-organ dysfunction. The fatal pathway is not identical for all viruses: patients with HCPS may deteriorate predominantly through pulmonary edema, myocardial dysfunction, and shock, whereas HFRS mortality is more closely associated with severe vascular leak, hypotension, renal failure, and complications of fluid imbalance. Case-fatality proportions vary by virus, healthcare access, recognition speed, and clinical setting; HFRS may range from below 1% to approximately 15%, while HCPS can reach 50% in some settings [52].

Recovery is often slower than the initial clinical phase suggests. Renal function, fatigue, exercise tolerance, and cardiorespiratory status may require follow-up after hospital discharge. Structured follow-up is particularly relevant after severe HFRS with acute kidney injury or HCPS requiring prolonged respiratory support [53].

Table 3: Comparative clinical features of hemorrhagic fever with renal syndrome and hantavirus pulmonary or cardiopulmonary syndrome.

S. No.	Clinical domain	HFRS	HPS / HCPS	References
1.	Typical geographic association	Europe and Asia	Americas	[54]
2.	Dominant organ syndrome	Renal and vascular	Pulmonary and cardiovascular	[55]
3.	Key early features	Fever, headache, myalgia, gastrointestinal symptoms	Fever, myalgia, gastrointestinal symptoms	[56]
4.	Major deterioration pattern	Hypotension, thrombocytopenia, acute kidney injury, oliguria	Rapid dyspnea, pulmonary edema, hypoxemia, shock	[57]
5.	Major laboratory	Thrombocytopenia,	Thrombocytopenia,	[58]

	clues	hemoconcentration, proteinuria, rising creatinine	hemoconcentration, evolving respiratory abnormalities	
6.	Critical care priorities	Hemodynamic assessment, careful fluids, renal support, electrolyte management	Oxygenation, cautious fluids, hemodynamic support, ventilatory escalation	[59]
7.	Recovery considerations	Renal recovery and fluid/electrolyte shifts	Pulmonary and cardiovascular recovery, fatigue and exercise tolerance	[60]

Table 3 contrasts the two major clinical syndromes without implying that they are pathophysiologically unrelated. Both arise from vascular and immune dysregulation, but the dominant organ manifestations determine the clinical priorities and the type of intensive support required [61].

8. Laboratory Diagnosis

8.1 Clinical and Epidemiological Suspicion

Because early symptoms overlap with common infections, laboratory diagnosis should be guided by a combined clinical and epidemiological assessment. A compatible exposure history, thrombocytopenia, elevated hematocrit or hemoconcentration, proteinuria, acute kidney injury, or rapidly progressive pulmonary edema can strengthen suspicion. Differential diagnosis should be tailored to local epidemiology and may include influenza, COVID-19, leptospirosis, dengue, severe bacterial infection, rickettsial disease, and other viral hemorrhagic or pulmonary syndromes [61].

Testing should be arranged promptly when hantavirus is clinically plausible. The early phase can be diagnostically difficult because antibody responses develop over time and viral RNA may be detectable only during a limited window. Repeated testing may therefore be appropriate when the initial result is negative but the clinical and exposure histories remain strongly suggestive [62].

8.2 Serological Diagnosis

Serology is a central diagnostic approach for hantavirus infection. Detection of hantavirus-specific IgM supports acute infection, while evidence of rising IgG titres or an appropriate seroconversion pattern can strengthen confirmation. Enzyme-linked immunosorbent assays are widely used because they can be standardized and adapted to public-health

laboratories. The interpretation of antibody tests should consider timing relative to symptom onset and the possibility of cross-reactive responses between related hantaviruses [63].

Serological testing is particularly valuable because symptomatic patients frequently mount measurable antibody responses early in the clinical course. Nevertheless, the best interpretation comes from pairing laboratory findings with exposure history, clinical syndrome, and regional virus circulation [64].

8.3 Molecular, Immunohistochemical, and Supporting Tests

Reverse transcription polymerase chain reaction (RT-PCR) can detect viral RNA during acute infection and is particularly informative early in illness or during outbreak investigations. Molecular assays also support strain characterization and genomic surveillance. Immunohistochemistry can assist diagnosis in tissue specimens under appropriate laboratory conditions, while next-generation sequencing and metagenomic approaches are increasingly useful for research, lineage tracking, and outbreak reconstruction rather than routine bedside diagnosis [65].

Routine hematology and biochemistry remain clinically important even when they are not pathogen-specific. Thrombocytopenia, leukocytosis, hemoconcentration, elevated creatinine, proteinuria, electrolyte abnormalities, and evidence of hepatic or myocardial injury can help define severity and guide supportive care. Table 2 compares the major diagnostic approaches by timing, principal use, and practical limitations. The table emphasizes that diagnosis is a layered process: no single test replaces clinical suspicion, exposure assessment, and appropriate timing [66].

Table 2: Complementary laboratory approaches for diagnosis and severity assessment in suspected hantavirus infection.

S. No.	Approach	Best-use context	Core information	Main limitation / consideration	References
1.	IgM serology	Acute	Evidence of recent	Sensitivity depends on	[67]

		symptomatic infection	immune response	timing; interpret with clinical context	
2.	IgG serology with paired or rising titres	Confirmation of recent infection	Seroconversion or increasing antibody response	Requires appropriately timed specimens	[68]
3.	RT-PCR	Early acute illness and outbreak investigation	Detection of hantavirus RNA	Window of viraemia can be limited; assay availability varies	[69]
4.	Immunohistochemistry	Selected tissue-based investigations	Localization of viral antigen	Specialized method and specimen constraints	[70]
5.	CBC and peripheral indices	Severity assessment and diagnostic support	Thrombocytopenia, leukocytosis, hemoconcentration	Not pathogen-specific	[71]
6.	Renal and serum biochemistry	HFRS severity assessment	Creatinine, electrolytes, renal injury pattern	Changes may overlap with other acute illnesses	[72]
7.	Chest imaging / oxygenation assessment	Suspected HPS/HCPS	Pulmonary edema and gas-exchange impairment	Findings require clinical correlation	[73]
8.	Genomic sequencing	Outbreak reconstruction and surveillance	Lineage assignment and relatedness	Primarily surveillance/research rather than routine bedside diagnosis	[74]

Table 2 shows why hantavirus diagnosis is best approached as a combination of pathogen-specific testing and nonspecific severity markers. Serology and RT-PCR provide complementary windows for confirmation, while hematological, renal, and respiratory assessments define the physiological consequences that determine the urgency of care [75].

8.4 Biosafety and Specimen Handling

Clinical laboratories must recognize that suspected hantavirus specimens can present a biological hazard. Procedures involving non-inactivated material should follow applicable high-containment and transport requirements established by national authorities and reference laboratories. Early coordination with public-health laboratories is advisable when specialized confirmatory testing is needed. This is particularly important during outbreaks because delays in specimen referral can prolong isolation decisions and complicate contact tracing [76].

9. Therapeutic Strategies and Clinical Management

9.1 Principles of Supportive Care

There is no globally approved curative antiviral treatment for hantavirus disease, so supportive care remains the foundation of management. The central clinical objective is to anticipate the physiological consequences of capillary leakage and maintain adequate oxygenation, perfusion, renal function, and

electrolyte balance without exacerbating edema. Management should occur in a setting capable of rapid escalation because deterioration may be abrupt once the cardiopulmonary or oliguric phase develops [77].

Fluid therapy requires particular caution. In HFRS, hemodynamic instability and renal failure can coexist with substantial vascular leak, making both under-resuscitation and fluid overload hazardous. In HCPS, excessive intravenous fluid can aggravate pulmonary edema and impair gas exchange. Serial assessment using blood pressure, oxygen saturation, urine output, laboratory values, bedside imaging where available, and clinical signs of intravascular volume is therefore more informative than fixed fluid targets [78].

9.2 Respiratory and Cardiovascular Support

Patients with HPS/HCPS may require supplemental oxygen, invasive mechanical ventilation, vasopressor support, and intensive hemodynamic monitoring. Because pulmonary edema and myocardial dysfunction can evolve quickly, early transfer to intensive care is appropriate when oxygenation, blood pressure, or work of breathing deteriorates. Mechanical ventilation should be guided by lung-protective principles and the patient's rapidly changing physiology rather than by a one-size-fits-all approach [79].

Extracorporeal membrane oxygenation (ECMO) has

been used in selected patients with refractory cardiopulmonary failure and can provide a bridge through the most severe phase of HCPS when delivered in experienced centers. Evidence is based largely on specialized-center experience rather than large randomized trials, so patient selection, timing, and institutional expertise remain critical [80].

9.3 Renal Support and Fluid-Electrolyte Management

Severe HFRS may produce acute kidney injury with oliguria, electrolyte disturbances, acid-base abnormalities, and fluid overload. Management includes close monitoring of urine output and renal indices, individualized fluid administration, and correction of clinically relevant electrolyte abnormalities. Renal replacement therapy, including hemodialysis, may be required when conventional supportive measures are insufficient or when life-threatening complications of kidney failure develop [81].

During the polyuric recovery phase, fluid and electrolyte requirements can change rapidly. Follow-up is therefore not simply a matter of documenting rising urine output; clinicians must also anticipate potassium, sodium, and volume losses and adjust replacement accordingly [82].

9.4 Antiviral Therapy

Ribavirin remains the best-studied antiviral option in hantavirus disease, but its role is limited. Evidence from early treatment of HFRS suggests that benefit is most plausible when therapy is initiated before

advanced disease, whereas controlled evidence has not established efficacy for HPS/HCPS. Consequently, ribavirin should not be regarded as a proven rescue therapy for advanced cardiopulmonary disease. Its use also requires consideration of regional practice, timing, contraindications, and specialist guidance [83].

The lack of a broadly effective antiviral reflects several development challenges. Hantaviruses are difficult to propagate for conventional screening, severe disease can progress faster than antiviral therapy can reverse established endothelial dysfunction, and animal models do not perfectly reproduce human disease. Current research therefore spans direct-acting polymerase and entry inhibitors, neutralizing monoclonal antibodies, host-directed strategies, and combinations designed to suppress viral replication before the inflammatory and vascular phases become irreversible [84].

9.5 Clinical Management Framework

Figure 2 presents a practical diagnostic and management pathway that links exposure assessment with laboratory confirmation and syndrome-specific supportive care. The figure is intentionally structured around early recognition because the therapeutic window for preventing secondary physiological injury is narrow. In clinical practice, a patient should move from suspicion to confirmatory testing while supportive management begins in parallel when disease severity warrants it; laboratory confirmation should not delay treatment of hypoxemia, shock, or acute kidney injury [85].

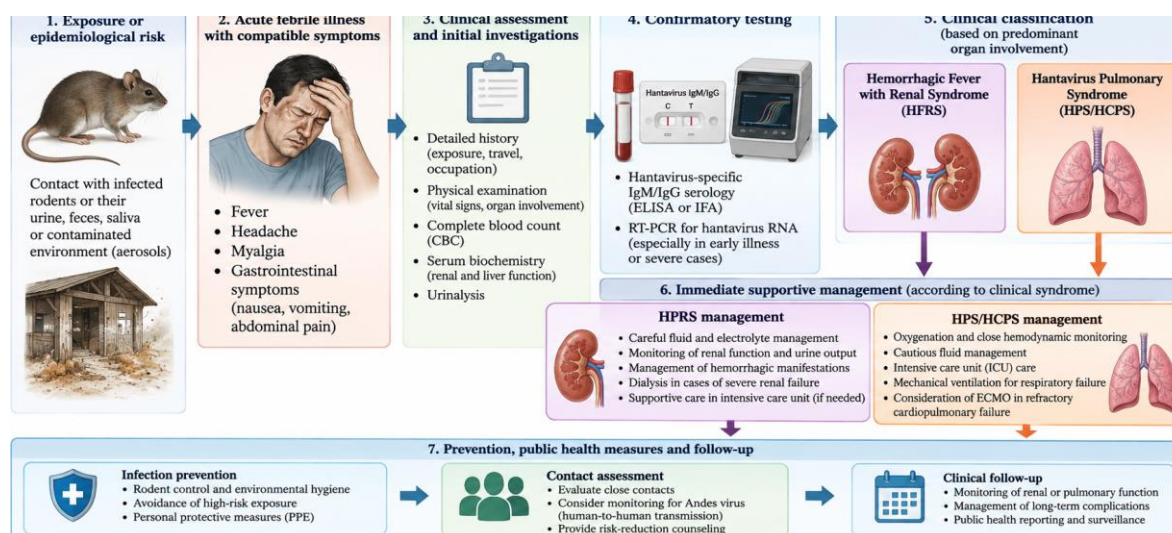


Figure 2: Diagnostic and clinical management pathway for suspected hantavirus infection, from exposure assessment and confirmatory testing to syndrome-specific supportive care and follow-up.

Figure 2 translates the review into a practical sequence for clinical decision-making. The pathway places exposure assessment and early testing alongside immediate supportive care, then separates

management priorities according to HFRS or HPS/HCPS before returning to prevention, contact assessment, and follow-up.

Table 4: Current and emerging therapeutic, preventive, and surveillance strategies for hantavirus disease.

S. No.	Intervention / strategy	Current role	Evidence status	Key limitation	References
1.	Supportive critical care	Foundation of treatment for both syndromes	Established clinical practice	Requires early recognition and specialist capacity	[86]
2.	Careful fluid management	Essential in HFRS and HCPS	Established physiological principle	Excess fluid can worsen pulmonary edema; under-resuscitation can worsen shock	[87]
3.	Mechanical ventilation	For severe hypoxemic respiratory failure	Supportive standard in severe HCPS	Management is technically demanding because physiology can deteriorate quickly	[88]
4.	ECMO	Selected refractory cardiopulmonary failure	Specialized rescue strategy	Limited to experienced centers; evidence largely observational	[89]
5.	Hemodialysis / renal replacement	Severe HFRS-associated kidney failure	Established supportive indication	Requires timely access and individualized fluid strategy	[90]
6.	Ribavirin	Most plausible when very early HFRS treatment is considered	Limited evidence; not proven for HPS/HCPS	Benefit is time-dependent and evidence is not definitive	[91]
7.	Regional inactivated HFRS vaccines	Prevention of Hantaan / Seoul-associated disease in selected settings	Used in China and the Republic of Korea	Limited global availability and incomplete cross-protection	[92]
8.	Monoclonal antibodies	Emerging early-treatment and prophylactic strategy	Preclinical / translational	Timing, breadth and clinical efficacy remain to be established	[93]
9.	mRNA / recombinant / DNA vaccines	Next-generation vaccine development	Experimental / clinical-development landscape	Need durable, broad protection across diverse hantaviruses	[94]
10.	Genomic surveillance	Outbreak detection and transmission reconstruction	Increasingly established public-health tool	Requires sequencing capacity, metadata and rapid analysis	[95]

Table 4 synthesizes current supportive care, preventive strategies, and emerging therapeutic approaches together with their principal translational limitations.

10. Prevention and Public Health Control

10.1 Rodent Control and Environmental Hygiene

The most reliable prevention strategy is reduction of

human contact with infected rodents and contaminated environments. Buildings should be inspected for rodent entry points, food should be stored securely, waste should be managed to reduce rodent attraction, and rodent infestation should be controlled using locally appropriate methods. High-risk enclosed spaces should be ventilated before cleaning, and dry sweeping or vacuuming of rodent-contaminated material should be avoided because it

can aerosolize infectious particles [96].

Safe cleaning practices are especially important in homes, farms, warehouses, cabins, laboratories, and abandoned buildings. Surfaces contaminated with rodent excreta should be appropriately disinfected and wet-cleaned using procedures consistent with public-health guidance. Prevention is therefore not simply a matter of eliminating rodents; it also depends on changing the way people interact with contaminated environments [97].

10.2 Occupational and Personal Protection

People working in agriculture, forestry, construction, military settings, wildlife research, pest control, and building maintenance may have repeated exposure opportunities. Risk reduction should combine environmental controls with appropriate personal protective measures and training in recognition of rodent contamination. The objective is to interrupt exposure before aerosolized particles reach the respiratory tract and to prevent contaminated material from contacting the eyes, mouth, or damaged skin [98].

Risk communication should be tailored to the exposure setting. Generic warnings are less effective than task-specific guidance, such as instructions for opening an abandoned structure, clearing a rodent-infested shed, handling contaminated materials, or responding to a suspected occupational exposure [99].

10.3 Surveillance, Early Warning, and One Health

Hantavirus surveillance is most informative when human case reporting is combined with reservoir and environmental monitoring. Molecular typing can clarify whether apparently separate cases are part of the same transmission chain, while rodent surveillance can identify shifts in virus prevalence or host distribution. Digital reporting systems and geographic information platforms can shorten the interval between clinical recognition and public-health action [100].

A One Health framework is especially relevant because human disease cannot be fully understood without information from animal hosts and their habitats. Collaboration among clinicians, microbiologists, epidemiologists, wildlife specialists, environmental scientists, and local communities can improve risk mapping and help identify ecological conditions that precede increases in human exposure [101].

10.4 Outbreak Response and Infection Prevention in Healthcare Settings

When a case is suspected, early notification and

contact assessment should be guided by the infecting virus and local public-health recommendations. For most hantavirus infections, the principal epidemiological concern is rodent exposure rather than routine person-to-person spread. Suspected Andes virus infection warrants more detailed assessment of close and prolonged contacts because limited human-to-human transmission has been documented. In healthcare settings, standard precautions remain central, with additional precautions guided by clinical procedures and public-health risk assessment [102].

The 2026 MV Hondius outbreak demonstrated the operational importance of coordinated contact tracing across borders. The completion of the follow-up period without additional linked cases illustrates that early identification, appropriate monitoring, and targeted precautions can interrupt secondary transmission even when the initial setting involves passengers from many countries [103].

11. Vaccines and Emerging Therapeutic Approaches

11.1 Current Vaccine Landscape

There is no globally deployed vaccine that provides broad protection against the major pathogenic hantaviruses. However, inactivated HFRS vaccines based on Hantaan and Seoul virus antigens have been used regionally in China and the Republic of Korea. These vaccines demonstrate that humoral protection is achievable for defined HFRS virus targets, but their geographic availability, antigenic breadth, and durability limit their generalizability to the full hantavirus landscape. Vaccines developed for Hantaan or Seoul virus should therefore not be assumed to provide equivalent protection against Puumala, Dobrava, Andes, or Sin Nombre viruses [104].

The main vaccine-development challenge is the combination of antigenic diversity and the need for durable neutralizing immunity. Current experimental strategies include recombinant or subunit approaches, DNA vaccines, viral vectors, mRNA platforms, and multivalent formulations designed to broaden the response. A successful next-generation vaccine will likely need to balance breadth, durability, manufacturing feasibility, safety, and compatibility with regional risk profiles [105].

11.2 Monoclonal Antibodies and Immunotherapeutic Strategies

Neutralizing antibodies directed toward hantavirus glycoproteins represent a promising therapeutic approach because the viral surface proteins are directly involved in cell attachment and entry. Passive immunotherapy is most attractive when administered

early, before vascular injury becomes self-sustaining. Monoclonal antibodies also provide mechanistic tools for defining protective epitopes and may support the rational design of vaccines that focus responses on conserved neutralization-sensitive regions [106].

Immunotherapeutic approaches require careful distinction between viral clearance and inflammatory control. Because severe disease involves dysregulated host responses, it is conceivable that the most effective future regimens will combine direct antiviral activity with strategies that reduce pathological endothelial signaling without compromising protective immunity [107].

11.3 Novel Antivirals and Host-Directed Approaches

The viral polymerase, glycoprotein-mediated entry pathways, nucleoprotein functions, and host factors required for replication are active areas for drug discovery. Screening efforts increasingly use structural biology, high-throughput methods, computational approaches, and replication assays to identify candidate inhibitors. Host-directed strategies may be advantageous when viral genetic diversity makes direct-acting compounds vulnerable to resistance, although host toxicity and pathway redundancy remain major barriers [108].

Translational progress will require models that reproduce clinically relevant vascular and cardiopulmonary phenotypes. Human endothelial models, organoids, ex vivo systems, and improved animal models can complement conventional cell culture and help distinguish compounds that merely reduce viral replication from those that prevent the physiological cascade leading to severe disease [109].

12. Recent Advances and Future Perspectives

12.1 Genomic Surveillance and Molecular Epidemiology

Next-generation sequencing is increasingly useful for reconstructing transmission chains, distinguishing viral lineages, identifying introductions, and supporting outbreak response. Genomic data become especially informative when combined with exposure history and temporal-geographic information. During unusual clusters, rapid sequencing can help determine whether cases share a common introduction or represent independent zoonotic events [110].

The practical future of genomic surveillance is likely to involve integration with routine public-health databases rather than stand-alone sequencing projects. Standardized metadata, interoperable reporting systems, and access to regional reference laboratories will determine whether genomic

information can meaningfully shorten outbreak-response intervals [111].

12.2 Rapid Diagnostics and Digital Epidemiology

Point-of-care or near-patient diagnostics could reduce delays caused by sample transport and centralized testing, particularly in remote endemic regions. The most useful platforms would combine high sensitivity during early illness with simple sample handling, robust quality control, and clear differentiation among clinically relevant hantavirus groups. Digital tools may further strengthen case finding by integrating symptoms, exposure history, laboratory results, and geospatial information [112].

Artificial intelligence and machine-learning approaches are potentially useful for ecological forecasting, anomaly detection, and prioritization of suspected cases, but their value depends on representative training data and careful validation. Predictive systems should support rather than replace epidemiological reasoning and laboratory confirmation [113].

12.3 Climate, Land Use, and Emerging Risk

Future hantavirus risk will remain closely tied to ecological change. Shifts in rainfall patterns, temperature, vegetation, agricultural practices, deforestation, urban expansion, and habitat fragmentation can modify reservoir populations or human exposure. The challenge is that the direction and magnitude of these effects differ between ecosystems. Consequently, future preparedness should focus on identifying local ecological indicators of increased spillover risk rather than assuming a universal climate-disease relationship [114].

International travel adds another layer of complexity. The 2026 MV Hondius outbreak showed that a rare secondary transmission phenotype can become operationally important when infected persons move rapidly across borders. Travel medicine, ship medicine, occupational health, and emergency preparedness systems should therefore retain awareness of hantavirus without overstating its baseline transmissibility [115].

12.4 Research Gaps and Translational Priorities

Several gaps remain. First, the correlates of durable and cross-protective immunity are incompletely defined, limiting vaccine optimization. Second, the mechanisms linking viral replication to severe endothelial dysfunction remain only partially resolved, especially the relative contribution of endothelial signaling, immune activation, platelets, complement,

and coagulation. Third, there is no standardized, globally accepted antiviral strategy. Fourth, surveillance is uneven across endemic regions, leaving uncertainty about the true burden and geographic expansion of infection.

Priority research should therefore connect molecular mechanisms with clinically measurable endpoints. Studies that integrate viral genomics, endothelial biology, host immunology, reservoir ecology, pharmacology, and clinical phenotyping are more likely to identify interventions that remain effective across virus lineages. Equally important is strengthening reference laboratories and regional preparedness so that scientific advances are translated into rapid diagnosis and supportive care at the point of need.

Conclusion

Hantavirus infection represents a model of an emerging zoonotic disease in which viral evolution, reservoir ecology, environmental change, host immunity, and healthcare capacity interact to determine human risk. Although the major clinical syndromes, HFRS and HPS/HCPs, differ in their dominant organ involvement, both are strongly influenced by dysregulated vascular permeability and host-response pathways. This shared biology provides a framework for understanding why severe disease can progress rapidly despite limited direct cytolysis of endothelial cells and why timely supportive management is central to survival.

Diagnostic capability has improved through serology, RT-PCR, and genomic methods, yet clinical recognition remains difficult during the early nonspecific phase. Treatment remains predominantly supportive, with careful fluid and hemodynamic management, respiratory support, renal replacement when indicated, and selected use of ECMO in refractory cardiopulmonary failure. Ribavirin has a limited evidence base and is not an established treatment for advanced HPS/HCPs. Regionally used inactivated HFRS vaccines demonstrate the feasibility of prevention, but broader vaccine development and

antiviral discovery remain unfinished priorities.

The 2026 MV Hondius outbreak further demonstrated the value of rapid international surveillance, diagnostic coordination, contact tracing, and risk communication while also confirming that Andes virus transmission between people remains limited and context-dependent. Future control of hantavirus disease will depend on a One Health strategy that links rodent ecology, environmental prevention, laboratory diagnosis, clinical preparedness, molecular surveillance, and innovation in vaccines and therapeutics. A deeper understanding of the mechanisms that convert viral infection into vascular and organ dysfunction will be particularly important for moving from supportive medicine toward targeted disease-modifying treatment.

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Author Contribution

M.A.: Writing-original draft; **G.M.:** Literature investigation; **S.T.:** Data curation; **M.A.:** Visualization.

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The authors declare that they used AI language tools (Gemini) to enhance this manuscript's linguistic clarity and readability. They carefully reviewed and edited all generated text to ensure accuracy and alignment with the research's intended meaning.

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