



## Review Article

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## Hantavirus disease: A review of global epidemiology, immunopathogenesis, clinical management, and future research priorities

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## ABSTRACT

Hantaviruses are rodent-borne zoonotic pathogens responsible for two major clinical syndromes: Hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome/cardiopulmonary syndrome. Although significant progress has been achieved in hantavirus research over recent decades, major challenges remain in surveillance, diagnostics, therapeutics, and vaccine development. This review comprehensively synthesizes current evidence on hantavirus virology, taxonomy, reservoir ecology, transmission dynamics, global epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, prevention, and One Health surveillance strategies. Particular emphasis is placed on the immunopathological mechanisms underlying endothelial dysfunction and vascular hyperpermeability, the hallmark features of severe disease. The review further explores how climate variability, land-use change, biodiversity loss, and rodent population dynamics shape spillover risk and geographic expansion. Current diagnostic approaches, including serology, RT-PCR, and next-generation sequencing, are critically evaluated alongside emerging point-of-care technologies. Therapeutic limitations are highlighted, particularly the absence of universally effective antivirals and globally approved vaccines. Key research gaps identified include inadequate surveillance in South Asia and Africa, insufficient understanding of Andes virus human-to-human transmission, limited validation of rapid diagnostics, and unresolved mechanisms of immune-mediated pathology. Adopting a One Health perspective, this review proposes priority research and public health directions to strengthen global preparedness, improve outbreak prediction, and accelerate development of effective diagnostics, therapeutics, and vaccines against hantavirus disease.

**KEYWORDS:** Hantavirus; Hemorrhagic fever with renal syndrome; Hantavirus pulmonary syndrome; Zoonotic diseases; One Health; Rodent-borne disease

## 1. Introduction

Hantaviruses are among the most significant yet underappreciated zoonotic pathogens affecting human populations globally[1]. First isolated in 1976 from the striped field mouse (*Apodemus agrarius*) near the Hantaan River in South Korea, which lent the founding member of the genus its name, these viruses have since been identified across every inhabited continent[2]. They cause two major clinical syndromes with divergent but pathophysiologically related manifestations. Hemorrhagic fever with renal syndrome (HFRS), predominantly caused by Hantaan, Seoul, Puumala, and Dobrava-Belgrade viruses, is characterized by acute kidney injury, thrombocytopenia, and hemorrhagic complications, with case fatality rates (CFRs) ranging from less than 1% for Puumala virus to approximately 15% for Hantaan virus[3,4]. Hantavirus pulmonary syndrome (HPS), caused by several New World hantaviruses, most notably Sin Nombre virus (SNV) in North America and Andes virus (ANDV) in South America, among others, manifests as rapidly progressive non-cardiogenic pulmonary edema with CFRs of 25%–40%[5,6].

Unlike many RNA viruses, hantaviruses do not cause apparent disease in their rodent reservoir hosts, establishing long-term persistent infections characterized by viraemia, antigenaemia, and

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viral shedding in saliva, urine, and feces[7]. Human infection occurs predominantly through inhalation of virus-contaminated aerosols, placing agricultural workers, forestry personnel, military personnel, and individuals engaged in rural activities at greatest risk[8,9]. The global burden of hantavirus infection is difficult to quantify precisely, owing to substantial underdiagnosis, limited surveillance infrastructure in endemic regions, and clinical overlap with other febrile illnesses[10,11].

The emergence of hantaviruses as public health threats is intrinsically linked to ecological, environmental, and socioeconomic drivers. Rodent population dynamics, shaped by climate variability (notably El Niño Southern Oscillation cycles), land-use change, and biodiversity loss, are primary determinants of spillover risk[12,13]. The progressive encroachment of human settlements into previously undisturbed habitats, combined with global climate warming, has expanded the geographic range of reservoir host species and increased the frequency of human-rodent contact[14,15]. Recent bibliometric analyses confirm that hantavirus research has grown substantially since the 1993 SNV discovery, yet critical gaps persist in vaccine development, antiviral therapy, diagnostic capacity, and surveillance, particularly in low- and middle-income countries (LMICs)[16].

This review addresses a timely need for a comprehensive, critical synthesis that not only catalogues existing knowledge but explicitly maps unresolved questions and proposes a structured agenda for future investigation. We adopt a One Health perspective, recognizing that sustainable progress against hantavirus disease requires integration of human, animal, and environmental health disciplines[17,18]. The review is structured to progress from virology and ecology through epidemiology, clinical science, diagnostics, and therapeutics, culminating in an analysis of critical research gaps and future directions.

A further complexity in the global clinical picture is the increasing recognition of infections with mixed or atypical clinical features that do not fit cleanly into the classical HFRS/HPS dichotomy. Cases which combine renal and pulmonary involvement and are sometimes accompanied by neurological or hepatic manifestations have been documented in parts of Asia, most notably in Nepal and Sri Lanka, and are thought to reflect infection with incompletely characterized or novel hantavirus strains[19,20].

## 2. Virology and taxonomy

### 2.1. Classification and genome organization

Hantaviruses are classified within the family Hantaviridae. Hantaviridae was formerly placed directly within the order Bunyavirales; however, following the 2024 reorganization ratified by the International Committee on Taxonomy of Viruses, Bunyavirales was elevated to the class Bunyaviricetes, and Hantaviridae is now

assigned to the order Elliovirales within this class[21]. The genome consists of three negative-sense, single-stranded RNA segments designated large (L), medium (M), and small (S). The L segment (~6 500 nucleotides) encodes the RNA-dependent RNA polymerase (RdRp); the M segment (~3 700 nucleotides) encodes the two surface glycoproteins Gn and Gc, which are critical mediators of host cell entry *via* beta-3 integrins; and the S segment (~1 700–2 100 nucleotides) encodes the nucleocapsid (N) protein, which encapsidates the genomic RNA and serves as the primary target antigen for serological diagnostics[2,22,23].

Unlike other related bunyaviral families, hantaviruses are not arthropod-borne; they are exclusively associated with small mammal reservoirs, primarily rodents of the families Cricetidae and Muridae, though insectivore-associated hantaviruses have been identified in shrews, moles, and bats[18,24]. Phylogenetic analyses broadly support co-speciation of hantaviruses with their rodent hosts, with New World hantaviruses clustering with Sigmodontinae and Neotominae rodents, and Old World viruses with Arvicolinae and Murinae species[21,25] (Figure 1).

### 2.2. Viral entry and replication

Hantavirus entry into endothelial cells is mediated through binding of the Gn/Gc glycoprotein complex to beta-3 integrin receptors, with subsequent internalization *via* clathrin-mediated or clathrin-independent endocytosis pathways. Replication occurs in the cytoplasm, with the RdRp performing transcription and genome replication. Viral particles are assembled and bud from the Golgi apparatus, with mature virions (~80–120 nm) released by exocytosis. A notable feature of hantavirus biology is the absence of cytopathic effect in reservoir hosts, attributed to efficient suppression of interferon-mediated antiviral responses, a mechanism incompletely understood and an active area of investigation[5,22].

## 3. Reservoir ecology and transmission dynamics

### 3.1. Rodent reservoir biology

Each hantavirus species is maintained by one or a few closely associated rodent reservoir species, in which persistent infection is established without overt disease. Infection dynamics within reservoir populations reflect complex interplays between host population density, age structure, sex ratio, and intraspecific behaviours[7,29]. Transmission among rodents occurs primarily through biting during territorial disputes, as well as through contaminated soil and nesting materials. Sexual transmission has been demonstrated experimentally, and maternal antibodies may confer temporary protection in juveniles[30,31].

Rodent population cycles driven by food availability, particularly mast events involving beech nuts and oak acorns in European

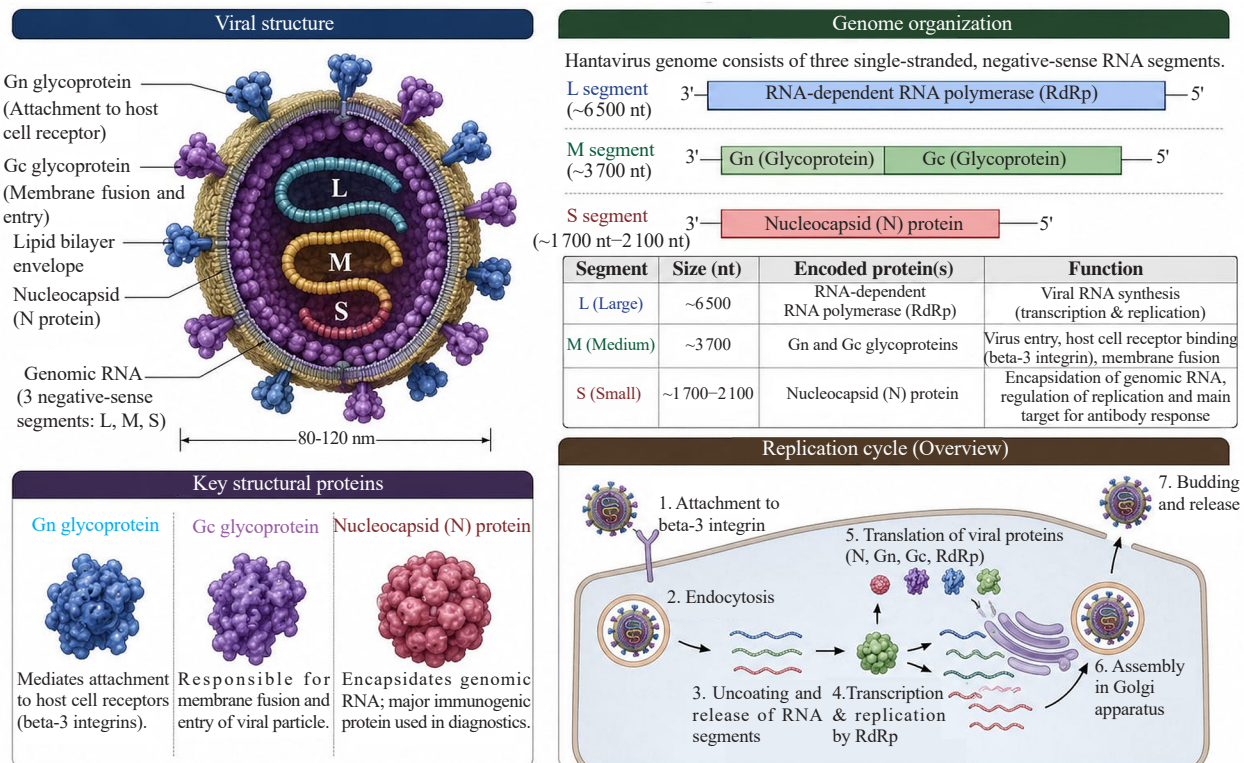


**Figure 1.** Viral structure, genome organization, and replication cycle of hantavirus[24–28].

forests, generate predictable epidemic cycles in human populations. In Fennoscandia, Puumala virus (PUUV) epidemics in humans follow the three- to five-year population cycles of the bank vole (*Myodes glareolus*) with a predictable one-year lag[32–34]. Mathematical models incorporating rodent population dynamics have demonstrated reasonable predictive power for human outbreak forecasting in Europe and China[35–37] (Figure 2).

### 3.2. Transmission to humans

The dominant route of human infection is inhalation of virus-containing aerosols generated from desiccated rodent excreta (urine, feces, saliva). Direct contact with rodents or their nesting materials, as well as rodent bites, can also transmit infection, though these routes are less common. Consumption of undercooked food contaminated by rodent excreta has been proposed but is poorly documented[9,38].

Human-to-human transmission is considered an exceptional feature of ANDV in South America. A systematic review by Toledo *et al.*[39] identified epidemiological and molecular evidence supporting person-to-person transmission of ANDV, particularly in household and nosocomial settings. This capacity absent or unconfirmed for all other hantaviruses is of paramount public health significance and warrants continued investigation. Proposed mechanisms include respiratory droplet transmission during the viraemic prodromal phase, though definitive experimental evidence remains elusive[39].

Occupational and behavioural risk factors significantly modulate individual exposure probability. Agricultural workers, foresters,

military personnel, hunters, campers, and rodent control workers are disproportionately affected[8,40]. Housing quality, sanitation standards, and grain storage practices are critical contextual determinants in LMIC settings[41].

### 3.3. Environmental and ecological drivers

The ecology of hantavirus transmission is profoundly shaped by environmental variability. Climate anomalies, particularly El Niño Southern Oscillation events, influence primary productivity, which in turn determines rodent abundance and hantavirus prevalence in reservoir populations[12,42]. Land-use change, specifically deforestation, agricultural expansion, and urbanization, alters the spatial relationship between rodent habitats and human settlements, generally increasing spillover risk[43,44]. The biodiversity dilution effect, whereby diverse mammalian communities reduce hantavirus prevalence in reservoir populations, has been empirically supported in several studies[45,46]. A detailed summary of ecological drivers is presented in Table 1.

## 4. Global epidemiology

### 4.1. Worldwide burden

Hantaviruses cause an estimated 150 000–200 000 human infections annually, with substantial geographic concentration in Asia, Europe, and the Americas[10,51]. China alone accounts for approximately

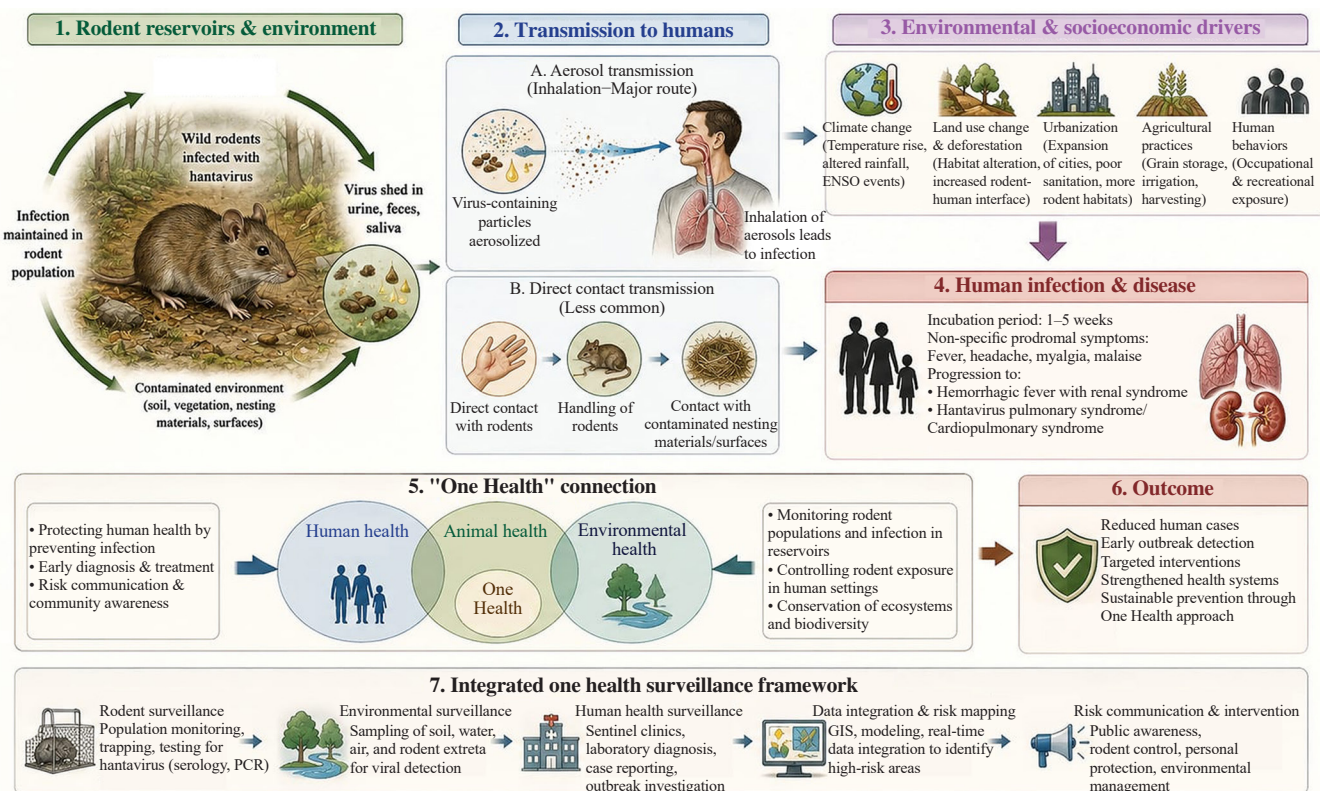


**Figure 2.** Transmission dynamics of hantavirus and the “One Health” connection[26–28].

70%-90% of globally reported HFRS cases, reflecting both genuine endemicity and a more developed surveillance infrastructure compared with other endemic regions[12,16]. Seroprevalence studies in non-epidemic populations indicate widespread subclinical or mild infection, suggesting that clinical case counts significantly underestimate total human exposure[11] (Figure 3).

#### 4.2. Asia

Asia is the epicentre of HFRS globally, with Hantaan virus and Seoul virus predominating in China, South Korea, and Russia[2,52]. China reports approximately 20 000-50 000 HFRS cases annually, concentrated in agricultural provinces of Shaanxi, Heilongjiang, and Shandong[12]. Korea was the site of the original HFRS recognition during the Korean War and remains an important endemic focus. Seoul virus, uniquely associated with the cosmopolitan Norway rat (*Rattus norvegicus*), has a global distribution but causes milder HFRS[52,53]. Critically, South Asia, including Bangladesh, India, Pakistan, Nepal, and Sri Lanka, lacks systematic, nationally coordinated hantavirus surveillance, despite the presence of commensal rodent species known to harbor hantaviruses[41,54]. Sri Lanka is, however, something of an exception within the region: although a national surveillance programme is still lacking, a substantial body of single-centre clinical and seroepidemiological

research has been published from the country over the past decade, making it one of the better-documented settings for hantavirus disease in South Asia[20,55]. This constitutes one of the most significant surveillance gaps identified in this review (Table 2).

#### 4.3. Europe

PUUV, transmitted by the bank vole, is the dominant hantavirus species in Europe, causing Nephropathia Epidemica, a usually mild form of HFRS prevalent in Fennoscandia, Germany, France, and the Balkans[3,56]. Germany has experienced marked HFRS surges in past years, with over 2 800 cases reported in 2010[57,58]. Dobrava-Belgrade virus, carried by *Apodemus flavicollis* and *Apodemus agrarius*, causes more severe HFRS in the Balkans and parts of Central Europe, with CFRs of 5%-12%[54]. Recent data from Hungary document continued PUUV circulation with phylogenetically diverse strains[59] (Table 2).

#### 4.4. The Americas

The discovery of SNV following the 1993 outbreak in the Four Corners region of the United States established HPS as a distinct clinical entity. Over 700 HPS cases have been confirmed in the United States, with approximately 36% CFR[15,21,60]. South

**Table 1.** Ecological and environmental drivers of hantavirus transmission dynamics.

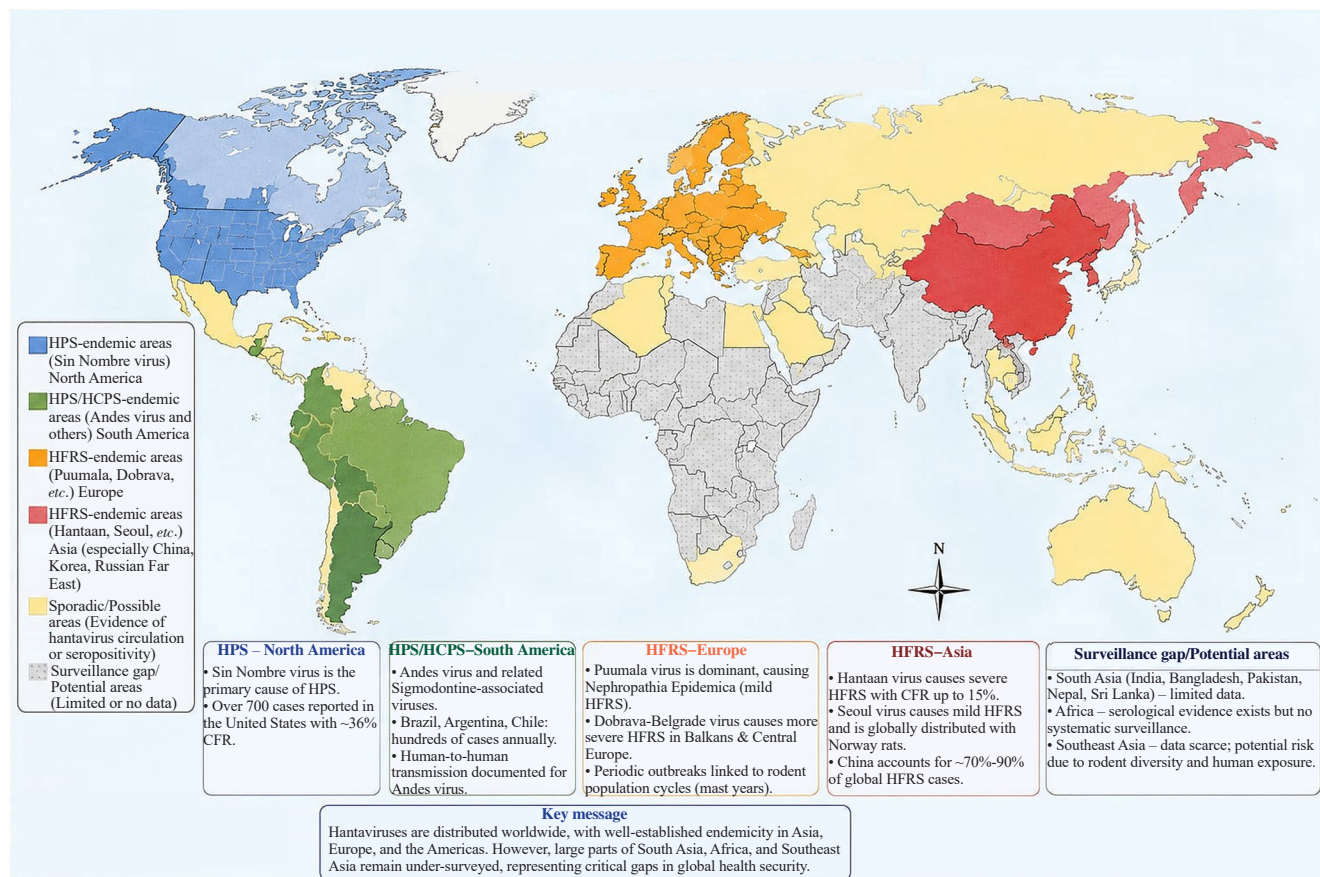
| Driver category                 | Mechanism of influence                                                                             | Reference |
|---------------------------------|----------------------------------------------------------------------------------------------------|-----------|
| Rodent population cycles        | Multi-annual mast events (beechnuts, acorns) → rodent outbreaks → increased human exposure         | [29,33]   |
| Climate variability (ENSO)      | El Niño-driven rainfall → vegetation boom → rodent density increase                                | [12,42]   |
| Land use change & deforestation | Forest fragmentation increases rodent-human interface; biodiversity loss elevates virus prevalence | [44,47]   |
| Urbanization                    | Urban rodent populations sustain Seoul virus; city growth prolongs epidemic duration               | [48]      |
| Biodiversity (dilution effect)  | Low host diversity → increased hantavirus prevalence in reservoir populations                      | [45,46]   |
| Seasonality & temperature       | Warmer springs extend rodent breeding; cold winters suppress populations                           | [32,49]   |
| Predator species richness       | Higher predator diversity limits rodent abundance and virus spillover                              | [50]      |

ENSO: El Niño Southern Oscillation.

**Table 2.** Major hantavirus species, rodent reservoirs, geographic distribution, associated clinical syndrome, and case fatality rate.

| Virus            | Disease     | Reservoir host                    | Geographic region | CFR (%) | Reference |
|------------------|-------------|-----------------------------------|-------------------|---------|-----------|
| Sin Nombre virus | HPS         | <i>Peromyscus maniculatus</i>     | North America     | 30-40   | [2]       |
| Andes virus      | HPS         | <i>Oligoryzomys longicaudatus</i> | South America     | 25-35   | [5]       |
| Puumala virus    | HFRS (NE)   | <i>Myodes glareolus</i>           | Europe            | <1      | [3]       |
| Hantaan virus    | HFRS        | <i>Apodemus agrarius</i>          | Asia              | 5-15    | [4]       |
| Seoul virus      | HFRS (mild) | <i>Rattus norvegicus</i>          | Worldwide         | 1-5     | [10]      |
| Dobrava-Belgrade | HFRS        | <i>Apodemus flavicollis</i>       | Balkans/Europe    | 5-12    | [58]      |
| Bayou virus      | HPS         | <i>Oryzomys palustris</i>         | SE United States  | ~35     | [6]       |
| Laguna Negra     | HPS         | <i>Calomys laucha</i>             | South America     | ~30     | [66]      |

HPS: hantavirus pulmonary syndrome; HFRS: hemorrhagic fever with renal syndrome; NE: Nephropathia Epidemica; CFR: case fatality rate.

**Figure 3.** Global distribution of HFRS and HPS/HCPS with surveillance gap regions[2,3,5,10,12,14]. HFRS: hemorrhagic fever with renal syndrome; HPS: Hantavirus pulmonary syndrome; HCPS: Hantavirus cardiopulmonary syndrome; CFR: case fatality rate.

America bears a disproportionate HPS burden; Brazil is the most affected country, with Andes and related Sigmodontine-associated viruses causing hundreds of cases annually[14,61,62]. Argentina and Chile have been focal points of ANDV activity, including documented household clusters compatible with human-to-human transmission[39,63] (Table 2).

#### 4.5. Africa and Oceania: Terra incognita

Serological evidence suggests hantavirus circulation in Africa and Southeast Asia, but formal surveillance systems are absent, and no well-characterized human disease epidemics have been described from these regions[27,64]. Africa harbors extensive Murinae rodent diversity and significant agricultural communities with rodent exposure, suggesting the existence of uncharacterized disease burden. This represents a critical surveillance gap with significant implications for global health security[65] (Table 2).

### 5. Pathogenesis and immunology

#### 5.1. Target cells and initial infection

Following inhalation, hantaviruses traverse the respiratory epithelium and establish primary infection in pulmonary endothelial cells and alveolar macrophages. Across the hantaviruses, the common pathophysiological endpoint, regardless of the specific virus species responsible, is profound vascular hyperpermeability: in HPS, this manifests as pulmonary edema, whereas in HFRS it manifests as renal and systemic hemorrhage. This permeability is not attributable to direct viral cytopathic effect, as hantaviruses do not lyse infected endothelial cells; rather, it results from immune-mediated disruption of endothelial barrier function[5,22,67].

#### 5.2. Immune pathology

The pathogenesis of hantavirus disease is fundamentally immunopathological. Massive influx of cytotoxic T lymphocytes and natural killer cells into infected tissues is a consistent finding in fatal cases. Virus-specific CD8<sup>+</sup> T cells generate high levels of pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , and interleukin-6, that collectively disrupt tight junctions between endothelial cells, increasing vascular permeability[5]. The magnitude of the T-cell response correlates with disease severity, and human leukocyte antigen class I haplotypes modulate both susceptibility and clinical outcome. Regulatory T-cell deficiency and excessive innate immune activation contribute to the cytokine storm observed in severe HPS[22]. Paradoxically, a robust humoral immune response, characterized by high-titer neutralizing

antibodies, is associated with survival, particularly when generated during the prodromal phase.

#### 5.3. Vascular permeability mechanisms

The molecular basis of hantavirus-induced vascular hyperpermeability remains incompletely resolved, constituting a major research gap. Proposed mechanisms include: (1) virus-induced downregulation of vascular endothelial-cadherin and other adherens junction proteins; (2)  $\beta$ -3 integrin signaling perturbation impairing vascular endothelial growth factor responses; (3) complement activation generating anaphylatoxins C3a and C5a; and (4) platelet activation and thrombocytopenia exacerbating haemostatic dysfunction[5,22]. Recent *in vitro* studies using human endothelial cell models and emerging organoid platforms offer promising avenues for mechanistic elucidation, though *in vivo* validation remains challenging given the absence of an ideal animal model (Figure 4).

#### 5.4. Renal pathology in HFRS

In HFRS, the kidney is the primary target organ[22]. Histopathological findings include tubulointerstitial nephritis, glomerular mesangial proliferation, and interstitial hemorrhage. Viral antigens are identified in tubular epithelial cells and glomerular endothelial cells. The oliguric phase reflects acute tubular necrosis and interstitial edema, with subsequent diuresis as edema fluid is mobilized. Long-term sequelae, including chronic kidney disease and hypertension, have been increasingly recognized in PUUV survivors[22].

### 6. Clinical manifestations

#### 6.1. HFRS

HFRS classically progresses through five clinical phases: febrile (days 1-5), hypotensive (days 3-6), oliguric (days 5-11), diuretic (days 12-14), and convalescent (weeks to months). The febrile phase is characterized by the abrupt onset of high fever, myalgia, headache, and back pain, with thrombocytopenia and proteinuria developing rapidly. The hypotensive phase carries the highest mortality risk, with capillary leak syndrome causing plasma volume depletion and shock. Oliguria with rising creatinine characterizes the oliguric phase; hemodialysis may be required. The diuretic phase marks recovery of renal function. The severity spectrum is broad: PUUV typically causes mild Nephropathia Epidemica, while Hantaan virus causes severe HFRS with CFRs approaching 15%[4,10,22]. The detailed comparison of HFRS and HPS features is provided in Table 3.

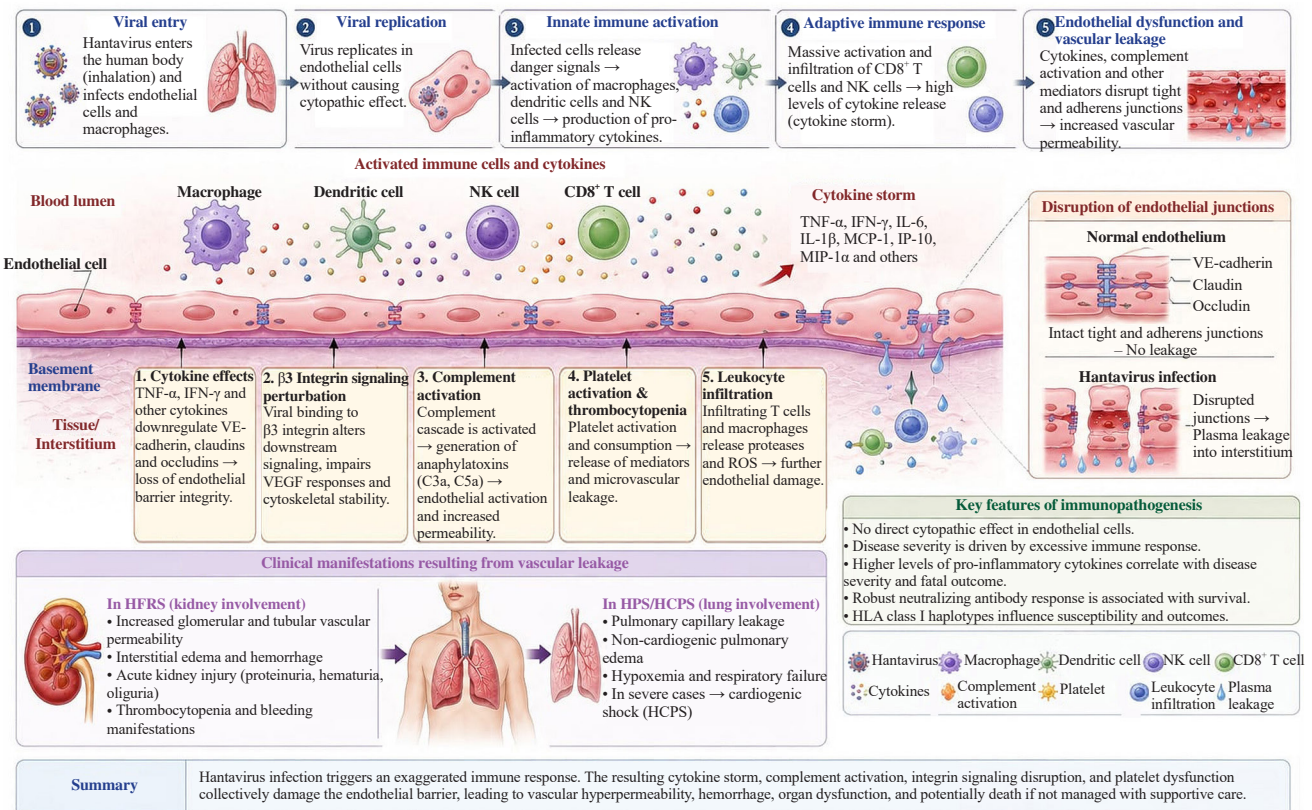


Figure 4. Immunopathogenesis of hantavirus-induced vascular hyperpermeability[68,69].

## 6.2. HPS

The pathogenesis of hantavirus disease is fundamentally immunopathological. Massive influx of cytotoxic T lymphocytes and natural killer cells into infected tissues is a consistent finding in fatal cases. Virus-specific CD8<sup>+</sup> T cells generate high levels of pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , and interleukin-6, that collectively disrupt tight junctions between endothelial cells, increasing vascular permeability[5]. The magnitude of the T-cell response correlates with disease severity, and human leukocyte antigen class I haplotypes modulate both susceptibility and clinical outcome. Regulatory T-cell deficiency and excessive innate immune activation contribute to the cytokine storm observed in severe HPS[22]. Paradoxically, a robust humoral immune response, characterized by high-titer neutralizing antibodies, is associated with survival, particularly when generated during the prodromal phase.

## 7. Diagnosis

### 7.1. Clinical diagnosis

Clinical diagnosis of hantavirus infection is challenging due to non-

specific initial manifestations. A high index of suspicion should be maintained in patients presenting with febrile illness accompanied by thrombocytopenia, renal impairment (HFRS), or unexplained pulmonary infiltrates (HPS), particularly those with occupational or recreational rodent exposure histories[5,22]. The clinical picture of hantavirus infection also overlaps substantially with leptospirosis and, to a lesser extent, dengue, particularly in tropical and subtropical settings where exposure risk and disease endemicity coincide; hantavirus infection has repeatedly been misdiagnosed as leptospirosis or dengue in such regions and should be considered in the differential diagnosis of compatible febrile illness even when dengue- or leptospirosis-specific testing is negative[51,70].

### 7.2. Laboratory diagnostics

Serological detection of hantavirus-specific IgM and IgG antibodies by enzyme-linked immunosorbent assay is the diagnostic standard in most clinical settings. IgM antibodies appear within three to five days of symptom onset, enabling early diagnosis. IgM antibodies typically remain detectable for approximately three to four months after infection, whereas IgG persists for years; consequently, a single positive IgM result alone is not sufficient to confirm acute infection, and diagnosis should ideally be corroborated by a four-fold rise in IgG titer between acute- and convalescent-phase paired sera, or

**Table 3.** Comparative clinical features of HFRS and HPS.

| Features                    | HFRS                                                   | HPS                                                    |
|-----------------------------|--------------------------------------------------------|--------------------------------------------------------|
| Causative viruses           | Hantaan, Seoul, Puumala, Dobrava                       | Sin Nombre, Andes, Bayou                               |
| Primary target organ        | Kidney (renal tubules)                                 | Lungs (pulmonary vasculature)                          |
| Incubation period           | 2-4 weeks                                              | 1-5 weeks                                              |
| Key clinical phases         | Febrile, hypotensive, oliguric, diuretic, convalescent | Prodromal, cardiopulmonary, diuretic, convalescent     |
| Hallmark finding            | Acute kidney injury, proteinuria, hematuria            | Non-cardiogenic pulmonary edema, bilateral infiltrates |
| Case fatality rate          | <1% (Puumala) to 15% (Hantaan)                         | 20%-40% (SNV); 25%-35% (ANDV)                          |
| Hemorrhage                  | Common (thrombocytopenia)                              | Uncommon                                               |
| Shock                       | Hypotensive phase (days 3-5)                           | Cardiogenic shock in severe HPS                        |
| Treatment                   | Ribavirin (some evidence), supportive dialysis         | Supportive; ECMO in severe cases                       |
| Human-to-human transmission | Not documented                                         | Documented for ANDV only                               |

SNV: Sin Nombre virus; ANDV: Andes virus; ECMO: extracorporeal membrane oxygenation.

**Table 4.** Diagnostic methods for hantavirus infection.

| Method                     | Principle                      | Sensitivity             | Limitation                                                                                                                      | Setting                                 |
|----------------------------|--------------------------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| IgM/IgG ELISA              | Antibody-antigen binding       | High (>90%)             | Window period; cross-reactivity; single IgM positivity alone is not confirmatory and should ideally be supported by paired sera | Clinical/reference laboratory (BSL-2)   |
| RT-PCR                     | Viral RNA detection            | Very high (acute phase) | Requires specialized lab; costly; narrow diagnostic window owing to short-lived viremia                                         | Clinical/reference laboratory (BSL-2)   |
| Immunofluorescence assay   | Fluorescent antibody binding   | Moderate-High           | Subjective interpretation; operator-dependent                                                                                   | Specialized clinical laboratory (BSL-2) |
| Immunoblot/Western blot    | Protein band detection         | High (confirmatory)     | Slow; labour-intensive                                                                                                          | Reference laboratory (BSL-2)            |
| Rapid lateral flow assay   | Antigen or antibody strip test | Moderate                | Low sensitivity in early infection; not widely validated for all strains                                                        | Field/POC                               |
| Neutralisation test (PRNT) | Virus-specific antibody titres | Gold standard           | Requires live-virus handling; slow                                                                                              | BSL-3 reference laboratory only         |
| Next-generation sequencing | Full genome characterisation   | Highest (strain-level)  | Expensive; bioinformatics expertise required                                                                                    | Research labs                           |

ELISA: enzyme-linked immunosorbent assay; PRNT: plaque reduction neutralization test; BSL: biosafety level; POC: point-of-care.

interpreted alongside a compatible clinical and exposure history[71]. Immunofluorescence assay and immunoblot techniques provide complementary specificity. The plaque reduction neutralization test represents the serological gold standard but requires biosafety level 3 laboratory infrastructure[22,53]. Molecular diagnosis by reverse transcription polymerase chain reaction (RT-PCR) targeting the S or M segment offers high sensitivity during the acute viremic phase but requires specialized facilities and is less accessible in endemic LMICs. A broadly reactive, nested RT-PCR assay targeting the more conserved L segment is also available and is increasingly used for pan-hantavirus screening and for identifying novel or divergent strains that S- or M-segment assays may fail to detect[72]. A key limitation of all RT-PCR-based approaches, however, is the short duration of detectable viremia, which is typically confined to the first few days of illness, leaving only a narrow window before viral RNA becomes undetectable in blood[71]. Next-generation sequencing enables strain-level characterisation and has revolutionized molecular epidemiology[59,65]. A comprehensive comparison of

diagnostic methods is provided in Table 4.

### 7.3. Diagnostic gaps in resource-limited settings

A critical unmet need exists for validated point-of-care (POC) rapid diagnostic tests for hantavirus infection in LMICs. Current rapid lateral flow assays lack sufficient sensitivity for early-phase diagnosis and have not been validated against the full diversity of circulating hantavirus strains[16]. CRISPR-based nucleic acid detection platforms and loop-mediated isothermal amplification assays represent promising emerging technologies that could enable field-deployable molecular diagnosis without cold-chain requirements, but their clinical validation against diverse hantavirus strains is incomplete. Cross-reactive antibody responses, particularly between Seoul virus and other Murinae-associated viruses, complicate serological interpretation in endemic regions where multiple hantavirus species co-circulate.

## 8. Treatment and clinical management

### 8.1. Supportive care

No specific antiviral therapy is universally approved for hantavirus infection. Management is primarily supportive, with careful attention to fluid balance, hemodynamic monitoring, and management of end-organ failure. For HFRS, renal replacement therapy (dialysis) is required in severe oliguria. For HPS, intensive respiratory support, including mechanical ventilation and, in refractory cases, venovenous extracorporeal membrane oxygenation, has improved outcomes at specialized centers[5].

### 8.2. Antiviral therapy

Ribavirin, a nucleoside analogue with broad-spectrum antiviral activity, has been evaluated in hantavirus infection. Evidence supporting its use in HFRS, particularly for Hantaan virus, is limited to early observational studies and a small number of clinical trials suggesting modest benefit when initiated within four days of onset[5]. For HPS, clinical trial evidence is largely negative; a randomized controlled trial of intravenous ribavirin for HPS in North America showed no benefit. These limitations, combined with ribavirin's adverse effect profile, highlight the urgent need for novel antivirals. Drug repurposing candidates, including favipiravir, remdesivir, and molnupiravir, have demonstrated *in vitro* activity against hantaviruses, but clinical data are absent[5,73].

### 8.3. Immunotherapy

Passive immunotherapy using convalescent plasma has been used empirically in ANDV hantavirus cardiopulmonary syndrome, with some observational evidence of benefit when administered early[5]. Monoclonal antibody therapy targeting hantavirus glycoproteins Gn and Gc is an active preclinical research area. The demonstration of potent neutralizing monoclonal antibodies with cross-reactive activity against multiple hantavirus species raises prospects for broadly protective immunotherapeutic products.

## 9. Prevention and public health measures

### 9.1. Environmental and behavioural prevention

In the absence of an approved vaccine, prevention relies on reducing human-rodent contact. Public health guidelines recommend rodent-proofing buildings, proper food storage, safe disposal of rodent nesting materials (using wet methods to avoid aerosol generation), and use of personal protective equipment, including N95

respirators, when cleaning rodent-infested spaces. Rodent control programmes using poison baiting and trapping reduce reservoir populations in peridomestic environments but are logistically challenging in rural agricultural settings[9,40].

### 9.2. Vaccination

The most impactful prevention gap is the absence of an internationally approved, broadly protective hantavirus vaccine. Inactivated whole-virus vaccines (Hantavax in South Korea; bivalent vaccines in China) are licensed for limited use in specific endemic regions, but demonstrate modest efficacy and limited immunogenicity duration, requiring repeated boosters[5,73]. DNA vaccines, virus-like particle vaccines, and mRNA-based platforms have demonstrated immunogenicity in preclinical models, but no candidate has advanced beyond Phase II clinical trials. The rapid development and deployment of mRNA vaccines during the SARS-CoV-2 pandemic provides a technological template that could be adapted for hantavirus vaccine development, representing a critical opportunity for accelerated investment[18].

### 9.3. One Health surveillance frameworks

Effective hantavirus prevention requires integration of human, animal, and environmental health monitoring within a One Health paradigm[17]. Integrated surveillance should combine rodent population monitoring, seroprevalence surveys in reservoir species, environmental sampling of hantavirus RNA, and human clinical surveillance in sentinel healthcare facilities. Geographic information systems and species distribution models can be used to map spillover risk and prioritize surveillance resources[15,35,74]. The development of the ArHa (Arenavirus and Hantavirus) host-pathogen database represents a step towards a harmonized global surveillance infrastructure[65].

## 10. Critical research gaps and future directions

Despite four decades of hantavirus research, fundamental scientific questions remain unresolved, and the global public health infrastructure to manage hantavirus disease is substantially inadequate.

### 10.1. Vaccine development

The absence of an approved, broadly protective hantavirus vaccine is the most critical gap in the prevention landscape. Current licensed vaccines (Hantavax, China bivalent vaccine) offer limited geographic coverage and suboptimal immunogenicity. No mRNA-based, virus-

like particle-based, or recombinant subunit vaccine candidate has advanced to Phase III trials. Investment in multi-antigen, cross-reactive vaccine platforms, capable of protection against both HFRS-causing and HPS-causing strains, is urgently needed[5,18,74].

### 10.2. Antiviral drug development

Randomized controlled trial evidence for any antiviral agent against hantavirus infection is lacking. Ribavirin's clinical benefit remains unproven in prospective trials for both HPS and severe HFRS. Systematic drug repurposing programmes leveraging existing antiviral libraries, combined with structure-based drug design targeting the hantavirus RdRp or glycoprotein entry mechanisms, are priority actions. High-throughput screening of approved antiviral compounds in biosafety level 3 cell-culture models could rapidly identify clinical candidates[5,73].

### 10.3. Surveillance in South Asia and Africa

The near-complete absence of systematic hantavirus surveillance in South Asia (Bangladesh, India, Pakistan, Nepal, Sri Lanka) and sub-Saharan Africa represents a critical blind spot in the global infectious disease landscape[41,54,64]. Commensal rodent species with hantavirus reservoir potential, including *Rattus rattus*, *Rattus norvegicus*, and multiple *Mus* species, are ubiquitous in these regions. Establishing sentinel serological surveillance in occupational risk groups (agricultural workers, abattoir workers, healthcare workers) and developing regional laboratory capacity for hantavirus diagnostics should be prioritized within the WHO regional frameworks.

### 10.4. POC diagnostics

The clinical management and outbreak response to hantavirus infection in LMICs is fundamentally limited by diagnostic inaccessibility. Current POC lateral flow assays lack sensitivity for early-phase diagnosis and have not been validated against the full spectrum of circulating strains[16]. Development and clinical validation of CRISPR-Cas12/13-based or loop-mediated isothermal amplification-based POC diagnostics for hantavirus, capable of being deployed in rural health facilities without refrigerated equipment, would represent a transformative advance. International regulatory frameworks for POC diagnostic validation in endemic settings should be established.

### 10.5. Pathogenesis research

The molecular mechanisms governing hantavirus-induced vascular hyperpermeability remain incompletely characterised.

Key unresolved questions include: the precise signaling pathways through which beta-3 integrin perturbation disrupts endothelial adherens junctions; the relative contributions of direct viral effects versus immune-mediated pathology to vascular permeability; the immunological correlates of protection distinguishing survivors from fatal cases; and the basis of sex-based differences in infection outcomes[30]. Human endothelial organoid models, single-cell RNA sequencing of patient peripheral blood mononuclear cells, and multi-parameter immunological profiling of longitudinal patient cohorts offer powerful tools for addressing these questions.

### 10.6. Human-to-human transmission

The biological basis of ANDV capacity for human-to-human transmission, unique among hantaviruses, is not understood. Characterization of the specific viral and host determinants enabling this transmission route, through comparative genomic and experimental studies, is a high-priority research question with direct implications for outbreak containment and infection prevention in healthcare settings[39].

### 10.7. Climate change modeling

Current predictive models linking climate change to hantavirus disease risk lack the spatial granularity and biological realism needed to inform local public health planning. Integration of climate projections with mechanistic rodent population-disease models, validated against multi-decadal empirical surveillance data, would substantially improve outbreak forecasting capacity. Long-term ecological monitoring platforms in key endemic regions are essential data inputs for such models[12,35,42].

## 11. Conclusion

Hantaviruses represent a persistent and likely expanding global public health threat, sustained by the ubiquity of their rodent reservoir hosts, the absence of approved preventive or curative interventions, and the inadequacy of surveillance systems in much of the world. This comprehensive review has delineated the current state of knowledge across the disciplines of virology, reservoir ecology, global epidemiology, pathogenesis, clinical medicine, diagnostics, and prevention, whilst explicitly mapping the critical gaps that constrain an effective global response.

The most urgent priorities are the development of a broadly protective mRNA or recombinant vaccine; the conduct of rigorous clinical trials for antiviral agents, including ribavirin and novel repurposed compounds; the establishment of integrated One Health surveillance networks in South Asia and sub-Saharan Africa; the

development and validation of field-deployable POC diagnostic tools; and the fundamental elucidation of the immunopathological mechanisms governing vascular permeability in hantavirus disease. The extraordinary advances in vaccine technology, genomic surveillance, and diagnostic platforms catalyzed by the COVID-19 pandemic provide unprecedented tools and institutional momentum that could be redirected to address these gaps.

A coordinated, multidisciplinary, and multi-sectoral response, grounded in One Health principles, is essential to reduce the burden of hantavirus disease. This will require sustained investment from national governments, international health organizations, and research funders, as well as meaningful engagement with affected communities and the integration of local ecological knowledge. The research agenda outlined in this review provides a structured framework for prioritizing these investments and accelerating progress toward hantavirus prevention and control.

### Conflict of interest statement

The author declares that there is no conflict of interest.

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