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REVIEW ARTICLE

Hantavirus Infections: Emerging Threats, Molecular Pathogenesis, and Advances in Therapeutic Strategies

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Abstract

Hantavirus infections are an emerging threat to global health with hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) with high case fatality rates. This review aims to analyse the emerging epidemiological trends, molecular pathogenesis and advances in treatment to inform future intervention strategies.

We reviewed hantavirus taxonomy in the family Hantaviridae, virology, global distribution associated with rodent reservoirs, and transmission dynamics with emphasis on outbreaks in Europe in 2025-2026 and novel reassortants. Molecular pathogenesis involves targeted entry thru beta3-integrins, immune escape by NSs and N proteins and vascular leak caused by cytokine dysregulation. Clinical symptoms include initial fever and muscle pain, shock and organ failure, diagnosed by IgM ELISA and RT-PCR.

Key findings include the lack of FDA-approved vaccines except China's Hantavax which is losing efficacy and the need for supportive care. Preclinical mRNA vaccines, monoclonal antibodies (e.g., JS02.2) and host-directed therapies (JAK inhibitors) however, provide 80-95% protection in models. Prevention relies on rodent control and surveillance.

In Conclusion, the integration of cryo-EM data, AI prediction of epitope mapping, and One Health strategies provides hope for universal hantavirus countermeasures, potentially avoiding climate change aggravated pandemics by 2030.

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INTRODUCTION

Hantaviruses, enveloped RNA viruses from the family *Hantaviridae* within the order *Bunyavirales*, pose a persistent yet often overlooked threat to global public health. Transmitted primarily through inhalation of aerosolized excreta from infected rodents, these zoonotic pathogens cause two major human syndromes: hemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus pulmonary syndrome (HPS) in the Americas. With over 200,000 annual HFRS cases reported in Asia alone predominantly from *Hantaan* and *Seoul* viruses and HPS outbreaks linked to *Sin Nombre* virus in the U.S., hantaviruses have reemerged as a formidable challenge amid climate-driven habitat shifts and urbanization [1].

Recent data underscore their escalating risks. In 2025, Europe saw a surge in *Puumala* virus cases in Scandinavia due to vole population booms from mild winters, while novel reassortants in East Asia raised alarms for enhanced transmissibility. These trends, exacerbated by global warming and intensified rodent-human interfaces, highlight hantaviruses as emerging threats with pandemic potential, as evidenced by the 1993 Four Corners outbreak that killed nearly 40% of infected individuals [2].

At the molecular level, hantaviruses hijack host pathways with precision. Their tri-segmented single-stranded RNA genome encodes nucleocapsid (N), glycoproteins (Gn/Gc), and RNA-dependent RNA polymerase (L) proteins, enabling immune evasion via interferon antagonism and endothelial dysfunction. Pathogenesis hinges on the virus's ability to induce vascular leakage through Gn/Gc-mediated platelet activation and vascular endothelial growth factor (VEGF) upregulation culminating in capillary leak syndrome, thrombocytopenia, and multi-organ failure. Recent cryo-EM structures (2024-2025) of Gn/Gc trimers have illuminated receptor-binding motifs for integrin αvβ3, paving the way for targeted interventions [3].

Despite their lethality, no FDA-approved vaccines or antivirals exist beyond supportive care. Ribavirin offers modest HFRS benefits but falters against HPS, while monoclonal antibodies and small-molecule inhibitors targeting the polymerase show promise in preclinical models.

CLASSIFICATION AND VIROLOGY OF HANTAVIRUS

Taxonomy and Classification

Hantaviruses belong to the family *Hantaviridae* within the order *Bunyavirales*, elevated to family status in 2016 from their prior genus designation under *Bunyaviridae*. They encompass the genus *Orthohantavirus*, with over 40 species phylogenetically grouped into clades corresponding to their rodent reservoirs: Eurasian (e.g., HFRS-causing *Hantaan*, *Puumala*, *Seoul*), American (*New World* or Neo-American, e.g., HPS-causing *Sin Nombre*, *Andes*), and minor clades like those in shrews and bats. Classification relies on

sequence divergence (>7% in L segment), reservoir host, and geographic distribution, with recent additions like *Bowman's Hill virus* reflecting expanded host ranges beyond rodents [4].

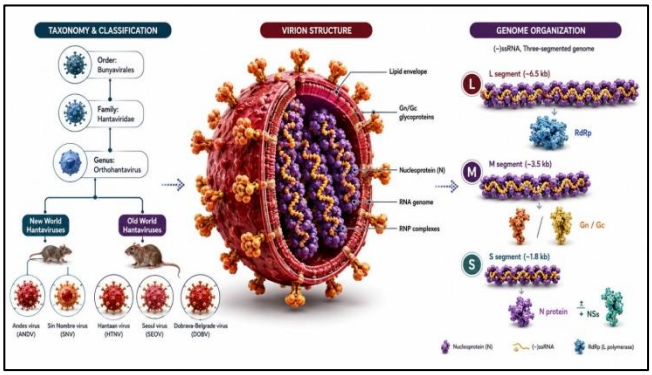


Figure 1: Classification and Virology of Hantavirus: Taxonomy, Virion Structure, and Genome Organization. (Source: Created by the authors using AI-assisted scientific illustration tools and manually refined for scientific accuracy)

This schematic depicts the hantavirus structure, highlighting its tri-segmented genome enveloped by glycoproteins Gn and Gc, which is central to its classification as an enveloped negative-sense RNA virus.

Virion Structure

Hantavirus particles are enveloped, spherical virions measuring 80–120 nm in diameter, featuring a lipid bilayer derived from host Golgi membranes studded with Gn and Gc glycoproteins. These surface proteins form heterotrimers critical for receptor binding (e.g., β3-integrins, DC-SIGN) and membrane fusion. The core contains three ribonucleocapsid segments encapsidated by nucleoprotein (N), housing the viral RNA-dependent RNA polymerase (L).

Transmission electron micrographs reveal hantavirus virions as textured spheres, illustrating their enveloped morphology and internal ribonucleoprotein complexes.

Genome Organization

The genome comprises three single-stranded, negative-sense RNA segments: L (6.8–12 kb, encoding RdRp), M (3.2–4.9 kb, encoding Gn, Gc, and sometimes NSM), and S (1–3 kb, encoding N and occasionally NSs via ambisense or leaky scanning). Total genome size is ~11–14 kb, with capped mRNAs generated via cap-snatching by L's endonuclease. Some species like *Puumala* express NSs for innate immune antagonism [7].

Replication Cycle

Replication occurs cytoplasmically: virions attach via Gn/Gc, enter via endocytosis, and fuse in late endosomes, releasing ribonucleocapsids. Primary transcription by L produces viral mRNAs; antigenome synthesis follows, enabling replication and secondary transcription. New ribonucleocapsids bud into Golgi, acquiring envelope and glycoproteins for exocytosis. The cycle exploits host lipid rafts and evades interferon via N and NSs proteins [8].

EPIDEMIOLOGY AND TRANSMISSION

Global Distribution

Hantaviruses are distributed worldwide, but are closely associated with specific rodent reservoirs in which they cause persistent infection without overt

disease. Asia carries the heaviest burden with > 200,000 cases per year of hemorrhagic fever with renal syndrome (HFRS) mainly caused by Hantaan virus (HTNV) in China and Korea, Seoul virus (SEOV) in urban rats throughout Eurasia and milder Puumala virus (PUUV) cases in Europe. In the Americas, the main hantavirus pulmonary syndrome (HPS) is caused by Sin Nombre virus (SNV) in deer mice in the western U.S. (almost 900 cases since 1993) and the highly lethal Andes virus (ANDV) in South America, particularly in Argentina and Chile [9].

Hantaviruses are distributed worldwide, with each virus associated with a specific rodent reservoir in which persistent infections occur without overt disease in the host. Asia is the most affected continent, with >200,000 annual cases of hemorrhagic fever with renal syndrome (HFRS), mainly due to Hantaan virus (HTNV) in China and Korea, Seoul virus (SEOV) in urban rats throughout Eurasia and milder Puumala virus (PUUV) cases in Europe. In the Americas, hantavirus pulmonary syndrome (HPS) is the most important disease, and is caused by Sin Nombre virus (SNV) in deer mice across the western U.S. (nearly 900 cases since 1993) and Andes virus (ANDV) in South America, particularly Argentina and Chile [10].



Figure 2: Peromyscus leucopus - white-footed deer mouse.

The deer mouse (*Peromyscus maniculatus*), shown here, serves as the primary reservoir for SNV, fueling HPS cases in rural North America through ecological overlap with human activity.

Transmission Routes

Humans are infected primarily thru inhalation of aerosolised virus from rodent urine, droppings or saliva, particularly when disturbing contaminated materials in enclosed spaces such as sheds or cabins. Other, less common, routes include rodent bites, ingestion of contaminated food, or mucosal contact with contaminated surfaces. Specifically, in Argentine clusters, ANDV is the only hantavirus that has demonstrated human-to-human transmission thru close contact via the respiratory route; no other strains have shown efficient person-to-person transmission, including healthcare workers [12].

Risk Factors and Recent Outbreaks

Key risks include rural occupations (farming, forestry), cleaning rodent-infested sites, and urban-

rural interfaces exacerbated by climate-driven rodent population surges (e.g., vole booms in post-mild-winter Europe). Males and some ethnic groups (e.g., American Indians in U.S. HPS) are disproportionately affected. Climate and travel-related emergence is highlighted by surges in PUUV incidence in Europe (e.g., Finland 2025), an 8-case/3-fatality cluster on an Atlantic cruise ship in 2026 traced to shipboard rats, and continued endemic HFRS in East Asia [13].

MOLECULAR PATHOGENESIS AND HOST IMMUNE RESPONSE

Attachment and Entry

Hantavirus entry starts with the binding of the virus to the surface of host cells, primarily via glycoproteins Gn and Gc displayed in tetrameric spikes on the envelope. Gc binds to β3-integrins (αvβ3 and αIIbβ3) that are abundant on endothelial cells, dendritic cells and platelets. Infection is inhibited 70-90% in plaque reduction assays and siRNA knockdown studies. Other receptors such as DC-SIGN (CD209) on dendritic cells and gC1qR help immune cells uptake. Cryo-EM structures reveal a class II fusion protein fold including ANDV Gc at 3.5 ? resolution. Receptor recognition is mediated by key motifs in domains I–III [14].

Virions are taken up by clathrin- and caveolin-independent macropinocytosis or endocytosis and directed to early endosomes upon binding. Late endosomes have a low pH (5.8–6.2), which triggers a conformational change in Gc that exposes fusion loops to mediate hemifusion and pore formation with the endosomal membrane. This is corroborated by fluorescence microscopy following pH-dependent colocalization with Rab7+ endosomes. Entry is blocked by Bafilomycin A1 by 80% [15].

Transmission electron microscopy of Sin Nombre virions reveals the enveloped nature of the virus, which is crucial to receptor-mediated entry into host cells.

Genome Release and Transcription

After fusion, the tri-segmented negative-sense RNA genome (L: ~6.5 kb RdRp; M: ~3.5 kb Gn/Gc ± NSm; S: ~1.8 kb N ± NSs) releases into the cytoplasm with associated nucleoproteins (RNPs). Primary transcription starts when L polymerase's endonuclease domain snatches 5' caps from host mRNAs, creating viral mRNAs that translate into N, Gn/Gc precursors, and L. Minigenome assays in Vero E6 cells show that cap-snatching efficiency relates to viral titer, with host Pol II transcripts being preferred. N protein stabilizes nascent vRNAs, as evidenced by IP-MS pulldowns [16].

Replication and Protein Processing

Once enough N is made, replication shifts to full-length antigenomes which accumulate in cytoplasmic inclusion bodies (viroplasms) where RdRp is active. Amplification results in excess vRNPs, as confirmed by FISH and metabolic labelling, with a 10-fold increase in vRNA by 24 h post infection (hpi). Gn/Gc precursors are processed in the Golgi, including furin cleavage of Gc, glycosylation (10-15 sites), and binding of Zn2+ in

the WRIS motif of Gn for maturation. Immunity is influenced by NSs (and in some cases ambisense S) and NSm (M frame-shift). NSs knockout mutants are more sensitive to interferon (IFN) in IFN competent cells [17,18].

Assembly and Egress

New RNPs associate with N and L and traffic to the Golgi, where they bud into vesicles. This results in a lipid envelope and glycoproteins and the production of filamentous virions (80-160 nm). The virus is released from the host cell by exocytosis . The filopodia help the virus to spread from cell to cell . Live-cell imaging and correlative light-EM reveal the presence of Golgi-derived vesicles and a 90% decrease in titer upon treatment with brefeldin A. As opposed to lytic human infection, reservoir rodents display tolerant immunity with asymptomatic replication [19,20].

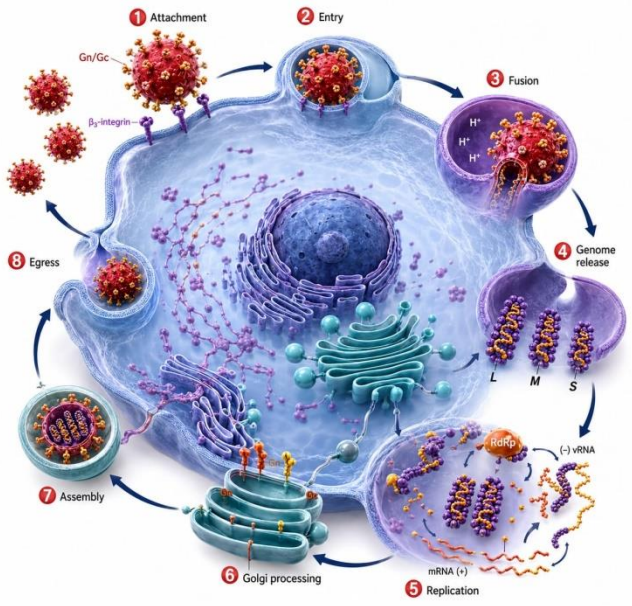


Figure 3: Hantavirus Replication Cycle: Molecular Events from Viral Entry to Egress. (Source: Created by the authors using AI-assisted scientific illustration tools and manually refined for scientific accuracy)

Immune evasion strategies of Hantavirus

Interferon Antagonism

Hantaviruses mainly evade type I interferon (IFN-I) responses via non-structural proteins NSs and N. NSs from Old World species such as Puumala and Tula viruses sequester RIG-I and MDA5 sensors in cytoplasmic aggregates, preventing IRF3 phosphorylation and IFN-β transcription. Knockout mutants have 100-fold reduced replication in IFN competent cells. The nucleoprotein N sequesters double-stranded RNA replication intermediates that would otherwise inhibit RIG-I activation and double-stranded RNA binding. N directly inhibits TBK1-IRF3 signalling, leading to a delay of IFN induction by 24–48 h [21].

Inhibition of JAK-STAT Pathway

After IFN production, hantaviruses disrupt signalling by binding STAT1/2 with the N protein, preventing nuclear translocation and ISG transcription. This is exemplified by reduced ISG15/IFIT1 expression in HTNV-infected cells despite high IFN levels. The Gn tail and NSm also block STAT2 phosphorylation, which enables the virus to keep replicating in interferon-treated cultures [22].

Modulation of Cell Death Pathways

Hantavirus N and Gc inhibit extrinsic apoptosis by upregulation of TRAIL-R2 decoy receptors and

inhibition of caspase-8 activation. This prolongs the life span of infected endothelial cells to generate progeny. They also inhibit necroptosis by mediating the degradation of RIPK3 by NSs and decrease pyroptosis by cleaving NLRP3 inflammasome components to reduce the release of IL-1β [23].

Adaptive Immune Evasion

Hantavirus N protein induces immune checkpoints, including PD-L1, on infected monocytes. This leads to T cell exhaustion with increasing level of PD-1/TIM-3 and associates with prolonged viremia in HFRS patients. Glycosylation and changes of glycoprotein Gc shape hide epitopes from neutralising antibodies, which limits early immune control [24].

Cellular Stress and Autophagy Interference

The N protein activates the PERK-eIF2α pathway to induce ER stress granules that sequester antiviral factors. It interacts with LC3 and inhibits autophagy flux, thus inhibiting RLR degradation and viral clearance. These together contribute to initial viral dissemination prior to the immunopathology created by overwhelming adaptive responses [25].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hemorrhagic fever with renal syndrome (HFRS) is endemic in Europe and Asia. It takes 2 to 6 weeks to go thru 5 stages. The prodrome of fever lasts 3 to 5 days and is characterised by high fever (>39°C), severe headache, myalgia, back and abdominal pain, nausea, and blurred vision. This stage is commonly accompanied by facial flushing, conjunctival injection, and petechiae. Hypotensive shock develops over hours to days. Symptoms include vascular collapse, tachycardia, and haemorrhage. Oliguric renal failure (3 to 7 days) causes uremia and fluid overload. After the diuresis (days) there is the recovery and then the convalescence [26,27].

The prodrome (3 to 6 days) resembles flu symptoms. Fever, severe muscle pain in thighs and hips, headache, gastrointestinal upset and dizziness. The cardiopulmonary phase (hours) is worse with cough, shortness of breath, low blood oxygen, non-cardiogenic pulmonary oedema, low blood pressure and shock due to capillary leak. Those who survive experience diuresis and recovery, but 50% report long-term fatigue [28].

These radiographs demonstrate the progression of HPS: early hazy opacities (a), rapid bilateral oedema (b), resolution with ventilation (c), and are representative of acute lung injury [29].

Diagnosis is based on epidemiology (exposure to rodents), serology (IgM by ELISA, rising IgG titers), RT-PCR for viral RNA (highest early in viremia), and immunohistochemistry on tissues. Early symptoms overlap with influenza, so repeat testing at 72 hours is required. CDC/WHO reference labs confirm diagnosis using plaque assays or sequencing. Thrombocytopenia (<100,000/μL), leukocytosis and hemoconcentration support clinical suspicion [30].

Table 1: Clinical Manifestations and Diagnosis of Hantavirus Infections.

Syndrome	Phase	Key Clinical Features	Laboratory Findings	Diagnostic Tests
HFRS (Asia/ Europe)	Febrile Prodrome (3–5 days)	High fever (>39°C), headache, myalgia, back pain, nausea, facial flushing, conjunctival injection	Thrombocytopenia (<100k/μL), hemoconcentration, proteinuria	IgM ELISA (early), RT-PCR (viremia peak)
	Hypotensive (hours–days)	Shock, hemorrhage (petechiae, epistaxis), tachycardia	Elevated creatinine, leukocytosis	4-fold IgG rise, IHC on biopsy
	Oliguric (3–7 days)	Renal failure, uremia, fluid overload, hypertension	Azotemia, hyperkalemia	Confirmatory plaque assay (reference labs)
	Diuretic/Convalescent	Polyuria, gradual recovery	Normalizing labs	
HPS (Americas)	Prodrome (3–6 days)	Fever, severe myalgia (thighs/back), headache, GI upset, dizziness	Thrombocytopenia, left shift, prolonged PT/PTT	Serology (IgM/IgG), RT-PCR
	Cardiopulmonary (hours)	Dyspnea, cough, hypoxemia, pulmonary edema, shock (38% CFR)	Hemoconcentration, hypoalbuminemia	Chest X-ray (edema), blood PCR
	Diuretic (days)	Fluid mobilization	-	-
	Convalescent	Fatigue (50% long-term)	-	-

PREVENTING AND ADDRESSING THE THREAT

Reducing contact between rodents and humans can prevent hantavirus infection. For most areas, no licensed vaccines exist except for the Hantaan virus formulation in China. The main strategies are to seal homes to prevent entry (gaps <6 mm), trap or clean infested areas with a 10% bleach solution, store food in metal containers, and avoid contact with rodents without gloves. Public health campaigns focus on the need for ventilation before cleaning and to high risk groups such as farmers according to CDC and WHO guidelines [31].

Global surveillance involves trapping rodents, serologic monitoring of reservoirs, and reporting human cases to WHO and CDC networks. Outbreak responses include contact tracing (human-human transmission is rare except for the Andes virus), provision of personal protective equipment (PPE) for healthcare workers and community notification after spikes such as during the 2025 European Puumala outbreaks. Climate modelling can forecast increases in rodent populations to support vector control efforts [32,33].

The Hantaan-Seoul bivalent vaccine (Hantavax) is 95-100% effective against severe HFRS in China, but its efficacy decreases after 6-12 months and booster vaccinations are required. mRNA vaccine platforms tested by Moderna and Pfizer (2024-2026) against Gn/Gc epitopes neutralise challenges in hamsters with 90% success. DNA and viral

vector vaccines are in Phase I/II trials for Sin Nombre/Andes [34].

Monoclonal antibodies (JS02.2 targeting Gc) are complemented by broad-spectrum antivirals (favipiravir analogues) and host-directed therapies (JAK inhibitors for cytokine storms). Artificial intelligence–based epitope mapping and cryo-EM structures can speed up the development of pan-hantavirus vaccines. Climate resilient surveillance and a One Health approach can address emerging threats and potentially prevent pandemics by 2030 [35,36].

CONCLUSION

Hantavirus infections are still a relevant zoonotic threat. Climate changes, complex immune evasion strategies, and high death rates underline the need for innovation beyond basic supportive care. The review addressed the virologic basis, global epidemiology with surges in 2025-2026, endothelial-focused pathogenesis involving β3-integrin entry and cytokine storms. It highlights advancements in diagnostics such as rapid IgM/RT-PCR. Rodent control and surveillance are the backbone for prevention but therapeutic approaches are improving with mRNA vaccines, monoclonal antibodies targeting Gc and host-directed JAK inhibitors that have shown promising preclinical results. Hantavax, China's vaccine, shows promise for vaccination despite waning immunity. Future directions include the integration of One Health approaches with cryo-EM structural studies, AI-based epitope predictions and predictive models for rodent populations to enable comprehensive countermeasures against hantaviruses. Addressing these strategies will enable us to convert this neglected threat into a manageable public health problem, safeguarding vulnerable populations against escalating environmental issues.

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