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SILENT SPILLOVER: THE GLOBAL THREAT OF HANTAVIRUS-A COMPREHENSIVE REVIEW

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Abstract:
Hantaviruses are negative sense single-stranded RNA zoonotic viruses that transmit diseases to humans from rodent, shrew, mole and bat reservoirs and are responsible for two serious clinical syndromes, haemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS), occurring in various geographical areas. Hantavirus infection is an important, though under-recognized, public health problem, with an estimated human incidence of 200,000 cases per year globally, which is far from being covered by the international surveillance and pandemic preparedness system. The evidence from peer-reviewed literature and surveillance databases and outbreak investigation reports retrieved between 1993 and 2026 was synthesized using PubMed/MEDLINE, Embase, Web of Science, WHO official reports, ECDC notification datasets, as well as other grey literature (LANL hantavirus database, Argentine Ministry of Health epidemiological bulletins). It was found that the taxonomy of hantavirus has been greatly expanded since its reclassification in 2017 from the genus Hantavirus to a new family Hantaviridae, which currently includes more than 53 recognized species in seven genera. China has the highest burden of HFRS in the world and Argentina experienced a significant HFRS epidemiological surge in 2025–2026. The distribution of reservoir species, immunopathological disease mechanisms driven by climate change through the integrin pathway and the lack of FDA approved vaccines or antiviral drugs, all point to the escalating threat of this issue. There is ongoing preclinical evaluation of new generation vaccine platforms such as mRNA, DNA and virus-like particle vaccines. Hantavirus is a largely under-recognized, yet manageable, public health threat to the world driven by climate change, land use change, and growing anthropological association with wild animals, which demands a One Health approach.

Keywords: *Hantavirus, Zoonotic transmission, Haemorrhagic fever with renal syndrome (HFRS), Hantavirus pulmonary syndrome (HPS), One Health, Climate change, Emerging infectious diseases*

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1. INTRODUCTION:

Hantavirus is a manageable but underutilized global public health problem, whose risk profile is constantly changing due to climate change, land-use modification, and the growing human–wildlife interface. To solve this, a multidisciplinary One Health solution is needed that brings together an integrated surveillance system across sectors, next generation vaccine development, rapid point-of-care diagnostics, and climate-adaptive rodent management. These efforts, as well as other measures, are much needed to enhance the preparedness, early detection, and reduce the increasing public health burden of hantavirus infection. (3,20,24).

A Korean War era (1950-1953) outbreak of severe hemorrhagic fever with acute renal failure (Korean hemorrhagic fever) along the Hantaan River is considered the time of clinical recognition of hantavirus as a separate disease entity. However, the history of the disease goes back almost as far as Soviet military physicians reported almost the same disease clusters, in the Khabarovsk region along the Amur River, in 1934; and clinical descriptions similar to those of HFRS have been found in Chinese medical literature dating back to the 12th century (3,4). However, the etiological agent, Hantaan virus (HTNV), was not isolated and characterized until 1978, when Ho Wang Lee and coworkers isolated and characterized the virus from striped field mice (Apodemus agrarius) trapped near the Hantaan River in South Korea (1) In 1993 the discovery of Sin Nombre virus during a fatal outbreak in the "Four Corners" region of the American Southwest completely changed the nature of hantavirus from a regional medical curiosity in Korea and the Soviet Union to a zoonotic threat that is widely distributed throughout the world and is ecologically complex. (2,4). Hantaviruses are now known to infect humans at an estimated rate of about 200,000 per year, spread over six continents of the inhabited world, and resulting in a spectrum of clinical disease, ranging from subclinical seroconversion to acute cardiopulmonary syndrome (CPS) with case fatality rates >40% for some of the HPS-causing hantaviruses. Yet, this pandemic footprint of (3,4,11) is almost certainly a massive undercount. The early febrile prodrome is shared with a wide range of diseases that include influenza, leptospirosis, rickettsia, severe sepsis, etc., and serological or molecular testing for confirmatory diagnosis is not widely available in most primary care environments in endemic low- and middle-income countries. The global surveillance structure is similarly weak and fragmented, and thus often generates an impression of the disease burden that differs from that which is actually occurring, which affects the rational allocation of research and public health resources (3,11,24,26).

There are a number of current realities that call for an updated evaluation of hantavirus as a worldwide risk. First, it has been found that the family Hantaviridae is far more diverse than the classical models of rodent viruses based on the tropically distributed genus Hantaan would lead one to expect; new virus variants are being documented in bats, shrews, moles, amphibians and even fish, raising fundamental questions about the origins of the mammal-infecting lineages and the potential for zoonotic spillover (7,8,9).

Category	Major Findings	Significance
Significance	Korean War outbreaks (1950–1953); Hantaan virus isolated in 1978.	Established hantavirus as a distinct human pathogen.
Global burden	~200,000 infections annually worldwide	Indicates substantial but likely underestimated disease burden
Taxonomic expansion	Discovery of hantaviruses in rodents, bats, shrews, moles, amphibians, and fish.	Challenges traditional rodent-centric paradigms.
Climate change	Temperature and precipitation shifts alter reservoir ecology.	Expands geographic areas at risk for outbreaks.
Therapeutic gap	No FDA-approved antiviral or vaccine for global use.	Supportive care remains the cornerstone of management.

Table 1 : *Key Milestones and Emerging Challenges in Hantavirus Research and Public Health*

Third, the recent spike in Argentine HPS cases in 2025–2026, in the urbanizing Buenos Aires metropolitan corridor rather than the more typical rural setting in the Argentinean Patagonian heartland, is an alarming shift toward a new epidemiological scenario involving periurban transmission dynamics that are not currently tracked by surveillance and response systems (23). Fourth, there are no FDA approved vaccines or antiviral compounds for any hantavirus infection, and supportive management is the main modality for a disease that progresses from prodrome to death in 72 hours or less (16,18,30).

These overlapping aspects of hantavirus biology, epidemiology, and public health are reviewed. The article starts with an updated taxonomy and genomic characterization of the bacteria, which reflects the reclassification of species discovered since 2017 and post-2017 epidemiological data (7,9,11). It then moves on to epidemiological burden analysis, pathogen-host-environment triad dynamics, projected risk due to climate change, molecular pathogenicity and immunology, clinical recognition and laboratory diagnosis, and the current therapeutic and vaccine landscape (9).

The review concludes with the provision of evidence-based recommendations for integrated surveillance, prevention and research prioritization within a One Health paradigm. Unlike past reviews, the current one pulls together the latest outbreak information, such as the unprecedented surge in Argentina in 2025–2026, the cruise ship outbreak, and new vaccine trial results with novel taxonomic discoveries and climate change model predictions all under one roof to provide a comprehensive understanding and response to a threat that has been underappreciated on a global scale. (22,23,30)

2. Taxonomy and Genomics

2.1 Family Hantaviridae: Post-2017 Reclassification

The reclassifications were of more than mere nomenclatorial tidiness of minds. It institutionalized the understanding that hantaviruses, as part of an evolutionary history that lasted for tens of millions of years, have co-evolved with a wide variety of host species, and that the host range and genetic diversity of hantaviruses is broader than the rodent model had suggested [7,9].

Such diversity has direct implications for risk assessment: non-rodent hantavirus lineages found in insectivores and bats are found in different ecological niches with different interfaces to humans, and their pathogenicity in people is largely unknown, though can not be ruled out on theoretical grounds alone as is the case with other bat-borne viruses like filoviruses and coronaviruses.2.2 Genome Architecture: Structure and Function of the Tripartite ssRNA Genome [8,9].

The hantaviruses have a tripartite, negative-sense single-stranded RNA (ssRNA) genome, with each segment (large, medium and small) packaged as a separate ribonucleoprotein (RNP) complex containing the viral RNA-dependent RNA polymerase (RdRp). This segmented genome structure, shared with other bunyaviruses, exhibits some unique features that have direct relevance in the context of viral replication, pathogenesis, and vaccine antigen design, specifically for hantaviruses. (11,26)

The RdRp (L protein) is encoded by the L segment (~6.5 kb) which functions in genome transcription and replication. In contrast to many negative sense RNA viruses, hantavirus RdRp initiates transcription by a cap-snatching process that involves the cleavage of short capped oligonucleotides from host mRNAs that is also associated with influenza viruses and has direct therapeutic implications, as cap-snatching inhibitors are a mechanistically rational antiviral target. This capping process is also carried out by the endonuclease domain of L protein, in its N-terminal region. (11,26)

The M segment can encode the glycoprotein precursor (GPC) that is co-translationally cleaved by signal peptidase to form two mature envelope glycoproteins, Gn (also called G1) and Gc (also called G2). These glycoproteins form heterodimeric structures on the viral lipid envelopes that are required for key initial events in cell entry, such as receptor binding and membrane fusion. The major antigens used in vaccine development programs are primarily Gn and Gc, which are the major targets for virus neutralising antibodies. In a few hantavirus species, the M segment also codes for a small non-structural protein (NSs) which seems to have a less defined role in hantavirus biology than its hantavirus counterpart in other bunyaviruses. (11,12,18)

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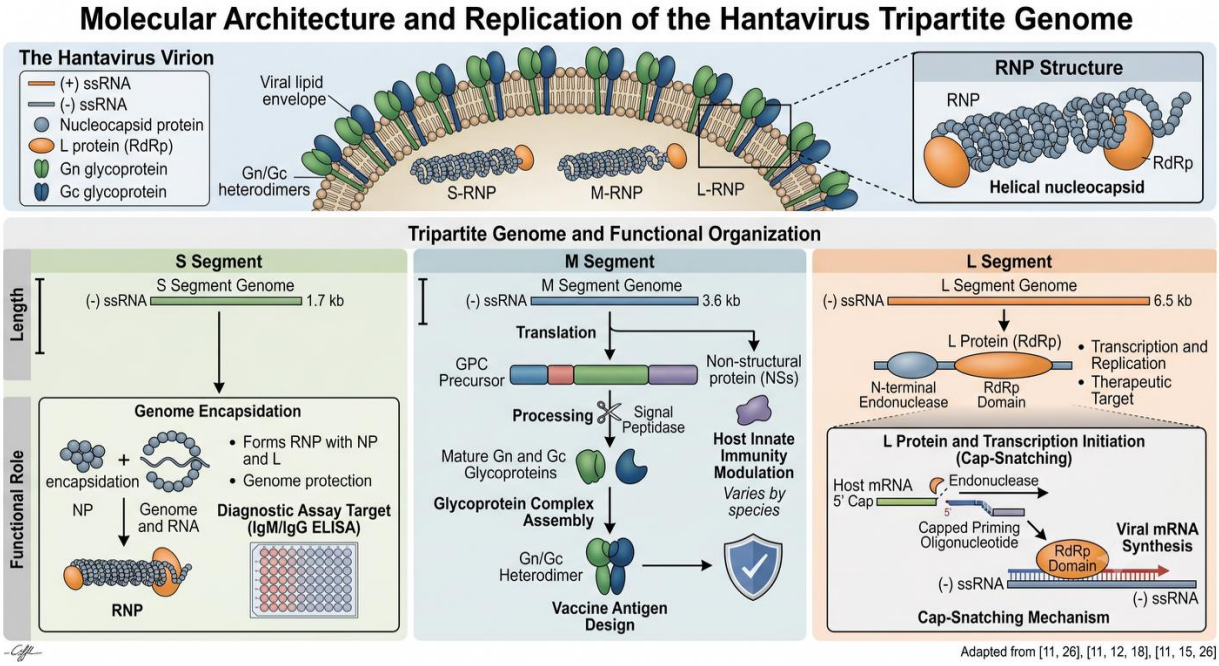

Figure 1: *Schematic representation of the molecular architecture, tripartite genome organisation and the replication strategy of hantaviruses, showing the structural organisation of the virion and the functions of S, M and L genomic RNA segments.*

2.3 Key Pathogenic Species

Among the 53-plus recognized hantavirus species, approximately a dozen have been unambiguously associated with human disease (3,11,26). In the Old World, Hantaan virus (HTNV, hosted by "Apodemus agrarius" in East Asia) causes the most severe form of HFRS with case fatality rates of 5–15% in hospitalized patients (3,10,26). The only truly global hantavirus is Seoul virus (SEOV) which is transmitted by the cosmopolitan rat (Rattus norvegicus) and R. rattus, and is responsible for under-appreciated cases of HFRS on every inhabited continent. (3,5,11).

Dobrava-Belgrade virus (DOBV) has at least four lineages, two of which have intermediate severity (Kurkino and Sochi) and one severe (Dobrava, hosted by "Apodemus flavicollis") with hemorrhagic and neurological complications. The Puumala virus (PUUV) is found in the bank vole "Myodes glareolus", spread from northern to central Europe and is responsible for the highest absolute hospitalizations with HFRS in Europe, despite causing a generally milder syndrome (5,21,24,26). In the New World, Sin Nombre virus (SNV)-hosted by the deer mouse "Peromyscus maniculatus" is responsible for the prototypic HPS with a case fatality rate of 36–38% in confirmed cases in the United States. (2,3,11)

The long-tailed pygmy rice rat "Oligoryzomys longicaudatus" in Chile and Argentina is the host species of Andes virus (ANDV), which is epidemiologically unique as the only hantavirus reported with sustained human-to-human transmission, thus presenting the highest public health risk(27). Other regional importance viruses in the New World comprises Laguna Negra virus from Bolivia and Paraguay, Black Creek Canal virus from Florida, USA and Bayou virus from Louisiana, USA (3,11,26).

2.4 Novel Species Discoveries (2023–2025)

Since 2023, metagenomic surveillance technologies have led to an astounding increase in known hantavirus diversity. New hantavirus species have emerged in increasingly varied host taxa, all overturning any preexisting notions of host range, co-evolutionary history, and spillover potential (7,8,9).

More interestingly, hantavirus-like sequences have been found in amphibians (the Southeast Asian and sub-Saharan anurans) and even in teleosts (fish) – a host range that is well outside the mammalian wall which had long been thought to be impenetrable. These sequences may be true replicating viruses that infect mammalian cells or may be highly divergent evolutionarily relics which are maintained in hosts without zoonotic potential (7,9).

Bats in Asia, Africa and South America have been found with multiple novel hantavirus species. In a few places, these bat-associated hantaviruses are phylogenetically more closely related to each other than to rodent-associated hantaviruses, suggesting

revisionist ideas that bats might be the true ancestral lineage of hantaviruses and the rodent lineages originated from them (9).

This is relevant for pandemic risk assessment, because bats are already known to be the evolutionary reservoir for several high impact human pathogens, such as SARS-CoV, SARS-CoV-2, MERS-CoV, Nipah, Hendra, Marburg and Ebola viruses (9).

2.5 Phylogenetics and Co-evolution with Rodent Hosts

The major evolutionary paradigm for rodent-borne hantaviruses is that they have been co-diverging, meaning that the phylogenies of hantavirus strains correspond to the phylogenies of their primary reservoir host species, thus suggesting millions of years of shared evolutionary history (9,11). Based on the concordant hantavirus and host phylogenies at the subfamily level Murinae, Arvicolinae, and Neotominae, this co-divergence hypothesis has been significantly modified by subsequent genomic studies, in which evidence for host switching, geographic isolation, and reticulate evolution in the hantavirus phylogeny were found at several nodes (6,9).

Experimental transmission of viruses from one sympatric rodent species to another has been demonstrated, and phylogeographic incongruence of some viral lineages and host lineages has been found, indicating a significant contribution from host switching to the current distribution of genetic variation (6,9,28). The hantaviruses are genetically diverse, with nucleotide sequence differences of more than 30% within the genus and 60% or more between genera (9,11).

These differences have practical significance with respect to serological assays that recognize the NP antigen and to vaccine cross-protection; thus antibodies to NP produced by one hantavirus may not cross-react with antigenically different viruses from different geographic areas (15,18) and vaccines containing glycoproteins from a single strain will not necessarily be effective against antigenically distinct viruses found in different geographic regions. The ability to develop broadly protective pan-hantavirus vaccine platforms is therefore a great scientific challenge, which has yet to be fully addressed. (18,19,30)

3. Pathogen–Host–Environment Triad

3.1 Reservoir Ecology and Host Specificity

The ecological basis of transmission of the hantavirus is a remarkably stable virus–reservoir relationship, where the primary host species is chronically infected and is asymptomatic. (3,11). Hantaviruses do not produce palpable disease in their natural reservoir hosts, and this is thought to be due to the general phenomenon of evolved immunological tolerance mediated by regulatory T-cell responses and type I interferon signalling pathways that block viral replication without eliminating the infection (11,12,28).

The reservoir is a persistent non-pathogenic infection in which virus is shed in urine, saliva and feces for long periods of time, and in some cases the entire lifetime of the infected person (3,11,28). Transmission within the reservoir population is primarily through direct, aggressive contact fighting, grooming and biting, and by environmental contamination of shared burrows and nesting areas, aerosol transmission is a secondary but epidemiologically important route in dense population situations (21,28).

3.2 Transmission Routes

The aerosol spread of dried rodent excrete-urine, feces, and saliva to humans is the main route of transmission of hantavirus, in enclosed or poorly ventilated areas where aerosolized viral particles can build up (3,11,26). Support for this aerosol route comes from epidemiological data, which also shows a temporal association between cases and enclosed activities such as opening cabins, cleaning barns, threshing grain and military bivouacking that were exposed to dried rodent urine, and experimental data that showed that dried rodent urine will keep infectious virus viable for several hours to days depending on the environmental conditions (temperature, humidity, and exposure to ultraviolet radiation)(3,21,28). The second route of direct inoculation is by biting from affected rodents, as has been observed in laboratory personnel, trappers and wildlife biologists (3,11). Eating food that has been contaminated with rodent feces has been suggested as a possible source of infection and is seldom cited as a major cause of infection when other evidence is lacking (3,11). Epidemiological uniqueness of Andes virus is its documented ability to cause sustained human-to-human transmission, which is not shared by any other known hantavirus, and which has been confirmed by phylogenetic analyses of clusters from epidemics where the virus transmission chain was incompatible with independent exposures from rodents (27).

Wells et al. described a family cluster of ANDV infections in 1996, and more recently, an outbreak on a cruise ship in 2025, where transmission was reported to have occurred within the confines of a cruise ship sailing in an area where ANDV is endemic, suggesting that close contact is required for human-to-human transmission and that it has been observed within households and healthcare settings. (22,27) Although the transmission of ANDV is well known to occur between humans, the

extent of such transmission seems significantly dampened when compared to respiratory viruses such as influenza, and sustained, large-scale transmission chains similar to those of pandemic respiratory viruses have not yet been reported, but as with other respiratory viruses, this is not a permanent epidemiological barrier and does not necessarily indicate that it will not be possible for human-to-human transmission to occur in the future, especially as the number of areas where rodents and humans may come into contact continue to grow. (22,27)

3.3 Rodent Population Dynamics: Climate-Driven Boom-Bust Cycles

In the mammalian host world, outbreaks of hantavirus in humans are not random in time, but rather consistently associated with pulses in the density of the reservoir rodent that temporarily reduce carrying capacity constraints on the dynamics of small mammal populations (3,20,21). A resource pulse that has been well documented is the masting phenomenon found in temperate forest systems, whereby the dominant tree species of the area, typically a European beech ("Fagus sylvatica") in the Old World and several oaks and pines in the Americas, produce large numbers of seeds synchronously, providing a massive food pulse to granivorous rodents (20,21).

Rodent population explosions can lead to as many as 20 times more rodents in a single breeding season in the reservoir than was previously observed, raising both the intra-specific contact rates (driving within-reservoir virus transmission) and the likelihood of human exposure to infectious excreta because of incursion of rodents into human-occupied spaces (20,21). In Scandinavia and central Europe the three-to-four-year periodicity of PUUV outbreaks is closely linked to the periodicity of bank vole population cycles, which is linked to forest seed production monitoring of beech mast, and this link is now well established and could be used to forecast the risk of outbreaks. (21,24). The ENSO events have a similar impact on rodent population dynamics and human outbreak risk in the Americas (3,20). The 1993 outbreak in the Four Corners area that resulted in hantavirus pulmonary syndrome was preceded by an unusual El Niño event in 1991-1992 that accompanied unusually high precipitation in the American Southwest, leading to an unusually high production pulse of piñon pine seeds and grassland vegetation, and hence a corresponding increase in "Peromyscus maniculatus" density (2,3,20). Local associations between ENSO-related precipitation variations and HPS outbreaks clusters have been reported numerous times in North and South America and have been documented as a potential early warning tool for the risk of HPS outbreaks (3,20).

4. Climate Change and Future Risk

4.1 Temperature, Precipitation, and HFRS Seasonality

Several epidemiological studies conducted in China, Finland, Germany, and Russia have found statistically significant links between climate and incidence patterns of HFRS, supporting the mechanistic pathways which link climate to outbreak risk (3,10,20,21). There are significant positive correlations between notification rates for HFRS and antecedent temperature and precipitation across several provinces in China, with a 2–6-month lag time, reflecting the time needed to pass through from a climate event that triggers a pulse in resources to higher rodent densities and increased human exposure (10,20). This implies the possibility of HFRS seasons being forecasted in advance of season onset and mobilization of preventive measures with sufficient lead time provided by warm climate anomalies associated with ENSO warm phases.

In Finland, the connections between autumn and spring variables, such as temperature and PUUV incidence respectively, and the availability of overwinter seeds and the survival of bank voles are sufficiently strong to form the basis of a validated outbreak early warning model which is now included in the country's national monitoring programme (21,24).

4.2 Predictive Modeling and 2050 Projections

Ecological niche models (ENMs) combining existing distribution data for reservoir species from the present day with predicted future climate from various IPCC scenarios give quantitative estimates of how the hantavirus transmission geography will change over the next few decades (3,20). A modeling study by Yeh et al. (31) was conducted using the LANL model to project HPS risk in 2050 for RCP 4.5 and 8.5 scenarios identified significant range expansion of HPS risk areas to include the Pacific Northwest, northern Rocky Mountain region and the Canadian Prairie provinces where reservoir populations of HPS are currently at low density but warming temperatures and changing precipitation patterns will be more favorable to "Peromyscus" population irruptions.

European ENMs suggest that the risk of PUUV occurs in the British Isles (where occasional locally introduced cases have been detected recently), the northern tier of Scandinavia and possibly Iceland where there have been established populations of bank vole, but no confirmed cases of PUUV. (20,21,24) The uncertainty ranges are quite large for these projections, due to model structure, species dispersal assumptions and the indirect effects of climate on reservoir ecology through vegetation changes, but the direction of projections across

models is consistent, suggesting geographic expansion of hantavirus risk is a near-certainty under plausible warming scenarios. (3,31,21)

5. Pathogenesis and Immunology

5.1 Viral Entry and Replication Cycle

The viral glycoprotein heterodimer Gn/Gc is responsible for viral entry into susceptible host cells, which include various cell types of the immune system, including endothelial cells, macrophages and dendritic cells, the important targets of productive infection in humans (11). The principal entry receptors for pathogenic hantaviruses have been found to be β3 integrins (αvβ3 and αIIbβ3) which bind to the RGD motif-like sequences in the Gn ectodomain of both Old World and New World pathogenic hantaviruses. In contrast, non-pathogenic hantaviruses bind to β1 integrins as their major receptor, and this is thought to be a mechanism explaining the different pathogenicity of virulent and avirulent hantaviruses, as β3 integrins are known to have critical roles in maintaining vascular permeability via interaction with VE-cadherin and other junctional proteins. Some hantaviruses have also been described as having a co-receptor or alternative entry factor, complement decay-accelerating factor (CD55 or DAF) (12,13).

5.2 Endothelial Tropism: The Vascular Core of Hantavirus Pathogenesis

The hallmark of the pathological process of hantavirus disease, whether it becomes HFRS or HPS, is increased vascular permeability leading to tissue oedema, hemorrhage, thrombocytopenia and organ dysfunction. This vascular pathology is consistent with the primary tropism of hantaviruses for endothelial cells of the microvasculature of target organs(26). The pulmonary phase of HPS is characterized by massive pulmonary edema and bilateral infiltrates, with pulmonary endothelium, specifically alveolar interstitium, as the main site of productive infection in HPS inducing hantaviruses. In the case of the viruses which cause HFRS, the primary target is the renal tubular and glomerular endothelium resulting in interstitial nephritis, proteinuria and renal failure typical of that syndrome(11).

5.3 Immunopathology: The CD8+ T-Cell Cytokine Storm

The most prominent model of hantavirus pathogenesis is immunopathological, with the actions of a large CD8+ cytotoxic T-lymphocyte (CTL) reaction directed against virally infected endothelial cells resulting in an excessive cytokine environment that can disrupt the endothelial barrier function, though not directly kill virally infected cells (14). Bronchoalveolar lavage fluid and lung tissue from people with HPS during the cardiopulmonary phase are extraordinary with exceptionally high numbers of virus-specific CD8+ T cells with an activated effector phenotype, and the plasma levels of pro-inflammatory cytokines such as tumor necrosis factor alpha, interferon gamma, IL-6, and CXCL10 are markedly increased (13). During this cytokine storm, the expression of the tight junction proteins, such as claudin and occludin, which normally maintain the integrity of the vascular barrier are downregulated, and the capillary barrier becomes more permeable through vascular endothelial growth factor (VEGF) mediated signaling, which is physiologically important to regulate the barrier integrity ; this leads to the massive pulmonary edema that overwhelms the respiratory reserve at the severe stage of HPS (11,12).

5.4 HFRS vs. HPS Pathogenesis Comparison

Although both diseases HFRS and HPS share the basic immunopathological process of increase in vascular permeability via CD8+ T-cell mediated cytokine action, there are important differences between the two diseases in the target organ involved, the spectrum of clinical disease, and the mechanism determining outcome. In HFRS, the main leakage site is renal interstitium and retroperitoneum, leading to oliguria, hematuria, proteinuria and severe cases to acute tubular necrosis that necessitates dialysis support. The severity gradient of HFRS is wide ranging from subclinical infection, detectable only serologically (common with PUUV), to fatal multiorgan failure (more common with HTNV and DOBV) and is partly influenced by viral factors, which may include the efficiency of type I interferon antagonism by different viral strains, and host genetic factors, most prominently the HLA class I haplotype (11,13).

Feature	Hemorrhagic Fever with Renal Syndrome (HFRS)	Hantavirus Pulmonary Syndrome (HPS/HCPS)
Principal causative viruses	Hantaan virus (HTNV), Seoul virus (SEOV), Dobrava-Belgrade virus (DOBV), Puumala virus (PUUV)	Sin Nombre virus (SNV), Andes virus (ANDV), Bayou virus, Black Creek Canal virus, Laguna Negra virus
Geographic distribution	Europe and Asia (Old World)	North and South America (New World)
Primary reservoir hosts	Murid rodents (*Apodemus*, *Rattus*, *Myodes*)	Sigmodontine rodents (*Peromyscus*, *Oligoryzomys*, *Oryzomys*)
Primary target organ	Kidney	Lung and cardiovascular system
Principal infected cells	Renal endothelial cells, tubular epithelial cells, monocytes/macrophages.	Pulmonary endothelial cells, alveolar macrophages, dendritic cells.
Dominant pathological mechanism	Immune-mediated vascular leakage affecting renal microvasculature.	Immune-mediated capillary leak affecting pulmonary microvasculature
Major cytokines implicated	TNF-α, IFN-γ, IL-6, IL-8	TNF-α, IFN-γ, IL-6, CXCL10, VEGF
Characteristic clinical syndrome	Fever, hemorrhage, thrombocytopenia, acute kidney injury.	Rapid pulmonary edema, hypoxemia, cardiogenic shock.
Long-term sequelae	Persistent renal dysfunction, hypertension, proteinuria	Reduced pulmonary function, fatigue, exercise intolerance

Table 2 : Comparative summary of the Epidemiology, pathogenesis, clinical manifestations, and management of hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS).

6. Clinical Features and Diagnosis

6.1 HFRS: Clinical Phases and Severity Spectrum

Hemorrhagic fever with renal syndrome has a characteristic clinical course in 5 phases (febrile, hypotensive, oliguric, diuretic, convalescent), but this textbook-like course is better seen in cases due to HTNV and may be abbreviated, incomplete or even not present in milder Puumala virus infections (10). The febrile phase (days 1-5) is characterized by sudden onset of fever (38.5-40C), severe headache, myalgia, and back pain often out of proportion to other findings due to retroperitoneal edema and renal capsular distention. Early signs include flushing of the face, injection of the conjunctiva, and Durozier spots (petechiae on soft palate) which are usually present by day three or four, and the thrombocytopenia is usually detectable by day three or four. Elevation of serum creatinine signaling the onset of renal involvement usually follows within the first week (26). The hypotensive phase (days 4–8) can cause a severe degree of circulatory dysfunction; vasopressor therapy may be necessary and irreversible renal cortical necrosis can be a potential complication. The oliguric phase (usually the most critical) may be accompanied by fluid retention, electrolyte disturbance, iatrogenic volume overload (pulmonary edema), and risk of hypertensive crisis due to the renin-angiotensin system's response to its perception of volume depletion (10,11,26).

6.2 Diagnostic Approaches

Several complementary methodologies can be used to confirm hantavirus infection in the lab, and each has different strengths in various clinical and epidemiological settings. The most common diagnostic method is serological detection of hantavirus NP-specific IgM and IgG antibody by ELISA or immunofluorescence assay (IFA); IgM is detected at or before onset of symptoms in HPS, reflecting the potential for a prolonged immunological incubation of the disease, and within the first few days of symptoms in HFRS (15). Sensitivity of acute-phase IgM ELISA is >95%, and serology is the laboratory method of choice for clinical case confirmation when quality-controlled reagents are used, for most pathogenic hantaviruses. Phylogenetically related hantaviruses create a problem of species specific serological attribution in endemic areas of co-circulation, such as the Balkans where PUUV and DOBV are co-circulating, and in South America where multiple sigmodontine-borne viruses are co-circulating (a practically important issue); in research and epidemiological contexts,

plaque reduction neutralization testing (PRNT) is necessary for species-specific identification (29).

Direct detection of the viral RNA by Reverse transcription PCR (RT-PCR) of conserved sequences of the S or M segment allows for high specificity and strain identification and phylogenetic characterization. Sensitivity of RT-PCR in clinical samples is also time-dependent, with the highest viral load during the febrile prodrome and dropping sharply after the onset of the cardiopulmonary phase, so RT-PCR is more likely to be positive when performed within the first five days of illness and may be negative by the time severe respiratory symptoms necessitate diagnostic testing in HPS. Monoclonal antibody capture assays to detect NP are a rapid alternative to PCR in resource-limited areas, and commercial strip tests similar to influenza rapid antigen detection assays have been tested with various hantavirus species and have shown good, though less than optimal, detection sensitivity profiles(11). Reliable and cost-effective diagnostics, especially for realizing point-of-care (POC) tests suitable for the primary care and field settings in LMICs, are of high priority and are an unmet need of a significant scale (26).

7. Treatment and Vaccine Landscape

7.1 Supportive Care: The Current Standard

The management of both HFRS and HPS is largely supportive, and has not changed significantly since hantavirus pulmonary syndrome was discovered in 1993. In HFRS, supportive care is aimed at maintaining hydration and electrolytes according to the various hemodynamic stages of the disease and renal replacement therapy (hemodialysis or continuous venovenous hemofiltration) is the ultimate therapy for severe acute kidney injury. The main issues in the clinical management are vasopressor support during the hypotensive phase, electrolyte abnormalities, especially hyperkalemia during the oliguric phase, and preventing problems associated with fluid overload(16,17).

For HPS/HCPS, the therapeutic goals are to support ventilation and stabilize the heart and blood pressure rhythmically in the cardiopulmonary phase. If respiratory failure occurs, lung-protective ventilation strategies (low tidal volume, permissive hypercapnia) that are recommended in the management of ARDS are used. In the absence of respiratory failure, patients with HPS will be admitted to hospital for monitoring and may be given appropriate ventilation, depending on their clinical status, prior to the onset of failure and thus may reduce the risk of death. Most importantly, the unique hemodynamic characteristics of HPS–cardiac depression: low output, high systemic resistance and normal filling pressures–suggest that the primary therapeutic benefit is mechanical support, rather than vasopressors alone. Extracorporeal membrane oxygenation (ECMO) has been used with life-saving success in severe cases of HCPS that are unresponsive to conventional ventilatory support and several case series from high resource centers in Chile, Argentina, and the United States have shown survival for patients who would otherwise have been predicted to die(17). Thus, the high specificity of the equipment and highly trained teams required to implement ECMO and their limited availability in the tertiary centers highlight the need to transfer patients as soon as their clinical condition deteriorates after an HPS diagnosis (40).

7.2 Ribavirin: A Qualified and Contested Antiviral

The nucleoside analogue ribavirin, which is known to have broad-spectrum antiviral activity by blocking viral RNA synthesis, and inducing error catastrophe has been tested as an antiviral in several clinical trials and observational studies of hantavirus infections, and shown to have variable efficacy and safety across different syndromes and geographic settings. A randomized controlled trial performed in China during the 1990s has shown that statistically significant mortality and reduction in the severity of renal complications was achieved when ribavirin was used in the febrile phase of the illness (within 4 days of onset); the evidence has led to its inclusion in the China national guidelines for treating HFRS. However, the methodological aspects of these trials are problematic, with a lack of clarity regarding the quality of the randomization and blinding process, and independent studies to confirm the efficacy of ribavirin for HFRS have not been conducted in rigorous trials, and thus its efficacy is challenged in evidence-based medicine schemes outside of China and South Korea(16,17).

Clinical evidence of the effectiveness of ribavirin is decidedly poor for HPS caused by SNV and ANDV. The most rigorous trial of intravenous ribavirin for HPS conducted in North America, a placebo-controlled trial, showed no significant effect on any clinical outcome and the proven toxicity of the drug (hemolytic anemia, teratogenicity) argues against its use in empirical therapy (26). This is pre-clinical data in the Syrian hamster model of ANDV-HCPS, suggesting that the lack of clinical benefit seen in the HPS trials was because the virus was diagnosed and treated at a late stage in infection and not because of a fundamental lack of antiviral activity; that is, very early treatment in the model was effective. Although this mechanistic proposal is speculative, it has left to us a persistent interest in the earlier antiviral intervention approaches (40).

7.3 Approved Vaccines: China and Korea

There are currently two licensed and available vaccines for hantavirus: a bivalent vaccine containing both Hantaan and Seoul virus produced on Vero cells manufactured in China (approximately two million doses annually); and a monovalent vaccine against Hantaan virus manufactured in South Korea (also produced in China, approximately two million doses annually), used mainly in high-risk populations of agricultural workers, military personnel, or residents of endemic rural areas in China and the Korean Peninsula (10). Both vaccines have been shown to be immunogenic in the vast majority of vaccinees based on induction of neutralizing antibody levels, and both vaccines require three doses of vaccine as a primary series; however, strong data on efficacy in the field are limited to a few RCTs. Based on the results of mass vaccination campaigns (in provinces in China with high HFRS burden), there is evidence of good level of protection, ranging from 60-95%, despite the limitations of the evidence base, indicating continued use of these vaccines in high-risk groups. The length of protection and requirement for booster doses are poorly understood (15).

8. Prevention, Surveillance, and Future Directions

8.1 Rodent Control Strategies

Since there are no approved vaccines to prevent hantavirus infection in most parts of the world, primary prevention of hantavirus transmission relies on behavioral change and environmental control measures to minimize human exposure to infected rodent excreta (20). Personal protective equipment advised in high risk settings are the use of N95 or FFP2 particulate respirators when cleaning areas where there is visible rodent activity, wetting down contaminated surfaces with dilute bleach (1:10) before cleaning to reduce aerosolization, wearing gloves when handling materials that may have been contaminated and ensuring that food is properly stored in rodent proof containers. Rodent exclusion programs are based on housing modification, which can involve sealing entry points greater than 6mm in diameter, elimination of food and harborage sources around dwellings and snap traps or glue boards in areas of active infestation, in both the rural agricultural and periurban environments (24).

8.2 Integrated Surveillance Systems

Multiple data streams (at different temporal and spatial scales) must be integrated to provide effective surveillance for hantavirus. Human case surveillance, which depends on reporting of clinical cases via the healthcare system, best indicates continued transmission, but is delayed by weeks to months from the actual epidemiological event, subject to the reporting of cases and to the detection of cases, and fails to capture the vast majority of human–virus encounters, which are subclinical seroconversions(36). Rodent seroprevalence surveillance systematic trapping and serological screening of reservoir populations in sentinel sites are able to give weeks to months of advance warning of the increased transmission risk before human case numbers begin to climb, allowing pre-emptive public health measures such as targeted rodent control and public education. Even earlier estimates of vegetation productivity indices, in particular, normalized difference vegetation index (NDVI) derived from satellite data, have been shown to be predictive of rodent population irruptions in the American Southwest, where 12-24 months of NDVI anomalies before case clustering of HPS have been observed (42).

8.3 Outbreak Response: Lessons from the 2025 Cruise Ship Cluster

The outbreak of Andes virus on the MV Hondius in January 2025 offers useful experience in responding to outbreaks in new transmission environments. The cluster - which eventually comprised several confirmed cases of HPS and necessitated emergency evacuation of the most severely affected patients to Chilean mainland hospitals - was identified through the ship's medical surveillance system, which was informed before departure of the risk of ANDV in the area the vessel was to sail through, as endemic territory. The 'real time' clinical management decisions made in the setting of rapid contact identification, respiratory isolation precautions for suspect cases, and a telemedicine consultation with Chilean infectious disease specialists, were crucial to the clinical management of this outbreak and a strategy that is now explicitly recommended by WHO guidance on hantavirus outbreak management for healthcare and congregate living facilities located in ANDV-endemic areas (37,38).

9. Discussion and Future Perspectives

The findings from this review are coming in from a variety of sources, which come together to several sobering lessons about the current situation of hantavirus as a global health threat. The burden of disease from Hantavirus is underappreciated as a global threat to human health, and the geographic and demographic distribution of the risk to humans for this disease is now being actively modified by anthropogenic factors such as climate change, land-use alteration and growing human-wildlife contact which will increase, not diminish, the geographic and demographic distribution of human exposure risk over the next decades. The scientific knowledge about the biology, molecular pathogenesis, and ecological transmission dynamics of hantavirus are well advanced, but the ability to translate and apply these knowledge to prevent illness and death from

hantavirus is still in its early stages. The lack of operational implementation of the knowledge is the major hurdle in hantavirus as a public health issue.

It is very paradoxical that the technological development of hantavirus vaccine is encouraging while the clinical and regulatory is discouraging. The mRNA, VLP, and monoclonal antibody platforms currently under study in the preclinical stage represent paradigm-shifting technology advances over the inactivated whole-virus vaccines that came before them and have the potential to provide more long-lasting, broadly cross-reactive and rapidly deployed protective product. The journey from promising preclinical findings to licensed medical products, however, involves conducting efficacy trials that would meet regulatory standards, which requires case numbers, GCP infrastructure and continued funding — that is not available on the scale required. The coordinated investment by national health agencies, international health organizations and philanthropic funders willing to see hantavirus as a legitimate pandemic threat and invest in it as such is needed to accelerate this journey.

Importantly, One Health, an approach that is often mentioned but not widely adopted in the field of infectious disease is the most inclusive and sustainable option to minimize hantavirus risk if it can be operationalized across the various sectors. The rodent reservoir is not a physical reality to be dealt with biologically, but an ecological system in a landscape that has been created by human decisions regarding land use, agriculture, housing and urban development. Climate change the dominant emerging driver of hantavirus risk geography is an anthropogenic process, whose mitigation would have cascading benefits for the trajectory of risk for hantavirus and dozens of other zoonotic pathogens. Making hantavirus surveillance and control a part of a wider agenda for health in an ecosystem and planet level approach is not only scientifically more correct but also politically more feasible as a way of gaining the multi-sectorial attention which is needed for the problem.

11. CONCLUSION:

Hantavirus is a worldwide zoonotic disease threat, ecologically complex, with a mortality component, whose epidemiology is changing as a result of climate change, land use changes and increasing human–wildlife interactions. The molecular biology of viral entry, as well as the ecological mechanisms underlying population irruptions of reservoirs are now firmly understood. The lack of knowledge is not the problem, but action – the development and approval of vaccines and antivirals, the availability of point-of-care diagnostics, the operationalisation of One Health surveillance and incorporation of hantavirus risk into climate adaptation planning. The Argentine surge in 2025–2026, the outbreak of hantavirus on cruise ships in Patagonia, and the potential northward and upward spread of reservoir species ranges as a result of the warming climate all indicate that the risk of hantavirus is increasing. It is possible now to develop full prevention and response capabilities while the case load is still relatively small. Neglected zoonotic threats have only ever come at a cost when they have been ignored when they have gone.

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