Review

Hantavirus Emergence in a Changing World: Virology, Pathogenesis, Surveillance, and One Health Preparedness

Maria E. Ramos-Nino , Nicolette Chiem , Prakash V. A. K. Ramdass *

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Hantavirus Emergence in a Changing World: Virology, Pathogenesis, Surveillance, and One Health Preparedness

Maria E. Ramos-Nino [1], Nicolette Chiem [2] and Prakash V. A. K. Ramdass [2,*]

[1] Department of Microbiology, Immunology, and Pharmacology, St. George's University School of Medicine, St. George P.O. Box 7, Grenada

[2] Department of Public Health and Preventive Medicine, St. George's University School of Medicine, St. George FZ818, Grenada

* Correspondence: prakash.ramdass@gmail.com; Tel.: (+473-439-2000)

Abstract

Hantaviruses are emerging rodent-borne pathogens that pose increasing global public health concerns due to their association with hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS), both of which can result in substantial morbidity and mortality. Environmental change, climate variability, urbanization, and land-use transformation are increasingly recognized as critical drivers of hantavirus emergence and transmission. This review summarizes current evidence regarding hantavirus virology, epidemiology, pathogenesis, clinical manifestations, diagnostics, surveillance systems, prevention strategies, and One Health preparedness approaches. Emphasis is placed on the influence of climate change and ecological disruption on rodent reservoir dynamics and spillover risk, as well as major surveillance and diagnostic gaps in tropical and Caribbean regions where hantavirus circulation may be underrecognized. Advances in molecular diagnostics, genomic surveillance, vaccine development, monoclonal antibody therapies, and climate-based early warning systems are also discussed. Existing evidence highlights the importance of integrated One Health surveillance systems that combine human, animal, and environmental monitoring to improve early detection and outbreak preparedness. Strengthening laboratory capacity, ecological surveillance, regional collaboration, and public health infrastructure will be essential for reducing the global burden of hantavirus infections and improving preparedness for future zoonotic disease threats.

Keywords: hantavirus; HFRS; HCPS; virology; disease surveillance; emerging infectious diseases; zoonoses; rodent-borne pathogens; climate change; pathogenesis; One Health

1. Introduction

The emergence and re-emergence of zoonotic infectious diseases continue to threaten global health, specifically in the setting of climate change, ecological disruption, urbanization, and increasing human mobility [1]. Among these pathogens, hantaviruses are an important group of rodent-borne viruses belonging to the family *Hantaviridae* that can cause severe and potentially fatal disease in humans [2]. Since the recognition of hantavirus cardiopulmonary syndrome (HCPS) in the southwestern United States in 1993, growing evidence of hantavirus circulation across Asia, Europe, and the Americas has increased concern regarding their epidemic potential and public health impact [3,4]. Hemorrhagic fever with renal syndrome (HFRS) accounts for thousands of hospitalizations annually, notably in Asia [5], while HCPS remains associated with high mortality rates that frequently exceed 30% in the Americas [6,7].

Hantaviruses are maintained in nature through persistent infection of specific rodent reservoir hosts, which shed virus in urine, feces, and saliva without developing significant disease [8]. Human

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infection most commonly occurs through inhalation of aerosolized viral particles from contaminated rodent excreta, although rodent bites and rare cases of person-to-person transmission, primarily involving Andes virus, have also been reported [9]. Consequently, hantavirus epidemiology is intricately linked to rodent ecology, environmental conditions, and patterns of human exposure [10].

Environmental and anthropogenic changes, such as climate variability, deforestation, urbanization, agricultural expansion, and land-use change, are increasingly influencing hantavirus transmission by altering rodent ecology and human–rodent interactions [11,12]. Climate-related events such as El Niño Southern Oscillation (ENSO) cycles and altered rainfall patterns have been linked to increased hantavirus incidence in endemic regions [13–15]. These concerns are especially relevant in tropical and subtropical regions, including parts of Latin America and many island nations in the Caribbean, where favorable ecological conditions and limited surveillance infrastructure may contribute to underdiagnosis [16]. This may occur because hantavirus infections can overlap clinically with other endemic febrile illnesses, such as dengue, leptospirosis, malaria, and rickettsial infections [17,18].

Furthermore, the coronavirus disease 2019 (COVID-19) pandemic highlighted the consequences of delayed pathogen detection, inadequate surveillance, and limited outbreak preparedness for emerging infectious diseases [19]. These lessons emphasize the need for integrated surveillance systems, improved diagnostic infrastructure, rapid data sharing, and coordinated public health responses [20]. In this context, a One Health approach, integrating human, animal, and environmental surveillance may enhance early detection of hantavirus circulation and strengthen preparedness, particularly in under-surveilled and resource-limited settings [21,22].

This review summarizes current evidence regarding hantavirus virology, epidemiology, pathogenesis, clinical manifestations, diagnostics, surveillance strategies, and prevention. Emphasis is placed on the environmental and ecological drivers of hantavirus emergence, surveillance and preparedness gaps in tropical and Caribbean regions, and the role of integrated One Health approaches in strengthening global preparedness and outbreak response.

2. Virology and Classification

2.1. Viral Structure and Genome Organization

Hantaviruses are enveloped, negative-sense, single-stranded RNA viruses belonging to the family Hantaviridae, order Bunyavirales **[23]**. The viral genome consists of three segments: small (S), medium (M), and large (L), encoding the nucleocapsid protein (N), the glycoprotein precursor (GPC, which is cleaved into Gn and Gc envelope glycoproteins), and the RNA-dependent RNA polymerase (L protein), respectively **[23]**. The nucleocapsid protein is highly immunogenic and serves as the primary target for serological diagnostics, while the glycoproteins mediate viral entry and are targets for neutralizing antibodies **[24]**.

2.2. Old World and New World Hantaviruses

Hantaviruses are classified into Old World and New World lineages based on their geographic distribution and phylogenetic relationships **[23]**. Old World hantaviruses, mostly found in Asia and Europe, are associated with HFRS and include Hantaan virus (HTNV) **[25]**, Seoul virus (SEOV) **[26]**, Puumala virus (PUUV) **[27]**, and Dobrava-Belgrade virus (DOBV) **[28]**. These viruses are carried by rodents of the family Muridae, with each virus typically associated with a specific rodent host **[29]**.

New World hantaviruses, found in the Americas, are associated with HCPS and include Sin Nombre virus (SNV) **[30]**, Andes virus (ANDV) **[31]**, and numerous other species **[32]**. These viruses are primarily carried by rodents of the family *Cricetidae*, subfamily *Sigmodontinae* **[29]**. The Andes virus is notable for being the only hantavirus with documented person-to-person transmission **[33]**. Major reservoir relationships and conceptual evolutionary associations among hantaviruses are shown in Figure 1.

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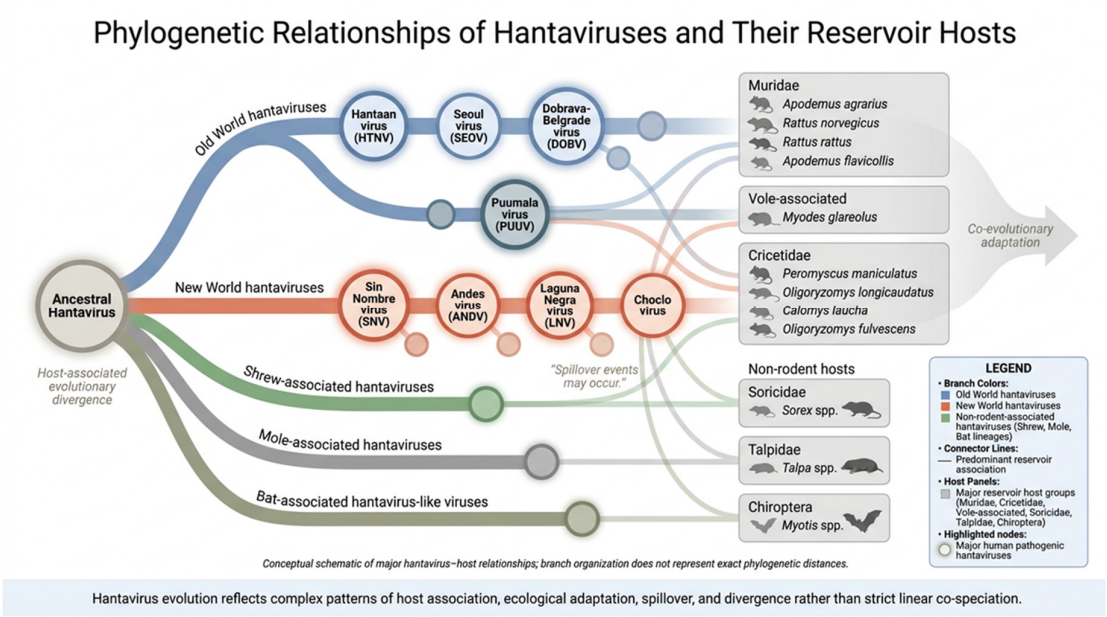

Figure 1. Conceptual evolutionary and reservoir host relationships of major hantaviruses. Schematic illustrating the evolutionary relationships and predominant reservoir host associations of major Old World hantaviruses (blue), including Hantaan (HTNV), Seoul (SEOV), Dobrava-Belgrade (DOBV), and Puumala (PUUV) viruses, and New World hantaviruses (red/orange), including Sin Nombre (SNV), Andes (ANDV), Laguna Negra (LNV), and Choclo viruses. Major rodent reservoirs and additional shrew-, mole-, and bat-associated hantavirus-like viruses are shown to highlight the ecological diversity and host-linked evolution of hantaviruses. The figure emphasizes the complex patterns of reservoir adaptation, divergence, and spillover.

2.3. Host Specificity and Viral Persistence

Each hantavirus species typically exhibits a high degree of host specificity, with persistent infection in a single primary rodent reservoir species **[6]**. The virus establishes chronic infection in the reservoir host without causing apparent disease, facilitating long-term viral shedding in urine, feces, and saliva **[34]**. This host-virus co-evolution has resulted in distinct geographic distributions of hantavirus species that mirror the distributions of their rodent hosts **[29]**. The major hantaviruses, their reservoirs, clinical syndrome, and geographic distribution are shown in Table 1.

Table 1. Major hantaviruses, reservoirs, clinical syndrome, and geographic distribution.

Virus	Lineage	Primary Reservoir	Syndrome	Geographic Distribution
Hantaan (HTNV)	Old World	*Apodemus agrarius*	HFRS (severe)	China, Korea, Russia
Seoul (SEOV)	Old World	*Rattus norvegicus*	HFRS (mild)	Global (urban)
Puumala (PUUV)	Old World	*Myodes glareolus*	NE/HFRS (mild)	Scandinavia, W. Europe
Dobrava-Belgrade (DOBV)	Old World	*Apodemus flavicollis*	HFRS (severe)	Balkans, C. Europe
Sin Nombre (SNV)	New World	*Peromyscus maniculatus*	HCPS	North America
Andes (ANDV)	New World	*Oligoryzomys longicaudatus*	HCPS	South America
Laguna Negra (LNV)	New World	*Calomys laucha*	HCPS	Paraguay, Bolivia
Choclo	New World	*Oligoryzomys fulvescens*	HCPS	Panama, Central America

Note: Adapted from [29].

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3. Global and Regional Epidemiology

3.1. Global Burden and Distribution

Hantavirus infections represent a notable global public health burden, with an estimated 150,000–200,000 hospitalizations annually, predominantly due to HFRS in Asia **[35]**. China accounts for the majority of global HFRS cases, with tens of thousands of cases reported annually **[36,37]**. The Republic of Korea, Russia, and several European countries also report substantial HFRS incidence **[38]**. In the Americas, HCPS cases are reported from Canada to southern Argentina, with the highest incidence in rural and peri-urban areas where human-rodent contact is frequent **[9]**. The global distribution of major hantaviruses and associated surveillance gaps is summarized in Figure 2.

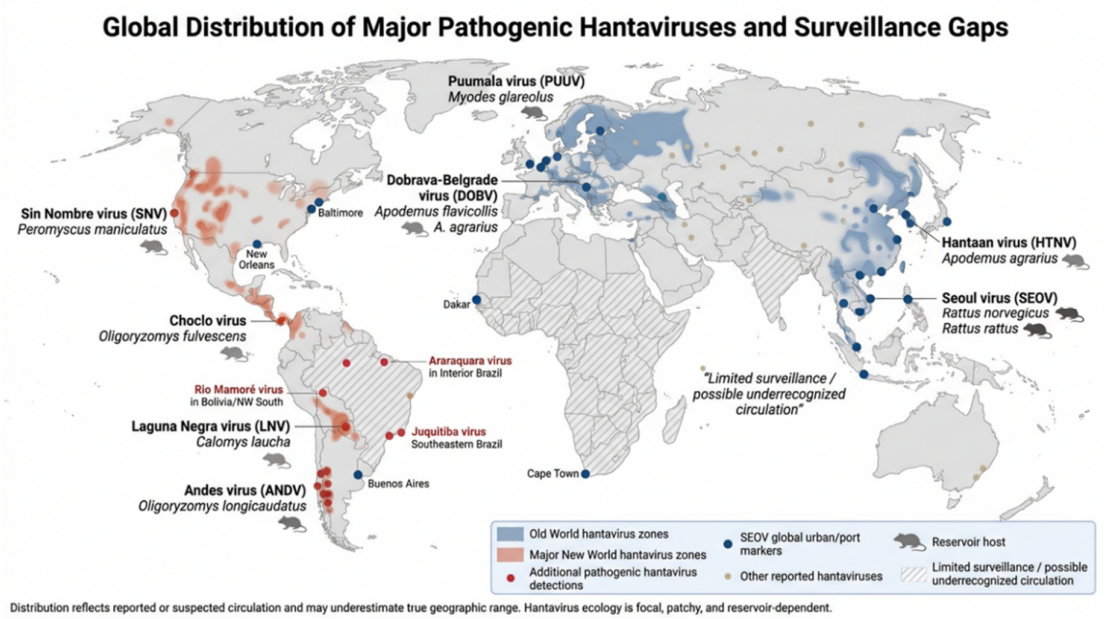

Figure 2. Global distribution of major pathogenic hantaviruses associated with human disease, highlighting the distinct geographic patterns of Old World hantaviruses linked to hemorrhagic fever with renal syndrome (HFRS) and New World hantaviruses associated with hantavirus cardiopulmonary syndrome (HCPS/HPS). Seoul virus (SEOV) is depicted as globally distributed due to its association with urban rats and international trade. Gray hatched regions indicate areas with limited surveillance and possible underrecognized circulation, including parts of tropical Africa, the Caribbean, tropical Latin America, and South and Southeast Asia. Distribution patterns are approximate and emphasize the focal and ecologically heterogeneous nature of hantavirus transmission.

3.2. Hemorrhagic Fever with Renal Syndrome (HFRS) Distribution

HFRS is endemic in Asia and Europe, with the highest burden in China, where Hantaan and Seoul viruses are the predominant causative agents **[39]**. The disease exhibits distinct seasonal patterns, with peak incidence typically occurring in late autumn and early winter, coinciding with increased rodent activity and agricultural harvests **[40,41]**. Puumala virus causes a milder form of HFRS known as nephropathia epidemica (NE) in Northern and Central Europe, with thousands of cases reported annually **[42,43]**. Climate variables, rodent population dynamics, and land-use changes have been associated with regional variations in HFRS incidence and transmission patterns **[44]**.

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3.3. Hantavirus Cardiopulmonary Syndrome (HCPS) Distribution

HCPS was first recognized in the southwestern United States in 1993 during an outbreak caused by Sin Nombre virus **[30]**. Since then, HCPS cases have been reported throughout the Americas, with notable endemic areas in Argentina, Chile, Brazil, Paraguay, and the United States **[8,45]**. The disease exhibits high case fatality rates, typically ranging from 20–32% **[46,47]**, with some outbreaks reporting rates exceeding 40–50% **[48,49]**. Environmental and climatic factors, including El Niño-associated rainfall variability and land-use change, have been linked to increased HCPS transmission risk in several endemic regions **[13,14]**.

3.4. Underrepresented Regions: Tropical and Caribbean Contexts

Despite the presence of diverse rodent populations and suitable ecological conditions, tropical and Caribbean regions remain significantly understudied with respect to hantavirus surveillance **[16,50]**. Limited seroprevalence studies and sporadic case reports suggest potential hantavirus circulation in these areas, but the true burden remains unknown due to inadequate diagnostic capacity, limited surveillance infrastructure, and low clinical awareness **[51,52]**. The Caribbean region, specifically, represents a major knowledge gap because systematic hantavirus surveillance remains largely absent despite the presence of both endemic and introduced rodent populations **[53]**.

4. Pathogenesis and Immunopathology

4.1. Viral Entry and Cellular Tropism

Hantaviruses enter human cells chiefly through interactions between viral glycoproteins (Gn and Gc) and cellular receptors, including integrins **[54]**. The primary cellular targets are vascular endothelial cells, where viral replication occurs without direct cytopathic effects **[55]**. This endothelial tropism is central to the pathogenesis of both HFRS and HCPS, as endothelial dysfunction leads to increased vascular permeability and the characteristic clinical manifestations of these diseases **[56,57]**.

4.2. Immune Response and Immunopathology

The pathogenesis of hantavirus disease is largely immune-mediated rather than directly cytopathic **[58]**. Following infection, both innate and adaptive immune responses are activated, with the production of pro-inflammatory cytokines, chemokines, and cellular immune responses **[59]**. While these responses are essential for viral control, excessive or dysregulated immune activation contributes to disease severity **[58]**. Neutralizing antibodies targeting the viral glycoproteins play a critical role in protection and recovery **[60]**. Studies have demonstrated that early and robust neutralizing antibody responses are associated with better clinical outcomes **[60]**. Conversely, delayed or inadequate antibody responses may contribute to severe disease **[61]**. T cell responses, especially CD8+ T cells, are also crucial for viral clearance but may contribute to immunopathology when dysregulated **[62]**. Key mechanisms contributing to hantavirus pathogenesis are summarized in Figure 3.

4.3. Vascular Permeability and Organ Dysfunction

The hallmark of hantavirus disease is increased vascular permeability resulting from endothelial dysfunction **[17]**. In HFRS, this manifests as capillary leakage in the kidneys, leading to acute kidney injury, proteinuria, and hematuria **[63]**. The disease typically progresses through five phases: febrile, hypotensive, oliguric, diuretic, and convalescent **[64]**. Severe cases may develop hemorrhagic complications, shock, and multi-organ failure **[65]**.

In HCPS, vascular permeability primarily affects the pulmonary vasculature, leading to non-cardiogenic pulmonary edema, respiratory failure, and cardiogenic shock **[66]**. The rapid progression from initial symptoms to respiratory failure and shock is characteristic of HCPS and contributes to its high mortality rate **[67]**. Myocardial dysfunction, likely mediated by immune mechanisms and

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cytokine storm, further complicates the clinical picture **[68]**. The clinical progression and major pathophysiologic differences between HFRS and HCPS are illustrated in Figure 4.

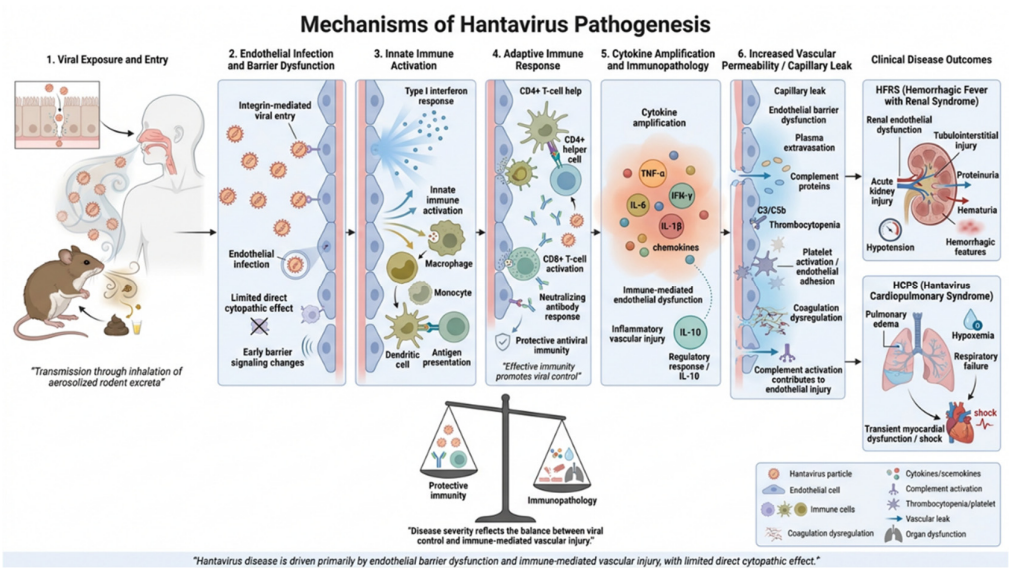

Figure 3. Mechanisms of hantavirus pathogenesis. An overview of the major mechanisms underlying hantavirus disease following inhalation of aerosolized rodent excreta. Hantaviruses initially infect endothelial cells through integrin-associated viral entry pathways. Early innate immune responses include type I interferon signaling, macrophage and monocyte activation, dendritic cell antigen presentation, and initiation of antiviral inflammatory pathways. Adaptive immune responses involve CD4+ helper T-cell activation, CD8+ cytotoxic T-cell responses, and neutralizing antibody production, which contribute to viral control but may also amplify vascular inflammation. Progression to severe disease is characterized by cytokine amplification and immune-mediated endothelial dysfunction involving inflammatory mediators such as TNF-α, IL-6, IFN-γ, IL-1β, chemokines, and regulatory cytokine responses including IL-10. These immune processes contribute to endothelial barrier dysfunction, complement activation, thrombocytopenia, platelet–endothelial interactions, coagulation dysregulation, and increased vascular permeability with plasma extravasation and tissue edema. Disease severity reflects the balance between antiviral immunity and immune-mediated vascular injury.

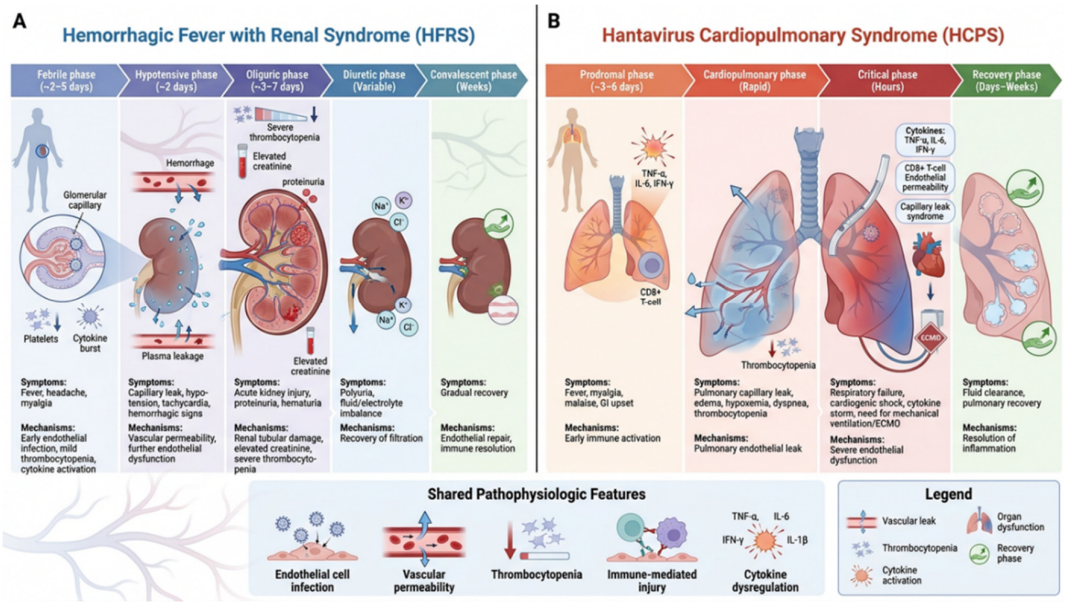

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Figure 4. Dual-panel schematic comparing the clinical progression and major pathophysiologic features of hemorrhagic fever with renal syndrome (HFRS)-Panel A, and hantavirus cardiopulmonary syndrome (HCPS)-Panel B.. Both syndromes share common mechanisms involving endothelial infection, immune-mediated inflammation, thrombocytopenia, and increased vascular permeability leading to capillary leak and organ dysfunction.

4.4. Host Genetic Factors

Host genetic factors, specifically human leukocyte antigen (HLA) polymorphisms, have been associated with susceptibility to and severity of hantavirus disease **[69]**. Certain HLA alleles have been linked to increased risk of severe disease, while others appear protective **[69]**. Understanding these genetic determinants may inform risk stratification and personalized approaches to clinical management **[70]**.

5. Environmental and Ecological Drivers

5.1. Climate Change and Hantavirus Emergence

Climate change is increasingly recognized as a major driver of hantavirus emergence by influencing rodent population dynamics, geographic distribution, and transmission risk **[11,14,15]**. Temperature changes, precipitation patterns, and ENSO events have been associated with increased hantavirus incidence and may support the development of climate-based early warning systems **[71,72]**. Climate-related expansion of rodent reservoirs into new habitats may further increase the risk of hantavirus spread to previously unaffected regions **[13]**. The interactions between climate variability, reservoir ecology, and hantavirus emergence are illustrated in Figure 5.

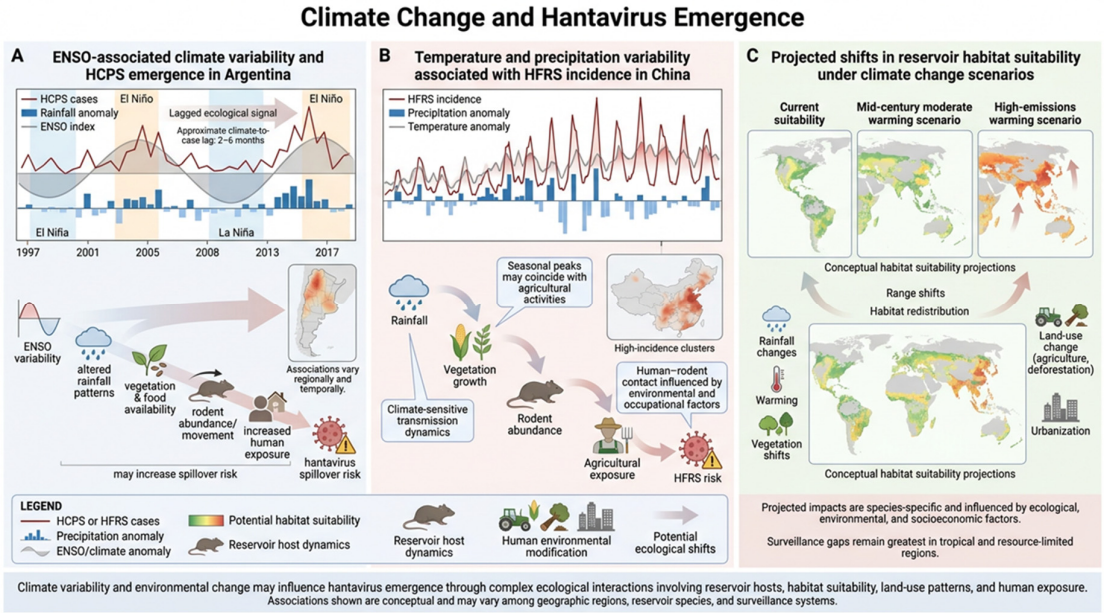

Figure 5. Climate change and hantavirus emergence. Conceptual overview of how climate variability, environmental change, and reservoir host ecology influence hantavirus emergence within a One Health framework. The figure illustrates the effects of El Niño Southern Oscillation (ENSO)-related rainfall variability on hantavirus cardiopulmonary syndrome (HCPS) in Argentina, climate-sensitive drivers of hemorrhagic fever with renal syndrome (HFRS) incidence in China, and potential shifts in reservoir habitat suitability under future climate change scenarios.

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5.2. Land Use Change and Agricultural Expansion

Anthropogenic land-use changes, such as deforestation, agricultural expansion, and urbanization, can alter rodent habitats and increase human exposure to hantaviruses **[14,41,71]**. Studies from Brazil and China have linked environmental modification and agricultural intensification to increased hantavirus transmission risk and shifts in disease epidemiology **[72,73]**.

5.3. Urbanization and Peri-Urban Transmission

Urbanization represents an increasingly vital driver of hantavirus transmission, especially for Seoul virus, which is carried by the Norway rat (*Rattus norvegicus*), a highly adaptable urban rodent **[26,74]**. Studies have documented Seoul virus circulation in urban rat populations in multiple countries, with sporadic human cases reported **[75,76]**. Long-term studies of urban rodent populations have revealed persistent hantavirus circulation in protected urban areas, with seroprevalence rates varying seasonally in association with rodent population dynamics and weather patterns **[77]**. These findings highlight the need for urban rodent control measures and surveillance in cities where human-rat contact is frequent **[78]**.

5.4. Biodiversity and Dilution Effects

The relationship between biodiversity and hantavirus risk is complex, as higher biodiversity may reduce transmission through dilution effects, whereas biodiversity loss may favor reservoir species and increase transmission risk **[79]**. Studies suggest that biodiversity, climate, and socioeconomic factors interact to influence hantavirus emergence and should be considered in prevention strategies **[80]**.

6. Clinical Manifestations and Diagnosis

6.1. Clinical Presentation of HFRS

HFRS typically presents with sudden onset of fever, headache, back pain, abdominal pain, and gastrointestinal symptoms **[81,82]**. The disease progresses through characteristic phases: febrile (3–7 days), hypotensive (hours to 3 days), oliguric (3–7 days), diuretic (days to weeks), and convalescent (weeks to months) **[83]**. Laboratory findings include thrombocytopenia, proteinuria, hematuria, and elevated creatinine **[82]**. Imaging findings in HFRS commonly include renal enlargement, perirenal fluid accumulation, and retroperitoneal edema, with hemorrhagic manifestations observed in severe disease **[84]**. The severity of HFRS varies by viral species, with Hantaan and Dobrava-Belgrade viruses typically causing more severe disease than Puumala virus **[85]**.

6.2. Clinical Presentation of HCPS

HCPS typically begins with a prodromal phase characterized by fever, myalgia, headache, and gastrointestinal symptoms lasting 3–6 days **[86]**. This is followed by rapid onset of respiratory distress, pulmonary edema, and cardiogenic shock **[87]**. Characteristic laboratory findings include thrombocytopenia, hemoconcentration, elevated lactate dehydrogenase, and immunoblastic lymphocytes **[8]**. Chest imaging reveals bilateral interstitial infiltrates and pleural effusions **[8]**. The rapid progression from initial symptoms to respiratory failure necessitates early recognition and intensive supportive care **[87]**. Survivors typically experience complete recovery, though convalescence may be prolonged **[86]**. The clinical differences between the two syndromes are shown in Table 2.

Table 2. Clinical differences between HFRS and HCPS.

Feature	HFRS	HCPS
Primary organ	Kidney	Lungs/Cardiovascular

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Clinical phases	5 (febrile, hypotensive, oliguric, diuretic, convalescent)	2 (prodromal, cardiopulmonary)
Key manifestations	AKI, hemorrhage, hypotension	Pulmonary edema, respiratory failure
Thrombocytopenia	Yes	Yes (severe)
Mortality	0.5–15%	30–50%
Associated viruses	HTNV, PUUV, SEOV, DOBV	SNV, ANDV, Choclo, Laguna Negra
Geographic focus	Asia, Europe	Americas

Note: Adapted from **[6,17,38,87]**.

6.3. Diagnostic Methods

Early and accurate diagnosis of hantavirus infection is critical for appropriate clinical management and public health response **[88,89]**. Diagnostic approaches include serological methods, molecular detection, and immunohistochemistry **[17,90]**.

6.3.1. Serological Diagnostics

Serological testing is the primary diagnostic approach for hantavirus infections, with Enzyme-linked immunosorbent assay (ELISA)-based detection of IgM and IgG antibodies commonly used for initial screening **[17]**. Confirmatory methods, namely immunofluorescence assays (IFA), Western blot, and microneutralization tests, can improve specificity and allow species-level identification; however, cross-reactivity among hantavirus species may complicate interpretation in regions where multiple strains co-circulate **[90]**.

6.3.2. Molecular Diagnostics

Reverse transcription polymerase chain reaction (RT-PCR) enables direct detection of hantavirus RNA and is extremely useful for early diagnosis before antibody seroconversion **[88]**. Real-time RT-PCR assays targeting conserved viral regions provide rapid and highly sensitive detection, although their utility is limited by the rapid decline in viral RNA after symptom onset **[89]**.

6.3.3. Point-of-Care and Field-Deployable Diagnostics

A proposed diagnostic workflow for suspected hantavirus infection is presented in Figure 6, and laboratory approaches for hantavirus detection are detailed in Table 3. Point-of-care (POC) diagnostics are increasingly crucial for hantavirus detection in resource-limited and outbreak settings **[91]**. Emerging approaches, comprising RT-LAMP and lateral flow immunoassays, offer rapid and field-deployable testing, although challenges related to sensitivity and specificity remain **[92]**. Ideal assays should provide rapid, accurate, and affordable detection with minimal equipment requirements **[93]**.

Table 3. Laboratory diagnostic approaches for hantavirus detection.

Method	Specimen	Timing	Sensitivity	Specificity	BSL Required
IgM ELISA	Serum	Acute (≥3 days)	85–95%	90–95%	BSL-2
IgG ELISA	Serum	Acute/convalescent	90–98%	90–98%	BSL-2
RT-PCR	Blood, tissue	Early acute	70–90%	>95%	BSL-2 (post-extraction)
Immunohistochemistry	Tissue	Any (autopsy)	80–95%	>95%	BSL-2
Viral culture	Blood, tissue	Acute phase	Variable	100%	BSL-3

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Rapid lateral flow	Whole blood	Acute phase	70–85%	85–95%	BSL-2

Note: Adapted from [89–91,94,95].

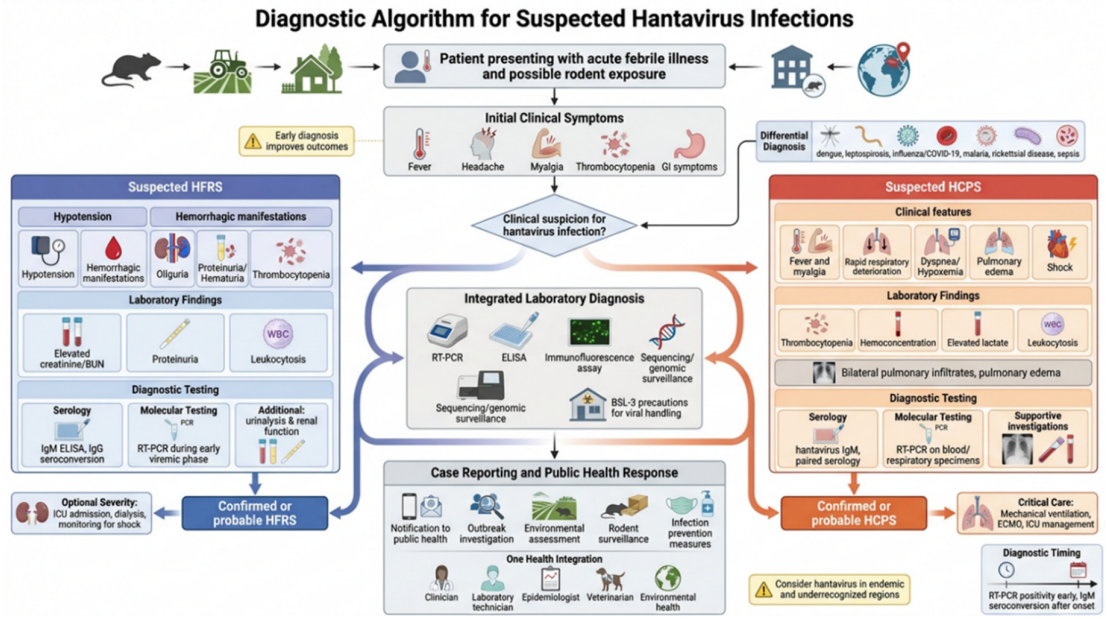

Figure 6. Diagnostic algorithm for suspected hantavirus infections. Clinical flowchart outlining the evaluation of suspected hantavirus infection based on epidemiologic exposure, clinical presentation, laboratory findings, and confirmatory testing. The algorithm differentiates between hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS), while incorporating common differential diagnoses with overlapping clinical features.

6.4. Diagnostic Challenges in Tropical and Caribbean Settings

Diagnostic capacity for hantavirus infections in tropical and Caribbean regions faces multiple challenges **[53]**. Limited availability of validated serological assays, lack of molecular diagnostic infrastructure, absence of reference laboratories, and limited awareness among healthcare providers all contribute to underdiagnosis **[96]**. Additionally, the potential circulation of uncharacterized hantavirus species in these regions may limit the performance of existing diagnostic assays developed for well-characterized species **[38]**. Strengthening laboratory infrastructure and improving clinician awareness are essential for enhancing early detection and surveillance capacity in these settings **[53]**. Differential diagnoses of hantavirus infection in tropical settings are listed in Table 4.

Table 4. Differential diagnosis of hantavirus infection in tropical settings.

Condition	Shared Features	Distinguishing Features	Key Test
Dengue fever	Fever, thrombocytopenia, myalgia	Rash, NS1 antigen, no renal failure	NS1 ELISA, RT-PCR
Leptospirosis	Fever, renal failure, myalgia	Jaundice, conjunctival suffusion	MAT, IgM ELISA
Malaria	Fever, thrombocytopenia, myalgia	Cyclic fever, splenomegaly	Blood smear, RDT
Influenza	Fever, myalgia, respiratory	No renal failure, no thrombocytopenia	Rapid influenza test
COVID-19	Fever, respiratory, myalgia	SARS-CoV-2 exposure, anosmia	RT-PCR

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Rickettsial disease	Fever, headache, thrombocytopenia	Rash, eschar, tick exposure	Serology, PCR
Hantavirus	Fever, thrombocytopenia, renal/pulmonary	Rodent exposure, pulmonary edema, AKI	IgM ELISA, RT-PCR

Note: Adapted from [38,94,97]**.**

7. Surveillance and Early Warning Systems

7.1. Current Surveillance Approaches

Hantavirus surveillance systems vary widely in scope and sophistication across different regions **[98]**. In countries with high disease burden, such as China and the Republic of Korea, national surveillance systems capture case data, conduct seroprevalence surveys, and monitor rodent populations **[82,83]**. These systems have generated valuable long-term datasets that have informed understanding of disease epidemiology and risk factors.

In contrast, many tropical and Caribbean countries lack systematic hantavirus surveillance, relying instead on passive case detection and sporadic research studies **[16]**. This surveillance gap limits understanding of disease burden, circulating viral species, and risk factors in these regions.

7.2. Integrated One Health Surveillance

The One Health approach integrates human, animal, and environmental surveillance systems to improve hantavirus monitoring, risk assessment, and outbreak preparedness **[21]**. Human surveillance focuses on clinical case detection and laboratory confirmation, while rodent surveillance evaluates reservoir distribution, population dynamics, and viral prevalence **[29]**. Environmental surveillance incorporates climate variability, land-use change, and ecological factors associated with transmission risk **[40]**. The integration of these surveillance streams improves early detection of changing transmission patterns and supports targeted public health interventions. The interconnected surveillance framework and data flows are illustrated in Figure 7.

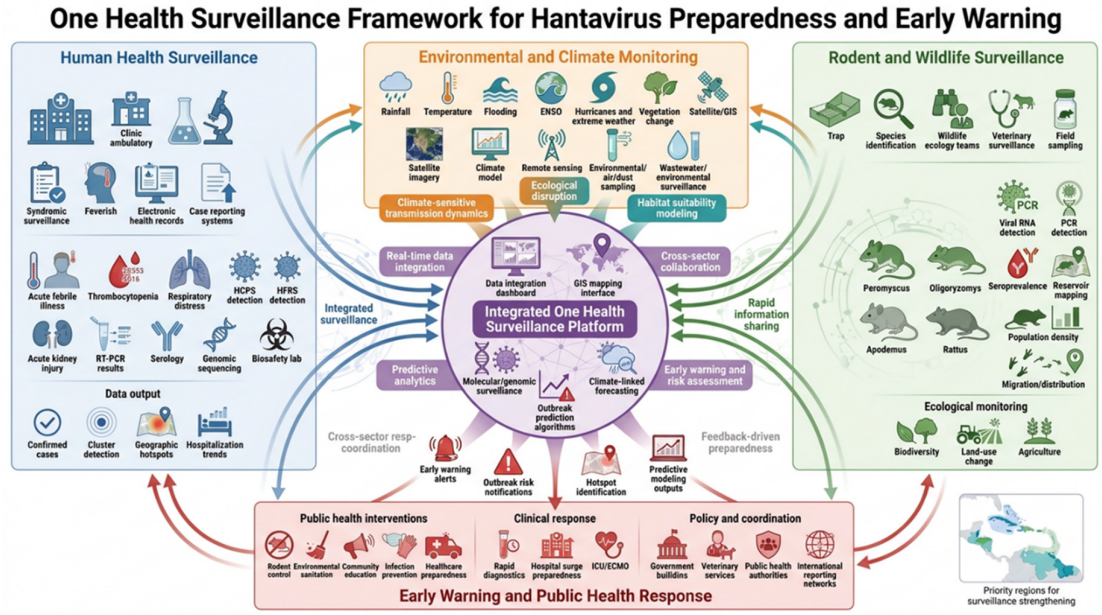

Figure 7. One Health surveillance framework for hantavirus preparedness and early warning. Integrated surveillance outputs support targeted public health interventions, including rodent control, clinician alerts, healthcare preparedness, and community education, particularly in under-surveilled regions.

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7.3. Climate-Based Early Warning Systems

Associations between climate variables and hantavirus incidence have prompted the development of climate-based early warning systems that integrate environmental data, rodent surveillance, and predictive models to identify periods of increased transmission risk **[11,13]**. Studies in China and the Americas suggest that temperature, precipitation, and El Niño patterns may help forecast outbreaks and support public health preparedness **[15]**.

7.4. Surveillance Priorities for Tropical and Caribbean Regions

Strengthening hantavirus surveillance in tropical and Caribbean regions requires improved epidemiological research, diagnostic capacity, healthcare awareness, and regional collaboration **[12,17]**. Integrating hantavirus monitoring into existing infectious disease surveillance systems may provide a practical and cost-effective approach to improving preparedness **[12]**. Major surveillance gaps and preparedness priorities are summarized in Figure 8, while surveillance challenges and proposed solutions are outlined in Table 5.

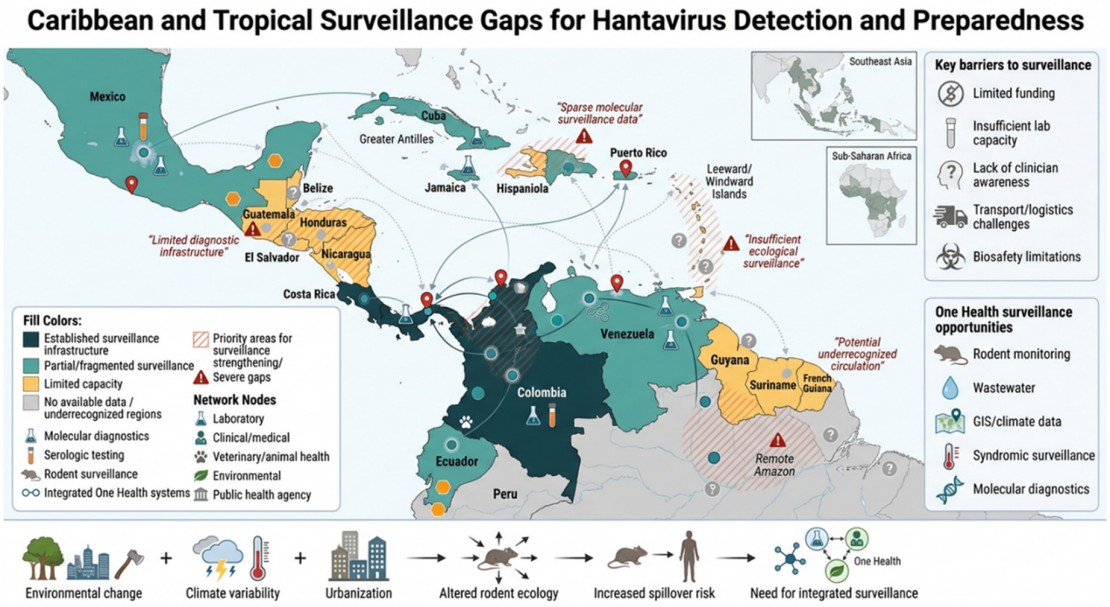

Figure 8. Surveillance gaps and preparedness priorities for hantavirus detection in Caribbean and tropical regions. Regional map illustrating variations in hantavirus surveillance capacity across the Caribbean basin and selected tropical regions of Central and South America. Areas with documented hantavirus activity and regions with limited surveillance infrastructure are highlighted to emphasize the potential for underrecognized transmission. The figure also identifies priority areas for strengthening laboratory capacity, rodent surveillance, clinician awareness, and environmental monitoring.

Table 5. Surveillance challenges and proposed solutions in Caribbean and tropical regions.

Challenge	Impact	Proposed Solution
Limited molecular diagnostics	Missed cases, delayed outbreak detection	Regional RT-PCR platform sharing, training programs
No baseline seroprevalence data	Unknown disease burden	Population-based serosurveys
Clinical overlap with dengue/leptospirosis	Systematic misdiagnosis	Multiplex diagnostic panels, clinician education
No rodent surveillance	Undetected reservoir activity	Integrated rodent trapping and molecular testing

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Fragmented reporting systems	Delayed outbreak recognition	Syndromic surveillance integration
Limited biosafety infrastructure	Inability to manage BSL-3 specimens	Biosafety capacity building, regional reference labs
Extreme weather events	Post-disaster exposure spikes	Disaster-response hantavirus surveillance protocols

Note: Authors synthesis based on **[6,37,38]**.

8. Prevention and Control

8.1. Prevention of Human Exposure

Primary prevention of hantavirus focuses on reducing human exposure to infected rodent excreta through rodent-proofing, sanitation, safe cleanup practices, use of personal protective equipment, and public education **[6,47]**. Enhanced precautions are crucial in high-risk occupational and outdoor settings, including farming, forestry, construction, and military activities **[38]**.

8.2. Rodent Control

Rodent control is an important strategy for reducing hantavirus transmission risk, although long-term effectiveness may be limited by ecological and logistical challenges **[99]**. Habitat modification, sanitation measures, trapping, and targeted rodent reduction programs are commonly used to reduce human exposure in high-risk settings **[71]**. The use of rodenticides may be effective in some contexts but raises concerns regarding environmental impact and non-target species exposure **[100]**. Integrated pest management (IPM) strategies that combine environmental sanitation, habitat reduction, surveillance, and selective rodent control are generally recommended for sustainable prevention efforts **[101]**. Urban rodent control is essential for preventing Seoul virus transmission associated with Norway rats in densely populated cities **[78]**.

8.3. Vaccines

No hantavirus vaccine is presently licensed outside China and the Republic of Korea, where inactivated vaccines against Hantaan and Seoul viruses have shown limited and short-lived immunity **[87,102]**. Several vaccine platforms, such as DNA, recombinant protein, viral vector, virus-like particle, and mRNA vaccines, are under investigation, with preclinical studies demonstrating promising protective immune responses and potential for rapid multivalent vaccine development **[103,104]**.

8.4. Therapeutics

There are currently no FDA-approved treatments for hantavirus infection, and management remains largely supportive, including dialysis for HFRS and mechanical ventilation or ECMO for severe HCPS cases **[105,106]**. Ribavirin may reduce mortality in HFRS when administered early, although evidence remains limited and benefits have not been demonstrated for HCPS **[17,102]**. Emerging immunotherapies, for example neutralizing monoclonal antibodies targeting viral glycoproteins, have shown promising protective effects in preclinical studies **[103,107]**.

9. Research Priorities and Future Directions

9.1. Surveillance and Diagnostic Innovation

Advancing surveillance and diagnostic capabilities is essential for improving hantavirus detection and outbreak preparedness, especially in underrepresented tropical and Caribbean regions. Priority areas include the development of genomic surveillance platforms, rapid point-of-care diagnostics, digital surveillance systems, and standardized reporting frameworks **[88,90]**. Artificial intelligence, machine learning approaches, and environmental monitoring tools may further improve outbreak prediction and risk mapping by integrating climate, ecological, and epidemiological data

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[89,91,108]. Collectively, these innovations may strengthen early detection and public health response capacity **[109]**.

9.2. Ecological and Environmental Research

Understanding hantavirus emergence requires integrated ecological, environmental, and epidemiological research. Key priorities include ecological niche modeling, longitudinal rodent surveillance, and studies evaluating the effects of climate change, biodiversity loss, land-use change, and environmental disruption on reservoir ecology and transmission risk **[110]**. Incorporating hantavirus risk assessments into environmental and land-use planning may help reduce future spillover risk **[71]**.

9.3. Pathogenesis and Immunology

Improving understanding of hantavirus pathogenesis and host immune responses is important for the development of vaccines and therapeutics. Key research priorities include identifying mechanisms of endothelial dysfunction, vascular permeability, and immune-mediated injury associated with severe disease **[56]**. Studies investigating protective immunity, host genetic susceptibility, and improved animal models may further support the development of targeted therapies and vaccine strategies **[69,70]**.

9.4. Vaccines and Therapeutics

Current research priorities for hantavirus vaccines and therapeutics focus on developing broadly protective and rapidly deployable countermeasures. Major areas of investigation include multivalent vaccines, mRNA vaccine platforms, monoclonal antibody therapies, and antiviral agents targeting viral replication or entry pathways **[102,103]**. Immunomodulatory therapies aimed at reducing excessive inflammatory responses may also improve outcomes in severe hantavirus disease **[86,87]**.

9.5. Capacity Building in Underrepresented Regions

Addressing hantavirus surveillance and research gaps in tropical and Caribbean regions requires sustained investment in laboratory infrastructure, workforce training, and regional collaboration **[53]**. Priority efforts include strengthening diagnostic and genomic surveillance capacity, improving outbreak investigation expertise, and establishing collaborative regional networks for data sharing and coordinated response activities **[96]**. Targeted funding and South–South collaboration may further support sustainable preparedness and surveillance development in under-resourced regions **[111,112]**.

10. One Health Framework for Hantavirus Preparedness

10.1. Integrating Human, Animal, and Environmental Health

The One Health framework recognizes the interconnected relationship between human, animal, and environmental health and is highly relevant to hantavirus preparedness **[113]**. Effective preparedness requires collaboration among public health agencies, veterinary services, environmental scientists, and wildlife experts to support integrated surveillance and coordinated outbreak response **[114]**. Shared surveillance systems that combine human case data, rodent ecology, and environmental monitoring may improve early detection of emerging transmission hotspots and support timely interventions.

10.2. Lessons from COVID-19 for Hantavirus Preparedness

The COVID-19 pandemic highlighted the importance of rapid surveillance, decentralized diagnostic capacity, international collaboration, and transparent public health communication for

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emerging infectious disease preparedness **[115]**. These lessons emphasize the need for integrated surveillance systems, rapid data sharing, and flexible public health infrastructure to strengthen hantavirus preparedness and outbreak response **[19,115]**.

10.3. Building Resilient Health Systems

Strengthening health systems for emerging infectious disease preparedness requires sustained investment in surveillance, laboratory diagnostics, outbreak response capacity, and workforce development **[24]**. Flexible public health infrastructure and coordinated partnerships among governments, academic institutions, and international organizations are essential for effective preparedness and response **[12]**. Resilient and adaptable health systems will be critical for responding to future hantavirus outbreaks and other emerging zoonotic threats. One Health preparedness strategies are shown in Table 6.

Table 6. One Health preparedness strategies for hantavirus surveillance.

Sector	Key Activities	Expected Outcomes
Human health	Case surveillance, clinician training, syndromic systems	Improved case detection, reduced diagnostic delays
Veterinary/wildlife	Rodent trapping, viral testing, species mapping	Reservoir identification, early outbreak warning
Environmental	GIS mapping, climate modeling, environmental sampling	Risk area identification, predictive modeling
Laboratory	RT-PCR capacity, serology, biosafety, reference labs	Rapid confirmation, quality-assured diagnostics
Public health policy	Regional networks, data sharing, standardized protocols	Coordinated outbreak response, harmonized surveillance
Research	Seroprevalence studies, genomic surveillance, vaccine development	Evidence base, preparedness tools

Note: Authors framework adapted from **[11,40,53,72,99]**.

11. Current Knowledge Gaps and Limitations

Important gaps remain in hantavirus surveillance, diagnostics, and disease recognition, most notably in tropical and resource-limited regions where infections may be underdiagnosed due to overlap with other endemic febrile illnesses and limited access to molecular and serological testing **[12,17]**. In addition, the ecological drivers of hantavirus emergence, including climate change, land-use change, and biodiversity loss, remain incompletely understood **[13–15,41]**.

Despite progress in vaccine and therapeutic research, no widely available vaccine or specific antiviral therapy currently exists **[102–104]**. Variability in surveillance systems, diagnostic methods, and case definitions further limits comparisons across regions and may underestimate the global disease burden, highlighting the need for strengthened surveillance, standardized reporting, and integrated One Health approaches **[21,22]**.

12. Conclusions

Hantaviruses remain critical emerging zoonotic pathogens with significant global health implications, primarily in regions where environmental change, urbanization, and climate variability are altering reservoir ecology and increasing opportunities for human exposure. The pathogenesis of hantavirus infections is driven largely by immune-mediated endothelial dysfunction and vascular permeability, leading to severe clinical syndromes including HFRS and HCPS. Despite advances in understanding hantavirus virology, immunopathology, diagnostics, and reservoir ecology, major gaps persist in surveillance infrastructure, diagnostic capacity, and epidemiological data. These gaps

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are especially evident in tropical and Caribbean regions, where hantavirus transmission may be underrecognized.

Recent progress in molecular diagnostics, genomic surveillance, vaccine platforms, monoclonal antibody therapies, and climate-informed risk modeling provides vital opportunities to improve early detection, preparedness, and outbreak response. However, sustained investment in laboratory infrastructure, ecological surveillance, workforce training, and regional collaboration remains essential. Integrated One Health approaches that combine human, animal, and environmental surveillance will be critical for strengthening global preparedness and reducing the impact of future hantavirus outbreaks and other emerging zoonotic threats.

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Abbreviations

The following abbreviations are used in this manuscript:

ANDV	Andes virus
COVID-19	Coronavirus disease 2019
DOBV	Dobrava-Belgrade virus
ECMO	Extracorporeal membrane oxygenation
ELISA	Enzyme-linked immunosorbent assay
ENSO	El Niño Southern Oscillation
FDA	Food and Drug Administration
HCPS	Hantavirus cardiopulmonary syndrome
HFRS	Hemorrhagic fever with renal syndrome
HLA	Human leukocyte antigen
HTNV	Hantaan virus
IFA	Immunofluorescence assay
LAMP	Loop-mediated isothermal amplification
LNV	Laguna Negra virus
MNT	Microneutralization test
NE	Nephropathia epidemica
NHP	Non-human primates
POC	Point-of-care
PUUV	Puumala virus
RT-PCR	Reverse transcription polymerase chain reaction

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SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SEOV	Seoul virus
SNV	Sin Nombre virus

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