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COMPREHENSIVE REVIEW OF GLOBAL ORTHOHANTAVIRUS OUTBREAKS: VIROLOGY, PATHOGENESIS, CLINICAL DYNAMICS, AND EVOLVING MANAGEMENT STRATEGIES

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ABSTRACT

Hantaviruses, members of the Orthohantavirus genus, pose an escalating threat to global public health, affecting over 200,000 individuals annually. They are characterized by two severe clinical syndromes: Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS). This review synthesizes recent virological, epidemiological, and therapeutic advancements, with a particular focus on the 2026 Andes virus (ANDV) cruise ship outbreak, which underscored the potential for person-to-person transmission in confined settings. Virologically, high-resolution cryo-electron microscopy has recently explained the 2.35 Å structure of the ANDV Gn–Gc tetramer, offering a blueprint for structure-based vaccine design. Pathogenesis is driven by host-mediated endothelial dysfunction and vascular leakage, primarily mediated by β3-integrin binding and VEGF-receptor 2 signaling, rather than direct viral cytopathic effects. Diagnosis remains a clinical challenge, relying on the identification of the "Classic Five" laboratory findings, including thrombocytopenia and hemoconcentration, and molecular confirmation via RT-PCR or serology. While current management is primarily supportive, utilising extracorporeal membrane oxygenation (ECMO) to achieve survival rates of approximately 80%, the therapeutic landscape is rapidly expanding. New developments include experimental antivirals (Favipiravir), novel biological platforms such as fibroblast-based immunomodulation, and thermally stable "ensilicated" mRNA vaccines designed for infrastructure-independent deployment. This article provides a comprehensive overview of these emerging trends, emphasizing the need for enhanced global surveillance and "One Health" strategies to mitigate future hantavirus spillover events.

KEYWORDS : Orthohantavirus; Hantavirus Pulmonary Syndrome (HPS); Hantavirus Cardiopulmonary Syndrome (HCPS); Hemorrhagic Fever with Renal Syndrome (HFRS);

INTRODUCTION

The genus Orthohantavirus, a member of the Hantaviridae family within the order Bunyavirales, represents a unique class of zoonotic pathogens that exert a significant and growing burden on global public health.[1] Unlike many other viral hemorrhagic fevers, hantaviruses are primarily transmitted via the inhalation of aerosolized excreta from persistently infected rodent, insectivores, or bat reservoirs rather than through arthropod vectors.[2] This transmission route links human infection risk to ecological shifts, rodent population dynamics, and anthropogenic changes in land use.[3] As of 2026, the emergence of the Andes virus (ANDV) cluster associated with a cruise ship environment has led to scientific inquiry into the mechanisms of human-to-human transmission, the structural biology of viral entry, and the urgent requirement for licensed therapeutics and vaccines.[4]

The clinical manifestations of hantavirus infection are broadly divided into two severe syndromes: Hemorrhagic Fever with Renal Syndrome (HFRS), predominant in Europe and Asia, and Hantavirus Pulmonary Syndrome (HPS), also referred to as Hantavirus Cardiopulmonary Syndrome (HCPS), primarily found in the Americas.[2] While HFRS exhibits a lower case fatality rate (CFR), ranging from less than 1% to 15%, HPS is among the most lethal viral infections known, with CFRs frequently exceeding 35% to 40% even in resource-rich clinical settings.[5] The pathogenesis of these diseases is characterized not by direct viral cytopathic effects, but by a complex, host-mediated dysregulation of the endothelial barrier, leading to systemic vascular leakage and subsequent organ failure.[4] This review provides a comprehensive analysis of recent available literature, from the foundations of the virus to the most recent clinical and epidemiological findings from 2024 through 2026.

Virological Fundamentals and Molecular Architecture

The Ortho hantavirus virion is an enveloped, pleomorphic particle with a diameter typically ranging from 80 to 160 nm.[3] Its structural complexity is defined by a tri-segmented, negative-sense, single-stranded RNA genome, which is encased within a lipid bilayer derived from the host's Golgi apparatus or plasma membrane.[1] The genome is organized into Large (L), Medium (M), and Small (S) segments, each performing critical functions in the viral replication cycle and host cell interaction.[2]

Genomic Segmentation and Protein Characterization

The S segment, which spans approximately 1,700 to 2,100 nucleotides, encodes the viral nucleoprotein (N). This protein is the most abundant viral component and plays a central role in encapsidating the three genomic RNA segments to form ribonucleoprotein (RNP) complexes. Beyond its structural role, the N protein is highly conserved across species, making it a primary target for diagnostic assays and a focus of vaccine candidates aimed at eliciting cross-reactive T-cell responses.[6]

The M segment, ranging from 3,613 to 3,707 nucleotides, encodes a glycoprotein precursor (GPC). This precursor is co-translationally cleaved by cellular signal peptidases in the endoplasmic reticulum into two mature glycoproteins, Gn and Gc. These glycoproteins are the primary determinants of viral entry and host range, forming heterodimers that subsequently oligomerize into tetrameric spikes that decorate the virion surface in a unique grid-like lattice.

The L segment, comprising approximately 6,500 nucleotides, encodes the RNA-dependent RNA polymerase (RdRp). This massive protein, roughly 2,160 amino acids long, is responsible for the transcription and replication of the viral genome in the host cytoplasm.[6] It utilizes a "cap-snatching" mechanism, where it cleaves the 5' caps from host messenger RNAs (mRNAs) to prime the synthesis of viral mRNA, effectively hijacking the host's translation machinery.[7] Table 1 summarizes the genomic segmentation and protein characteristics of Orthohantavirus, including the three RNA segments (L, M, and S), their encoded proteins, and key structural and functional features.

Table 1. Summary of the Genomic Segmentation and Protein Characteristics of Orthohantavirus

Genomic Segment	Size (Nucleotides)	Encoded Protein	Biological Function

Large (L)	~6,500	RdRp	Genome replication and transcription; cap-snatching.6
Medium (M)	3,613 - 3,707	GPC (Gn and Gc)	Viral attachment, receptor binding, and membrane fusion.1
Small (S)	1,700 - 2,100	Nucleoprotein (N)	RNA encapsidation and RNP formation.6

Recent studies have advanced the understanding of hantavirus architecture. In 2024 and 2025, researchers employed virus-like particle (VLP) systems and cryo-electron microscopy to determine the 2.35 Å resolution structure of the membrane-embedded Andes virus (ANDV) Gn–Gc tetramer. This study identified earlier uncharacterized features of the tetramer's organization and its pH-sensing mechanisms, which are critical for triggering the conformational changes required for membrane fusion within the acidic environment of the endosome.[1]

These structural revelations have significant implications for vaccine design. Immunization of murine models with self-amplifying replicon RNA (repRNA) encoding ANDV-VLPs elicited high levels of glycoprotein-binding antibodies. Furthermore, the discovery of dimers of tetramers in various flexing conformations provides a structural basis for the pleomorphic nature of the virus, allowing it to adapt its lattice structure to accommodate various virion shapes and sizes.[1]

Epidemiology and Outbreak Dynamics

The epidemiology of hantavirus is characterized by its zoonotic nature, where each viral species is typically associated with a specific primary small mammal reservoir.[8] The geographic distribution of these reservoirs dictates the regional incidence of HFRS and HPS.[2]

Old World Hantaviruses: HFRS and NE

In Eurasia, the primary pathogenic hantaviruses include Hantaan virus (HTNV), Seoul virus (SEOV), Puumala virus (PUUV), and Dobrava-Belgrade virus (DOBV).[2]

- **Hantaan Virus (HTNV):** Carried by the striped field mouse (Apodemus agrarius), HTNV is the primary cause of severe HFRS in Asia, particularly in rural China and South Korea. Outbreaks are often seasonal, correlating with agricultural activities that disturb rodent habitats.[9]
- **Seoul Virus (SEOV):** Uniquely among hantaviruses, SEOV is carried by the brown rat (Rattus norvegicus), a species with a global distribution due to its cohabitation with humans in urban environments. Consequently, SEOV-related HFRS cases are reported worldwide. Recent phylogenetic studies indicate that SEOV M and S segments are evolving at higher rates than HTNV, potentially increasing their genetic diversity and adaptability.[9]
- **Puumala Virus (PUUV):** Endemic to Europe and parts of Russia, PUUV is carried by the bank vole (Myodes glareolus). It causes a milder form of HFRS known as nephropathia epidemica (NE), characterized by low fatality rates but high morbidity.[2]
- **Dobrava-Belgrade Virus (DOBV):** Carried by the yellow-necked wood mouse (Apodemus flavicollis), DOBV causes severe HFRS in Southeastern Europe with a CFR of approximately 10% to 12%.[2]

New World Hantaviruses: HPS and HCPS

In the Americas, hantaviruses such as Sin Nombre virus (SNV) and Andes virus (ANDV) are the primary agents of HPS/HCPS.[6]

- **Sin Nombre Virus (SNV):** The deer mouse (Peromyscus maniculatus) is the primary reservoir for SNV, which causes the majority of HPS cases in the United States and Canada.[10] Between 1993 and 2023, the United States reported 890 laboratory-confirmed cases, with 94% occurring west of the Mississippi River.[11]
- **Andes Virus (ANDV):** Found in South America (Argentina, Chile), ANDV is carried by the long-tailed pygmy rice rat (Oligoryzomys longicaudatus).[3] ANDV is clinically distinct as it is the only hantavirus strain with documented, albeit rare, person-to-person transmission.[1]

Table 2 summarizes the reservoirs, epidemiological distribution, and disease severity associated with various Hantavirus species, highlighting their principal animal hosts, geographic occurrence, and clinical outcomes in humans.

Table 2. Summary of the Reservoirs, Epidemiological Distribution, and Disease Severity Associated With Various Hantavirus Species

Types	Virus	Reservoir	Region	Syndrome Severity
Old-world hantaviruses	HTNV	Apodemus agrarius	Asia	Severe HFRS.9
	SEOV	Rattus norvegicus	Global	Moderate HFRS.9
	PUUV	Myodes glareolus	Europe	Mild HFRS (NE).2
	DOBV	Apodemus flavicollis	Europe	Severe HFRS.2
New-world hantaviruses	SNV	Peromyscus maniculatus	United States and Canada	HPS/HCPS .10
	ANDV	Oligoryzomys longicaudatus	South America (Argentina, Chile)	HPS/HCPS . 3

The 2026 Andes Virus Outbreak:

On May 2, 2026, the World Health Organization (WHO) was notified of a cluster of severe acute respiratory illness (SARI) among passengers and crew of the cruise ship MV Hondius. This outbreak represented a significant epidemiological event due to the suspected human-to-human transmission of ANDV in a confined environment.[5]

As of May 8, 2026, eight cases were reported, including six confirmed and two probable cases, with three fatalities (CFR 38%). The index case was an adult male who had traveled in rural Argentina before boarding the ship on April 1. Subsequent cases included close contacts and crew members, such as the ship's doctor and a guide, who developed symptoms approximately 20 to 30 days after the index case's onset, aligning with known incubation periods.[5] Table 3 has details of reported cases from the Andes virus (ANDV) outbreak as of May 8, 2026, including case counts, geographic locations, dates of reporting, and associated clinical outcomes.

Table 3 : Details of Reported Cases from the Andes Virus (ANDV) Outbreak as of May 8, 2026

Case ID	Status	Outcome	Key Detail
Case 1	Probable	Deceased	Travel in rural Argentina; died onboard April 11.5
Case 2	Confirmed	Deceased	Close contact of Case 1; died in Johannesburg April 26.5
Case 3	Confirmed	Critical	Medically evacuated from Ascension Island to ICU.5
Case 4	Confirmed	Deceased	Died onboard May 2; ANDV confirmed post-mortem.5
Case 5	Confirmed	Stable	Ship doctor; symptoms onset April 30.5

Case 6	Confirmed	Stable	Ship guide; symptoms onset April 27.5

The international response to the MV Hondius outbreak involved the CDC, ECDC, WHO, and health authorities from over 23 nations, illustrating the complexities of managing a person-to-person transmissible hantavirus in the context of global travel.[5]

Pathogenesis: The Mechanism of Vascular Dysfunction

The defining feature of hantavirus pathogenesis is systemic vascular leakage, which occurs despite the absence of direct cytopathic effects on infected cells. This indicates that the clinical manifestations are driven by host-mediated immune responses and the localized dysregulation of the endothelial barrier.[4]

Endothelial Entry and Integrin Interaction

Hantaviruses primarily target endothelial cells, which form the vital fluid barrier within the vasculature.[6] Entry is mediated by cellular receptors, most notably β3-integrins.[12] Pathogenic hantaviruses bind to $\alpha v\beta 3$ integrins, which are critical regulators of vascular integrity.[12] This binding is believed to inhibit the normal function of these integrins, sensitizing the endothelial cells to the effects of vascular endothelial growth factor (VEGF).[13]

VEGF Signaling and Adherens Junctions

The interaction between the virus and endothelial cells triggers a signaling cascade that specifically enhances VEGF-directed permeabilizing responses. In ANDV infections, there is a documented increase in the phosphorylation of VEGF-receptor 2 (VEGFR2). This leads to the downregulation and degradation of vascular endothelial (VE)-cadherin, a major component of adherens junctions.[6] When VE-cadherin is lost, the tight contacts between endothelial cells are disrupted, allowing plasma to leak into the interstitial spaces of the lungs (in HPS) or the kidneys and other tissues (in HFRS).[4]

Kallikrein-Kinin System and Bradykinin

Recent research has also identified the role of the kallikrein-kinin system in hantavirus pathogenesis. Infection with HTNV or ANDV can result in the activation of this system, leading to the liberation of bradykinin. Bradykinin is a potent inducer of vascular permeability, and its overproduction further exacerbates the systemic leakage. This is clinically relevant, as bradykinin receptor antagonists have shown early potential in improving outcomes in some hantavirus cases.[13]

Role of Inflammatory Mediators and Fibroblasts

Severe hantavirus disease is characterized by an uncontrolled inflammatory response, often referred to as a "cytokine storm". High levels of inflammatory cytokines contribute to endothelial barrier dysfunction and progressive tissue damage. In critical HPS cases, the resulting terminal lung damage resembles that seen in severe Acute Respiratory Distress Syndrome (ARDS). Recent investigations suggest that fibroblasts, which are central to tissue repair and regeneration, might be utilized to modulate these inflammatory cascades and restore endothelial integrity.[14]

Clinical Symptoms and Disease Progression

Hantavirus infections present with a predictable but rapidly escalating series of symptoms, making early recognition difficult but vital for survival.[10]

Hantavirus Cardiopulmonary Syndrome (HCPS) Staging

HCPS typically follows a four-stage clinical progression[10]:

1. **Prodromal Phase (3–5 Days):** Patients experience non-specific viral symptoms, including fever, chills, and severe myalgias, particularly in the large muscle groups of the thighs, hips, and back. Gastrointestinal symptoms like nausea, vomiting, and diarrhea are common, but respiratory symptoms are usually absent at this stage.[10]
2. **Cardiopulmonary Phase:** This phase is marked by the sudden onset of respiratory distress, non-cardiogenic pulmonary edema, and cardiovascular collapse.[4] Most patients develop hypotension and hypoxia within 24 hours of clinical presentation.[10]
3. **Diuretic Phase:** In survivors, there is a rapid resolution of the capillary leak, characterized by brisk diuresis as the body clears pulmonary and interstitial fluid.[10]
4. **Convalescent Phase:** Clinical improvement is usually swift, though patients may suffer from long-term fatigue and reduced pulmonary capacity for weeks or months.[10]

Hemorrhagic Fever with Renal Syndrome (HFRS) Staging

HFRS classically progresses through five distinct phases[6]:

1. **Febrile Phase (1–7 Days):** Symptoms include high fever, severe headache, back and abdominal pain, and often a characteristic flushing of the face.[6]
2. **Hypotensive Phase (1–3 Days):** Blood pressure drops rapidly, and thrombocytopenia becomes pronounced. Severe cases can lead to shock.[6]
3. **Oliguric Phase (2–6 Days):** Renal function deteriorates, leading to decreased urine output and high levels of blood urea nitrogen and creatinine.[6]
4. **Polyuric Phase (~2 Weeks):** Urine output increases significantly as renal function begins to recover.[6]
5. **Convalescent Phase (3–6 Months):** A long period of recovery marked by lethargy and a gradual return to baseline health.[6]

Prognostic Indicators

Clinicians use several key indicators to assess the risk of mortality in hantavirus patients. Poor prognostic signs include plasma lactate levels greater than 4.0 mmol/L and a cardiac index of less than 2.2 L/min/m^2.[10] Additionally, elevated creatinine levels and the presence of significant infiltrates on chest radiographs are associated with increased mortality in New World infections.[15] Table 4 has the list of prognostic indicators used to predict clinical outcomes in patients infected with hantavirus, including laboratory parameters, clinical features, and markers associated with disease severity and mortality.

Table 4: Prognostic Indicators of Hantavirus Infection

Indicator	Value for Poor Prognosis	Significance
Plasma Lactate	> 4.0 mmol/L	Indicator of severe tissue hypoxia and metabolic acidosis.10
Cardiac Index	< 2.2 L/min/m^2	Signifies severe myocardial depression and shock.10
Thrombocytopenia	Severe (Platelets < 50k)	Correlates with the severity of vascular leakage.10
Creatinine	Elevated	Indicates significant renal impairment, common in both HFRS and HPS.15

Laboratory Diagnosis and Clues

Because early hantavirus symptoms are non-specific, laboratory diagnosis is essential for distinguishing it from other febrile illnesses like influenza, leptospirosis, or COVID-19.[5]

The "Classic Five" Lab Findings

Healthcare workers are trained to identify a cluster of five laboratory findings that, when appearing together, are highly suggestive of HCPS[10]:

1. **Thrombocytopenia:** A rapid decline in platelet count.
2. **Hemoconcentration:** An increased hematocrit level due to plasma loss from the vasculature.

3. **Left Shift without Toxic Granulation:** Increased immature white blood cells.
4. **Immunoblasts (>10%):** Large, atypical lymphocytes reflecting intense immune activation.
5. **Rapid Onset Respiratory Compromise:** Rapid development of pulmonary edema on imaging.

Confirmatory Diagnostic Methods

The definitive diagnosis of hantavirus infection requires specific laboratory tests, typically conducted in specialized public health or reference laboratories.[10]

- **Serology:** Enzyme-linked immunosorbent assay (ELISA) is used to detect IgM and IgG antibodies.[10] IgM is typically positive at the onset of symptoms. A four-fold rise in IgG titers between acute and convalescent phases is also confirmatory.[10]
- **Molecular Testing (RT-PCR):** Reverse transcription-polymerase chain reaction is highly effective during the acute phase of illness when viremia is present.[2] PCR can identify the specific viral species and strain, which was critical in characterizing the 2026 ANDV cruise ship outbreak.[5]
- **Immunohistochemistry (IHC):** Used primarily in post-mortem cases or tissue biopsies to detect hantaviral antigens in endothelial cells.[10]

Innovations in Diagnostics

The global point-of-care (POC) diagnostics market is rapidly integrating AI to improve the interpretation of infectious disease assays. While not yet standard for hantavirus, AI-based early warning systems, like those cleared by the FDA for sepsis, offer a roadmap for reducing lead time in identifying the severe immune responses characteristic of HCPS.[16]

Infection Prevention and Control (IPC)

In the absence of licensed vaccines or cures, IPC is the primary mechanism for preventing hantavirus outbreaks and protecting healthcare workers.[4]

Rodent Exclusion and Environmental Cleaning

Preventing human exposure to rodent excreta is the most effective way to control hantavirus. This involves a "Seal Up, Trap Up, Clean Up" approach.[18]

- **Seal Up:** Holes as small as 6 mm (the width of a pencil) should be sealed with steel wool or metal flashing to prevent rodent entry into homes and cabins.[18]
- **Trap Up:** Snap traps are recommended over glue or live traps to minimize contact with live rodents and their aerosolized excreta.[18]
- **Clean Up:** Contaminated areas must be aired out for 30 minutes before cleaning.[18] Never sweep or vacuum rodent droppings.[10] Instead, spray the area with a 10% bleach solution (one part bleach to nine parts water) and let it soak for at least 5 minutes before wiping with paper towels or a mop.[10]

Clinical IPC for Andes Virus

The risk of person-to-person transmission for ANDV requires enhanced clinical IPC measures compared to other hantaviruses.[10] Table 5 has the Summary of enhanced infection prevention and control measures for managing suspected hantavirus infection cases, including recommended precautions, personal protective equipment, environmental controls, and procedures to minimize transmission risk.

Table 5: Summary of Enhanced Infection Prevention and Control Measures for Managing Suspected Hantavirus Infection Cases

Precaution Category	Requirement	Applicable Scenario
Standard Precautions	Gowns, gloves, eye protection	Suspected non-ANDV hantavirus (e.g., SNV, HTNV).10
Airborne Precautions	Fit-tested N95 or PAPR; AIIR	Aerosol-generating procedures for any hantavirus.10
Dry VHF PPE	Fluid-resistant gown (AAMI 3/4), gloves, eye/face protection, N95/PAPR	All suspected and confirmed ANDV cases.10
Isolation	Strict isolation in AIIR	Confirmed ANDV cases.10

Therapeutic Landscape and Clinical Trials

Current hantavirus management is primarily supportive.[6] However, the 2026 outbreak has accelerated interest in several experimental therapies and novel therapeutic platforms.

Supportive Management and ECMO

Early referral to an intensive care unit (ICU) is the most critical factor in improving survival.[5]Management strategies include:

- **Judicious Fluid Administration:** Over-aggressive fluid resuscitation can worsen non-cardiogenic pulmonary edema. Vasopressors are preferred for managing hypotension.[10]
- **Extracorporeal Membrane Oxygenation (ECMO):** For patients in severe respiratory failure, early transfer to an ECMO-capable facility has been shown to increase survival to approximately 80% even in cases of cardiopulmonary collapse.[10]

Experimental Antivirals

- **Favipiravir (T-705):** A prodrug that is converted into a purine nucleotide analog, selectively inhibiting the RdRp. It has shown 100% survival in lethal ANDV hamster models.[6]
- **Vandetanib:** This drug targets the phosphorylation of VEGFR2, acting as a host-directed antiviral to maintain the structural integrity of endothelial adherens junctions.[6]
- **Ribavirin:** While previously the standard of care for HFRS, clinical trials for HPS have generally shown it to be ineffective.[19]

Innovative Biological Therapies

- **Fibroblast Therapy:** In May 2026, FibroBiologics announced the expansion of its fibroblast-based therapeutic platform to target HPS. Preclinical studies in ARDS models suggest that fibroblasts can modulate the hyperinflammatory "cytokine storm" and promote tissue repair in the lungs.[14]
- **NanoViricides (NV-387):** A novel nanomaterial that mimics host cell membrane receptors (Sulfated Proteoglycans). It is designed to engulf and neutralize virus particles, preventing them from infecting cells—a mechanism termed "Re-Infection Inhibition".[20]

Vaccine Development Pipeline

The search for a hantavirus vaccine has faced decades of funding shortages, but the 2026 outbreak and recent technological leaps have moved several candidates into the spotlight.[21]

MVA-Hanta Vaccine Trial

A Phase I clinical trial is currently underway in the United Kingdom, testing a new vaccine based on the Modified Vaccinia Ankara (MVA) platform. This study involves 24 healthy adults receiving three increasing doses 28 days apart to assess safety and cellular immunogenicity, specifically T-cell responses to hantavirus nucleoprotein peptides.[22]

Ensilication and mRNA Technology

Researchers at the University of Bath are developing a "completely new" vaccine against Hantaan disease. This

vaccine utilizes mRNA technology and a patented process called "Ensilication," where active proteins are wrapped in protective silica cages. This innovation allows the vaccine to remain stable at ambient temperatures, eliminating the need for a "cold chain" and making it ideal for deployment in remote or tropical regions.[23]

Virus-Like Particles (VLPs) and repRNA

Advancements in VLP technology have allowed for the creation of self-amplifying replicon RNA (repRNA) vaccines.[1] These vaccines elicit high titers of neutralizing antibodies by mimicking the structural organization of native hantavirus glycoproteins while remaining non-infectious.[1]

Table 6 enlists hantavirus vaccines currently under development, outlining candidate types, target viral strains, platforms or technologies used, and their stages of preclinical or clinical evaluation.

Table 6: List of Hantavirus Vaccines Currently Under Development

Vaccine Candidate	Platform	Development Phase	Key Innovation
MVA-Hanta	Modified Vaccinia Ankara	Phase I Human Trial	Uses established smallpox/mpox vaccine vector.22
University of Bath	Ensilicated mRNA	Preclinical / animal testing	Thermal stability without refrigeration.23
VLP-repRNA	RNA-based VLPs	Preclinical	Elicits robust, broadly neutralizing antibodies.1
ICONE Subunit	E. coli Subunit (NP)	Developing phase	Focuses on conserved nucleocapsid proteins.6

Emerging Global Trends and Africa's Surveillance Gap

While hantavirus research has historically centered on Asia, Europe, and the Americas, recent reports have highlighted the existence of rodent reservoirs and human disease in Africa. [24]

African Hantaviruses

Confirmed African hantaviruses include Sangassou, Tanganya, Azagny, and Mouyassué. These are primarily carried by African wood mice and other reservoirs such as Mastomys and Cricetomys species. Human cases remain rarely reported on the continent, likely due to a lack of specialized diagnostic facilities and limited surveillance, resulting in hantavirus being a significant cause of "undifferentiated febrile illness" that goes unrecognized.[24]

The Role of South Africa in the 2026 Response

South Africa's National Institute for Communicable Diseases (NICD) played a central role in the 2026 cruise ship response, confirming the presence of the Andes strain in multiple patients medically evacuated to the country.[5] This capacity for molecular detection and international coordination underscores the necessity for regional centers of excellence in managing emerging viral threats.[24]

CONCLUSION: The Path Forward

Hantaviruses remain a formidable challenge to global health, characterized by their high mortality rates and the complex ecological factors that drive their emergence.[4] The 2026 cruise ship outbreak has fundamentally altered the understanding of Andes virus transmission dynamics, highlighting the vulnerability of travelers and the potential for hantaviruses to bridge the gap between rural spillover and international transmission.[5]

The scientific community has made significant strides in defining the high-resolution structure of the viral glycoproteins and the molecular mechanisms of vascular dysfunction.[1] These insights are now fueling a diverse pipeline of vaccines from mRNA and ensilicated proteins to viral vectors—and novel therapeutics such as fibroblast modulation and nanoviricides.[14]

Moving forward, global readiness will depend on three pillars:

1. **Enhanced Surveillance:** Strengthening the detection of hantavirus in regions like Africa and Southeast Asia where the burden is likely under-recognized.[24]
2. **Rapid Diagnostics:** Developing point-of-care tools integrated with AI to provide earlier identification of severe cases.[16]
3. **Vaccine Equity:** Ensuring that the next generation of vaccines, such as those utilizing thermally stable ensilication, are accessible to the vulnerable populations in rural and resource-limited environments. [23]

As ecological changes and human movement continue to reshape the risk landscape, the integration of "One Health" surveillance with cutting-edge virological research will be essential to preventing future outbreaks from escalating into global crises.

Keywords:
Orthohantavirus; Hantavirus Pulmonary Syndrome (HPS); Hantavirus Cardiopulmonary Syndrome (HCPS); Hemorrhagic Fever with Renal Syndrome (HFRS); Andes virus (ANDV); 2026 MV Hondius Outbreak; Vascular Leakage and Endothelial Dysfunction; Ensilicated mRNA Vaccines; Fibroblast Therapy; Cryo-electron Microscopy (Cryo-EM); RNA Interference (RNAi); Zoonosis

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