Narrative Review

narra R

Narrative Review

Progress in antiviral and vaccine strategies against hantavirus: Current advances and future perspectives

Aswin R. Khairullah[1], Moh R. Afnani[2], Bima P. Pratama[3], Syahputra Wibowo[4], Indira P. Negari[5], Abdul H. Furqoni[6], Kartika A. Fauzia[7], Siti Fauziyyah[8], Rangga A. Prastika[2], Muhammad 'A. Kurniawan[3], I MDM. Adnyana[9], Sukma Sahadewa[2,10], Fara D. Durry[2,11], Volta K. Setiawan[12], Abhishek Singh[13], Vikash Jakhmola[13], Abdugani Abdurasulov[14], Maksim Rebezov[14,15], Nitin Sharma[16], Arif NM. Ansori[2,13,17*] and Rollando Rollando[18*]

[1]Research Center for Veterinary Science, National Research and Innovation Agency (BRIN), Bogor, Indonesia; [2]Drug and Vaccine Innovation Research Group, Virtual Research Center for Bioinformatics and Biotechnology, Surabaya, Indonesia; [3]Research Center for Process Technology, National Research and Innovation Agency (BRIN), Banten, Indonesia; [4]Eijkman Research Center for Molecular Biology, National Research and Innovation Agency (BRIN), Bogor, Indonesia; [5]Research Center for Vaccine and Drugs, National Research and Innovation Agency (BRIN), Bogor, Indonesia; [6]Center for Biomedical Research, National Research and Innovation Agency (BRIN), Bogor, Indonesia; [7]Research Center for Preclinical and Clinical Medicine, National Research and Innovation Agency (BRIN), Bogor, Indonesia; [8]Applied Master's Program in Food Security, Lampung State Polytechnic, Bandar Lampung, Indonesia; [9]Department of Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi, Indonesia; [10]Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia; [11]Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jawa Timur, Surabaya, Indonesia; [12]Medical Biotechnology Research Group, Virtual Research Center for Bioinformatics and Biotechnology, Surabaya, Indonesia; [13]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India; [14]Department of Veterinary Medicine and Biotechnology, Osh State University, Osh, Kyrgyz Republic; [15]Faculty of Biotechnology and Food Engineering, Ural State Agrarian University, Yekaterinburg, Russia; [16]Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, India; [17]Postgraduate School, Universitas Airlangga, Surabaya, Indonesia; [18]Faculty of Health Sciences, Universitas Ma Chung, Malang, Indonesia

*Corresponding authors: ansori.anm@gmail.com (ANMA) and ro.llando@machung.ac.id (RR)

Abstract

Hantaviruses are rodent-associated zoonotic RNA viruses responsible for hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS), two clinically distinct diseases characterized by vascular dysfunction and potentially severe organ failure. Their geographic distribution, antigenic diversity, and variable clinical outcomes complicate the development of broadly applicable medical countermeasures. The aim of this narrative review is to critically examine the molecular rationale, current evidence, and translational readiness of antiviral and vaccine strategies against hantavirus infections. Antiviral approaches include ribavirin, favipiravir, RNA interference, neutralizing monoclonal antibodies, and investigational host-directed therapies, with particular attention to differences between human clinical evidence and findings from cell culture or animal models. Vaccine strategies are evaluated across regionally implemented inactivated vaccines, live-attenuated vaccines, DNA candidates assessed in early-phase human trials, recombinant protein, viral vector, and messenger RNA platforms that remain predominantly preclinical. The review also distinguishes vaccine immunogenicity, experimental protection, durability of immune responses, and clinical effectiveness. Major barriers to translation include virus-specific therapeutic responses, narrow treatment windows, targeted delivery, antigenic diversity, and the absence of validated correlates of protective immunity. This review highlights the experimental and clinical evidence needed to advance promising antiviral and vaccine candidates toward effective strategies for prevention and treatment of hantavirus infections.

Keywords: Hantavirus, hemorrhagic fever with renal syndrome, hantavirus cardiopulmonary syndrome, antiviral agents, vaccines

Copyright: © 2026 by the authors.
This is an open access article distributed under the terms and conditions of the CC BY-NC 4.0.

Received: August 10, 2026 - Accepted: October 29, 2026 - Published online: November 6, 2026

Introduction

Hantaviruses are enveloped, tripartite, negative-sense RNA viruses within the family *Hantaviridae*. The genome comprises small (S), medium (M), and large (L) segments that encode proteins required for viral replication and host-cell entry [1]. Rodents are the principal reservoirs of human-pathogenic hantaviruses, and their distribution and transmission are shaped by reservoir ecology and environmental conditions [2]. Ecological analyses based largely on Chinese surveillance further emphasize that environmental variability and host population dynamics can influence hantavirus transmission [3].

Human infection is associated primarily with two major clinical syndromes: hemorrhagic fever with renal syndrome (HFRS), most commonly reported in Asia and Europe, and hantavirus cardiopulmonary syndrome (HCPS), predominantly reported in the Americas [4,5]. HFRS is characterized by fever, vascular instability, hemorrhagic manifestations, and varying degrees of acute kidney injury [4]. In contrast, HCPS may progress rapidly to noncardiogenic pulmonary edema, respiratory failure, and circulatory shock [5]. These geographic patterns are associated with differences in circulating viral species and their reservoir hosts. Moreover, changes in land use, land cover, and human–rodent interactions may further modify exposure risks [6-8].

Human infection usually follows inhalation of aerosols contaminated with urine, feces, or saliva from infected rodents, particularly during activities that disturb contaminated materials [9]. Epidemiological investigations have identified residential, occupational, and recreational exposures among patients with HCPS in the United States [10]. Human-to-human transmission is uncommon but has been documented for Andes virus, typically in circumstances involving close or prolonged contact [9,11]. Accordingly, current prevention strategies primarily focus on reducing human exposure to infected rodents and their excreta, particularly in potentially contaminated residential and occupational environments [12].

Vascular endothelial cells are major targets of pathogenic hantaviruses, and clinically significant vascular leakage can develop without extensive direct virus-mediated cytolysis [13]. Altered vascular endothelial growth factor signaling has been implicated in endothelial barrier integrity in experimental systems [14]. Innate and adaptive immune responses contribute to viral control but may also exacerbate inflammation and vascular dysfunction, suggesting that therapeutic strategies may need to address both viral replication and dysregulated host responses [15,16].

Recent surveillance data illustrate the continuing, geographically heterogeneous disease burden. In China, national surveillance recorded 3,271 cases of epidemic hemorrhagic fever and 16 deaths in 2025 [17]. In the European Union/European Economic Area (EU/EEA), 1,885 hantavirus infections were reported in 2023, corresponding to a notification rate of 0.4 cases per 100,000 population [18]. In the Americas, the Pan American Health Organization reported 229 confirmed cases of hantavirus pulmonary syndrome and 59 deaths through epidemiological week 47 of 2025, corresponding to a reported case-fatality proportion of 25.7% [19]. These figures originate from different years, surveillance systems, and case definitions and should not be interpreted as directly comparable estimates of regional incidence or disease lethality.

Despite this burden, supportive management remains the cornerstone of clinical care, and no antiviral has demonstrated consistent efficacy across HFRS and HCPS [9]. A randomized clinical trial conducted in China reported reduced mortality and selected complications among patients with HFRS receiving intravenous ribavirin [20]. However, a placebo-controlled trial in HCPS did not establish a clinical benefit during the cardiopulmonary phase, underscoring why treatment findings cannot be generalized across syndromes or disease stages [21]. Favipiravir has shown antiviral activity and improved survival under selected preclinical conditions [22]. RNA interference has suppressed Andes virus replication in cultured cells [23]. Neutralizing monoclonal antibodies have conferred protection in selected animal challenge models, but their efficacy in patients remains unconfirmed [24]. Collectively, these findings illustrate the different levels of evidence supporting current antiviral candidates, ranging from clinical investigation to in vitro and animal-model studies [25].

Prevention faces similar translational challenges. Inactivated vaccines targeting HFRS-associated hantaviruses have been implemented in China [26], while Hantavax is an authorized

inactivated Hantaan virus vaccine in South Korea [27]. In contrast, a bivalent Hantaan/Puumala DNA vaccine has reached phase IIa clinical evaluation for safety and immunogenicity, without demonstrating clinical effectiveness against naturally acquired infection [28]. Recombinant protein, viral vector-based, and messenger RNA vaccine platforms have been investigated predominantly in preclinical studies, and the breadth and durability of vaccine-induced protection remain important evidence gaps [29].

Accordingly, the aim of this narrative review is to critically evaluate the molecular rationale, evidence levels, and translational limitations of current hantavirus antiviral and vaccine strategies. The discussion first summarizes mechanisms relevant to therapeutic targeting and antigen design, then compares clinically investigated interventions with preclinical and exploratory approaches, assesses the development status of vaccine platforms, and identifies priorities for further experimental and clinical validation.

Virology and pathogenesis of hantavirus

Genome organization and viral structure

The hantavirus genome comprises three RNA segments, each encoding proteins with distinct roles in the viral life cycle. The S segment encodes the nucleocapsid (N) protein, which encapsidates viral RNA and participates in viral RNA synthesis [1]. The M segment encodes a glycoprotein precursor processed into the surface glycoproteins Gn and Gc, which mediate viral attachment and membrane fusion [30]. Because Gn and Gc contain neutralizing antibody epitopes, they represent important targets for antibody-based interventions and vaccine antigen design [31–33]. Furthermore, the ability of Gn and Gc to self-assemble into virus-like particles in experimental expression systems provides a potential platform for vaccine antigen presentation [34].

The L segment encodes the RNA-dependent RNA polymerase (RdRp), which is responsible for viral messenger RNA (mRNA) transcription and genome replication [1]. During transcription, the viral transcription machinery uses short capped RNA primers acquired from host transcripts through cap-snatching to synthesize mRNA from negative-sense genomic RNA (vRNA) [35]. In contrast, genome replication proceeds through primer-independent synthesis of a full-length positive-sense complementary RNA (cRNA), or antigenome, from the vRNA template [36]. The antigenome subsequently serves as an intermediate template for producing new negative-sense genomic RNA, rather than functioning as a protein-coding transcript [37]. These mechanistically distinct steps identify RdRp and viral RNA synthesis as relevant targets for direct-acting antivirals. In addition, experimental evidence demonstrating interactions between N and RdRp highlights the importance of the viral replication complex in RNA synthesis [38].

Viral entry and host interaction

Hantavirus entry begins with Gn/Gc-mediated interactions with host-cell entry factors, followed by endocytosis and membrane fusion within endosomal compartments [13,30]. Earlier cell-based studies implicated αvβ3 integrins in entry by certain HFRS-associated hantaviruses [39]. In contrast, protocadherin-1 (PCDH1) has been experimentally identified as a critical entry factor for Andes virus and Sin Nombre virus in pulmonary endothelial cells. Disruption of PCDH1 expression also conferred protection against Andes virus challenge in hamsters [40]. These findings indicate that entry-factor dependence differs among hantaviruses and should not be represented as a single universal receptor pathway. For Hantaan virus, clathrin-dependent receptor-mediated endocytosis was demonstrated in a cell-based investigation, although this pathway should not be assumed to operate identically in all hantaviruses [41]. Gn and Gc contribute complementary functions to viral attachment, membrane fusion, and virion assembly [42].

Following entry, pathogenic hantaviruses primarily target vascular endothelial cells, where infection can impair barrier function without extensive direct viral cytolysis [13]. Experimental studies have linked enhanced vascular endothelial growth factor (VEGF) signaling to increased endothelial permeability [14]. Specifically, Andes virus infection of human lung endothelial cells has been associated with increased VEGF production and reduced junctional VE-cadherin,

contributing to endothelial barrier disruption [43]. The resulting vascular leakage contributes to renal involvement in HFRS and pulmonary and cardiovascular complications in HCPS [4, 5, 44]. Furthermore, pathogenic hantaviruses have been shown to promote platelet adherence to infected endothelial cells in experimental systems, suggesting an additional mechanism contributing to vascular dysfunction [45]. The connections between viral entry, endothelial dysfunction, and organ involvement are summarized in **Figure 1**.

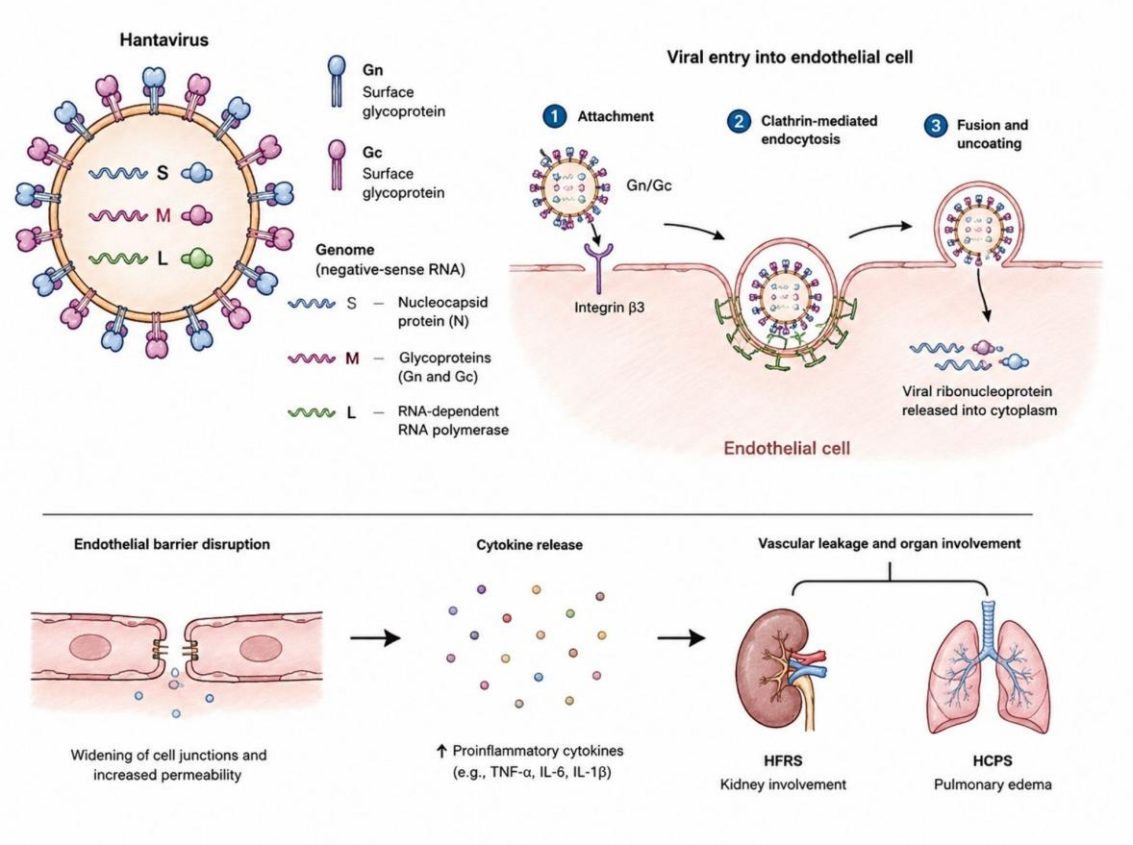


Figure 1. Hantavirus structure, entry, and endothelial pathogenesis.

Immunopathogenesis

Host immune responses contribute to both control of hantavirus infection and the development of vascular injury. Innate recognition involving retinoic acid-inducible gene I (RIG-I)-like receptors activates type I interferon signaling and restricts Hantaan virus replication in experimental systems [46]. However, hantaviruses can modulate these antiviral pathways, and the outcome reflects interactions between viral replication and host immune regulation [37]. In a Hantaan virus model, viral interference with TRIM25-associated RIG-I-like receptor signaling was reported as a mechanism of innate immune antagonism [47]. Clinical observations in patients with Puumala virus infection further demonstrate the involvement of both innate and adaptive immune responses during hantavirus infection [48]. In addition, neutralizing antibodies targeting the Gn/Gc glycoproteins can inhibit viral entry and represent important components of vaccine development and passive immunotherapy, although their protective breadth varies depending on the antibody and viral species [24,31].

Adaptive immune responses, particularly virus-specific T-cell responses, may contribute to viral control but can also participate in immunopathology. In an endothelial-cell culture model, hantavirus-specific cytotoxic T lymphocytes increased permeability of infected endothelial monolayers, suggesting a potential mechanism of immune-mediated endothelial injury [49]. However, the extent to which this experimental mechanism contributes to vascular pathology in patients remains incompletely established. Dysregulated inflammatory mediators and VEGF-associated signaling may further impair endothelial junctions and amplify vascular leakage [14,15, 50]. These findings highlight the need to distinguish protective antiviral immunity from potentially harmful immune-mediated responses and support the investigation of

complementary therapeutic strategies that suppress viral replication while preserving protective immunity and endothelial integrity.

Current antiviral strategies against hantavirus

Current management of hantavirus infection relies primarily on supportive and organ-directed care, including respiratory and hemodynamic support and renal replacement therapy when clinically indicated [9]. Although several antiviral candidates have been investigated, their levels of supporting evidence and clinical development vary substantially. Ribavirin has undergone human clinical testing, with different outcomes reported between HFRS and HCPS [20,21]. In contrast, favipiravir [22], RNA interference-based approaches [23], and neutralizing monoclonal antibodies [24] remain supported predominantly by preclinical evidence from cell-based and animal studies. Additional compounds identified through cell-based screening have demonstrated potential to interfere with hantavirus entry, although their therapeutic relevance remains to be established [51]. The current evidence for these interventions, distinguishing supportive clinical management from clinically investigated, preclinical, and exploratory therapeutic approaches, is summarized in **Table 1**. The proposed antiviral targets and intervention points are illustrated in **Figure 2**; these represent potential therapeutic strategies rather than interventions with established clinical efficacy.

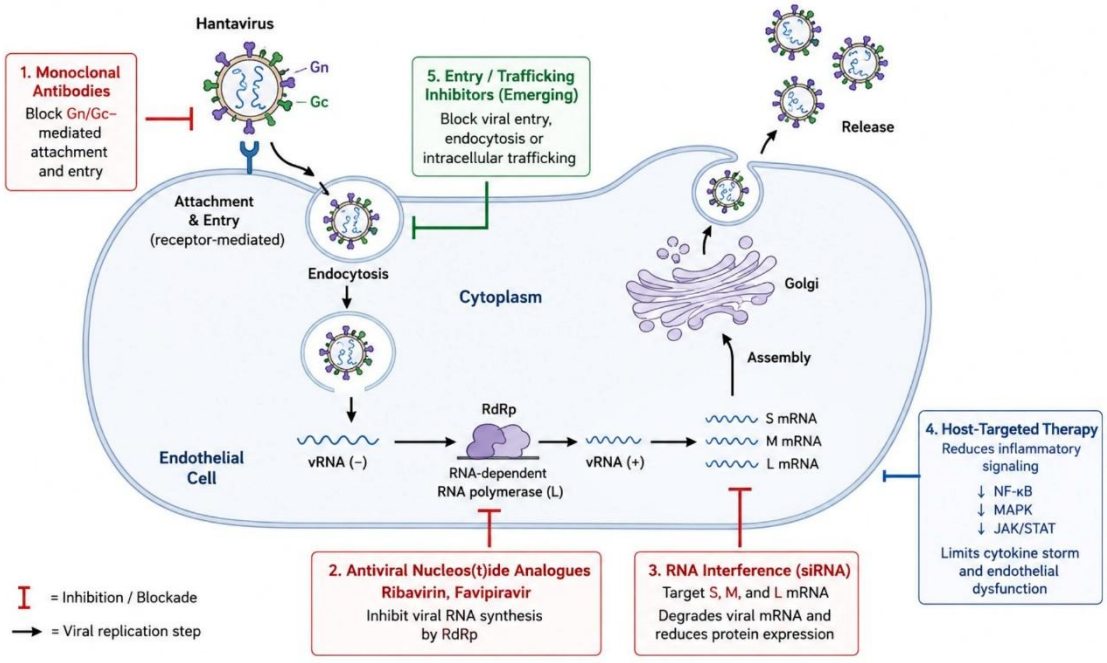


Figure 2. Mechanistic overview of antiviral strategies against hantavirus.

Ribavirin and conventional antivirals

Ribavirin is a nucleoside analogue that interferes with viral RNA synthesis through several proposed mechanisms, including inhibition of inosine monophosphate dehydrogenase (IMPDH), depletion of intracellular guanosine triphosphate pools, and effects on viral polymerase activity or mutagenesis [52]. Although these mechanisms provide a rationale for its antiviral activity, clinical outcomes differ by syndrome, hantavirus species, and disease stage. Thus, mechanistic plausibility alone cannot substitute for evidence of benefit in patients. Consistent with a mutagenesis-related mechanism, a Hantaan virus cell-culture study linked ribavirin exposure to increased viral RNA mutational frequency, supporting a mutagenesis-related mechanism under the conditions tested [53].

For HFRS, a randomized, double-blind, placebo-controlled trial conducted in China enrolled 242 patients and reported reduced mortality and fewer oliguric and hemorrhagic complications in the ribavirin-treated group [20]. These findings suggest a potential benefit in selected cases

treated early, but do not establish equal efficacy against all HFRS-associated hantaviruses. This limitation is illustrated by a separate randomized, open-label trial of Puumala virus-associated HFRS, in which ribavirin did not improve viral load kinetics, and adverse events were more frequent among treated patients [54]. Differences in study populations, causative viruses, clinical stages, and outcomes limit generalization from one HFRS trial to another. A meta-analysis of available ribavirin studies emphasized that heterogeneous syndromes, study designs, and disease stages restrict pooled conclusions [55]. Observational experience with intravenous ribavirin in Korean HFRS patients provides additional human context but does not have the evidentiary strength of a placebo-controlled trial [56].

Evidence in HCPS is less supportive of ribavirin's clinical efficacy. A placebo-controlled trial in North America found no convincing improvement in its principal clinical outcome among confirmed HCPS cases treated during the cardiopulmonary phase [21]. However, the relatively small number of confirmed cases and premature termination of the trial limit its ability to exclude potential benefits from treatment initiated during earlier disease stages. Nevertheless, ribavirin activity observed in Andes virus experimental models must not be presented as proof of efficacy in patients [57]. Its potential use must also be weighed against adverse effects, including hemolytic anemia and reproductive toxicity [20,54]. Overall, the available evidence does not support ribavirin as a universally effective treatment for hantavirus infections, highlighting the importance of virus-specific and disease-stage-dependent clinical evaluation.

Favipiravir and broad-spectrum antivirals

Favipiravir (T-705) is a nucleoside analogue antiviral that undergoes intracellular conversion to an active ribofuranosyl triphosphate metabolite, which interferes with RdRp-mediated viral RNA synthesis [52]. In hantavirus experiments, favipiravir inhibited Hantaan virus replication in cell culture, while separate experiments showed reductions in viral RNA and infectious titers for Andes virus and Sin Nombre virus [22,52]. These findings demonstrate in vitro antiviral activity against selected hantaviruses but do not establish clinical efficacy in humans. Pharmacological studies of favipiravir describe its intracellular activation and activity against RNA virus polymerase systems [67], while its broader antiviral development history is informative for candidate selection but does not constitute hantavirus-specific clinical evidence [68].

In Andes virus-infected Syrian hamsters, oral favipiravir reduced viral RNA and antigen levels and improved survival at selected doses [22]. Importantly, the protective effect was strongly dependent on treatment initiation: administration beginning on or before day 4 after exposure improved survival, whereas treatment initiated on days 5 or 6 failed to prevent lethal disease. This loss of protection coincided with the onset of detectable viremia in the experimental model [22]. These findings suggest that the therapeutic window may be a critical determinant of favipiravir efficacy, although the observed timing cannot be directly extrapolated to human infection.

Clinical efficacy in either HFRS or HCPS remains inadequately confirmed, and no reliable conclusion can be drawn that favipiravir is clinically superior or safer than ribavirin for hantavirus infection [9,52]. Dose selection, tolerability, use after symptom onset, and activity across different hantavirus species require further clinical evaluation. Favipiravir should therefore be described as a preclinical antiviral candidate rather than an established treatment.

RNA interference and gene silencing approaches

RNA interference (RNAi) offers a sequence-specific strategy to suppress viral gene expression. Small interfering RNA (siRNA) directed against transcripts associated with the S, M, or L genome segments can guide the RNA-induced silencing complex (RISC) to complementary target RNA, leading to sequence-dependent cleavage and reduced viral protein expression [23]. Chiang et al. demonstrated inhibition of Andes virus replication by selected siRNAs in Vero E6 cells and human lung microvascular endothelial cells [23]. Although these results establish antiviral activity in cell-based models, their clinical applicability remains unproven.

Further evidence of antiviral activity has emerged from animal models. Plasmids expressing short hairpin RNA (shRNA) targeting Hantaan virus reduced viral replication and improved outcomes in experimental mouse infection studies [58]. A separate investigation used an antibody-based chimeric protein to deliver antiviral siRNA into infected cells and reported reduced virus-associated intracranial disease in a mouse model [59].

Table 1. Hantavirus therapeutic strategies: Mechanisms of action, levels of evidence, clinical development status, and limitations

Strategy	Representative agents/approaches	Primary mechanism of action	Molecular/clinical target	Evidence level/development status	Evidence-supported key findings	Limitations / translational gaps
Supportive and organ-directed care	Respiratory support, hemodynamic stabilization, renal replacement therapy as indicated	Support of organ function; no specific inhibition of viral replication	Pulmonary, cardiovascular and renal dysfunction	Established clinical care	Core clinical management for HFRS and HCPS when indicated [9].	Not a direct-acting antiviral; advanced support may be resource-intensive.
Conventional antiviral — ribavirin	Intravenous ribavirin	Nucleoside analogue; IMPDH inhibition, guanosine pool depletion, and interference with viral RNA synthesis	Host IMPDH and viral RNA synthesis	Clinically evaluated; syndrome- and stage-dependent	A randomized trial found reduced mortality/complications in selected HFRS patients; Puumala HFRS trial did not demonstrate virological benefit; clinical efficacy in HCPS is unestablished [20,21,54].	Limited/generalization-sensitive clinical evidence; hemolytic anemia; reproductive toxicity; treatment timing.
Broad-spectrum antiviral — favipiravir	Favipiravir (T-705)	Active ribonucleotide metabolite interferes with RdRp-mediated RNA synthesis	Viral RdRp	Preclinical (cell culture and animals)	Antiviral activity against selected hantaviruses; improved Andes virus hamster survival when treatment began before detectable viremia [22,52].	Adequate human clinical confirmation absent; animal timing window and dosing are not directly transferable.
RNA interference — siRNA/shRNA	Segment-targeted siRNA; shRNA plasmids; targeted siRNA delivery	RISC-dependent, sequence-specific silencing of complementary viral RNA	S-, M- and L-derived viral transcripts	Preclinical (cell culture and mouse studies)	Reduced Andes virus replication in cultured cells; Hantaan virus shRNA and targeted siRNA delivery showed protective effects in distinct mouse models [23,58,59].	Endothelial delivery, RNA stability, endosomal escape, off-target effects, immune activation and model relevance [60].
Host miRNA modulation	Candidate miRNA mimics/inhibitors	Proposed modification of host transcripts implicated in infection or inflammation	Host microRNA regulatory pathways	Experimental/exploratory	Host miRNA profiles change in cell- and virus-dependent patterns during hantavirus infection [61].	Expression changes do not establish therapeutic efficacy; pleiotropic effects and specificity unresolved.
Neutralizing mAbs	ADI-42898, ADI-65534, JL16/MIB22	Inhibition of Gn/Gc-mediated attachment or fusion	Viral Gn/Gc epitopes	Preclinical (neutralization and animal challenge)	Selected antibodies protect in pre- or post-exposure models; some protect Andes virus-infected hamsters after	No established human efficacy; breadth of in vivo cross-protection, timing, escape and safety uncertain.

Strategy	Representative agents/approaches	Primary mechanism of action	Molecular/clinical target	Evidence level/development status	Evidence-supported key findings	Limitations / translational gaps
					detectable replication [24,62,63].	
Convalescent immune plasma	High-neutralizing-titer plasma from recovered patients	Passive delivery of polyclonal neutralizing antibodies	Viral glycoproteins and virions	Limited human clinical evaluation (nonrandomized)	Nonrandomized multicentre Andes virus HCPS study suggested possible benefit [64].	Cannot establish causality; donor variability, supply, and transfusion-related risks.
Host-directed pathway modulation	Investigational inhibitors of inflammatory/endothelial signaling	Proposed modulation of dysregulated host immune and vascular responses	NF-κB, MAPK, JAK/STAT and related pathways	Experimental/exploratory	Mechanistic rationale exists from studies of endothelial leakage and innate responses [14,15,37].	Drug- and pathway-specific efficacy missing; risk of disrupting protective immunity.
VEGFR2-directed approach — vandetanib	Vandetanib	Inhibition of VEGFR2-associated signaling implicated in endothelial permeability	Host VEGFR2 and vascular barrier	Preclinical (cell culture and hamster studies)	Modest delay in disease progression and reduced pleural effusion in Andes virus hamsters after pretreatment [65].	No proven survival or symptomatic human treatment benefit; toxicity and timing concerns.
Natural protein candidate — lactoferrin	Bovine lactoferrin	Interference with early viral adsorption to host cells	Virus–cell attachment	Preclinical (cell culture and suckling mice)	Reduced hantavirus focus formation and improved survival following prophylactic administration in a suckling-mouse model [66].	No human clinical efficacy; largely prophylactic experimental evidence; pharmacology undetermined.
Combination-based approaches	Lactoferrin + ribavirin; ribavirin + favipiravir; proposed antiviral/host-directed regimens	Potential interference with complementary viral or host processes	Multiple targets depend on selected agents	Experimental/early preclinical	Combined lactoferrin/ribavirin inhibited focus formation in vitro; ribavirin/favipiravir showed additive inhibition in cell culture [52,66].	No demonstrated clinical synergy, safety, optimal dosing, or benefit over monotherapy.

Gn/Gc: hantavirus envelope glycoproteins; HCPS: hantavirus cardiopulmonary syndrome; HFRS: hemorrhagic fever with renal syndrome; IMPDH: inosine monophosphate dehydrogenase; JAK/STAT: Janus kinase/signal transducer and activator of transcription; L: large; M: medium; MAPK: mitogen-activated protein kinase; mAbs: monoclonal antibodies; miRNA: microRNA; NF-κB: nuclear factor kappa B; RdRp: RNA-dependent RNA polymerase; RISC: RNA-induced silencing complex; RNA: ribonucleic acid; S: small; shRNA: short hairpin RNA; siRNA: small interfering RNA; VEGFR2: vascular endothelial growth factor receptor 2.

Despite these encouraging findings, the experimental models do not fully reproduce the clinical manifestations of HFRS or HCPS, and the therapeutic efficacy of these approaches in humans remains unestablished. Several barriers complicate the translation of RNAi-based approaches into clinical applications, including RNA degradation and clearance, inadequate delivery into infected tissues, inefficient endosomal escape, possible off-target silencing, innate immune activation, and viral sequence variability [60]. Selective delivery to infected vascular endothelial cells is particularly challenging, and proposed lipid, polymeric, or targeted delivery systems require hantavirus-specific efficacy and safety testing rather than extrapolation from other diseases [60]. In addition to direct viral RNA silencing, hantavirus infection has been associated with virus- and cell type-specific alterations in host microRNA (miRNA) expression profiles [61]. However, these expression changes do not establish a therapeutic role for miRNA mimics or inhibitors, which remain exploratory approaches requiring functional validation.

Monoclonal antibody-based therapy

Neutralizing monoclonal antibodies (mAbs) target Gn/Gc epitopes and can block viral attachment or membrane fusion, thereby preventing entry of viral ribonucleoprotein complexes into the cytoplasm [24,31]. Their experimental applications must be differentiated by administration timing: pre-exposure prophylaxis, post-exposure prophylaxis before advanced illness, and therapeutic intervention after viral replication is established. To date, hantavirus-specific mAbs have predominantly preclinical evidence, rather than validated efficacy in patients. Reviews of hantavirus entry mechanisms provide a rationale for targeting glycoprotein-mediated membrane fusion, while emphasizing virus-dependent entry pathways [69].

Pre-exposure protection has been observed in selected animal challenge systems, while post-exposure experiments demonstrate that certain antibodies remain protective after inoculation [24]. For example, ADI-42898 neutralized multiple hantavirus glycoprotein pseudotypes or entry systems in laboratory assays and protected animals challenged with Andes virus or Puumala virus [24]. However, neutralization of multiple viruses in vitro must be distinguished from direct demonstration of protection against each virus in vivo. Reviews of hantavirus humoral immunity distinguish neutralizing-antibody responses from demonstrated protection in specific experimental models [70]. Earlier recombinant human antibodies targeting Hantaan virus Gc (historically termed G2) demonstrated virus-specific neutralization in laboratory assays [71].

Beyond prophylaxis, selected mAbs have also demonstrated therapeutic potential when administered after infection has been established. Williamson *et al*. reported complete survival following treatment with the JL16/MIB22 antibody combination on days 5 and 9 after infection, whereas later administration on days 8 and 10 yielded weaker, statistically inconclusive protection [62]. An engineered antibody, ADI-65534, provided substantial protection in the Andes virus hamster model when administered after detectable viral replication, supporting an experimental therapeutic window beyond immediate post-exposure administration [63]. These results remain specific to the tested antibody, virus, and animal model, and should not be interpreted as demonstrated efficacy in symptomatic human disease.

The breadth of antibody-mediated protection also requires careful interpretation, as cross-binding, cross-neutralization, and cross-protection represent distinct experimental outcomes [24,63]. Although conserved Gn/Gc epitopes offer a rationale for broadly active antibodies, efficacy against untested species, resistance through viral escape, dosing, pharmacokinetics, and human safety remain uncertain. Convalescent immune plasma should be distinguished from purified mAbs: a nonrandomized multicentre study in Andes virus-associated HCPS suggested possible clinical benefit, but its design did not establish causality or validate mAb treatment [64]. Antigenic mapping of human hantavirus antibodies has revealed distinct patterns of glycoprotein recognition and neutralization breadth, supporting candidate-specific rather than universal claims [72].

Host-targeted antiviral strategies

Host-directed approaches aim to modify cellular factors involved in hantavirus infection or vascular injury rather than directly inhibiting viral components. Endothelial barrier dysfunction, VEGF-related signaling, and inflammatory responses provide mechanistic reasons to investigate vascular-stabilizing and immunomodulatory interventions [14,15]. However, mechanistic

involvement in disease does not demonstrate that pharmacological inhibition of an individual pathway improves clinical outcomes. Hantavirus-focused evidence on vascular and lymphatic endothelial responses provides a mechanistic rationale for exploring host-directed interventions, but does not establish clinical treatment efficacy [73].

NF-κB, MAPK, and JAK/STAT pathways have roles in innate immune signaling and inflammation, but their modulation may also impair protective antiviral responses [37]. Similarly, targeting host-cell entry factors requires virus-specific evaluation, as β3-integrin-associated entry mechanisms and PCDH1 dependence differ among hantaviruses [39,40]. Thus, candidate host-directed inhibitors remain exploratory for hantavirus treatment and require evidence of selective efficacy, appropriate timing, and acceptable safety in disease-relevant models.

Investigational antiviral and host-directed candidates

Vandetanib is a multitarget kinase inhibitor investigated experimentally for its effects on VEGF receptor 2 (VEGFR2)-associated endothelial signaling, rather than as a proven direct inhibitor of hantavirus entry or RNA synthesis. In an Andes virus-infected hamster model, pretreatment modestly affected the timing of disease progression and reduced pleural effusion, but did not establish a meaningful survival benefit [65]. Accordingly, these results do not support therapeutic efficacy after symptom onset in patients, and potential drug toxicity further limits clinical extrapolation.

Another investigational approach involves lactoferrin, an iron-binding glycoprotein with reported antiviral activity in experimental hantavirus models. In studies involving Seoul virus, pretreatment interfered predominantly with viral adsorption, while prophylactic administration increased survival in a suckling-mouse model [66]. However, these findings primarily support a prophylactic effect under experimental conditions rather than therapeutic activity against established infection. They should not be interpreted as evidence of clinical efficacy in HFRS or HCPS or of clinically established anti-inflammatory effects. Its effective human dose, delivery, and safety in hantavirus disease remain unresolved.

Combining different antiviral agents represents a further investigational strategy aimed at targeting complementary stages of viral infection. Lactoferrin pretreatment followed by ribavirin enhanced inhibition of hantavirus focus formation in vitro [66]. In a separate Hantaan virus cell-culture study, ribavirin plus favipiravir exhibited an additive antiviral interaction; this is not evidence of synergistic clinical efficacy [52]. Importantly, additive inhibition in vitro does not establish pharmacological synergy or improved clinical outcomes. Proposed combinations of direct-acting antivirals with host-directed agents remain insufficiently validated for hantavirus disease and require carefully designed studies addressing drug interactions, treatment timing, and toxicity.

Taken together, the clinical evidence for ribavirin in selected HFRS settings is distinct from predominantly preclinical findings for favipiravir, RNAi, mAbs, vandetanib, and lactoferrin. No tested strategy should be described as broadly effective across hantavirus syndromes without appropriately matched clinical evidence. These approaches, according to their mechanisms of action, evidence levels, key findings, and translational limitations, are presented in **Table 1**. Furthermore, small-molecule screening against hantavirus infection has generated experimental hits that likewise require mechanistic and in vivo validation [74].

Progress in hantavirus vaccine development

Hantavirus vaccine development comprises platforms with markedly different regulatory statuses and levels of supporting evidence. Inactivated whole-virus vaccines have been licensed and implemented in selected endemic settings for prevention of HFRS, whereas DNA vaccine candidates have entered human trials and recombinant protein, viral vector, and mRNA platforms remain predominantly preclinical [26,27,28,29]. An important distinction throughout this section is that vaccine-induced antibody responses, experimental protection, duration of measurable immunity, and effectiveness against naturally acquired disease are different endpoints. Accordingly, **Table 2** classifies each approach by its developmental status, immunological mechanism, demonstrated findings, and unresolved limitations.

Inactivated vaccines

Inactivated whole-virus vaccines contain chemically inactivated viral antigens and primarily stimulate antigen-specific humoral immunity without introducing a replicating hantavirus. Hantavax, an inactivated Hantaan virus vaccine, has been licensed and used in South Korea, while China has implemented distinct inactivated formulations against HFRS-associated hantaviruses [26,27]. These vaccines represent the most extensively used hantavirus vaccine platforms in humans; however, their regulatory approval and epidemiological applications remain geographically restricted and should not be interpreted as evidence of broad protection against HCPS-associated hantaviruses [29]. An earlier study described production and immunogenicity of an inactivated Hantaan virus preparation derived from suspension-cultured Vero cells, providing formulation-specific preclinical and manufacturing context [88].

Importantly, vaccine immunogenicity does not necessarily translate into protection against clinical disease. In a study of 226 healthy adults receiving Hantavax, seroconversion following two primary doses was 90.14% by immunofluorescence assay (IFA), but only 23.24% by plaque reduction neutralization test (PRNT50); one month after a booster, corresponding seropositivity was 87.32% and 45.07% [75]. A later phase III trial involving 320 adults reported neutralizing-antibody seroconversion of 80.97% after a modified three-dose primary schedule, supporting the importance of dose timing and assay choice for interpreting immunogenicity [76]. Nevertheless, neither study directly established protection against naturally acquired HFRS. Earlier Hantavax research also documented antibody responses in vaccinated adults, although the relationship between serological responses and clinical protection remained unresolved [89].

Antibody persistence is also distinct from the duration of clinical protection. In the longitudinal Hantavax study, mean detectable seropositivity persisted for 735 days by PRNT50 and 845 days by IFA, but these values measure antibody detectability rather than the duration of vaccine effectiveness [75]. The need for boosters and the extent of sustained protection therefore cannot be inferred from seropositivity alone.

Observational studies provide a separate, less uniform body of evidence concerning clinical effectiveness. An early Korean case-control study estimated vaccine effectiveness of 25%, 46%, and 75% after one, two, and three doses, respectively, but the confidence intervals for all three estimates included no effect [77]. A subsequent case-control study among South Korean military personnel reported adjusted effectiveness of 58.9% (95% confidence interval (CI): 2.3–82.7%) against HFRS, suggesting possible protection in that specific population [78]. In contrast, a retrospective study of vaccinated and unvaccinated HFRS patients did not show a statistically significant reduction in severe renal outcomes [79]. Together, these findings support cautious discussion of regional vaccine effectiveness rather than universal efficacy or guaranteed prevention of severe disease.

Live-attenuated vaccines

Live-attenuated vaccines are intended to replicate in a restricted manner while presenting a broad set of viral antigens. Although this mechanism could theoretically stimulate both humoral and cellular responses, hantavirus-specific development remains exploratory rather than clinically established [29]. Key barriers include establishing genetically stable attenuated strains, managing potential reversion or altered tissue tropism, and demonstrating safety in relevant disease models. No live-attenuated hantavirus vaccine is licensed for human use, and its clinical protective efficacy has not been established.

Recombinant protein vaccines

Recombinant protein and subunit approaches present selected hantavirus antigens, principally Gn/Gc or antigenic domains, without requiring propagation of infectious vaccine virus. Correct antigen folding and preservation of conformational epitopes are especially important because many protective neutralizing antibodies recognize structural features of the surface glycoproteins [30,31]. Such antigens may be combined with adjuvants or displayed multivalently, although their clinical utility remains unproven [29].

Table 2. Hantavirus vaccine platforms: Immunological mechanisms, evidence levels, development status, and major limitations

Vaccine platform	Representative examples/approaches	Mechanism of action	Major immune response	Evidence level/development status	Advantages / evidence-supported findings	Limitations/evidence gaps
Inactivated whole-virus vaccines	Hantavax (South Korea); distinct HTNV/SEOV formulations (China)	Inactivated antigens stimulate immune recognition without viral replication	Binding and neutralizing antibodies, with schedule-dependent booster responses [75,76]	Regionally licensed/implemented; human immunogenicity studies and observational effectiveness data	Human antibody responses vary by IFA and PRNT50 [75,76]; observational HFRS effectiveness estimates are heterogeneous [77,78,79]	Waning antibody responses; no validated protection threshold; geographic/strain limits; uncertain durable clinical protection.
Live-attenuated vaccines	Exploratory attenuated hantavirus candidates	Controlled replication would present multiple viral antigens	Potential humoral and cellular responses (theoretical)	Exploratory; no licensed human hantavirus product	Platform rationale only; no established human efficacy for hantavirus [29]	Reversion risk, genetic stability, biosafety, suitable animal models, and manufacturing feasibility.
Recombinant protein and subunit vaccines	Engineered Gn/Gc proteins or domains; nanoparticle-displayed GnH	Noninfectious glycoprotein antigens stimulate antigen-specific immune responses	Antibody binding and neutralization in selected animal experiments	Preclinical; computational epitope designs are earlier-stage	A GnH nanoparticle elicited neutralization of ANDV/CHOV pseudotypes, not SNV [80]; candidate ANDV epitopes were predicted in silico [81]	No proven human effectiveness; conformational integrity, adjuvants, durability, and heterologous protection require validation.
DNA vaccines	Bivalent HTNV/PUUV plasmid vaccines; ANDV glycoprotein DNA	Intracellular plasmid transcription produces mRNA for antigen translation	Neutralizing antibodies; cellular responses evaluated by candidate	Human clinical studies: published phase I and phase IIa; unlicensed	HTNV/PUUV phase IIa enrolled 120 adults [28]; ANDV phase I enrolled 48 [82], assessing safety and immunogenicity	Prevention of naturally acquired infection unproven; delivery, dose, durability, cross-strain breadth unresolved.
Viral vector-based vaccines	Adenovirus-ANDV; recombinant VSV-ANDV; VSV-HTNV glycoproteins	Viral vectors express hantavirus antigens in vaccinated host cells	Candidate-specific neutralizing and cellular responses	Preclinical; virus challenge models	Selected adenovirus and VSV constructs protected hamsters against ANDV challenge; VSV-HTNV reduced viral burden in mice [83,84,85]	No clinical efficacy; vector immunity, replication-competent-vector safety, and heterologous protection unknown.
mRNA vaccines	HTNV prefusion-stabilized glycoprotein mRNA-LNP; ANDV mRNA candidates	LNP-mediated cytoplasmic translation of mRNA-encoded antigens	Neutralizing antibodies and experimental immune memory	Preclinical; animal studies	HTNV mRNA-LNP protected mice in a challenge study [86]; ANDV mRNA candidates have been	Human efficacy not established; stability, dose, durability, safety, and cross-strain challenge evidence are needed.

Vaccine platform	Representative examples/approaches	Mechanism of action	Major immune response	Evidence level/development status	Advantages / evidence-supported findings	Limitations/evidence gaps
					investigated preclinically [87]	
Structure-guided and nanoparticle antigen design	ANDV-GnH nanoparticles; linear B-cell epitope prediction	Multivalent antigen display and epitope selection seek to focus recognition	Selected neutralizing responses; predicted epitopes are unvalidated	Preclinical (protein immunogen) or in silico (epitope prediction)	ANDV-GnH elicited restricted pseudotype cross-neutralization [80]; ANDV epitope candidates were predicted computationally [81]	No evidence of universal vaccine protection; heterologous live challenge and experimental epitope validation needed.
Prime–boost and adjuvant optimization	Hantavax schedule changes; experimental heterologous prime–boost	Repeated or heterologous antigen exposure seeks to improve immune memory	Antibody boosting; regimen-dependent B- and T-cell responses	Human immunogenicity evidence for Hantavax schedules; novel regimens preclinical	Modified Hantavax schedule increased neutralizing antibody responses [76]; experimental mRNA-LNP boosting increased titers in mice [86]	Immunogenicity does not prove clinical protection; ideal timing, safety, durability, and costs remain uncertain.

ANDV: Andes virus; CHOV: Choclo virus; Gc: hantavirus glycoprotein Gc; Gn: hantavirus glycoprotein Gn; GnH: Gn head domain; HFRS: hemorrhagic fever with renal syndrome; HTNV: Hantaan virus; IFA: indirect immunofluorescence assay; LNP: lipid nanoparticle; mRNA: messenger RNA; PRNT50: 50% plaque reduction neutralization test; PUUV: Puumala virus; RNA: ribonucleic acid; SEOV: Seoul virus; SNV: Sin Nombre virus; VSV: vesicular stomatitis virus.

A Gn head-domain nanoparticle immunogen derived from Andes virus induced neutralizing antibodies in mice against pseudotyped viruses bearing Andes and Choclo virus glycoproteins, but not against the tested Sin Nombre virus pseudotype [80]. This finding demonstrates limited cross-neutralization in an experimental assay rather than established protection against heterologous live-virus infection or clinical disease. At an earlier discovery stage, an immunoinformatics study of Andes virus glycoprotein predicted and structurally mapped candidate linear B-cell epitopes, including surface-accessible candidates for subsequent experimental testing [81]. Similarly, another computational study proposed multi-epitope hantavirus vaccine constructs based on predicted immunological properties [90]. However, these predictions remain preliminary and require experimental validation of antigenicity, antibody recognition, immunogenicity, and protective efficacy before their potential as vaccine candidates can be established.

DNA vaccines

DNA vaccines deliver plasmids encoding hantavirus antigens, usually glycoproteins. Following cellular uptake, the DNA is transcribed into mRNA and the resulting mRNA is translated to produce antigen. These sequential processes should not be described as direct translation of the plasmid itself [1, 29]. DNA vaccination can therefore stimulate antigen-specific humoral and cellular responses without administering intact infectious hantavirus.

Clinical development of hantavirus DNA vaccines has progressed beyond preclinical evaluation. A randomized phase IIa trial evaluated a bivalent Hantaan virus/Puumala virus DNA vaccine delivered by intramuscular electroporation in 120 healthy adults, measuring safety and neutralizing antibody responses across dose schedules [28]. Separately, a randomized phase I study of an Andes virus DNA vaccine administered by needle-free injection enrolled 48 adults and reported neutralizing antibody responses with generally acceptable short-term tolerability [82]. The latter trial evaluated immunogenicity and safety rather than disease prevention.

These clinical studies support feasibility and early-phase human immunogenicity, but none establishes protection from naturally acquired hantavirus infection or reduction of HFRS or HCPS incidence. Delivery methods, dosing schedules, durability, and breadth against antigenically distinct species remain unresolved. Accordingly, DNA vaccines are clinically evaluated candidates, not licensed or clinically proven preventive interventions.

Viral vector-based vaccines

Viral vector-based vaccines use a recombinant carrier to express hantavirus antigens in vaccinated hosts. In preclinical studies, adenoviral vectors expressing hantavirus proteins conferred protection against lethal Andes virus challenge in Syrian hamsters [83]. Similarly, recombinant vesicular stomatitis virus expressing Andes virus glycoproteins protected hamsters against lethal challenge after experimental vaccination [84]. These studies demonstrate animal protection rather than clinical vaccine efficacy. In another experimental platform, a recombinant modified vaccinia Ankara multivalent vaccine reduced viral burden in a mouse infection model; this is not evidence of disease prevention in humans [91].

A more recent VSV-based Hantaan virus glycoprotein candidate induced neutralizing antibodies and reduced viral burden after Hantaan virus challenge in mice; the study additionally measured persistence of antibody responses within the experimental follow-up [85]. However, this finding cannot establish durable immunity in humans, and neutralizing activity against another species should not be interpreted as heterologous challenge protection without direct testing. Vector immunogenicity, replication competence, manufacturing consistency, and the potential impact of anti-vector immunity require candidate-specific safety and efficacy assessment before clinical translation. Experience with adenoviral vector platforms in other pathogens shows that pre-existing anti-vector immunity can modify vaccine responses, a consideration that requires candidate-specific evaluation for hantavirus vaccines [92].

mRNA vaccine approaches

mRNA vaccines encode viral antigens that are translated after delivery into host-cell cytoplasm; lipid nanoparticles (LNPs) can protect the mRNA and facilitate cellular uptake. The Gn/Gc complex is a principal antigenic target for hantavirus mRNA vaccine designs [30]. Unlike plasmid

DNA vaccines, this platform does not require nuclear entry for antigen expression, although formulation stability, reactogenicity, and appropriate antigen conformation remain important development considerations. General mRNA-vaccine research highlights formulation quality and delivery characteristics as determinants of immunogenicity, although these considerations require hantavirus-specific testing [93].

In 2026, prefusion-stabilized Hantaan virus glycoprotein constructs delivered as DNA or LNP-encapsulated mRNA elicited neutralizing antibodies and protected mice in an Hantaan virus challenge model [86]. A separate 2026 report described single-dose mRNA vaccine candidates targeting Andes virus in preclinical research [87]. These findings provide hantavirus-specific experimental support for mRNA vaccine development, but no clinical effectiveness or licensed human indication can be inferred from animal-model protection. Cross-species protection, durability, dosing, safety, and feasibility of use in endemic populations require further evaluation.

Immunological correlates of protection

Neutralizing antibodies against Gn/Gc are important candidate markers of protective immunity, but their detection must not be equated with demonstrated vaccine-mediated clinical protection [24,31]. Binding antibody assays such as IFA, live-virus neutralization assays such as plaque reduction neutralization test, and pseudovirus-based assays quantify different properties and cannot be treated as interchangeable outcomes. A 2026 systematic review of hantavirus vaccine trials emphasized the substantial differences between antibody readouts and the absence of a validated human correlate or surrogate of protection [94]. Structural analysis of antibody-mediated hantavirus glycoprotein targeting provides additional support for evaluating epitope accessibility rather than relying on binding titres alone [95].

Although protection against experimental viral challenge provides stronger functional evidence than antibody induction alone, such findings remain dependent on the animal model, viral species, and experimental conditions. Similarly, the persistence of neutralizing antibodies or memory responses does not establish a corresponding duration of protection in humans [75,85]. T-cell responses and balanced innate signaling may contribute to protection, yet excessive inflammatory activity is also implicated in hantavirus-associated vascular injury [15,49]. Future vaccine studies therefore need standardized immunological assays, heterologous challenge where justified, longitudinal follow-up, and ultimately studies measuring clinically meaningful human outcomes.

Taken together, the evidence supports three distinct levels of vaccine readiness: regionally implemented inactivated vaccines with human observational effectiveness data, DNA candidates with early-phase human safety and immunogenicity findings, and other platforms supported mainly by preclinical results. The comparative development status of these platforms, together with their immunological responses and remaining protection gaps, is illustrated in **Figure 3**. Development of broadly protective vaccines will require direct testing across relevant viral species rather than inference from conserved epitopes, cross-binding, or cross-neutralization alone [29,80].

Challenges in antiviral and vaccine development

Despite advances in hantavirus therapeutics and vaccine research, several barriers impede the transition from mechanistic discovery to broadly applicable interventions. Genetic and antigenic diversity across hantavirus species complicates the selection of conserved antiviral targets and vaccine epitopes [2,24]. Comparative structural studies have documented differences in virion morphology and organization among Old World and New World hantaviruses [96]. Consequently, neutralization of selected viral species or recognition of a conserved epitope cannot be assumed to confer protection against all HFRS- and HCPS-associated viruses [63,80]. Furthermore, evolutionary analyses highlight substantial genetic variation across hantavirus lineages, emphasizing the need for continued genomic surveillance and evaluation of antigenic breadth [97,98].

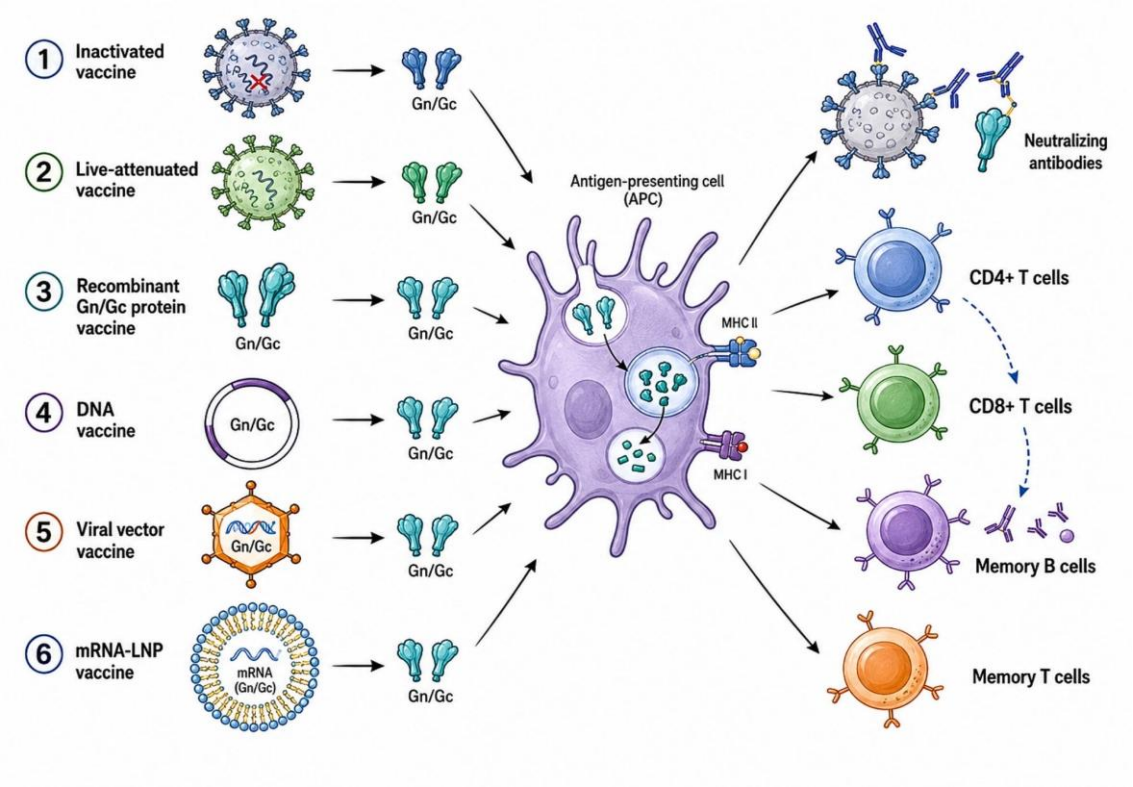


Figure 3. Comparative landscape of hantavirus vaccine platforms and immune protection.

The limited availability of disease-relevant models is another important constraint. The Syrian hamster model reproduces several features of severe Andes virus-associated cardiopulmonary disease and has enabled challenge experiments with antivirals, antibodies, and vaccine candidates [99]. However, outcomes in this model should not be generalized to all hantaviruses or to the full clinical spectrum of HFRS. Other laboratory models may permit viral replication or immunological evaluation without reproducing the clinically important renal or pulmonary manifestations of human disease [100]. Differences in model susceptibility and disease manifestations also complicate comparisons across experimental studies. Standardized endpoints, including viral burden, endothelial dysfunction, survival, and treatment timing, are therefore needed to improve the interpretability of preclinical studies. Previous reviews focused on hantavirus-associated renal disease caution that pulmonary and renal manifestations may not be reproduced equally across available experimental models [101].

The translation of early antiviral effects into treatment of patients is further limited by differences in viral species, exposure-to-treatment intervals, and disease stage. The contrasting clinical findings for ribavirin in selected HFRS cases and in HCPS during the cardiopulmonary phase illustrate why syndrome-specific trials and precisely defined treatment windows are essential [20,21]. In addition, severe hantavirus disease is often uncommon and geographically concentrated, making recruitment, appropriate control groups, and sufficiently powered efficacy studies difficult [19,100]. Multicenter collaboration and prospectively specified clinical endpoints are needed to distinguish antiviral activity from improvements in patient outcomes.

Research infrastructure and product delivery impose additional constraints. Work involving infectious hantaviruses and experimental challenges requires risk-appropriate containment and specialized expertise; containment requirements depend on the agent and procedure rather than a single universal biosafety designation [102]. For RNA-based therapeutics, efficient delivery to infected endothelial cells, intracellular release, and avoidance of off-target effects remain unresolved [60]. Although nanoparticle systems have potential advantages for drug stability and tissue delivery in broader antiviral research, these advantages require direct verification for hantavirus-specific therapeutic products [103]. Historical biosafety assessments for hantavirus laboratory and postmortem work likewise emphasize evaluating the specific exposure procedure and associated hazards [104].

Vaccine implementation also presents practical limitations beyond immunogenicity. Regionally used inactivated vaccines have yielded variable observational effectiveness estimates, whereas DNA and newer platforms still lack direct evidence of protection against naturally acquired human infection [28,77,78]. Differences among neutralization assays, the absence of validated human correlates of protection, and limited longitudinal follow-up hinder comparisons across platforms [75,94]. Manufacturing consistency, cost, dosing requirements, and distribution infrastructure should be evaluated alongside safety and efficacy, particularly for the settings where hantavirus exposure is concentrated [29].

Future perspectives and novel therapeutic directions

Future research should prioritize the validation of hantavirus-specific findings rather than assume that general technological advances will yield clinically effective interventions. Computational screening provides one possible route to candidate identification: molecular docking and molecular dynamics have been used to investigate putative inhibitors of the Hantaan virus RdRp endonuclease domain [105]. However, predicted target binding is not equivalent to biochemical enzyme inhibition, suppression of infectious virus, or therapeutic efficacy. Artificial intelligence (AI) and machine learning (ML) approaches are increasingly discussed in antiviral lead prioritization, but their demonstrated performance in other viral systems does not validate hantavirus-specific drug discovery [106,107]. Candidate molecules should be tested sequentially in biochemical assays, infected-cell experiments, relevant animal models, and pharmacological and safety studies before clinical evaluation.

Nanotechnology offers two distinct applications that should not be conflated. Multivalent protein nanoparticles can display selected Gn/Gc antigens and have elicited cross-neutralizing antibodies against particular viral glycoprotein pseudotypes in mice [80]. In contrast, lipid nanoparticles serve as carriers for nucleic acid vaccines, and preclinical Hantaan virus mRNA formulations have induced neutralizing responses and protection in mouse challenge studies [86]. Neither result establishes the effectiveness of nanoparticle-delivered antiviral drugs, and both vaccine approaches still require assessments of human safety, durability, and protective breadth. Delivery principles developed for other antiviral medicines may guide formulation research but remain an extrapolation until tested specifically against hantavirus infection [60,103].

Broadly protective hantavirus vaccination is a compelling but unresolved goal. The identification of neutralizing antibody epitopes and structural features of the Gn/Gc complex provides a rationale for structure-guided antigen design [24,63]. High-resolution structural analysis of Andes virus glycoprotein tetramers has further clarified the molecular organization of potential antigenic targets [108]. Nevertheless, an epitope that is conserved or recognized by an antibody does not necessarily elicit similarly broad protection when presented as a vaccine antigen. The experimentally restricted cross-neutralization observed with a Gn nanoparticle immunogen and the computational status of proposed Andes virus B-cell epitopes illustrate the need to distinguish antigen design, antibody recognition, and heterologous challenge protection [80,81]. Future candidates should undergo head-to-head neutralization analyses, suitable heterologous challenge studies, and longitudinal assessment of immune responses before broad or universal protection is claimed.

A related priority is the development of clinically informative biomarkers. Studies of innate immunity, endothelial permeability, and inflammatory responses have identified pathways associated with hantavirus pathogenesis [14,15,46]. Genomic, transcriptomic, proteomic, and emerging metabolomic methods may help characterize disease heterogeneity and generate candidates for patient stratification [109]. However, the available evidence does not establish a validated biomarker-guided algorithm for selecting ribavirin, immunomodulatory treatment, or supportive care for individual patients. Prospective, adequately sized patient cohorts, repeated sampling across disease stages, and independent validation will be necessary before precision medicine approaches can be considered clinically applicable.

Translational research should also address treatment strategies directly. For antiviral candidates and neutralizing antibodies, clinically meaningful endpoints must be assessed relative to symptom onset and established viral replication, rather than inferred from administration

before experimental challenge [22,62,63]. Combination regimens should be evaluated for genuine pharmacological interactions and safety; additive effects observed in cell culture do not establish clinical synergy [52,66]. Successful programs will need reproducible experimental results, clinically relevant pharmacokinetics, and study designs that can accommodate differences between HFRS and HCPS.

Beyond individual countermeasures, hantavirus prevention benefits from a One Health approach that integrates rodent reservoirs, environmental change, and human exposure. Reviews of hantavirus ecology emphasize how environmental conditions and reservoir dynamics affect transmission risk [110]. Broader epidemiological evidence supports connecting virological surveillance with human case detection and exposure assessment [111]. Such integrated information may help target prevention and identify emerging risks, but the performance of predictive models and the benefit of proposed interventions still require independent evaluation [2,6].

Methodological lessons from research on other emerging zoonotic infections may also inform hantavirus research. For example, vaccine development for Nipah virus has highlighted challenges in translating preclinical findings into clinical applications, conducting efficacy trials during unpredictable outbreaks, and establishing interpretable immunological endpoints [112]. Although these experiences offer useful methodological insights, their findings cannot be extrapolated to establish antiviral or vaccine efficacy against hantaviruses. Hantavirus-specific experimental and clinical validation remains essential.

Conclusion

Antiviral research has identified several intervention points, but the levels of evidence supporting available candidates remain markedly different. Ribavirin has demonstrated clinical benefit in selected HFRS settings, particularly with early treatment, yet its effectiveness has not been established for HCPS and cannot be generalized across viruses or disease stages. Favipiravir has inhibited hantavirus replication and improved outcomes in selected preclinical models, but adequate clinical confirmation remains lacking. RNA interference has suppressed viral replication in cultured cells and experimental animals; targeted delivery, sequence specificity, and safety remain major barriers to translation. Neutralizing monoclonal antibodies have demonstrated pre-exposure, post-exposure, and treatment-related protection in selected animal models, but human therapeutic efficacy and broad cross-protection remain unconfirmed.

Vaccine development has likewise progressed at unequal levels of clinical maturity. Inactivated vaccines are licensed and used in selected endemic countries, with variable human observational effectiveness data. DNA vaccine candidates have undergone phase I and IIa human studies primarily assessing safety and immunogenicity, while recombinant protein, viral vector-based, and mRNA platforms remain predominantly preclinical. Vaccine-induced antibodies, protection in an animal challenge model, persistence of measurable immunity, and prevention of clinical disease are distinct outcomes. Antigenic diversity and the lack of validated human correlates of protection continue to impede the development of broadly protective vaccination strategies. Overall, supportive care remains central to hantavirus management, and investigational antivirals and vaccines require stronger, syndrome-specific evidence. Priorities include standardized preclinical models, optimized treatment timing and delivery, well-designed human studies, direct assessment of heterologous vaccine protection, and coordinated surveillance. Emerging computational and biomarker-based technologies require direct hantavirus-specific validation.

Acknowledgments

The authors thank Jalan Tengah, Indonesia (https://jalantengah.site) for providing manuscript editing and native English proofreading services.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Virtual Research Center for Bioinformatics and Biotechnology (VRCBB), Indonesia (https://jalantengah.site/vrcbb/) (Grant No. RG/26/05/04).

Underlying Data

Not applicable.

Declaration of artificial intelligence use

Generative artificial intelligence (ChatGPT, OpenAI, Grammarly) was used to assist with language editing, manuscript organization, and drafting support. The authors remain responsible for verifying the scientific accuracy, source citations, and final content of the manuscript.

How to cite

Khairullah AR, Afnani MR, Pratama BP, *et al*. Progress in antiviral and vaccine strategies against hantavirus: Current advances and future perspectives. Narra Rev 2026; 2 (3): e43 - http://doi.org/10.52225/narrarev.v2i3.43.

References

1. Meier K, Thorkelsson SR, Quemin ERJ, Rosenthal M. Hantavirus replication cycle—an updated structural virology perspective. Viruses 2021;13(8):1561.
2. Jonsson CB, Figueiredo LTM, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev 2010;23(2):412-441.
3. Tian H, Stenseth NC. The ecological dynamics of hantavirus diseases: From environmental variability to disease prevention largely based on data from China. PLoS Negl Trop Dis 2019; 13(2):e0006901.
4. Jiang H, Du H, Wang LM, Wang PZ, Bai XF. Hemorrhagic fever with renal syndrome: Pathogenesis and clinical picture. Front Cell Infect Microbiol 2016;6:1.
5. MacNeil A, Nichol ST, Spiropoulou CF. Hantavirus pulmonary syndrome. Virus Res 2011;162(1-2):138-147.
6. Moirano G, Botta A, Yang M, *et al*. Land-cover, land-use and human hantavirus infection risk: A systematic review. Pathog Glob Health 2024;118(5):361-375.
7. Peters CJ, Simpson GL, Levy H. Spectrum of hantavirus infection: Hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. Annu Rev Med 1999;50(1):531-545.
8. Hjelle B, Torres-Pérez F. Hantaviruses in the Americas and their role as emerging pathogens. Viruses 2010;2(12):2559-2586.
9. World Health Organization. Hantavirus. Geneva: WHO; 2026.Available from: https://www.who.int/news-room/fact-sheets/detail/hantavirus. Accessed: 30 October 2026.
10. de St Maurice A, Ervin E, Schumacher M, *et al*. Exposure characteristics of hantavirus pulmonary syndrome patients, United States, 1993–2015. Emerg Infect Dis 2017;23(5):733-739.
11. Toledo J, Haby MM, Reveiz L, *et al*. Evidence for human-to-human transmission of hantavirus: A systematic review. J Infect Dis 2022;226(8):1362-1371.
12. Krüger DH, Schönrich G, Klempa B. Human pathogenic hantaviruses and prevention of infection. Hum Vaccin 2011;7(6):685-693.
13. Noack D, Goeijenbier M, Reusken CBEM, *et al*. Orthohantavirus pathogenesis and cell tropism. Front Cell Infect Microbiol 2020;10:399.
14. Gavrilovskaya IN, Gorbunova EE, Mackow NA, Mackow ER. Hantaviruses direct endothelial cell permeability by sensitizing cells to vascular permeability factor VEGF, while angiopoietin 1 and sphingosine 1-phosphate inhibit hantavirus-directed permeability. J Virol 2008;82(12):5797-5806.
15. Saavedra F, Díaz FE, Retamal-Díaz A, *et al*. Immune response during hantavirus diseases: Implications for immunotherapies and vaccine design. Immunology 2021;163(3):262-277.
16. Manigold T, Vial P. Human hantavirus infections: Epidemiology, clinical features, pathogenesis and immunology. Swiss Med Wkly 2014;144(1):w13937.

17. National Disease Control and Prevention Administration (China). National overview of notifiable infectious diseases in 2025. Beijing: NCDPA; 2026. Available from: https://www.ndcpa.gov.cn/jbkzzx/c100016/second/content/content_2099411934094200832.html. Accessed: 30 October 2026.
18. European Centre for Disease Prevention and Control. Hantavirus infection. In: Annual epidemiological report for 2023. Stockholm: ECDC; 2025. Available from: https://www.ecdc.europa.eu/en/publications-data/hantavirus-infection-annual-epidemiological-report-2023. Accessed: 30 October 2026.
19. Pan American Health Organization. Epidemiological alert: Hantavirus pulmonary syndrome in the Americas Region. Washington (DC): PAHO; 2025.
20. Huggins JW, Hsiang CM, Cosgriff TM, *et al*. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis 1991;164(6):1119-1127.
21. Mertz GJ, Miedzinski L, Goade D, *et al*. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. Clin Infect Dis 2004;39(9):1307-1313.
22. Safronetz D, Falzarano D, Scott DP, *et al*. Antiviral efficacy of favipiravir against two prominent etiological agents of hantavirus pulmonary syndrome. Antimicrob Agents Chemother 2013;57(10):4673-4680.
23. Chiang CF, Albariño CG, Lo MK, Spiropoulou CF. Small interfering RNA inhibition of Andes virus replication. PLoS One. 2014;9(6):e99764.
24. Mittler E, Wec AZ, Tynell J, *et al*. Human antibody recognizing a quaternary epitope in the Puumala virus glycoprotein provides broad protection against orthohantaviruses. Sci Transl Med 2022;14(636):eabl5399.
25. Dheerasekara K, Sumathipala S, Muthugala R. Hantavirus infections-treatment and prevention. Curr Treat Options Infect Dis 2020;12(4):410-421.
26. Zheng Z, Li Z, Huang X, *et al*. Hemorrhagic fever with renal syndrome and diversity and distribution of hantaviruses—China, 2014–2023. China CDC Wkly 2025;7(25):858-862.
27. Korea Pharmaceutical Information Center. Hantavax injection (inactivated Hantaan virus vaccine). Republic of Korea: KPIC. Product information sourced from the Ministry of Food and Drug Safety. Available from: https://www.health.kr/drug/A11AKP08G3541. Accessed: 30 October 2026.
28. Hooper JW, Paolino KM, Mills K, *et al*. A phase 2a randomized, double-blind, dose-optimizing study to evaluate the immunogenicity and safety of a bivalent DNA vaccine for hemorrhagic fever with renal syndrome delivered by intramuscular electroporation. Vaccines 2020;8(3):377.
29. Chai S, Wang L, Du H, Jiang H. Achievement and challenges in orthohantavirus vaccines. Vaccines 2025;13(2):198.
30. Guardado-Calvo P, Rey FA. The surface glycoproteins of hantaviruses. Curr Opin Virol 2021; 50:87-94.
31. Rissanen I, Krumm SA, Stass R, *et al*. Structural basis for a neutralizing antibody response elicited by a recombinant Hantaan virus Gn immunogen. mBio 2021;12(4):e02531-20.
32. Muyangwa M, Martynova EV, Khaiboullina SF, *et al*. Hantaviral proteins: Structure, functions, and role in hantavirus infection. Front Microbiol 2015;6(1):1326.
33. Royster A, Ren S, Ali S, *et al*. Modulations in the host cell proteome by the hantavirus nucleocapsid protein. PLoS Pathog 2024;20(1):e1011925.
34. Acuña R, Cifuentes-Muñoz N, Márquez CL, *et al*. Hantavirus Gn and Gc glycoproteins self-assemble into virus-like particles. J Virol 2014;88(4):2344-2348.
35. Cheng E, Mir MA. Signatures of host mRNA 5′ terminus for efficient hantavirus cap snatching. J Virol 2012;86(18):10173-10185.
36. Durieux Trouilleton Q, Barata-García S, Arragain B, *et al*. Structures of active Hantaan virus polymerase uncover the mechanisms of Hantaviridae genome replication. Nat Commun 2023;14:2954.
37. LaPointe A, Gale M Jr, Kell AM. Orthohantavirus replication in the context of innate immunity. Viruses 2023;15(5):1130.
38. Cheng E, Wang Z, Mir MA. Interaction between hantavirus nucleocapsid protein (N) and RNA-dependent RNA polymerase (RdRp) mutants reveals the requirement of an N-RdRp interaction for viral RNA synthesis. J Virol 2014;88(15):8706-8712.
39. Gavrilovskaya IN, Brown EJ, Ginsberg MH, Mackow ER. Cellular entry of hantaviruses which cause hemorrhagic fever with renal syndrome is mediated by beta3 integrins. J Virol 1999;73(5):3951-3959.
40. Jangra RK, Herbert AS, Li R, *et al*. Protocadherin-1 is essential for cell entry by New World hantaviruses. Nature 2018;563(7732):559-563.

41. Jin M, Park J, Lee S, *et al*. Hantaan virus enters cells by clathrin-dependent receptor-mediated endocytosis. Virology 2002;294(1):60-69.
42. Cifuentes-Muñoz N, Salazar-Quiroz N, Tischler ND. Hantavirus Gn and Gc envelope glycoproteins: Key structural units for virus cell entry and virus assembly. Viruses 2014;6(4):1801-1822.
43. Shrivastava-Ranjan P, Rollin PE, Spiropoulou CF. Andes virus disrupts the endothelial cell barrier by induction of vascular endothelial growth factor and downregulation of VE-cadherin. J Virol 2010;84(21):11227-11234.
44. Hepojoki J, Vaheri A, Strandin T. The fundamental role of endothelial cells in hantavirus pathogenesis. Front Microbiol 2014;5(1):727.
45. Gavrilovskaya IN, Gorbunova EE, Mackow ER. Pathogenic hantaviruses direct the adherence of quiescent platelets to infected endothelial cells. J Virol 2010;84(9):4832-4839.
46. Kell AM, Hemann EA, Turnbull JB, Gale M Jr. RIG-I-like receptor activation drives type I IFN and antiviral signaling to limit Hantaan orthohantavirus replication. PLoS Pathog 2020;16(4):e1008483.
47. Zhao Y, Che L, Pan M, *et al*. Hantaan virus inhibits type I interferon response by targeting RLR signaling pathways through TRIM25. Virology 2024;589(1):109942.
48. Klingström J, Smed-Sörensen A, Maleki KT, *et al*. Innate and adaptive immune responses against human Puumala virus infection: Immunopathogenesis and suggestions for novel treatment strategies for severe hantavirus-associated syndromes. J Intern Med 2019;285(5):510-523.
49. Hayasaka D, Maeda K, Ennis FA, Terajima M. Increased permeability of human endothelial cell line EA.hy926 induced by hantavirus-specific cytotoxic T lymphocytes. Virus Res 2007;123(2):120-127.
50. Terajima M, Ennis FA. T cells and pathogenesis of hantavirus cardiopulmonary syndrome and hemorrhagic fever with renal syndrome. Viruses 2011;3(7):1059-1073.
51. Mayor J, Torriani G, Engler O, Rothenberger S. Identification of novel antiviral compounds targeting entry of hantaviruses. Viruses 2021;13(4):685.
52. Mayor J, Engler O, Rothenberger S. Antiviral efficacy of ribavirin and favipiravir against Hantaan virus. Microorganisms 2021;9(6):1306.
53. Severson WE, Schmaljohn CS, Javadian A, Jonsson CB. Ribavirin causes error catastrophe during Hantaan virus replication. J Virol 2003;77(1):481-488.
54. Malinin OV, Platonov AE. Insufficient efficacy and safety of intravenous ribavirin in treatment of haemorrhagic fever with renal syndrome caused by Puumala virus. Infect Dis 2017;49(7):514-520.
55. Moreli ML, Marques-Silva AC, Pimentel VA, da Costa VG. Effectiveness of the ribavirin in treatment of hantavirus infections in the Americas and Eurasia: A meta-analysis. Virusdisease 2014;25(3):385-389.
56. Rusnak JM, Byrne WR, Chung KN, *et al*. Experience with intravenous ribavirin in the treatment of hemorrhagic fever with renal syndrome in Korea. Antiviral Res 2009;81(1):68-76.
57. Safronetz D, Haddock E, Feldmann F, *et al*. In vitro and in vivo activity of ribavirin against Andes virus infection. PLoS One 2011;6(8):e23560.
58. Liu YY, Chen LJ, Zhong Y, *et al*. Specific interference shRNA-expressing plasmids inhibit Hantaan virus infection in vitro and in vivo. Acta Pharmacol Sin 2016;37(4):497-504.
59. Yang J, Sun JF, Wang TT, *et al*. Targeted inhibition of hantavirus replication and intracranial pathogenesis by a chimeric protein-delivered siRNA. Antiviral Res 2017;147:107-115.
60. Reschke M, Piotrowski-Daspit AS, Pober JS, Saltzman WM. Nucleic acid delivery to the vascular endothelium. Mol Pharm 2022;19(12):4466-4486.
61. Shin OS, Kumar M, Yanagihara R, Song JW. Hantaviruses induce cell type- and viral species-specific host microRNA expression signatures. Virology 2013;446(1-2):217-224.
62. Williamson BN, Prescott J, Garrido JL, *et al*. Therapeutic efficacy of human monoclonal antibodies against Andes virus infection in Syrian hamsters. Emerg Infect Dis 2021;27(10):2707-2710.
63. Mittler E, Serris A, Esterman ES, *et al*. Structural and mechanistic basis of neutralization by a pan-hantavirus protective antibody. Sci Transl Med 2023;15(700):eadg1855.
64. Vial PA, Valdivieso F, Calvo M, *et al*. A non-randomized multicentre trial of human immune plasma for treatment of hantavirus cardiopulmonary syndrome caused by Andes virus. Antivir Ther 2015;20(4):377-386.

65. Bird BH, Shrivastava-Ranjan P, Dodd KA, *et al*. Effect of vandetanib on Andes virus survival in the hamster model of hantavirus pulmonary syndrome. Antiviral Res 2016;132:66-69.
66. Murphy ME, Kariwa H, Mizutani T, *et al*. Characterization of in vitro and in vivo antiviral activity of lactoferrin and ribavirin upon hantavirus. J Vet Med Sci 2001;63(6):637-645.
67. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci 2017;93(7):449-463.
68. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther 2020;209(1):107512.
69. Mittler E, Dieterle ME, Kleinfelter LM, *et al*. Hantavirus entry: Perspectives and recent advances. Adv Virus Res 2019;104(1):185-224.
70. Engdahl TB, Crowe JE Jr. Humoral immunity to hantavirus infection. mSphere 2020;5(4):e00482-20.
71. Koch J, Liang M, Queitsch I, *et al*. Human recombinant neutralizing antibodies against hantaan virus G2 protein. Virology 2003;308(1):64-73.
72. Engdahl TB, Binshtein E, Brocato RL, *et al*. Antigenic mapping and functional characterization of human New World hantavirus neutralizing antibodies. Elife 2023;12(1):e81743.
73. Mackow ER, Gorbunova EE, Dalrymple NA, Gavrilovskaya IN. Role of vascular and lymphatic endothelial cells in hantavirus pulmonary syndrome suggests targeted therapeutic approaches. Lymphat Res Biol 2013;11(3):128-135.
74. Hall PR, Leitão A, Ye C, *et al*. Small molecule inhibitors of hantavirus infection. Bioorg Med Chem Lett 2010;20(23):7085-7091.
75. Song JY, Woo HJ, Cheong HJ, *et al*. Long-term immunogenicity and safety of inactivated Hantaan virus vaccine (Hantavax) in healthy adults. Vaccine 2016;34(10):1289-1295.
76. Song JY, Jeong HW, Yun JW, *et al*. Immunogenicity and safety of a modified three-dose priming and booster schedule for the Hantaan virus vaccine (Hantavax): A multi-center phase III clinical trial in healthy adults. Vaccine 2020;38(50):8016-8023.
77. Park K, Kim CS, Moon KT. Protective effectiveness of hantavirus vaccine. Emerg Infect Dis 2004;10(12):2218-2220.
78. Jung J, Ko SJ, Oh HS, *et al*. Protective effectiveness of inactivated hantavirus vaccine against hemorrhagic fever with renal syndrome. J Infect Dis 2018;217(9):1417-1420.
79. Yi Y, Park H, Jung J. Effectiveness of inactivated hantavirus vaccine on the disease severity of hemorrhagic fever with renal syndrome. Kidney Res Clin Pract 2018;37(4):366-372.
80. Ramos KE, Mariano MC, Mittler E, *et al*. Hantavirus GnH nanoparticle immunogen elicits a cross-neutralizing antibody response in mice. ACS Infect Dis 2025;11(11):3061-3070.
81. Nariswari HK, Afnani MR, Syahputra MFA, *et al*. In silico prediction and structural mapping of linear B-cell epitopes in Andes virus glycoprotein as potential vaccine candidates. J Trop One Health 2026;1.
82. Paulsen GC, Frenck R Jr, Tomashek KM, *et al*. Safety and immunogenicity of an Andes virus DNA vaccine by needle-free injection: A randomized, controlled phase 1 study. J Infect Dis 2024;229(1):30-38.
83. Safronetz D, Hegde NR, Ebihara H, *et al*. Adenovirus vectors expressing hantavirus proteins protect hamsters against lethal challenge with Andes virus. J Virol 2009;83(14):7285-7295.
84. Brown KS, Safronetz D, Marzi A, *et al*. Vesicular stomatitis virus-based vaccine protects hamsters against lethal challenge with Andes virus. J Virol 2011;85(23):12781-12791.
85. Zhang H, Liu H, Wei J, *et al*. Single dose recombinant VSV based vaccine elicits robust and durable neutralizing antibody against Hantaan virus. npj Vaccines 2024;9:28.
86. Ye W, Dang Y, Wang Y, *et al*. Prefusion-stabilized Hantaan virus glycoprotein nucleic acid vaccine elicits potent neutralizing antibody responses via germinal center activation. Nat Commun 2026;17:3972.
87. Meyer M, Kuzmin IV, Dews EA, *et al*. Single-dose mRNA vaccines against Andes hantavirus. Lancet 2026;407(10547):2495-2497.
88. Choi Y, Ahn CJ, Seong KM, *et al*. Inactivated Hantaan virus vaccine derived from suspension culture of Vero cells. Vaccine 2003;21(17-18):1867-1873.
89. Cho HW, Howard CR. Antibody responses in humans to an inactivated hantavirus vaccine (Hantavax). Vaccine 1999;17(20-21):2569-2575.

90. Ismail S, Abbasi SW, Yousaf M, *et al*. Design of a multi-epitopes vaccine against hantaviruses: An immunoinformatics and molecular modelling approach. Vaccines 2022;10(3):378.
91. Aram M, Graham V, Kennedy E, *et al*. A multi-valent hantavirus vaccine based on recombinant modified vaccinia Ankara reduces viral load in a mouse infection model. Vaccines 2025;13(3):270.
92. Fausther-Bovendo H, Kobinger GP. Pre-existing immunity against Ad vectors: Humoral, cellular, and innate response, what's important? Hum Vaccin Immunother 2014;10(10):2875-2884.
93. Quan Y, Yang H, Li W, Li L. mRNA vaccines: immunogenicity and quality characteristics. J Nanobiotechnol 2025;24:6.
94. Cioni G, Calò GL, Imperiali G, *et al*. Vaccines against hantavirus infections: A systematic literature review. Vaccines 2026;14(10):898.
95. Rissanen I, Stass R, Krumm SA, *et al*. Molecular rationale for antibody-mediated targeting of the hantavirus fusion glycoprotein. Elife 2020;9(1):e58242.
96. Parvate A, Williams EP, Taylor MK, *et al*. Diverse morphology and structural features of Old and New World hantaviruses. Viruses 2019;11(9):862.
97. Plyusnin A, Morzunov SP. Virus evolution and genetic diversity of hantaviruses and their rodent hosts. Curr Top Microbiol Immunol 2001;256(1):47-75.
98. Ramsden C, Melo FL, Figueiredo LM, *et al*. High rates of molecular evolution in hantaviruses. Mol Biol Evol 2008;25(7):1488-1492.
99. Safronetz D, Ebihara H, Feldmann H, Hooper JW. The Syrian hamster model of hantavirus pulmonary syndrome. Antiviral Res 2012;95(3):282-292.
100. Liu R, Ma H, Shu J, *et al*. Vaccines and therapeutics against hantaviruses. Front Microbiol 2020;10:2989.
101. Mir S. Hantavirus induced kidney disease. Front Med 2022;8(1):795340.
102. D'Souza MH, Patel TR. Biodefense implications of New-World hantaviruses. Front Bioeng Biotechnol 2020;8:925.
103. Delshadi R, Bahrami A, McClements DJ, *et al*. Development of nanoparticle-delivery systems for antiviral agents: A review. J Control Release 2021; 331:30-44.
104. Nolte KB, Foucar K, Richmond JY. Hantaviral biosafety issues in the autopsy room and laboratory: Concerns and recommendations. Hum Pathol 1996;27(12):1253-1254.
105. Faisal S, Badshah SL, Sharaf M, Abdalla M. Insight into the Hantaan virus RNA-dependent RNA polymerase inhibition using in-silico approaches. Mol Divers 2023;27(6):2505-2522.
106. Kolarič A, Jukič M, Bren U. Machine learning in antiviral drug design. Bioorg Med Chem 2026;132:118426.
107. Du S, Hu X, Li P, *et al*. Antiviral drug discovery and development: Challenges and future directions. Signal Transduct Target Ther 2026;11:69.
108. Guo L, McFadden E, Slough MM, *et al*. High-resolution in situ structures of hantavirus glycoprotein tetramers. Cell 2026;189(9):2731-2747.e15.
109. Najafi S, Jojani M, Najafi K, Roviello GN. Omics approaches in hantavirus research: Current advances, challenges, and future perspectives. BioTech 2026;15(3):58.
110. Guterres A, de Lemos ERS. Hantaviruses and a neglected environmental determinant. One Health 2018;5:27-33.
111. Jiang H, Zheng X, Wang L, *et al*. Hantavirus infection: A global zoonotic challenge. Virol Sin 2017;32(1):32-43.
112. Chatterjee S, Mahata J, Firdous A, *et al*. Nipah virus vaccine development: Current platforms, preclinical evidence, and clinical translation. Front Drug Discov 2026;6.