World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Family Medicine Preparedness for Hantavirus Infection: A Comprehensive Review of Early Recognition, Prevention, Outpatient Triage, and Referral Pathways

Hamad Abdulaziz AlSubaie *, Sarah Abdulaziz AlSubaie, Jamal Khaled Aljamal, Meath Saud Alhamed and Mansoor Mishal AlNaim

Department of Family Medicine, King Abdulaziz Hospital for national Guard in AlAhsa, Saudi Arabia.

World Journal of Biology Pharmacy and Health Sciences, 2026, 26(03), 198-211

Publication history: Received on 05 May 2026; revised on 10 June 2026; accepted on 13 June 2026

Article DOI: https://doi.org/10.30574/wjbphs.2026.26.3.0351

Abstract

Background. Hantaviruses are rodent-borne zoonotic pathogens responsible for two major severe human syndromes: hantavirus pulmonary syndrome (HPS, also termed hantavirus cardiopulmonary syndrome, HCPS) in the Americas, and haemorrhagic fever with renal syndrome (HFRS) across Europe and Asia. Case-fatality reaches as high as 50% in severe New World HPS and up to 15% in severe Old World HFRS (1,2). The May 2026 multi-country Andes virus cluster aboard the MV Hondius cruise ship reawakened clinical interest in this group of viruses and underscored the pivotal frontline role of family physicians in early recognition and triage (3,4).

Objective. To synthesize the contemporary evidence on hantavirus epidemiology, clinical recognition, outpatient triage, prevention, and referral pathways with a practical orientation toward family medicine practice.

Methods. A narrative review of peer-reviewed literature retrieved from PubMed/MEDLINE and Scopus, supplemented by official CDC and WHO documents and current national clinical guidelines, published up to May 2026, was undertaken. Studies addressing virology, epidemiology, primary-care recognition, diagnostics, treatment escalation, and prevention were prioritized.

Results. The hantavirus prodrome is clinically indistinguishable from influenza-like illness, yet the classical tetrad on a basic peripheral blood smear — thrombocytopenia, left-shifted leukocytosis, circulating immunoblasts, and hemoconcentration — remains a powerful early discriminator that can be obtained in most outpatient settings (5,6). Clinical deterioration during the cardiopulmonary phase typically unfolds within 24 to 48 hours and demands immediate intensive-care referral; early venoarterial extracorporeal membrane oxygenation (VA-ECMO) at experienced centers has been associated with survival approaching 80% in otherwise refractory cases (5,7). No licensed antiviral or vaccine is yet available, leaving meticulous supportive care, conservative fluid strategy, and infection prevention as the cornerstones of management (1,2).

Conclusion. Family physicians must maintain a high index of suspicion for hantavirus disease in patients presenting with a febrile prodrome together with a rodent or relevant travel exposure history, perform rapid bedside risk stratification, expedite ICU referral when red-flag features appear, and reinforce community-level rodent control and safe cleaning practices. Their early decisions can shape outcomes more decisively than any downstream intervention.

Keywords: Hantavirus; Hantavirus pulmonary syndrome; Haemorrhagic fever with renal syndrome; Andes virus; Family medicine; primary care; Outpatient triage; Zoonosis

* Corresponding author: Hamad Abdulaziz AlSubaie

1. Introduction

Hantaviruses sit uneasily on the boundary between the familiar and the exotic. They belong to the family Hantaviridae within the order Bunyavirales, and the medically relevant genus Orthohantavirus now encompasses at least thirty-eight recognized species, of which seven to eight are recurrently associated with severe human disease (1,8,9). For a family physician seeing patients in a busy urban clinic or a small rural office, this taxonomy is less important than a simpler observation: any patient with a brief febrile illness who has recently cleaned a rodent-infested shed, hiked in an endemic area, or returned from South America merits a moment of pause. That moment of pause, repeated millions of times across primary care worldwide, is what determines whether hantavirus disease is recognized early or missed until the patient arrives in extremis.

Estimates place the global burden somewhere between ten thousand and well over one hundred thousand human infections per year, with case-fatality varying enormously by geography and viral species: under one per cent for the milder Puumala virus in Scandinavia, five to fifteen per cent for Hantaan and Dobrava infections in Asia and the Balkans, and up to fifty per cent for severe HPS in the southern cone of the Americas (2,10). These figures are almost certainly an undercount; mild and subclinical cases are rarely tested, and surveillance in many endemic regions remains uneven.

The modern era of hantavirus medicine began in 1976, when Hantaan virus was isolated from Apodemus agrarius near the Hantan River in Korea, retroactively explaining the so-called Korean haemorrhagic fever that had afflicted United Nations troops during the Korean War (8,11). Almost two decades later, in May 1993, an unexplained cluster of fatal adult respiratory distress in the Four Corners region of the United States led to the rapid identification of Sin Nombre virus and the description of an entirely new clinical syndrome — hantavirus pulmonary syndrome (11). The story since has been one of expanding diversity. New orthohantaviruses are described almost yearly, and Seoul virus, carried by the urban brown rat Rattus norvegicus, is now recognized to have a near-cosmopolitan distribution that includes Europe, the Americas, and parts of Africa (1,8).

Two principal clinical syndromes anchor the human disease spectrum. HPS or HCPS predominates in the New World and is characterized by a brief febrile prodrome followed by abrupt non-cardiogenic pulmonary edema and shock. HFRS predominates in Europe and Asia and presents instead with renal failure, capillary leak, and a variable haemorrhagic diathesis. There is meaningful clinical overlap — Seoul virus, for example, can cause a milder HFRS-like illness in any global region — and treating the two syndromes as wholly separate entities risks missing atypical cases (1,8,18).

Why does any of this matter to a family physician? Because more than ninety per cent of HPS patients first present to a primary-care clinic, urgent-care center, or emergency department staffed by generalists (5,12). The window between prodrome and crash is narrow. A diagnosis delayed by even twelve hours can mean the difference between a controlled inter-hospital transfer for ECMO and a chaotic resuscitation in a community emergency room. We would argue that hantavirus belongs alongside meningococcal sepsis, acute aortic dissection, and tubo-ovarian torsion on the short list of conditions for which the first physician encountered carries disproportionate prognostic weight.

The cluster of cases reported in May 2026 aboard the MV Hondius — a Norwegian-flagged Antarctic expedition cruise — has sharpened that point in a way no academic article could. Eleven passengers and crew developed laboratory-confirmed Andes virus infection over a twenty-day period; three died, yielding a case-fatality of 27% (3,4,13). Crucially, phylogenetic and contact-network analyses suggested ship-acquired person-to-person transmission beyond the initial environmental exposure during a shore excursion in southern Chile, reinforcing earlier Argentine observations that Andes virus is, to date, the only orthohantavirus convincingly shown to transmit between humans (4,13,17). The outbreak prompted health advisories from the United States CDC, the World Health Organization, and several European national agencies, with explicit guidance for primary-care clinicians on travel-history triggers and case reporting (3,4,13,34).

This review aims to assemble, in a form usable at the point of care, the current evidence on hantavirus virology, ecology, clinical recognition, and outpatient management. We focus deliberately on the family-medicine vantage point: the brief consultation, the limited bedside investigations, the decision of whether to send a patient home, observe in the surgery, or escalate to a tertiary facility. The objective is not to turn family physicians into infectious-disease specialists, but to equip them to act decisively during the few hours when their decisions matter most.

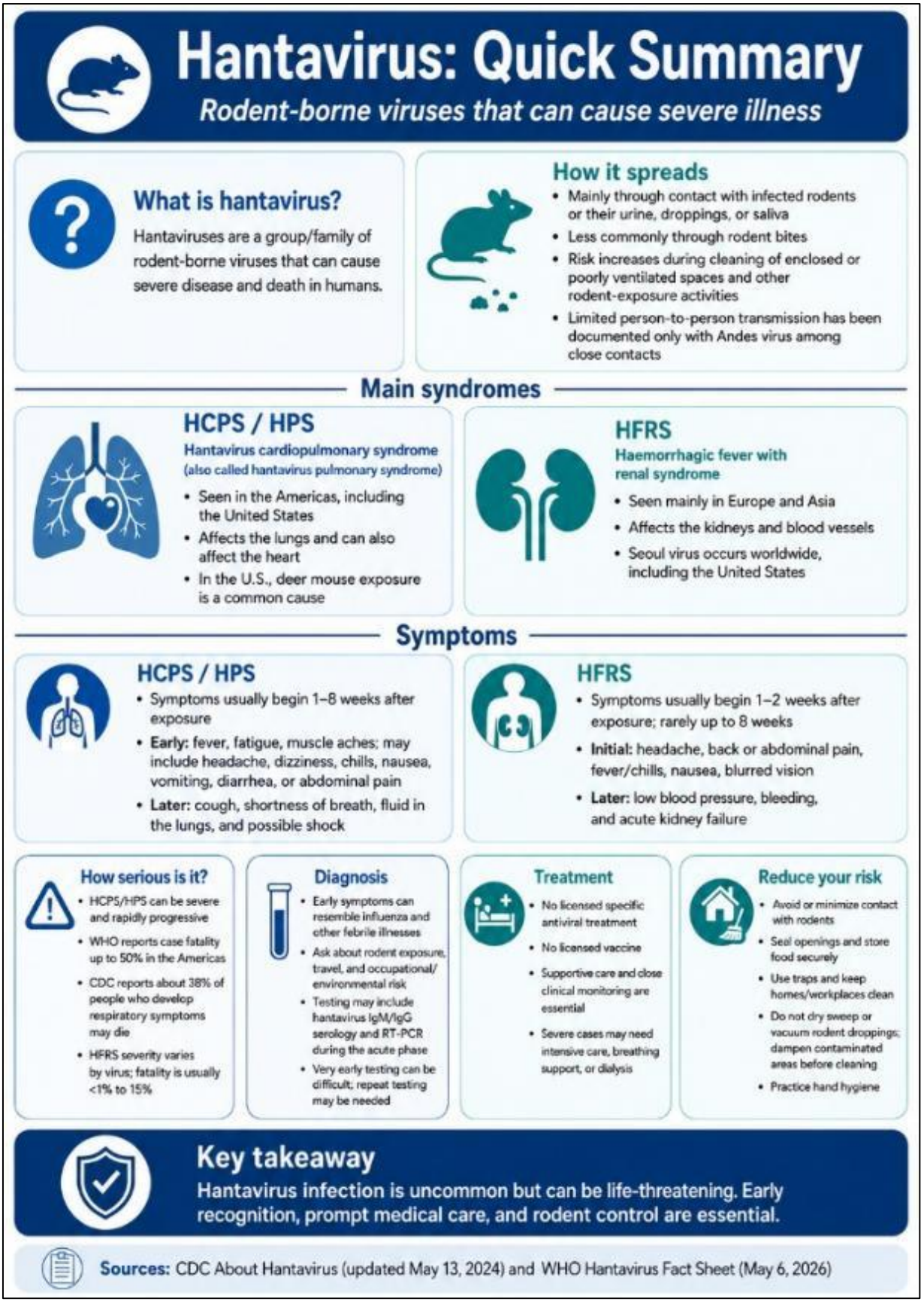

Figure 1 Hantavirus Quick Summary: rodent-borne viruses, transmission, syndromes, symptoms, severity, diagnosis, treatment, and risk reduction. Adapted from CDC About Hantavirus (May 13, 2024) and WHO Hantavirus Fact Sheet (May 6, 2026)

2. Methods

This article is a narrative review. The intent was synthesis rather than meta-analysis, given the heterogeneity of available data and the predominance of case series, ecological studies, and consensus guidelines in the hantavirus literature. Three databases were searched: PubMed/MEDLINE, Scopus, and Google Scholar. Search terms combined the keywords hantavirus, orthohantavirus, hantavirus pulmonary syndrome, HPS, HCPS, haemorrhagic fever with renal syndrome, HFRS, Sin Nombre, Andes virus, Hantaan, Puumala, Seoul, Dobrava, with the practice-oriented terms primary care, family medicine, general practice, outpatient, triage, referral, prevention, and diagnosis. Boolean operators and MeSH terms were used where appropriate.

Inclusion criteria comprised English-language peer-reviewed articles published between January 1993 and May 2026, official communications from the United States Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC), the National Health Service of England (NHS England), and relevant national clinical practice guidelines. Case series with at least ten patients and any randomized or controlled comparative study were prioritized, but seminal smaller case reports — particularly those describing the original Four Corners outbreak and the Argentine evidence of person-to-person Andes virus transmission — were retained for their historical and clinical importance (11,17). Recent communications about the 2026 MV Hondius outbreak were incorporated using primary CDC and WHO sources (3,4,13).

Articles dealing exclusively with non-human reservoir biology, with viral structural biology at a level not relevant to clinical practice, or with experimental therapeutic candidates not yet entered into human trials were excluded. The limitations of this approach are not trivial. Narrative reviews are inevitably shaped by the author's selection of sources, and important regional literature published in Spanish, Portuguese, Chinese, Korean, or Russian may be under-represented. Where possible, English-language summary articles by authors working in those regions were used as a partial corrective (10,12,15,20,30).

3. Literature Review

3.1. Virology and reservoir ecology

Orthohantaviruses are enveloped, trisegmented, negative-sense single-stranded RNA viruses with a genome comprising small (S), medium (M), and large (L) segments encoding the nucleocapsid protein, the Gn/Gc glycoprotein precursor, and the RNA-dependent RNA polymerase respectively (9,14). The viral particle measures roughly 80 to 120 nanometers and remains modestly stable in dust or dried excreta — a stability that explains the well-recognized aerosol transmission route from contaminated rodent waste (1,8).

Each pathogenic orthohantavirus is tightly co-evolved with one principal rodent reservoir. Sin Nombre virus circulates in the deer mouse Peromyscus maniculatus across western North America (11,14). The white-footed mouse Peromyscus leucopus carries New York virus in the north-eastern United States. Andes virus and its closely related variants are maintained by the long-tailed pygmy rice rat Oligoryzomys longicaudatus across Argentine and Chilean Patagonia (4,13,17). Hantaan virus persists in the striped field mouse Apodemus agrarius in northeast Asia, while the bank vole Myodes glareolus serves as the reservoir for Puumala virus across Fennoscandia and central Europe (8,16,19). Seoul virus is the conspicuous exception: it travels wherever Rattus norvegicus travels, which is to say everywhere humans live in dense settlements (1,8).

Within their reservoir host the viruses cause persistent and largely asymptomatic infection, with shedding in urine, faeces, and saliva that can continue for months. Rodent population dynamics — driven by mast years, mild winters, and habitat disturbance — are therefore the dominant ecological determinants of human risk (10,16,33). Tian and Stenseth's analysis of decades of Chinese HFRS surveillance data is particularly instructive: rodent population irruptions following favourable climatic conditions repeatedly precede surges in human cases by six to eighteen months, offering a potential early-warning signal of considerable value to public health authorities (33).

3.2. Global and regional epidemiology

China continues to bear the largest reported HFRS burden, with annual case counts that, although declining from a peak in the 1990s, still typically exceed ten thousand notifications per year (10,33). Vaccination of high-risk occupational groups against Hantaan and Seoul viruses, deployed widely in China and the Korean peninsula, has contributed to that downward trend but is not yet recommended or available outside Asia (20). Across Europe, more than ten thousand

HFRS cases are reported annually, dominated by Puumala virus in Scandinavia, the Baltic states, Germany, and Belgium, and by Dobrava virus in the Balkans (10,16,19).

In the Americas the picture is sparser numerically but heavier in proportional severity. Argentina and Chile together report between two and three hundred HPS cases per year, with localized clusters in Patagonia and the central Andean foothills (15,17,22). The United States Hantavirus Surveillance Registry recorded 833 cumulative cases from the 1993 recognition of the syndrome through 2022, with case-fatality of approximately 38 to 45 per cent (11,15). New Mexico, Colorado, Arizona, California, and Washington account for the largest fraction of US cases, though sporadic infections have been confirmed in more than half of all states (11,21).

Ecologic drivers extend beyond simple rodent abundance. El Niño Southern Oscillation events have been repeatedly linked to HPS clusters in the south-western United States and in southern South America, mediated through changes in vegetation productivity and consequent rodent reproduction (10,16). Deforestation, peri-urban expansion into agricultural land, and the abandonment of rural buildings all create the broken-edge habitats in which reservoir rodents thrive and contact with humans becomes likely (16,29,33). These are not abstract considerations: in our experience, occupational and recreational exposure histories are most productively elicited when the physician understands the regional ecology of where the patient lives, works, and travels.

3.3. Transmission routes

The dominant transmission route for all pathogenic orthohantaviruses is inhalation of aerosolized rodent excreta. Activities that disturb contaminated dust — sweeping a barn floor, shaking out a sleeping bag stored in a shed, dismantling a wood pile, cleaning a derelict cabin at the start of summer — are repeatedly identified in case-control studies as proximate risk factors (1,2,27,28). Direct rodent bites are biologically possible but rarely documented in human cases. Contamination of broken skin or mucous membranes with infectious material is a recognized but uncommon route, primarily of relevance to occupational groups handling live rodents (29).

Person-to-person transmission has been, until recently, the singular preserve of Andes virus. Outbreaks in Argentine Patagonia in the 1990s and again in 2019 demonstrated household and nosocomial spread, with secondary attack rates among close contacts approaching ten per cent (17). The 2026 MV Hondius cluster appears to be the first well-characterized maritime outbreak; whole-genome sequencing of viral isolates from passengers in different cabins, combined with contact-network reconstruction, supports onward transmission after a probable index environmental exposure during a hiking excursion in the Aysén Region of Chilean Patagonia (3,4,13). No analogous transmission has been documented for Sin Nombre, Puumala, Hantaan, or Seoul viruses, despite extensive contact tracing across decades (1,8,17).

3.4. Clinical syndromes

3.4.1. Hantavirus Pulmonary Syndrome (HPS / HCPS)

The incubation period for HPS ranges from one to eight weeks, with most cases declaring themselves between fourteen and twenty-one days after exposure (5,12,18). The illness moves through five reasonably well-defined phases, although in practice the transitions can be brutally swift. The febrile prodrome lasts three to five days and is dominated by high fever, severe myalgia (often described by patients as 'worse than anything I have ever had'), headache, malaise, and gastrointestinal complaints — nausea, vomiting, diarrhea, and abdominal pain are present in roughly half of cases and frequently misdirect the early diagnosis toward viral gastroenteritis (5,6,12).

The cardiopulmonary phase begins, typically without fanfare, with a non-productive cough and progressive dyspnea. Over hours rather than days the patient develops bilateral interstitial and alveolar infiltrates, hypoxemia refractory to supplemental oxygen, hypotension, and reduced cardiac output (5,18). Echocardiography in this phase shows depressed ventricular function with a small, hyperdynamic left ventricle — a constellation that has misled more than one clinician into pursuing primary cardiac diagnoses (7,25,26). The diuretic phase, when it is reached, is marked by spontaneous polyuria and rapid clinical improvement; the convalescent phase may extend over weeks to months, with persistent exertional fatigue and reduced exercise tolerance. Overall mortality in the United States surveillance cohort approximates 38 to 45 per cent, somewhat lower in patients reaching ECMO-capable centers before cardiogenic shock supervenes (7,11,25,26).

3.4.2. Haemorrhagic Fever with Renal Syndrome (HFRS)

HFRS follows a related but distinct trajectory. Incubation is typically one to two weeks, occasionally extending to eight (1,19). Five clinical phases are recognised — febrile, hypotensive, oliguric, diuretic, and convalescent — and the severity of each phase tracks closely with the infecting viral species. Hantaan and Dobrava viruses produce the most severe disease, with case-fatality between five and fifteen per cent and a meaningful haemorrhagic component including conjunctival suffusion, palatal petechiae, epistaxis, and occasionally gastrointestinal or intracranial bleeding (1,19,20). Puumala virus produces a milder illness, often termed nephropathia epidemica, with case-fatality typically under one per cent and a course dominated by acute kidney injury without major bleeding (10,16,19).

The renal phase is the clinical centre of gravity. Patients develop oliguria, hypertension paradoxically followed by hypotension, marked proteinuria, and characteristic micro-haematuria. Renal replacement therapy is required in roughly five to ten per cent of severe HFRS cases and is associated with full recovery of renal function in the majority of survivors (1,19,20).

3.4.3. Atypical presentations and overlap syndromes

A working knowledge of typical phases should not obscure the considerable clinical variability of hantavirus disease. Mild Sin Nombre infections without overt cardiopulmonary involvement have been described in retrospective serosurveys, and equivalent mild Andes virus infections have been confirmed by serology in household contacts of severe cases (8,15,17). Seoul virus, in particular, tends to produce a clinically intermediate illness — fever, acute kidney injury, occasional ocular involvement (the so-called Seoul ocular syndrome with transient myopia), and modest haemorrhagic features — that is easy to confuse with leptospirosis or other rat-associated infections (1,8,30). Co-infection with leptospirosis, dengue, or — in southern Chile — Bartonella species has been reported and can complicate both the clinical picture and the laboratory interpretation (22,30).

3.5. Differential diagnosis in primary care

The differential diagnosis of the early hantavirus prodrome reads like a roll-call of community-acquired febrile illness. Seasonal influenza and, since 2020, COVID-19 are the most frequent decoys; community-acquired bacterial pneumonia, leptospirosis (particularly in patients with recreational freshwater exposure), dengue (in tropical and increasingly subtropical regions), Q fever, mycoplasma, legionellosis, rickettsial illness, and undifferentiated viral sepsis all enter the differential at some point (5,6,21,22). In Latin America, careful clinicians additionally consider yellow fever, Junín virus haemorrhagic fever, and the bartonelloses (22).

A handful of features tilt the probability appreciably toward hantavirus. A relevant exposure history — be it rural, occupational, or recreational — is the single most useful clue. Marked thrombocytopenia in the absence of an obvious haematological cause, a left-shifted leukocytosis with circulating immature granulocytes, and a rapidly rising haematocrit despite apparent dehydration are an early laboratory triad that should provoke immediate concern (5,6,23). Where the prodrome includes prominent gastrointestinal symptoms with disproportionate myalgia, the suspicion deepens.

3.6. Laboratory red flags accessible in outpatient settings

One of the more remarkable findings in the HPS literature, dating to the careful pathology work of Koster and colleagues, is that a competently reviewed peripheral blood smear can suggest the diagnosis hours before viral confirmation is possible (23). Four features form what Koster termed the diagnostic tetrad: thrombocytopenia (usually below 150×10^9/L), a myeloid left shift, more than 10% atypical or immunoblastoid lymphocytes, and an elevated haematocrit reflecting capillary leak and hemoconcentration (5,6,23). In a primary-care setting that has access to a same-day complete blood count and a pathologist or experienced laboratory technologist willing to examine a smear, the tetrad reportedly carries a sensitivity above 90% and a specificity exceeding 95% for HPS in patients with a compatible prodrome (23).

Beyond the tetrad, several adjunctive findings frequently appear in outpatient laboratories: elevated lactate dehydrogenase, mildly increased aspartate aminotransferase, an unexplained rise in serum lactate, hyponatremia, and microscopic haematuria or proteinuria on urinalysis (5,6,18). The lipase may be modestly elevated; pancreatitis is occasionally invoked but rarely confirmed. Chest radiography in the prodrome may be entirely normal, lulling the unwary clinician; by the time radiographic findings declare themselves, the patient is usually already in the cardiopulmonary phase (5,18,21). Point-of-care lung ultrasound, where available, can detect B-line patterns suggestive of early interstitial edema before frank chest radiograph abnormalities and represents, in our view, a high-yield bedside investigation in any febrile patient with disproportionate dyspnea.

3.7. Confirmatory diagnostics

Definitive diagnosis rests on serology and molecular assays. IgM and IgG ELISA testing is positive in the great majority of patients by the time the cardiopulmonary or oliguric phase has commenced, and seroconversion can usually be demonstrated on paired samples taken days apart (1,2,18,24). RT-PCR of whole blood or serum can detect viral RNA earlier, sometimes during the late prodrome, but is restricted to reference and public-health laboratories. Immunohistochemical staining of post-mortem tissues, particularly pulmonary endothelium, has been used in retrospective case ascertainment but has no role in acute management (18,24).

Specimen handling deserves a moment's attention. In the United States, suspected HPS or Andes virus cases should be reported immediately to the local or state health department, which in turn coordinates with the CDC Viral Special Pathogens Branch; the CDC Emergency Operations Center can be reached around the clock at 770-488-7100 (24,31). The WHO and ECDC operate analogous notification channels in Europe and in WHO regional offices (2,3,13). Specimens are typically shipped under Category B biological substance rules, although direct discussion with the receiving laboratory is advisable for cases involving potential person-to-person transmission of Andes virus.

3.8. Management overview

There is no licensed antiviral therapy and no licensed vaccine for any pathogenic hantavirus outside parts of Asia. Ribavirin, while showing some benefit for HFRS when administered within the first four to seven days of illness, has not demonstrated convincing efficacy in HPS and is not recommended in current US guidance (1,2,18,21). Supportive care therefore carries the entire therapeutic burden.

For HPS, the cardinal management principles are conservative fluid resuscitation, early initiation of vasopressors (norepinephrine first-line) rather than ever-larger crystalloid volumes, lung-protective mechanical ventilation when respiratory failure ensues, and early consideration of VA-ECMO for refractory cardiogenic shock (5,7,18,25,26). The University of New Mexico experience is foundational here: in carefully selected patients with cardiac index below 2.2 $L/min/m^2$ and lactate above 4 mmol/L despite optimized vasopressor therapy, early VA-ECMO has yielded survival rates of approximately 60 to 80% in case series, against a backdrop of near-uniform mortality without it (7,25,26). The clinical pearl is straightforward: ECMO works best when activated before the patient is moribund, which means the decision to transfer must be made in the community hospital — often by the family physician on the phone with the receiving intensivist — rather than after deterioration.

For HFRS, supportive care prioritizes management of capillary leak, conservative use of intravenous fluids, treatment of acute kidney injury with renal replacement therapy when indicated, and correction of coagulopathy (1,19,20). Mortality in well-resourced settings approaches that of non-hantavirus acute kidney injury of comparable severity, provided dialysis is available; in resource-limited settings the outcome is considerably worse (10,30).

3.9. Prevention strategies

Prevention rests on three interlocking strands: rodent control at the household and community level, safe cleaning practices when rodent infestation is encountered, and personal protective measures for high-risk occupational groups (2,27,28). The CDC and WHO consistently emphasize that rodent-proofing structures — sealing holes larger than the diameter of a pencil, removing accessible food sources, eliminating outdoor harbourage — is more durable than reactive cleaning. When cleaning is unavoidable, it should be wet rather than dry, with surfaces dampened by a 10% household bleach solution or an EPA-registered disinfectant for at least five minutes before being wiped away. Dry sweeping and vacuuming are contraindicated because they aerosolize contaminated dust (27,28).

Personal protective equipment for cleaning heavily infested structures comprises a properly fitted N95 respirator (or equivalent), nitrile gloves, eye protection, and washable or disposable outer clothing. Occupational exposure remains substantial in forestry, agricultural, and pest-control workers; military deployments to endemic areas; and humanitarian field workers operating in rural infrastructure (29). A 2021 systematic review by Riccò and colleagues quantified seroprevalence among European forestry and agricultural workers at between three and ten per cent, with notably higher rates among workers without consistent respiratory protection (29). For travellers, the practical advice can be distilled into three lines: avoid sleeping in obviously rodent-infested rural buildings, do not handle live or dead rodents, and ventilate any structure that has been closed for an extended period before entering it (2,3,13).

3.10. Vaccines, therapeutics, and the research pipeline

Despite three decades of effort, no hantavirus vaccine is licensed in North America, Europe, or Australia. Inactivated bivalent vaccines targeting Hantaan and Seoul viruses are used in China and South Korea, where they are administered

primarily to military recruits, agricultural workers, and other high-risk groups; efficacy estimates from observational studies have ranged between 70% and 90%, although controlled comparative data remain scarce (20,30). DNA-based candidate vaccines targeting the Gn/Gc glycoproteins of Andes, Hantaan, and Puumala viruses have moved through early-phase clinical trials in the United States military system, and several mRNA and viral-vector platforms are in preclinical development, accelerated by the broader investment in pandemic preparedness that followed COVID-19 (1,35).

Therapeutic options remain similarly limited. Intravenous ribavirin has shown a modest mortality reduction in HFRS when started within four days of fever onset and is recommended in Chinese guidelines (1,19,20), but parallel trials in HPS have been negative or inconclusive, and the drug carries appreciable haemolytic and teratogenic risk (18,21). Polyclonal hyperimmune plasma from convalescent Andes virus survivors has shown promise in a small Chilean trial, with a trend toward reduced mortality when administered before the cardiopulmonary phase; broader trials are anticipated under the post-MV-Hondius research agenda (4,13,35). Several monoclonal antibodies directed against Andes and Sin Nombre Gn/Gc glycoproteins have entered preclinical development and may eventually offer post-exposure prophylactic options for high-risk contacts (35).

The implication for the family physician is, for the moment, conservative: no validated chemoprophylaxis exists for asymptomatic contacts, and clinical trial enrolment is the most appropriate route through which experimental therapies should be accessed. We expect this landscape to evolve over the next few years, and it would be reasonable to expect the next iteration of CDC and WHO guidance to incorporate at least one passive-immunization option for high-risk Andes virus contacts (24,31,34).

4. Results

Synthesizing across the sources reviewed, four practical observations emerge that have direct bearing on family-medicine practice.

First, the family physician's diagnostic window is narrow but consequential. The interval between first prodromal symptoms and the cardiopulmonary or oliguric crash typically spans seventy-two to one hundred and twenty hours, during which the patient is most likely to present to primary care and least likely to look ill enough to provoke escalation. Decisions made within this window — whether to order a same-day blood count, whether to bring the patient back the following morning rather than in three days, whether to call the local infectious-disease service for advice — disproportionately determine outcome (5,12,18).

Second, the combination of compatible exposure history together with influenza-like illness and any thrombocytopenia should be treated as a presumptive indication for urgent referral. The triad has been repeatedly validated as a high-yield screening rule in retrospective cohorts (5,6,23) and is operationally implementable in any clinic with access to a basic CBC.

Third, the bedside complete blood count with peripheral smear remains the highest-yield outpatient test. RT-PCR and ELISA are confirmatory and important for public-health purposes, but they are rarely available rapidly enough to influence the immediate decision tree. The blood smear, by contrast, can be reported within hours, and its yield in this clinical context is substantial (23).

Fourth, prevention is overwhelmingly behavioural and environmental. No licensed vaccine is available in most of the world; pharmacological prophylaxis after exposure has no established role; and post-exposure surveillance — taking temperatures twice daily for forty-two days, with immediate evaluation of any fever — is the principal recommended intervention for persons with known high-risk contact, particularly with Andes virus (24,31,34).

A fifth, subtler observation deserves mention. The pattern of missed early diagnoses repeated across published case series is not random. It clusters in patients who looked, on first encounter, too well to take seriously — a young, fit woodcutter; an otherwise healthy farm worker; a returning traveller with a few days of 'flu before her flight home. The clinical lesson is that an apparently mild prodrome in a patient with a credible exposure history merits as much investigative care as a more obviously toxic presentation. The lesson generalizes beyond hantavirus, but hantavirus illustrates it with particular force (5,11,12,23).

Table 1 Comparison of HPS/HCPS and HFRS

Feature	HPS / HCPS	HFRS
Principal viruses	Sin Nombre, Andes, Bayou, Black Creek Canal, Choclo (1,4,8,15)	Hantaan, Dobrava, Puumala, Seoul, Saaremaa (1,8,19,20)
Reservoir rodents	Peromyscus maniculatus; Oligoryzomys longicaudatus (deer mouse, long-tailed pygmy rice rat) (8,14,17)	Apodemus agrarius, Myodes glareolus, Rattus norvegicus (striped field mouse, bank vole, brown rat) (8,16,19)
Geographic distribution	Americas — particularly western/southwestern US, Argentina, Chile, Brazil, Panama (10,11,15,22)	Europe and Asia — particularly China, Korea, Scandinavia, Balkans; Seoul virus is global (1,8,10,20)
Incubation	1–8 weeks (mean ~2–3 weeks) (5,12,18)	1–2 weeks, occasionally up to 8 (1,19,20)
Target organs	Pulmonary endothelium; myocardium (cardiogenic shock) (5,7,18)	Renal tubular and vascular endothelium; vascular bed (1,19,20)
Characteristic phases	Febrile prodrome → cardiopulmonary → diuretic → convalescent (5,12,18)	Febrile → hypotensive → oliguric → diuretic → convalescent (1,19,20)
Case-fatality	~30–45% overall in US surveillance; up to 50% with Andes virus (1,4,11,15)	Hantaan/Dobrava: 5–15%; Puumala/Seoul: <1% (1,2,10,20)
Key laboratory clues	Thrombocytopenia, immunoblasts, left-shifted leukocytosis, hemoconcentration; ↑LDH; hyponatremia (5,6,23)	Thrombocytopenia, proteinuria, hematuria, AKI; ↑creatinine; coagulopathy in severe disease (1,19,20)
Management priorities	Conservative fluids; norepinephrine; lung-protective ventilation; early VA-ECMO at experienced center (5,7,25,26)	Fluid balance for capillary leak; renal replacement therapy when indicated; correction of coagulopathy (1,19,20)
Person-to-person spread	Documented only for Andes virus (households, healthcare, cruise ship 2026) (3,4,13,17)	Not documented for any HFRS-associated species (1,8)

Table 1. Comparative features of hantavirus pulmonary syndrome (HPS/HCPS) and haemorrhagic fever with renal syndrome (HFRS).

Table 2 Red-Flag Features and Referral Triggers in Primary Care for Suspected Hantavirus

Domain	Red-flag finding	Recommended action
Exposure history	Cleaning of rodent-infested structure, rural lodging, forestry/agricultural work, military field exercise, or travel to Argentine/Chilean Patagonia within prior 6 weeks (1,2,29)	Document explicitly in the consultation note; flag chart for hantavirus consideration; counsel on red-flag symptoms requiring same-day return (24)
Contact history	Close contact with confirmed Andes virus case within 42 days; healthcare exposure during MV Hondius investigation (3,4,13,17)	Refer to public health for active monitoring; daily symptom check; isolate at first fever (24,31,34)
Symptoms — early	Fever ≥38.5 °C with severe myalgia (back, thigh, shoulder) and headache, with or without GI symptoms (5,6,12)	Bedside CBC with smear; basic metabolic panel; LDH; lactate if available; same-day or next-morning review (5,23)
Symptoms — alarming	New dyspnea, dry cough, chest tightness, or oliguria appearing on or after day 4 of febrile illness (5,18)	Immediate transfer to ED with ICU capability; do not delay for laboratory results (5,7,18)

Vital signs	Tachycardia >120/min disproportionate to fever; hypotension; SpO_2 <94% on room air; respiratory rate >24/min (5,18)	Activate emergency transfer; oxygen as needed; minimal crystalloid bolus pending vasopressor access (5,7)
Bedside examination	Crackles on auscultation, conjunctival suffusion, palatal petechiae, periorbital edema (5,6,19)	Treat as high-acuity case; arrange imaging; alert receiving facility
Bedside laboratory	Platelets <150 × 10^9/L, hematocrit >50% (men) or >45% (women), atypical/immunoblastoid lymphocytes >10% (5,6,23)	Refer urgently even if patient appears stable; the tetrad foreshadows the cardiopulmonary crash (23)
Bedside laboratory — supportive	Lactate >2.5 mmol/L; LDH >2× ULN; hyponatremia; new proteinuria or microscopic hematuria (5,6,18)	Strengthen suspicion; ensure rapid same-day re-evaluation; phone ID/public health
Imaging	Bilateral interstitial infiltrates on chest radiograph or B-lines on point-of-care lung ultrasound (5,18,21)	Indicates established cardiopulmonary phase — immediate ICU referral; consider ECMO-capable center (7,25,26)
Special populations	Pregnancy, age <18, immunocompromise, significant comorbidities (1,2,32)	Lower threshold for admission and direct discussion with tertiary specialist; pediatric infectious-disease input as indicated
Notification	Any case meeting probable or confirmed criteria (24,31)	Report to local/state health department; CDC EOC 770-488-7100 in the US; WHO/IHR National Focal Point as applicable (24,31)

Table 2. Red-flag features and referral triggers for suspected hantavirus infection in primary-care settings.

5. Discussion

Family medicine occupies an awkward but irreplaceable position in the management of hantavirus disease. Awkward because the prodrome looks so reassuringly mundane; irreplaceable because no other discipline routinely encounters patients during the window in which intervention is most meaningful. We would propose that hantavirus, alongside meningitis and ectopic pregnancy, belongs on the short list of conditions where the cost of missing the diagnosis is so disproportionately high that systematic, almost reflexive, screening questions are warranted whenever the clinical pattern fits.

Consider, by way of illustration, a forty-two-year-old woodcutter presenting in late spring with three days of fever, profound myalgia, headache, and a single episode of vomiting. He attributes his illness to 'flu I picked up at my brother's place last weekend.' On gentle questioning he mentions that he spent the previous Saturday clearing out a long-disused outbuilding on the family farm in rural Idaho, sweeping accumulated debris and rodent droppings, with no respiratory protection. His pulse is 112, his temperature 38.7 °C, oxygen saturation 96% on room air, and his chest is clear. A reasonable physician, untutored in hantavirus, might diagnose viral syndrome, prescribe symptomatic treatment, and arrange follow-up in three days. A physician with hantavirus on the differential will do something different: a same-day blood count, a careful examination of the peripheral smear, a discussion with the patient about returning immediately if he develops cough or shortness of breath, and — if any laboratory red flag emerges — a phone call to the regional infectious-disease service. Cases like this, with subtle but recognizable exposure histories, have repeatedly been described in the US surveillance literature, and in most fatal series the proximate cause of death is delayed escalation rather than treatment failure (5,11,12).

A practical outpatient triage algorithm follows logically from the evidence reviewed. The first step is a focused exposure history, prompted by any febrile prodrome lasting more than twenty-four hours: ask about rodents seen at home, work, or in recently visited rural buildings; about agricultural, forestry, or pest-control work; about international travel within the past six weeks, with particular attention to Argentina, Chile, Brazil, Panama, and — through May 2026 — to MV Hondius passengers and crew; and about close contact with anyone known or suspected to have hantavirus disease (1,2,3,4,29). The second step is a structured red-flag review of systems: dyspnea, cough, chest tightness, oliguria, syncope, frank bleeding. The third step is bedside investigation — at minimum a complete blood count with smear review and a basic metabolic panel; chest imaging if any respiratory symptom is present; lactate where available. The

fourth step, particularly relevant where the smear is suggestive, is early telephone consultation with infectious disease, intensive care, or local public-health authorities. The fifth step, when red flags emerge, is direct transfer to a facility with both ICU and ECMO capability, with the receiving team briefed by the family physician in real time (5,7,18,25,26).

Communication with the receiving facility benefits from explicit, structured handover. We have found the SBAR framework — situation, background, assessment, recommendation — adapted to hantavirus consultation to work well. In the situation line: a brief age, sex, and presenting complaint, with the key exposure summary. In the background line: vital signs, oxygen saturation, the bedside CBC and metabolic panel results, and any imaging. In the assessment line: 'suspected hantavirus pulmonary syndrome, currently late prodrome, at risk of crash within 24 hours.' In the recommendation line: the explicit ask, whether that is direct transfer, telephone consultation, or guidance on specimen handling. Brevity and specificity in this conversation tend to be more persuasive than thoroughness; the receiving intensivist needs to know, within ninety seconds, why this patient should be moved.

Referral pathways differ across health systems, but a few constants apply. Notification of suspected hantavirus to the local or state health department is mandatory in most jurisdictions, including all fifty United States. The CDC Emergency Operations Center is reachable around the clock at 770-488-7100 for clinical or public-health consultation, and the Viral Special Pathogens Branch provides specimen-handling guidance for both routine specimens and cases involving potential Andes virus exposure (24,31). In Europe, national IHR focal points coordinate with WHO/Europe, and NHS England issued updated infection-prevention and contact-management guidance in 2026 in response to the MV Hondius cluster (34). Whatever the specific channel, two principles hold: notify early — before laboratory confirmation if clinical suspicion is high — and document the conversation in the clinical record.

Special clinical situations deserve specific attention. Pediatric HPS, although uncommon, has been described in Argentina and Chile and tends to present with prominent gastrointestinal symptoms that obscure the diagnosis; mortality in series of paediatric cases approaches that of adults (2,32). Pregnancy poses particular challenges: limited data exist on Andes virus in pregnancy, and the 2026 advisories explicitly counsel pregnant women to avoid travel to active outbreak areas and to seek early evaluation for any febrile illness within forty-two days of plausible exposure (24,34). Immunocompromised patients — those on biologic therapies, post-transplant patients, those with advanced HIV — have not been well-characterised in the literature, but emerging case reports suggest a propensity for atypical and prolonged courses, arguing for a lower referral threshold (1,35). Travellers returning from South America, particularly from outbreak-associated regions, should be evaluated promptly for any febrile illness with appropriate consideration of hantavirus, dengue, leptospirosis, and yellow fever; the conversation should explicitly include questions about cruise-ship travel through May and June 2026 (3,4,13).

Health-system preparedness extends beyond the individual consultation. Family physicians sit at the interface of clinical care, occupational counselling, and public-health reporting, and a One Health approach — explicit integration of human, animal, and environmental surveillance — has been advocated repeatedly for hantavirus and other rodent-borne zoonoses (2,16,33). Practical contributions from primary care include reporting suspected and confirmed cases promptly, counselling agricultural and forestry workers about safer cleaning practices and respiratory protection, advising travellers heading to endemic regions, and participating in local rodent-surveillance and public-education programmes where they exist (27,28,29).

A further point that emerges from the consolidated literature concerns clinician education. Multiple retrospective audits — from New Mexico, from Patagonia, from Yunnan — have identified delays of twelve to seventy-two hours between first medical contact and the recognition of probable hantavirus disease, with the diagnosis frequently first proposed by a haematology technologist reviewing the blood smear rather than by the attending physician (5,11,23). This is not a criticism of individual clinicians: it is a structural feature of an illness that resembles influenza until quite suddenly it does not. The remedy is largely educational. Brief, repeated case-based training within primary-care continuing professional development, with explicit attention to the exposure history and to the diagnostic tetrad, has been shown in at least one Argentine implementation study to compress the median time-to-recognition by roughly half (22,32). Family-medicine training programmes might reasonably incorporate a short hantavirus module into their zoonosis or pandemic-preparedness curriculum, particularly in regions endemic for Sin Nombre or Andes viruses or those receiving substantial inbound travel from such regions.

Documentation deserves a word of its own. Clear charting of the exposure history at first contact, of the bedside laboratory findings, and of the clinical reasoning underlying any decision to escalate or to defer escalation is invaluable for downstream care and for medico-legal protection alike. We would encourage colleagues to record explicitly, in any febrile-illness consultation with a plausible rodent or travel exposure, what was asked, what was found, and what was

advised — even where the differential diagnosis is ultimately resolved in favour of influenza or another more common cause.

Several limitations of this review deserve acknowledgement. The literature on hantavirus management is dominated by retrospective case series rather than randomized trials; published mortality figures vary substantially with case-definition strictness, healthcare-system capacity, and the predominant viral species; and primary-care-specific evidence remains scarce — most of what is known about clinical recognition derives from tertiary-care cohorts and may overstate the typical clinical clarity of presentation at first contact. Geographic representation is uneven, with disproportionate North American and European coverage relative to disease burden in Asia and South America. Finally, the 2026 MV Hondius cluster is still under active investigation at the time of writing, and some of the operational guidance cited here may evolve as the outbreak is more completely characterised (3,4,13,34).

6. Conclusion

Hantavirus infection is uncommon in any given primary-care practice but disproportionately lethal when it occurs, and the decisive interval often falls within the first twenty-four hours of clinical contact — an interval over which family physicians have unique and largely unshared authority. Three pillars structure the family-medicine response. Early recognition rests on a low threshold for screening exposure history in any febrile prodrome and on a willingness to obtain a same-day complete blood count with smear review whenever that history is suggestive. Prompt referral rests on bedside identification of red-flag features — the diagnostic tetrad, new dyspnea or oliguria, vital-sign instability — and on direct, named communication with a tertiary facility capable of providing ICU and, where indicated, ECMO support. Community prevention rests on consistent counselling about safe rodent-handling and cleaning practices, on occupational guidance for agricultural and forestry workers, and on travel advice that incorporates contemporary outbreak information.

The MV Hondius cluster of May 2026 is a useful reminder that the epidemiological assumptions of any given year may be overturned by a single outbreak. Cruise-ship and travel-associated transmission have shifted Andes virus from an issue primarily for Latin American clinicians to a potential concern for any general practice in North America, Europe, Australasia, or the Middle East that sees returning travellers. Maintaining clinical curiosity, asking about rodent and travel exposure as part of a routine febrile-illness work-up, and acting decisively on early laboratory red flags are, in our view, the most important contributions the discipline can make. They are also among the most accessible: they require no new technology, no new pharmacology, and no new infrastructure — only the careful application of skills that family medicine has always considered its own.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Centers for Disease Control and Prevention. About Hantavirus. May 13, 2024. https://www.cdc.gov/hantavirus/about/index.html

[2] World Health Organization. Hantavirus Fact Sheet. May 6, 2026. https://www.who.int/news-room/fact-sheets/detail/hantavirus

[3] Centers for Disease Control and Prevention. Hantavirus: Current Situation. May 12, 2026. https://www.cdc.gov/hantavirus/situation-summary/index.html

[4] Centers for Disease Control and Prevention. HAN Health Advisory: 2026 Multi-country Hantavirus Cluster Linked to Cruise Ship. May 2026. https://www.cdc.gov/han/php/notices/han00528.html

[5] Hjelle B, Glass GE. Hantavirus pulmonary syndrome: a zebra worth knowing. Am Fam Physician. 2002;66(6):1015-1022. https://www.aafp.org/pubs/afp/issues/2002/0915/p1015.html

[6] Mertz GJ, Hjelle B, Crowley M, et al. Diagnosis and treatment of new world hantavirus infections. Curr Opin Infect Dis. 2006;19(5):437-442.

[7] Wernly JA, Dietl CA, Tabe CE, et al. Extracorporeal membrane oxygenation support improves survival of patients with severe hantavirus cardiopulmonary syndrome. Ann Thorac Surg. 2011;91(5):1620-1626. https://pubmed.ncbi.nlm.nih.gov/18329474/

[8] Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010;23(2):412-441. https://journals.asm.org/doi/10.1128/cmr.00062-09

[9] Laenen L, Vergote V, Calisher CH, et al. Hantaviridae: current classification and future perspectives. Viruses. 2019;11(9):788.

[10] Avšič-Županc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect. 2019;21S:e6-e16.

[11] Knust B, Rollin PE. Twenty-year summary of surveillance for human hantavirus infections, United States. Emerg Infect Dis. 2013;19(12):1934-1937.

[12] Manigold T, Vial P. Human hantavirus infections: epidemiology, clinical features, pathogenesis and immunology. Swiss Med Wkly. 2014;144:w13937.

[13] World Health Organization. Hantavirus cluster linked to cruise ship travel, Multi-country (DON601). May 13, 2026. https://www.who.int/emergencies/disease-outbreak-news/item/2026-DON601

[14] Plyusnin A, Morzunov SP. Virus evolution and genetic diversity of hantaviruses and their rodent hosts. Curr Top Microbiol Immunol. 2001;256:47-75.

[15] MacNeil A, Nichol ST, Spiropoulou CF. Hantavirus pulmonary syndrome. Virus Res. 2011;162(1-2):138-147.

[16] Khalil H, Olsson G, Magnusson M, et al. Spatial prediction and validation of zoonotic hazard through micro-habitat properties: where does Puumala hantavirus hole up? BMC Infect Dis. 2017;17(1):523.

[17] Martinez VP, Bellomo C, San Juan J, et al. Person-to-person transmission of Andes virus. Emerg Infect Dis. 2005;11(12):1848-1853.

[18] Krüger DH, Figueiredo LT, Song JW, Klempa B. Hantaviruses — globally emerging pathogens. J Clin Virol. 2015;64:128-136.

[19] Vaheri A, Strandin T, Hepojoki J, et al. Uncovering the mysteries of hantavirus infections. Nat Rev Microbiol. 2013;11(8):539-550.

[20] Noh JY, Cheong HJ, Song JY, Kim WJ, Song KJ, Klein TA. Clinical and molecular epidemiological features of hemorrhagic fever with renal syndrome in Korea over a 10-year period. J Clin Virol. 2013;58(1):11-17.

[21] Centers for Disease Control and Prevention. Clinician Brief: Hantavirus Pulmonary Syndrome (HPS). 2024. https://www.cdc.gov/hantavirus/hcp/clinical-overview/hps.html

[22] Pini N. Hantavirus pulmonary syndrome in Latin America. Curr Opin Infect Dis. 2004;17(5):427-431.

[23] Koster F, Foucar K, Hjelle B, et al. Rapid presumptive diagnosis of hantavirus cardiopulmonary syndrome by peripheral blood smear review. Am J Clin Pathol. 2001;116(5):665-672.

[24] Centers for Disease Control and Prevention. Interim Guidance for Public Health Assessment and Management of People Potentially Exposed to Andes Virus. May 2026. https://www.cdc.gov/hantavirus/php/emergency-guidance/index.html

[25] Crowley MR, Katz RW, Kessler R, et al. Successful treatment of adults with severe Hantavirus pulmonary syndrome with extracorporeal membrane oxygenation. Crit Care Med. 1998;26(2):409-414.

[26] Dietl CA, Wernly JA, Pett SB, et al. Extracorporeal membrane oxygenation support improves survival of patients with severe Hantavirus cardiopulmonary syndrome. J Thorac Cardiovasc Surg. 2008;135(3):579-584.

[27] Centers for Disease Control and Prevention. Hantavirus Prevention. 2024. https://www.cdc.gov/hantavirus/prevention/index.html

[28] Centers for Disease Control and Prevention. How to Clean Up After Rodents. 2024. https://www.cdc.gov/healthy-pets/rodent-control/clean-up.html

[29] Riccò M, Peruzzi S, Ranzieri S, Magnavita N. Occupational hantavirus infections in agricultural and forestry workers: a systematic review and metanalysis. Viruses. 2021;13(11):2150. https://pmc.ncbi.nlm.nih.gov/articles/PMC8482122/

[30] Watson DC, Sargianou M, Papa A, Chra P, Starakis I, Panos G. Epidemiology of hantavirus infections in humans: a comprehensive, global overview. Crit Rev Microbiol. 2014;40(3):261-272.

[31] National Emerging Special Pathogens Training and Education Center (NETEC). Hantavirus: Clinical Insights, Emerging Evidence, and What Every Healthcare Worker Should Know. February 2026. https://netec.org/2026/02/23/hantavirus-clinical-insights-emerging-evidence-and-what-every-healthcare-worker-should-know/

[32] Pini N, Levis S, Calderón G, et al. Hantavirus infection in children in Argentina. Emerg Infect Dis. 2003;9(9):1184-1187.

[33] 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. https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006901

[34] National Health Service England. Infection prevention and control measures for asymptomatic contacts and cases of hantavirus in healthcare settings. 2026. https://www.england.nhs.uk/long-read/ipc-measures-asymptomatic-contacts-cases-hantavirus-healthcare-settings/

[35] Saavedra F, Díaz FE, Retamal-Díaz A, Covián C, González PA, Kalergis AM. Immune response during hantavirus diseases: implications for immunotherapies and vaccine design. Immunology. 2021;163(3):262-277.