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RETHINKING THE DEAD-END: A REVIEW OF HUMAN-TO-HUMAN HANTAVIRUS TRANSMISSION

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ABSTRACT

Background: Hantaviruses have long been classified as strictly rodent-borne zoonotic pathogens, with humans serving as incidental, dead-end hosts. However, outbreaks of Andes virus (ANDV) in South America challenge this uniform paradigm, presenting clear evidence of person-to-person transmissibility.

Objective: This narrative review synthesizes the epidemiological, clinical, and molecular evidence surrounding human-to-human hantavirus transmission, highlighting the biological dichotomy between strictly zoonotic lineages and transmissible strains.

Methodology: A comprehensive search of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar was conducted for literature published between 1990 and 2026. Studies focusing on outbreak investigations, cohort surveillance, case series, and molecular phylogenetics of clinically significant hantaviruses (including Hantaan, Puumala, Sin Nombre, and Andes viruses) were reviewed and analyzed narratively.

Results: The literature demonstrates a definitive, lineage-dependent separation in transmission potential. Old World hantaviruses (e.g., Hantaan, Puumala) and the New World Sin Nombre virus show an absolute absence of confirmed interhuman transmission, even in high-risk nosocomial or close household settings. Conversely, Andes virus demonstrates reproducible secondary transmission, primarily confined to close family contacts, intimate partners, and specific healthcare scenarios involving aerosol-generating procedures. Molecular sequencing confirms directional transmission via identical viral genomic segments within ANDV clusters. However, all hantavirus transmission chains remain short, with an estimated reproductive number (R_0) below 1.0, indicating a lack of sustained epidemic potential.

Conclusion: Hantavirus transmission is a strain-dependent process. While the majority of lineages remain strictly zoonotic, Andes virus represents a distinct exception capable of short-chain, human-to-human propagation under high-contact conditions. These findings underscore the need for targeted infection-control protocols and risk-stratified public health responses.

KEYWORDS: Hantavirus, Andes virus, Disease Transmission, Infectious, Hantavirus Pulmonary Syndrome, Hemorrhagic Fever with Renal Syndrome, Zoonoses

1. INTRODUCTION

Hantaviruses are enveloped, negative-sense, single-stranded RNA viruses belonging to the family *Hantaviridae* within the order *Bunyavirales* (1). Unlike most other bunyaviruses, which are vector-borne pathogens transmitted by arthropods, hantaviruses maintain a highly co-evolved, persistent relationship with specific small mammal reservoirs, primarily rodents, insectivores, and bats (2-4). Human infection typically occurs through the inhalation of aerosolized viral particles shed in the excreta, saliva, or urine of chronically infected reservoirs (5). Depending on the specific viral lineage and geographic region, hantavirus infection manifests as one of two distinct, severe clinical syndromes: Hemorrhagic Fever with Renal Syndrome (HFRS) in the Old World (Europe and Asia) or Hantavirus Cardiopulmonary Syndrome (HCPS)-also frequently termed Hantavirus Pulmonary Syndrome (HPS)-in the New World (the Americas) (6,7). Both syndromes are characterized by microvascular dysfunction, increased capillary permeability, and severe immunopathological cascades, often resulting in high case-fatality rates (8-10).

For decades, a central tenet of hantaviridae epidemiology was that humans act exclusively as incidental, dead-end hosts (11,12). Outbreaks of HFRS driven by Hantaan virus (HTNV) or Puumala virus (PUUV), as well as early outbreaks of HCPS driven by Sin Nombre virus (SNV) in North America, consistently demonstrated that individual cases could be mapped back to direct environmental exposure to rodent reservoirs, with no evidence of onward transmission to healthcare personnel or household contacts (13-17). However, the identification of Andes virus (ANDV) during outbreaks in Argentina and Chile in the late 1990s fundamentally challenged this rigid paradigm (14,18,19). Epidemiological clusters of HCPS emerged where secondary infections occurred in individuals with absolutely no history of direct rodent or rural environmental exposure, suggesting a direct human-to-human transmission pathway (18,21).

This observed divergence in transmissibility creates a profound biological and public health dichotomy within the genus. While the structural and regulatory mechanisms governing endothelial cell dysfunction appear conserved across pathogenic hantaviruses, the specific host-pathogen interactions that facilitate viral shedding into human respiratory secretions and subsequent acquisition by close contacts remain poorly understood (8,20). This variation carries crucial clinical implications, particularly concerning nosocomial infection control, emergency airway management, and the design of localized public health interventions (20,22). A nuanced, comprehensive understanding of these lineage-specific transmission mechanics is vital to moving past uniform, generalized hantavirus transmission assumptions and preparing for emerging viral variants (23,24).

This narrative review evaluates the accumulated evidence surrounding human-to-human hantavirus transmission from 1990 through 2026. By contrasting the strictly zoonotic profile of Old World lineages and Sin Nombre virus against the reproducible, short-chain interhuman transmissibility of Andes virus, this paper delineates the factors governing transmission risk, analyzes the vital role of molecular phylogenetics in confirming transmission directionality, and addresses the critical implications for contemporary clinical practice and global health security.

2. METHODOLOGY

This article was conducted as a narrative review of the published literature on human-to-human transmission of hantaviruses. Relevant scientific publications were identified through searches of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, supplemented by reference tracking of key articles and reports from international public health organizations, including the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the Pan American Health Organization (PAHO). Literature published between 1990 and 2026 was considered to provide both historical and contemporary perspectives on hantavirus transmission dynamics.

The review focused on epidemiological investigations, outbreak reports, cohort studies, case series, and molecular studies describing potential transmission events among humans. Particular attention was given to studies examining Andes virus, Hantaan virus, Puumala virus, Sin Nombre virus, and other clinically important hantavirus species. Publications were examined for evidence related to transmission patterns, exposure histories, diagnostic approaches, molecular findings, and infection-control implications.

The collected literature was reviewed and synthesized narratively, with emphasis placed on comparing transmission characteristics among different hantavirus lineages and evaluating the strength of evidence supporting person-to-person transmission. Findings were organized according to major themes, including viral species, transmission settings, molecular evidence, and public health significance. This approach allowed for a comprehensive discussion of the current understanding of hantavirus transmission while identifying areas requiring further research.

3. RESULTS

The compiled literature reveals a definitive, lineage-dependent separation in hantavirus interhuman transmission capacity. While the vast majority of lineages demonstrate no capacity for sustained horizontal transmission, Andes virus (ANDV) in South America constitutes a distinct exception, backed by coupled epidemiological and molecular evidence confirming limited secondary propagation within high-contact networks.

3.1 Evidence Across Old World Hantaviruses

Epidemiological tracking of Old World hantaviruses-predominantly Hantaan (HTNV), Puumala (PUUV), and Dobrava-Belgrade (DOBV) viruses-demonstrates an absolute absence of person-to-person transmissibility (5,6,12). Across extensive outbreak investigations in Europe and Asia, secondary cases among household cohorts and clinical staff were uniformly absent (6,11). Case clustering was invariably tracked to shared environmental exposure to rodent reservoirs rather than horizontal human vectors (5,12). Even within intensive care units managing advanced Hemorrhagic Fever with Renal Syndrome (HFRS), longitudinal surveillance has failed to document secondary seroconversion among heavily exposed contacts, solidifying the strictly zoonotic status of these strains (11,12,16,17).

3.2 Evidence for Sin Nombre Virus

Similarly, surveillance data for the premier North American New World lineage, Sin Nombre virus (SNV), show no indication of horizontal propagation (10,13). Detailed evaluations of close family dynamics and medical personnel exposed to index Hantavirus Pulmonary Syndrome (HPS/HCPS) cases have repeatedly failed to identify secondary clusters (10,15). Given the severe respiratory manifestations of SNV, intensive surveillance has focused on nosocomial risks during high-risk, aerosol-generating procedures (e.g., endotracheal intubation) (20). Despite these high-exposure scenarios, longitudinal monitoring has failed to confirm a single horizontal transmission event, corroborating the status of SNV as an exclusive rodent-borne zoonosis (15,20).

3.3 Andes Virus and Evidence of Secondary Transmission

In stark contrast, Andes virus exhibits a highly divergent transmission profile (14,18). Outbreak investigations in Argentina and Chile repeatedly document distinct clinical clusters driven by true human-to-human transmission pathways (18,19,21). Epidemiological mapping indicates that ANDV propagation is highly localized, occurring almost exclusively among household cohorts, romantic partners, and primary caregivers experiencing sustained, close-quarters contact with symptomatic index patients (21,25). Longitudinal cohort data define the secondary

incubation period as 11 to 45 days, consistent with person-to-person incubation dynamics rather than point-source environmental acquisition (19,25).

Definitive validation of direct horizontal transmission is provided by high-resolution molecular phylogenetics. Reverse transcription-polymerase chain reaction (RT-PCR) amplification and viral sequencing have consistently exposed identical or near-identical genomic structures across the S, M, and L RNA segments of index and secondary cases within defined micro-clusters (18,23,26). This absolute sequence identity effectively rules out independent spillover from genetically diverse rodent populations, mathematically confirming directional human transmission chains (19,26). Risk-factor regression models indicate that intensive caregiving, prolonged face-to-face proximity, and direct contact with infectious respiratory secretions or saliva are the primary variables driving transmission (22,23,25).

3.4 Healthcare-Associated Transmission

Nosocomial propagation has been meticulously documented across several major ANDV outbreaks (20,22). While the baseline risk to medical staff remains low, a small, highly significant cohort of confirmed nosocomial transmission events is verified in the literature (20,23). These transmissions are heavily correlated with specific high-risk clinical events, including emergency airway management without appropriate personal protective equipment (PPE), extended unshielded bedside care during the late symptomatic phase, and direct mucosal exposure to respiratory droplets (20,22). In these instances, molecular typing has confirmed direct viral transmission from hospitalized patients to attending healthcare personnel, rendering nosocomial ANDV transmission a distinct, context-dependent occupational hazard (22,23).

3.5 Transmission Dynamics and Epidemic Potential

Despite the clear horizontal capacity of ANDV, mathematical and epidemiological modelling reveals that human hantavirus transmission chains are structurally short and self-limiting (5,23). No empirical evidence supports sustained, community-wide propagation or autonomous epidemic amplification driven exclusively by human networks (7,23). In settings where ANDV transmission occurs, transmission lines typically terminate abruptly after one or two sequential generation links (23,26). The basic reproductive number (R_0) for ANDV consistently falls well below the critical threshold of 1.0, indicating that the virus lacks the inherent efficiency to maintain permanent human outbreaks without continuous spillover reinforcement from its primary reservoir, *Oligoryzomys longicaudatus* (5,23).

3.6 Overall Pattern of Evidence

In summary, the peer-reviewed evidence establishes a clear, binary division in hantavirus transmission mechanics. Old World strains (HTNV, PUUV, DOBV) and North American New World lineages (SNV) operate strictly within a zoonotic model where humans represent an evolutionary dead end. Conversely, Andes virus occupies a separate epidemiological niche, characterized by a biologically reproducible, though inefficient, capacity for short-chain human-to-human transmission under specific high-exposure, close-contact conditions (18,23). Beyond this localized exception, the global epidemic potential of hantaviruses within the human population remains exceptionally low (5,24).

4. DISCUSSION

This synthesis reinforces the paradigm that the majority of clinically significant hantaviruses-including Old World lineages (HTNV, PUUV, DOBV) and the New World SNV-are strictly zoonotic pathogens (5,6,10,12). For these lineages, empirical data uniformly fail to demonstrate horizontal transmission among household or healthcare cohorts, solidifying the status of humans as evolutionary dead-end hosts (11,15). Conversely, Andes virus (ANDV) constitutes a distinct biological exception, demonstrating a reproducible capacity for short-chain, person-to-person transmission within high-contact clusters (18,21). High-resolution molecular phylogenetics has provided definitive validation of this pathway, revealing near-identical genomic sequences between index and secondary cases that rule out coincidental point-source co-exposure (19,26).

The mechanistic divergence driving ANDV transmissibility likely stems from unique host-pathogen dynamics. Evidence suggests ANDV exhibits an enhanced tropism for human respiratory tissues, resulting in elevated viral loads within upper and lower respiratory secretions compared to non-transmissible lineages (8,20). Additionally, strain-specific modulation of the early host innate immune response may provoke heightened viral shedding during late prodromal and early symptomatic phases, enabling transmission via respiratory droplets or close mucosal contact (20,23). Despite this capacity, ANDV remains an inefficient respiratory pathogen; its basic reproductive number (R_0) remains below 1.0, meaning transmission chains are self-limiting and incapable of autonomous epidemic propagation without rodent reservoir spillover (5,23).

A critical methodological challenge across the reviewed literature is distinguishing true horizontal transmission from shared environmental exposure. While early outbreak investigations relied on serology and clinical histories-which lack the granularity to establish transmission directionality-modern molecular epidemiology has resolved these diagnostic ambiguities through real-time genomic sequencing (18,22). Clinically, these findings mandate a risk-stratified approach to infection control. Standard precautions suffice for Old World strains and SNV, but suspected or confirmed ANDV cases require strict, enhanced isolation protocols and respiratory protection, especially during high-risk, aerosol-generating procedures (20,22).

Several limitations temper these conclusions, including the retrospective design of historical outbreak reports, recall bias in exposure tracking, and regional disparities in molecular diagnostic capacities (22,26). Furthermore,

the true incidence of secondary transmission may be underestimated due to a historic lack of prospective surveillance for mild or asymptomatic cases (25). To resolve these gaps, future research must integrate real-time genomic sequencing with prospective contact tracing, implement robust cohort studies in high-exposure settings, and utilize advanced human respiratory tissue models to fully elucidate the molecular determinants of ANDV phenotypes.

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