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Emerging Hantavirus Threats: Clinical Manifestations and Strategies for Mitigation

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ABSTRACT

The rapid increase in global trade and travel has facilitated the evolution of various viral pathogens, enabling them to adapt to new hosts and expand their environments. Among these emerging viruses are the hantaviruses, which are primarily transmitted by small rodents, particularly rats. When these viruses are transmitted to humans, they can lead to two major clinical syndromes: renal syndrome associated with hemorrhagic fever and Hantavirus cardiopulmonary syndrome. Humans are generally infected through exposure to aerosols from contaminated rodent urine, feces, or saliva. While human-to-human transmission is rare, the virus's spread is highly dependent on rodent hosts. Hantaviruses belong to the family Bunyaviridae, specifically the genus *Orthohantavirus*, and are characterized as single-stranded, negative-sense RNA viruses enveloped in the order Bunyavirales. Although hantavirus research is progressing globally, it remains limited. The recent emergence of the coronavirus has spurred further research into hantaviruses, aiming to curb viral spread through new vaccines. This review highlights the pathophysiology, molecular mechanisms of hantavirus progression, and recommended measures to protect public health.

Keywords: *Orthohantavirus*, Negative-sense RNA virus, Coronavirus, Public health, Hantavirus, Bunyavirales

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Introduction

Infections have the potential to be viral and are a significant threat to global health, posing serious risks to human life [1-3]. The ongoing emergence of zoonotic pathogens continues to be a major public health concern, contributing to a variety of health issues. Amid the current global crisis caused by the Coronavirus and the resulting emphasis on social distancing, there has been increased awareness about viruses in general. Among these, Hantaviruses, which have been causing widespread concern, have garnered more attention as emerging pathogens in regions such as America, Asia, and Europe. Hantaviruses primarily affect small mammals, with humans becoming infected through exposure to contaminated aerosols or by direct contact with rodent droppings [4]. Once transmitted from rodents to humans, these viruses can lead to serious clinical conditions such as Hemorrhagic Fever with Renal Syndrome (HFRS), which is predominantly seen in Asia and Europe, and Hantavirus Cardiopulmonary Syndrome (HCPS/HPS), which is more common in the Americas [5]. The virus was

first identified during a major outbreak near the Hantan River in South Korea in 1976, and it has since been acknowledged as Hantavirus [6].

The Hantavirus genome consists of three key RNA segments: S, M, and L. These segments are encapsulated within a nucleocapsid protein (N), which is a precursor glycoprotein (GPC) and forms a ribonucleoprotein (RNP) complex along with RNA-dependent RNA polymerase (RdRp). This complex is enclosed in a lipid envelope with glycoprotein spikes known as Gn and Gc [7]. The S RNA segment encodes the nucleocapsid (N) protein, while the M RNA segment is processed to produce the envelope glycoproteins G1 and G2. The L RNA segment functions as the viral transcriptase/replicase enzyme. The N protein plays a crucial role in mRNA transcription and translation, initiating replication. Additionally, the N protein is required in trimeric form for effective translation in eukaryotic cells [8, 9].

The glycoproteins of pathogenic hantaviruses can interfere with the induction of INF-β and TBK-1 through their virulence factors located on the G1 cytoplasmic tail [10]. The N protein also influences the dimerization of protein kinase R (PKR) and inhibits its phosphorylation, which is essential for PKR's enzymatic activity. PKR plays a critical role in inhibiting viral replication and maintaining an antiviral state. It triggers the production of interferons (IFNs) by up-regulating NF-κB and IRF1 [11, 12]. In this review, we will explore the role of the N protein in regulating the antiviral state, outline the transmission cycle of the virus, discuss available vaccines, and provide an overview of conventional therapies for the prevention of Hantavirus infections **(Figure 1)**.

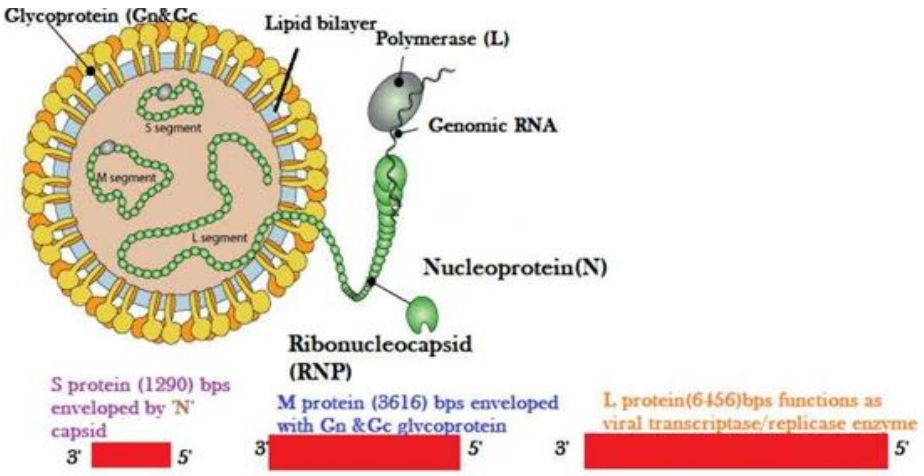

Figure 1. The organization of the Hantavirus genome with an outer decorated lipid envelope and a protected genome inside with nucleocapsids is considered as the N protein.

Results and Discussion

Hantavirus transmission lifecycle

Hantaviruses, classified under the Bunyaviridae family, are closely related to arboviruses and are primarily maintained within specific rodent hosts, known as roboviruses. The presence and spread of Hantavirus are largely determined by the distribution of these rodent reservoirs [13]. The primary natural hosts for Hantaviruses are murid rodents, which belong to the Rodentia order and Muridae family. These rodents are further classified into subfamilies such as Murinae, Arvicolinae, and Sigmodontinae. To date, there is no evidence suggesting that Hantaviruses can be transmitted by non-rodent hosts **(Figure 2)**.

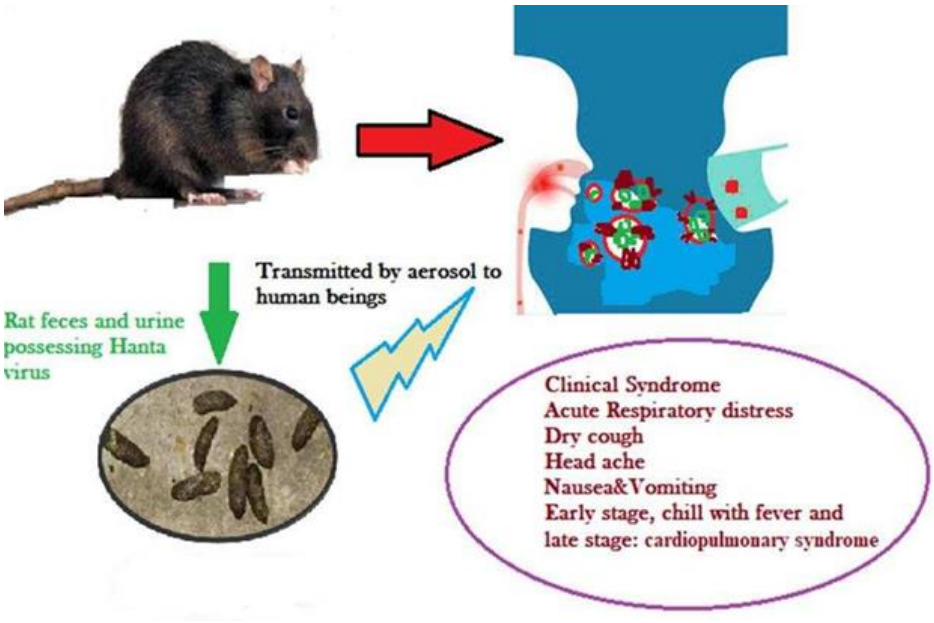

Figure 2. Schematic diagram depicting the life cycle transmittance of Hantavirus

Glycoprotein trafficking

For a virus to infect a host, it must first penetrate the cell membrane. The glycoproteins of Hantavirus play a crucial role in this process by interacting with cell surface receptors and cleverly evading the endocytic pathway. This is achieved through the fusion of viral and host cell membranes [14]. A diagram summarizing the interaction and trafficking of glycoproteins is presented in **Figure 3**. Hantaviruses bind to specific receptors on the cell surface, including β3 integrins, decay-accelerating factor (DAF)/CD55, and the receptor for the globular head domain of complement C1q (gC1qR)/p32 [15]. Upon binding to the cell membrane, the virus induces clustering of these receptors, which increases membrane acidity and activates signaling pathways. This leads to membrane invagination, forming an endocytic vesicle that facilitates the virus's entry into the host cell [16].

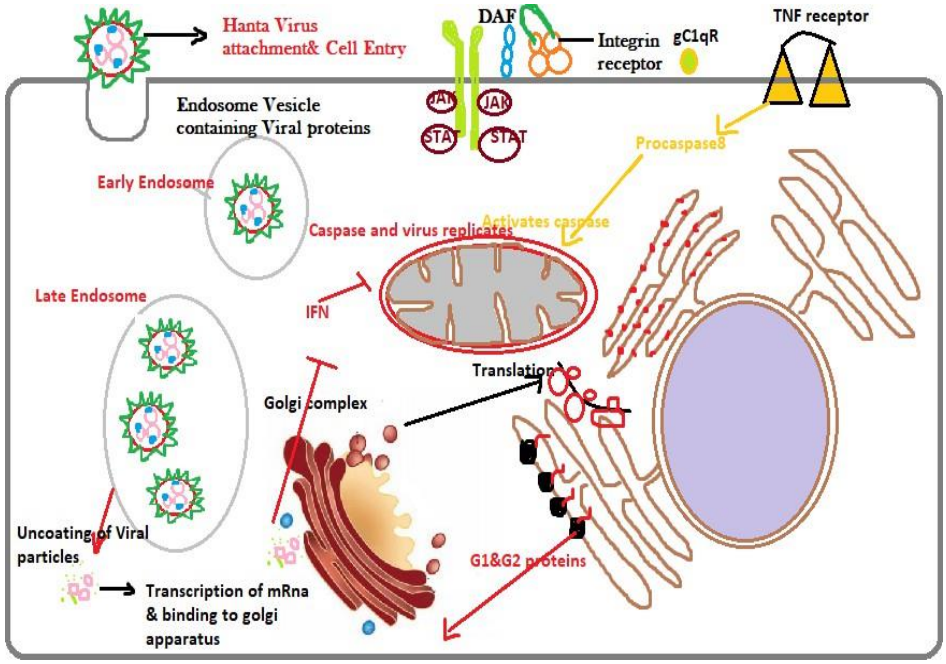

Figure 3. Hantavirus regulation mechanism with RNA binding and Ribonucleoproteinassembly during the trafficking process in the Golgi complex.

Hantavirus can infect various types of cells, including macrophages, epithelial cells, endothelial cells, follicular dendritic cells, and lymphocytes, through the attachment of viral glycoproteins to the host's cell surface receptors

[17]. Research has shown that β-receptors specifically interact with the G1 and G2 viral glycoproteins, which are responsible for triggering clinical illnesses such as HFRS and HPS. The viral trafficking process involves the formation of endolysosomal vesicles, where the virus begins to uncoat, releasing its three essential ribonucleoproteins (RNPs) into the cytoplasm. Once the viral RNA-dependent RNA polymerase (RdRp) is released, primary transcription starts, followed by translation of S and L mRNA transcripts on free ribosomes. The M-segment transcript, on the other hand, is translated on membrane-bound ribosomes and matures in the rough endoplasmic reticulum. Among these proteins, the N protein is the most abundant and plays an important role in regulating the virus cycle, including translation, trafficking, and assembly [18].

Recent studies have highlighted that the N protein, through its interaction with host cells, gradually modulates the immune response to the infection [19]. The maturation of the *Bunyavirus*/*Orthohantavirus* glycoproteins occurs in the Golgi complex, where the Gn and Gc glycoproteins undergo N-glycosylation. The Gn glycoprotein is vital for supporting trafficking within the Golgi apparatus. Notably, the expression of Gn alone leads to partial localization within the Golgi, while Gc expression is associated with localization in the endoplasmic reticulum [20].

Role of glycoprotein-induced virulence mechanism

When viral particles enter the human body, the innate immune system is activated to reduce viral replication, with Type I interferons (IFNs) playing a central role in providing direct antiviral defense by stimulating natural killer (NK) cells. However, viruses have developed mechanisms to evade detection and elimination by the immune system, particularly by suppressing the transcription of type I IFN. Studies have shown that the G1 protein cytoplasmic tail of pathogenic hantaviruses interferes with the induction of IFN-β by binding to TRAF3, thereby blocking the phosphorylation of IRF3, a crucial step in the immune response mediated by the RIG-I/TBK1 pathway. This process is depicted in a schematic diagram **(Figure 4)**, where TRAF3, an E3 ubiquitin ligase, forms a complex with TBK1 essential for IRF3 phosphorylation. By mimicking non-pathogenic proteins, the N-glycoproteins of the virus disrupt antiviral responses in infected cells, ultimately promoting viral replication.

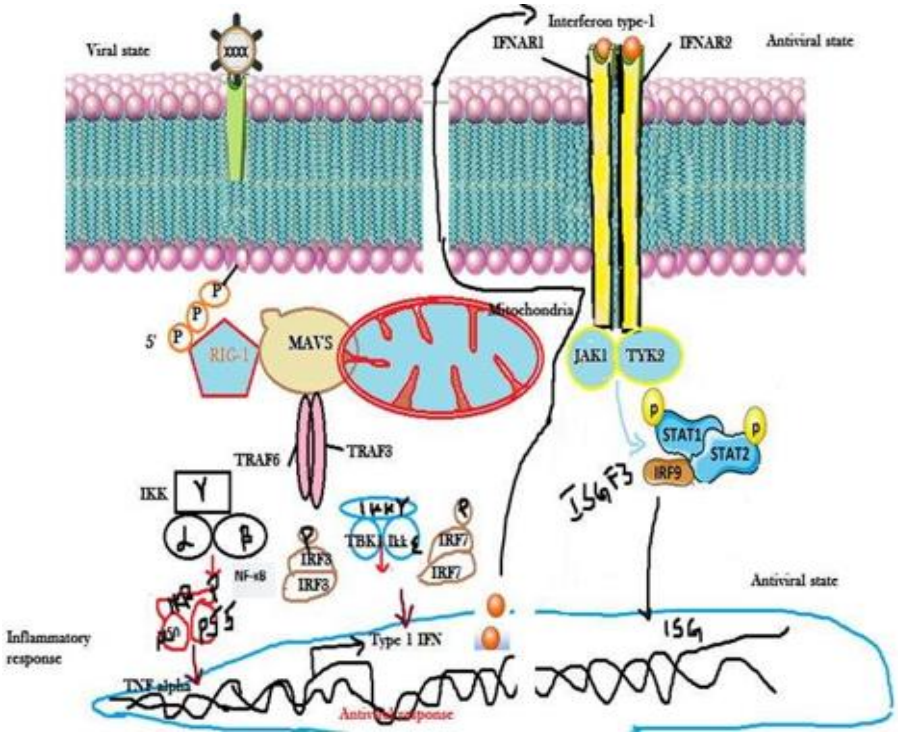

Figure 4. Schematic diagram illustrating the transcriptional activation of Interferon stimulated genes (ISGs) by JAK/STAT signaling pathway

Classification and geographical distribution of old and new hantavirus

The recognition of Hantaviruses was largely due to two significant outbreaks of disease that occurred in the 1950s. The first outbreak, during the Korean War, affected over 3,000 UN troops, leading to what became known as

Korean hemorrhagic fever, now commonly referred to as hemorrhagic fever with renal syndrome (HFRS). The second major outbreak occurred in the United States in 1993 in the Four Corners region, where a new clinical syndrome called Hantavirus pulmonary syndrome (HPS) or Hantavirus cardiopulmonary syndrome (HCPS) was identified. These outbreaks resulted in considerable mortality rates, with HFRS causing about 12% mortality and HPS having a much higher mortality rate of approximately 60%. The responsible agent for the disease was identified as the Hantaan virus (HTNV), which was primarily transmitted by the striped field mouse, serving as its main reservoir. Subsequently, other HFRS-related viruses were identified across Europe, Asia, and the United States.

Further investigations revealed the presence of HTNV and HTNV-like viruses in urban environments, contributing to cases of HFRS linked to rodents such as *Apodemus agrarius*, *A. peninsulae*, and Seoul virus (SEOV), which were found in regions like Far East Russia, China, and South Korea during the early 1980s, as shown in **Table 1**. Additionally, new findings highlighted the emergence of other viruses like Dobrava virus (DOBV) and Dobrava-like viruses, which were connected to the old-world Hantaan virus within the Apodemus genus, causing outbreaks in Europe. In Europe, another milder form of HFRS, called nephropathia epidemica (NE), which was first described in the 1930s, was linked to Puumala virus (PUUV), carried by the bank vole (*Myodes glareolus*), previously known as *Clethrionomys glareolus*.

The recognition of Hantavirus outbreaks causing HFRS has heightened global awareness, particularly due to the alarming rise of this illness in China, with an estimated 150,000 cases reported annually. In contrast, the Sin Nombre virus (SNV), a New World virus from the subfamily Sigmodontinae, was quickly found within a few weeks in most parts of the United States. The detection of the virus became possible.

To date, more than 29 different hantaviruses have been identified as causing hemorrhagic illnesses. These diseases are transmitted from rodent reservoirs to humans in areas where these rodent hosts are prevalent **(Table 1)**. While hantaviruses continue to exist in the Middle East, Africa, and Asia, they remain largely undetected in certain regions. Recent studies have also identified shrew-borne hantaviruses across the globe. One notable discovery is the Thottapalayam virus (TPMV), which was isolated from the Asian house shrew (*Suncus murinus*) and is currently identified as the only known shrew-borne hantavirus. These findings have garnered significant attention from researchers and public health officials alike, spurring efforts to explore treatments and raise awareness among the public.

Table 1. Geographic distribution and associated diseases of Old World and New World Hantavirus strains.

Group and Subfamily	Viral Strain	Abbreviation	Geographic distribution	Rodent host	Associated disease
Old World Murinae	Hantaan Virus	HTNV	China, South Korea, Russia	*Apodemus agrarius*	HFRS
	Dobrava-Belgrade Virus	DOBV	Balkans	*Apodemus flavicollis*	HFRS
	Seoul Virus	SEOV	Worldwide	Rattus	HFRS
	Saaremaa Virus	SAAV	Europe	*Apodemus agrarius*	HFRS
	Amur Virus	AMRV	Far East Russia	*Apodemus peninsulae*	HFRS
	Soochong Virus	SOOV	South Korea	*Apodemus peninsulae*	HFRS
Arvicolinae	Puumala Virus	PUUV	Europe, Asia, Americas	*Clethrionomys glareolus*	HFRS/NE
	Khabarovsk Virus	KHAV	Far East Russia	*Microtus fortis*	HFRS
	Muju Virus	MUJV	South Korea	*Myodes regulus*	HFRS
	Prospect Hill Virus	PHV	Maryland	*Microtus pennsylvanicus*	HFRS
	Tula Virus	TULV	Russia/Europe	*Microtus arvalis*	HFRS
	Isla Vista Virus	ISLAV	North America	*Microtus californicus*	HFRS
	Topografov Virus	TOPV	Siberia	*Lemmus sibericus*	HFRS
New World Sigmodontinae or Neotominae	Sin Nombre Virus	SNV	North America	*Peromyscus maniculatus*	HPS
	Monongahela Virus	MGLV	North America	*Peromyscus leucopus*	HPS

	New York Virus	NYV	North America	*Peromyscus leucopus*	HPS
	Black Creek Canal Virus	BCCV	North America	*Sigmodon hispidus*	HPS
	Bayou Virus	BAYV	North America	*Oryzomys palustris*	HPS
	Limestone Canyon Virus	LSCV	North America	*Peromyscus boylii*	HPS
	Playa de Oro Virus	OROV	Mexico	*Oryzomys couesi*	HPS
	Catacamas Virus	CATV	Honduras	*Oryzomys couesi*	HPS
	Choclo Virus	CHOV	Panama	*Oligoryzomys fulvescens*	HPS
	Calabazo Virus	CALV	Panama	*Zygodontomys brevicauda*	HPS
	Rio Segundo Virus	RIOSV	Costa Rica	*Reithrodontomys mexicanus*	HPS
	Cano Delgadito Virus	CADV	Venezuela	*Sigmodon alstoni*	HPS
	Andes Virus	ANDV	Argentina, Chile	*Oligoryzomys longicaudatus*	HPS
	Bermejo Virus	BMJV	Argentina	*Oligoryzomys chocoensis*	HPS
	Pergamino Virus	PRGV	Argentina	*Akodon azarae*	HPS
	Lechiguanas Virus	LECV	Argentina	*Oligoryzomys flavescens*	HPS
	Maciel Virus	MCLV	Argentina	*Bolomys obscurus*	HPS
	Oran Virus	ORNV	Argentina	*Oligoryzomys longicaudatus*	HPS
	Alto Paraguay Virus	-	Paraguayan Chaco	*Holochilus chacoensis*	Zika virus disease in pregnant women
	Ape Aime Virus	AAIV	Eastern Paraguay	*Akodon montensis*	Unknown
	Itapúa Virus	-	Eastern Paraguay	*Oligoryzomys nigripes*	HPS
	Rio Mamore Virus	RIOMV	Bolivia, Peru	*Oligoryzomys microtis*	HPS
	Araraquara Virus	-	Brazil	*Bolomys lasiurus*	HPS
	Juquitiba Virus	JUQV	Brazil	*Oligoryzomys nigripes*	HPS
	Jaborá Virus	JABV	Brazil, Paraguay	-	HPS

Hantavirus evolution and analysis

The phylogenetic studies of Hantavirus, along with their corresponding rodent hosts, have highlighted a deep, long-standing co-evolutionary relationship between the viruses and their rodent reservoirs. The analysis, which focuses particularly on the connection between Old World and New World Hantavirus **(Figure 5)**, sheds light on the evolution of these viruses. It also addresses ecological factors that contribute to their emergence and the spread of zoonotic diseases, which can spill over into human populations. Human activities, such as deforestation, agricultural expansion, colonization, and urbanization, have significantly increased the risk of vector-borne diseases for both humans and domestic animals. These environmental and ecological shifts often reduce the diversity of rodent populations but simultaneously promote increased interactions among host species, facilitating more hantavirus transmission events. Consequently, this situation can lead to a chain reaction, amplifying virus transmission among rodents and increasing the risk of human infections.

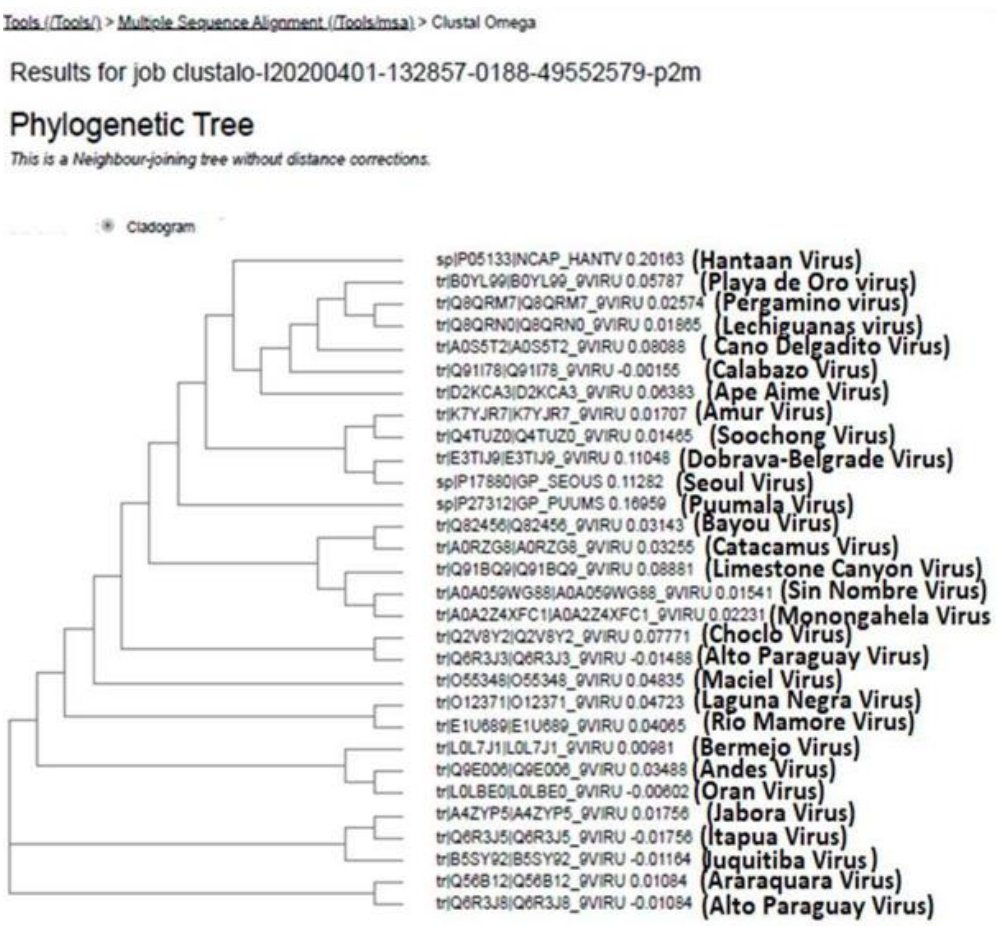

Figure 5. Phylogenetic analysis for studying the evolutionary relationship between Old and New World Hanta Virus using CLUSTAL (Omega).

Treatment of hantavirus

Upon infecting host cells, Hantaviruses elicit a strong immune response in humans. However, both Old World and New World Hantaviruses share common pathological features that contribute to the severity of the viral infection. Ribavirin, a drug previously studied for its antiviral properties against Bunyaviridae and Arenaviridae viruses, showed effectiveness in reducing mortality rates in animal models, including suckling mice infected with HTNV. Some studies conducted in China with HFRS patients demonstrated that Ribavirin improved the prognosis when administered early in the disease [21-28]. However, when used during the later stages of the disease, Ribavirin had no significant clinical benefit and even caused anemia in patients.

Currently, there are no approved post-exposure treatments for hantavirus infections, but various strategies are being explored, particularly those targeting the viral replication cycle and enhancing the host's immune response to manage HFRS or HCPS. Several antiviral drugs, antibodies, subunits, and even novel small molecules have been tested for their potential to combat Hantavirus. Although these treatments have shown protective effects in laboratory settings, their clinical application faces challenges. Additionally, several host-targeting therapies have been developed to make vascular function better and restore immune balance, though their therapeutic efficacy remains uncertain. Various studies have also explored plant-based treatments for HCV, but research on easy methods for treating HFRS/HPS is still lacking.

Conclusion

This research sheds light on the evolutionary trajectory of the Hantavirus genus and its transmission through small mammals, particularly rodents, which serve as primary reservoirs. The review provides a fresh perspective on understanding the evolution of the Hantavirus and the phylogenetic connections between the Old World and New World strains. Given the growing risk posed by emerging Hantaviruses, especially those with zoonotic origins, it

is crucial to pursue effective treatments and discover new, low-toxicity plant-based remedies. Additionally, future investigations should prioritize strategies to limit the transmission of the virus from rodent hosts.

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Ethics Statement: None

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