

Sin Nombre Virus and the Emergence of Other Hantaviruses: A Review of the Biology, Ecology, and Disease of a Zoonotic Pathogen

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Aim of the article

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This article reviews recent discoveries related to the Sin Nombre virus (SNV) and other New World hantaviruses, with a focus on their biology, transmission, ecology, and the Hantavirus Pulmonary Syndrome (HPS) they cause.

Relevance:

HPS has a high mortality rate and limited treatment options. Understanding the biology and transmission of the virus is crucial for preventing outbreaks in North America and potentially in Latin America.



History

Sin Nombre Virus, formerly known as Muerto Canyon Virus or Four Corners Virus, is a negative-sense single-stranded RNA (-ssRNA) virus belonging to the order *Bunyavirales* and the family *Hantaviridae*.

It is associated with various diseases.

Old World hantaviruses, such as Hantaan, Puumala, Dobrava, and Seoul, cause Hemorrhagic Fever with Renal Syndrome (HFRS), which has a fatality rate of less than 1%.

New World hantaviruses, including Sin Nombre, Monongahela, New York, Bayou, and Black Creek Canal (North America), as well as Andes, Araraquara, Laguna, and Choclo (South America), cause Hantavirus Pulmonary Syndrome (HPS), with a fatality rate ranging from 30% to 60%.

The virus was first detected in the U.S. in 1993 in the Four Corners region (FCR), with most cases identified in New Mexico and Arizona.

Geographical distribution

The geographical distribution of hantaviruses is determined by their rodent reservoirs. For Sin Nombre Virus (SNV), the primary reservoir is the common deer mouse, *Peromyscus maniculatus*.

Table 1. New World hantaviruses and their known reservoirs.

Virus	Reservoir	Location
Sin Nombre virus	<i>Peromyscus maniculatus</i>	USA
Monongahela virus	<i>Peromyscus maniculatus</i>	USA
New York virus	<i>Peromyscus leucopus</i>	USA
Bayou virus	<i>Oryzomys palustris</i>	USA
Black Creek Canal virus	<i>Sigmodon hispidus</i>	USA
Andes virus	<i>Oligoryzomys longicaudatus</i>	Argentina and Chile
Araraquara virus	<i>Necomys lasiurus</i>	Brazil
Laguna Negra virus	<i>Calomys laucha</i>	Paraguay
Choclo virus	<i>Oligorizomys fulvescens</i>	Panama



Emergence of Sin Nombre Virus (SNV)

In 1993, an SNV outbreak occurred in the Four Corners Region (FCR), characterized by severe pulmonary symptoms, primarily affecting young, previously healthy individuals.

The index case was a 19-year-old Navajo man who presented with acute respiratory distress, marked by significant pulmonary edema.

The patient's fiancée had recently died of a similar illness.

Five other similar cases in the region were reported, all with recent close contact with rodents.

The virus was isolated through blind passaging in deer mice, followed by subsequent passaging and adaptation in Vero E6 cells.

The isolated strain, designated NRM11, was obtained from deer mouse lung tissue.



Emergence of Sin Nombre Virus (SNV)

A nationwide call to report any cases led to the identification of a spectrum of New World hantaviruses (NWHVs) responsible for HPS in the U.S., including Bayou (Louisiana), Black Creek Canal (Florida), and New York-1 (NY).

Since 1993, the annual range of reported SNV cases in the U.S. has been 10-50, with approximately 850 cases reported across 39 states to date.

While the total number of cases remains low, the fatality rate is high, ranging from 30% to 60%.

Factors contributing to the prevalence of SNV include seasonal changes (e.g., in Chilean rice rats, infections are more common between spring and summer).

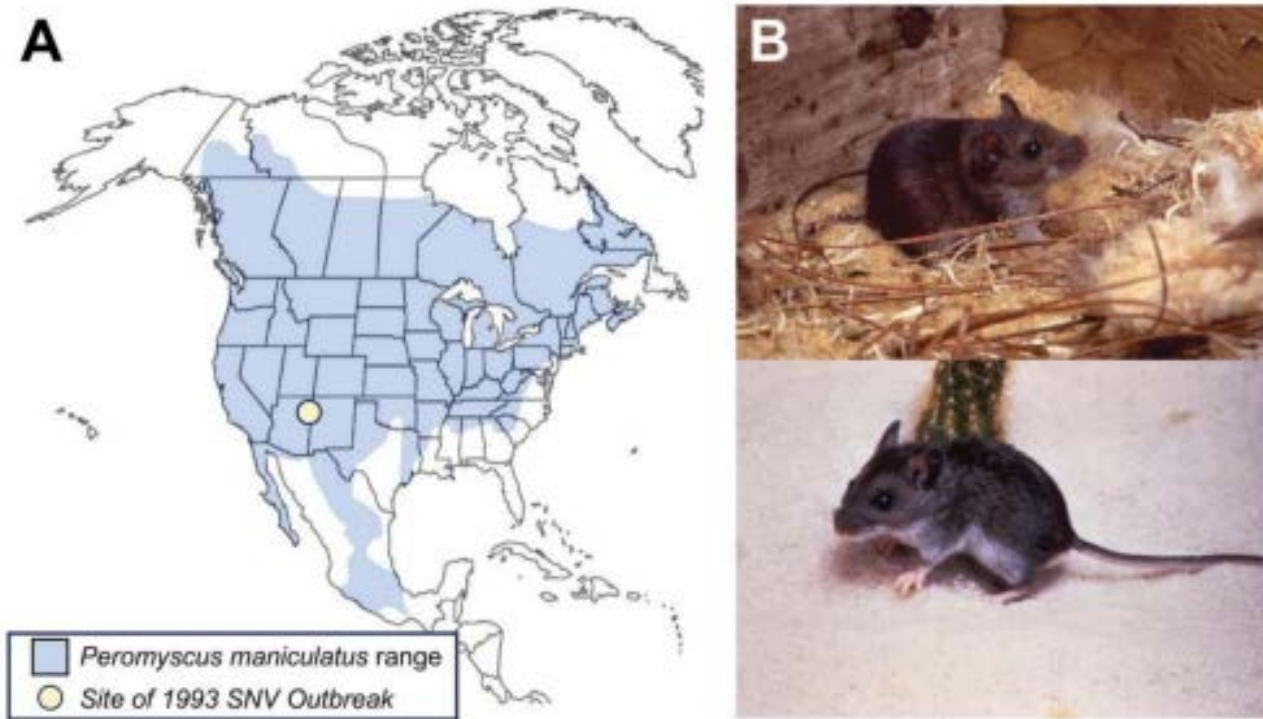
Human activities, such as agriculture, increase interactions with rodents.

In 2012, a small HPS outbreak occurred in Yosemite National Park, resulting in three deaths.

In June 2021, a case of SNV was reported in Michigan.

Transmission and ecology

Figure 1. Geographic range of the deer mouse (*Peromyscus maniculatus*).
(A) The geographic range of *P. maniculatus* in North America is shown in blue. A yellow dot marks the location of the 1993 SNV outbreak in the Four Corners region.
(B) Adult *P. maniculatus* mice (images courtesy of the CDC).



Virus structure and genome organization

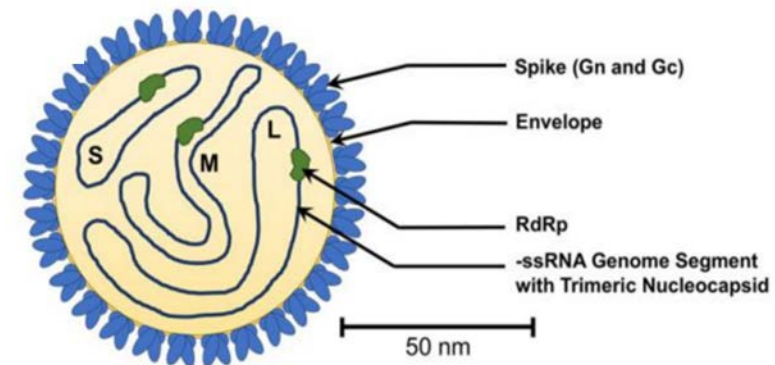
The virions are spherical or pleomorphic, with an envelope covered in spike proteins composed of the glycoproteins Gn and Gc.

The genome is single-stranded negative-sense RNA (-ssRNA) and consists of three segments:

- **S (2.06 kb):** Encodes the nucleocapsid protein.
- **M (3.70 kb):** Encodes a glycoprotein precursor that is processed into Gn and Gc.
- **L (6.56 kb):** Encodes the viral RNA-dependent

RNA polymerase (RdRp or L protein).

The nucleocapsid forms trimers that assemble into a helical structure, with a positively charged groove that binds the genomic RNA.



Orthohantavirus Sin Nombre Virus
12.3 kb -ssRNA Genome

Small (S) Segment – encodes viral nucleocapsid

3' — **N** — 5' (2.06 kb)

Medium (M) Segment – encodes glycoprotein precursor (Gn + Gc)

3' — **GPC** — 5' (3.70 kb)

Large (L) Segment – encodes viral RNA polymerase (RdRp)

3' — **RdRp** — 5' (6.56 kb)

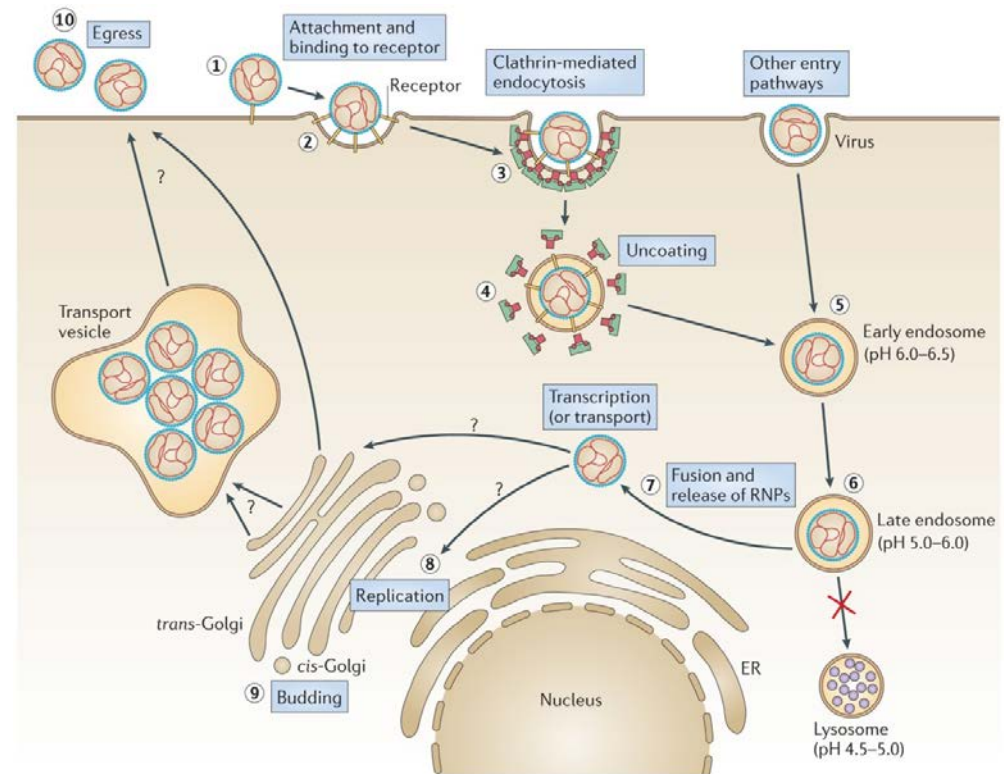
Virus entry

The virus enters endothelial cells using beta-3 integrin.

Old World hantaviruses (OWH) have been shown to utilize clathrin-coated vesicles for entry.

New World hantaviruses (NWH) enter through endocytic vesicles, and the acidification of the endosome induces a conformational change in Gc.

This change releases the fusion peptide, allowing for fusion with the host cell membrane and the release of the viral genomic RNA into the cytoplasm.



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Virus transcription

The three segments of the SNV genome are transcribed at different times post-infection.

N gene is the first to be transcribed at four hours post-infection (HPI) in Vero E6 cells.

The glycoprotein precursor (GPC) mRNA is detected around 32 HPI.

L protein is detected at 48 HPI.

Transcription relies on "prime and realign" strategy for at least some transcripts.

Cap snatching of host cytoplasmic transcripts occurs at cytoplasmic processing bodies.

GPC mRNA contains a poly(A) tail that is templated by eight uridine (U) residues.

In contrast, the N and L mRNAs lack a poly(A) tail, and a stem-loop structure may terminate their transcription.

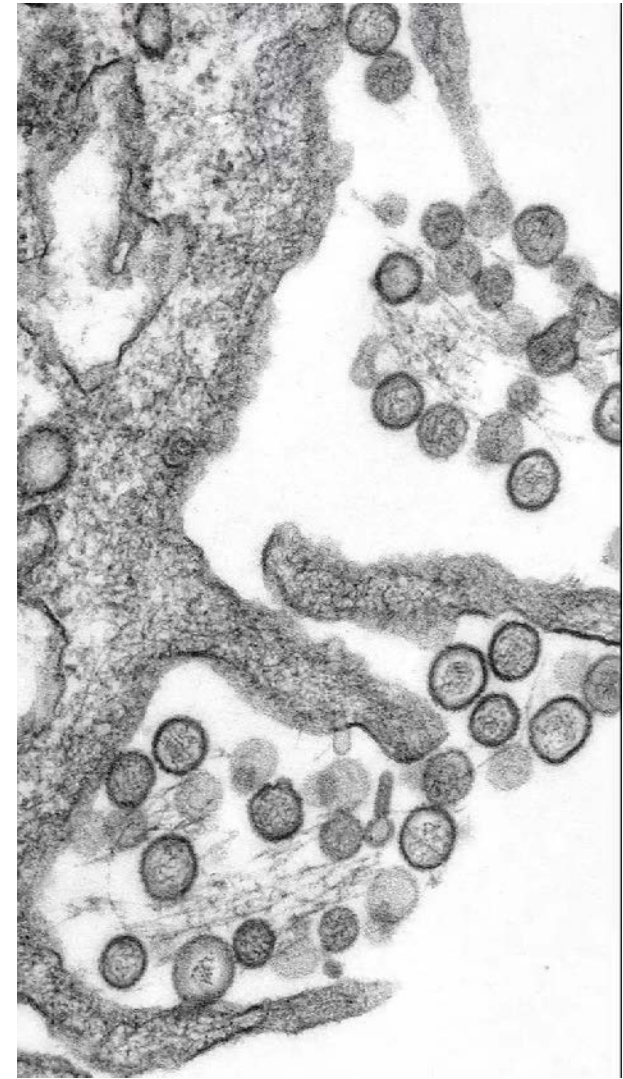
Virus particle formation

SNV has been observed to produce both granular and filamentous inclusion bodies in the cytoplasm of infected cells.

While Old World hantaviruses bud at intracytoplasmic membranes, such as the Golgi apparatus, SNV virions bud at the plasma membrane.

The virions of SNV are roughly spherical, with a diameter of approximately 112 nm, featuring a dense lipid envelope and closely spaced surface projections, averaging less than 10 nm each, along with filamentous nucleocapsids.

A study conducted in 2019 reported that the round particles had a diameter of 90 nm, while the tubular particles had a diameter of 85 nm and an average length of 180 nm. Both strains exhibited irregular morphologies, but there was a normal distribution of tubular and rounded particles.



Virus particle formation

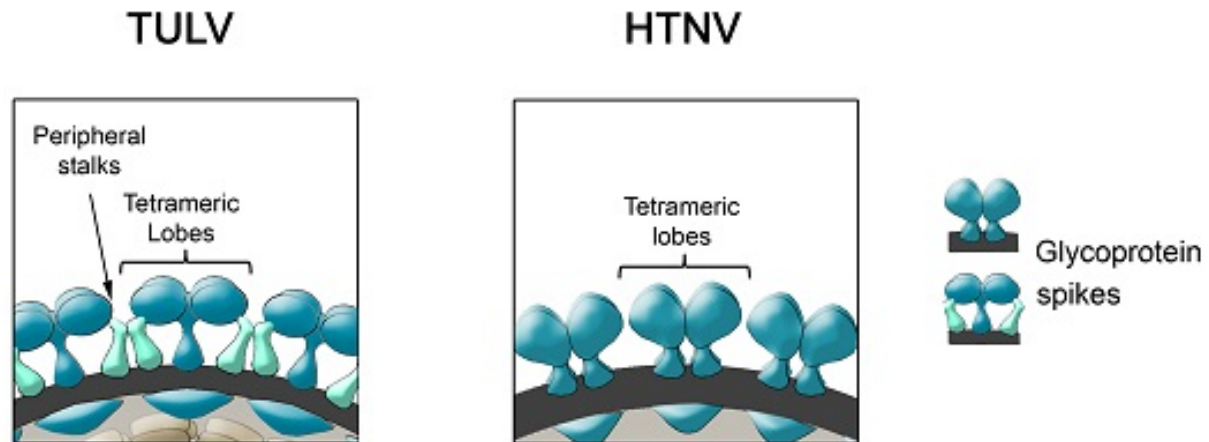
During SNV replication, the GPC protein is co-translationally cleaved in the endoplasmic reticulum by the host signal peptidase, resulting in an N-terminal fragment (Gn) and a C-terminal fragment (Gc).

The glycoproteins (Gn and Gc) arrange into a heterodimer, with Gn forming the stalk and Gc forming the globular head. These heterodimers then assemble into tetrameric spikes.

These spikes create a lattice that covers most of the virion surface, leaving only small areas of the membrane exposed.

The spike-to-spike interactions on the membrane may contribute to the curvature of the virion.

The spike glycoprotein is classified as a class II fusion protein.

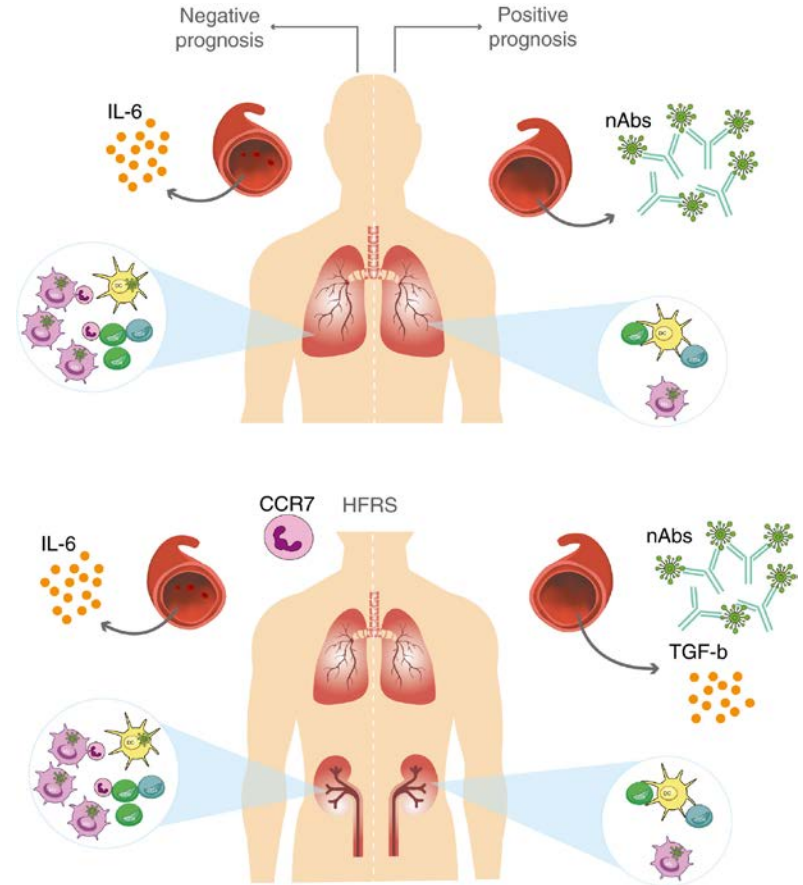


Evasion of innate immunity

NYV cytoplasmic tail of the Gn fragment has been shown to inhibit RIG-I- and TBK1-directed interferon responses by blocking the formation of TBK1-TRAF3 complexes.

This inhibition delays the innate immune response, allowing for virus replication and spread within the host.

Additionally, SNV Gn is degraded in the host cell through the host's autophagy machinery, which counteracts immune evasion and allows for the later induction of type I interferons.



Ecology of SNV

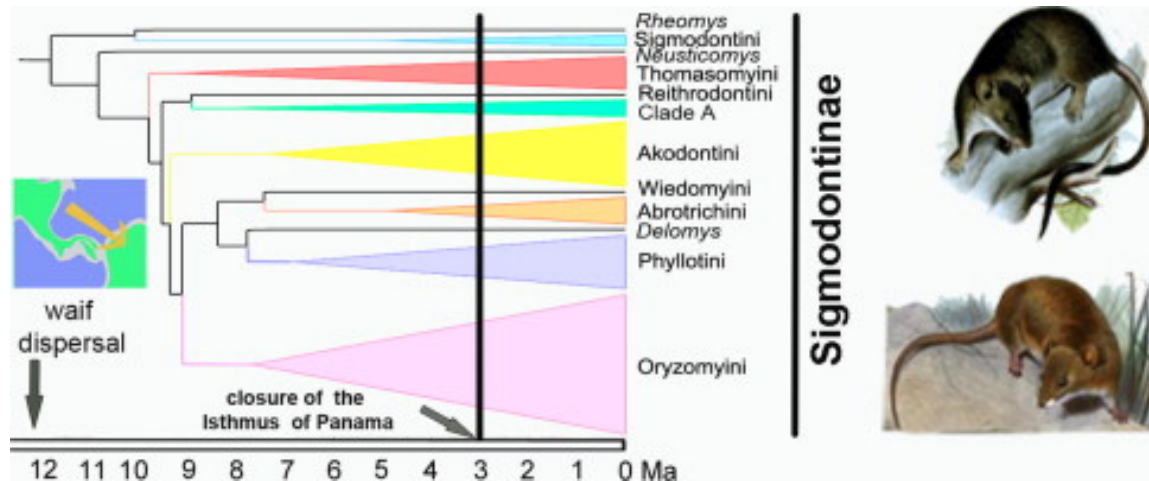
Members of the Hantaviridae family use arthropod vectors, hantaviruses typically infect rodents.

The Sigmodontinae subfamily is the largest group of rats and mice in the western hemisphere, and are the reservoirs for hantaviruses that cause HPS.

It is currently unclear why HPS-causing viruses exist solely in the Americas.

Peromyscus maniculatus (deer mouse) is the primary rodent host of Sin Nombre virus (SNV).

There is speculation that most, if not all, American rodents within the Sigmodontinae group will eventually be found to carry a characteristic hantavirus, many of which may cause a form of HPS.





Ecology of SNV

Most rodents are considered dead-end hosts for SNV replication.

A 1999 study demonstrated that woodrats (*Neotoma lepida*) are susceptible to SNV infection. The viral levels in the bloodstream of these and other dead-end hosts are low enough to mitigate concerns regarding transmission to other organisms.

Peromyscus maniculatus is primarily found in rural areas, with only a few cases reported in suburban regions. All cases have been associated with direct exposure to deer mouse urine, feces, and saliva.

Male deer mice exhibit higher seropositivity, and fluctuations in IgG antibody titers have been positively correlated with changes in their population.

Rates of seroconversion are highest during late summer and mid-winter, coinciding with the breeding season.

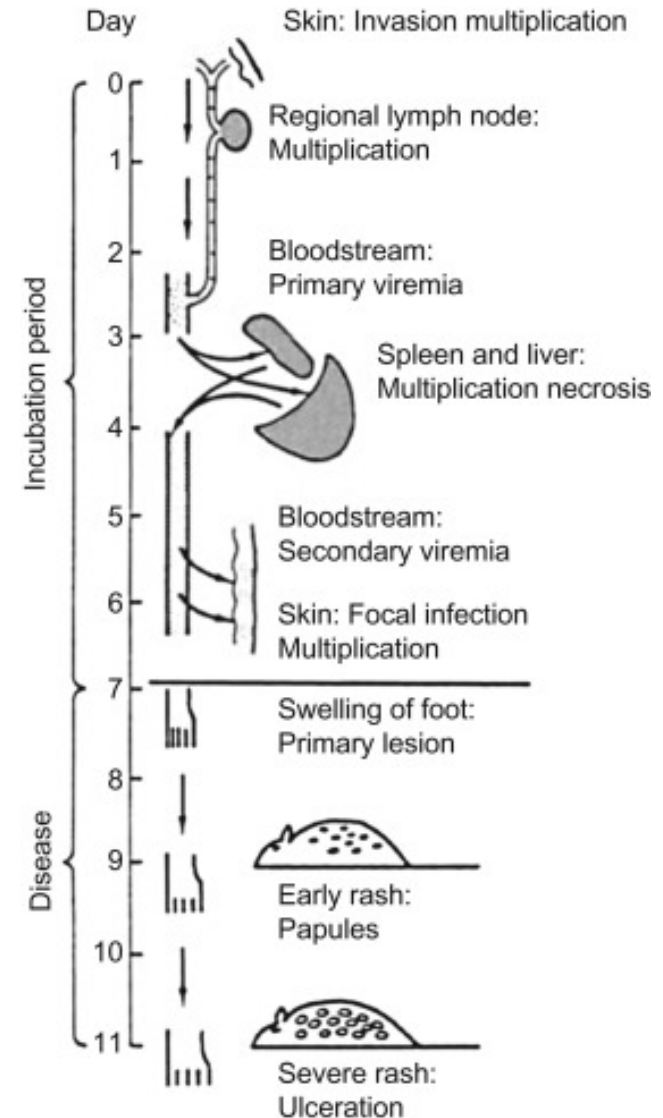
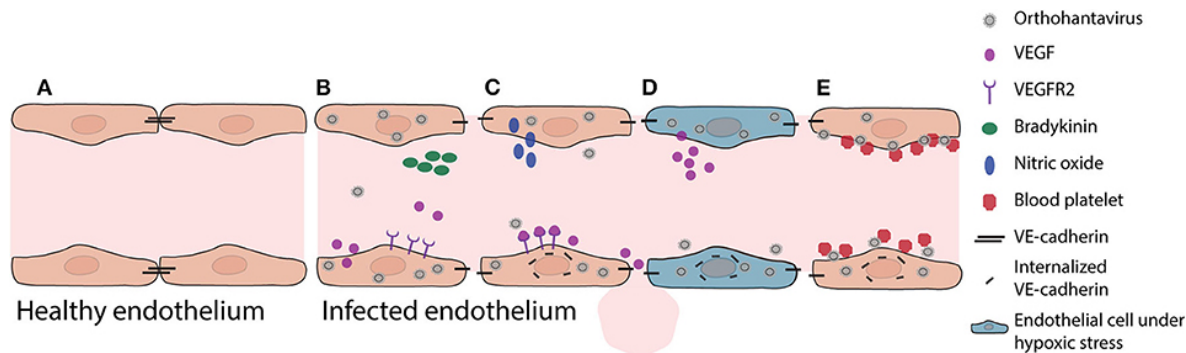
It remains unclear how climate change, shifts in human population centers, and agricultural practices impact the prevalence of deer mice and other hantavirus vectors.

Transmission of SNV

Sin Nombre virus (SNV) is transmitted among rodents, where it causes a persistent infection.

SNV has not been detected in the bloodstream; instead, it is found in endothelial cells in the lungs, heart, kidneys, and brain.

This finding suggests that the heart, lungs, and brown adipose tissue are the primary sites of SNV replication during persistent infection.





Transmission of SNV

Rodent-to-rodent transmission occurs through contact with bodily fluids, during confrontations between animals, or during grooming behaviors.

Rodent-to-human transmission can occur through bites or the aerosolization of virus particles found in urine, feces, and saliva, which can then be inhaled by humans, leading to infection of the terminal bronchioles or alveoli.

Shortly after this initial infection, significant viremia becomes detectable, resulting in a systemic infection of the pulmonary endothelia and, less frequently, other parts of the body.

As of now, human-to-human transmission has not yet been confirmed.



Clinical presentation and symptoms of HPS

Symptoms of Hantavirus Pulmonary Syndrome (HPS) typically onset within 1 to 8 weeks following exposure to the virus.

The prodromal period and initial disease presentation are characterized by fever, myalgia, headache, cough, nausea, vomiting, chills, and dizziness.

A report from the 1994 Four Corners outbreak indicated that all patients exhibited both fever and myalgia, along with an elevated respiratory rate (greater than 20 breaths per minute) at the time of admission.

The mean duration of symptoms prior to hospitalization during this outbreak was found to be 5.4 days.

HPS illness then rapidly progresses to pulmonary edema, hypoxemia, tachycardia, and hypotension within a 24 to 48-hour period, often coinciding with acute respiratory failure and interstitial edema.

In the Four Corners outbreak, the mean duration between the first onset of symptoms and death was 8 days, with a case fatality rate of 76%.

Clinical presentation and symptoms of HPS

Early hospitalization is crucial for maximizing survival and recovery chances.

Survivors of the Four Corners outbreak generally did not exhibit hypotension, while fatal cases showed severe hypotension (systolic blood pressure ≤ 85 mmHg).

Gastrointestinal symptoms can aid in differentiating Hantavirus Pulmonary Syndrome (HPS)-associated acute respiratory distress syndrome from other viral pneumonia

Table 2. Clinical presentation and symptoms of HPS.

Period of Disease	Symptoms
Prodromal	Fever
	Myalgia
	Headache
	Cough
	Nausea
	Vomiting
	Chills
	Dizziness
Disease Onset	Elevated Respiratory Rate
	Pulmonary Edema
	Hypoxemia
	Tachycardia
	Hypotension
	Acute Respiratory Failure
	Interstitial Edema



Clinical presentation and symptoms of HPS

Since the initial outbreak in 1993, there have been over 700 cases of Hantavirus Pulmonary Syndrome (HPS) reported to date.

Although the mortality rate remains high at 38%, Sin Nombre virus (SNV) does not always lead to severe disease, and there have been reports of asymptomatic cases of HPS.

Patients with SNV who do not develop serious illness may experience fatigue, myalgia, and shortness of breath.

These symptoms could result from an overactive immune response or potentially harmful therapies administered in the hospital.

Some follow-up studies on survivors of SNV infection have shown decreased airflow in small airways, increased residual lung volume, and reduced capacity for oxygen diffusion.

Detection and diagnosis

A combination of a positive serological test result, the identification of viral antigens in histological samples, or amplifiable viral RNA in either blood or tissue—along with a compatible history of Hantavirus Pulmonary Syndrome (HPS)—is diagnostic for HPS according to the CDC.

The sera of patients can retain hantavirus-specific antibodies for years. Serological studies indicate that subclinical or inapparent infections with the virus are rare.

Antiserum is utilized in Western blot analyses

Table 3. Diagnostic options for treating HPS.

Diagnostic Method	Description
Serological Testing/ELISA	Detection of IgM antibodies specific to hantavirus; a four-fold rise in IgG antibody is considered diagnostic for hantavirus disease.
Immunohistochemical and Western Blot	Positive detection of viral antigen in histological samples; detection of hantaviral antigens by Western blot using hantavirus-specific antisera.

ELISA, Enzyme-linked immunosorbent assay; Ig, Immunoglobulin.

Therapeutic options for HPS

Treatment options for HPS are limited if not initiated prior to the onset of viremia.

Supportive care in an ICU with close monitoring is essential.

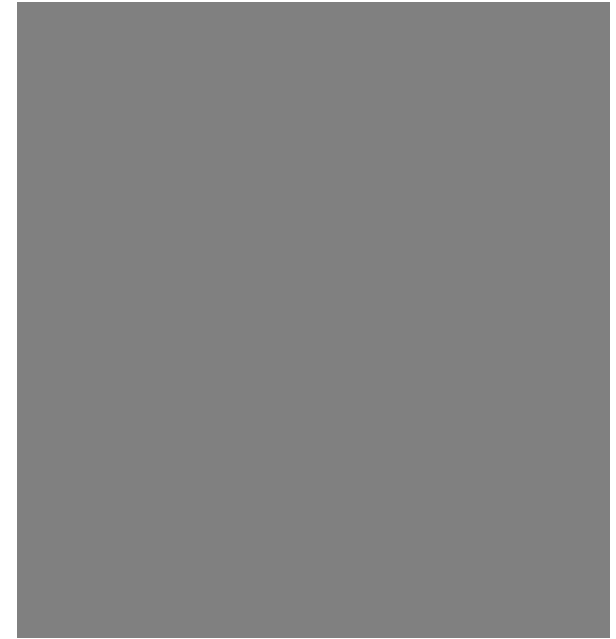
Supplemental oxygen should be provided for hypoxia as the disease progresses into the cardiopulmonary phase.

It is important not to administer excessive fluids due to the impacts of HPS on endothelial integrity and potential edema.

Ribavirin has shown protective effects against lethality and can reduce disease severity, even after prolonged periods of ANDV infection.

However, emergency use during the Four Corners outbreak found no significant benefit.

Once the disease progresses beyond the initial prodromal period and enters the cardiopulmonary phase, Ribavirin becomes ineffective.



Ribavirin

Broad-spectrum antiviral drug with activity against several RNA and some DNA viruses.

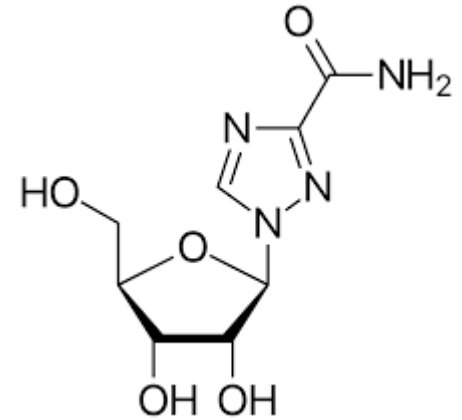
It is a nucleoside analog that interferes with viral replication through multiple mechanisms.

Ribavirin has shown protective effects against lethality and can reduce disease severity, even after prolonged periods of ANDV infection.

However, emergency use during the Four Corners outbreak found no significant benefit.

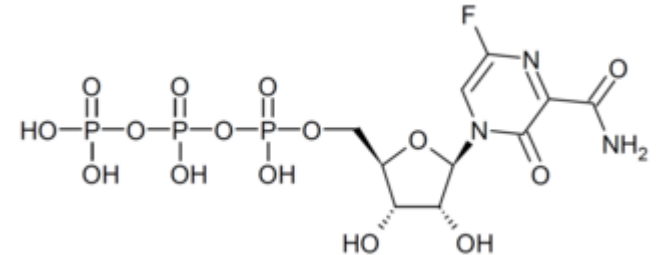
Once the disease progresses beyond the initial prodromal period and enters the cardiopulmonary phase, Ribavirin becomes ineffective.

- Used in:
 - Chronic Hepatitis C Virus (HCV)
- Respiratory Syncytial Virus (RSV)
- Lassa Fever and Other Viral Hemorrhagic Fevers
- Arenaviruses and Bunyaviruses



Therapeutic options for HPS

Favipiravir (also known as T-705) is an antiviral drug that works by inhibiting viral RNA-dependent RNA polymerase (RdRp)—an enzyme essential for the replication of many RNA viruses



Favipiravir has shown efficacy against SNV reducing the detection of RNA in blood and antigens in the lungs.

It has also been effective against ANDV, offering protection against lethality and reducing RNA levels in blood and lung antigens.

However, it is ineffective once viremia has begun.

Also used for:

- Influenza viruses
- Ebola virus (experimental)
- SARS-CoV-2 (investigational)



Therapeutic options for HPS

Vandetanib was initially explored as a treatment for HPS due to the increased endothelial permeability and edema associated with the disease.

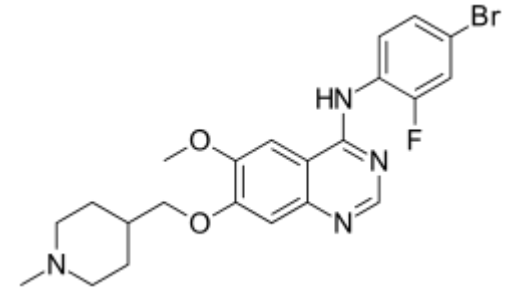
Is an oral tyrosine kinase inhibitor (TKI) used primarily in the treatment of certain types of thyroid cancer.

Has shown *in vitro* antiviral activity against some viruses by targeting host pathways rather than viral enzymes.

Inhibition of virus-induced cellular signaling through EGFR inhibition, which some viruses (e.g., coronaviruses, herpesviruses) use to facilitate entry or replication.

Inhibition of virus-induced cellular signaling through RET and VEGFR pathway interference, possibly affecting virus-induced angiogenesis and inflammation.

Pretreatment with Vandetanib has been shown to delay lethality and increase survival rates.



Therapeutic options for HPS

Methylprednisolone may help limit the proinflammatory response associated with hantavirus infection.

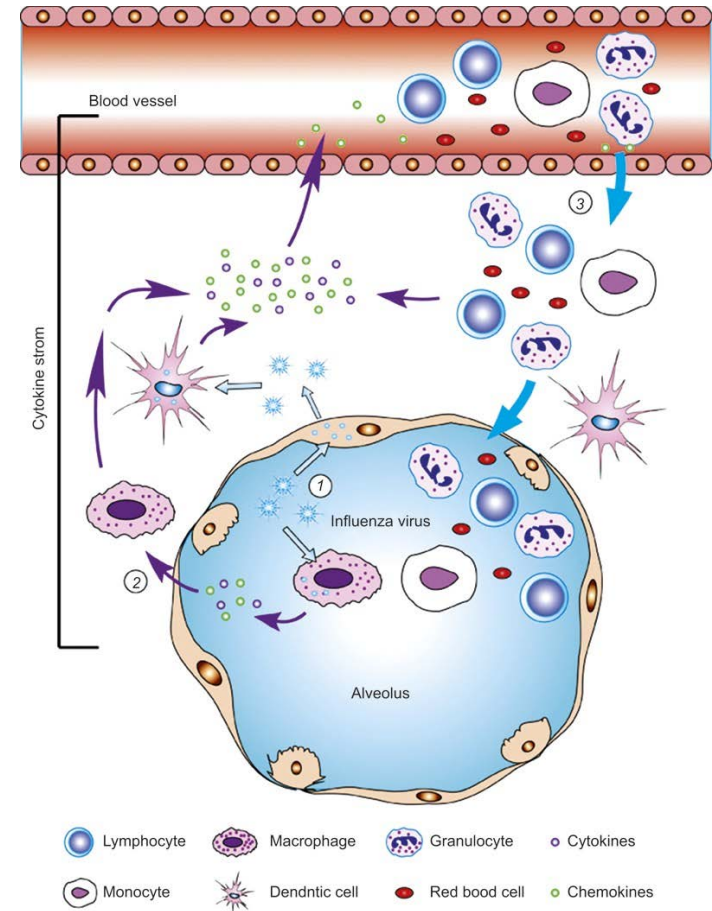
Synthetic corticosteroid (glucocorticoid) with potent anti-inflammatory and immunosuppressive properties.

For severe or critical COVID-19 (patients needing oxygen or mechanical ventilation) as it reduces cytokine storm and lung inflammation.

Herpesvirus Infections (e.g., VZV, HSV, EBV) in severe CNS infections (e.g., herpes encephalitis or VZV-related vasculitis), reduces inflammation and edema.

Viral Myocarditis where it suppresses harmful immune-mediated myocardial damage.

It can worsen viral infections if used inappropriately or too early (e.g., during viremia).





Inmunotherapy

Both natural infections and immunizations can induce protective neutralizing antibodies.

Efforts to map the antigenic sites on the binding glycoproteins of Sin Nombre virus (SNV) and the Andes virus have been successful.

These advancements are contributing to the development of prophylactic treatment options.



Hantavirus vaccine development

There are currently no approved vaccines for hantaviruses, and commercial development is unlikely due to the low incidence of Hantavirus Pulmonary Syndrome (HPS).

A viral vector employing a vesicular stomatitis virus backbone expresses the glycoprotein precursor (GPC) of the Sin Nombre virus and the GPC of the Andes virus (ANDV). This approach induces cross-reactive antibody responses and provides protection against lethal challenges in an ANDV model.

Deer mice showed reduced viral RNA in both the blood and lungs, along with decreased transmission.

It may be possible to immunize wild vectors through a baiting strategy.

Prevention of HPS

Avoid or minimize contact with rodents.

Seal any holes or entry points to prevent their entry and hiding spots.

Maintain a clean habitat, ensuring it is free of food and potential nesting materials.

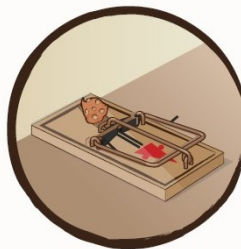
Set traps in areas where signs of rodent infestation are present.

You Can Prevent Hantavirus

**How to Protect Yourself and Your Family
from **Hantavirus Pulmonary Syndrome**
in the United States**



SEAL UP!



TRAP UP!



CLEAN UP!





Discussion and future outlook

Globally, there is an increasing incidence of emerging viral pathogens.

As of the end of 2021, the CDC reported a total of 850 cases of hantavirus pulmonary syndrome (HPS) in the USA since 1993.

It remains unclear how climate change and demographic shifts—such as the ongoing migration from rural to urban settings—will affect rodent populations and the potential for virus transmission to humans.

Awareness of hantaviruses and their associated diseases is low among people living within the geographic ranges of these pathogens.

Antigenic similarities between SNV and ANDV might allow recombination among New World hantaviruses following co-infection events.

The availability of rodent models for studying infections of both SNV and ANDV has been instrumental in understanding pathogenesis within these vectors and evaluating potential therapeutics and vaccines to mitigate disease.



Conclusions

Sin Nombre virus (SNV) and other New World hantaviruses have the potential to cause severe disease.

Since their transmission occurs through different rodent vectors, it remains unclear how changes in human demographics and climate change will impact viral abundance and exposure events in the future.

While our understanding of hantaviruses has significantly expanded over the past few decades, further research is needed to better understand the biology, ecology, and pathogenesis of these viruses.

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