

# Hantavirus: Past and Future

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**Abstract:** *Hantaviruses have been known to exist for over 40 years, Hantavirus is cause of the hemorrhagic fever and renal syndrome. Hantavirus was first recognized as an infectious disease in the early 1950s when a cluster of 3000 United Nation troops stationed in Korea was struck by a mysterious illness. Many genomes, proteins play different roles in Hantaviruses such as genomic RNAs also receptors that is Clq receptor (gClqR) or G1 and G2 glycoproteins. Previous studies show that individuals suffering from Hantavirus pulmonary syndrome disease. In recent years, there are no US FDA – approved vaccines against Hantaviruses. China and South Korea, in both countries, the use of vaccines, combined have been researched; DNA vaccines targeting the genome segment, subunit vaccines that use recombinant Gn, Gc and N protein of virus. Virus like particle vaccines that contain viral protein but lack genetic material. These, only DNA vaccines have entered into clinical trials. Our aim this review is to display Past and Future Hantavirus, and effect of Hantavirus Pulmonary Syndrome.*

**Keywords:** Hantavirus, Rodent reservoirs, Hemorrhagic fever, Renal syndrome

Contribution / Originality: This study is of very different studies which have consideration for genetical treatment of Hantavirus. This contributes information about changes in Hantavirus life cycle which open new aspects for further research work.

## 1. Introduction

Hantavirus are a family of viruses spread mainly by rodents and can cause varied disease syndromes in people worldwide. Infection with any Hantavirus can produce Hantavirus disease in people. [1] Hantaviruses in the Americas are known as “NEW WORLD” Hantaviruses and may cause Hantavirus pulmonary syndrome (HPS). Other Hantaviruses, known as “OLD WORLD” Hantaviruses, are found mostly in Europe and Asia and may cause hemorrhagic fever with renal syndrome (HFRS).

Each Hantavirus serotype has a specific rodent host species and is spread to people via aerosolized virus that is shed in urine, waste matter and Saliva, and less frequently by a bite from an infected host. The most important Hantavirus in the United States that can cause HPS is the Sin Nombre virus, spread by the deer mouse. Hantavirus pulmonary syndrome (HPS) is a Severe, sometimes deadly, respiratory disease in humans caused by infection with Hantaviruses. cases of human Hantavirus infection occur isolated, usually in rural areas where forests, fields and farms offer suitable habitat for the virus’s rodent hosts. Areas around the home or work where rodents may live for example houses, outbuildings and sheds are potential sites where people may be exposed to the virus. In the US and Canada, the Sin Nombre Hantavirus is responsible for the majority of cases of Hantavirus infection. The host of the Sin Nombre virus is the deer mouse (*peromyscusmaniculatus*), present through the Western and central US and Canada. [2, 3]

Several other Hantaviruses are capable of causing Hantavirus infection in the US. The New York Hantavirus, carried by the white footed mouse, is associated with HPS cases in northeastern in US. The Black Creek Hantavirus, carried by the cotton rat, is found in the southeastern US. Cases of HPS have been confirmed to a different place in the Americas, including Canada Argentina, Bolivia, Brazil, Panama, and Uruguay.

The Hantaviruses that cause human illness in the United States are not known to be transmitted by any types of

animals other than certain species of rodents. Dogs and cats are not known to carry Hantavirus; however, they may bring infected rodents in to a contact with people if they catch such animals and carry them home. [4]

In the United States, deer mice (along with cotton rats and rice rats in the southeastern states and the white footed mouse in the Northeast are reservoirs of the Hantaviruses. The rodents shed the virus in their urine, droppings, and saliva. The virus is mainly transmitted to people when they breath in air contaminated with the virus. When fresh rodent urine, droppings or existing materials are mixed up, tiny droplets containing the virus get into the air. This process is known as “airborne transmission” [5].

The Hantavirus that cause human illness in the United states cannot be transmitted from one person to another person.

### Early symptoms

Early symptoms include fatigue, fever and muscle aches, especially in the large muscle groups – thighs, hips, back, and sometimes shoulders. These symptoms are universal. There may also be headaches, dizziness, and abdominal problems, such as nausea, vomiting, diarrhea.

### Late symptoms

Four to 10 days after the initial phase of illness, the late symptoms of HPS appear. These include coughing and shortness of breath, with the sensation. HPS can be fatal. It has a mortality rate of 38percent. [6]

### Diagnosing HPS

Diagnosing HPS in an individual who has only been infected a few days is difficult, because early symptoms such as fever, muscle aches, and fatigue are easily confused with influenza. However, if the individual is experiencing fever and fatigue and has a history of potential rural rodent exposure, together with shortness of breath, would be strongly suggestive of HPS. If the individuals are experiencing these symptoms they should see their physician immediately and mention their potential rodent exposure.

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## 2. Treating HPS

There is no specific treatment, cure, or vaccine for Hantavirus infection. However, we do know that if infected individuals are recognized early and receive medical care in an intensive care unit, they may do better. In intensive care, patients are given oxygen therapy to help them through the period of severe respiratory distress. [7]

The earlier the patient is brought in to intensive care, the better. If patient is experiencing full distress, it is less likely the treatment will be effective. [8]

Hemorrhagic fever with renal syndrome (HFRS) is a group of clinically similar illness caused by Hantavirus from the family Bunyaviridae. HFRS includes diseases such as Korean hemorrhagic fever, and nephropathia epidemica. The viruses that cause HFRS include Hantaan, Dobrava, Saaremaa, Seoul, and puumala. [9]

HFRS is found throughout the world. Hantaan virus is widely distributed in eastern Asia, particularly in China, Russia, and Korea. Puumala virus is found in Scandinavia, Western Europe, and western Russia. [10]

Hantaviruses are carried and transmitted by rodents. People can become infected with these viruses and develop HFRS after exposure to aerosolized urine, droppings, or saliva of infected rodents or after exposure to dust from their nests. Transmission may also occur when infected urine or these other materials are directly introduced into broken skin or onto the mucous membranes of the eyes, nose, or mouth. In addition, individuals who work with live rodents can be exposed to Hantaviruses through rodent's bites from infected animals. Transmission from one human to another may occur, but is extremely rare. [11]

Rodents are the natural reservoir for Hantaviruses. Known carriers include the striped field mouse the reservoir for both the Saaremaa and Hantaan virus; the brown or Norway rat the reservoir for Seoul virus; the bank vole, the reservoir for Puumala virus; and the yellow necked field mouse which carries Dobrava virus develop within 1 to 2 weeks after exposure to infectious material, but in rare cases, they may take up to 8 weeks to develop [12]. Initial symptoms begin suddenly and include intense headache, back and abdominal pain, fever, chills, nausea and blurred vision. Individuals may have flushing of the face, inflammation or redness of the eyes, or a rash. Later symptoms can include low blood pressure, acute shock, vascular leakage, and acute kidney failure, which can cause severe fluid overload. The severity of the disease varies depending upon the virus causing the infection. Hantaan and Dobrava virus infection usually cause severe symptoms. [13]

Several laboratory tests are used to confirm a diagnosis of HFRS in patients with a clinical history compatible with the disease. Such patients are determined to have HFRS if they have serologic test results positive for Hantavirus infection, evidence of Hantavirus antigen in tissue staining and microscope examination, or evidence of Hantavirus RNA sequences in blood or tissue. [14]

Supportive therapy is the mainstay of care for patients with Hantavirus infections. Care includes careful management of the patient's fluid (hydration) and electrolyte (e.g. sodium, potassium, chloride) levels, maintenance of correct oxygen and blood pressure levels, and appropriate treatment of any secondary infections. Dialysis may be required to correct severe fluid overload. Intravenous ribavirin an antiviral drug, has been shown decrease illness and death associated with HFRS if used very early in the disease. Depending upon which virus is causing the HFRS, death occurs in less than 1 % to as many as 15 % of patients. Fatality ranges from 5-15% for HFRS caused by Hantaan virus, and it is less than 1% for disease caused by puumala virus. [15, 16] Rodent control is the primary strategy for preventing Hantavirus infections. Rodent populations near human communities should be controlled, and rodents should be excluded from homes. Individuals should avoid contact with rodent urine, droppings, saliva, and waste material and the safety measures described below should be followed when cleaning rodent infested areas. [17]

## 3. Outbreak

### Outbreak History (The First Outbreak)

In May 1993, an outbreak of an unexplained pulmonary illness occurred in the southwestern United States, in an area shared by Arizona, New Mexico, Colorado and Utah known as "The Four Corners". A young, physically fit Navajo man suffering from shortness of breath was rushed to a hospital in New Mexico and died very rapidly [18]. While reviewing the results of the case, medical personnel discovered that the young man's fiancée had died a few days before after showing similar symptoms, a piece of information that proved key to discovering the disease.

Hantaviruses are a family of viruses spread mainly by rodents and can cause varied disease syndromes in people worldwide. Infection with any Hantavirus can produce Hantavirus disease in people. Hantaviruses in the Americas are known as "New World" and may cause Hantavirus pulmonary syndrome (HPS). Other Hantaviruses, known as "Old World" Hantaviruses are found mostly in Europe and Asia and may cause hemorrhagic fever with renal syndrome (HFRS).

Each Hantavirus serotype has a specific rodent host species and is spread to people via aerosolized virus that is shed in urine, feces and saliva, and less frequently by a bite from an infected host. The most important Hantavirus in the United States that can cause HPS is the *Sin Nombre* Virus, spread by the deer mouse. Hantaviruses are enzootic viruses that maintain persistent infections in their rodent hosts without apparent disease symptoms. The spillover of these viruses to humans can lead to one of two serious illnesses, Hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome. In recent years, there has been an improved understanding of the epidemiology; pathogenesis and natural history of these viruses following an increase in the number of outbreaks in the Americas. In this review, current concepts regarding the ecology of and disease associated with these serious human pathogens are presented. [19, 20]

In the past century, two major outbreak of disease led to discovery of Hantaviruses in the Old and New Worlds. The first outbreak occurred during the Korean War (1950 to 1953), wherein more than 3, 000 United Nations troops fell ill with Korean hemorrhagic fever with Renal syndrome (HFRS). [21] The second outbreak of disease occurred in the Four Corners region of the United states in 1993 and was initially referred to as Four Corners disease, which is now called Hantavirus pulmonary syndrome (HPS) or Hantavirus cardiopulmonary syndrome (HCPS). These viruses can cause serious disease in humans and have reached mortality rates of 12% (HFRS) and 60% (HPS) in some outbreaks. In 1978, nearly 25 years after the recognition of HFRS, the etiological agent for this disease, Hantaan virus (HTNV), and its reservoir, the striped field mouse (*Apodemusagrarius*), This landmark study launched the recognition of additional HFRS – related viruses in Asia, Europe and the United states.

Surveillance efforts showed the presence of HTNV and HTNV – like viruses in *Apodemusagrarius* and *A. peninsulae* rodents in Far East Russia, China and South Korea and distinct virus, Dobrava virus (DOBV), and Dobrava –like viruses harbored by *Apodemusflavicollis*, *A. agrarius*, and *A. ponticus* in Europe. In the 1980s, it was discovered that urban cases of HFRS were caused by the rat – borne Seoul virus (SEOV) in Asia and in Europe, nephropathiaepidemic (NE), which is a milder form of HFRS described in the 1930s, was discovered to be caused by another Hantavirus, *puumala* virus (PUUV), harbored by

the bank vole, *Myodesglareolus* (previously known as *clethrionomysglareolus*). The discovery of these Hantaviruses has led to the appreciation that worldwide, there may be many as 150, 000 cases of HFRS each year, with more than half occurring in China.

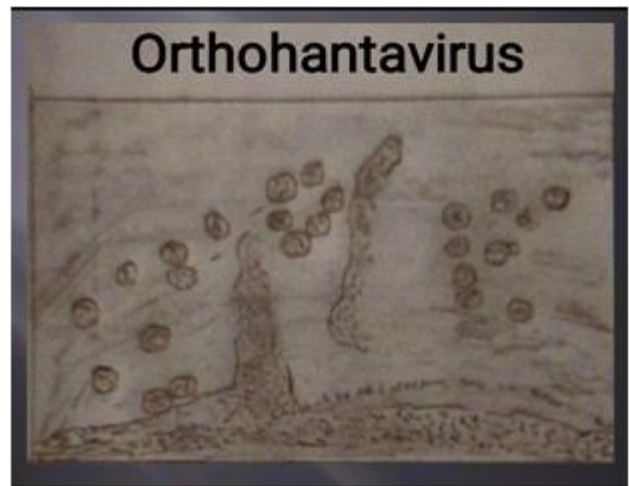
In contrast to these early pioneering efforts that led to the discovery of HTNV, the etiological agent of HPS, *Sin Nombre* virus (SNV) was identified within weeks of the Four Corners outbreak.

Technological advancements in molecular biology contributed largely to the ability of investigators to rapidly isolate and characterize this newly discovered virus. However, it was the weak cross – reactivity of human sera with the antigen from an Old world Hantavirus that provided the first clue due to the possible causative agent of HPS. Since the Four Corners outbreak, more than 2000 cases of HPS have occurred in sporadic clusters throughout the Americas and have led to the discovery of many different strains of these viruses and their rodent reservoirs. At present, over 21 Hantaviruses that cause illness in humans ranging from protein urea to pulmonary edema and frank hemorrhage illness when transmitted from their rodent reservoirs to humans have been identified across the globe. Additional Hantaviruses may remain undiscovered, since in many countries, Hantavirus infections are likely to go undetected and not reported, especially in Africa, the Middle East, and the Indian subcontinent. [22, 23]

**Table 1:** Information related to Group, subfamily, Geographic distribution and Associated disease.

Group and Subfamily	Virus isolate or strain	Abbreviation	Geographic distribution	Rodent host	Associated disease
Old world Murinae	Hantaan virus	HTNV	China, South Korea	<i>Apodemusagrarius</i>	HFRS
	Dobrava-Belgrade virus	DOBV	Balkans	<i>Apodemusflavicollis</i>	HFRS
	Seoul virus	SEOV	Worldwide	<i>Rattus</i>	HFRS
	Saaremma virus	SAAV	Europe	<i>Appodemusagrarius</i>	HFRS
	Amur virus	AMRV	Far East Russia	<i>Apodemuspeninsulae</i>	HFRS
	Soochong virus	-	South Korea	<i>Apodemuspeninsulae</i>	Unknown
Arvicolinae	Puumala virus	PUUV	Europe, Asia, and Americas	<i>Clethrionomysglareolus</i>	HFRS
	Khabarovsk virus	KHAV	Far East Russia	<i>Microtus fortis</i>	Unknown

This is especially evident with the discovery of shrew-borne Hantaviruses around the globe. Until these seminal discoveries, Thottapalayam virus (TPMV), a long unclassified virus isolated from the Asian house shrew (*suncusmurinus*), was the only known shrew – borne Hantavirus. Clearly, these and other Hantaviruses deserve the attention of research scientists and public health officials with respect to their impact on public health and the quest for treatments and to promote public awareness of those Hantaviruses that cause illness in humans. Here, we present a review of these fascinating viruses, with our major focus being on the ecology of and disease caused by these serious human pathogens.



**Figure 1:** OrthoHantavirus

Figure 1 OrthoHantavirus is a genus of single stranded, enveloped, negative sense RNA viruses in the family Hantaviridae of the order *Bunyvirales*. Member of these genus may be called orthoHantaviruses or simply

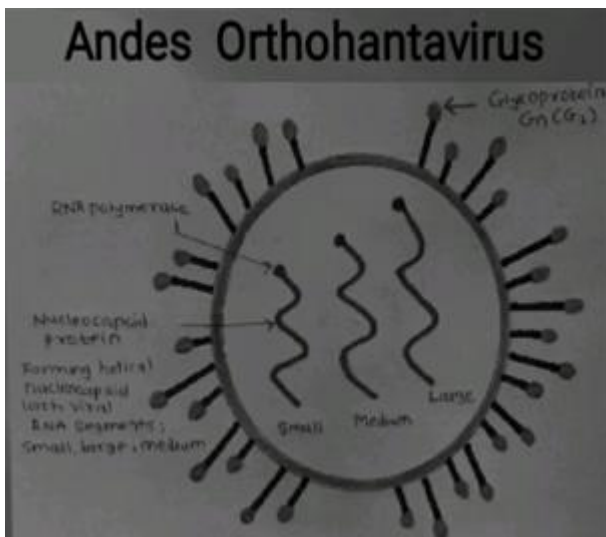
Hantaviruses. They normally cause infection in rodents, but do not cause disease in them. Humans may become infected with Hantaviruses through contact with rodent urine, saliva or waste material. Some stains cause potentially fatal diseases in human, such as Hantavirus hemorrhagic fever with renal syndrome (HFRS) or Hantavirus pulmonary syndrome (HPS), while others have not been associated with known human disease. HPS is a respiratory illness associated with the inhalation of aerosolized rodent excreta (urine and waste material) contaminated by Hantavirus particles.

**Table 2:** Composition of the Rank and Virus

Virus
Classification

**RANKVIRUS**

Realm	Riboviria
Kingdom	Orthornavirae
Phylum	Negarnaviricota
Class	Ellioviricetes
Order	Bunyavirales
Family	Hantaviridae
Subfamily	Mammantavirinae
Genus	OrthoHantavirus



**Figure 2:** Andes Hantavirus

Figure 2 Human infections of Hantaviruses have almost entirely been linked to human contact with rodent excrement however human to human transmission of the Andes virus was reported in South America.

**4. Taxonomy**

OrthoHantaviruses belong to the Hantaviridi family and members of both the family and of the genus are called Hantaviruses. The genus also belongs to the subfamily Mammantavirinae, the mammalian Hantaviruses, with three other genera OrthoHantaviruses specifically are mammalian Hantaviruses that are transmitted among rodents. The genus has 36 recognized species as of 2019. The type species of the genus is the Hantaanorthohantavirus.

**5. Characteristics**

**Structure**

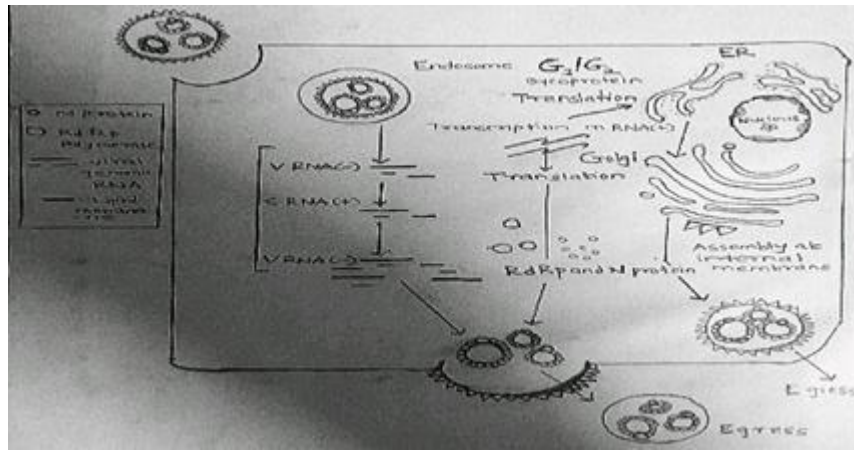
Hantavirus virions are about 120 -160 nanometers (nm) in diameter. The lipid double layer of the viral envelope is about 5nm thick and is embedded with viral surface proteins to which sugar residues are attached. These Glycoproteins known as Gn and Gc are encoded by the M segment of the viral genome. They tend to associate with each other and have both an interior tail and the exterior domain that extends to about 6nm beyond the envelope surface. Inside the envelope are the nucleocapsids. These are composed of many copies of the nucleocapsid protein N, which interact with three segments of the genome to form helical structure. [88] The virally encoded RNA polymerase also found in interior. The density of the virions is 1.18 gram per cubic centimeter. These features are common to all members of the Hantaviridae family.

**Genome**

The genome of Hantaviruses is negative –sense, single-stranded RNA. Their genomes are composed of three segments: the small (S), medium (M), large (L) segments. [90] The genomic RNAs of Hantaviruses are thought to complex with N protein to form helical nucleocapsids, the RNA component of which circularize due to sequence complementarity between the 5’ and 3’ terminal sequences of genomic segments. No non structural proteins are known, unlike the other genera in this family. At the 5’and 3’ of each segment are short non coding segment in all sequences at the 5’ end is 37-51 nucleotides. The 3’ non coding regions differ: L segment 38-43 nucleotides; M segment 168-229 nucleotides; and S segment 370-730 nucleotide. The 3’ end of the S segment is conserved between the genera suggesting a functional role.

The G1 (or Gn) and G2 (Gc) glycoproteins from hetero-oligomers and are then transported from the endoplasmic reticulum to the Golgi complex where glycolysation is completed. The L protein produces nascent genomes by replication via a positive – sense RNA intermediate. Hantavirus virions are believed to assemble by association of nucleocapsids with glycoproteins embedded in membrane and released by exocytosis.





**Figure 3:** Life cycle of Hantavirus

Figure. 3. Viral entry into host cells initiates by binding to surface cell receptors. Integrins are main receptors for Hantaviruses in vitro but complement decay accelerating factor (DAF) and globular heads of complement C1q receptor (gC1qR) have mediated attachment in cultured cells too. Entry may proceed through a number of possible routes, including clathrin-dependent endocytosis, clathrin-independent receptor mediated endocytosis, and micropinocytosis. Viral particles are then transported to late endosomes. Gc-mediated membrane, triggered by low pH, releases the nucleocapsid into the cytoplasm. After the release of the nucleocapsid in to cytoplasm, the complexes are targeted to the ER-Golgi Intermediate compartments (ERGIC) through microtubular associated movement resulting in the formation of viral factories at ERGIC.

These factories then facilitate transcription and subsequent translation of the viral proteins. Transcription of viral genes must be initiated by association of the viral proteins. Transcription of viral genes must be initiated by association of the L protein with the three nucleocapsid species. In addition to transcriptase and replicase functions, the viral L protein is also thought to have an endonuclease activity that cleaves cellular messenger RNAs (mRNAs) for the production of capped primers used to initiate transcription of viral mRNAs. As a result of this cap snatching, the mRNAs of Hantaviruses are capped and contain non template 5'-terminal extensions.

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### Pathogenesis

The pathogenesis of Hantavirus infection is unclear as there is a lack of animal models to describe it (rats and mice do not seem to acquire severe disease). While the primary site of viral replication in the body is not known, in HFRS the main effect is in the blood vessels while in HPS most symptoms are associated with the lungs. In HFRS, there are increased vascular permeability and decreased blood pressure due to

endothelial dysfunction and the most dramatic damage is seen in the kidneys, whereas in HPS, the lungs, spleen, and gall bladder are most affected. Early symptoms of HPS tend to present similarly to the flu (muscle aches, fever and fatigue) and usually appear around 2 to 3 weeks after exposure. Later stages of the disease (about 4 to 10 days after symptoms start) include difficulty breathing, shortness of breath and coughing.

### 6. Evolution

Findings of significant compatibility between genetic of Hantaviruses and genetic of their rodent reservoirs have led to the theory that rodents, although infected by the virus, are not harmed by it because of long -standing Hantavirus rodent host co-evolution, although findings in 2008 led to new hypotheses regarding Hantavirus evolution. Various Hantaviruses have been found to infect multiple rodent species, and cases of cross-species transmission (host switching) have been recorded. Additionally, rates of substitution based on nucleotide sequence data reveal that Hantavirus biological group and rodent subfamilies may not have diverged at the same time. Analysis in 2014 suggested a common origin for these viruses ~2000 years ago. The association with particular rodent families appears to have been more recent. The viruses carried by the *Arvicolinae* and *Murinae* subfamilies originated in Asia 500-700 years ago. These subsequently spread to Africa, Europe, North America and Siberia possibly carried by their hosts. The species infecting the *Neotominae* subfamily evolved in Brazil 400 years ago. Their ancestors may have been a *Neotominae* - associated virus from northern South America. [24]

The evolution of shrew-borne Hantaviruses appears to have involved natural occurrences of homologous recombination events of genome segments. The evolution of Tula orthohantavirus carried by the European common vole also appears to have involved homologous recombination events. [25, .26]

### 7. Prevention

According to the CDC, the best prevention against contracting Hantavirus is to eliminate or minimize contact with rodents in the home, workplace, or campsite. As the

virus can be transmitted by rodent saliva, excretions, and bites, control of rats and mice in areas frequented by humans is key for disease prevention. General prevention can be accomplished by disposing of rodent nests, sealing any cracks and holes in homes where mice or rats could enter, setting traps, or laying down poisons or using natural predators such as cats in the home [27].

The Hantaviruses remain infectious in the environment varies based on factors such as the rodent's diet, temperature, humidity, and whether indoors or outdoors. The viruses have been demonstrated to remain active for two to three days at normal room temperature, while ultraviolet rays in direct sunlight kills them within a few hours. However, rodent waste material or urine of indeterminate age should always be treated as infectious. [28]

## 8. Vaccine

As of 2020, there are no US FDA – approved vaccines against Hantaviruses. However, whole virus inactivated bivalent vaccines against Hantaan virus and Seoul virus are available in China and South Korea. In both countries, the use of vaccines, combined have been researched : DNA vaccines targeting the M genome segment and the S genome segment, subunit vaccines that use recombinant Gn, Gc, and N protein of the virus, virus vector vaccines that have recombinant Hantavirus protein inserted in them, and virus like particle vaccines that contain viral protein but lack genetic material. Of these, only DNA vaccines have entered into clinical trials. [29]

## 9. Treatment

*Ribavirin* may be a drug for HPS and HFRS but its effectiveness remains unknown, still, spontaneous recovery is possible with supportive treatment. People with suspected Hantavirus infection may be admitted to the hospital, given oxygen and mechanical ventilation support to help them breathe during the acute phases of Hantavirus, has only been studied in mice, hamsters, and rats. There are no reports of controlled clinical trials. [30]

## 10. Conclusion

Hantavirus is the disease which is maintained within the rodent population, specifically the deer mouse. The information shows the Hantavirus is a cause of hemorrhagic fever. Hantavirus pulmonary syndrome is serious disease that occur after contact with infected rodent. It is concluded that the *Ribavirin* drug for Hantavirus pulmonary syndrome o it is effective. Hantavirus may have simple reservoir. Also Hantavirus infections are increasingly as a cause of disease worldwide. Recent year, 2020, there are no US FDA-approved vaccines against Hantaviruses. In the treatment, there are no reports of controlled clinical trials. The regions especially affected by hemorrhagic fever with renal syndrome include China, Russia, Europe, and the highest region incidence of Hantavirus pulmonary syndrome include Argentina, Chile, United States, Canada. Also identified the years after then and are collectively referred to as the Past and Future Hantavirus. It is completely infect endothelial

cells in their rodent reservoirs and humans. Also so far, there is no cure for this virus but patients are diagnosed early on they can be provided intensive care. Medical professionals advise rodent control as the primary measure to stop the spread of Hantavirus.

## 11. Acknowledgements

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