

# Zoonotic Hantaviridae with global public health significance

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## Abstract

*Hantaviridae* currently encompasses seven genera and 54 species. Multiple hantaviruses, such as *Hantaan virus*, *Seoul virus*, *Dobrava-Belgrade virus*, *Puumala virus*, *Andes virus*, and *Sin Nombre virus*, are highly pathogenic to humans. They cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome or hantavirus pulmonary syndrome (HCPS/HPS) in many countries. Some hantaviruses infect wild or domestic animals without causing severe symptoms. Rodents, shrews, and bats are reservoirs of various mammalian hantaviruses. Studies on the genomics, taxonomy, evolution, replication, transmission, pathogenicity, and control of hantaviruses, as well as patient treatment, have made significant advances in recent years. Meanwhile, novel hantaviruses infecting bats, rodents, shrews, amphibians, and fish have been identified. This systematic review compiles these advancements to aid researchers and the public in better recognizing this zoonotic virus family with global public health significance.

## Review

### Zoonotic *Hantaviridae* with global public health significance

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## ABSTRACT

*Hantaviridae* currently encompasses seven genera and 54 species. Multiple hantaviruses, such as *Hantaan virus*, *Seoul virus*, *Dobrava-Belgrade virus*, *Puumala virus*, *Andes virus*, and *Sin Nombre virus*, are highly pathogenic to humans. They cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome or hantavirus pulmonary syndrome (HCPS/HPS) in many countries. Some hantaviruses infect wild or domestic animals without causing severe symptoms. Rodents, shrews, and bats are reservoirs of various mammalian hantaviruses. Studies on the genomics, taxonomy, evolution, replication, transmission, pathogenicity, and control of hantaviruses, as well as patient treatment, have made significant advances in recent years. Meanwhile, novel hantaviruses infecting bats, rodents, shrews, amphibians, and

fish have been identified. This systematic review compiles these advancements to aid researchers and the public in better recognizing this zoonotic virus family with global public health significance.

**Key words**

*Hantaviridae* ; hemorrhagic fever with renal syndrome; hantavirus cardio pulmonary syndrome; taxonomy; evolution; pathogenicity; systematic review

**1. Introduction**

In 2017, *Bunyaviridae* was officially upgraded to *Bunyavirales* , and the genus *Hantavirus* in *Bunyaviridae* was upgraded to *Hantaviridae* .<sup>1</sup> Multiple hantaviruses, such as *Hantaan virus* (HTNV), *Seoul virus* (SEOV), *Dobrava-Belgrade virus* (DOBV), *Puumala virus* (PUUV), *Andes virus* (ANDV), and *Sin Nombre virus* (SNV), are highly pathogenic to humans.<sup>2</sup> They cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome or hantavirus pulmonary syndrome (HCPS/HPS) worldwide (Table 1).<sup>3</sup> This review compiles recent advancements in the research of *Hantaviridae* in order to aid researchers and the public in better understanding this virus family with global public health significance.

**Table 1.** Human diseases caused by hantaviruses.

Disease	Affected organs
Hemorrhagic fever with renal syndrome (HFRS)	Kidney, spleen, liver, brain, blood
Hantavirus cardiopulmonary syndrome or hantavirus pulmonary syndrome (HCPS/HPS)	Lung, heart, spleen, liver, blood

\*: HTNV: *Hantaan virus* ; SEOV: *Seoul virus* ; DOBV: *Dobrava-Belgrade virus* ; TULV: *Tula virus* ; PUUV: *Puumala virus* ; ANDV: *Andes virus* ; SNV: *Sin Nombre virus* ; CHOV: *Choclo virus* ; LNV: *Laguna Negra virus* .

**2. Diseases caused by hantaviruses**

Hantaviruses pathogenic to humans have been classified into Old World hantaviruses (OWHVs) and New World hantaviruses (NWHVs) based on their geographical distribution. OWHVs, the major etiological agents of HFRS, include HTNV, SEOV, and DOBV viruses, which are distributed in Asia and Europe. NWHVs, the major etiological agents of HCPS/HPS, include ANDV and SNV viruses, which are distributed in South America and North America.<sup>4</sup> Globally, about 150,000 to 200,000 HFRS or HCPS/HPS cases are reported annually, with case fatality rates (CFR) between 1%-15% (HFRS) to 30%-50% (HCPS/HPS).<sup>5</sup>

HFRS was first documented in Korea in 1951.<sup>2</sup> This disease is usually divided into five phases, including fever, hypotension, oliguria, polyuria, and recovery, with the hallmark feature of acute kidney injury, after the incubation period of 2-3 weeks. Acute kidney injury may cause kidney swelling, proteinuria, and hematuria.<sup>6</sup> Symptoms of HFRS include fever, headache, low back pain, visual impairment, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, and bloody stool), and proteinuria.<sup>3</sup> Meanwhile, hemorrhagic symptoms caused by thrombocytopenia include petechiae of the skin and mucosa, hematuria, hemoptysis, conjunctival congestion, gastrointestinal bleeding, and even intracranial hemorrhage. Disseminated intravascular coagulation (DIC) may also occur in severe HFRS cases. The hypotension phase is characterized by sudden hypotension and shock caused by microvascular leakage, which may lead to sudden deaths.<sup>5</sup> The oliguria phase is caused by renal failure, with the symptoms of oliguria (usually <400 mL/day) and proteinuria.

In the diuretic phase, renal function gradually recovers with an increase in urine output. While renal function can recover completely after a long recovery period, chronic renal failure and hypertension may also occur.<sup>7</sup> In addition to the typical renal disease caused by HFRS, some patients present with extrarenal symptoms, such as acute respiratory distress syndrome (ARDS), cholecystitis, pericarditis, and encephalitis.<sup>6</sup> Infection with PUUV in humans can lead to a mild form of HFRS termed nephropathia epidemica (NE).<sup>8</sup>

HCPS/HPS was first documented in North America in 1993.<sup>3</sup> This disease is usually divided into the prodromal, cardiopulmonary, and recovery phases, with the hallmark features of microvascular leakage and ARDS, after the incubation period of 1-7 weeks.<sup>3</sup> The prodromal symptoms are similar to the fever phase of HFRS, such as fever, headache, myalgia, nausea, and vomiting. It also includes flu-like symptoms (e.g., cough and dyspnea) accompanied by thrombocytopenia.<sup>5</sup> The cardiopulmonary phase lasts for several days with tachycardia, arrhythmias, and cardiogenic shock. Leakage of pulmonary capillaries in this phase can cause respiratory failure, pulmonary edema, hypotension, bilateral pulmonary infiltration, and pleural effusion. Acute kidney injury and proteinuria also occur in some HCPS/HPS patients. HCPS/HPS can lead to acute deaths during the cardiopulmonary phase.<sup>9</sup>

HTNV was first discovered in South Korea in 1978.<sup>10</sup> HTNV is mainly distributed in China, South Korea, Russia, and Vietnam.<sup>5,11</sup> More than 90% of global HFRS cases are reported from mainland China, with most of them being caused by HTNV.<sup>12</sup> About 9,000-12,000 HFRS cases are reported in China each year, with a CFR of approximately 1%. These cases are distributed throughout China.<sup>13</sup> In South Korea, about 400-600 cases of HFRS are reported annually, with a CFR 1%-2%.<sup>14</sup>

SEOV was first discovered in South Korea in 1982.<sup>15</sup> While SEOV mainly circulates in China and South Korea, it is the only hantavirus that is globally distributed.<sup>16</sup> This is consistent with the global distribution of its hosts Norway rats (*Rattus Norvegicus*).<sup>17</sup> SEOV infection accounts for about 25% of HFRS cases worldwide, with a CFR less than 1%.<sup>3</sup>

DOBV was first discovered in Slovenia in 1992.<sup>18</sup> It is mainly distributed in Slovenia, Czech Republic, Poland, Russia, Serbia, Greece, Germany, Denmark, France, and other European countries.<sup>19</sup> The pathogenicity of DOBV varies according to its genotypes. The Dobrava and Sochi genotypes are highly pathogenic, with a CFR of 10%-15%.<sup>20</sup> The Kurkino genotype is less virulent and causes only mild HFRS, with a CFR of 0.3%-0.9%. The Saaremaa genotype does not cause mortality.<sup>19</sup>

PUUV was first discovered in Finland in 1980.<sup>21</sup> PUUV is mainly distributed in central, northern, and eastern European countries.<sup>5</sup> It caused more than 3000 HFRS cases each year in Europe between 2010 and 2020. They are usually mild, with a CFR of 0.1%-0.4%.<sup>3,5</sup>

ANDV was first discovered in Argentina in 1995.<sup>22</sup> ANDV is mainly distributed in Argentina and Chile and causes dozens of HCPS/HPS cases annually with a CFR about 40%. ANDV can be transmitted among humans.<sup>23</sup>

SNV was first detected in 1993 in the USA.<sup>24</sup> SNV circulates in the USA, Canada, and Mexico, and causes dozens of HCPS/HPS cases annually with a CFR of 30%-35%.<sup>25,26</sup>

Other viruses in *Orthohantavirus*, such as *Tula virus* (TULV) in many Eurasia countries,<sup>27</sup> *Bayou virus* (BAYV) in USA,<sup>28</sup> *Choclo virus* (CHOV) in Panama,<sup>29</sup> and *Laguna Negra virus* (LANV) in South America,<sup>30</sup> have been identified as pathogenic to humans.

### 3. Morphology and genomics of hantaviruses

Hantavirus virions are usually spherical with a quasi-symmetric icosahedral lattice (T=12). The diameter of the virions is 120-160 nm.<sup>31</sup> The lipid bilayer of the viral envelope is about 5 nm thick. The surface spikes embedded in the viral envelope are composed of the glycoproteins Gn and Gc. Each spike is formed by a tetramer of Gn and Gc (Figure 1 ) extending from the lipid bilayer to about 10 nm. Inside the envelope are the nucleocapsids composed of many copies of the nucleocapsid protein N, which interact with the three segments of the viral genome and the viral RNA-dependent RNA polymerase (RdRp).<sup>32</sup>

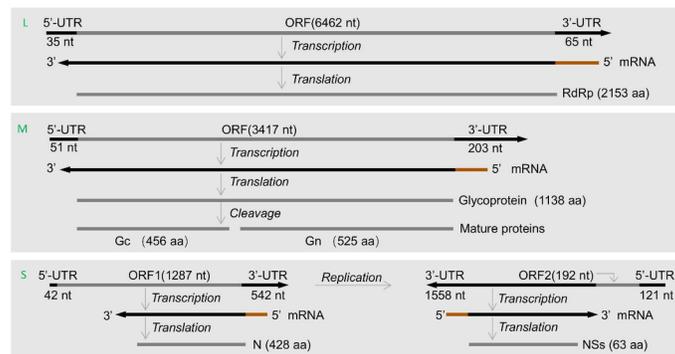
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image1.emf available at <https://authorea.com/users/575418/articles/647735-zoonotic-hantaviridae-with-global-public-health-significance>

**Figure 1.** The external (A) and interior (B) structures of hantaviruses with three genomic RNA segments (L, M, and S).

Like most members of *Bunyavirales*, hantaviruses genome encompasses large (L), medium (M), and small (S) single-stranded negative-sense RNA (-ssRNA) segments, consisting of about 10,000-15,000 nucleotides in total (Figure 2).<sup>33</sup> The L segment encodes RdRp that mediates the transcription and replication of viral genomic RNA. The M segment encodes a glycoprotein precursor (GPC), which is co-translated and cleaved by host cell signal peptidases to Gn and Gc.<sup>34</sup> Gn and Gc bind to cell receptors, regulate immune responses, and induce protective antibodies.<sup>4</sup> The S segment encodes the N protein, which binds to and protects the viral RNA molecules. The S segment of some *orthohantaviruses* (e.g., ANDV, PUUV, SNV, TULV, and LANV) encodes a nonstructural protein (NS), which inhibit the production of interferon in host cells.<sup>35</sup>

The terminal untranslated region (UTR) sequences of the genomic segments of hantaviruses are highly conserved and complementary. They form stalk structures and participate in the replication and transcription of viral genomic RNA (vRNA).<sup>36,37</sup>



**Figure 2.** The three genomic RNA segments (L, M, and S) of an Andes virus and their encoding proteins. Their sequence accession numbers in GenBank are NC003468, NC003467, and NC003466.<sup>38</sup> Brown lines represent the 5'-methylated cap and some nucleotides transferred from host cell mRNAs to the viral mRNAs. ORF: open reading frame. UTR: untranslated region.

## 4. Taxonomy and distribution of hantaviruses

The *Hantaviridae* Study Group of the International Committee on Taxonomy of Viruses (ICTV) designated the method DEmARC for classifying the new hantavirus genera and species. DEmARC uses the phylogenetic relationships and pairwise evolutionary distances (PED) values of the concatenated S and M segment sequences, calculated with the maximum likelihood method and the Whelan and Goldman (WAG) substitution model. The PED cutoff value of 0.1 is used for species demarcation in *Hantaviridae*.<sup>39</sup>

In 2018, only one virus genus (*orthohantavirus*) was classified in *Hantaviridae*. In 2019, three new virus genera (*Loanvirus*, *Mobatvirus*, and *Thottimvirus*) in *Hantaviridae* were classified. In 2023, four subfamilies (*Actantavirinae*, *Agantavirinae*, *Mammantavirinae*, and *Repantavirinae*), seven genera (*Actinivirus*, *Agnathovirus*, *Loanvirus*, *Mobatvirus*, *Orthohantavirus*, *Thottimvirus*, and *Reptillovirus*), and 54 species in *Hantaviridae* were classified (Table S1) (Figure 3).<sup>40,41</sup> *Robina virus* which was reported in Australia in

2017, may belong to the *Mobatvirus* genus and needs to be reclassified (Figure 3).<sup>42</sup> These taxa were consistent with the phylogenetic relationships in their RdRp genes (Figure 3),<sup>43</sup> and they are largely consistent with their host distribution and conserved sequences at the genome termini.<sup>39</sup> The ICTV *Hantaviridae* Study Group will reclassify in 2023-2024 and only evaluate those viruses with complete genome sequences.<sup>44</sup>

The genus *Actinovirus* covers five species of fish viruses, with four identified in China in 2018 and one identified in Europe in 2020.<sup>45</sup> The genus *Agnathovirus* covers one species of fish virus identified in China in 2018.<sup>45</sup> The genus *Loanvirus* covers two species of bat viruses identified in China in 2013 and Czech Republic in 2015, respectively.<sup>46,47</sup> The genus *Mobatvirus* covers three species of bat virus identified in Vietnam, China, and Philippines, respectively, in 2015-2016,<sup>48-50</sup> besides one mole virus identified in Poland in 2014 and one shrew virus identified in Russia in 2019.<sup>51,52</sup> The genus *Orthohantavirus* covers 38 species with hosts in rodents, moles, shrews, and humans.<sup>40</sup> As mentioned above, HTNV, SEOV, DOBV, PUUV, SNV, and ANDV are widely distributed and highly pathogenic to humans.<sup>2</sup> The genus *Thottimvirus* covers two species of shrew viruses identified in India in 2007 and in Japan in 2008.<sup>53,54</sup> The genus *Reptillovirus* covers one species of gecko virus identified in China in 2018.<sup>45</sup>

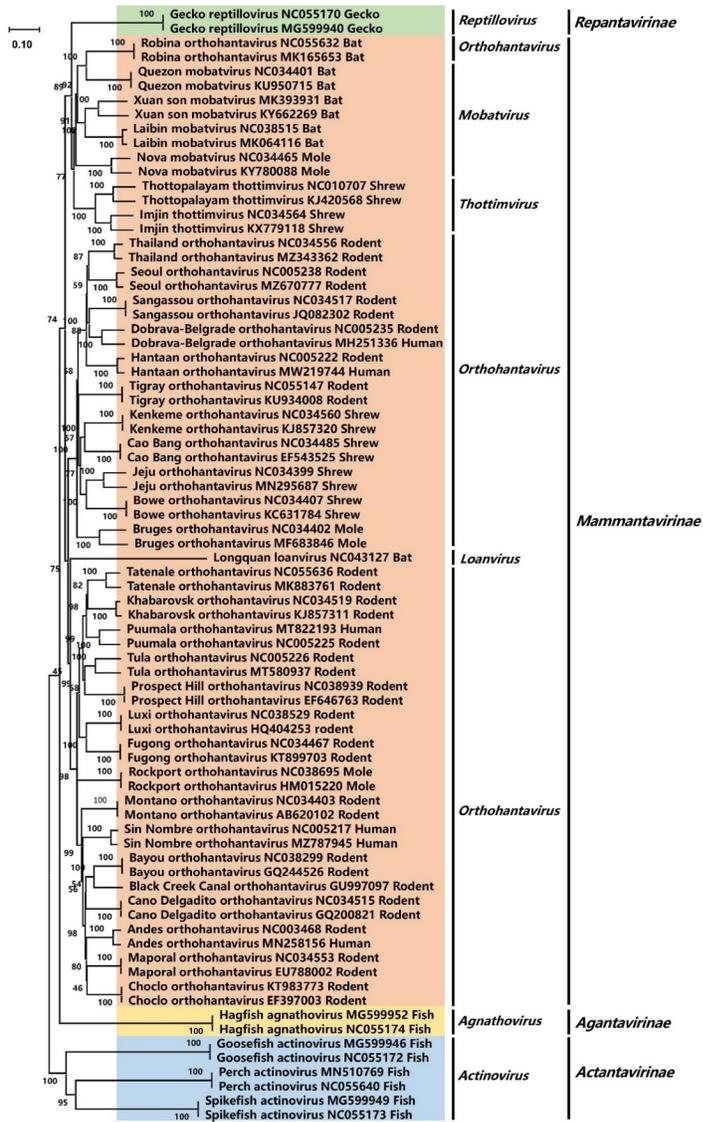
Some species of hantaviruses have been classified into several lineages. For example, the HTNVs isolated from China were classified into 10 lineages as per their S or M genomic segment sequences.<sup>55</sup> SEOVs were classified into six lineages (1-6) as per their M genomic segment sequences. Lineages 1, 2, 3, and 5 of SEOVs were isolated from China, while lineage 4 included isolates from China, South Korea, Japan, Singapore, Vietnam, and the USA. Lineage 6 SEOVs were isolated from the UK except for one strain from Brazil.<sup>56</sup>

## 5. Evolution of hantaviruses

Numerically, the most common events in the genomic evolution of hantaviruses are single-nucleotide substitutions. Nucleotide insertions and deletions, including those leading to frameshift mutations, are important in the evolution of hantaviruses, particularly in the macroevolution (e.g., inter-species evolution) of hantaviruses.<sup>57</sup>

Like other viruses with multiple genomic segments, hantaviruses can utilize genomic recombination and reassortment to rapidly change their genomic sequences. Genomic reassortment and recombination events frequently occur in nature and have been demonstrated in *in vitro* experiments. These events have facilitated the adaptation of hantaviruses to multiple hosts and ecosystems.<sup>4,58</sup>

Recombination events in the S or M segment in OWHVs (e.g., HTNV, SEOV, ANDV, TULV, and PUUV) have been recorded.<sup>55,58</sup> A recombinant HTNV strain A16 isolated from Shaanxi Province in China had a parent from a hantavirid species other than HTNV,<sup>55</sup> suggesting that recombinant events in hantaviruses can occur among different hantavirid species.



**Figure 3.** Phylogenetic relationships among 78 species in *Hantaviridae*, calculated with the software MEGA 11.0, the amino acid sequences of the viral RdRp gene, the Neighbor-joining method, and the Poisson model. Bootstrap values were calculated using 1000 replicates.

Reassortment events of NWHVs (e.g., SNV) in rodents in the USA have been recorded. These events mainly exchange the viral S or M segments.<sup>4,58</sup> ANDV-SNV reassortment events and HTNV-SEOV reassortment events were experimentally confirmed.<sup>58</sup> 19.1% of PUUV genomes obtained from rodents in 2005–2009 were identified as reassortants.<sup>4</sup>

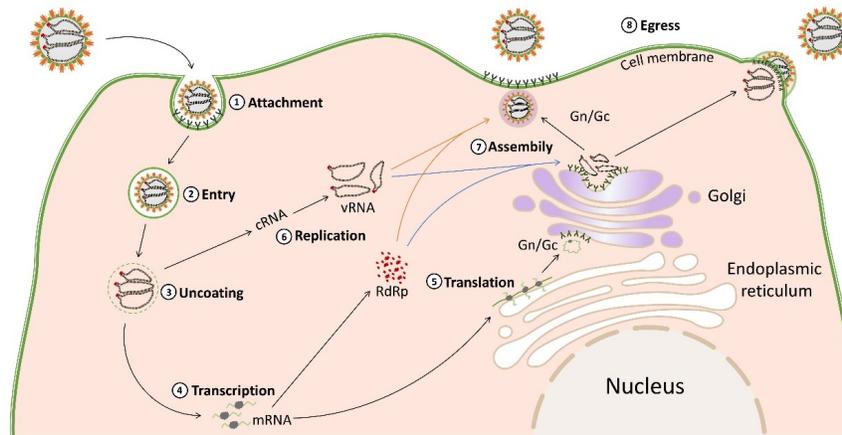
The evolution of hantaviruses was likely driven by host adaptation and geographical isolation.<sup>59</sup> Pathogenic hantaviruses were isolated from various rodent species. For instance, HTNV has been isolated from *Apodemus agrarius*, SEOV from *Rattus norvegicus*, PUUV from *Myodes glareolus*, ANDV from *Oligoryzomys longicaudatus*, and SNV from *Peromyscus maniculatus*. It has been believed for a long time that rodents are the original hosts of various hantaviruses and that one hantavirus species circulates largely in one rodent species.<sup>2</sup> Although recent studies suggested that one hantavirus species can circulate in a few rodent

species (Table S1), the genera and species of *Hantaviridae* are largely consistent with their host species, and orthohantaviruses have evolved into different species in the hosts of *Murinae*, *Arvicolinae*, *Neotominae*, and *Sigmodontinae* subfamilies.<sup>59</sup> Meanwhile, HTNV and SEOV have formed multiple lineages corresponding to their geographic distribution.<sup>56</sup>

Multiple studies have shown that mammalian hantaviruses may originate from hantaviruses in shrews, bats, or moles,<sup>46</sup> which might come from reptile or fish hantaviruses.<sup>45</sup>

## 6. Replication of hantaviruses

The replication processes of hantaviruses in host cells include attachment to host cells and internalization, membrane fusion, transport and release into the cytoplasm, transcription, replication, translation of the genome, and assembly and release of the virion (Figure 4).<sup>60</sup> Vascular endothelial cells and macrophages are the primary sites of hantavirus replication.<sup>61</sup>



**Figure 4.** Schematic overview of the replication of some hantaviruses.

The attachment and entry of hantaviruses into host cells are mediated by the binding of viral glycoproteins to host cell surface receptors.<sup>61</sup> Some hantaviruses attach and enter host cells through integrins (e.g.,  $\alpha V\beta 3$  and  $\alpha V\beta 1$ ), which are transmembrane heterodimer glycoproteins composed of  $\alpha$  and  $\beta$  subunits.<sup>60</sup> In addition to integrins, decay acceleration factors (e.g., DAF/CD55) and complement receptors (e.g., gC1qR/P32) have also been proposed as candidate cell attachment factors for some hantaviruses.<sup>60</sup> Protocadherin-1 likely played a role in the attachment and entry of all NWHVs in the last two years.<sup>62</sup> After attachment to cell surface receptors, hantaviruses rely on several pathways for entry, including macropinocytosis and endocytosis, which are either clathrin-, calveolin-, or cholesterol-dependent.<sup>60</sup> For instance, HTNV and SEOV are internalized by clathrin-mediated endocytosis. ANDV can be internalized through cholesterol-mediated micropinocytosis.<sup>60</sup>

After internalization, virions form clathrin-coated vesicles, which can be formed with clathrin-coated cell membranes.<sup>61</sup> Virions are then transported to the early endosomes, and eventually to the late endosomes and lysosomal compartments. The membrane fusion of the viral envelope with the endosome is accompanied by a decrease in pH value, from the weak acidity of the early endosome to the strong acidity of the late endosome. Hantavirus requires acidity (pH 5.8-6.3) for membrane fusion.<sup>63</sup> Gc is a type II viral fusion protein. The conformational change of Gc is triggered by endosomal acidification, and then the Gc fusion peptide is inserted into the endosomal membrane, leading to further conformational change, which mediates the fusion of the viral envelope and endosomal membrane.<sup>64</sup>

The fusion of the viral envelope and endosomal membrane promotes the release of the viral ribonucleoproteins (RNP) complex into the cytoplasm, initiating the transcription and replication of the viral genome.<sup>31</sup> RdRp

mediates the transcription and replication of the viral genome, and the replication of the hantavirus genome only occurs in the cytoplasm.<sup>7</sup> Both the 5'- and 3'- ends of vRNA have non-coding regions (NCR), which are complementary sequences. vRNA replicates into complementary RNA (cRNA), which serves as a template for vRNA replication. Genome replication starts from scratch and proceeds through forward cRNA, which replicates out vRNA and is encapsulated by nucleocapsid (N) proteins to form RNPs.<sup>61</sup>

N proteins play a variety of roles in the viral replication cycle. They participate in transcription together with viral RdRp to promote mRNA translation.<sup>31</sup> RdRp initiates transcription through a unique cap-snatching mechanism that produces the viral mRNAs. The N-terminal of the L protein has endonuclease activity, which can cut capped primers from mRNA of host cells and be used to synthesize viral mRNAs (cap-snapping).<sup>31</sup> The viral mRNAs transcribed from the L and S segments of the genome are translated on episomal ribosomes, and the viral mRNAs transcribed from the M segments in membrane-bound ribosomes are translated in the endoplasmic reticulum (ER) and rough endoplasmic reticulum (RER).<sup>65</sup>

The viral GPC is cleaved in the ER into the Gn and Gc glycoproteins at the conserved pentapeptide motif WAASA,<sup>31</sup> which are further glycosylated in the ER and transported to the Golgi complex, where they form heterodimers.<sup>66</sup> Gn and Gc are modified by N-glycan chains, which stabilize the spike structure and play a key role in the virion assembly.<sup>64</sup> All virions are assembled in the Golgi apparatus, and the newly synthesized virions bud into the Golgi pool, during which the cytoplasmic tail of Gn interacts with the RNP complex.<sup>60</sup> The virions are then transported to the cell membrane, where they are released by exocytosis. Hantaviruses are usually assembled at the Golgi apparatus, and some hantaviruses could be assembled at the plasma membrane by fusion of viral vesicles and cell membranes.<sup>31</sup>

The host mechanisms of innate and acquired immunity in mammals are crucial to inhibiting hantavirus replication.<sup>67</sup> Despite various advances in this field in recent years, many key aspects of hantaviruses replication cycle remain unknown, particularly regarding the mechanisms involved in genome replication, transcription, translation, and viral assembly.

## 7. Transmission of hantaviruses

Although hantaviruses can be inactivated by heating at 60°C for 30 minutes, organic solvents, hypochlorite solvents, or ultraviolet light,<sup>5</sup> they are relatively stable in the external environment. They can survive for 10 days at room temperature and more than 18 days at low temperatures (e.g., 4°C).<sup>12</sup> This facilitates the transmission of hantaviruses.

Different from the fact that various bunyaviruses (e.g., Rift Valley fever virus) are transmitted by insects, human hantaviruses are mainly transmitted by rodents.<sup>45,54,68</sup> Hantaviruses usually cause asymptomatic and persistent infections in rodents, except that Syrian hamsters infected with ANDV can show typical symptoms of HCPS/HPS. Rodents, shrews, moles, and bats are the reservoirs of some hantaviruses, which can transmit the virus horizontally and vertically.

Infected animals can spread hantaviruses to other sensitive animals through aerosols or droplets formed from their excreta or secretions (feces, urine, saliva), through the consumption of contaminated food, or through biting and scratching.<sup>69,70</sup> They can also transmit the hantavirus through the fecal-oral route, and females can transmit the virus through the placenta or suckling.<sup>71</sup> Mating and fighting among sensitive animals also aids in virus transmission.<sup>72</sup>

Rodents can also transmit hantaviruses to humans through aerosols or droplets formed from their excreta and through the consumption of contaminated food.<sup>3</sup> Rodent bites and scratches are important for virus transmission to humans.<sup>73</sup> The prevalence rate of hantaviruses (e.g., SEOV) is up to 80% among traders who cultivate and breed rodents and those who keep pet rodents (e.g., rats and mice).<sup>74,75</sup> An outbreak of SEOV in North America with 31 confirmed cases of infection resulted from contact with pet rats.<sup>73</sup>

ANDV is currently the only known hantavirus that can be transmitted from humans to humans. It usually occurs after close contact with an infected person.<sup>76</sup> ANDV may be secreted into human saliva and transmitted through the respiratory tract via airborne droplets released by coughing or sneezing.<sup>77</sup> Studies have

shown that ANDV can also be transmitted to newborns through breast milk, and transmission between humans can also occur through the digestive tract or placenta.<sup>78</sup>

Investigations have shown that HFRS can be transmitted to animals or humans through the bites of mites.<sup>79,80</sup> Investigations have also shown that pigs can be infected with HTNV without severe symptoms,<sup>81</sup> and sows can vertically transmit the virus through the placenta.<sup>82</sup> A swine breeder was infected with hantavirus, but with no history of mite bites or rodent infestation in the living environment, so the pig-to-human transmission of the virus could be possible.<sup>83</sup> However, the relevant investigations have been neglected, possibly because they were published in Chinese.

HTNV and PUUV antibodies have been detected in cattle, deer, and rabbits. SNV antibodies have been detected in cats and dogs.<sup>84</sup> The roles of these mammalian hosts in the ecology of hantaviruses remain unknown.

## 8. Pathogenesis of hantaviruses

Human infections with hantaviruses can cause acute diseases, and the severity varies by viral species and strains.<sup>3,19,20</sup> HFRS mainly affects the kidney and blood vessels, and HCPS/HPS mainly affect the heart and lung.<sup>67</sup> Other organs and systems, such as the nervous system, spleen, and liver, can also be affected.<sup>85</sup>

In both animals and humans, hantavirus infection mainly occurs in renal or pulmonary endothelial cells (ECs) and macrophages.<sup>65</sup> The main pathogenesis of HFRS and HCPS/HPS covers increased vascular permeability and acute thrombocytopenia.<sup>5</sup> Infection begins with the interaction between hantavirus glycoproteins (Gn and Gc) and  $\beta$ -integrin receptors (e.g.,  $\alpha v \beta 1$  and  $\alpha v \beta 3$ ) on target cell membranes.<sup>86</sup> Immature dendritic cells located near epithelial cells transport virions from lymphatic vessels to local lymph nodes, to infect more ECs. These cells act as antigen-presenting cells and induce immune activation, especially those associated with macrophages and CD8<sup>+</sup> T lymphocytes.<sup>5</sup> Delayed type I interferon response leads to higher virus titers.<sup>87</sup> After immune activation, cytotoxic T lymphocytes produce pro-inflammatory cytokines that can damage the infected endothelial cells, leading to increased vascular permeability and inflammatory reactions.<sup>88</sup> Activation of complements and release of pro-inflammatory cytokines, such as interferon (IFN), interleukins (IL-1, IL-6, and IL-10), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), play a crucial role in changing endothelial cell permeability.<sup>86</sup> Different hantaviruses elicit different immune responses. High levels of cytotoxic CD8<sup>+</sup> T lymphocytes can be detected in HFRS patients. Elevated IL-6 levels are associated with thrombocytopenia and renal failure.<sup>86</sup>

Human leukocyte antigen (HLA) is responsible for presenting viral antigens to T lymphocytes. Genetic susceptibility to severe HFRS disease is related to the HLA type, and different hantaviruses are associated with different HLA haplotypes.<sup>65</sup>

Natural reservoir hosts of hantaviruses often exhibit asymptomatic persistent infection with hantaviruses, which may result from the innate immunity of the reservoir hosts.<sup>85</sup> In rodents, it is possible that T lymphocytes can be regulated with the immune receptor NLRC3, leading to persistent viral infection without symptoms, and the lack of such an immune regulation in humans leads to disease.<sup>89</sup>

The lack of obvious symptoms in natural hosts and the lack of suitable animal models restricted research on the pathogenesis of HTNV and SEOV to humans.<sup>90</sup> HTNV infected *Nlrc3*<sup>-/-</sup> mice can develop clinical symptoms and pathological changes resembling those seen in patients with HFRS, suggesting a new model for studying the pathogenesis of HTNV. Monkeys can be infected with PUUV through laboratory infection with similar symptoms to NE and can be used as an animal model of NE.<sup>85</sup> Research into the pathogenesis of HCPS/HPS has been aided with the hamster model, which mimics the pulmonary capillary leak and the hypotension characteristic of human HCPS/HPS.<sup>5</sup>

## 9. Diagnosis and treatment of hantavirus infections

Epidemiological information and clinical symptoms are useful for the initial diagnosis of hantavirus infections. Confirmation of hantavirus infections should be based on clinical symptoms, epidemiological information,

and detection of the nucleic acids, proteins, and/or antibodies specific to the associated hantavirus.<sup>65</sup>

No specific antivirals have been approved for HFRS and HCPS/HPS in the USA or Europe.<sup>5</sup> However, some antivirals, including ribavirin, fapilavir, and lactoferrin, have displayed varying efficacy in the treatment of hantavirus infections.<sup>91</sup>

Prophylactic administration of ribavirin and fapilavir in early infection or post-exposure has shown some efficacy.<sup>92</sup> Both ribavirin and fapilavir have shown anti-hantavirus activity in vivo and in vitro.<sup>5,91</sup> Ribavirin has proven effective in the early treatment of HFRS with some limitations, including toxicity to humans and animals at high doses and the potential to cause hemolytic anemia.<sup>92</sup> Fapilavir is superior to ribavirin without the side effect associated with anemia.<sup>77</sup> Fapilavir was evaluated in an ANDV/SNV-infected hamster model, where oral administration twice daily at 100 mg/kg significantly reduced the viral RNA load in the blood and the antigen load in the lung. Oral administration of fapilavir before the onset of viremia prevented HCPS, whereas delayed administration had no protective effect.<sup>91</sup>

Antibodies include monoclonal and polyclonal antibodies.<sup>91</sup> Monoclonal antibodies that are effective against hantaviruses have been demonstrated in hamster models and suckling mouse models.<sup>91</sup> Monoclonal antibodies have been proven effective for treatment of HCPS/HPS induced by ANDV infection in hamster models.<sup>93</sup> Polyclonal antibodies produced by DNA-vaccinated bovines have also displayed protective effects in animal models.<sup>65</sup>

Supportive treatment can be used to maintain fluid and electrolyte balance in HFRS patients, while blood transfusions can control bleeding and improve clotting in DIC cases. For HCPS/HPS patients, oxygen supplementation is usually required.<sup>5</sup>

## 10. Prevention and control of hantaviruses

Prevention and control of hantaviruses pathogenic to humans rely on education and actions to block the viral transmission and protect humans.

Epidemiological surveillance and analysis play key roles in identifying risky regions and factors that contribute to hantavirus transmission. To mitigate this risk, rodenticides, traps, and cats can be employed for targeted control of rodents. Additionally, cleaning and disinfecting human living environments can prevent contamination of food and other items with hantaviruses from rodent excreta or secretions.

People at high risk of infection with hantaviruses, such as those working in agriculture, forestry, or animal husbandry, should take protective measures, including wearing masks or face coverings.<sup>94</sup> No vaccines for hantaviruses have been approved worldwide, with the exception of the Republic of Korea (ROK) and mainland China. In the ROK, an inactivated vaccine (Hantavax) has been marketed since 1990 to prevent HFRS caused by HTNV and SEOV, which requires a three- or four-dose regimen.<sup>95</sup> A similar bivalent inactivated vaccine was marketed in 1994 in mainland China.<sup>96</sup> Approximately 2 million doses of HFRS inactivated bivalent vaccine are used annually in mainland China, with vaccine-induced immunity lasting up to 33 months.<sup>97</sup>

In recent years, multiple types of new vaccines for hantaviruses have been investigated in laboratories. For instance, a vaccinia virus recombinant vector vaccine expressing the glycoproteins Gn and Gc of HTNV elicited neutralizing antibodies against both HTNV and SEOV in hamster models, although the vaccine had no cross-protection against PUUV.<sup>98</sup> Various DNA vaccines expressing the genomic glycoproteins of OWHVs and NWHVs have also been investigated in hamster models.<sup>91</sup>

## 11. Discussion

From the panorama of hantaviruses depicted above, hantaviruses circulate in various mammals (e.g., bats, rodents, shrews, and moles), amphibians, and fish widely in the world, and some hantaviruses are highly pathogenic to humans. They usually infect humans through animal-to-human transmission. In recent years, the taxonomy of *Hantaviridae* has been greatly expanded and revised, and research targeting various aspects of this important virus family has made significant progress.

In the years to come, numerous research advances in *Hantaviridae* can be anticipated. Novel genera or species within this family will be discovered, particularly from novel regions or host species. For instance, the suspected novel hantaviruses *Rusne virus* from the root vole in Lithuania and *Academ virus* from moles in Russia were reported recently.<sup>99,100</sup> Some genomic segments of important known hantaviruses (e.g., *Lena virus* and *El Moro Canyon virus*) will be sequenced and analyzed. The structures and functions of more proteins of hantaviruses will be revealed. More evolutionary and ecological features of hantaviruses, including the roles of pigs and mites, in hantavirus transmission, will be further explored, and the phylogenetic distribution and pathogenesis of more hantaviruses will be clarified. More vaccines (e.g., mRNA vaccines) and other measures to control highly pathogenic hantaviruses will be evaluated. The panorama of hantaviruses depicted in this review can be a valuable reference for these explorations.

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## AUTHOR CONTRIBUTIONS

Rui-Xu Chen, Huan-Yu Gong, Xiu Wang, Ming-Hui Sun, and Yu-Fei Ji wrote the first version of this manuscript under the direction of Jian-Wei Shao and Ji-Ming Chen. Rui-Xu Chen drew the tables and figures. Ji-Ming Chen conceived, designed, and financially supported this study and revised this manuscript. All the authors have checked and agreed on the submitted version of this manuscript.

## DATA AVAILABILITY STATEMENT

The data that supporting the findings of this study are available from the corresponding author upon reasonable request.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

## SUPPORTING INFORMATION

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