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Review

# Hantavirus infections

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ABSTRACT

Over the past few decades understanding and recognition of hantavirus infection has greatly improved worldwide, but both the amplitude and the magnitude of hantavirus outbreaks have been increasing. Several novel hantaviruses with unknown pathogenic potential have been identified in a variety of insectivore hosts. With the new hosts, new geographical distributions of hantaviruses have also been discovered and several new species were found in Africa. Hantavirus infection in humans can result in two clinical syndromes: haemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS) caused by Old World and New World hantaviruses, respectively. The clinical presentation of HFRS varies from subclinical, mild, and moderate to severe, depending in part on the causative agent of the disease. In general, HFRS caused by Hantaan virus, Amur virus and Dobrava virus are more severe with mortality rates from 5 to 15%, whereas Seoul virus causes moderate and Puumala virus and Saaremaa virus cause mild forms of disease with mortality rates <1%. The central phenomena behind the pathogenesis of both HFRS and HCPS are increased vascular permeability and acute thrombocytopenia. The pathogenesis is likely to be a complex multifactorial process that includes contributions from immune responses, platelet dysfunction and the deregulation of endothelial cell barrier functions. Also a genetic predisposition, related to HLA type, seems to be important for the severity of the disease. As there is no effective treatment or vaccine approved for use in the USA and Europe, public awareness and precautionary measures are the only ways to minimize the risk of hantavirus disease. **T. Avšič-Županc, CMI 2016;▪:1**

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## Introduction

Since its first description in Chinese writings 900 years ago, the disease resembling hantavirus infection came to the attention of the world during the Korean conflict (1950–53). More than 3000 United Nations troops fell ill with Korean haemorrhagic fever, which is commonly referred to as haemorrhagic fever with renal syndrome (HFRS). However, the causative agent of the disease remained unknown until the early 1980s, when Lee *et al.* reported on Hantaan virus (HTNV), present in the lungs of its natural reservoir, the striped field mouse (*Apodemus agrarius*) [1]. Although the milder form of HFRS, nephropathia epidemica (NE), has been known in Fennoscandia since the early 1930s, its aetiological agent Puumala virus (PUUV) was found in bank voles (*Myodes glareolus*) in Finland only in 1980 [2]. Another important milestone of hantavirus infection was the outbreak that occurred in the Four Corners region of the USA in 1993 with the disease called hantavirus cardiopulmonary syndrome (HCPS) [3]. The causative agent of HCPS, Sin Nombre virus (SNV) and other pathogenic hantaviruses including Andes virus (ANDV) have been reported in North and South America [4].

Pathogenic hantaviruses, in nature carried by a specific rodent host species, can cause severe disease in humans with mortality rates from 12% (HFRS) [5] to 40% (HCPS) [6]. Both diseases are acute febrile infections, usually acquired through inhalation of aerosols or dust particles contaminated with virus containing rodent excreta [7]. HFRS is characterized by renal failure and haemorrhagic manifestations that vary from petechiae to severe internal bleeding. Pneumonia and cardiovascular dysfunction are characteristics of HCPS. Increased permeability of microvascular endothelium seems to be a common effect of hantavirus infection. In the complex pathogenesis of hantavirus infection it is suggested that not the direct viral cytopathology, but immune mechanisms may play an important role [8].

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At present, over 28 hantaviruses that cause disease in humans, ranging from acute renal failure to pulmonary oedema and severe haemorrhagic illness, have been identified around the world. While around 1000 HCPS cases have been reported, it is estimated that more than 100 000 HFRS cases occur worldwide each year. In many countries hantaviral infections are undetected and not reported, so additional hantaviruses may remain undiscovered. Hantaviruses and the diseases they cause deserve the attention of researchers and public health officials, and increased clinician awareness with regard to their impact on public health.

## General properties of hantaviruses

Hantaviruses are enveloped RNA viruses, spherical in shape with a diameter of 80 to 120 nm, and they form a separate genus within the *Bunyaviridae* family. The genome comprises three negative-sense, single-stranded RNAs that share a 3′ terminal sequence of the genome segments. The three segments, S (small), M (medium) and L (large), encode the nucleoprotein (N), envelope glycoproteins (Gn and $G_C$), and the L protein or viral RNA-depended RNA polymerase, respectively [9]. Like other enveloped viruses, hantaviruses are readily inactivated by heat (30 min at 60°C), detergents, UV irradiation, organic solvents and hypochlorite solutions. Hantaviruses infect endothelial, epithelial, dendritic and lymphocyte cells by the attachment of the viral glycoprotein to the cell surface receptors. Until now, it is considered that $\beta_1$-integrin interacts with viral $G_n$ of apathogenic hantaviruses, while $\beta_3$-integrin interacts with the glycoprotein of pathogenic hantaviruses [10,11]. Hantaviruses replicate in the cytoplasm and the glycoproteins are targeted to the Golgi complex, where most hantaviruses bud. However, SNV has been shown to bud at the plasma membrane [4]. Hantaviruses found in Eurasia and in America share common features of their life cycles, but based on recent studies it was suggested that they may have evolved differently in specific interaction with the host cell machinery [7].

## Hantavirus ecology

In contrast to other Bunyaviruses, hantaviruses are not transmitted by an arthropod vector, but are carried and transmitted to humans by persistently infected rodent or insectivore hosts and even bats (Fig. 1). Therefore, it is not surprising that the ecology and geographical distribution of hantaviruses relate to the distribution of their natural reservoir. The hantavirus prototype strain, HTNV, was first isolated from the striped field mouse, *Apodemus agrarius*, in 1976 [1]. The discovery of the aetiological agent of HFRS in South Korea prompted research all over the world, which resulted in the discovery of other HFRS-associated novel viruses in the Old World. Hantaviruses have since been discovered to circulate not only in Asia and Europe, but also in both Americas and Africa (detailed review in refs [7,8]).

In general it is accepted that infection of the natural host is inapparent and does not produce disease. Despite that, a few studies have described some negative impact of hantavirus infection on the hosts' survival [12], the slower growth of infected animals [13,14] and the presence of histopathological changes in infected tissues [15]. Understanding the ecology of hantaviruses requires an interdisciplinary research approach, which links laboratory experiments with results obtained from field studies involving wild-caught animals. Hantaviruses are usually closely associated with a single rodent (insectivore) species, which is a result of a co-evolution of the virus and the host [16]. The infection of other animals such as moose [17], red fox [18], or domestic cat and dog [19,20] is considered to be a spillover with minor or non-existent risk for human infection [21]. But a spillover infection of a sympatric host seems to be a common incident [22–24] promoted by complex biogeographic and anthropogenic pressures on the environment (reviewed in ref. [7]). Because spillover infection enables natural reassortment and origination of new hantavirus species, this might also be important with regard to public health [24].

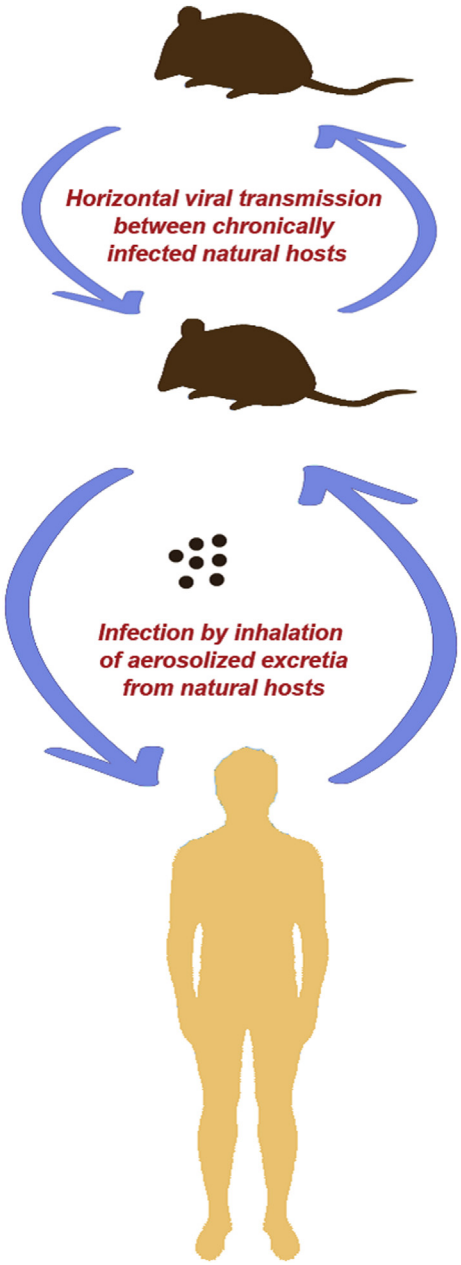


**Fig. 1.** Hantavirus life cycle and spillover infection to humans. In nature hantaviruses are circulating via horizontal transmission between chronically infected natural host reservoirs (mice, rats, voles). Most human infections occur when contaminated aerosolized rodent excreta are inhaled.

### *Old World hantaviruses*

Several hantaviruses that have been demonstrated to circulate in Europe and Asia belong to the so-called 'Old World hantaviruses', and they are carried by animal species of four rodent genera

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*Myodes*, *Microtus*, *Apodemus* and *Rattus*, and also by two insectivore families: Soridae and Talpidae.

The most widely distributed rodent reservoir in Europe is the bank vole *Myodes glareolus*, the carrier of PUUV [2], which inhabits the whole continent with the exception of the Mediterranean region [4]. In Asia two other species of vole host hantaviruses: *Myodes rufocanus*, the carrier of Hokkaido virus (HOKV) in Japan [25] and *Myodes regulus*, carrier of Muju virus (MJUV) in Korea [26]. Despite some seroprevalence studies the virulence towards humans of HOKV and MJUV is still undetermined [26].

Another group of voles, from the genus *Microtus* are populating North America, Europe and Asia [27]. Namely, several hantavirus serotypes have been isolated from *Microtus* spp. not only in Europe: Khabarousk and Vladivostok virus isolated from *Microtus fortis* [28,29] and Tula virus from *Microtus arvalis* and *Microtus levis* (previously *Microtus rossiaemeridionalis*) [30], but also in America: Prospect Hill virus from *Microtus pennsylvanicus* [31], Isla Vista virus from *Microtus californicus* [32] and Bloodland Lake virus from *Microtus ochrogaster* [33]. In Siberia a hantavirus is hosted by lemmings, called Topografov virus isolated from *Lemmus sibiricus* in 1996 [34]. Although, there is some evidence of possible human infection with Tula virus [35,36] currently no clinical disease has been clearly associated with any *Microtus*-carried hantaviruses [37].

A severe form of HFRS is related with *Apodemus* mouse-borne hantaviruses in Asia and Europe. In Asia the presence of HTNV and HTNV-like viruses (Amur/Soochong virus) was demonstrated in *Apodemus agrarius* and *Apodemus peninsulae* in Far East Russia, China and South Korea [38–40]. On the other hand, the *Apodemus* mice are also widely spread in Europe hosting different hantaviruses, which reveals a complex ecology and evolution. The severe form of HFRS, with high mortality rate, was reported in the Balkan region in the early 1950s. The etiologic agent, Dobrava virus (DOBV) was characterized in 1992, after isolation from its rodent host *Apodemus flavicollis* captured in Dobrava village, Slovenia [41]. Later, a new DOBV-like virus was isolated from *A. agrarius* captured in Tula region in European Russia [42]. Molecular and phylogenetic analyses have shown that this is a new lineage of DOBV, named DOBV-Aa, which causes a mild to moderate form of HFRS in Central Europe [43,44]. Another DOBV-like isolate was recovered from *A. agrarius* captured on the Saaremaa island of Estonia [45]. This new genetic lineage was also accepted as a new virus species, named Saaremaa virus (SAAV) [46], after it was found in a natural reservoir in several different European countries [5]. Until now, infection with SAAV has been confirmed using serological methods in only three HFRS patients, albeit no molecular evidence has yet been postulated [47]. In addition, a fourth lineage of DOBV-like virus was detected in *Apodemus ponticus* from Sochi district, Russia [48]. It is unusual for a hantavirus, but DOBV has already been found in three different *Apodemus* species and although all lineages share high amino acid sequence similarity, they can be separated phylogenetically and also seem to possess different virulence towards humans [48].

Another hantavirus is present worldwide, Seoul virus (SEOV) harboured by *Rattus norvegicus* [49]. Its global distribution is the result of host dispersion all over the world. In Europe, SEOV persistence was demonstrated in a population of *R. norvegicus* captured in France, but no human infection in Europe has been reported [50]. In contrast to other hantaviruses, SEOV experienced only a minor geographical variation [7,51]. In Asia distinct lineages of SEOV-related hantaviruses were found: Gou virus, harboured by *Rattus rattus* [52], Serang virus is carried by *Rattus tanezumi* [53] and Thailand virus, from *Bandicota indica* [54].

### *New World hantavirus*

A second group of hantaviruses are so-called 'New World hantavirus', which were first recognized in 1993, after an outbreak of an acute pulmonary distress syndrome in America. The causative agent was named SNV and isolated from the common deer mouse, *Peromyscus maniculatus* [3]. Soon after, many new hantaviruses were isolated from different mice and rats inhabiting the Americas [55]. In South America, the most important hantavirus is ANDV, which is the main causative agent of HCPS in Argentina [56] and the only hantavirus for which an ability to spread from human to human has been described [57,58]. Altogether, there are more than 30 new hantavirus strains and genetic lineages throughout the Americas, which have been recently review in detail by Jonsson *et al.* [7].

### *Insectivore-borne hantaviruses*

Although several studies have shown the presence of antibodies that cross-react with Eurasian hantaviruses in African populations, until 2006 the African continent was a blank spot on the hantavirus map [59]. The first African hantavirus was named Sangassou virus and was found in African wood mouse, *Hylomyscus simus* [59]. Soon after that, another African hantavirus (Tanganya virus) was isolated, surprisingly from a shrew host, *Crocidura theresae*, in Guinea [60]. For a long time hantaviruses were believed to be rodent-borne pathogens, but since 2006 several new shrew and mole-borne hantaviruses have been discovered. Above that, historically the first discovered hantavirus, Thottapalayam virus, in 1964, was isolated from Asian house shrew (*Suncus murinus*) and was placed in the genus Hantavirus, based on its morphological features [61,62]. Besides Africa and Asia, also in Europe several insectivores were identified as hantavirus hosts. The most spread shrew-borne hantavirus in Europe is Seewis virus, first isolated from *Sorex araneus* in Switzerland [63]. Shortly thereafter, Seewis virus was found in different *Sorex* sp. in several countries in Europe [64–66]. Nothing is known about the pathogenicity of shrew-borne or mole-borne hantaviruses, but concerning the low amino acid similarities between rodent- and shrew-borne hantaviruses this is not a surprise (reviewed in ref. [8]). The first serological assay to detect Thottapalayam virus has shown the presence of antibodies in a febrile patient in Thailand [67]. Finally, we can conclude that additional research will reveal hantavirus evolution and significance for human health.

Quite recently, hantaviruses were molecularly detected in bats from Sierra Leone and Cote d'Ivoire [68,69]. Even though hantaviruses detected in bats are distinct from other hantaviruses, the role of bats as novel hosts or as spillover infection is still under research. Nonetheless, these findings underline the complex evolutionary history of hantaviruses.

## Hantavirus phylogeny

Hantaviruses are associated with their natural reservoir hosts, mainly rodents, but also insectivores (shrews and moles) and bats. The chronically and probably asymptomatically infected animals may excrete the virus in their urine, faeces and saliva for months. The genetic and serological relation of hantaviruses follows that of their natural reservoir; these viruses have probably coevolved with their rodent hosts for millions of years [70]. They are considered to be one of the best examples of a long-term association between RNA virus and the host. However, some analyses have proposed that similarities between the phylogenies of hantaviruses and their natural hosts are a result of a more recent history, probably a result of host switching and local adaptation, rather than joint host and

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virus co-evolution [71]. In addition to host switching events between closely related rodent species, recent findings on insectivore-associated hantaviruses call for revaluation of the co-divergence concept [72].

The association between hantaviruses and their natural hosts reflects also in their phylogeny. Rodent-associated hantaviruses form three major evolutionary clades that correspond to the three Muridae subfamilies of their natural hosts. Phylogenetic analyses show that the viruses carried by Arvicolinae (voles), Sigmondontinae (New World rats and mice) and Murinae (Old World rats and mice) rodent subfamilies each form a separate branch. Insectivore-associated hantaviruses and their carriers from families Sorcidae (shrews) and Talpidae (moles) form a fourth evolutionary clade. Bioinformatics analysis of a hantavirus recently detected in an African insectivorous bat, *Nycteris hispida* (family Nycteridae), showed high degrees of identity to shrew- and mole-associated hantaviruses. The genetic variation within a certain hantavirus type is related to geographic distribution and distance, which may depend on the ancestral migration routes of the corresponding rodent reservoir [4]. Recently, several novel hantaviruses with unknown pathogenicity for humans have been identified in Africa in a variety of insectivores. These insectivore hantaviruses share very low amino acid sequence similarity with rodent-borne hantaviruses and consequently probably no serological cross-reactivity either. This explains why they have remained undiscovered for such a long period [8].

## Epidemiology of hantavirus infections

Humans do not belong to the natural host range of hantaviruses, and infection generally occurs accidentally by inhalation of virus-containing aerosols from rodent excretions such as urine, faeces and saliva [73,74]. Although the aerosol route of infection is undoubtedly the most common, human infection after a rodent bite has also been reported [75]. Person-to-person transmission was considered unlikely until 1996, when reports regarding transmission of ANDV in an HCPS outbreak in Argentina changed this perception [76,77].

The risk of contracting hantavirus from rodents is related to closeness of contact. People who live or work in close contact with infected rodents are at increased infection risk, with occupations such as animal trappers, mammalogists, forestry workers, farmers and military personnel at highest risk [78–80]. Humans are usually infected from aerosolized rodent excreta when working with hay and crops during harvesting, cutting wood inside dusty woodsheds, cleaning cellars, barns, sheds or summer cottages in the autumn, especially when these spaces are poorly ventilated [5].

The time and space distribution of hantavirus infections in man mirror the distribution of their rodent hosts. Hence HFRS cases are reported in Europe and Asia, while HCPS has only been described in the Americas, with different hantaviruses being found where their hosts predominate [7,73]. Today, approximately 100 000 HFRS cases are estimated to occur annually, with China being the most endemic country, accounting for 70–90% of all HFRS cases (40 000–60 000 cases annually in the past few years) [81,82]. It should however be kept in mind that asymptomatic or non-specific mild infections probably outnumber the symptomatic, characteristic infections. In addition, hantavirus disease is not notifiable in all the countries where clinical cases occur [5].

### *Epidemiology of HFRS in Eurasia*

Seven hantaviruses have been associated with HFRS so far (Table 1). In Asia severe cases of HFRS are caused by HTNV and Amur/Soochong virus, with mortality rates up to 15%, whereas infections with SEOV result in moderate disease course with case

**Table 1**
List of medically important hantaviruses

| Group | Virus | Geographic distribution | Rodent carrier | Disease |
|---|---|---|---|---|
| Old World hantaviruses | Amur/Soochong | Far East Russia | *Apodemus peninsulae* | HFRS |
| | Dobrava | Balkans | *Apodemus flavicollis* | HFRS |
| | Hantaan | Russia, China, South Korea | *Apodemus agrarius* | HFRS |
| | Puumala | Europe, Asia | *Myodes glareolus* | HFRS (NE) |
| | Luxi | China | *Eothenomys miletus* | HFRS |
| | Saaremaa | Europe | *Apodemus agrarius* | HFRS |
| | Seoul | South Korea | *Rattus* | HFRS |
| | Tula | Europe, Russia | *Microtus arvalis* | HFRS* |
| New World hantaviruses | Anajatuba | South America | *Oligoryzomys fornesi* | HCPS |
| | Araucaria | South America | *Oligoryzomys nigripes, Oxymycterus judex, Akodon montensis* | HCPS |
| | Araraquara | Brazil | *Bolomys lasiurus* | HCPS |
| | Bayou | North America | *Oryzomys palustris* | HCPS |
| | Bermejo | Argentina | *Bolomys lasiurus* | HCPS |
| | Black Creek Canal | North America | *Sigmodon hispidus* | HCPS |
| | Castelo dos sonhos | South America | *Oligoryzomys eliurus* | HCPS |
| | Choclo | Panama | *Oligoryzomys fulvescens* | HCPS |
| | Itapua | South America | *Oligoryzomys nigripes* | HCPS |
| | Juquitiba | Brazil | *Oligoryzomys nigripes* | HCPS |
| | Laguna Negra | Argentina, Bolivia, Paraguay | *Calomys laucha* | HCPS |
| | Lechiguanas | Argentina | *Oligoryzomys flavescens* | HCPS |
| | Maporal | South America | *Oligoryzomys delicatus* | HCPS |
| | Monongahela | North America | *Peromyscus leucopus* | HCPS |
| | Neembucu | South America | *Oligoryzomys chacoensis* | HCPS |
| | New York | North America | *Peromyscus leucopus* | HCPS |
| | Oran | Argentina | *Oligoryzomys longicaudatus* | HCPS |
| | Paranoa | South America | Not known | HCPS |
| | Rio Mamore | Bolivia, Peru | *Oligoryzomys microtis* | HCPS |
| | Sin Nombre | North America | *Peromyscus maniculatus* | HCPS |

HCPS, hantavirus cardiopulmonary syndrome; HFRS, haemorrhagic fever with renal syndrome; NE, nephropathia epidemica.
* Association with the disease not definitely confirmed.

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fatality rates of 1–2%. Annually, from 40 000 to 60 000 cases are reported, 99% of them from China [7,73,83].

In Europe, more than 9000 HFRS cases per year are reported, with PUUV infections being the most predominant. In general, PUUV infections occur throughout central and northern Europe, the Balkans and Russia within the range of the *Myodes glareolus* habitat and result in a mild form of HFRS, known as NE. Most PUUV-associated cases have been diagnosed in parts of European Russia, Finland and Sweden. In recent years NE has been fairly common also in Belgium and Germany, followed by Norway, France, Hungary, Austria, Slovenia and others [4,5,84].

Severe cases of HFRS in Europe are caused by DOBV, carried by *A. flavicollis*, and have so far been identified only in the Balkan region, although the host distribution is much wider [85–89].

SAAV (and/or DOBV-Aa) carried by *A. agrarius* has been recognized as a distinct causative agent of a mild form of HFRS, reported in Russia, Germany and Slovakia [35,48,90,91]. In contrast to DOBV-HFRS cases in the Balkans, where mortality rates up to 12% have been reported [86], and no fatal cases were associated with the SAAV caused HFRS. Recently, another lineage of DOBV was identified in *A. ponticus* in the Sochi region in European Russia and was associated with a moderate-to-severe form of HFRS [48]. The broad spectrum of clinical diseases caused by the four different DOBVs, despite their close genetic resemblance, could perhaps be explained by the three different rodent species that represent their natural reservoirs.

Tula virus has been associated with human infections in the Czech Republic, Switzerland and Germany, but this association has not been unequivocally demonstrated [35,36,92].

Through in sero-epidemiological surveys, human hantavirus infections have also been reported in Italy [93], Latvia [94], Lithuania [95], Moldova [96], Spain [97] and the UK [98], but no clinical cases have been registered in these countries.

### *Epidemiology of HCPS in the Americas*

Since HCPS was first recognized as a hantaviral disease in the Four Corners area in May 1993, clinical cases have also been confirmed in Argentina, Bolivia, Brazil, Canada, Chile, Panama, Paraguay and Uruguay and at least 15 hantaviruses have been associated with HCPS. Approximately 200 cases of HCPS per year are reported jointly in North and South America. Even though the number of reported cases is considerably smaller than that of HFRS, the average case fatality in HCPS is around 40%. SNV is now known to be the predominant cause of HCPS in the USA, whereas in South America the most important causative agent is ANDV [7,99]. ANDV is so far also the only hantavirus with reported person-to-person transmission with high mortality rates [57,58,77,100]. In addition, it has been suggested that HCPS-associated viruses, like HFRS-causing viruses, may cause unrecognized, asymptomatic or subclinical infections. Namely, a high prevalence of antibodies against HCPS-causing hantaviruses was reported in some populations despite rare clinical cases [101,102].

### *Hantavirus infection in Africa*

In Africa, the first serological evidence of hantavirus infections was obtained in 1984, when Gonzalez *et al.* demonstrated hantavirus antibodies in humans and rodents in Benin, Burkino Faso, Central African Republic and Gabon [103]. Since then, human hantavirus infections have been demonstrated through serological surveys also in Senegal, Nigeria, Egypt, Djibouti and Guinea [104–108]. However, only a single case of possible HFRS in Africa has been reported in the literature to date [109].

## Hantavirus-associated diseases/clinical syndromes

Hantavirus infection in humans can result in two clinical syndromes: HFRS or HCPS caused by Old World or New World hantaviruses, respectively. The differences between the hantavirus-associated diseases are caused by the fact that different vascular beds are predominantly affected, namely renal medulla capillaries during HFRS and pulmonary capillaries during HCPS. On the other hand, the initial symptoms of all hantavirus infections are similar, including an abrupt onset of high fever, malaise, myalgia and other flu-like symptoms. Common factors of HFRS and HCPS are also increased vascular permeability leading to hypotension, thrombocytopenia and leucocytosis with a left shift [21,55,110].

### *Hemorrhagic fever with renal syndrome*

The clinical presentation of HFRS varies from subclinical, mild, and moderate to severe, depending in part on the causative agent of the disease. In general, HFRS caused by HTNV, Amur/Soochong virus or DOBV are more severe with mortality rates from 5 to 15%, whereas SEOV causes moderate disease and PUUV and SAAV cause mild forms of disease with mortality rates <1%. Nevertheless, an individual case of PUUV infection may be severe, an individual HTNV infection may be mild, and infections are commonly subclinical seroconversion [7,111,112].

A typical course of HFRS can be divided into five distinct phases: febrile, hypotensive, oliguric, polyuric and convalescent (Fig. 2). These phases are better distinguished in severe forms of disease caused by HTNV and DOBV. After an incubation period between 2 and 4 weeks, the disease starts abruptly with high fever, chills, headache, backache, abdominal pains, nausea and vomiting. Somnolence and visual disturbances (blurred vision) are frequently reported. This febrile phase usually lasts 3 to 7 days. Towards the end of this phase conjunctival haemorrhages and fine petechiae occur initially on the palate. The hypotensive stage can last from several hours to 2 days. In severe cases, hypotension, even shock, may develop rapidly and one-third of HFRS deaths are associated with fulminant irreversible shock at this stage. Thrombocytopenia and leucocytosis are characteristic of this phase and if severe haemorrhagic disease occurs, its onset is at this stage. Haemorrhagic manifestations can include petechiae on the skin and mucosa, ecchymoses, conjunctival suffusion, haematemesis, epistaxis, haematuria, melaena and fatal intracranial haemorrhages. In the oliguric phase, which lasts 3–7 days, blood pressure becomes normalized, while kidney function is transiently decreased, leading to oliguria or even anuria, proteinuria, abnormal urinary sediment, including microscopic haematuria, and azotaemia. During the oliguric phase, which is usually accompanied by abdominal or back pain, patients with severe symptoms have to be treated by haemodialysis. One-half of fatalities occur during this phase. Typical laboratory findings are elevated levels of serum creatinine and urea. In the polyuric phase, renal function starts to recover and urinary output increases. The onset of the diuretic phase is a positive prognostic sign for the patient. It can last for days or weeks with patients passing several litres of urine per day. Convalescence, characterized by recovery of clinical and laboratory markers, is usually prolonged and can last for up to 6 months. Full recovery is usually reached and longer-lasting complications are rare but can include chronic renal failure and hypertension [98,111,113]. In children, the clinical picture closely mimics that in adults but is often less severe. However, abdominal manifestations are registered more often [114–116].

In milder forms of HFRS caused by SEOV, *A. agrarius*-associated DOBV (DOBV-Aa), SAAV or in NE caused by PUUV the five phases of HFRS are not easily distinguishable. The clinical picture of PUUV

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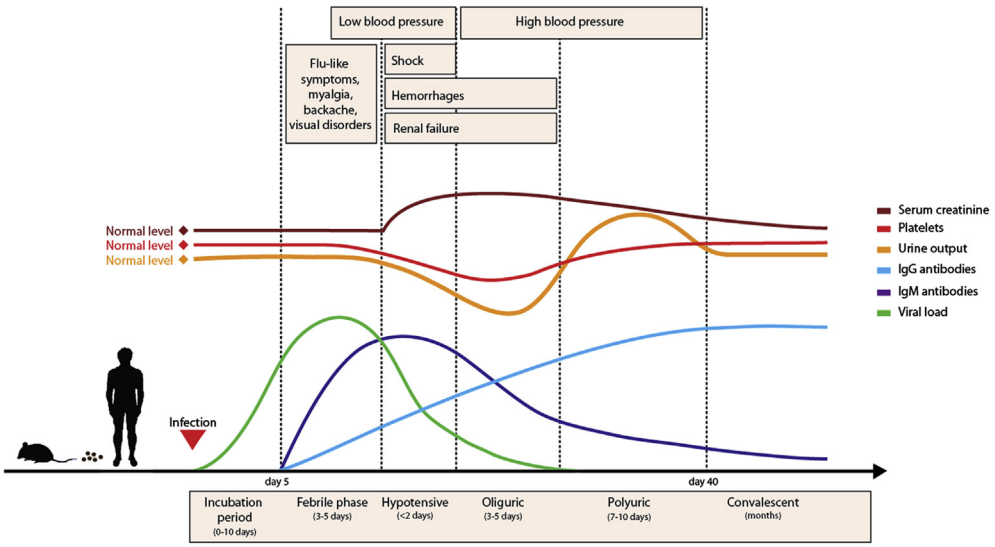


**Fig. 2.** Schematic representation of hantavirus infection kinetics with a clinical course of the disease in humans. A typical course of haemorrhagic fever with renal syndrome (HFRS) can be divided into five distinct phases: febrile, hypotensive, oliguric, polyuric and convalescent. After the infection viral load starts to peak and with the onset of the first clinical symptoms, the antibodies rise. Hallmark laboratory findings that are substantial with development of HFRS are decreases in platelets and urine output and increase in serum creatinine level.

infection is basically similar to DOBV, but shows a limited spectrum of symptoms resulting in lower mortality rates (0.1%). In NE, severe haemorrhagic manifestations and shock usually do not occur, but mild haemorrhagic symptoms such as petechiae are seen in about one-third of patients. Instead of full-blown shock syndrome, hypotension is observed. Although most patients have signs of kidney function failure, it is generally less prominent than in HFRS caused by more virulent hantaviruses, with oliguria or anuria manifesting in less than half of the patients. Altogether, since the clinical course of NE is often uncharacteristic and resembles more a febrile disease with abdominal pain, it is often not diagnosed as NE [117,118].

Infection with SEOV causes a moderate form of HFRS with clinical presentation and course very similar to HFRS caused by HTNV. However, SEOV infections are often associated with the presence of hepatitis, which is generally not present in other hantavirus infections [113,119].

### *Hantavirus cardiopulmonary syndrome*

In comparison with HFRS, HCPS is a more severe disease with higher case fatality rates, from about 30 to 50%. The clinical course of HCPS generally progresses through three phases: prodromal, cardiopulmonary and convalescent, and clinical manifestations can vary from mild hypoxaemia to respiratory failure with cardiogenic shock [120].

The prodromal phase is usually a short non-specific illness with flu-like symptoms such as high fever, chills, myalgia, nausea, headache, vomiting, abdominal pain and diarrhoea. This is followed by a rapid progression to the cardiopulmonary phase with abrupt onset of progressive cough, shortness of breath and tachycardia. Patients develop acute non-cardiac pulmonary oedema and hypotension. Bilateral infiltrates develop rapidly, sometimes associated with pleural effusions, causing respiratory failure and making mechanical ventilation mandatory. In severe cases this stage is complicated by cardiogenic shock, lactic acidosis and massive haemoconcentration. Patients can die within hours of hospitalization. Patients who survive the acute phase of the disease enter the polyuric stage, which is accompanied by the resolution of the pulmonary oedema. Although convalescence is slow and patients often complain about weakness, fatigue and impaired exercise tolerance, the recovery is generally complete, without any sequelae [99,110,120].

Although renal disease is usually assigned to HFRS and lung disease to HCPS, the increased medical knowledge about the clinical courses of HFRS and HCPS has resulted in the conclusion that both syndromes partly overlap. Namely, the numbers of reported HFRS cases with lung involvement and HCPS cases with renal and/or haemorrhagic involvement are continuously growing [121–123].

## Hantavirus pathogenesis

In both animals and humans hantavirus infections mainly occur in pulmonary or renal endothelial cells and macrophages, albeit the viral antigen is present also in many different organs [124,125]. In contrast to humans, animals tend to be persistently infected throughout their entire lifespan and still capable of transmitting the virus to other animals and humans. Therefore, the lack of apparent disease in the natural host and the lack of proper animal models have limited our understanding of hantavirus pathogenesis [126]. Until recently, there was no animal model for HFRS, because the Syrian hamster model used for ANDV and HCPS [127] is not applicable to HFRS. However, cynomolgus monkeys infected with wild-type PUUV strains produce disease symptoms that resemble NE clinical pathology [128,129].

The central phenomena behind the pathogenesis of both HFRS and HCPS are increased vascular permeability and acute thrombocytopenia with marked permeability of microvascular beds [11,130]. Hantavirus replication occurs in the vascular endothelium but does not seem to cause direct cytopathic effects [131–133]. The hantavirus replication cycle is rather slow, resulting in late viraemia on days 5 to 10 after infection [134], which would suggest virus persistence rather than the acute lytic progression seen in other viral haemorrhagic fevers [11]. In human kidney tissues of patients with NE the viral antigen was detected along with inflammatory cell infiltrations and tubular damage, suggesting that viral replication together with the immune response are involved in tissue injury [133,135]. The peritubular area of the distal nephron is the main site where an increased expression of several cytokines and

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endothelial adhesion molecules is seen [135]. The renal involvement in acute NE is characterized by markedly decreased glomerular filtration rate and renal plasma flow. Increased glomerular permeability leads to massive proteinuria and is a sign of tubular dysfunction [136].

It is not yet completely understood how hantaviruses disseminate in the human body, after inhalation, the infection begins with an interaction of $G_n$ and $G_c$ surface proteins with β-integrin receptors at the target cell membrane [137,138]. It has been shown that both pathogenic (HTNV, SEOV, PUUV, SNV) and non-pathogenic (Tula virus, Prospect Hill virus) hantaviruses infect human endothelial cells, but they use a different integrin receptor ($\alpha_v\beta1$ versus $\alpha5$ $\beta_3$) [137]. Probably immature dendritic cells play a pivotal role in hantavirus dissemination, as they express $\beta_3$-integrin receptors and are located in the vicinity of epithelial cells [139]. They can also serve as vehicles for the transport of the virions through the lymphatic vessels to the regional lymph nodes, where after further replication virions can reach endothelial cells [110]. These cells allow virus replication, which induces immune activation, especially by macrophages and $CD8^+$ T cells [7]. It has been shown that a type I interferon response has been delayed in cells infected with pathogenic hantaviruses, resulting in higher viral titres [110]. Inflammatory cytokine and chemokines produced by antiviral innate immune response can act as double-edged sword. Increased levels of interleukin-10, interferon-γ and tumour necrosis factor-α in serum samples were found in both DOBV- and PUUV-infected patients. In addition, the significantly higher levels of interleukin-10 and tumour necrosis factor-α were detected in patients with a more severe clinical course of the disease [140]. In NE patients the disease severity is characterized by elevated pro-inflammatory cytokines interleukin-6 and tumour necrosis factor-α, but low immunosuppressive transforming growth factor-$\beta_1$ levels. The upregulation of transforming growth factor-$\beta_1$ in the late phase of acute PUUV infection suggests a protective immunoregulatory role [141]. In NE patients cytotoxic T cells may contribute to the capillary damage via immunopathology, also by increased concentrations of nitric oxide and tumour necrosis factor-α [142,143]. In contrast with other haemorrhagic fever viruses, which inhibit maturation of infected dendritic cells, hantaviruses induce their maturation and so elicit a vigorous T-cell response during acute infection [144]. In NE patients the cytotoxic T-lymphocyte response enhanced the number of activated $CD8^+$ T cells and reversed $CD4^+$ versus $CD8^+$ T-cell ratio, which coincides with the onset of clinical disease [145–147]. A mixed pattern of T helper type 1 and T helper type 2 immune response patterns, high levels of proinflammatory cytokines and their insufficient suppression by regulatory cytokines leads to the harmful effect of immune response in HFRS-infected patients [110]. Hantavirus pathogenesis is likely to be a complex multifactorial process that includes contributions from immune responses, platelet dysfunction and the deregulation of endothelial cell barrier functions [11]. Above that, a genetic predisposition towards severe HFRS disease was shown to be related to HLA type, but different hantaviruses were associated with different HLA haplotypes. A genetic predisposition towards a severe form of HFRS caused by PUUV infection was shown to be associated especially with haplotype HLA-B*8 DRB1*03:02 [148–151]. The same HLA haplotype was again correlated with a severe course of HCPS after ANDV infection [152]. In addition, HLA haplotype HLA-B*35 was more frequent in severe disease progression in patients infected with DOBV, especially in fatal cases [151]. The same HLA type has already been reported in correlation with a severe form of HCPS induced by SNV [144].

## Diagnosis and treatment

The diagnosis of HFRS and HCPS is based on clinical and epidemiological data and laboratory tests. The symptoms that should alert the physician to a possible hantavirus infection are high fever, headache, abdominal and back pains and pathological laboratory findings with leucocytosis, thrombocytopenia, increased serum creatinine, proteinuria and haematuria. However, it is almost impossible to diagnose hantavirus infections solely on clinical grounds, especially in cases with mild and moderate clinical symptoms, as the early signs of the disease are non-specific [5,73].

Laboratory diagnosis of acute hantavirus infections is based on serology as virtually all patients have IgM and usually also IgG antibodies present in serum at the onset of symptoms. The most commonly used serological tests are indirect IgM and IgG ELISA as well as IgM capture ELISAs, which have higher specificity than indirect ELISAs. Indirect immunofluorescence assays are also regularly used for diagnostics but have lower specificity [113,153]. In addition, rapid 5-minute user-friendly immunochromatographic IgM-antibody tests have been developed and are available commercially [154,155].

The hantavirus infection can also be confirmed by detection of hantavirus genome in blood or serum samples by RT-PCR. Both traditional and quantitative RT-PCR are used to detect viraemia [156–158]. Although the presence of viraemia varies, viral RNA can usually be detected if an acute sample is available. It has also been suggested that higher viraemia is found in more severe hantavirus infections (DOBV, SNV, ANDV), compared with milder infections, caused by PUUV [134,150,159–161]. In addition, with detection of viral RNA, hantavirus infection has been confirmed even before the presence of specific antibodies [100,159].

At present, no specific U.S. Food and Drug Administration-approved therapy is available for either HFRS or HCPS; the treatment is primarily supportive. It is recommended that patients with HCPS and severe HFRS should be moved to an intensive care unit for close monitoring and care. Maintaining the fluid and electrolyte balance together with circulatory volume is very important and must be carefully monitored according to the patient's fluid status, amount of diuresis and kidney function to avoid dangerous over hydration (for patients that are anuric and with leaky capillaries). HFRS patients with severe renal insufficiency, which is associated with severe fluid retention and pulmonary oedema, may need dialysis treatment. If extensive thrombocytopenia and bleeding are present, platelet transfusions can be used [99,111,120]. In HCPS, supplemental oxygen, mechanical ventilation when indicated, fluid management, and the appropriate use of pressors are crucial [99].

Ribavirin was shown to possess anti-hantaviral activity *in vitro* and *in vivo* and was proven effective in treatment of suckling mice infected with HTNV [162]. Ribavirin has been used in the treatment of HFRS in China and clinical studies on Chinese HFRS patients suggest that ribavirin therapy can significantly reduce the mortality rate if given in the first 5 days after onset of symptoms [163,164]. In a recent report by Rusnak *et al.*, it has been confirmed that administration of intravenous ribavirin early in the course of HFRS reduces the occurrence of oliguria and the severity of renal insufficiency [165]. Intravenous ribavirin has also been examined for the treatment of HCPS. However, in a few limited trials treatment with ribavirin had no clinical benefit for the patients [166,167].

## Prevention

One of the major risk factors for infection is living close to forested areas and cleaning up around houses or sheds [168]. In addition, occupational exposures, such as construction or forest workers, farmers and soldiers are at increased risk [80,168–170].

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The preventive measures are based mainly on rodent control, reducing rodents' shelter and food sources near human housing, eliminating rodents inside homes and avoiding contact with potentially contaminated areas. Apart from using standard precaution measures, the only way of minimizing the risk of hantavirus disease could be effective vaccines, but up to now no vaccines were approved for wide use in Europe or the USA. In Asia, the Republic of Korea, Hantavax® has been used for a number of years. The vaccine is derived from formalin-inactivated HTNV-infected suckling mouse brain, but frequent booster doses are needed for protective immunity [171]. In China, several different formalin-inactivated vaccines from animal tissues have been produced and used, but none has been approved for use in European countries (reviewed in ref. [172]). Apart from that, only two molecular vaccines against HFRS have been tested in humans, the first was recombinant vaccinia-vectored vaccine expressing the M segment of HTNV [173] and the second plasmid DNA [174]. The advantage of DNA vaccines is that they offer an easy way to construct multivalent vaccines and they are able to induce long-lasting humoral and cellular immunity. Such vaccine, using an M segment construct of HTN and PUUV, is currently in Phase I clinical trials in the USA to determine the safety, tolerability and immunogenicity [175,176].

## Conclusions

Hantavirus infections belong to the increasing group of emerging zoonotic infectious diseases. Over the past few decades the understanding and recognition of hantavirus infection has greatly improved worldwide. Both, the amplitude and the magnitude of hantavirus outbreaks have been increasing. This could be explained by better clinical awareness, development of sensitive diagnostic tests, intensive research on reservoir and changing climatic conditions. Although some are newly detected, hantaviruses are old viruses, but environmental changes may affect the geographic distribution, abundance and the dynamic of the carrier rodent species, and hence the epidemiology of hantavirus disease. Although, today we can only speculate how extensive environmental and climatic changes will be, hantavirus infections will remain a public health threat. Therefore, further research on hantavirus pathogenesis, diagnostics, antiviral and vaccine development are needed.

## Transparency declaration

The authors declare that they have no conflicts of interest.

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