Review Article

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Microbiological and epidemiological review of Hantavirus: A Review

Hardi Fattah Marif [1] and Kwestan Najm Ali[1*]

[1] Department of Clinic and Internal Medicine, College of Veterinary Medicine, University of Sulaimani, Sulaimani City, Kurdistan-Iraq.

*Corresponding author: kwestan.ali@univsul.edu.iq, Phone number: +964-07701598448

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Abstract

Hantaviruses are rodent viruses that have a world-wide distribution. Rodents and insectivores act as asymptomatic, chronic, persistently infected carrier hosts, whereas humans are dead end hosts and may exhibit symptoms after an incubation period of between one and six weeks. Hantaviruses infect humans and causing either hemorrhagic fever with renal syndrome (HFRS) or Hantavirus cardiopulmonary syndrome (HCPS). Due to the absence of the treatment and approved vaccine in the USA, European and Asian countries, the public awareness and precautions are the only way of minimizing the risk of Hantavirus infection. This review provides a microbiological and epidemiological summary of the Hantavirus diseases in rodents and human beings. We concluded that the disease is a serious zoonotic disease the affect animals and humans and the mortality rate is really high. A wide range of different diagnostic tests play an important role in the diagnosis of the Hantavirus.

Keywards: Hantavirus, HFRS, HCPS and vaccine.

المراجعة الميكروبيولوجية والوبائية لفيروس هانتا

الخلاصة

فيروسات هانتا هي فيروسات قوارض منتشرة في جميع أنحاء العالم. يمكن أن تصيب الزبابة والشامات والخفافيش والعديد من أنواع القوارض. هذه الخزانات في الغالب بدون أعراض. ومع ذلك ، يمكن لبعض فيروسات هانتا التي تنقلها القوارض أن تصيب البشر وتتسبب إما في الحمى النزفية المصحوبة بمتلازمة الكلى (HFRS) أو متلازمة فيروس هانتا القلبية الرئوية (HCPS) لم يتم الإبلاغ عن أي لقاحات أو علاجات حالية معتمدة من إدارة الغذاء والدواء الأمريكية. نظرًا لغياب العلاج واللقاح المعتمد في الولايات المتحدة الأمريكية والدول الأوروبية والآسيوية ، فإن الوعي العام والاحتياطات هي الطريقة الوحيدة لتقليل مخاطر الإصابة بفيروس هانتا. تقدم هذه المراجعة ملخصًا ميكروبيولوجيًا ووبائيًا لأمراض فيروس هانتا في القوارض والبشر. علاوة على ذلك ، نقدم معلومات حول الاختبارات الخاصة بتشخيص أمراض فيروس هانتا في الإنسان والحيوان.

Introduction

Hantaviruses are negative-sense RNA viruses belong to the family Bunyaviridae (1). The genus Hantavirus consists of multiple species, 21 species have been confirmed to cause clinical and symptomatic disease in humans (2). The Hantavirus genome is segmented, containing small, medium and large (S, M and L) segments. The segments code for essential structural proteins including nucleocapsid (N) protein (S segment), two glycoproteins Gn and Gc (M segment) and an RNA-dependent RNA-polymerase (L segment). The genome segments are surrounded by N proteins to form ribonucleoproteins within a lipid envelope displaying spikes formed of Gn and Gc proteins (3) (Figure 1).

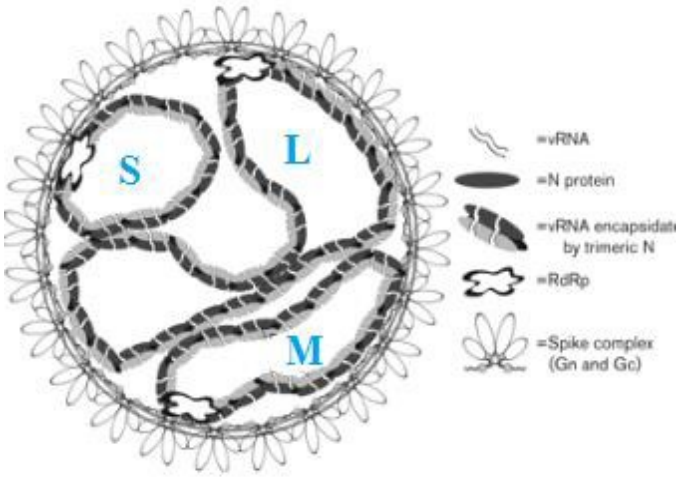

Figure 1: Hantavirus structure. Adapted from (3)

1-Characteristics of the Disease

We can divide Hantaviruses into two groups, which have different clinical signs. Old World Hantaviruses cause Hantavirus Haemorrhagic Fever with Renal Syndrome (HFRS), and New World Hantaviruses cause Hantavirus Cardiopulmonary Syndrome (HPS). Hantavirus Cardiopulmonary Syndrome is found mainly in the United States (Figure 3). It can cause severe disease with cardiopulmonary symptoms and a mortality rate of up to 50% (4). The Hantaviruses causing this syndrome include Sin Nombre, Andes, New York and Bayou (Table 1). Haemorrhagic Fever Renal Syndrome is Eurasian in origin and produces symptoms in a five stage clinical course. Mortality with this syndrome is up to 12%. A subset of milder disease caused by the Puumala virus is also recognised. The syndrome, known as Nephropathia Epidemica, is associated with mortality rates as low as 0.1% (4).

2-Transmission

Hantaviruses can produce chronic and persistent infections in rodent. Hantaviruses have involved with the rodent hosts, resulting in little or no pathology. The viral transmission across the species barrier results in human infections.

2-1. Direct transmission

a. By the entrance of the virus into an oral or ocular mucous membranes after having direct hand contact with rodent urine, droppings, or saliva. (5).

b. Biting by an infectious animals is considered a form of virus transmission to humans. This may happen rarely (6, 7).

2-2. Indirect transmission

a. Human infection by inhalation of infectious material aerosolized rodent excretion is considered to the most common route. This mostly occurs during the cleaning process of the dirty places, dusts, and debris that contaminated with rodent urine, droppings or nesting material (8, 9).

b. Another theorized point to cause human infection is the ingestion of contaminated food.

c. Person to person - extremely rare; it has been reported in a single outbreak of Andes virus in Argentina in 1996 (10).

3.Pathogenesis

In Rodents:

Hantavirus infection can be fatal in neonates, although maternal antibodies provide transient protection. In adults, viraemia is rapidly cleared; however viral antigens have been detected in endothelial cells and macrophages in a range of organs (including the lungs and kidneys) without causing clinical disease. There is an age dependent outcome in adults, which is associated with immune mediated mechanisms (11, 12). Studies have shown that cytotoxic T cells are essential for viral clearance, however, investigations into cell mediated immunity in rodents indicate suppression of pro-inflammatory and effector T cells by regulatory T cells, indicating humoral immunity alone may protect adult rodents from clinical disease. This immune response is in stark contrast to that of human patients.

In Humans:

The mechanisms of Hantavirus pathogenesis are complex and many of the underlying mechanisms that cause disease are still unresolved. Viral entry is via the respiratory route and it has been assumed that the respiratory tract is the primary site of viral replication. However, identification of the viral antigen in endothelial cells early in the course of infection suggests that these cells are the primary target of the virus. In the later stages of infection virus is found in the parenchyma of numerous organs. Notably, for Seoul virus, this is the kidneys.

Hantavirus binds to endothelial cells via β3 integrins (13, 14), which regulate vascular permeability. In in-vitro studies, however, Hantavirus replication within an endothelial cell monolayer does not demonstrate cytopathic effects or alteration in endothelial cell permeability, indicating that other factors contribute to the pathogenesis of the virus (15).

In addition to infection of endothelial cells, studies have shown that patients with Haemorrhagic Fever with Renal Syndrome (HFRS) have virus present in 2-20% of peripheral blood cells, primarily macrophages and B cells. The infection of macrophages, in particular, is important during the hypotensive phase of infection, as infected macrophages up-regulate production of pro-inflammatory cytokines, mainly TNF-α, which exerts a potent effect on vascular tone. Indeed the level of TNF–α is inversely correlated with blood pressure, i.e. high levels of TNF-α result in lowered blood pressure (15). Studies have also demonstrated that T cells,

whilst important in viral clearance and hence patient recovery, also play an important role in progression of disease (16); that is once levels of CD8+ cells exceed a certain threshold further excessive production of TNF-α and interferon mediates increased vascular permeability, leading to leakage (15).

The pathogenesis of HFRS renal failure is poorly understood but has been attributed to the deposition of immune complexes and immune cell infiltrates, comprising primarily of neutrophils, within the kidney parenchyma (17). An increase in these complexes is observed during the oliguric and polyuric phases of the disease (Figure 1) leading to necrosis, haemorrhage and ischaemia. The acute transient renal failure is characterised by varying degrees of azotaemia, haematuria, proteinuria, polyuria and reduced concentration ability. Recovery of renal function may range from several weeks to months (18**,** 19).

4.Diagnosis

The diagnostic tests of Hantavirus infection are different depending on the stages of infection at presentation due to the short viraemic phase of infection.

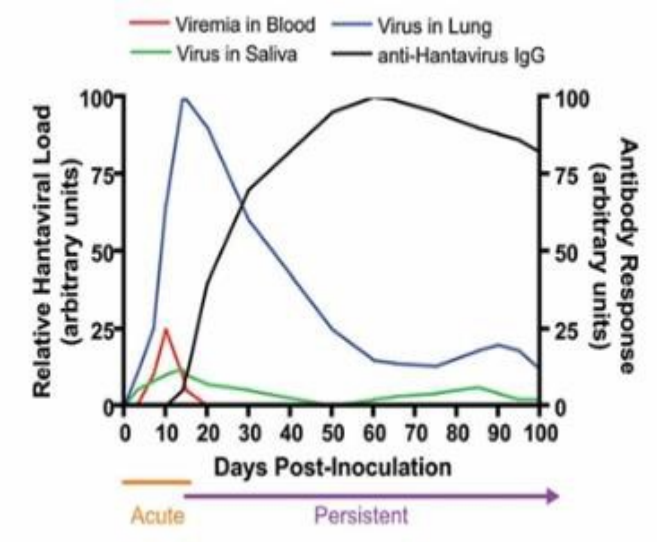

Figure 2: Kinetics of Hantavirus infections Adapted from (20).

4-1. Serological Symptomatic Panel

a. Microscopic agglutination test (MAT)

MAT is the Gold Standard test requiring two serum samples (21). The sera are incubated with live antigen suspensions of UK endemic Leptospira serovars at 29oC +/- 1oC, for 2-4 hours. Dark field microscopic examination of the serum-antigen mix assesses agglutination, and the titers are determined. The end point is the highest dilution of serum at which 50% agglutination occurs.

Tests are considered to be positive in the presence of clinical signs if:

1. A negative first test is followed by a positive second test.

2. There is a four-fold rise in antibody titer between the first and second tests.

3. An IgM reading on the first test that is several fold above the standard cut-off (1:100) indicates a positive test and negative the need for a second sample.

b. Indirect Immunofluorescence Assay (IFA)

Serology for Hantavirus infections is determined by IFA, as described by (22). Briefly, reference viral strains are propagated in Vero E6 cells (ATCC CRL 1586)1b and fixed on slides. This antigen is incubated with patient sera and fluorescein labelled rabbit anti-human IgM serum (Sigma-Aldrich) 2b diluted 1 in 28 in PBS containing Evan's blue.

c. Enzyme-linked Immunosorbent Assay (ELISA)

The most common serological tests for Hantaviruses are indirect IgG and IgM enzyme-linked immunosorbent assays (ELISAs) as well as IgM capture ELISAs. The rapid IgM capture ELISA developed by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Centers for Diseases Control and Prevention (CDC) are effective for the diagnosis of HFRS and HPS (2). These tests take about 4 to 6 h when performed by trained personnel. Virus-infected lysates or purified N protein can be used as an antigen in ELISAs. ELISAs have been developed for the South American Hantaviruses as well (23).

Virus Isolation

The virus can be isolated from blood samples as previously described by (24) Patient serum can be incubated with Vero E6 cells (Sigma-Aldrich) 2b and blind passaged three times in monolayers with minimal essential media. Confirmation of Hantavirus presence can be achieved by PCR of the blind passaged cells.

PCR

Following virus culture, RNA can be extracted using RNeasy Kit and tested with (PCR) using Superscript III Platinum One step qRT-PCR kit 4b, as described by (25).

Genome Sequencing

Genome sequencing can be performed to further elucidate a potential relationship between human cases and Hantavirus species carried by the local rodent population.

The S-segment of Hantaviruses is less variable and therefore allows for easier tracing of evolutionary change, thus assisting the identification of the origin of the virus. Standard Sanger sequencing on a 3130XL sequencer (Life Technologies) 4b can be undertaken as described by (25).

Epidemiological Review

Worldwide Distribution

Distribution of Hantaviruses can be separated into "New World' viruses, found in the Americas and "Old World' viruses, found in Eurasia. This evolution of viruses has led to two separate disease processes occurring in the two regions; HPS in the Americas and HFRS in Eurasia (Figure 4).

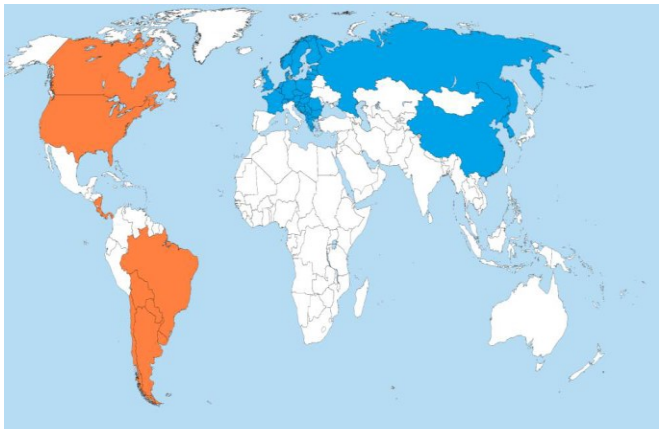

Figure 3: World distribution of Hantavirus Pulmonary Syndrome (orange) and Haemorrhagic Fever with Renal Syndrome (blue).

During the twentieth century, two large disease outbreaks resulted in the discovery of Hantavirus diseases. Korean Haemorrhagic Fever (renamed Haemorrhagic Fever with Renal Syndrome by the World Health Organisation in 1982) was responsible for the death of 3200 US soldiers stationed in Korea from 1951-1954 (26). In 1978, Hantaan virus was isolated by (22) and was identified to be the aetiological agent responsible for Korean Haemorrhagic Fever (22). In 1993, a disease outbreak in the Four Corners region of the USA resulted in identification of Hantavirus Pulmonary Syndrome (previously known as Four Corners disease). Within weeks of the Four Corners outbreak, Sin Nombre virus was isolated as the causative agent and cross-reaction of patient sera with HFRS Hantavirus antigen indicated the relation of the two seemingly different diseases (2). This previously unknown relationship between the two disease presentations led to the discovery of numerous other viruses within the Hantavirus family. There have been reports of Hantavirus outbreaks throughout Europe, Asia and the Americas since World War I, and each year 150,000 people are hospitalised globally with Hantavirus, although many other infections occur undetected (Figure 4). Serological investigation indicated that there were strong evidences of hantaviral infections in humans in Kuwait (27).

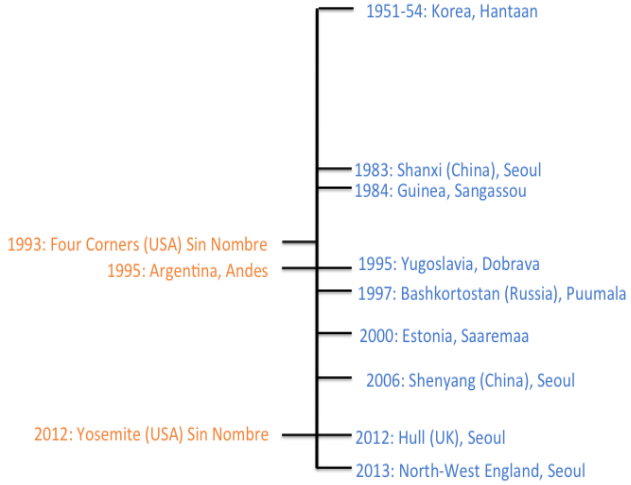

Figure 4: Events of Hantaviral Significance in the 20th Century, HFRS (blue), HPS (orange).

Each species of Hantavirus has a specific reservoir host (Table 1). However, spill over into other wildlife populations may occur and, as such, further maintain the virus within the wild (2). Rodents and insectivores act as asymptomatic, chronic, persistently infected carrier hosts, whereas humans are dead end hosts and may exhibit symptoms after an incubation period of between one and six weeks (28,4). Virus particles are excreted in urine and faeces of rodents and can survive in the environment for 12-15 days within bedding materials (28).

Table 1: Hantaviruses and their host species, geographical range, disease syndrome and reference source (Adapted from 29)

Virus	Reservoir Host	Distribution	Disease
Andes	Oligoryzomys longicaudatus (Long tailed pygmy rice rat)	Argentina	HPS
Dobrava-Belgrade	Apodemus flavicollis (Yellow-neck mouse)	Balkans	HFRS
Hantaan	Apodemus agrarius (Striped field mouse)	China, Russia, Korea	HFRS
Prospect Hill	Microtus pennsylvanicus (Meadow vole)	United States, Canada	None
Puumala	Myodes glareolus (Bank vole)	Scandinavia, Europe, Russia	HFRS (Nephropathia Epidemica (NE))
Saaremaa	Apodemus agrarius (Striped field mouse)	Baltics, Europe, Russia	HFRS (Nephropathia Epidemica (NE))
Sangassou	African wood mouse (Hylomyscus simus)	Guinea	Unknown
Seoul	Rattus norvegicus (Brown rat)	Worldwide	HFRS
Sin Nombre	Peromyscus maniculatus (Deer mouse)	United States, Canada	HPS
Tula	Microtus arvalis (European common vole)	Europe	Unknown

From Rodents to Insectivores

There is growing evidence that Hantaviruses do not exclusively infect rodents as reservoir hosts. Insectivore hosts for genetically distinct Hantaviruses have been described recently. These viruses include (30, 31, 32, 33).

- Azagny and Imjin carried by the Ussuri White-toothed shrew (Crocidura lasiura)
- Oxbow carried by the American shrew mole (Neurotrichus gibbsii)
- Seewis carried by the Eurasian common shrew (Sorex araneus)
- Tanganya carried by Therese's shrew (Crocidura theresae)

The individual reservoir host of the different Hantaviruses influences the epidemiology and ecology of human infection. Although Hantaviruses are most commonly recognised in a rural setting, the urban habitat of the brown rat (Rattus norvegicus) has allowed Seoul virus to disseminate throughout human populations in the urban environment. Indeed, epidemiological studies of brown rat migration implicate the species in the worldwide spread of Seoul virus (34).

Farm workers, military personnel and woodchoppers have all been identified as having an increased risk of contracting Hantavirus due to the outdoor nature of their work. Studies on Hantavirus epidemiology have demonstrated that males are over-represented with male to female ratios of between 2:1 and 3:1. Most infection occurs in the 20-40 year old age group. Infections can occasionally occur in children. This pattern of infection is likely to be due to differences in occupation and lifestyle between men and women (35).

Increases in human cases of Hantavirus in Europe have been associated with pullulation of the rodent reservoir. Climatic variations can result in a mast year in which food available to the rodent is abundant; this increase in food supply leads to improved survival and reproductive success, and

a population increase is observed the following year (36).

2.3. Hantavirus in Mainland Europe

Dobrava virus, carried by the yellow-necked mouse, causes the most severe form of HFRS and seems to be restricted to the South East of the continent in the Balkans. Puumala is the most common agent of HFRS in Europe (37), due to its host, the bank vole, being the most abundant mammal on the continent. Seoul virus is found continent-wide due to its hosts, the black and brown rats, spreading globally via international shipping. Seoul virus causes disease in urban areas, whereas Dobrava and Puumala tend to be more rural.

2.4 .Hantavirus cases in humans in the UK

Several Hantavirus cases in humans have previously been reported in the UK (Table 1).

Prevalence studies

A study of zoonotic diseases in farmers found a seroprevalence of 4.7% in 1991. Farmers were chosen for the study as it was thought that they were more likely to encounter zoonotic disease. However, it should be noted that because of this the seroprevalence in the general population is likely to be much lower (38).

In 1994, investigations were undertaken regarding the seroprevalence of Hantavirus infection in Northern Ireland. Serum from 627 of these patients, who had presented to hospital for conditions such as renal impairment, rashes, lymphadenopathy or abdominal pain, was tested along with serum from 100 were seemingly healthy controls. 16 of the 727 (2.2%) people tested showed antibodies to Hantavirus. This study provided evidence for existence of Hantaviruses in Northern Ireland, although it was not possible to determine the species responsible (39).

Hantaviruses in wild rodents

Following the 1991 cases of Hantavirus in Somerset patients, rodents in the Somerset area were sampled for Hantavirus antibodies. At the time of publishing, 4 of 100 rats and 1 of 102 mice had tested seropositive (40).

Webster *et al.* (1995) conducted a study of the prevalence of various parasites in Rattus norvegicus in 1995. They found 5 of 127 rats to be positive for Hantavirus serologically, using IgG, IFA and IgG ELISA (41).

From September 2009 to November 2011, Pounder *et al.* (2013) trapped 495 rodents and tested them for Hantavirus using PCR on lung tissue. All samples were negative except for one male Microtus agrestis (field vole), which was collected from near Tattenhall in Cheshire. The sample from the vole was sequenced and compared to known Hantaviruses, demonstrating the greatest degree of similarity to other Arvicolinae-associated Hantaviruses. Phylogenetic analyses provided evidence that the virus discovered was actually novel and the authors propose to call it Tatenale (42).

Jameson *et al.,* (2013) reported the first confirmed Hantavirus infection known to be

pathogenic to man in a wild rat in the UK in 2013. Hantavirus was identified in a patient in Yorkshire, and rodents were trapped at the patient's residence and tested for Hantavirus. Two of the four Rattus norvegicus were shown to be positive for presence of Hantavirus RNA, and sequencing showed the virus was Seoul-like.

The reports of Hantaviruses circulating in wild rodent populations in the UK suggest the potential for outbreaks of disease in human populations. Therefore it may be important for clinicians to include Hantavirus as a differential diagnosis in cases of acute renal failure.

Hantaviruses in pets

In 1990 a serological survey for Hantavirus antibodies in cats was conducted. 157 pet and feral cats were tested, of which 15 (9.6%) were seropositive. Among the 81 chronically ill cats sampled, 19 (23%) had antibodies to Hantavirus (43). Whilst these results appear to suggest Hantavirus exposure may be widespread amongst feline populations, as yet there is no confirmation of how Hantavirus may contribute to feline disease, or whether cats may shed the virus and be a source of infection to humans.

In 2013, confirmation of Hantavirus in a patient in North Wales prompted testing of two pet rats, owned by the patient's fiancée, for Hantavirus. Blood and urine samples were taken, and real time PCR was performed, demonstrating the presence of Hantavirus. The rats were euthanized and viral RNA was extracted from the lungs. Sanger sequencing was performed on the viral RNA, which showed the virus to be a Seoul-like virus, similar to but not identical to the strain involved in the Yorkshire case in 2012. The breeder had cared for the pet rats during the period of the man's illness, and subsequently 21 rats from the breeder's colony were tested, by the same methods, for Hantavirus. Seven of the 21 rats demonstrated viral RNA, and preliminary sequencing is suggestive of the same strain present in the 2 rats originally tested (25).

In 1994, McKenna et al., (1994), investigated seroprevalence of Hantavirus infection in Northern Ireland. At this time, there had been no documented cases of Hantavirus infection in humans in Northern Ireland. Sera from 727 patients was tested; 627 of these patients had presented to hospital for conditions such as renal impairment, rashes, lymphadenopathy or abdominal pain, whilst 100 were seemingly healthy controls. 16 of the 727 (2.2%) people tested showed antibodies to Hantavirus. This study provided evidence for the existence of Hantaviruses in Northern Ireland, although it was not possible to determine the species responsible (39).

Conclusion

Depending on the previous studies on Hantaviruses we concluded that the disease is a serious zoonotic disease the affect animals and humans and Hantavirus knowledge, understanding and recognition all over the world are mostly progressed in the last few decades. The hosts of the Hantaviruses are small rodents. This

virus can enter to the human body through aerosols inhalation and can cause Hemorrhagic Fever Renal Syndrome (HFRS), Hantavirus cardiopulmonary syndrome (HCPS) and the mortality rate is really high. A wide range of different diagnostic tests play an important role in the diagnosis of the Hantavirus. Many studies have been reported to curb the transmission of the Hantavirus and focus on having distance between humans and host rodents because there is no approved vaccines and treatments (except Hantavax, which is licensed for human use only in the Republic of Korea).

References

1. Prist RP, Uriarte M, Tambosi RL, Prado A, Pardini R, D´Andrea SP, Metzger PJ. Landscape, Environmental and Social Predictors of Hantavirus Risk in São Paulo, Brazil. Plosone. 2016; 11(10): 1-18.
2. Jonsson CB, Figueiredo LTM, Vapalahti O. A global perspective on Hantavirus ecology, epidemiology and disease. Clinical Microbiology Reviews. 2010; 23:412.
3. Hepojoki J, Strandin T, Lankinen H, Vaheri A. Hantavirus structure - molecular interactions behind the scene. Journal of General Virology; 2012; 93:1631-1644.
4. Muranyi W, Bahr U, Zeier M, van der Woude FJ. Hantavirus infection. Journal of the American Society of Nephrology. 2005; 16:3669-3679.
5. Figueiredo MTL, de Souza MW, Ferrés M, Enria AD. Hantaviruses and cardiopulmonary syndrome in South America. Virus Research. 2014;187:43-54
6. Michalski A, Niemcewicz M, Bielawska-Dro´zd A, Nowakowska A, Gawe J, Pitucha G, Joniec J, Zielonka K, Marciniak-Niemcewicz A, Kocik J. Surveillance of Hantaviruses in Poland: A Study of Animal Reservoirs and Human Hantavirus Disease in Subcarpathia. Vector-borne and zoonotic diseases. 2014; 14 (7): 514-522
7. Hjelle B, Jenison S, Goade D et al. Hantaviruses: clinical microbiologic, and epidemiologic aspects. Critical Reviews in Clinical Laboratory Sciences. 1995; 32:469–508.
8. Olsson GE, Hjertqvist M, Lundkvist A, Hornfeldt B. Predicting high risk for human hantavirus infections, Sweden. Emerg Infect Dis. 2009; 15: 104-6.
9. Olsson GE, White N, Ahlm C, Elgh F, Verlemyr AC, Juto P, Palo RT. Demographic factors associated with Hantavirus infection in bank voles (Clethrionomys glareolus). Emerging Infectious Diseases. 2002; 8:924–929.
10. Martinez VP, Bellomo C, San Juan J, Pinna D, Forlenza R, Elder M, Padula PJ. Person-to-person transmission of Andes

virus. Emerging Infectious Diseases. 2005; 11:1848-1853.

11. Avsic-Zupanc T, Saksida A, Korva M. Review: Hantavirus infections. Clinical Microbiology and Infection. 2019; 21:e6-e16.
12. Kanerva M, Mustonen J and Vaheri. Pathogenesis of Puumala and other Hantavirus infection.Reviews in Medical Virology. 1998; 8: 67-86.
13. López R, Pérez-Araos R, Salazar A, Ulloa LA, Vial C, Vial AP, Graf J. Hemodynamic and Pulmonary Permeability Characterization of Hantavirus Cardiopulmonary Syndrome by Transpulmonary Thermodilution. Viruses. 2019; 11 (900): 1-12.
14. Gavrilovskaya IN, Apekina NS, Bernshtein AD et al. Pathogenesis of haemorrhagic fever with renal syndrome virus infection and mode of horizontal transmission of Hantavirus in bank voles. Archives of Virology Supplement. 1990; 1:57-62.
15. Khaiboullina SF, Morzunov SP, St. Jeor ST. Hantaviruses: Molecular biology, evolution and pathogenesis. Current Molecular Medicine. 2005; 5:773-790.
16. Terajima M, Ennis FA. T Cells and pathogenesis of Hantavirus cardiopulmonary syndrome and haemorrhagic fever with renal syndrome. Viruses. 2011; 3: 1059-1073.
17. Cosgriff T. Mechanisms of disease in Hantavirus infection: Pathophysiology of haemorrhagic fever with renal syndrome. Reviews of Infectious Diseases. 1991; 13:97-107.
18. Hepojoki J, Vaheri A, Strandin T. The fundamental role of endothelial cells in hantavirus pathogenesis. Frontiers in Microbiology/Virology. 2014; 5:1-7.
19. Lee HW. Clinical features of haemorrhagic fever with renal syndrome in Korea. Reviews of Infectious Diseases. 1989; 11: 864-876.
20. Easterbrook JD, Klein SL. Immunological mechanisms mediating Hantavirus persistence in rodent reservoirs. PLoS Pathogens. 2008; 4:11.
21. Goris AGM, Hartskeerl AR. Leptospirosis Serodiagnosis by the Microscopic Agglutination Test. Current protocols in microbiology. 2014; 32 (1): 12E.5.1-12E.5.18.
22. Lee HW, Lee P-W, and Johnson KM. Isolation of the aetiologic agent of Korean hemorrhagic fever. Journal of Infectious Diseases; 1978; 137:298–308.
23. Padula JP, Rossi MC, Della Valle OM, Martinez VP, Colavecchia BS, Edelstein A, Miguel DS, R. D. Rabinovich DR, Segura LE. Development and evaluation of a solid-phase enzyme immunoassay based on Andes hantavirus recombinant nucleoprotein. J. Med. Microbiol. 2000; 49:149-155.

24. Lee HW. Virus isolation. In: Lee HW, Calisher C, Schmaljohn C (editors) Manual of haemorrhagic fever with renal syndrome and Hantavirus pulmonary syndrome Seoul. WHO Collaborating Centre for Virus Reference and Research (Hantavirus). 1999; 74-79.
25. Jameson LJ, Taori SK, Atkinson B, Levick P, Featherstone CA, van der Burgt G, McCarthy N, Hart J, Osborne JC, Walsh AL, Brooks TJ, Hewson R. Pet rats as a source of Hantavirus in England and Wales. Euro Surveillance. 2013; 18:9.
26. Bi Z, Formenty HBP, Roth EC. Review Article Hantavirus Infection: a review and global update. J Infect Developing Countries. 2008; 2(1):3-23.
27. Pacsa SA, Elbishbishi AE, U.C. Chaturvedi CU, Chu YK, Mustafa SA. Hantavirus-speci¢c antibodies in rodents and humans living in Kuwait. FEMS Immunology and Medical Microbiology. 2002; 33:139-142.
28. Kallio ER, Klingstrom J, Gustafsson E, Manni T, Vaheri A, Henttonen H, Vapalahti O, Lundkvist A. Prolonged survival of Puumala Hantavirus outside the host: Evidence for indirect transmission via the environment. Journal of General Virology. 2006; 87:2127-2134.
29. Schmaljohn, CS, Nichol ST, Bunyaviridae. In "Fields virology" (D.M. Knipe, P.M. Howley, D.E. Griffin, R.A. Lamb, M.A. Martin, R.B., and S.S.E., Eds. 2007; 2: 1741–1789.
30. Kang HJ et al. Evolutionary insights from a genetically divergent Hantavirus harboured by the European Common Mole (Talpa europaea). PLoS ONE. 2009; 4:7.
31. Kang HJ, Bennett SN, Hope AG, Cook JA, Yanagihara R. Shared ancestry between a newfound mole-borne hantavirus and Hantaviruses harboured by cricetid rodents. Journal of Virology. 2011; 85:7496-7503.
32. Klempa B et al. Novel Hantavirus sequences in shrew, Guinea. Emerging Infectious Diseases. 2007; 13: 520–522.
33. Song JW et al. Newfound Hantavirus in Chinese Mole Shrew, Vietnam. Emerging Infectious Diseases 2007: 13:1784–1787.
34. Lin XD, Guo WP, Wang W, Zou Y, Hao ZY, Zhou DJ, Dong X, Qu YG, Li MH, Tian HF, Wen JF, Plyusnin A, Xu J, Xhang YZ. Migration of Norway rats resulted in the worldwide distribution of Seoul Hantavirus today. Journal of Virology. 2012; 86: 972-981.
35. Hart CA, Bennett M. Hantavirus infections: epidemiology and pathogenesis. Microbes and Infection. 1999; 1:1229−1237.
36. Clement J, Vercauteren J, Verstraeten WW, Ducoffre G, Barrios J, Vandamme AM, Maes P, Van Ranst M. Relating increasing Hantavirus incidences to the

changing climate: the mast connection. International Journal of Health Geographics. 2009; 8:1.

37. Olsson GE, Leirs H, Henttonen H. Hantavirsuses and their hosts in Europe: reservoirs here there, but not everywhere. Vector-borne and Zoonotic Diseases; 2010; 10:549-561.
38. Coleman TJ. The Public Health Laboratory Service (PHLS) and its role in the control of zoonotic disease. Acta Tropica. 2000; 76:71–75.
39. McKenna P, Clement J, Matthys P, Coyle PV, McCaughey C. Serological evidence of Hantavirus disease in Northern Ireland. Journal of Medical Virology. 1994; 43:33-38.
40. Pether JVS, Lloyd G. The clinical spectrum of human Hantavirus infection in Somerset, UK. Epidemiology and Infection. 1993; 111: 171-175.
41. Webster JP, MacDonald DW. Parasites of wild brown rats (Rattus norvegicus) on UK farms. Parasitology. 1995; 111:247-255.
42. Pounder KC, Begon M, Sironen T, Henttonen H, Watts PC, Voutilainen L, Vapalahti O, Klempa B, Fooks AR, McElhinney LM. Novel Hantavirus in wildlife, United Kingdom. Emerging Infectious Diseases. 2013; 19:673-675.
43. Bennett M, Lloyd G, Jones N, Brown A, Trees AJ, McCracken C, Smyth NR, Gaskell CJ, Gaskell RM. Prevalence of antibody to Hantavirus in some cat population in Britain. Veterinary Record. 1990; 127:548-549.