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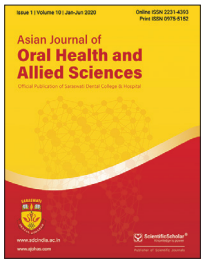

*Review Article*

# Hantavirus: An emerging global threat

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## ABSTRACT

Hantaviruses (HVs) are globally emerging pathogens that can cause varied disease syndromes worldwide. HV infections spread to humans from their natural reservoirs, rodents. HV infection can cause severe diseases such as HV pulmonary syndrome or "HV cardiopulmonary syndrome" and "hemorrhagic fever with renal syndrome" in humans through contact with infected rodents urine, feces, saliva, and blood droppings. There has been significant improvement in the understanding of the epidemiology, pathological process, and environmental history of HV infectious after an increase in the number of outbursts in the United States of America and Pan-American countries. Many cases have been reported in India also since 1964. The main objective of this paper is to present an overview of the HV infection, which can be an emerging global threat.

**Keywords:** Emerging diseases, Hantavirus, India

## INTRODUCTION

Recently, many published reports highlighted the threat of evolving human infections. Among them, zoonotic infections transmitted to humans are a significant source of emerging viral infectious epidemics.[1-3]

Emerging diseases are "previously unknown infectious diseases that occur as outbreaks, or known diseases that are rapidly increasing in incidence or geographic range in the past two decades, or are persistent infectious diseases that cannot be controlled." Reemerging diseases are "infectious diseases that reappear after a significant decline because of the breakdown in public health measures or change in behavior that allows disease return or in case of new strains of organism appears."[4,5] Hantaviruses (HVs) are globally emerging pathogens that can cause varied disease syndrome worldwide.[5] HVs are enveloped negative-sense, single-stranded RNA viruses of family Bunyaviridae that can spread to humans from rodents, which are their natural reservoirs.[4,5] This paper intends to present an overview of HV that may emerge as a global threat in future.

## MATERIALS AND METHODS

Related literature was searched using electronic database MedLine/PubMed database and Google Scholar, with emphasis on peer-reviewed journals till April 2020 using medical subject headings "HV," "HV and Endemic diseases," "HV and Epidemic diseases," "HV and Emerging diseases," and "HV and India." Search engine MedLine/PubMed when searched for "HV" revealed 4319 papers, and search when was filtered for "HV and Endemic diseases," "HV and Epidemic diseases," "HV

and Emerging diseases," and "HV and India" showed 300, 207, and 44 articles. Titles and abstracts of relevant articles in the English language were screened, and relevant full-text articles along with the full text of "best match papers" suggested by PubMed were shortlisted. Pertinent gray literature from other electronic databases were also included for additional information after proper scrutinization.

## HV SPREAD TO HUMAN

HV can infect humans through contact with infected rodents urine, feces, saliva, and blood droppings. Deer mouse, white-footed rat, hispid cotton rat, and rice rat are the natural hosts of HV and develop persistent infection.[5,6] HV spreads mainly by infected rodents, usually in rural or unused buildings, or other work-related areas such as construction sites, forests, farms, or parks that offer suitable habitat for the virus rodent hosts. It can also spread through recreational (camping/hiking) or household exposures while living close to rodent infestations or during cleaning rodent-infected areas.[6,7] The infected rodent shed mainly transmits the virus to humans when they breathe in virus-contaminated air in a particular area, where rat's fresh shed gets mixed up with dust, and tiny virus-infected droplets develop in the air where rodents have been active. Bites or scratches of the infected rodents may also spread infections to humans.[5,6,8]

## HV INFECTIOUS DISEASES

### *Old world HV infection*

Ancient Chinese literature of around 960 AD mentions a similar hemorrhagic fever with renal syndrome (HFRS) caused by "Old World HV." HFRS was first reported during the Korean Conflict between 1951 and 1954 among the 3200 United Nation armed troops.[7] A long-standing unclassified *Thottapalayam virus* (TPMV) was 1st time isolated in 1964 from the spleen of *Suncus murinus* (Asian House Shrew) in Vellore, India.[7,9] Korean hemorrhagic fever was a rare disease transmitted from the striped field rodent (*Apodemus agrarius*) found near the Han River of South Korea in 1978.[9] Asian HV prototype, HV (HTNV), was named after rodents caught near the Han River.[5] In 1982, HV genus was identified in the Bunyaviridae family viruses, which included viruses causing HFRS. Earlier HVs were considered as Old World HV that mostly found in Europe and Asia.[6] A milder form of HFRS, nephropathic epidemics caused by HV, *Puumala virus* (PUUV), *Tula virus,* and *Dobrava-Belgrade virus* (DOBV) were reported in Europeans.[10] In Asia, HFRS caused by wild brown-rats born Seoul HV (SEOV) was discovered in the 1980s, and conclusive evidence of circulating SEOV in brown or Norway rats (*Rattus norvegicus*) was reported in January 2015.[11]

### *New world HV infection*

In 1993, the inherent HV found in the New World as a non-pathogenic *Prospect Hill virus*.[9] Subsequently, with an outbreak of unexplained acute respiratory distress (later on called as HV pulmonary syndrome [HPS] or HV cardiopulmonary syndrome [HCPS]), in the four corners (Arizona, New Mexico, Colorado, and Utah) of the Southwestern United States (US), HV became an important concern and known as "New World HV."[6,7,9] Shortly, most important HV causing HPS or HCPS was isolated from the deer mouse (*Peromyscus maniculatus*) in the US, named Sin Nombre virus (SNV).[6,7] Later on, another HV, which was similar to SNV, Andes virus (ANDV), was also discovered in the USA.[9]

### *Pathogenesis and clinical features of HV infections*

Major manifestations vary depending on infecting serotype. Virus gets infection into humans body through inhalation of HV-infected rodents material. It primarily infects macrophages and endothelial cells of respiratory and renal system.[9] Pathogenesis of HV disease is largely attributed to "cytokine storm."[5] Early signs and symptoms are non-specific.[5,9] The incubation period of 2–4 weeks is followed by a febrile phase. The clinical course of HFRS can be divided into febrile (3–7 days), hypotensive (2 days), oliguric (3–7 days), polyuric, and convalescent (can last up to 6 months). HCPS is more severe than HFRs, and a typical course of HCPS consists of prodromal, cardiopulmonary, and convalescent phases. The clinical picture in the early stages of HCPS may be similar to other viral infections. A great overlap in the clinical presentations of HFRS and HCPS has also been reported.[5]

At present, serological assays with recombinant HV antigens and indirect immunoglobulin M (IgM) and immunoglobulin G (IgG)-ELISA are advocated for laboratory diagnosis. In both HFRS and HCPS, increased hematocrit, leukocytosis, thrombocytopenia, hematuria, proteinuria, and serum creatinine can be observed.[5,9,10]

## WORLDWIDE EPIDEMIOLOGICAL SCENARIO OF HV INFECTION

In the USA, since its first identification in 1993 among three residents of New Mexico till January 2017, 728 laboratory-confirmed cases of HV infections had been reported in 36 US.[12] On June 6, 2002, a total of 318 cases in 31 US, with a case fatality of 37%, were reported.[6] Ten confirmed cases of HV infections were reported in National Park Service in November 2012. Another outbreak of the Seoul virus infecting 17 individuals among 7 US was reported in January 2017.[12]

HPS cases have also been reported in South American and other North American countries, as in Balkans, Northern Sweden, Argentina, Poland, Chile, Bolivia, Brazil, Serbia, United Kingdom, Panama, Germany, and Russia. In Europe, a gradual increase in the incidence of HV infections was observed, and 3754 confirmed HV cases were recorded in the year 2014.[13] Since 1997, an average of 83 HPS cases annually reported in Argentina, and after 2011, the annual cases were twice the previously recorded annual average. Between the years 2013, and 2018, a total of 114 confirmed cases of HPS reported with a fatality rate of 18.6%.[14-16] Southern Argentina reported having 29 laboratory-confirmed HPS cases and the death of 11 individuals between October 28, 2018 and January 20, 2019.[16] Since 1994, an active follow-up of HPS has begun in Canada. Till January 2015, a total of 109 confirmed cases and 27 deaths because of HPS have been reported in Canada.[17,18] In Chile, on an average of 67 cases reported annually since 1995.[14] In 2011, the total number of cases increased to 93, and during the year 2018, eight confirmed cases were reported in Chile that include two deaths.[14,16] In 2019, one first confirmed case of human-to-human HV spread in the Los Lagos Region of Chile with a travel history to Epuyén was reported.[16]

In the Chaco region of Paraguay, HPS cases were 1st time detected in 1995, and since then, the total number of reported cases was 56, 18, and 2 in 2011, 2012, and 2013, respectively. Confirmed cases have been reported in Panama since 1999, with an average of 12 cases/year. A total of 16 cases in 2012 and 14 confirmed cases in 2013 had been reported afterward. The annual average number of confirmed reported cases in Uruguay was 9, since 1997.[13,14] In Northern Uruguay, the first case was reported in 2010.[14] In Venezuela, a total of 8 confirmed cases were reported in 1999, and since 2007, every year, there has been an increase in the number of confirmed cases.[19] Small outbreaks occurred in Bolivia between 2002 and 2012, and in 2018, a total of 40 cases were reported in Santa Cruz and Tarija region of Bolivia.[20] Between 1993 and 2007, a total of 884 confirmed cases were reported in Brazil,[21] and after 2015, HPS cases were decreased annually.

With the highest incidence and morality of HFRS, China accounts for above 90% of HFRS cases worldwide.[13] In the Shaanxi Province of Northeastern China, the first case of HFRS was reported in 1931.[22,23] From 1950 to 2007, approximately 1.56 million HFRS cases have been reported, and 46,427 people have died from this disease with a fatality rate of 3%, and it spread like a pandemic in all 31 provinces of China, Hong Kong, and Taiwan.[22,24] In China, the current case fatality rate of 1.13% has been observed for HFRS by HTNV and SEOV.[13] From 2006 to 2017, the highest incidence of HFRS was reported in Shaanxi Province, with around 4.51 cases/100,000 cases. By November 20, 2017, 878 persons were reported to get HFRS in Shaanxi Province.[13]

According to Global Times, "When the world is trying to find the solution for the coronavirus 2019 (COVID-19) pandemic, a HV confirmed man from China's Yunnan Province died on March 15, 2020, due to HPS disease, while traveling in a public transport bus from Yunnan to the Shandong Province. All the fellow passengers on the bus have been tested for the HV in view of the risk of human-to-human transmission."[25] The report suggested a recent HV outbreak in China. Szabo *et al*.[26] summarized case fatality rate of 10–15% for HFRS by HTNV in Asia, 30–50% for HPCS by ANDV in Uruguay, up to 12% for HFRS by DOBV in Europe, 0.1–0.4% for HFRS by PUUV in Europe, 30–50% for HCPS by SNV in USA and Canada, and 1–2% for HPCS by SEOV worldwide.

## HV INFECTIONS IN INDIA

First indigenous Indian HV species, TPMV, was isolated in 1964 in South India from the spleen of a non-rodent house shrew, during studies of Japanese encephalitis.[5,6,27] Chandy *et al*.[28] reported serological evidence of HV infection among the South Indian population. They reported that 14.7% of 152 individuals with febrile illness and 5.7% of 87 voluntary healthy donors were positive anti-HV IgM positive.[28] This study suggested the possibility of asymptomatic and symptomatic HV infections in the South Indian population.[28,29] HV-specific IgM has been detected as early as 3 days after onset of illness.[30] Another seroprevalence study revealed higher HV specific IgG in the risk group (11%) as compared to a healthy blood donor group (4%) conducted in risk group versus healthy blood donor group.[5,31] Clement *et al*.[32] gave the first evidence of fatal HV nephropathy in India. They reported 12% SEOV-positive antibodies and 5% PUUV-positive antibodies in South Indian patients imitating leptospirosis-like illness from Chennai and Cochin.[32]

Many reports from different regions of the nation are suggesting ocular involvement in HV infection,[33] coinfection of tuberculosis with HV causing renal disease in children,[29] and HPS in a postpartum woman has also been published in the past two decades.[34] In 2008, 28 individuals from the Irula community in Tamil Nadu's Vellore district reported HV infection. In 2016, a 12-year-old boy reported to have bleeding from the lungs, who later Mumbai died of the HV disease.[35]

*Bandicota indica* (Muridae), the known reservoir for Thailand HV (THAIV) causing HFRS in Thailand, is also found in India.[36] The first laboratory evidence for rodent-associated HV conducted at multiple sites in South India revealed THAIV and HTNV confirmed HV antibodies in 9 out of 83 rodents.[5,37] Recently, many Indian molecular level studies are also published that may help in a better understanding of HV infection.[38,39]

## PREDICTING THE HVs OUTBREAK

The majority of viruses coexist in the immediate environment surrounding the man and are often sustained within other species without producing any human disease. Due to disturbances in the natural ecological equilibrium, these viruses, from time to time, can emerge or remerge in humankind, resulting in periodic diseases or outbreaks.[40] Similarly, due to the natural ecological process, humans may get HV infections from rats, where it harbors without any apparent disease. The risk of human-to-human transmission is always there and may result in the development of a pandemic-like situation. Wells *et al.*[41] revealed one such outbreak report of nosocomial human to human transmission of HV in Argentina in 1997.

PubMed search until April 2020 showed 44 papers on "HV infections in India," whereas first case in India was reported in 1964. HV infections are underdiagnosed in India due to the lack of detailed studies.[40] Literature suggested the presence of HV infections in the Indian population with preponderance in South Indian states. Limited and exorbitantly priced diagnostic kits, lack of awareness, and lack of interprofessional collaborations may place these regions on the potential risk of an epidemic outbreak.[5] It may take another 70–75 years in future for it to outbreak like COVID-19 in India. There is an urgent need to start anti-HFRS/HPS programs, including rodent surveillance and its control, public health education, and environmental management. Indian researchers and public health workers should work together to make sure that HV does not become a significant public health concern in the near future.[42] Otherwise, the TPMV/HFRS/HPS/SNV diseases may emerge or reemerge as an epidemic disease in some locations of the South and Middle West states of India.

## TREATMENT AND PREVENTION OF HV INFECTION

HVs are most widely distributed as zoonotic rodent-borne disease, and there is no definitive treatment available for HV infections.[40] Although many efforts have been made, still there are no approved and effective anti-HV drugs yet, and ongoing research is in progress on nucleic acid vaccines.[27] Ribavirin has been used in clinical trials that decrease the fatality of HFRS, but not in HCPS.[27,34,40] Enhancing host interferon responses throughout the early phase may be a new treatment strategy for HRRS/HCP, but more work is needed to translate it into clinical practice.[13] Symptomatic and supportive therapy is the best way to control advancement toward life-threatening conditions.[27] Physicians should include HV infections in the differential diagnosis of acute febrile illness in patients with a history of contact with rodents.[37]

It is wise to avoid all contact with rodents when possible, as the prevention of exposure to rodent excreta is the best way to avoid infection. Decontamination of human residences if signs of rodent activities are noticed, a habit of keeping rodents as pets should discouraged, and proper food storage practices should be maintained.[27] Preventive procedures can be implemented to control the HV infections through demonstration of the experiments in simple, practical, and inexpensive ways in rural dwellings. People who are engaged in outdoor activities should take precautions to reduce possible exposure to potentially rodent infectious materials. Geographic differentiation of rodent and human populations with varying housing types, customs, and culture may require modifications as per local requirement.

Active surveillance, research strengthening, improvement in the medical sector, public awareness to minimize human exposure to HV-infected rodents through social outreach program amongst the common man and rural people are required to control the HV infections. Conscientious collaboration amongst the medical technologists, microbiologists, virologists epidemiologists, physicians, environmentalists, civic bodies, as well as policymakers for developing, and timely implementation of a systematic approach to prevent, identify, diagnose, manage and foresee any emergent situation in the near future is of paramount importance.

## CONCLUSION

The concerned government health departments should continuously review the effective implementation of precautionary measures. More scientific research is needed to translate basic sciences research into clinical practice. The best way to combat HV infection is to minimize contact with rodents at home, workplace, and during outdoor activities, and by taking all the precautions to reduce possible exposure to potentially rodent infectious materials, as prevention is better than cure. So for this, there is an easy way to do this– it is known as "Seal Up! Trap Up! Clean Up!"

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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### Conflicts of interest

There are no conflicts of interest.

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