



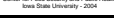



S l i d e 1	<p style="text-align: center;">Hantavirus</p> 	<p>Hantavirus is an RNA virus in the Bunyaviridae family. It is recognized as causing hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS) in humans. Rodents are the reservoir host and transmit the disease horizontally within their species and vertically to humans through aerosolized infectious particles from their excrement. HPS is now recognized as a pan-American zoonosis, with an expanding clinical spectrum, caused by many novel New World hantaviruses with distinct rodent hosts.</p>
S l i d e 2	<p style="text-align: center;">Overview</p> <ul style="list-style-type: none"> • Organism • History • Epidemiology • Transmission • Disease in Humans • Disease in Animals • Prevention and Control 	<p>In today's presentation we will cover information regarding the organism that causes hantavirus and its epidemiology. We will also talk about the history of the disease, how it is transmitted, species that it affects (including humans), and clinical and necropsy signs observed. Finally, we will address prevention and control measures for hantavirus.</p>
S l i d e 3	<p style="text-align: center;">The Organism</p> 	
S l i d e 4	<p style="text-align: center;">Hantaviruses</p> <ul style="list-style-type: none"> • Family Bunyaviridae <ul style="list-style-type: none"> - RNA virus - Genus <i>Hantavirus</i> <ul style="list-style-type: none"> • Only genus not arthropod-borne • Transmitted by murid rodents • More than 25 hantavirus species  	<p>Hantavirus is a three segmented RNA virus in the family Bunyaviridae. Hantaviruses are transmitted by rodents and are the only virus in the Bunyaviridae family that are not transmitted by arthropods. There are more than 25 antigenically different viral species, each associated with a single rodent species. Photo: Electron micrograph of Sin Nombre (without a name) hantavirus, the most common serotype seen in the U.S.</p>
S l i d e 5	<p style="text-align: center;">Hantaviruses</p> <ul style="list-style-type: none"> • Lipid envelope <ul style="list-style-type: none"> - Deactivated by ordinary disinfectants • A "viral hemorrhagic fever" <ul style="list-style-type: none"> - Hantavirus Pulmonary Syndrome (HPS) - Hemorrhagic Fever with Renal Syndrome (HFRS) 	<p>Due to the lipid envelope, it is easily killed by common disinfectants, such as chlorine, iodine, acetone, ethanol. Ultraviolet irradiation, low pH, and temperatures at or above 37°C (98.6°F) will also deactivate it. The classic presentation of signs results, in some cases, in a viral hemorrhagic fever, which can precipitate in the respiratory system (HPS) or renal system (HFRS).</p>

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Hantaviruses in the Old World

Serotype	Host	Location
Hantaan	<i>Apodemus agrarius</i> (striped field mouse)	Asia, Far East Russia
Dobrava	<i>A. agrarius</i> , <i>A. flavicollis</i> (yellow neck mouse)	Europe Balkans
Seoul	<i>Rattus norvegicus</i> , <i>R. rattus</i> (Norway brown rat, roof rat)	Worldwide
Puumala	<i>Clethrionomys glareolus</i> (red bank vole)	Europe

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The hantaviruses previously recognized as causing Hemorrhagic Fever with Renal Syndrome (HFRS) in the old world are Hantaan, Dobrava, Seoul, and Puumala. Hantaan, Dobrava, and Seoul are subfamily Murinae associated viruses, whereas Puumala is a Subfamily Arvicolinae associated virus. The infections the rodents carry are lifelong, yet asymptomatic and transmitted horizontally among others of their species. The geographic distribution of human HFRS cases is also specific to the serotype and is listed under location. It is thought that murid rodents have probably harbored inapparent hantavirus infections for thousands or more years. It is unknown whether any of the animals other than the natural rodent hosts are epidemiologically important. Numerous other hantaviruses have been identified but not linked to human disease.

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Hantaviruses in the New World

Serotype	Host	Location
Sin Nombre	<i>Peromyscus maniculatus</i> (deer mouse)	Central & West U.S., Canada
Monongahela	<i>Peromyscus maniculatus</i> (deer mouse)	Eastern U.S., Canada
New York	<i>Peromyscus leucopus</i> (white-footed mouse)	Eastern U.S., Canada
Bayou	<i>Oryzomys palustris</i> (rice rat)	SE U.S.
Black Creek Canal	<i>Sigmodon hispidus</i> (cotton rat)	SE U.S.

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Most of the hantavirus infection in North America are associated with rodents of the family *Muridae*, subfamily *Sigmodontinae*. The subfamily *Sigmodontinae* associated viruses are highly diverse and constitute the majority of HPS cases in North America. As many as 3 hantaviruses can be found in a particular geographic site, each circulating in its own rodent reservoir. Spillover hosts are believed to have little or no impact on hantaviral distribution or associated disease. However, rodents other than the primary reservoirs can play an important carrier role which reflects some adaptation of the virus to the rodent host and not just geographic isolation of the virus type. There are many SNV-like viruses, such as Monongahela and New York, with different genetic lineages within North America. Most causes of HPS can be linked to the rodent lineage *Peromyscus* spp. For example the white footed mouse, *Peromyscus leucopus* and *boylii* can be important reservoirs for Sin Nombre in the western U.S.

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Hantaviruses in the New World

Serotype	Host	Location
Andes	<i>Oligoryzomys longicaudatus</i> (long-tailed pygmy rice rat)	Argentina/Chile
Oran	<i>O. longicaudatus</i>	NW Argentina
Lechiguanas	<i>O. flavescens</i>	Central Argentina
HU39694	Unknown	Central Argentina
Laguna Negra	<i>Calomys laucha</i>	Paraguay/ Bolivia
Juquitiba	Unknown	Brazil

*Numerous other hantaviruses have been identified but not linked to human disease

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South American cases of HPS are listed here with their serotypes and rodent host, if known. These are subfamily Sigmodontinae associated viruses. The Andes virus has been associated with several HPS cases in Patagonia with possible person to person transmission of the disease. The host is the long tailed pygmy rice rat, *Oligoryzomys longicaudatus*. Oran, Lechiguanas, and HU39694 are all subfamily relation to the Andes virus serotype and their host and location of HPS cases are listed. Laguna Negra was associated with a large outbreak of HPS in Paraguay and its rodent host is *Calomys laucha*.

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This map depicts the geographic distribution of the various hantaviruses in the Western Hemisphere. The host vector is listed with the virus name.

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History



Hantaviruses are not new diseases, but rather, newly emerging diseases.

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Hantaviruses in Our Past

- American Civil War
- World Wars I and II
- 1913, 1932
 - Russia reported cases
- 1934
 - Sweden - Nephropathia Endemica
- 1950's
 - Reports of Korean Hemorrhagic Fever

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Hantavirus disease outbreaks have occurred as far back as American Civil War times. There are records of a hemorrhagic fever syndrome (HFRS) during World War I and II. What is thought to be the first outbreaks of hantavirus causing HFRS were reported in Russia in 1913 and 1932. Japanese troops in Manchuria reportedly had cases in 1932 and cases referred to as Nephropathia Epidemica (NE) in Sweden appeared in 1934. Western medicine diagnosed Korean Hemorrhagic Fever (KHF) during the Korean War in the 1950's.

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Hemorrhagic Fever with Renal Syndrome (HFRS)

- 1951-1954: Korean War
 - 3,200 U.N. troops develop disease
 - Hantaan River separated N. & S. Korea
- 1977
 - Hantaan agent isolated and characterized
 - 1990: 94% of serum samples from soldiers in 1950's had antibodies
- 1979
 - Seoul virus found in Japan and Europe


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HFRS was first recognized by western physicians from 1951 to 1954 when 3,200 cases of a debilitating, acute, febrile illness were reported among United Nations forces in Korea. The soldiers were living in foxholes while stabilizing the contested border between North and South Korea and had close contact with rodents. The mortality rate was 10-15% so the Hemorrhagic Fever Commission of the United States Army began an enormous investigation. H. Lee, P. Lee, and K. Johnson are credited with finding the antigen in the lungs of a Korean field mouse (*Apodemus agrarius coreae*). Isolation of the organism occurred in 1977 and named Hantaan for the river that runs near the 38th parallel separating North and South Korea. Much to the credit of the Hemorrhagic Fever Commission, over 600 serum samples from 245 soldiers were preserved until 1990. It resulted in 94% of the samples having antibodies to Hantaan, almost 40 years after the outbreak. In 1979, a virus similar to Hantaan was causing hemorrhagic fever in laboratory workers that had contact with rats in Japan and Europe. This virus was carried by *Rattus norvegicus*, *R. rattus* and named Seoul virus after the site of the initial studies. The ongoing risk of shipping these laboratory rats worldwide lead to the dissemination of the Seoul virus.

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U.S.: Four Corners Outbreak



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The converging point of Colorado, Utah, Arizona, and New Mexico's state borders became the location of the 1993 Four Corners Outbreak of Hantavirus Pulmonary Syndrome (HPS). The Navajo Nation Indian Reservation in New Mexico had the first fatalities. The Navajo tribal belief is such that mice were responsible for bringing seeds to the earth, allowing humans to survive. Mice are thought of as the "landlords of the world" and are highly respected in Navajo culture. Avoidance of rodent contact and housecleaning efforts took on a whole new education effort in this area of the United States.

The Four Corners Outbreak

- May 1993
 - First clinical case
 - Abrupt fever, myalgia, pulmonary edema
- June 1993
 - 12 fatalities
 - Unexplained Adult Respiratory Distress Syndrome (ARDS)
 - Sera cross-reacted with Hantaan, Seoul, Puumala virus
 - Rodents trapped - deer mouse main reservoir

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Several young and healthy members of the Navajo Nation in New Mexico presented to the Indian Health Service physicians with a sudden onset of respiratory failure in May 1993, and by June, twelve people had died. It was originally diagnosed as unexplained Adult Respiratory Distress Syndrome (ARDS). Clinical signs included an abrupt fever, myalgia, headache, and cough, followed by acute progressive pulmonary edema, leading to respiratory failure and hypotension and death 2-10 days after onset. The Department of Public Health for New Mexico along with the Centers for Disease Control and Prevention became involved and set up surveillance and testing. Initial results of acute and convalescent sera against Hantaan, Seoul, and Puumala virus antigens showed cross-reactive antibodies. It had taken a pulmonary form which was unlike any other clinical presentation of hantavirus. Nearly 1700 small mammals representing 31 species were subsequently captured and tested. Almost half of the mammals captured were deer mice (*Peromyscus maniculatus*) and 30% had antibody the now named Sin Nombre Virus.

The Four Corners Outbreak

- Winter and spring 1993
 - Drought for several years followed by snow and rain
 - Vegetation blossomed and rodent population grew tenfold
- Virus isolated and named
 - Sin Nombre Virus (SNV)
- Newly emerging virus has been present since 1959
 - 38 year old Utah man

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The sudden outburst of cases is attributed to the weather patterns that occurred in the Four Corners area. Prior to 1993 there had been a drought for several years. By spring of that year, heavy snows and rainfall helped drought-stricken plants and animals to revive and grow in larger-than-usual numbers. With plenty of vegetation for food and protection, the deer mice reproduced so rapidly that there were ten times more mice in May 1993 than there had been in May of 1992. An increase in mice numbers, coupled with their high infection rate, increased the risk to humans who shared habitats with mice in rural areas. The virus was isolated 1 month after the first report of cases and named Muerto Canyon virus, then Four Corners virus, and finally Sin Nombre Virus (SNV – “virus without a name”). Cases did occur prior to 1993, but a sharp rise in 1993 led to recognition of the disease. One of the prior cases was a 38 year old Utah man that had died from an illness compatible with hanta in 1959. Researches located his lung tissue and utilizing current technology, were able to isolate SNV in 1994. Earliest case diagnosed by immunohistochemistry in postmortem tissues was a patient who died in 1978.

Epidemic Curve of Four Corners Outbreak

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An epidemic curve of the first 100 cases of HPS in the Four Corners outbreak through December of 1994. It shows that HPS did occur prior to the major outbreak in 1993 but it took the cluster of clinical cases to realize the potential threat to human health.

Recent Cases

- May 2003: Montana
 - Three cases
 - Two deaths
 - Contracted virus from rodents in home
 - First cases since fall of 2001
 - Overall cases in Montana
 - Virus first appeared in state in 1993
 - 20 cases
 - 5 deaths

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In May 2003, three cases of hantavirus in humans were reported in Montana within a two week period. Two of the individuals died, the other was hospitalized and recovered. The people are thought to have contracted the virus from rodents in their homes. These cases were the first reported in Montana since the fall of 2001. Overall (including these cases), Montana has had 20 cases of hantavirus with 5 deaths since the virus first appeared in the state in 1993.

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Epidemiology



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Common Rodent Reservoirs

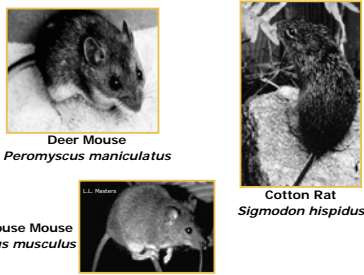
- United States, except the Southeast
 - Deer mouse (*Peromyscus maniculatus*)
- Southeast United States
 - Cotton rat (*Sigmodon hispidus*)
 - Rice rat (*Oryzomys palustris*)
- Eastern
 - White-footed mouse (*Peromyscus leucopus*)
- House mouse not a carrier!

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As noted previously, the natural host of hantavirus is rodents. The deer mouse (*Peromyscus maniculatus*) is the primary carrier in all areas of the United States, except the southeast. There the carriers tend to be the cotton rat (*Sigmodon hispidus*) and the rice rat (*Oryzomys palustris*). The eastern United States also deals with the white-footed mouse (*Peromyscus leucopus*). It is important to remember that the house mouse is not a carrier. It is unknown whether any of the animals other than the natural rodent hosts are epidemiologically important.

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Deer Mouse
Peromyscus maniculatus

Cotton Rat
Sigmodon hispidus

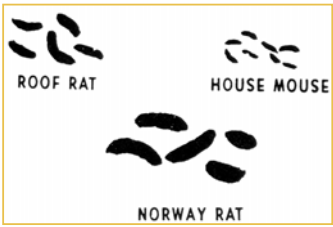
House Mouse
Mus musculus

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The deer mouse, *Peromyscus maniculatus*, is approximately six inches long from its nose to the tip of its tail. It has a white belly and is grayish to light brown on top. It has large ears and a furry tail that is white on its underside. In contrast, the house mouse, *Mus musculus*, is grayish to light brown without a white belly and it has scales on its tail, versus hair. House Mouse photo taken by L. L. Masters
<http://www.ndis.nrel.colostate.edu/escop/photos/mammals.html>

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ROOF RAT

HOUSE MOUSE

NORWAY RAT

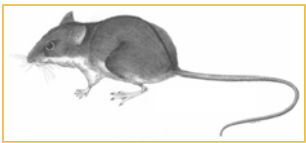
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This depicts the different feces of a Norway rat, the roof rat, and the house mouse. It is important to remember that not all types of rodents carry hantavirus. None of these rodents have been associated with HPS in humans. It can be tough to tell what kind of rodents you have so play it safe -- clean up the infestation and rodent-proof your home or workplace.

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Hantaan Virus Reservoir



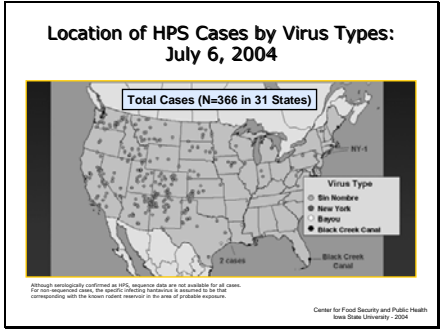
Striped field mouse
Apodemus agrarius

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The striped field mouse, *Apodemus agrarius*, is the rodent reservoir for Hantaan virus in Asia and far east Russia. Source: Burt WH, Grossenheider RP. Peterson field guides. A Field Guide to the Mammals. 3rd ed. New York, New York. Houghton Mifflin Company. 1980

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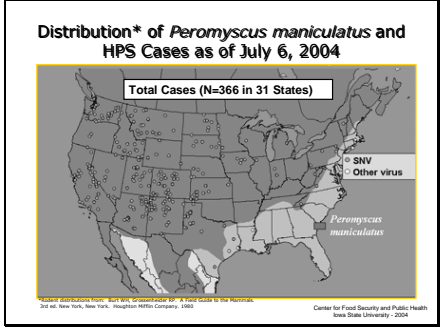
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This map depicts the 366 cases of HPS and their causing virus type in the United States. Although serologically confirmed as HPS, sequence data are not available for all cases. For non-sequenced cases, the specific infecting hantavirus is assumed to be that corresponding with the known rodent reservoir in the area of probable exposure. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/epislides/episl7.htm>.

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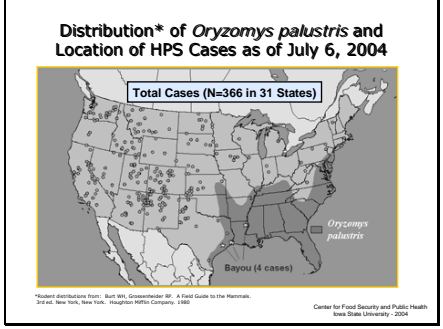
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The green shaded area depicts the geographic distribution in Canada, the United States, and Mexico of the deer mouse, *Peromyscus maniculatus*. Sin Nombre Virus was responsible for almost all of the 366 cases in 31 states. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/epislides/episl7.htm>.

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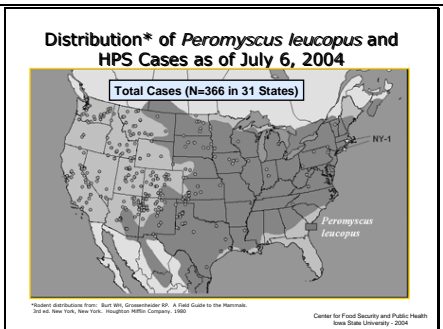
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The green shaded area depicts the geographic distribution in Canada, the United States, and Mexico of the rice rat, *Oryzomys palustris*. Given this widespread distribution, only four cases of Bayou Virus caused HPS. Sin Nombre Virus was responsible for almost all of the 366 cases in the United States. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/epislides/episl7.htm>.

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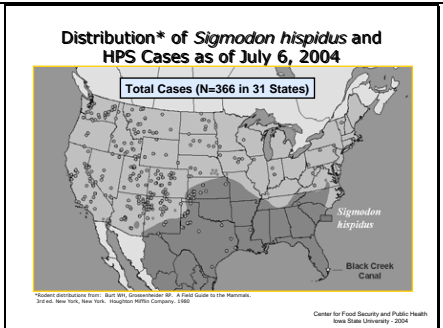
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The green shaded area depicts the geographic distribution in Canada, the United States, and Mexico of the white footed mouse, *Peromyscus leucopus*. Given this widespread distribution, only two cases of New York-1 Virus caused HPS. Sin Nombre Virus was responsible for almost all of the 366 cases in the United States. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/epislides/episl7.htm>.

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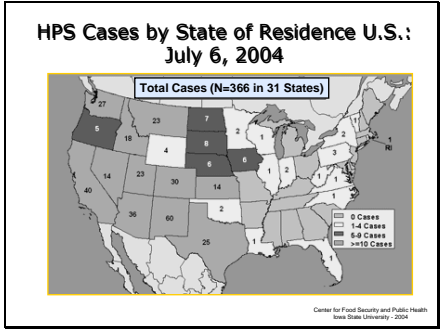
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The green shaded area depicts the geographic distribution in Canada, the United States, and Mexico of the cotton rat, *Sigmodon hispidus*. Given this widespread distribution, only one case of Black Creek Canal Virus caused HPS. Sin Nombre Virus was responsible for almost all of the 366 cases in the United States. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/epislides/episl7.htm>.

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This map depicts the distribution of the 366 cases of HPS in 31 states, with a concentration area in the southwest. The gray color indicates that state has never had a case of HPS; yellow indicates that state has had 1-4 cases; green indicates there has been 5-9 cases; orange indicates that state has had 10 or more cases of HPS. This could reflect either a higher mouse density, a higher rate of mouse infection, or more sharing of habitats by humans and deer mice. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/epislides/episl7.htm>.

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- HPS Case Count**
- North & South America
 - 1500 cases
 - United States and Canada
 - Sin Nombre Virus
 - Majority of cases
 - Others implicated
 - Andes, Monongahela, Black Creek Canal, Bayou, and New York viruses
 - Rodent-to-human transmission
- Center for Food Security and Public Health
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More than 1500 cases of HPS have been reported in North America and South America. There are currently 5 known viruses that have resulted in 387 human cases since 1959 in the United States and Canada. Most of those have been caused Sin Nombre, but also Andes, Monongahela, Black Creek Canal, Bayou, and New York virus are implicated in HPS. Rodent-to-human transmission has been implicated in causing disease.

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- HPS Case Count, U.S.**
- United States
 - 31 states have reported cases
 - Occur throughout the year
 - More common in spring-summer
 - 75% of patients reside in rural areas
 - 62% male; 38% female
 - Mean age of confirmed case is 37
 - Mortality rate 38%
 - Notifiable disease
- Center for Food Security and Public Health
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HPS cases have occurred in 31 of the lower 48 United States and appear to be more common in the spring and summer. Approximately 75% of the afflicted continues to be people in rural settings, with 62% of the cases being male and 38% female. The mean age of confirmed case patients is 37 (range: 10-75 years). Mortality is at 38% which is much greater than HFRS. HPS is a notifiable disease in the United States. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/epislides/episl7.htm>.

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- Non-Sin Nombre HPS Viruses**
- Black Creek Canal Virus
 - Cotton rat (*Sigmodon hispidus*)
 - One case in a Florida man
 - Bayou Virus
 - Rice rat (*Oryzomys palustris*)
 - 4 cases in Louisiana, Texas
 - New York-1 Virus
 - Deer mouse (*P. maniculatus*), white footed mouse (*P. leucopus*)
 - 2 cases in New York
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Case count of non-Sin Nombre causes of HPS in the U.S. The first of these three viruses, Black Creek Canal virus (BCCV), is associated with the cotton rat (*Sigmodon hispidus*); a single case of infection with this virus has been described in Dade County, Florida. Investigations of cases of HPS in Louisiana and Texas have yielded the unique viral sequence of a second, Bayou virus. This virus sequence has now been associated with the rice rat (*Oryzomys palustris*). Finally, cases of HPS in the northeastern United States have been caused by New York-1 virus that is similar to SNV, but distinct enough to suggest that it is a variant found in the eastern third of the United States. This virus is associated with both the deer mouse, *P. maniculatus*, and the white footed mouse, *P. leucopus*. To date, most of the human cases of HPS have been associated with the SNV.

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Rodent Exposures and HPS 70 confirmed HPS cases

Peridomestic exposure	69% (48/70)
Peridomestic & occupational exposure	19% (13/70)
Peridomestic & recreational exposure	9% (6/70)
Occupational exposure	4% (3/70)
Entering/cleaning rodent-infested structures	9% (6/70)


Armstrong, L.R. et al., JID 1995, 172 (October) Center for Food Security and Public Health
Iowa State University - 2004

Based on 70 confirmed cases of HPS, probability of being exposed based on activity is illustrated. Those who had the most cases (69%) were exposed in or around the home. Occupational exposure was the lowest at 4%. In another study that looked at seroprevalence of SNV antibodies it was found that among 239 samples taken from U.S. mammalogists and rodent workers with varying degrees of rodent exposure, the seroprevalence was only 1.14%.

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Risk of Contracting HPS

- Relatively low
- Contact with rodent excrement puts you at greatest risk
 - Cleaning a rodent infested dwelling
 - Opening or cleaning buildings that have been closed for a while
 - Especially over winter



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The risk associated with contracting HPS is relatively low. It is often associated with an increased numbers of rodents in and around the house. Anything that puts you in contact with rodent droppings, urine or nesting materials can place you at risk for infection. Indoor exposure has been linked to rodents in the home or near dwellings, especially in colder months. Opening or cleaning buildings that have been closed up for a period of time, such as cabins, sheds, barns, storage facilities that may have become rodent infested also increases the risk of exposure. See prevention and control for proper handling of these situations. Photo <http://www.cdc.gov/ncidod/diseases/hanta/images/hv081m.jpg>

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Risk of Contracting HPS

- Work, play, or live in closed spaces where rodents are actively living
- Hikers and campers
- Construction and utility workers
 - Enter crawl spaces under buildings
 - No serological evidence in 522 samples
- Traveling to and within hantavirus areas is not a risk factor

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Poor housing conditions, agricultural activities, wilderness camping, and other outdoor activities have help predispose people to the spread of infection if rodents are actively living in those same areas. Hikers and campers can also be exposed when they use infested trail shelters or camp near other rodent habitats. Construction and utility workers can be exposed when they work in crawl spaces under houses or in vacant buildings that may have a rodent population. Out of 522 samples taken from various occupational groups with frequent contact with rodents and their excreta (farm workers, laborers, professionals, home repairers, service industry and park service workers, heating and plumbing contractors, utility workers, and technicians) there was no serological evidence of SNV infection. Travel to and within all areas where hantavirus infection has been reported is not considered a risk factor for infection with HPS. However, recent research results show that many people who have become ill with HPS got the disease after having been in frequent contact with rodents and/or their droppings for some time. In addition, many people who have become ill reported that they had not seen rodents or their droppings at all.

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HPS U.S. Descriptive Demographic Statistics: July 6, 2003

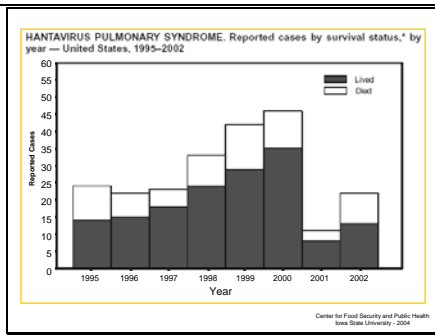
Characteristics	Total	
	N	366 (100%)
Gender		
Male	227	(62%)
Female	139	(38%)
Race		
White	284	(78%)
American Indian	71	(19%)
Black	6	(2%)
Asian	3	(1%)
Ethnicity		
Hispanic	45	(12%)
Case Fatality		
Dead	135	(37%)
Age (years)		
Mean	= 37 [10-75]	

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This depicts the demographic statistics of HPS in the United States as of July 6, 2003. Out of 366 reported cases, the majority have been reported in Caucasian people, while the Four Corners Outbreak primarily occurred in American Indians. Mortality rate is 37% and the mean age of people affected is 37. Many infections have occurred in lower socioeconomic people due to poorer housing and agricultural activities which increases their risk of exposure. Suburbanization, wilderness camping, and other outdoor activities have spread infection to persons of middle-upper incomes. Data as of July 6, 2004 at <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/episodes/epis17.htm>.

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This chart illustrates the survival status of HPS cases in the United States from 1995 to 2002. There was a record low number of cases reported to the CDC in 2001, but the number increased in 2002. Data from the National Center for Infectious Diseases; found in the Summary of Notifiable Diseases 2002, CDC website.

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Cases of HPS caused by the Andes virus have occurred in Paraguay, Uruguay, Chile and Argentina. Argentina was the first country to suspect person-to-person transmission. Several South American countries have isolated hantavirus and they are distinctly different from those found in the United States. Person-to-person transmission was thought to occur in Argentina. Outbreaks of HPS are often associated with a change in the rodent population, natural disasters, such as fires or floods, changes in the climate or weather patterns, and natural predators.

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HFRS

- Worldwide
 - 150,000–200,000 cases/yr
- Korean Hemorrhagic Fever
 - South Korea
 - 300-700 cases annually
 - Eastern China
 - ~100,000 cases annually
- Outbreaks linked to contact with field rodents during planting and harvesting of crops

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There is a worldwide distribution of people afflicted with hemorrhagic fever with renal syndrome and approximately 150,000 to 200,000 hospitalizations are reported each year. More than half of these are in China where hantavirus has been recognized since 1931. Korean Hemorrhagic Fever reportedly causes 300-700 cases of HFRS annually in South Korea. Eastern China reports about 100,000 cases annually. HFRS outbreaks in Asia and Europe are linked to contact with field rodents through the planting and harvesting of crops.

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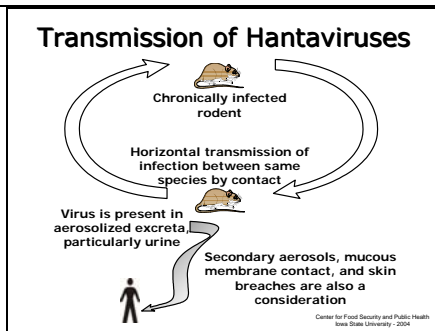
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Transmission

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Transmission occurs through inhalation of aerosolized virus particles from rodent excrement. Transmission of hantavirus infection starts with the reservoir host, a chronically infected rodent. Rodents shed the viral particles in their urine, feces, and saliva. Humans become infected when they disturb the microenvironment of rodents and breathe the tiny droplets in the air of these infected particles, a process called aerosolization. Direct contact with rodent excreta on human mucous membranes or through skin abrasions may also result in transmission. The virus particles can contaminate food consumed by humans and cause infection, and in very rare cases, a bite from an infected rodent can precipitate the disease. Horizontal transmission occurs between rodents of the same species and to man. Vertical transmission is negligible or absent and infection is asymptomatic and not deleterious to the rodent reservoir.

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Transmission of Hantaviruses

- Non-rodent animals may test positive
 - Do not excrete viral particles
 - Some species may introduce rodents into domestic setting
- Person-to-person transmission rare
 - Not through blood transfusion or vectors
 - Southern Argentina case
- Lab acquired (several cases)

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Seroprevalence in non-rodent animals is often low. A total of 164 species of mammals and birds have shown evidence of hantavirus infection. In 200 samples from cats in Austria, 5% were positive and cat ownership has been described as a risk factor for hantavirus disease in China. Research has failed to demonstrate the excretion of infectious particles from these species. Some species, such as the dog and cat, remain a bigger risk factor for bringing infected rodents into a domestic setting. A study involving 396 health care workers in the southwest United States demonstrated nosocomial transmission was not a factor in disease spread. Exposure to bodily fluids of an infected person could result in secondary transmission as was the suspected case in Southern Argentina. An outbreak of Andes virus Hantavirus Pulmonary Syndrome occurred in 1995 in the towns of El Bolson and Bariloche when a Buenos Aires physician apparently contracted the infection after minimal exposure to an infected patient. Person-to-person transmission of HFRS in Asia and HPS in the United States have not been reported. Therefore, CDC guidelines for management of HPS patients in the U.S. recommend standard precautions. There have been several lab-associated outbreaks of HFRS.

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Disease in Humans



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Chances of becoming infected are low. Flu-like signs appear 1-2 weeks after infection. Sin Nombre is most common cause of HPS.

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Clinical Signs of HPS

- Incubation period
 - 14-17 days
- Early stage
 - Fatigue, fever, myalgia, headache
 - Lasts 3-5 days
 - Half of the patients experience headaches, dizziness, chills, nausea, vomiting, diarrhea, abdominal pain

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Incubation time is mostly between 14 to 17 days. Initial signs include fatigue, fever, myalgia of the large muscle groups (thighs, hips, back, shoulders), and headache lasting 3 to 5 days. About half of the patients will experience headaches, dizziness, chills, and various gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal pain. CDC Infectious Disease Pathology Activity
www.cdc.gov/ncidod/diseases/hanta/hps/noframes/printgenlsection.htm

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Clinical Signs of HPS

- Later stage
 - 4 to 10 days after initial signs
 - Coughing and shortness of breath
 - Rapidly progressive, non-cardiogenic pulmonary edema and severe hypotension
 - Hospitalization and ventilation required usually within 24 hours

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Four to ten days after initial clinical signs, coughing and shortness of breath due to a rapidly progressive, non-cardiogenic pulmonary edema and severe hypotension. As the disease progresses rapidly, hospitalization and ventilation are necessary within 24 hours. Even with today's technology, approximately 40% of patients die within the first 48 hours due to uncorrected hypoxia and shock. CDC All About Hantavirus
www.cdc.gov/ncidod/diseases/hanta/hps/noframes/phys/clinical.htm

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Clinical Signs of HPS

- Tachypnea, tachycardia
- Hypotension
- Crackles or rales on lung examination
- Lowered albumin, elevated hematocrit
- Elevated WBC count
- Platelet count below 150,000 units

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Additional signs of HPS include increased respiratory and heart rates, lowered blood pressure. Lung auscultation often reveals crackles or rales, and radiographs are warranted. CBC and blood chemistry should be run every 8 to 12 hours to monitor WBC count and platelet count. As pulmonary edema increases, the serum albumin values are lowered with a rise in hematocrit. The WBC count is often elevated while the platelet count falls below 150,000 units.

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HPS Radiographic Findings

- Bilateral interstitial infiltrates
 - Moderate to rapid progression
- Bilateral alveolar infiltrates
- Pleural effusion
- Normal heart size

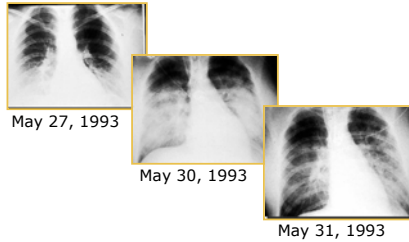


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In HPS, the lung is the target organ and due to increased vascular permeability, a distinctive bilateral pulmonary edema ensues. Radiographic findings include bilateral interstitial infiltrates that will have moderate to rapid progression as demonstrated by sequential radiographs. Bilateral alveolar infiltrates with pleural effusion are also found, but the heart will remain normal in size.

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Radiographic Progression of HPS



Source: Dr. L. Ketai

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These radiographs demonstrate the progression of HPS in the lung of a patient. They were taken on May 27, May 30, and May 31, 1999 (courtesy of L. Ketai). The chest radiograph occasionally may be normal very early in the pulmonary phase of HPS, but it soon progresses to the more typical pattern of bilateral interstitial or alveolar pulmonary edema. The findings differ from those of adult respiratory distress syndrome in that indications of interstitial edema (Kerley B lines, peribronchial cuffing) are more common and the distribution is more central in HPS.

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HPS National Surveillance Inclusion Criteria

- Healthy person with febrile illness;
- Unexplained acute respiratory distress syndrome OR bilateral interstitial lung infiltrates
- Supplemental oxygen OR death from unexplained respiratory illness
- AND noncardiogenic pulmonary edema at autopsy
- AND no identifiable, specific cause of death

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Hantavirus Pulmonary Syndrome is part of a national surveillance program and the specific case definition is as follows: A previously healthy person presenting with a febrile illness with a temperature at or above 101°F (38.3°C), unexplained Adult Respiratory Distress Syndrome, radiographic evidence of bilateral interstitial infiltrate that develops within one week of hospitalization, and respiratory compromise that requires supplemental oxygen. If sudden death occurs before supplemental oxygen and noncardiogenic pulmonary edema is present on autopsy without an identifiable, specific cause of death, diagnosis can be made.

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HPS National Surveillance Exclusion Criteria

- Predisposing underlying medical condition
- Acute illness that explains the respiratory disease

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Exclusion criteria are important in HPS clinical case definitions and include the presence of a predisposing underlying medical condition or an acute illness that explains the respiratory disease.

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HPS National Surveillance

- Confirmation requires meeting all inclusion and exclusion criteria
- Plus laboratory confirmation
 - Positive serology
 - Positive PCR
 - Positive IHC

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Confirmation of HPS disease requires meeting all the inclusion and exclusion criteria plus laboratory confirmation such as positive serology via the presence of hantavirus specific immunoglobulin M or rising titers of immunoglobulin G, positive polymerase chain reaction for hantavirus RNA, or positive immunohistochemistry for hantavirus antigen.

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Clinical Signs of HFRS

- Febrile phase
 - Abrupt onset of chills, lethargy, sustained high fever
 - Headache, myalgia, vomiting, diarrhea
 - Thrombocytopenia, petechial hemorrhages
- Hypotensive phase
 - Increased hematocrit
 - Sinus bradycardia

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There are five phases of Hemorrhagic Fever with Renal Syndrome characterized as febrile, hypotensive, oliguric, diuretic, and convalescent. In the febrile phase, onset is sudden and follows with chills despite a sustained high fever, lethargy, headache, myalgia, vomiting and diarrhea. Thrombocytopenia is often a clue to diagnosis, while the conjunctiva and skin show petechiae. The hypotensive phase often results in an increased hematocrit with sinus bradycardia even with the fever.

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Clinical Signs of HFRS

- Oliguric phase
 - Lowered urine output
 - Increased serum urea and creatinine
 - Death due to circulatory or renal failure
- Diuretic phase
 - Spontaneous
- Convalescent phase
 - Unable to concentrate urine

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There are five phases of the disease characterized as febrile, hypotensive, oliguric, diuretic, and convalescent. In the oliguric phase, urine output decreases leading to higher serum concentrations of urea and creatinine. Metabolic acidosis occurs due to the electrolyte imbalance. Death occurs 75% of the time in the first 10 days, generally during the oliguric phase of the disease due to circulatory or renal failure. The diuretic phase occurs spontaneously and as a result renal function can return to normal. The convalescent phase can last weeks to months with the patient unable to concentrate urine.

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Other HFRS Clinical Signs

- Hantaan, Seoul, Dobrava viruses
 - Severe hemorrhagic complications
- Puumala virus
 - Nephropathia Epidemica
 - Acute febrile disease with renal involvement
 - Transient thrombocytopenia

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Hantaan, Seoul, Dobrava viruses have severe hemorrhagic complications during the oliguric phase. Puumala virus causes a condition known as nephropathia epidemica that causes an acute febrile disease with renal involvement and a transient thrombocytopenia.

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Diagnosis

- Serology
 - ELISA used by CDC
 - IgM, IgG
- Immunohistochemistry
 - Detects viral antigen in tissues
- Virus isolation
- Various others



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The CDC uses ELISA to detect the presence of IgM in acute-phase serum or a four-fold rise in IgG antibody titer from acute- and convalescent-phase sera. Acute-phase serum as an initial diagnostic specimen may not yet have IgG but it is long lasting, and has been used in serologic investigations of the epidemiology of the disease. Immunohistochemistry can be used on formalin fixed tissues to detect hantavirus antigen when serum is unavailable. Virus isolation was accomplished using a serum sample from a seronegative child 2 days before clinical onset of signs of HPS. Other tests include the polymerase chain reaction for hantavirus RNA, currently experimental, a Western blot assay using recombinant antigens and isotype-specific conjugates for IgM-IgG differentiation and rapid immunoblot strip assay (RIBA) which is an investigational prototype assay used to identify serum antibody to recombinant proteins and peptides specific for SNV and other hantaviruses.

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HPS Treatment

- Early, aggressive intensive care
- Avoidance of hypoxia
 - Assisted ventilation
- Electrolyte balance
- Maintaining normal blood pressure
- Ribavirin has questionable efficacy
- Careful monitoring

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Treatment of patients with HPS requires early and aggressive intensive care, focusing on electrolyte balance, oxygenation of the blood, and maintaining blood pressure. Antiviral drugs, such as ribavirin, have questionable efficacy, possibly due to the late introduction after disease onset.

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HPS Prognosis

- Patients can recover
 - With early supportive care
- Grave prognosis
 - If undiagnosed or do not seek treatment
- Chronic lung and heart damage
 - Can result depending on the type and aggressiveness of supportive care

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The Four Corners Outbreak, due to the difficulty in identifying the type of hantavirus, had a grave prognosis for many of the initial victims. History of exposure leads to a more rapid diagnosis, and therefore treatment. Early aggressive supportive care is needed for a successful resolution of symptoms. Without treatment, the prognosis for HPS is grave. With supportive care and symptom targeted therapy, patients can recover from the disease. Chronic lung and heart damage can result, again depending on the type and aggressiveness of supportive care.

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Case

- February 2000
 - 61 year old rural Vermont resident
 - Episodes of fever, chills, syncope
 - Hospitalized
 - Swollen lymph node, sore knee
 - Abnormal CBC, normal lung radiographs
 - Progressed to respiratory failure
 - Interstitial edema, mechanical ventilation

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In February 2000, a previously healthy 61 year old rural Vermont resident was hospitalized. Previous signs included three syncopal episodes, one week of chills with a fever less than or equal to 102° F (39° C), gastrointestinal upset with anorexia and right knee pain. Physical exam findings upon entering the hospital were a slightly elevated temperature at 99.3° F (37.4° C), pulse was 90 bpm, blood pressure 135/90mmHg, clear lung sounds, and a swollen non-tender lymph node under the left jaw. CBC showed an elevated hematocrit, lowered platelet count and normal WBC count with 83% granulocytes. Initial radiographs were clear but 1 day later revealed interstitial edema leading to onset of respiratory failure, hypoxemia, and hypotension which required mechanical ventilation.

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Case

- Renal insufficiency, DIC
 - Released after 23 days
- Initial diagnosis
 - Adult Respiratory Distress Syndrome with sepsis
- Further Investigation
 - Contact with rodent excrement
 - Paired serum samples positive for SNV
- 5% of HPS cases occur east of Mississippi River


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Renal insufficiency and DIC (disseminated intravascular coagulation) ensued. The patient was released after 23 days in the hospital, 16 of which were in intensive care. Diagnosis: ARDS (Adult Respiratory Distress Syndrome), and sepsis of unknown etiology. After further investigation, it was discovered that this patient cleaned a mouse nest from a woodpile 2 months previous to the illness, as well as having seen mice in the basement and trapping two under the kitchen counter. Paired serum samples submitted to the CDC for ELISA, IgM, and IgG testing, revealing SNV antibodies. The Vermont Department of Health discovered mice droppings in the cellar and under the kitchen counters. Rodents were trapped by the USDA in a five mile radius of the patient's home and tested serologically at CDC for hantaviral antibodies. 43 rodents were tested and only two of five deer mice were found positive. Only 5% of the 284 cases of confirmed HPS occurred east of the Mississippi River.

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Disease in Animals

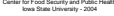


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Disease in Animals

- Rodents
 - Reservoir
 - Asymptomatic carriers
 - Antigen present in virtually all organs
 - Infectious for life
- Other mammals seronegative




Rodents are the reservoir for hantavirus but are asymptomatic carriers. They carry an abundance of viral antigens in their blood, kidneys, liver, fat, nervous tissue, and lungs which makes them infectious for life and can transmit to other rodent species and to man. Other mammals such as carnivores were tested and all were seronegative to SNV.

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Prevention and Control

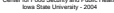


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HPS Prevention

- Limit exposure to mouse excrement
- Control rodents indoors
- Control rodents outdoors
- Use safety precautions when cleaning rodent infested areas
- Minimize your exposure when enjoying outdoor activities





The most effective way to prevent the risk of HPS is to limit exposure to rodents and their excreta, both inside the home and out. Utilizing proper precautions when in situations where mouse excreta exists will also decrease the risk of exposure. It is important to remember to minimize your exposure when enjoying outdoor activities.

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Control Mice Indoors

- Prevent access to food sources
 - Keep food preparation and cooking areas clean
 - Cover pet and human food overnight
 - Store garbage in tightly covered or elevated container
- Rodent trapping

Control mice inside the home by keeping food preparation and cooking areas clean, do not leave human or pet food out overnight, and store garbage in containers with tight lids or elevate it. Set traps for the rodents who have entered. Mouse trap photo www.cdc.gov/ncidod/diseases/hanta/images/hv115m.jpg

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Prevent Entry Indoors

Seal holes with steel wool or use sheet metal around foundation




Clear away brush from foundation

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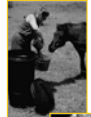

Seal any holes in the foundation with sheet metal or use steel wool around piping. Prevent mice from entering the home by clearing away brush and debris from the foundation. It is important to also “rodent proof” any buildings you are trapping mice. Trapping alone will actually increase the chance of exposure to an infected excrement because trapping without blocking the entry of new mice merely increases the number of mice who inhabit the buildings. Steel wool photo www.cdc.gov/ncidod/diseases/hanta/images/hv125m.jpg, sweeping foundation photo www.cdc.gov/ncidod/diseases/hanta/images/hv128m.jpg

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Control Mice Outside

- Eliminate nesting sites
 - Elevate woodpiles and garbage cans
- Eliminate food sources
 - Store in tight containers
 - Cover uneaten food at night
- Encourage natural predators
 - Non-poisonous snakes, owls, hawks

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Control the number of rodents outside by eliminating possible nesting sites and shelter areas in or around dwellings. If necessary, locate those items at least 100 feet from the home. Trap outside if necessary but remember to use insecticide on trapped rodents to kill fleas in plague endemic areas. Eliminate possible food sources by storing them in tight containers, elevating them, and cover or remove uneaten food at night. Another control mechanism is to encourage natural predators, such as non-poisonous snakes, owls, and hawks.

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Safely Clean Up Rodent Areas

- Wear rubber gloves
- Avoid sweeping or vacuuming initially
- Spray contaminated materials with disinfectant
- Seal dead rodents and excrement in bags and dispose
- Disinfect gloves before removal and Wash Hands!

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Safety precautions need to be taken when cleaning up areas where rodents once inhabited. It is wise to allow the area to air out while not stirring up dust particles. Wear latex rubber gloves, and possibly a face mask, to prevent contact and inhalation of virus particles. Avoid sweeping, vacuuming, or stirring dust until area is wet with disinfectant. The entire contaminated area should then be sprayed with household disinfectants such as a 10% bleach solution. This will disinfect dead rodents and more importantly, their infectious excrement. A 10% bleach solution can be made by adding 1 1/2 cups bleach to 1 gallon water. Then seal any dead rodents and the other materials in a bag and dispose of properly. Disinfect gloves before removal and wash hands thoroughly. Spraying rodent feces. Photo www.cdc.gov/ncidod/diseases/hanta/images/hv144m.jpg.

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Minimizing Outdoor Exposure

- Avoid contact with rodents
- Do not camp near rodent burrows
- Keep campsite clean
- Tightly seal all food
- Air out unused cabins before entering
- Avoid sleeping on the bare ground



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While enjoying outdoor activities, it is important to remember some simple steps to minimize your exposure to potentially infectious rodents. First of all, avoid all contact with rodents. Do not feed or handle them even if they appear friendly. Avoid camping near rodent burrows, and keep your campsite clean and food containers tightly sealed. It is best to air out any buildings, such as an unused cabin, before entering or cleaning. If possible, avoid sleeping on the bare ground as this enhance your chance of being exposed during slumber. Campsite photo www.cdc.gov/ncidod/diseases/hanta/images/hv155m.jpg

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Other Measures

- Use N-100 (HEPA) filters on respirators
 - Effective in removing virus particles less than 5 microns
 - Not tested in transmission of HPS

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Recent changes in the nomenclature and certification of the type of filters used in respirators include the discontinuation of the HEPA designation and the designation of new classes of filters. The N-100 (99.97) is equivalent to the previous HEPA filter. Use of an N-100 filter should provide the same protection as the HEPA filter. Due to the nature of the virus, no studies have been able to test the efficacy of either the HEPA or N-100 filters in protecting against HPS transmission. Available evidence suggests that HPS is transmitted by inspiring small (less than 5 micron) viral particles in aerosols which the N-100 is the most effective in removing.

Internet Resources

- CDC All About Hantavirus
 - www.cdc.gov/ncidod/diseases/hanta/hps/noframes/phys/clinical.htm
- CDC Infectious Disease Pathology Activity
 - www.cdc.gov/ncidod/diseases/hanta/hps/noframes/printgenlsection.htm

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