

1. Hantavirus pulmonary syndrome (HPS), caused by a previously unknown hantavirus, was first recognized in May 1993. The disease begins with nonspecific symptoms that can include fever, muscle aches, headache, abdominal pain, nausea, and vomiting, followed later by coughing and shortness of breath. The symptoms usually occur between 1 and 6 weeks after exposure to virus-laden rodent excreta. The disease rapidly progresses to cardiac and respiratory failure, requiring that the patient receive intensive care.

Family Bunyaviridae 5 genera, 250 species			
<u>Genus</u>	<u>Human disease</u>		
Bunyavirus	LaCrosse encephalitis, others		
Phlebovirus	Rift Valley fever, sandfly fever		
Nairovirus	Crimean-Congo hemorrhagic fever		
Tospovirus	Plant virus, no known human disease		
Hantavirus	Hemorrhagic fever with renal syndrome		
	Hantavirus pulmonary syndrome		

2. Family Bunyaviridae: Hantaviruses are members of the family Bunyaviridae, which consists of 5 genera and 250 species. Hantaviruses can cause hantavirus pulmonary syndrome (HPS) or hemorrhagic fever with renal syndrome (HFRS). The 5 genera of Bunyaviridae include *Bunyavirus*, *Phlebovirus*, *Nairovirus*, *Tospovirus*, and *Hantavirus*.

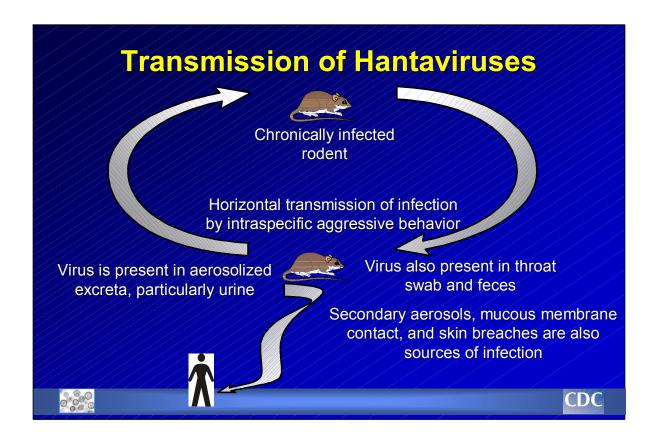
#### **Characteristics of Hantaviruses**

- No arthropod vector established
   Unique among genera of Bunyaviridae
- Rodent hosts
   Genus and possibly species specific
- Transmission
   Aerosolization of rodent excreta

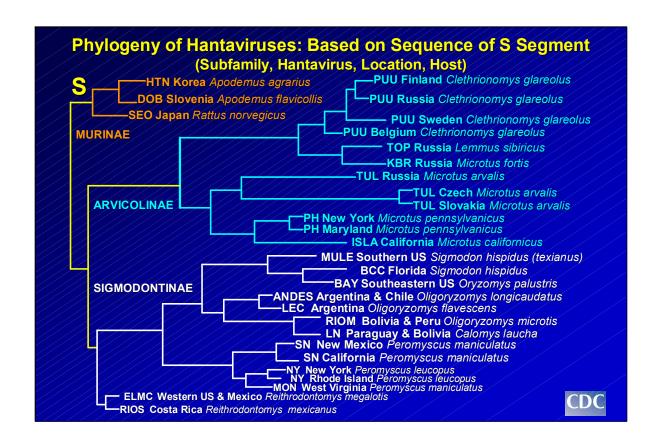


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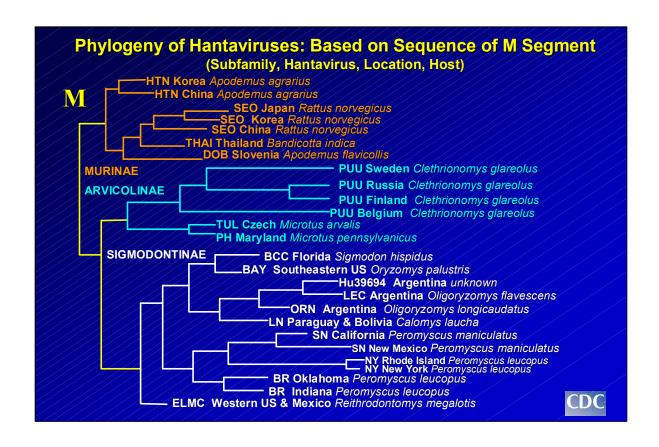
3. Characteristics of Hantaviruses: Hantaviruses are unique among Bunyaviridae genera in that they are not associated with an arthropod vector. In general, a distinct rodent species is the reservoir for each hantavirus. Transmission of hantaviruses to humans most often occurs via inhalation of aerosolized, virusladen rodent excreta.



4. Transmission of Hantaviruses: The virus is horizontally transmitted between rodents through intraspecific aggressive behaviors, such as biting. The virus is transmitted to humans from aerosolized rodent excreta, particularly urine. Transmission to humans also can occur from inhalation of secondary aerosols, and from rodent bites or other direct contact of infectious material with mucous membranes or broken skin.



5. Phylogeny of Hantaviruses, Based on the Sequence of the S Segment (one of three genomic RNA segments): This phylogenetic tree depicts the relationship among the viruses, the primary rodent reservoir of the virus, and the geographic origin of the characterized virus.



6. Phylogeny of Hantaviruses, Based on the Sequence of the M Segment (one of three genomic RNA segments): This phylogenetic tree depicts the relationship among the viruses, the primary rodent reservoir of the virus, and the geographic origin of the characterized virus.

<u>Virus</u>	<u>Host</u>	<u>Location</u>	Disease
Hantaan	Apodemus agrarius	Asia, Far East Russia	HFRS
Dobrava	Apodemus flavicollis Apodemus agrarius	Balkans Europe	HFRS
Seoul	Rattus norvegicus Rattus rattus	Worldwide	HFRS
Subfam	ily Arvicolinae asso	ciated viruses	
<u>Virus</u>	<u>Host</u>	<u>Location</u>	<u>Diseas</u>
Puumala	Clethrionomys glareolu	s Europe	HFRS

7. Hantaviruses in the Old World: At least four Old World hantaviruses -- Hantaan, Dobrava, Seoul, and Puumala viruses -- can cause hemorrhagic fever with renal syndrome (HFRS) and are endemic in parts of Europe and Asia. Murine rodents carry Hantaan, Dobrava, and Seoul viruses. An Arvicoline rodent species carries Puumala virus, which causes a milder form of HFRS. Numerous other Old World hantaviruses have been identified but have not been linked to human disease.

#### **Hantaviruses in the New World (1) Subfamily Sigmodontinae associated viruses** Virus Host Location Disease Sin Nombre **HPS** Peromyscus maniculatus West & Central U.S. & Canada Monongahela Peromyscus maniculatus Eastern U.S. & **HPS** Canada New York Peromyscus leucopus Eastern U.S. **HPS** Bayou Oryzomys palustris Southeastern U.S. HPS Black Creek Canal Sigmodon hispidus Florida **HPS** Numerous other hantaviruses have been identified but not linked to human disease CDC

8. Hantaviruses in the New World -- North America: Hantaviruses in the New World are associated with hantavirus pulmonary syndrome (HPS). Sigmodontine rodents carry the hantaviruses that cause HPS and are found throughout the Americas. Sin Nombre virus, carried by *Peromyscus maniculatus*, is the predominant cause of HPS in the United States and Canada. Mononghela, New York, Bayou, and Black Creek Canal viruses also cause HPS and are found in eastern Canada and eastern and southeastern United States. Numerous other hantaviruses have been identified but have not been linked to human disease.

<u>Virus</u>	<u>Host</u>	<u>Location</u>	<u>Diseas</u>
Andes	Oligoryzomys longicaudatus	Argentina & Chile	HPS
Oran	Oligorozomys longicaudatus	Northwestern Argentin	<b>a</b> //
Lechiguanas	Oligoryzomys flavescens	Central Argentina	
Hu39694	Unknown	Central Argentina	
Laguna Negra	Calomys laucha	Paraguay & Bolivia	HPS
Bermejo	Oligoryzomys chacoensis	Northwestern Argentina	HPS
Juquitiba	Unknown	Brazil	HPS
Choclo	Oligoryzomys fulvescens	Panama	HPS

9. Hantaviruses in the New World - South and Central America: In South and Central America, hantaviruses that have been identified as causing HPS are Andes virus in Argentina and Chile; Andes-like viruses including Oran, Lechiguanas, and Hu39694 in Argentina; Laguna Negra virus in Bolivia and Paraguay; Bermejo virus in Argentina; Juquitiba virus in Brazil; and Choclo virus in Panama. Numerous other hantaviruses have been identified but have not been linked to human disease.



10. A map of Western Hemisphere shows the distribution of New World hantaviruses and their associated rodent hosts. The viruses in bold print cause disease in humans including: Sin Nombre, Choclo, Orán, Andes, New York, Bayou, Black Creek Canal, Juquitiba, Laguna Negra, Hu39694, and Lechiguanas.

#### Virus (Rodent Host)

Sin Nombre (Peromyscus maniculatus)

Muleshoe (Sigmodon hispidus)

Isla Vista (Microtus californicus)

El Moro Canyon (Reithrodontomys megalotis)

Calabazo (Zygodontomys brevicauda)

Choclo (Oligoryzomys fulvescens)

Caño Delgadito (Sigmodon alstoni)

Rio Mamore (Oligoryzomys microtis)

Orán (Oligoryzomys longicaudatus)

Bermejo (Oligoryzomys chacoensis)

Andes (Oligoryzomys longicaudatus)

New York (Peromyscus leupous)

Prospect Hill (Microtus pennsylcanicus)

Bloodland Lake (Microtus ochrogaster)

Bayou (Oryzomys palustris)

Black Creek Canal (Sigmodon hispidus)

Rio Segundo (Reithrodontomys mexicanus)

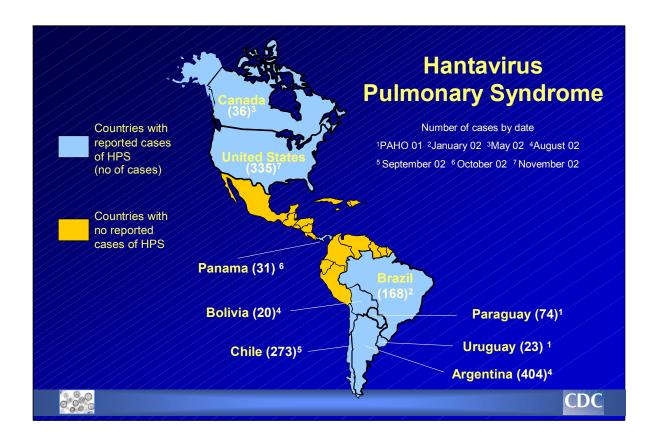
Juquitiba (Unknown host)

Laguna Negra (Calomys laucha)

Maciel (Necromys benefactus)

Hu39694 (Unknown host)

Lechiguanas (Oligoryzomys flavescens)



11. A map of Western Hemisphere shows the number of cases of Hantavirus Pulmonary Syndrome in the respective country.

#### **Country (Number of Cases)**

Argentina (404)

**Brazil** (168)

Bolivia (20)

Canada (36)

Chile (273)

Panama (31)

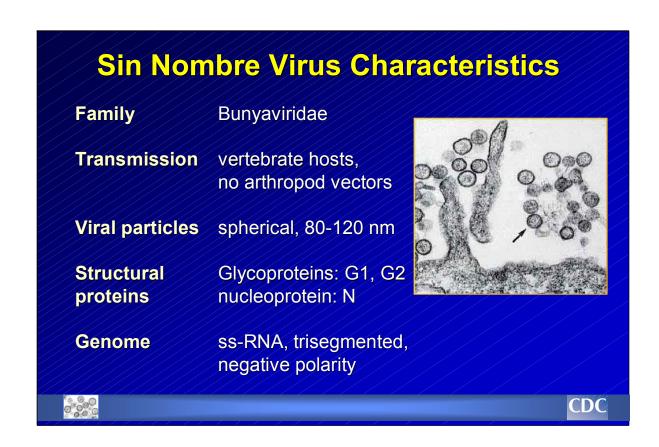
Paraguay (74)

United States (335)

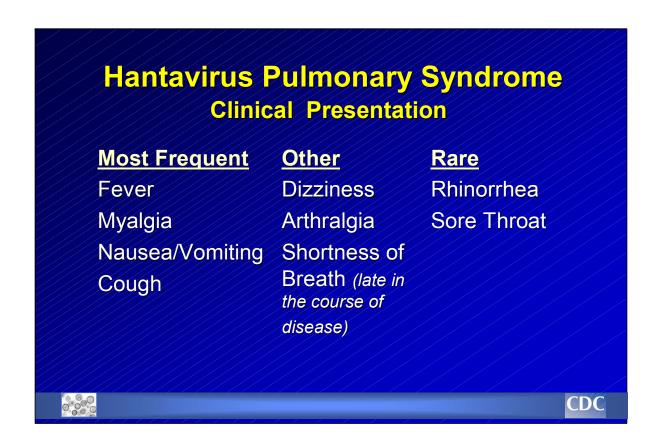
Uruguay (23)



12. Deer Mouse (*Peromyscus maniculatus*) and Cotton Rat (*Sigmodon hispidus*): The deer mouse is the primary rodent host for Sin Nombre virus, the main etiologic agent of HPS in North America. The cotton rat is the primary rodent host for the Black Creek Canal virus. Infected rodents show no visible evidence of acute or chronic infection.



13. Characteristics of Sin Nombre Virus: Sin Nombre virus belongs to the family Bunyaviradae and contains three genomic RNA segments of negative polarity. The virion of Sin Nombre virus is spherical and is 80-120nm in diameter. The virion contains two glycoproteins, G1 and G2, located on the outer surface, which are the nucleoprotein and the viral polymerase.



14. Clinical Presentation of HPS: Most frequent symptoms include fever, myalgia, nausea/vomiting, and cough. Other symptoms include dizziness, arthralgia, and shortness of breath. Rhinorrhea and sore throat are rarely seen.

## Hantavirus Pulmonary Syndrome Physical Examination

- Tachypnea
- Tachycardia
- Hypotension
- Crackles or rales on lung examination



CDC

15. Physical Examination Findings of HPS: Typical findings include fever, tachypnea, tachycardia, hypotension, and crackles or rales on lung examination.

### Hantavirus Pulmonary Syndrome Radiographic Findings

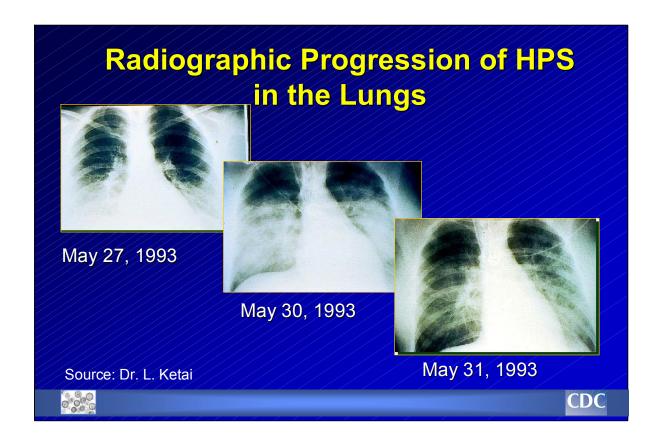
- Bilateral interstitial infiltrates
   moderate to rapid progression
- Bilateral alveolar infiltrates
- Pleural effusion





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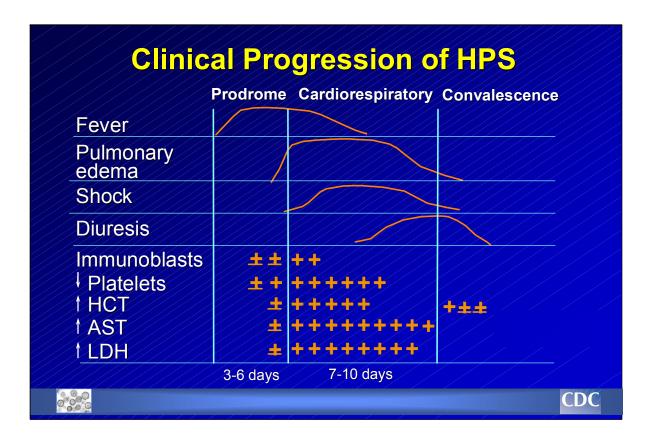
16. Radiographic Findings of HPS: Findings usually include interstitial edema, Kerley B lines, hilar indistinctness and peribronchial cuffing with normal cardiothoracic ratios. HPS begins with minimal changes of interstitial pulmonary edema and rapidly progressing to alveolar edema with severe bilateral involvement. Pleural effusions are common and are often large enough to be evident radiographically.



17. Radiographic Progression of HPS in the Lungs: These chest X-rays of an HPS patient were taken on May 27, May 30, and May 31, 1993. Approximately one-third of patients show evidence of pulmonary edema in the initial radiograph. Forty-eight hours after the initial radiograph, virtually all patients demonstrate interstitial edema and two-thirds have developed extensive bibasilar or perihilar airspace disease (courtesy of L. Ketai).

# Hematology Low platelet count Atypical lymphocytes (immunoblasts) Elevated LDH Left shift on WBC differential Elevated AST (SGOT) Elevated WBC Elevated WBC CDC

18. Common Laboratory Findings: Notable hematological findings include low platelet count, immunoblasts, left shift on WBC differential, elevated WBC, and elevated hematocrit. The large atypical lymphocyte shown here is an example of one of the laboratory findings that, when combined with a bandemia and dropping platelet count, are characteristic of HPS. Notable blood chemistry findings include low albumin, elevated lactate dehydrogenase (LDH), elevated aspartate aminotransferase (AST or SGOT) and elevated alanine aminotransferase (ALT or SGPT).



19. Clinical Course of HPS: Clinical course of HPS starts with a febrile prodrome that may ultimately lead to hypotension and end-organ failure. The onset of the immune response precedes severe organ failure, which is thought to be immunopathologic in nature. Hypotension does not result in shock until the onset of respiratory failure, but this may reflect the severe physiologic impact of lung edema.

#### **HPS Management**

- Early aggressive intensive care
- Early use of inotropic agents (Dobutamine)
- Early ventilation
- Careful monitoring
  - Oxygenation
  - Fluid balance
  - Blood pressure



CDC

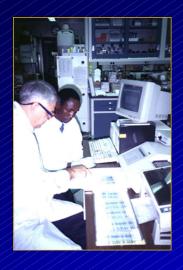
20. HPS Patient Management: Treatment of patients remains supportive in nature. Early aggressive intensive care is imperative, and may include early use of inotropic agents, such as dobutamine, to augment myocardial contractivity. Patients require early ventilation and careful monitoring of oxygenation, fluid balance, and blood pressure.

## ICU Monitoring and Therapy Early use of inotropic agents Mechanical ventilation Judicious volume resuscitation Early PA catheter

21. ICU Monitoring and Therapy: Because of the rapid progression of the disease, patients should be quickly transferred to a fully equipped emergency facility when necessary. Patients should be closely and continually monitored by a physician so that life-supporting procedures can be performed. Inotropic agents, mechanical ventilation, early PA catheterization and judicious volume resuscitation are elements of supportive care.

SOS 6/95

## Hantavirus Pulmonary Syndrome Laboratory-confirmed Diagnosis



- SerologyIgMIgG
- Immunohistochemistry
- Reverse transcription and polymerase chain reaction (RT-PCR)

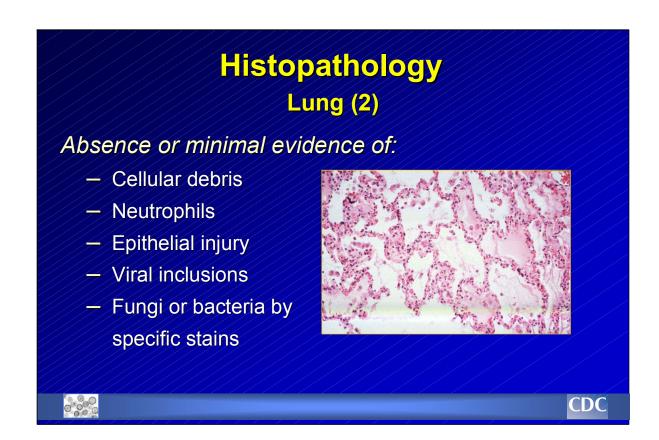


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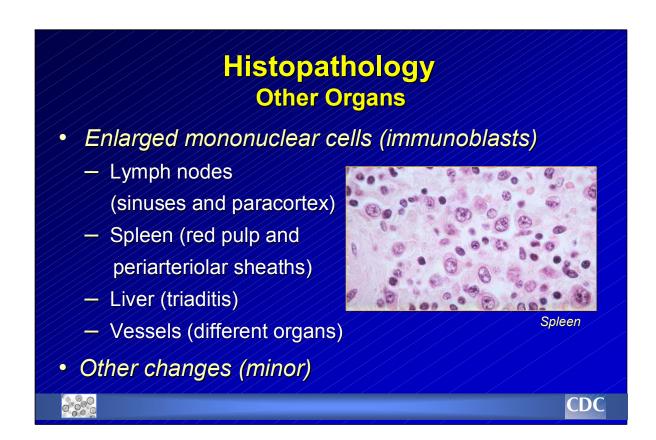
22. Laboratory Confirmation of HPS: HPS can be diagnosed several ways. CDC uses an enzyme-linked immunosorbent assay (ELISA) to detect IgM antibodies to SNV and to diagnose acute infections with other hantaviruses. An IgG test is used in conjunction with the IgM-capture test. A four fold rise in IgG antibody titer between acute- and convalescent-phase sera or the presence of IgM in acute-phase sera are diagnostic for hantaviral disease. Note that acute-phase serum sent as an initial diagnostic specimen may not yet have IgG. IgG antibody is long lasting, and sera of patients retrospectively identified appear to have retained antibody for many years. The RT-PCR technique allows for classification of distinct viruses prior to viral isolation. Immunohistochemical staining is used for postmortem or retrospective diagnosis.

# Histopathology Lung (1) Interstitial Pneumonitis - Congestion - Interstitial infiltrate of enlarged mononuclear cells (immunoblasts) - Intra-alveolar and septal edema - Focal hyaline membranes

23. Histopathology Lungs (1): No single pathognomonic lesion will permit histopathologic diagnosis of HPS. Lungs are dense and rubbery, usually weighing twice as much as the average lung. In most cases there is a mild to moderate interstitial pneumonitis with variable degrees of congestion, edema, and mononuclear cell infiltration. Focal hyaline membranes are observed, as well as extensive intra-alveolar and septal edema.



24. Histopathology Lungs (2): In typical cases, neutrophils are scanty and the respiratory epithelium remains intact. There is no evidence of cellular debris, nuclear fragmentation, viral inclusions, fungi or bacteria by specific stains.



25. Histopathology of Other Organs: Typical histopathologic findings that may be seen in lymphoid tissues of HPS patients include the presence of immunoblasts within the red pulp and periarteriolar sheaths of the spleen; in the paracortex and sinuses of lymph nodes; and in the peripheral blood.

### Rodent Exposure 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 9% (6/70) structures

Armstrong, L.R. et al., JID 1995; 172 (October)





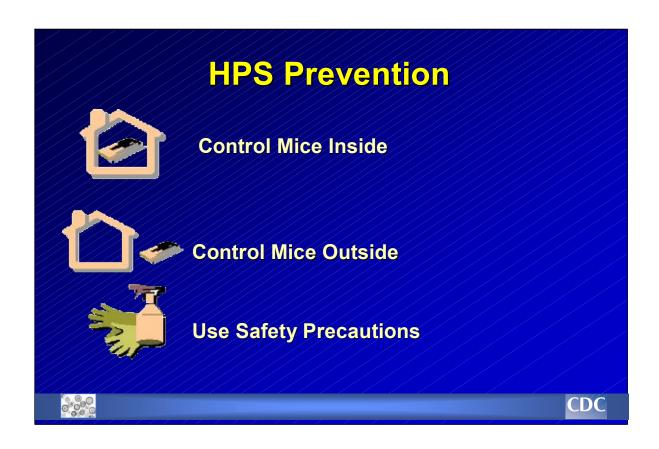
26. Rodent Exposure Data from 70 confirmed HPS Cases: A review of confirmed HPS cases was conducted to characterize rodent exposure. Of 70 confirmed HPS cases, 69% had peridomestic exposure; 19% had both peridomestic and occupational exposure; 9% had peridomestic and recreational exposure; 4% had occupational exposure; and 9% had rodent exposure while entering and cleaning rodent-infested structures.

#### Prevalence of SNV IgG Antibodies in **Select U.S. Populations** Risk group Postive/tested (%) Location/time Forest workers<sup>1</sup> 0/143 SW US, 1993 Health care workers<sup>2</sup> 0/396 SW US, 1993 3/299 (1.0%) SW US, 1993 Prodromal HPS<sup>3</sup> 3/239 (1.3%) SW US, 1993 Contacts<sup>4</sup> Rural OCC5 1/522 (0.2%) SW US, 1994 Rodent workers<sup>6</sup> 8/932 (0.9%) US, 1994 Total 15/2531 (0.6%) 2. Vitek et al, 1996 3. Simonsen et al, 1995 1. Vitek et al. 1996 4. Zeitz et al, 1995 5. Zeitz et al, 1995 6. Armstrong et al, 1995 CDC

27. Seroprevalence of SNV IgG Antibodies in Select U.S. Populations: Studies focusing on select high-risk groups showed a total prevalence of SNV antibodies of 0.6% (15/2531). Antibody prevalence was 0% (0/143) for forest workers; 0% (0/396) for health care workers; 1% (3/299) for prodromal HPS patients during initial 1993 outbreak; 1.3% (3/239) for contacts of HPS patients; 0.2% (1/522) for rural OCC; and .9% (8/932) for rodent workers.

<u>Country</u>	Positive/tested (%)	<u>Time</u>
Paraguay <sup>1</sup>	44/345 (12.8%)	1995
Western Paraguay <sup>2</sup> (Indian Population)	78/193 (40.4%)	1993-1995
Argentina <sup>3</sup>	<1%	1996
Salta Province <sup>2</sup> (Indian Population)	38/222 (17.1%)	1993-1995
Chile <sup>3</sup>	2 13%	1997

28. Prevalence of SNV IgG Antibodies in Select South American Populations: Prevalence of hantavirus antibodies in select South American populations varies from region to region. Studies demonstrated an antibody prevalence of 12.8% (44/345) in Paraguay; 40.4% (78/193) among an Indian population in Western Paraguay; <1% in Argentina; 17.1 % (38/222) among an Indian population in the Salta province, Argentina; and 2-13% in Chile.

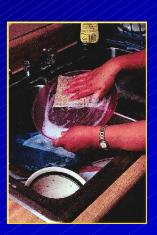


29. HPS Prevention: Overview Slide. The best method to prevent HPS is to limit human-rodent contact. Mice should be controlled inside and outside of the home. Safety precautions should be used when cleaning in areas with evidence of rodent infestation.



#### **Control Mice Inside**

- Eliminate food sources
  - Wash dishes and clean the floor and counters
  - Put pet food and water away at night
  - Store food / garbage in containers with tight lids



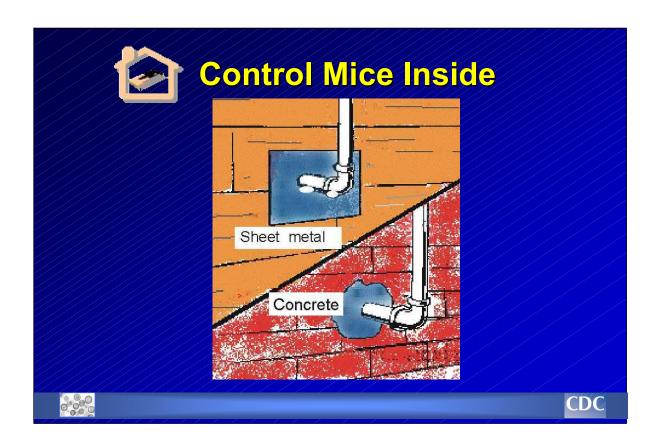


CDC

30. Control Mice Inside: Eliminate food sources by washing dishes, cleaning floors and counter. Put pet food and water away at night. Store food and garbage in containers with tight lids.



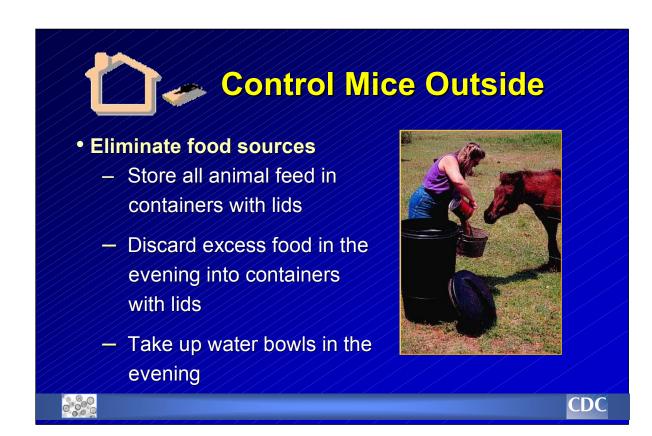
31. Prevent Mice from Entering Homes and Buildings: Clear brush and grass from around foundation. Seal holes that mice may use to enter buildings and use flashing around the base of the house. Keep snap traps, baited with peanut butter, set continuously.



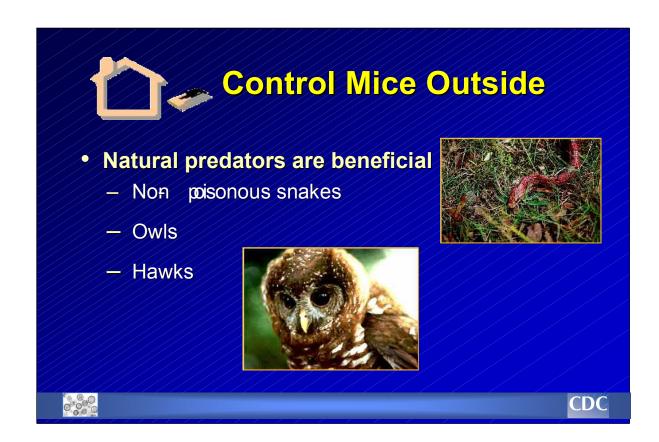
32. Use sheet metal or concrete to seal holes around pipes leading into homes.



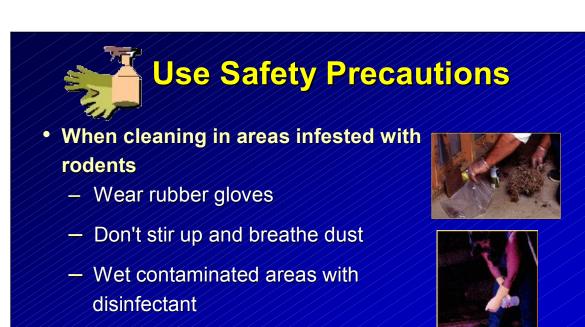
33. Control Mice Outside: Eliminate possible nesting sites. Elevate hay, woodpiles, and garbage cans and place them at least 100 feet from the house. Eliminate junk or things that provide shelter to rodents.



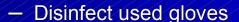
34. Control Mice Outside: Eliminate food sources. Store all animal feed in containers with lids. Discard excess food in the evening into containers with lids. Do not leave water bowls out at night.



35. Natural rodent predators, such as non-poisonous snakes, owls, and hawks, may be beneficial in the control and reduction of rodents outside the home.



Dispose of dead animals properly







36. Use Safety Precautions: When cleaning in areas infested with rodents, use a disinfectant, wear rubber gloves and do not stir up and breathe dust. Dispose of dead animals properly. Disinfect used gloves before removing, and wash hands thoroughly with soap and water.

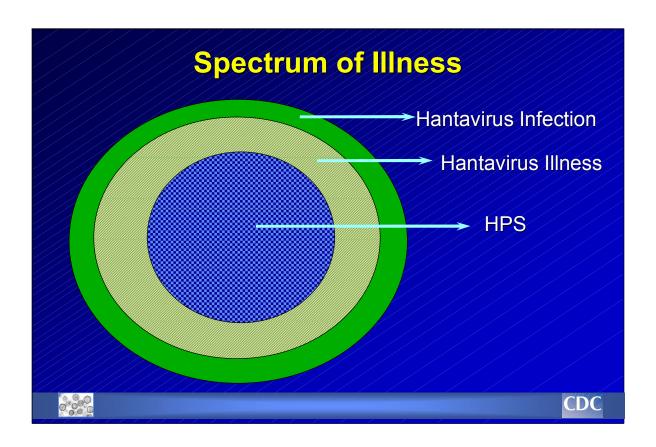


- When enjoying outdoor activities
  - Avoid contact with rodents
  - Stay away from rodent burrows or nests
  - Keep campsite clean and food tightly sealed
  - Open unused cabins and air out before entering or cleaning
  - Avoid sleeping on bare ground





37. Use Safety Precautions When Enjoying Outdoor Activities: avoid contact with rodents, stay away from rodent burrows or nests, and keep campsites clean and food tightly sealed. Open doors and windows of unused cabins and air out for at least half an hour before entering or cleaning. Avoid sleeping on bare ground.



38. Hantavirus Spectrum of Illness: Hantavirus infections can be asymptomatic, cause a mild hantaviral illness or HPS (hantavirus pulmonary syndrome).

## HPS National Surveillance HPS Case Definition

- Febrile illness (T ≥ 38.3°C)
- Unexplained ARDS or bilateral infiltrates following hospitalization
- Supplemental oxygen

or

- Noncardiogenic pulmonary edema at autopsy
- No identifiable specific cause of death

MMWR 1993; 42: 816-820



CDC

39. HPS National Surveillance -- HPS Case Definition: HPS is a febrile illness with a temperature of 38.3°C or greater, characterized by bilateral interstitial pulmonary infiltrates, respiratory compromise usually requiring supplemental oxygen, and clinically resembling acute respiratory distress syndrome. An autopsy may reveal noncardiogenic pulmonary edema with no identifiable specific cause of death.

## HPS National Surveillance Mild Hantaviral Illness Case Definition

- Febrile illness (T > 38.0° C)
- No bilateral diffuse interstitial or alveolar infiltrates



CDC

40. HPS National Surveillance -- Mild Hantaviral Illness: This case definition includes febrile illness of a temperature of 38.0°C or greater without bilateral diffuse interstitial or alveolar infiltrates.

## HPS National Surveillance Comments

- Full clinical spectrum of HPS is undefined
- Cases with mild pulmonary disease
- Cases with accompanying renal disease
- Depending on resources, screening criteria could include:
- Mild pulmonary disease
- Unexplained acute febrile renal disease
- Other febrile syndromes



CDC

41. HPS National Surveillance -- Comments: The full clinical spectrum of HPS is undefined. HPS cases can have a mild pulmonary disease or involve a renal component. Depending on resources, more sensitive screening criteria could include mild pulmonary disease, unexplained acute febrile renal disease, and other febrile syndromes.

#### **Shipping**

#### Safety

- Label as infectious substance and/or human blood precautions
- Double container with absorbent material sufficient for volume being sent
- Plastic tubes preferable over glass

#### Conditions

- Sera -- room temperature or cold pack
- Clot or buffy coat -- dry ice
- Fresh tissues (1-cm cubes) -- dry ice
- Formalin-fixed tissue and blocks -- room temperature (don't freeze)



CDC

42. Shipping Guidelines for Diagnostic Specimens – Safety: Label specimens as "infectious substance". Use a double layered container with absorbent material between layers sufficient to absorb the volume being sent. Use plastic tubes rather than glass. Shipping conditions: Serum samples should be shipped at room temperature or on cold packs. Clot or buffy coat specimens should be shipped on dry ice. Fresh tissue should be in 1cm cubes and on dry ice. Formalin-fixed tissues and paraffin blocks should be at room temperature and not frozen.

#### **Submitting Specimens**

#### For details on:

- Specimen types and volumes
- HPS Case Report Forms
- National Surveillance Laboratory Specimen Forms

Call 404-639-1511

or

Visit www.cdc.gov/ncidod/diseases/hanta/hps/index.htm





43. Submitting Specimens: For details on specimen types and volumes for submission, HPS case reports, and national surveillance laboratory specimen forms, call 404-639-1511, or visit <a href="www.cdc.gov/ncidod/diseases/hanta/hps/index.htm">www.cdc.gov/ncidod/diseases/hanta/hps/index.htm</a>