UWTASP
tele-antimicrobial stewardship program

Hantavirus (and some Ebola*)

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June 16, 2026

*if there is time!

Project ECHO

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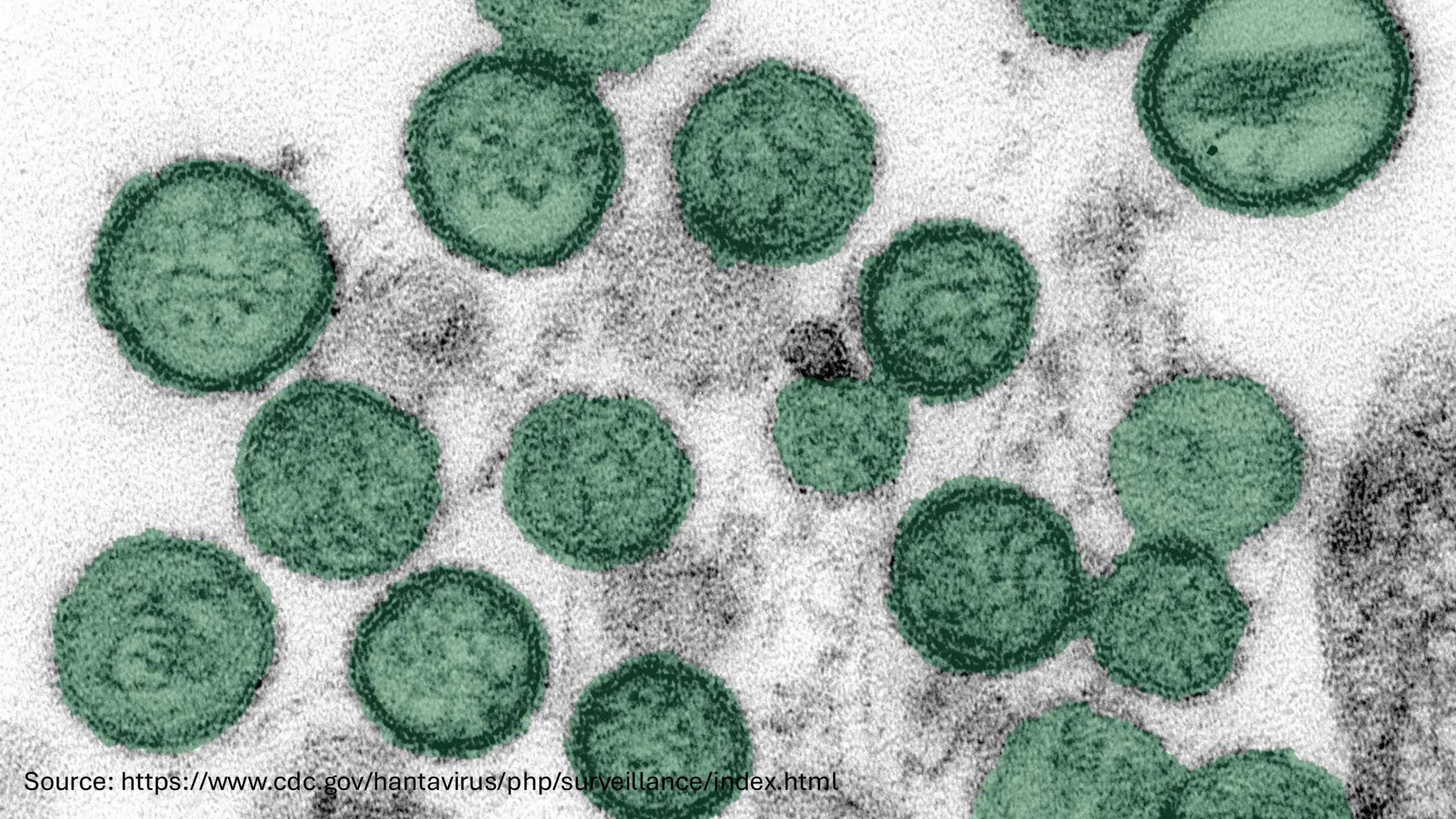

Source: https://www.cdc.gov/hantavirus/php/surveillance/index.html

Learning Objectives

- Understand the basic virology and epidemiology of hantaviruses, with emphasis on Andes and Sin Nombre viruses
- Recognize clinical presentations of Hantavirus Pulmonary Syndrome (HPS)
- Know how to diagnose hantavirus infection
- Manage HPS patients in resource-limited settings
- Implement prevention strategies for high-risk populations

What is Hantavirus?

Genus: *Orthohantavirus*

Family: *Hantaviridae*

Order: *Bunyavirales*

Type: Negative-sense, single-stranded RNA

Envelope: Lipid bilayer with glycoproteins

Genome: 3 segments (S, M, L)

Key Facts

- Rodent-borne viruses
- No arthropod vectors
- Found worldwide
- Cause hemorrhagic fever with renal syndrome (HFRS) or pulmonary syndrome (HPS)
- Person-to-person transmission rare (except Andes)

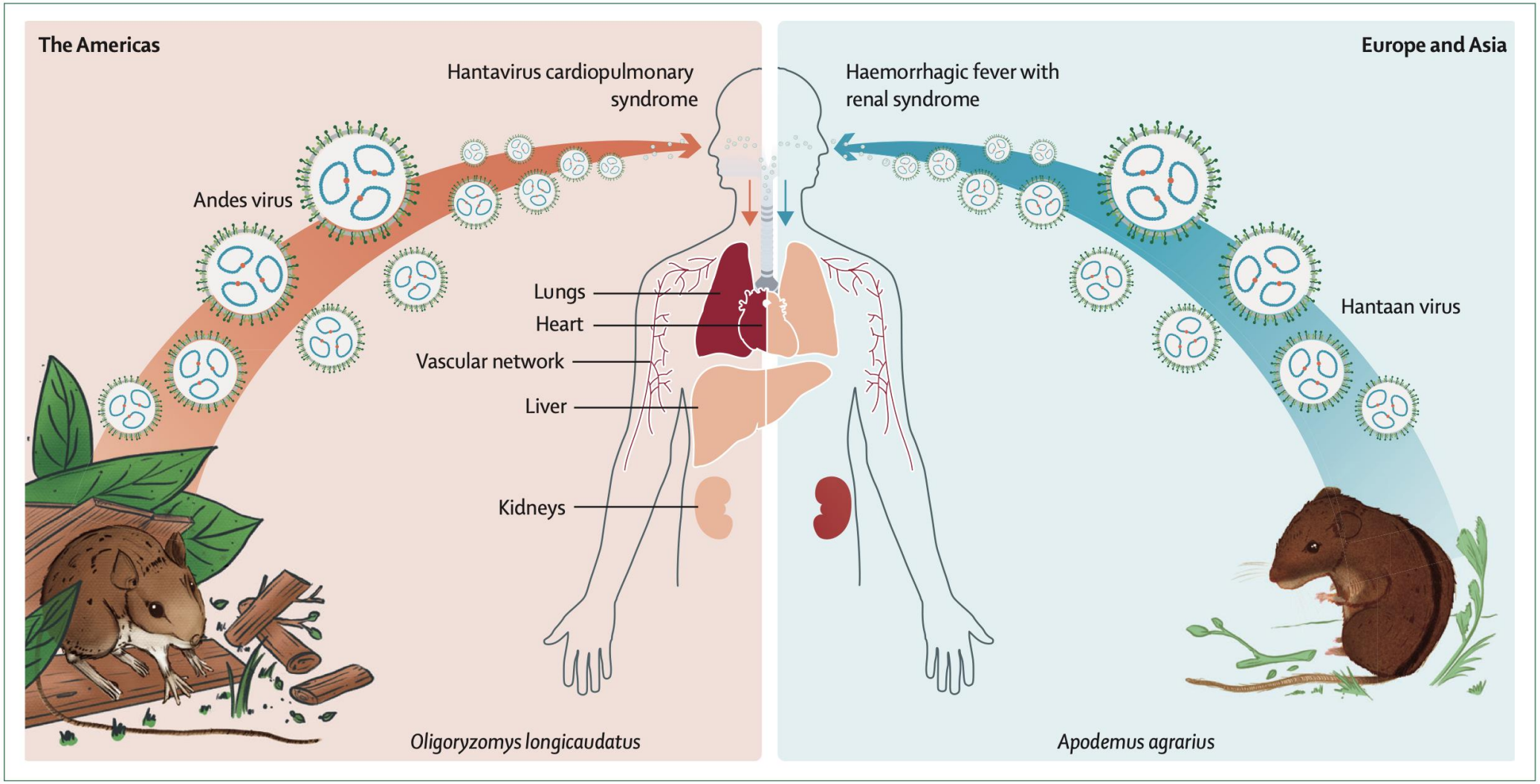

Figure 1: **Hantavirus transmission from rodents to humans**
Transmission mainly occurs via inhalation of aerosolised viral particles shed in rodent urine, faeces, and saliva. Organ and organ system involvement differs in magnitude according to the infecting virus. Andes virus, Hantaan virus, and their rodent host species shown in the figure are representative of pathogenic hantaviruses and rodent hosts present throughout the Americas, Europe, and Asia.

Source: https://doi.org/10.1016/S1473-3099(23)00128-7

	Rodent host	Syndrome	Case fatality rate (%)	Country
The Americas				
Sin Nombre virus	*Peromyscus maniculatus*	HCPS	35%	USA, Canada
Andes virus	*Oligoryzomys longicaudatus*	HCPS	21·4–35·9%	Argentina, Chile
Araraquara virus	*Bolomys lasiurus*	HCPS	44·5%	Brazil
Choclo virus	*Oligoryzomys fulvescens*	Fever, HCPS	12–15%	Panama
Laguna Negra virus	*Calomys laucha*, *Calomys callosum*	Fever, HCPS	11·7%	Paraguay, Argentina, Bolivia, Peru
Juquitiba virus	*Oligoryzomys nigripes*	HCPS	32·5%	Brazil
Europe and Asia				
Hantaan virus	*Apodemus agrarius*	HFRS	1%	China
Puumala virus	*Myodes glareolus*	HFRS (NE)	0·1–0·4%	Finland, Sweden, Belgium, Germany, France, Russia, northeast Europe
Dobrava virus	*Apodemus flavicollis*, *Apodemus ponticus*	HFRS	9·8–12·0%	Balkans, southeast Europe
Seoul virus	*Rattus norvegicus*	HFRS	<1%	Worldwide
Tula virus	*Microtus arvalis*	HFRS	..	Russia, Europe

All information was obtained from several sources.[8,19–28] HCPS=hantavirus cardiopulmonary syndrome. HFRS=haemorrhagic fever with renal syndrome. NE=nephropathia epidemica.

Table: **Common or important hantaviruses causing disease in the Americas, and Europe and Asia**

Source: https://doi.org/10.1016/S1473-3099(23)00128-7

Andes Virus (ANDV)

Source: https://www.pbs.org/newshour/health/operator-of-hantavirus-hit-ship-will-say-by-weeks-end-when-the-vessel-will-resume-cruises

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Person-to-person transmission of ANDV has been documented in Argentina and Chile.[58–63] In 2018–19, a person-to-person transmission outbreak affected 34 patients in Argentina, 11 of whom died.[59] A prospective study in Chile followed 476 household contacts of 76 confirmed ANDV cases for 5 weeks, and found 16 additional patients with a secondary attack rate of 3·4%. The risk of infection was 17·6% among sex partners of an index case, compared with 1·2% for other household contacts.[58] Rare nosocomial transmission has also been reported.[62,63] Based on these reports, risk factors for person-to-person transmission could include being a sexual partner, tongue kissing, and sleeping in the same room largely just before or during the febrile prodrome. In addition, attending a social gathering with a symptomatic person was identified as a risk factor in the 2018–19 Argentina outbreak.[59] ANDV has been detected in saliva from rodents and humans,[64,65] and is more resistant to inactivation by saliva than PUUV or HTNV.[66]

Source: https://doi.org/10.1016/S1473-3099(23)00128-7

Andes Virus (ANDV)

Geography

- South America
- Argentina (Junín)
- Chile
- Brazil
- Paraguay

Epidemiology

- Rodent host: Long-tailed pygmy rice rat (*Oligoryzomys*)
- Mortality: 30-40%
- Person-to-person transmission documented
- Rural/agricultural settings

Clinical Presentation

- Primarily HCPS (not HFRS)
- Prodrome: 1-5 weeks
- Rapid respiratory deterioration
- High mortality if untreated

Sin Nombre Virus (SNV)

Geography

- North America
- USA (West to Midwest)
- Canada
- Mexico & Central America

Epidemiology

- Rodent host: Deer mouse (*Peromyscus*)
- Mortality: 30-40%
- Peak: spring-early summer
- No person-to-person transmission

Clinical Presentation

- HCPS (not HFRS)
- Prodrome: 1-5 weeks
- Rapid cardiopulmonary compromise
- High case-fatality rate

The New England
Journal of Medicine

Volume 330 APRIL 7, 1994 Number 14

HANTAVIRUS PULMONARY SYNDROME: A CLINICAL DESCRIPTION OF 17 PATIENTS WITH A NEWLY RECOGNIZED DISEASE

JEFFREY S. DUCHIN, M.D., FREDERICK T. KOSTER, M.D., C.J. PETERS, M.D., GARY L. SIMPSON, M.D., PH.D., BRUCE TEMPEST, M.D., SHERIF R. ZAKI, M.D., PH.D., THOMAS G. KSIAZEK, D.V.M., PH.D., PIERRE E. ROLLIN, M.D., STUART NICHOL, PH.D., EDITH T. UMLAND, M.D., RONALD L. MOOLENAAR, M.D., SUSAN E. REEF, M.D., KURT B. NOLTE, M.D., MARGARET M. GALLAHER, M.D., JAY C. BUTLER, M.D., ROBERT F. BREIMAN, M.D., AND THE HANTAVIRUS STUDY GROUP*

Abstract *Background.* In May 1993 an outbreak of severe respiratory illness occurred in the southwestern United States. A previously unknown hantavirus was identified as the cause. In Asia hantaviruses are associated with hemorrhagic fever and renal disease. They have not been known as a cause of human disease in North America.

Methods. We analyzed clinical, laboratory, and autopsy data on the first 17 persons with confirmed infection from this newly recognized strain of hantavirus.

Results. The mean age of the patients was 32.2 years (range, 13 to 64); 61 percent were women, 72 percent were Native American, 22 percent white, and 6 percent Hispanic. The most common prodromal symptoms were fever and myalgia (100 percent), cough or dyspnea (76 percent), gastrointestinal symptoms (76 percent), and headache (71 percent). The most common physical findings were tachypnea (100 percent), tachycardia (94 percent), and hypotension (50 percent). The laboratory findings included leukocytosis (median peak cell count, 26,000 per cubic millimeter), often with myeloid precursors, an increased hematocrit, thrombocytopenia (median lowest platelet count, 64,000 per cubic millimeter), prolonged prothrombin and partial-thromboplastin times, an elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, and proteinuria. Rapidly progressive acute pulmonary edema developed in 15 of the 17 patients (88 percent), and 13 patients, all of whom had profound hypotension, died (case fatality rate, 76 percent). Increases in the hematocrit and partial-thromboplastin time were predictive of death.

Conclusions. Infection with a newly described hantavirus causes the hantavirus pulmonary syndrome, which is characterized by a brief prodromal illness followed by rapidly progressive, noncardiogenic pulmonary edema. (N Engl J Med 1994;330:949-55.)

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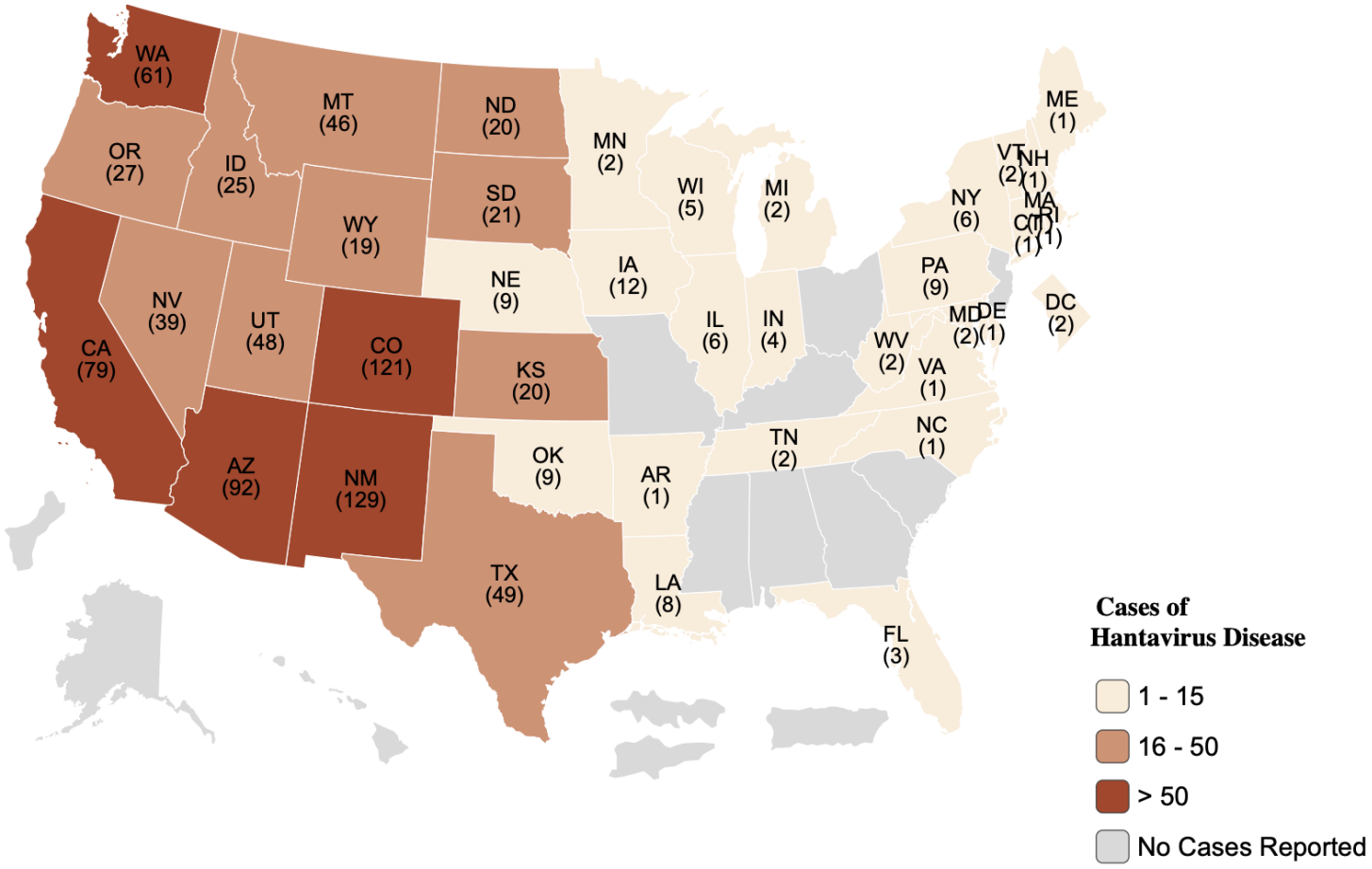
Illnesses considered in the initial differential diagnosis included pneumonic plague, leptospirosis, inhalational anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral community-acquired pneumonias, legionellosis, meningococcemia and other sepsis syndromes, and illnesses caused by viruses not commonly seen in the United States (flavivirus, arenavirus, and bunyavirus). There was no evidence of exposure to known toxic agents. Laboratory tests for bacterial and viral pathogens and a variety of toxic agents were negative, and the initial autopsy findings suggested that bacterial or parasitic causes were unlikely.

Source: https://www.nejm.org/doi/pdf/10.1056/NEJM199404073301401

Map of U.S. Cumulative Cases of Hantavirus by State through 2023

All cases through 2023 | Single year cases, by month and cumulative



Source: https://www.cdc.gov/hantavirus/data-research/cases/index.html

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Viral Structure & Replication

Virion Structure

- Spherical, 90-120 nm diameter
- Lipid envelope with G1 & G2 surface glycoproteins
- Ribonuxcleoprotein complexes with 3 RNA segments
- L protein = RNA-dependent RNA polymerase
- N protein = nucleocapsid protein

Replication

- Entry via receptor-mediated endocytosis
- β3 integrins are cellular receptors
- Transcription & replication in cytoplasm
- Budding through Golgi apparatus
- Infected cells die via apoptosis

Transmission to Humans

Primary Routes of Transmission:

- Inhalation of aerosolized virus from infected rodent urine, feces, or saliva (most common)
- Contact with infected rodent materials → broken skin/mucous membranes
- Rarely: direct bite from infected rodent
- Person-to-person transmission: Andes virus documented (healthcare exposure)

High-Risk Exposures in Rural Settings:

Cleaning barns/sheds; stored grain; contaminated bedding; rodent droppings; occupational exposure (farmers, ranch workers, seasonal laborers)

Epidemiology: Seasonality & Risk Factors

Seasonal Pattern

- SNV: Spring-early summer (April-July)
- Peak after mild winters (more rodents)
- Increased rodent activity outdoors
- Higher human exposure during farming/cleanup

High-Risk Groups

- Agricultural workers
- Outdoor laborers
- Rural residents
- Campers/hikers in endemic areas
- Healthcare workers (Andes exposure)

Pathogenesis: How Hantavirus Causes Disease

Phase 1: Infection (0-5 days)

Virus replicates in lungs, primarily in capillary endothelium and other tissues

Phase 2: Viremia & Immune Response (days 5-10)

Detectable IgM; immune activation drives vascular permeability and endothelial dysfunction

Phase 3: Pulmonary Edema & Shock (days 10+)

Capillary leak → pulmonary edema, thrombocytopenia, hypotension, shock

Key Feature: ENDOTHELIAL DYSFUNCTION

Direct viral damage + immune-mediated injury → vascular permeability, coagulopathy, thrombocytopenia, and hemodynamic collapse

Clinical Presentation: Prodromal Phase (1-5 weeks)

Symptoms

- Fever (often >38.5°C / >101°F)
- Myalgias (especially back & legs)
- Headache
- Chills
- Malaise & fatigue
- Nausea, vomiting, abdominal pain
- Diarrhea or constipation

Exam Findings

- Fever
- Minimal respiratory findings initially
- Normal or slightly elevated WBC
- Thrombocytopenia (early sign)
- Hemoconcentration (elevated Hct)
- Elevated creatinine/BUN (varies)
- No rash

Clinical Presentation: Cardiopulmonary Phase (HPS)

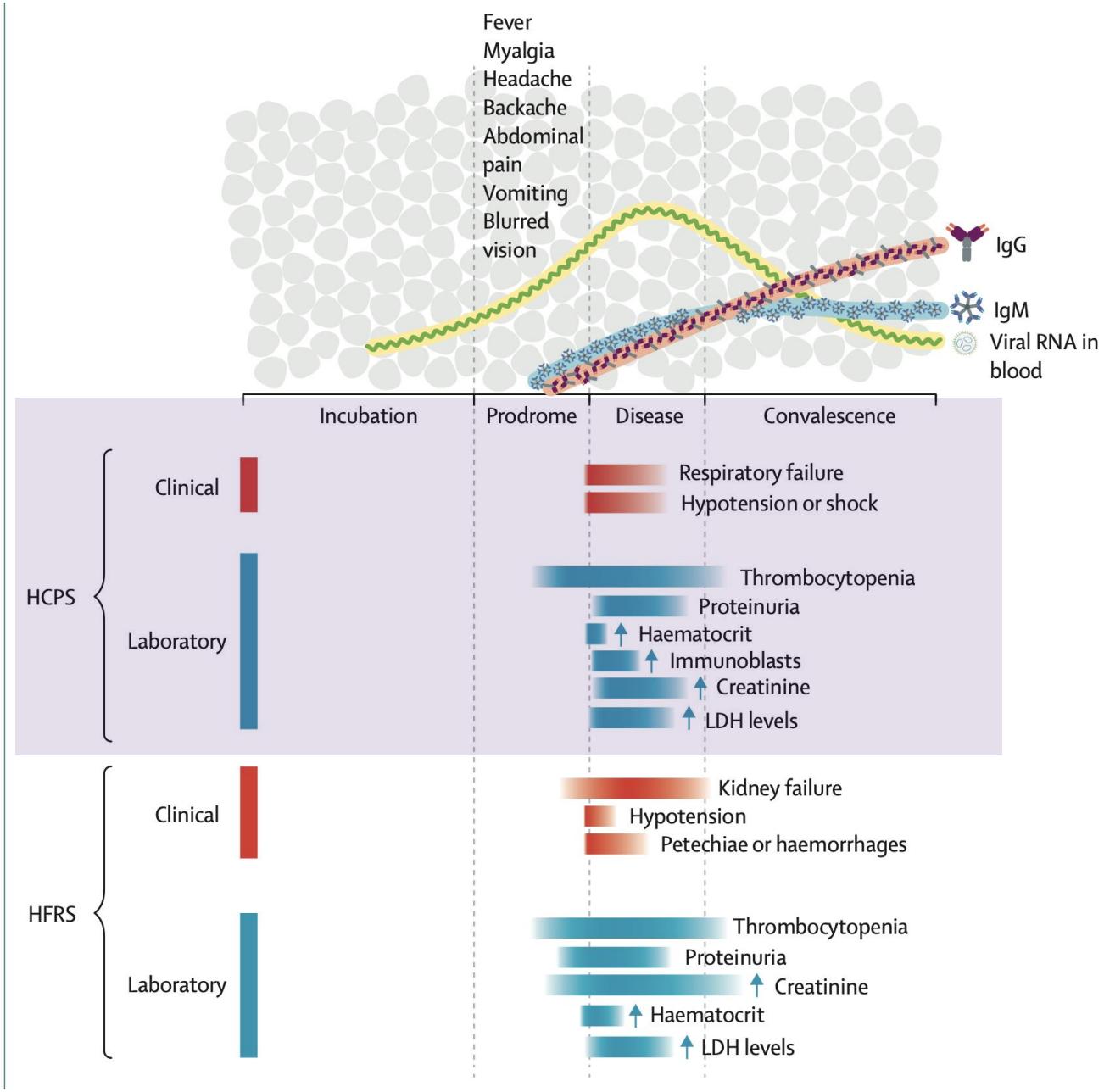
Respiratory Findings

- Cough (onset ~4-10 days)
- Dyspnea, tachypnea
- Crackles (basilar)
- CXR: bilateral interstitial infiltrates → pulmonary edema
- Hypoxemia, respiratory failure
- Normal cardiac silhouette

Shock & Organ Failure

- Hypotension → cardiogenic shock
- Myocardial depression
- Severe thrombocytopenia (<50K)
- Coagulopathy (↑PT/INR)
- Acute kidney injury
- Multi-organ failure

Sin Nombre



Source: https://doi.org/10.1016/S1473-3099(23)00128-7

Diagnosis: Clinical Suspicion

Think Hantavirus When You See:

- Febrile patient with rural/occupational exposure to rodents
- Fever → rapid respiratory symptoms (4-10 days later)
- Bilateral pulmonary infiltrates on CXR
- Thrombocytopenia + hemoconcentration
- Hypotension in the setting of pulmonary edema (unusual!
- Hypoxia out of proportion to CXR findings (capillary leak)

⚠ RED FLAG: Pulmonary edema WITHOUT elevated cardiac pressures suggests endothelial permeability disease

Diagnosis: Laboratory & Serologic Tests

Serologic Tests (Most Common in Clinical Practice):

- IgM ELISA: Present at symptom onset; confirms recent infection
- IgG ELISA: Appears later; indicates past/current infection
- Immunofluorescence antibody (IFA) assay: Reference method
- Western blot: Confirmatory test

Other Tests:

- RT-PCR (respiratory secretions, serum): Early diagnosis during viremia
- Immunohistochemistry: Post-mortem or autopsy diagnosis

Note: Send serum for serologic testing to CDC for hantavirus testing via state health departments. Coordinate with public health.

Diagnosis: Laboratory & Serologic Tests

UW Lab: Hantavirus Antibodies, IgG and IgM (Sendout)

Two major groups of hantaviruses are recognized based on clinical presentation. The first group includes Sin Nombre Virus (SNV), which causes hantavirus pulmonary syndrome, a severe and sometimes fatal form of acute respiratory distress. A second group of hantaviruses (including Seoul, Hantaan, Dobrava, and Puumala) causes hemorrhagic fever with renal syndrome, a condition not typically seen in the United States. **Sera are initially screened for IgG and IgM antibodies recognizing the nucleocapsid protein common to all hantaviruses.** All Hanta IgM positive samples from US residents will be sent to a Public Health Laboratory for SNV-specific IgM. Samples that are Hanta IgG positive but IgM negative are not subjected to SNV-specific IgM testing, since the lack of IgM rules out acute SNV infection. A positive Hanta IgM result but a negative SNV-specific IgM antibody result may indicate either reactivity to a hantavirus other than SNV or false positive reactivity. A small number of SNV IgM positive (but Hanta IgG negative) samples represent false positive reactivity associated with acute cytomegalovirus or Epstein Barr virus infection.

Management: Supportive Care

Early Recognition → ICU Admission

- Oxygen therapy & mechanical ventilation (if needed)
- Fluid management is CRITICAL -> Avoid fluid overload (worsens pulmonary edema)
- Judicious vasopressor support for hypotension
- Monitor for disseminated intravascular coagulation (DIC)
- Platelet & coagulation factor transfusion if needed
- Renal replacement therapy for AKI
- Cardiac support (may need **ECMO** in severe cases)

Challenge: Balancing fluid resuscitation with avoiding pulmonary edema; high mortality even with aggressive supportive care (~30-40%)

Management: Antivirals & Specific Therapy

Ribavirin

- Nucleoside analog (broad-spectrum antiviral)
- IV formulation: Most evidence for early treatment
- Dosing: 10 mg/kg × 3 doses, then 5 mg/kg × 4 doses over 10 days
- Modest mortality benefit (~30-50% reduction) if started early (first 7 days)?
- Side effects: Hemolytic anemia, teratogenic (avoid in pregnancy)

Other Considerations

- Inotropes (dopamine, norepinephrine) for shock management
- **ECMO for severe cardiopulmonary failure (if available)**
- Convalescent plasma: Limited data; not routinely recommended
- Immunoglobulin: No proven benefit

Vaccines & Prophylaxis

Current Status:

- No licensed vaccines available in North America or South America
- Inactivated vaccines available in South Korea, China (for Hantaan virus, variable efficacy)
- Research ongoing: mRNA vaccines, DNA vaccines show promise
- Post-exposure prophylaxis: No proven benefit; supportive care remains standard

Prevention:

- Rodent control in buildings & surrounding areas
- Avoid exposure to infected rodents, their droppings, or contaminated materials
- PPE for high-risk activities (N95 mask, gloves, eye protection)
- Seal rodent entry points in buildings
- Proper ventilation when cleaning contaminated areas

Prevention for Rural Health Providers

Community Education

- Educate farmers & ranchers about risk
- Seasonal reminders (spring cleanup)
- Proper PPE for high-risk activities
- Safe rodent control practices

Healthcare Infection Control

- Standard precautions for suspected HPS
- Airborne precautions for Andes virus (person-to-person)
- Educate healthcare workers on risk
- Notify public health of suspected cases

Occupational Health

- Screen for hantavirus risk in occupational histories
- Provide PPE & training for high-risk workers
- Ensure proper ventilation in work areas
- Record exposures for surveillance

Case Reporting & Resources

- Report suspected cases to local health dept.
- CDC Hantavirus Hotline: available 24/7
- Early consultation improves outcomes

Ebola Virus: Overview

Classification

Family: ***Filoviridae***

Genus: *Ebolavirus*

Negative-sense RNA

Filamentous virions

Bat reservoir (likely)

Key Characteristics

- Zoonotic spillover events from wildlife
- Human-to-human transmission via blood/body fluids
- No arthropod vector
- Mortality: 25-90% depending on species & outbreak
- Viral hemorrhagic fever

Ebola Species: Focus on Bundibugyo

Five Identified Species:

- Zaire (EBOV): Africa; highest mortality (60-90%); largest outbreaks
- Sudan (SUDV): Africa; mortality 40-50%
- Bundibugyo (BDBV): Uganda; mortality ~40%; smaller outbreaks
- Taï Forest (TAFV): Côte d'Ivoire; one documented case
- Reston (RESTV): Philippines, USA laboratory exposure; no human deaths

Bundibugyo Ebolavirus (BDBV)

First identified: 2007 in Bundibugyo District, Uganda. Limited outbreaks (2007, 2012, 2018-2019). Mortality ~40%. Presents similarly to Zaire Ebola. Transmitted human-to-human via direct contact with blood/body fluids; higher risk for healthcare workers during outbreaks.

Quick Comparison: Hantavirus vs. Ebola

Feature	Hantavirus (HPS)	Ebola (BDBV)
Transmission	Aerosolized rodent urine/feces	Direct contact with blood/fluids
Incubation	1-5 weeks	2-21 days (avg 8-10)
Onset	Fever → respiratory symptoms	Fever → GI/hemorrhagic symptoms
Mortality	30-40%	~40% for BDBV; up to 90% for Zaire
Geographic risk	Rural North/South America	Central/West Africa
Healthcare Risk	Supportive care; rare person-to-person	Very high; body fluid exposure
Treatment	Supportive; ribavirin (marginal benefit)	Supportive care; monoclonal antibodies

Key Takeaways

- Hantavirus = severe, progressive respiratory disease in rural/occupational exposures
- Prodrome (fever/myalgia) → cardiopulmonary collapse in 4-10 days
- Key features: Bilateral infiltrates + hypotension + thrombocytopenia + normal cardiac size
- Early recognition & ICU management (fluid balance, vasopressors, mechanical support) crucial
- Ribavirin may reduce mortality if started early
- Prevent via rodent control, PPE, education of high-risk populations

Resources & References

Online Resources:

- CDC Hantavirus: www.cdc.gov/hantavirus
- CDC Emergency Operations Center: 1-770-488-7100
- State Health Department (for local guidance)
- Infectious Diseases Society of America (IDSA) guidelines

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