

HOW MANY PEOPLE DIED YEARLY OF HANTAVIRUS IN THE LAST 10 YEARS AND WHERE

Hantavirus deaths vary significantly by region due to the different viral strains present. Globally, between **10,000 and 100,000 cases** occur annually, primarily in Asia and Europe. [\[1, 2, 3, 4, 5\]](#)

Regional Death and Fatality Data (2014–2024)

Region [1, 2, 3, 4, 5, 6, 7, 8]	Disease Type	Yearly Death Estimate / Trends	Case Fatality Rate (CFR)
Americas	Hantavirus Pulmonary Syndrome (HPS)	~80 deaths (est. from ~200 yearly cases)	~40% - 50%
Asia (mostly China)	Hemorrhagic Fever with Renal Syndrome (HFRS)	Thousands of cases annually; deaths vary by strain	1% - 12%
Europe	Nephropathia Epidemica (NE/HFRS)	Very low yearly deaths (e.g., 3 deaths in EU/EEA in 2023)	<1% (for PUUV strain)

Yearly Breakdown & Locations

- **The Americas:** HPS is primarily found in **Argentina, Brazil, Bolivia, Chile, Panama, Paraguay, Uruguay, and the United States**.
 - **United States:** Averages **roughly 30 cases per year**, with about **one-third** resulting in death. Most cases occur in western states like **New Mexico, Colorado, and Arizona**.
 - **2025 Data:** Eight countries in the Americas reported **59 deaths** from 229 confirmed cases.
- **Europe:** Cases are most frequent in **Finland and Germany**, which together account for over 60% of European infections. While cases can number in the thousands (e.g., **4,249 cases in 2017** across the EU), the dominant Puumala virus strain is rarely fatal.
- **Asia:** China and the Republic of Korea continue to report thousands of HFRS cases annually, though incidence rates have been declining. [\[1, 2, 4, 5, 6, 7, 8, 9\]](#)

Recent Outbreak Note (2026)

An unusual outbreak occurred in early 2026 on the cruise ship *MV Hondius*, originating in **Argentina**, resulting in **3 confirmed deaths** as of May 2026. [\[1, 2, 3, 4, 5\]](#)

Are you looking for **prevention tips** for a specific region, or would you like to see a list of the **most recent outbreaks**?

hantavirus

Hantaviruses are a group of zoonotic viruses primarily carried by rodents (mice, rats, and voles) that can cause severe respiratory or kidney disease in humans. **Most people become infected by breathing in air contaminated with virus particles from infected rodent urine, droppings, or saliva.** [\[1, 2, 3\]](#)

Current Global Situation (May 2026)

As of mid-May 2026, health officials are responding to a significant cluster of cases linked to the cruise ship **MV Hondius**. [1, 2]

- **Strain:** The outbreak involves the **Andes virus**, a specific South American strain.
- **Human-to-Human Spread:** Unlike most hantaviruses, the Andes strain is unique because it can spread between people through close, prolonged contact.
- **Impact:** Cases have been identified globally, including in France and the UK, following the repatriation of passengers. The **CDC** is currently monitoring dozens of individuals in the U.S. who may have been exposed. [1, 2, 3, 4, 5]

Transmission and Risk Factors

Most infections occur when contaminated dust is stirred up in enclosed spaces, such as during the cleaning of long-unused buildings like sheds, cabins, or barns. [1, 2]

- **Inhalation:** Breathing in aerosolized virus particles (most common).
- **Direct Contact:** Touching contaminated surfaces and then touching your eyes, nose, or mouth.
- **Bites:** Rarely, through a bite from an infected rodent. [1, 2, 3]

Symptoms and Disease Types

Symptoms typically develop 1 to 8 weeks after exposure. Early signs often mimic the flu: fever, fatigue, muscle aches (especially in the back and thighs), headaches, and abdominal pain. The disease typically progresses into one of two syndromes depending on the strain: [1, 2, 3, 4, 5]

Syndrome [1, 2, 3, 4]	Primary Region	Major Symptoms	Fatality Rate
Hantavirus Pulmonary Syndrome (HPS)	Americas	Severe breathing difficulties, lung/heart failure	Up to 50%
Hemorrhagic Fever with Renal Syndrome (HFRS)	Europe & Asia	Bleeding, kidney failure, low blood pressure	1% – 15%

Prevention and Treatment

There is currently **no specific vaccine or antiviral treatment** for hantavirus. Treatment focuses on supportive care, such as oxygen therapy or dialysis, which is most effective when started early. [1, 2, 3]

According to the [World Health Organization \(WHO\)](#), prevention is the best defense:

- Seal holes in your home to keep rodents out.
- Use a disinfectant or bleach solution when cleaning rodent-infested areas instead of sweeping or vacuuming, which can kick up infectious dust.
- Wear gloves and masks in high-risk environments. [1, 2, 3]

Would you like to know more about the **symptoms** to watch for or the **specific cleaning protocols** recommended by health authorities?

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- Hantavirus - World Health Organization (WHO)

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- Hantavirus - frequently asked questions

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when has the hantavirus discovered

The virus was first identified in **1976** by South Korean virologist **Dr. Ho Wang Lee**. It was isolated from a field mouse found near the **Hantan River** in South Korea, which is why it was named "Hantaan virus". [1, 2, 3, 4]

While the virus itself was discovered in the 1970s, it has a longer history: [1, 2, 3]

- **1950s:** During the **Korean War**, more than 3,000 UN troops fell ill with a mysterious "hemorrhagic fever". This illness was later confirmed to be caused by the Hantaan virus after Dr. Lee successfully isolated it.
- **1982:** The World Health Organization (WHO) officially named the disease **Hemorrhagic Fever with Renal Syndrome (HFRS)**.
- **1993:** A different strain of hantavirus, now known as the **Sin Nombre virus**, was discovered in the U.S. following a deadly outbreak in the **Four Corners** region. This marked the first time the virus was recognized in North America as the cause of **Hantavirus Pulmonary Syndrome (HPS)**. [1, 2, 3, 4, 5, 6, 7]

Historians believe the disease is much older, with descriptions of similar symptoms appearing in Chinese medical texts as early as **960 AD**. [1]

Would you like to know more about the **different strains** of the virus found in various parts of the world?

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- Hantavirus Pulmonary Syndrome—The 25th Anniversary of ...

Abstract. During the spring of 1993, a mysterious respiratory disease struck the Four Corners region of the southwestern United St...

National Institutes of Health (.gov)

- Hantaviruses - PMC

In 1978, the etiologic agent of Korean Hemerologic fever was isolated from small infected field rodent Apodemus agrarius near Hant...

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- Orthohantavirus - Wikipedia
New World hantaviruses assemble near the cell membrane and obtain their envelope from it as they leave the cell by budding from it...

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history of outbreaks?

The history of hantavirus is marked by several pivotal outbreaks that shifted how scientists understand the virus, moving from a regional concern in Asia to a recognized global health threat. [\[1, 2\]](#)

1. The Korean War (1950–1953)

The first modern encounter with the virus occurred when roughly **3,000 UN troops** in Korea developed a mysterious hemorrhagic fever. [\[1, 2\]](#)

- **Impact:** The disease caused high fever, internal bleeding, and kidney failure, resulting in hundreds of deaths.
- **Outcome:** Although clinical studies were extensive, the actual virus remained unknown for another two decades until Dr. Ho Wang Lee isolated it in 1976 from a field mouse near the Hantan River. [\[1, 2, 3, 4\]](#)

2. The "Four Corners" Outbreak (1993)

Before 1993, hantavirus was thought to only exist in the "Old World" (Europe and Asia) and primarily affect the kidneys. This changed when a cluster of healthy young people in the **U.S. Southwest** (Arizona, Colorado, New Mexico, and Utah) began dying of sudden, severe respiratory failure. [\[1, 2, 3\]](#)

- **Discovery:** Scientists identified a new strain, **Sin Nombre virus**, carried by deer mice. This established **Hantavirus Pulmonary Syndrome (HPS)** as a new, highly lethal disease in the Americas.
- **Stigma:** The outbreak was initially dubbed the "Navajo disease," which caused significant social and economic backlash for the Navajo Nation. [\[1, 2, 3, 4, 5\]](#)

3. Epuyén, Argentina (2018–2019)

An outbreak in the small town of Epuyén highlighted the unique danger of the **Andes strain**.

- **Human-to-Human Transmission:** This event confirmed that the Andes strain could spread between people. A "superspreader" event at a birthday party led to 34 cases and 11 deaths.
- **Containment:** The outbreak was eventually stopped through strictly enforced self-quarantines and isolation. [\[1, 2\]](#)

4. MV Hondius Cruise Ship (May 2026)

A recent global alert was triggered by an outbreak on the cruise ship **MV Hondius** while traveling from Argentina to Cape Verde. [\[1, 2\]](#)

- **Current Status:** As of May 8, 2026, there are **eight confirmed or suspected cases and three deaths**.
- **Global Response:** Passengers have been quarantined in several countries, including the U.S., UK, and Australia. Genomic testing confirms the virus is the Andes strain, but experts believe

the risk to the general public remains low as it requires very close, prolonged contact to spread. [\[1, 2, 3\]](#)

Would you like to see a **map of the regions** where different hantavirus strains are most commonly found?

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17 sites

- What the (rather brief) history of hantavirus reveals about its spread
12 May 2026 — The first known outbreak came during the Korean War in the 1950s, when around 3,000 United Nations troops developed a mysterious i...

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- What is Hantavirus? | ABC NEWS
11 May 2026 — with more on the virus. and its pandemic. potential here's the ABC's health reporter co-host Dr norman Swan. well nobody knew it e...

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yes

Hantaviruses are geographically divided into two major groups: **New World** hantaviruses (found in the Americas) and **Old World** hantaviruses (found in Europe and Asia). The distribution is tied to the specific rodent hosts that carry each strain. [\[1, 2, 3, 4\]](#)

Global Distribution of Major Strains

- **The Americas (New World):** These strains primarily cause **Hantavirus Pulmonary Syndrome (HPS)**.
 - **Sin Nombre virus:** The most common cause of HPS in North America, primarily in the Western U.S. and Canada, carried by the deer mouse.
 - **Andes virus:** Found in South America (Argentina and Chile). It is the only strain known to spread between humans.
- **Europe & Asia (Old World):** These strains primarily cause **Hemorrhagic Fever with Renal Syndrome (HFRS)**.
 - **Hantaan virus:** Primarily found in East Asia (China, South Korea, Russia), carried by the field mouse.
 - **Puumala virus:** Found in Northern and Central Europe, causing a milder form of HFRS called Nephropathia Epidemica.
 - **Dobrava virus:** Found in the Balkans and Eastern Europe, often causing more severe HFRS.

- **Seoul virus:** Unique because it is carried by the brown rat, which has traveled globally via ships. As a result, Seoul virus cases are reported worldwide, including in urban areas of the Americas. [[1](#), [2](#), [3](#), [4](#), [5](#), [6](#), [7](#), [8](#), [9](#), [10](#), [11](#), [12](#)]

Recent Outbreak Context (2026)

As of May 2026, the **Andes virus** has gained international attention due to cases linked to the **MV Hondius cruise ship**. Health authorities in countries like the **UK, France, Germany, Singapore, and the U.S.** are monitoring individuals following the ship's departure from Argentina. [[1](#), [2](#)]

Map data ©2026 [Terms](#)

2000 km

Americas (New World - HPS)

Eurasia (Old World - HFRS)

Would you like to know more about the **specific rodent species** that carry these viruses in your area?

Centers for Disease Control and Prevention officials prepare a containment suit for a hantavirus field study in 2004. Smith Collection/Gado / CDC via Gado / Getty Images file

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May 12, 2026, 10:00 PM GMT+1

By [Aria Bendix](#)

Scientists think the hantavirus, the [deadly pathogen that has infected 11 passengers](#) on a Dutch cruise ship, could be as old as humans. But much of their understanding of human cases comes from a handful of outbreaks within the past century.

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The first known **outbreak came during the Korean War in the 1950s, when around 3,000 United Nations troops developed a mysterious illness that scientists would later recognize as hantavirus.**

But it wasn't until some 20 years later, in 1978, that scientists linked the virus to a rodent near the Hantan river in South Korea, which gave hantavirus its name.

The first cases in North America were diagnosed in 1993. And in 1996, an outbreak in Argentina marked the first confirmed instance of person-to-person transmission.

Hantavirus is rarer, but far deadlier than respiratory viruses like Covid or flu. Only one strain, which is not found locally in the U.S., is capable of passing between humans. That strain is the one involved in the cruise ship outbreak, which has forced passengers from across the world to quarantine.

The limited number of past outbreaks could offer clues about how the cruise ship passengers got sick — but doctors who have studied hantavirus said there's more to learn.

"Because the disease is so incredibly rare, it's been very difficult to study in the sense that we don't really have the numbers," said Dr. Charles Chiu, a professor of laboratory medicine and infectious diseases at University of California, San Francisco.

Fewer than 900 cases were reported in the U.S. from 1993 to 2023. Cases can also be hard to investigate because many people die quickly after developing symptoms. Up to half of hantavirus cases can be fatal, depending on the strain and method of transmission.

"The current outbreak will teach us more, because we've had very few of these events with more than a handful of patients," said Dr. Gregory Mertz, emeritus professor of internal medicine at the University of New Mexico.

Here's what we know about the major outbreaks over the last several decades.

Outbreaks in the Four Corners and Yosemite

In 1993, public health officials began investigating a mysterious cluster of illnesses in the "Four Corners" region of the United States, where Arizona, Colorado, New Mexico and Utah meet.

The [first case to raise alarm](#) was a 19-year-old long distance runner in New Mexico whose fiancée had just died of an unknown respiratory illness. The man sought medical care twice — first with a fever, muscle aches, chills, headache and fatigue, then with vomiting and diarrhea. But each time, his physical exam was normal, so he was sent home. He died after [attending his fiancée's funeral](#).

"There were physicians that recognized, through seeing or hearing about multiple cases, that maybe we were seeing something that we didn't understand and we hadn't learned about in medical school," said Mertz, who helped investigate the outbreak.

The Centers for Disease Control and Prevention ultimately confirmed the illnesses as hantavirus based on antibody testing and autopsies.

At the time, the virus wasn't known to infect humans in North America. But this particular strain — known as "Sin Nombre" — was linked to a deer mouse that had become more prevalent in the Four Corners after unusually heavy rain and snow that spring. By August 1993, around 30 [cases had been identified in the southwestern U.S.](#), 20 of whom died.

A deer mouse during a biological survey at Follenby Pond near Tupper Lake, N.Y. **The hantavirus disease is carried in the feces, urine and saliva of deer mice and other rodents and on airborne particles and dust.** Mike Lynch / Adirondack Daily Enterprise via AP file

Most human cases of hantavirus in North America are the Sin Nombre strain and are acquired through contact with the aerosolized urine, feces or saliva of infected rodents. The strain involved in the cruise ship outbreak, the Andes strain, is not found in North America and is linked to the pygmy rice rat that's native in parts of Argentina and Chile.

“You have to be kind of unlucky to get Sin Nombre virus ... There’s this little window where the virus is still viable, but the mouse pee or the feces are dry enough that they can be stirred up into the air and people can inhale it,” said Dr. Tom Boo, the public health officer for Mono County, a rural area in California that has recorded 27 hantavirus cases since 1993 — the most in the state.

In 2012, 10 people contracted the Sin Nombre strain after staying overnight at Yosemite National Park in California. All but one camper slept in cabins that were later found to have rodents in the wall insulation. Three of the campers died.

Recommended

[HEALTH NEWS Americans from hantavirus cruise ship remain in quarantine to monitor for symptoms, CDC says](#)

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“Some campers who maybe did not air out the cabin may have had a higher exposure to the virus, which led to the infection,” said Chiu, who helped sequence the virus and test people during the outbreak.

Hantavirus gained further attention last year after Betsy Arakawa, the wife of Oscar-winning actor Gene Hackman, [died of the virus](#) at the couple’s home in Santa Fe, New Mexico. Hackman died roughly a week later. Authorities said at the time that the actor, who had advanced Alzheimer’s, may not have been aware of his wife’s passing. A state assessment [found rodents and rodent feces on the property](#), but not in the main living quarters.

Human-to-human transmission in Argentina

The Andes strain is the only hantavirus known to spread from person to person.

The first recognized cases occurred in 1996 across [three towns in southern Argentina](#). Three of the 18 cases were doctors caring directly for an infected patient.

Scientists learned more about human transmission after so-called “super-spreader” events in Argentina in 2018 and 2019. The events led to 34 infections and 11 deaths.

The outbreak started after a person attended a birthday party for 90 minutes with a fever and muscle aches, and presumably infected five others.

Another infected person attended her husband’s wake while she had a fever. Ten people who had close contact with her became ill.

Passengers watch epidemiologists board the hantavirus-stricken cruise ship MV Hondius in Praia, Cape Verde, on Wednesday.^{AP}

Public health authorities eventually contained the outbreak by isolating symptomatic patients and telling their close contacts to stay home. Before those measures were taken, one infected person was spreading the virus to about two others, on average.

A [2020 paper in the New England Journal of Medicine](#) determined that patients with a high viral load were more likely to spread the virus, and that transmission was more likely to occur at massive social gatherings or if someone had extensive contact with an infected person.

“There is a possibility of spread in an enclosed, cramped space,” Chiu said.

The cruise ship outbreak meets that criteria, he said — especially if people shared a room with an infected person or had a drink with them at the bar for several hours.

“At least in terms of the behavior of the virus currently, how we’re seeing these cases evolve, there’s nothing that’s inconsistent with what we already know about the virus or suspect about this virus,” Chiu said.

Hantavirus infection

Bottom of Form

From Wikipedia, the free encyclopedia

This article is about the disease. For the virus, see [Orthohantavirus](#). For the 2026 outbreak, see [MV Hondius hantavirus outbreak](#).

Hantavirus infection

Other names Hantavirus disease



The cotton rat, [Sigmodon hispidus](#), is a hantavirus carrier that becomes a threat when it enters human habitation in rural and suburban areas.

Specialty	Infectious disease
Symptoms	HFRS: Headache, abdominal pain, fever, nausea, bleeding, kidney failure^[1] HPS: Tiredness, fever, muscle pain, cough, shortness of breath^[2]
Usual onset	1 to 8 weeks following exposure ^{[1][2]}
Types	Hemorrhagic fever with renal syndrome (HFRS) Hantavirus pulmonary syndrome (HPS)^[3]
Causes	orthohantaviruses spread by rodents ^[4]
Diagnostic method	Blood tests ^[4]
Prevention	Rodent control ^[4]
Treatment	Supportive care ^[4]
Frequency	HFRS 100,000 cases per year, HPS < 50 cases per year ^[4]
Deaths	HFRS 12%, HPS 40% ^[4]
Named after	Hantan River in South Korea

Hantavirus infection or **hantavirus disease** is an [infectious disease](#) of [humans](#) caused by [viruses](#) in the [Orthohantavirus](#) genus of viruses. It can result in [hemorrhagic fever with renal syndrome](#) (HFRS) or [hantavirus pulmonary syndrome](#) (HPS).^[3] Symptoms of HFRS generally include [headache](#), [abdominal pain](#), [fever](#), nausea, bleeding, and [kidney failure](#).^[1] Symptoms of HPS include tiredness, fever, [muscle pain](#), cough, and [shortness of breath](#).^[2] Onset of initial symptoms is generally 1 to 8 weeks following exposure.^{[1][2]}

HFRS is due to [Old World hantaviruses](#) while HPS is due to [New World](#) hantaviruses.^[3] More than 28 specific hantaviruses cause disease in humans.^[4] The disease is typically spread when

people breathe in air contaminated by [rodent](#) droppings.^[4] The underlying mechanism of both forms of the disease involves [low platelets](#) and [leaky blood vessels](#).^[4] [Diagnosis](#) is based on blood tests, typically [serology](#).^[4]

Treatment is primarily [supportive care](#).^[4] This may include [oxygen therapy](#), [mechanical ventilation](#), [dialysis](#), or [platelet transfusions](#).^[4] [Ribavirin](#) may be useful if given early in HFRS.^[4] The risk of death is around 12% with HFRS and around 40% with HPS.^[4]

About 100,000 cases of HFRS occur a year, while about 1,000 cases of HPS have been identified since it was first detected in 1993.^[4] While descriptions of what is believed to be hantavirus infections date back to around 1000 AD,^[4] the virus that causes the disease was not discovered until 1976, in the [Hantan River](#) area of South Korea.^{[4][5]}

In April 2026, an outbreak of hantavirus infection caused by the [Andes virus was identified on the Dutch cruise ship MV Hondius](#).

Signs and symptoms

Initial symptoms

After an [incubation period](#) of 2–4 weeks, the typical illness for all hantaviruses starts with non-specific symptoms which may include high fever, chills, headache, backache, abdominal pains, nausea, and vomiting.^[6]

Hemorrhagic fever with renal syndrome

Main article: [Hantavirus hemorrhagic fever with renal syndrome](#)

Hemorrhagic fever with renal syndrome (HFRS) is caused chiefly by hantaviruses in [Asia](#) and [Europe](#). Clinical presentation varies from subclinical to fatal, depending on the virus. After an incubation period of 2 to 4 weeks, symptoms appear. Then bleeding under the skin begins, often paired with low blood pressure, followed by further internal bleeding throughout the body. [Renal dysfunction](#) leading to further health issues, which may cause death, then begins.^[4] A milder form of HFRS occurs in Europe, and is called "nephropathia epidemica" (NE).^[7]

Hantavirus pulmonary syndrome

Main article: [Hantavirus pulmonary syndrome](#)

Hantavirus pulmonary syndrome (HPS), also called hantavirus cardiopulmonary syndrome (HCPS), is usually caused by hantaviruses in the [Americas](#). After an incubation period of 16 to 24 days, symptoms appear. After a few days of symptoms similar to HFRS, there is sudden onset of progressive, or productive, coughing, shortness of breath, and elevated heart rate, due to [fluid buildup in the lungs](#). These symptoms are accompanied by impairment of [lymphoid organs](#). Death from [cardiovascular shock](#) may occur rapidly after the appearance of severe symptoms.^{[4][8]} While HCPS is typically associated with New World hantaviruses, the [Puumala virus](#) in Europe has also, rarely, caused the [syndrome](#).^[7]

Cause

The cause is viruses within [Orthohantavirus](#), a genus of single-stranded, enveloped, [negative-sense RNA viruses](#) in the family [Hantaviridae](#) of the order [Elliovirales](#).^[9] They normally cause infection in [rodents](#), but do not cause disease in them.^[9] Humans may become infected with hantaviruses through contact with rodent urine, saliva, or feces. While many hantaviruses cause

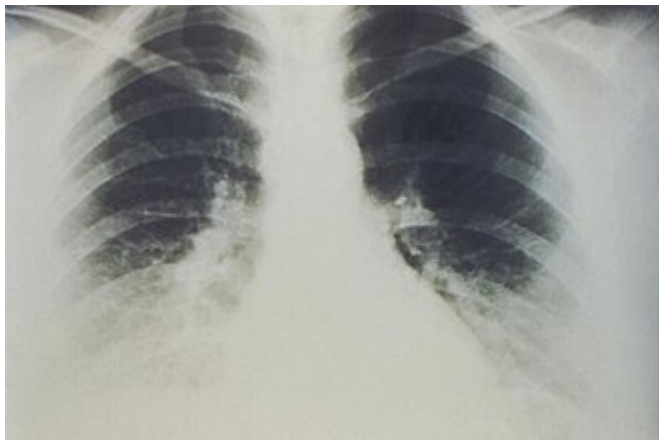
either of the two diseases, some are not known to cause illness, such as the [Prospect Hill virus](#).^[8]

Transmission

Hantaviruses are transmitted by contact with the bodily fluids of rodents, particularly from saliva from bites and especially from inhalation of viral particles from urine and feces in [aerosols](#). The manner of transmission is the same for both diseases caused by hantaviruses. Among the HCPS-causing hantaviruses is the [Andes virus](#), which is the only hantavirus confirmed to be capable of spreading from person to person, though this is rare.^{[4][8]}

Infections have almost entirely been linked to contact with rodent excrement; however, in 2005 and 2019, human-to-human transmission of the [Andes virus](#) was reported in South America.^[10]

Diagnosis



A chest x-ray showing the **early stages of bilateral pulmonary effusion due to hantavirus pulmonary syndrome (HPS). HPS begins with interstitial pulmonary edema, progressing to alveolar edema with severe bilateral involvement. Pleural effusions are common.**

In terms of the evaluation of this infection the following is done:^[11]

- Chest X-ray (pulmonary edema)
- Blood workup (thrombocytopenia)
- Immunofluorescent or immunoblot assay (ELISA utilizing IgM)

Prevention

The best prevention against contracting hantavirus is to eliminate or minimize contact with rodents in the home, workplace, or campsite.^[12] As the virus can be transmitted by rodent saliva, excretions, and bites, control of rats and mice in areas frequented by humans is key for disease prevention. General prevention can be accomplished by disposing of rodent nests, sealing any cracks and holes in homes where mice or rats could enter, setting traps, or laying down poisons or using natural predators such as cats in the home.^[13]

The duration that hantaviruses remain infectious in the environment varies based on factors such as the rodent's diet, temperature, humidity, and whether indoors or outdoors. The viruses have been demonstrated to remain active for two to three days at normal room temperature, while ultraviolet rays in direct sunlight kill them within a few hours. However, rodent droppings or urine of indeterminate age should always be treated as infectious.^{[14][15][16]}

Vaccine

Main article: [Hantavirus vaccine](#)

Whole virus [inactivated](#) bivalent vaccines against Hantaan virus and Seoul virus are available in [China and South Korea](#). In both countries, the use of the vaccine, combined with other preventive measures, has significantly reduced the incidence of hantavirus infections. Apart from these vaccines, four types of vaccines have been researched: DNA vaccines targeting the M genome segment and the S genome segment, subunit vaccines that use recombinant Gn, Gc, and N proteins of the virus, virus vector vaccines that have recombinant hantavirus proteins inserted in them, and virus-like particle vaccines that contain viral proteins but lack genetic material. Of these, only DNA vaccines have entered into clinical trials.^{[17][18]} As of 2026 there was no vaccine for the Andes hantavirus.^[19]

Treatment

[Ribavirin](#) may be a drug for HPS and HFRS but its effectiveness remains unknown; still, spontaneous recovery is possible with supportive treatment. People with suspected hantavirus infection may be admitted to the hospital and given oxygen and mechanical ventilation support to help them breathe during the acute pulmonary stage with severe respiratory distress.^{[13][20]} Immunotherapy, administration of human neutralizing antibodies during acute phases of Hantavirus, has only been studied in mice, hamsters, and rats. There are no reports of controlled clinical trials.^[21]

Epidemiology

Hantavirus infections have been reported from all continents except Australia. Regions especially affected by hemorrhagic fever with renal syndrome include [China](#), the [Korean Peninsula](#), [Russia](#) (Hantaan, Puumala and Seoul viruses), and northern and western [Europe](#) ([Puumala](#) and Dobrava virus). Regions with the highest incidences of hantavirus pulmonary syndrome include [Argentina](#), [Chile](#), [Brazil](#), the [United States](#), [Canada](#), and [Panama](#).

Africa

In 2010, a novel hantavirus, [Sangassou virus](#) was isolated in Africa which causes hemorrhagic fever with renal syndrome.^[22]

Asia

In [mainland China](#), Hong Kong, the [Korean Peninsula](#) and [Russia](#), hemorrhagic fever with renal syndrome is caused by Hantaan, Puumala and Seoul viruses.^[23]

Australia

As of 2005, there were no human infections reported in Australia, though rodents were found to carry antibodies.^[24]

Europe

In Europe two hantaviruses – Puumala and Dobrava-Belgrade viruses – are known to cause hemorrhagic fever with renal syndrome.^[25] Puumala usually causes a generally mild disease, [nephropathia epidemica](#), which typically presents with fever, headache, gastrointestinal symptoms, impaired renal function and blurred vision. Dobrava infections are similar, except that they often also have hemorrhagic complications.

Puumala virus is carried by its rodent host, the [bank vole](#) (*Clethrionomys glareolus*), and is present throughout most of Europe, except for the Mediterranean region. There are four known Dobrava virus genotypes, each carried by a different rodent species. Genotype Dobrava is found in the [yellow-necked mouse](#) (*Apodemus flavicollis*); genotypes Saaremaa and Kurkino in the [striped field mouse](#) (*Apodemus agrarius*), and genotype Sochi in the [Black Sea field mouse](#) (*Apodemus ponticus*).

In 2017 alone, the Robert Koch Institute (RKI) in Germany received 1,713 notifications of hantavirus infections.^[26]

North America

Canada

The primary cause of the disease in Canada is Sin Nombre virus-infected deer mice. Between 1989 and 2014, there were a total of 109 confirmed cases, with the **death rate estimated at 29%.**^[27] The virus exists in deer mice nationwide, but cases were concentrated in western Canada (British Columbia, Alberta, Saskatchewan and Manitoba) with only one case in eastern Canada. In Canada "[a]ll cases occurred in rural settings and approximately 70% of the cases have been associated with domestic and farming activities."^[27]

United States

As of January 2017, 728 cases of hantaviral disease had been reported in the United States cumulatively since 1995, across 36 states, not including cases with presumed exposure outside the United States. More than 96% of cases have occurred in states west of the [Mississippi River](#). The top 10 states by number of cases *reported* (which differs slightly from a count ordered by the state of original *exposure*) were [New Mexico](#) (109), [Colorado](#) (104), [Arizona](#) (78), [California](#) (61), [Washington](#) (50), [Texas](#) (45), [Montana](#) (43), [Utah](#) (38), [Idaho](#) (21), and [Oregon](#) (21); **36% of the total reported cases have resulted in death.**^[28]

Mexico

In Mexico, rodents have been found to carry hantaviruses include [Thomas's giant deer mouse](#) (*Megadontomys thomasi*), the [pack rat](#) *Neotoma picta*, [Orizaba deer mouse](#) (*Peromyscus beatae*), [Western harvest mouse](#) (*Reithrodontomys megalotis*) and [Sumichrast's harvest mouse](#) (*Reithrodontomys sumichrasti*).^[29]

South America

Agents of HPS found in [South America](#) include the [Andes virus](#) (also called Oran, Castelo de Sonhos – Portuguese for "Castle of Dreams", Lechiguanas, Juititaba, Araraquara, and Bermejo virus, among many other synonyms), which is the only hantavirus that has shown an interpersonal form of transmission, and the Laguna Negra virus, an extremely close relative of the previously known Rio Mamore virus.

Rodents that have been shown to carry hantaviruses include [Abrothrix longipilis](#) and [Oligoryzomys longicaudatus](#).^[30]

2026 MV *Hondius* hantavirus outbreak

Main article: [MV *Hondius* hantavirus outbreak](#)

On 3 May 2026, a suspected outbreak of hantavirus was reported aboard the cruise ship [MV Hondius](#) in the Atlantic Ocean, resulting in three deaths. While the ship had departed Argentina three weeks prior, it was located off the coast of [Cape Verde](#) at the time the outbreak gained international attention.^[31] The following day, the [World Health Organization](#) issued a statement confirming that **"seven cases (two laboratory confirmed cases of hantavirus and five suspected cases) have been identified, including three deaths, one critically ill patient and three individuals reporting mild symptoms"**. The ship was carrying a total of 147 passengers and crew at the time of the report.^[32] While anchored off the coast of [Praia](#), Cape Verde, authorities barred passengers from disembarking to protect national public health.^[33]

On 6 May, an eighth case was identified, while the ship was on its way to the [Canary Islands](#).^[34]

History

12th-century Chinese texts describe diseases with clinical features similar to hantavirus infection.^{[7][35]} In late [medieval England](#), a mysterious [sweating sickness](#) swept through the country in 1485, just before the [Battle of Bosworth Field](#). Noting that the symptoms overlap with hantavirus pulmonary syndrome, several scientists have theorized that the virus may have been the cause of the disease.^{[36][37]} The hypothesis was criticized because sweating sickness was recorded as being transmitted from human to human, whereas hantaviruses were not known to spread in this way.^[38]

[Trench nephritis](#) during [World War I](#) may have been hantavirus infection.^[39]

The first clinical recognition was in 1931 in [Northeast China](#).^[7] Around the same time in the 1930s, [nephropathia epidemica](#) was identified in Sweden.^[7]

HFRS came to the recognition of western physicians during the [Korean War](#) between 1951 and 1954 when more than 3,000 [United Nations](#) soldiers fell ill in an outbreak.^[35] In 1976, the first pathogenic hantavirus, the [Hantaan virus](#), was isolated from rodents near the [Hantan River](#) in [South Korea](#). Other prominent hantaviruses that cause HFRS, including the [Dobrava-Belgrade virus](#), [Puumala virus](#), and [Seoul virus](#), were identified in the years after then and are collectively referred to as the Old World hantaviruses.^{[7][35]}

In 1993, an [outbreak of HCPS](#), then unrecognized, occurred in the [Four Corners](#) region of the United States and led to the discovery of the [Sin Nombre virus](#). Since then, approximately 43 hantavirus strains, of which 20 are pathogenic, have been found in the Americas and are referred to as the New World hantaviruses. This includes the [Andes virus](#), one of the primary causes of HCPS in South America and the only hantavirus known to be capable of person-to-person transmission.^[7]

In March 2025, it was determined that [Betsy Arakawa](#), the wife of actor [Gene Hackman](#), had died the previous month to [hantavirus pulmonary syndrome](#).^{[40][41]}

In April 2026, an [outbreak occurred](#) on the cruise ship [MV Hondius](#) causing the death of three passengers on board. The ship was heading from [Ushuaia](#), Argentina, to [Cape Verde](#).^[42]

See also

- [1993 Four Corners hantavirus outbreak](#)
- [2012 Yosemite hantavirus outbreak](#)

- [MV Hondius hantavirus outbreak](#)

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1993 Four Corners hantavirus outbreak



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1993 Four Corners hantavirus outbreak



The [Four Corners Monument](#), at the spot where the borders of Arizona, Colorado, New Mexico, and Utah meet

Disease	Hantavirus pulmonary syndrome
Pathogen	Sin Nombre virus
Source	Western deer mouse
Location	Four Corners region, United States
Date	1993
Confirmed cases	33 in Four Corners states; 48 nationwide
Recovered	16 in Four Corners states; 21 nationwide
Deaths	17 in Four Corners states;

	27 nationwide
Fatality rate	52% in Four Corners states; 56% nationwide

An outbreak of [hantavirus disease](#) occurred in 1993 in the [United States](#), primarily in the [Four Corners](#) region of [Arizona](#), [Colorado](#), and [New Mexico](#). Before 1993, hantaviruses that cause disease in humans, native to rodents, were known to spread mainly in Asia and Europe and to cause [hemorrhagic fever with renal syndrome](#). The outbreak in 1993 led to the discovery of hantaviruses from the [Western Hemisphere](#) that could cause disease and revealed the existence of a second disease caused by them: [hantavirus pulmonary syndrome](#) (HPS). In the Four Corners states, 17 of the 33 HPS cases in 1993 resulted in death, a 52% [case fatality rate](#). Nationwide that year, 27 of the 48 HPS cases resulted in death, a 56% case fatality rate.

The earliest confirmed cases of HPS in 1993 occurred in March, but the outbreak was not discovered until May when a young [Navajo](#) couple died within days of each other due to sudden respiratory failure. Investigators quickly found other people with the same symptoms as the couple. Further investigation discovered a new hantavirus, [Sin Nombre virus](#) (SNV), as the cause and identified the [western deer mouse](#) as its [natural reservoir](#). Public health officials gave advice on how to prevent infection, and the antiviral drug [ribavirin](#) was tested on suspected cases. While the first cases to be identified were in the Four Corners region, more cases were identified outside of the area as the year went on but not in the Four Corners state [Utah](#). Before research in 1993 showed that SNV was not spread between people, there was widespread fear that HPS was contagious. Consequently, Native Americans of the Four Corners region, especially the Navajo, experienced discrimination and racism during the outbreak.

The 1991–1992 [El Niño](#) indirectly caused the outbreak by producing a warmer-than-usual 1992–1993 winter and increased rainfall in the spring of 1993 in the Four Corners region. This increased the amount of vegetation available for rodents for food and shelter, which led to a significant increase in their numbers. The increased population density of rodents allowed SNV to spread more easily, and with a much larger population, interactions with people were more likely to occur. Further research has uncovered HPS cases before the outbreak as far back as 1959. Since the outbreak, hantaviruses that cause HPS have been identified throughout the Americas. In North America, SNV is the most common cause of the disease. HPS infections are rare, but they have a case fatality rate ranging from 12% to 45%, varying by virus. Treatment is supportive, and prevention is based on minimizing contact with rodents.

Background

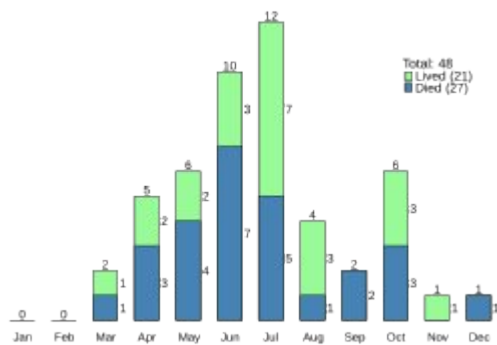


The Four Corners states are highlighted and include a circle to indicate the location of the Four Corners.

The [Four Corners](#) refers to the region surrounding the four-state border between southwestern Colorado, northwestern New Mexico, northeastern Arizona, and southeastern Utah.^{[1][2]} Most of the area is divided into [reservations](#) for Native American nations and tribes, namely the [Navajo Nation](#), [Hopi Reservation](#), [Ute Mountain Ute Tribe](#), [Southern Ute Indian Reservation](#), [Zuni Indian Reservation](#), and [Jicarilla Apache Nation](#).^[3] This sparsely populated area^[4] is part of the [Colorado Plateau](#), a desert region with mountains, [canyons](#), and [sedimentary rock](#) formations.^{[1][5]}

Hantaviruses are a group of [viruses](#) that constitute the [taxonomic family Hantaviridae](#). Hantaviruses that cause disease in humans are native to rodents and assigned to the [genus Orthohantavirus](#). Each species of hantavirus is usually transmitted by one rodent species.^[6] Before the 1993 Four Corners outbreak, [Old World](#) hantaviruses were known to cause [hemorrhagic fever with renal syndrome](#) (HFRS) and nephropathia epidemica, a milder form of HFRS, in Asia and Europe.^{[7][8]} Before this outbreak, [New World](#) hantaviruses were not known to infect or cause illness in humans.^{[9][10]}

Course of outbreak



HPS frequency in the US in 1993 by month^[11]
HPS frequency in the US in 1993 by state and territory^[11]

After HPS was discovered in May 1993,^[12] the outbreak was confirmed to have started earlier, in March.^{[11][13]} A dozen more cases were reported, mostly among the Navajo, in the weeks after the discovery.^[12] The outbreak continued to worsen through June and peaked in July before a sharp decline in August.^{[11][13]} HPS was first reported outside the Four Corners in Texas, in June.^{[14][15]} By mid-August, 23 hantavirus infections had been confirmed in the Four Corners region. In the [Southwest](#), 20 of the 30 confirmed cases resulted in death, a 67% case fatality rate.^[16] As the year went on, an increasing number of cases were identified outside the Four Corners region.^{[12][17]} By October, 60 cases of hantaviral disease had been reported nationwide, about half in the Four Corners region. Thirty-nine of these cases were confirmed by laboratory testing, 25 of which led to death.^{[12][18]}

From August to December, new reports of HPS were relatively low, except for a spike in October.^{[11][13]} By the end of the year, 48 cases had been confirmed nationwide, 27 of which resulted in death.^[11] **This 56% case fatality rate was similar across age, sex, and race,^[19] and it declined as physicians learned to quickly recognize HPS, identify less severe cases, and effectively treat HPS.^[20] Most of the infected were male, and, in the Four Corners region, all of the infected either lived in or visited rural areas before falling ill.** Of the 33 cases to occur in 1993 in Arizona, Colorado, and New Mexico, 26 occurred during the height of the outbreak from April to July, and 17 died, a 52% case fatality rate. The only Four Corners state where no HPS was identified in 1993 was Utah.^{[11][21]}

Outbreak investigation

Discovery

On May 11, 1993, a 19-year-old Navajo man, a competitive long-distance runner, visited the hospital in [Crownpoint, New Mexico](#),^[22] for [fever](#), muscle pain, chills, headache, and [malaise](#). He was given an [antibiotic](#), a drug for [influenza A](#), and a [painkiller](#) and discharged from the hospital. He returned two days later due to persistent symptoms, vomiting, and diarrhea and was discharged with no change in treatment.^[23] On the morning of May 14, he was traveling with his family from Crownpoint to [Gallup, New Mexico](#), when he became severely [short of breath](#). They stopped their car in [Thoreau, New Mexico](#), about 30 miles (42 km) east of Gallup, and contacted emergency services. By the time help arrived, he had collapsed due to [respiratory failure](#). An ambulance crew performed CPR as he was taken to the Gallup Indian Medical Center, where he was found to have fluid buildup in his lungs ([pulmonary edema](#)). Despite efforts to resuscitate him, he died. The death of the young man due to sudden respiratory failure confused medical staff.^{[12][22][24]}

Gallup, New Mexico, where the outbreak was first noticed by investigators

Because the man's death was highly unusual, it was required by law to be reported to the New Mexico Office of the Medical Investigator (OMI) in [Albuquerque](#), where [autopsies](#) are conducted. The deputy medical investigator in Gallup, Richard Malone, was called in to investigate his death. Malone had investigated a similar death of a 30-year-old Navajo woman a few weeks earlier, in April, at the same medical facility in Gallup. The woman's death, attributed to [pulmonary edema](#), was examined [post mortem](#) by [University of New Mexico](#) (UNM) [pathologist](#) Patricia McFeeley, who worked with the New Mexico OMI. The woman's lungs were filled with [blood plasma](#) and more than twice as heavy as usual. Test results were negative for known infections that could have caused her death. Malone contacted McFeeley on the day of the man's death to discuss the similarities between the two cases, and she agreed to perform an autopsy on the deceased man once permission was obtained from his family.^{[12][24]}

Malone spoke to the parents of the deceased man and hoped to receive information about what could have caused his death. They told Malone that their son collapsed while they were on their way to the funeral of his fiancée. She had died five days earlier, on May 9, at the hospital in Crownpoint^[25] with the same symptoms as her fiancé. Since Crownpoint is on the Navajo reservation, the medical facility there was not required to report her death to the New Mexico OMI and did not do so.^{[12][26]} Furthermore, due to her history of [asthma](#), her death was not considered alarming at first.^[27] After updating McFeeley on the situation, Malone convinced the families of the deceased to have the couple's bodies examined in autopsy. Later that day, McFeeley reported a possible outbreak of an unknown and deadly respiratory illness to the [state health department](#) in [Santa Fe](#) and prepared for autopsy. The autopsies of the couple showed only severe pulmonary edema with no explanation for the cause of illness.^{[12][28]}

Expanded scope

Scientists from the CDC helped identify the cause of the outbreak. Pictured is the CDC's headquarters in Atlanta, Georgia.

Malone then contacted Bruce Tempest, the medical director of Gallup Indian Medical Center. Tempest recalled having been involved in at least two discussions with physicians who had cared for young, previously healthy tribal members who suddenly died from an unknown respiratory illness. Malone and Tempest agreed that the situation required further action, so they searched for more cases.^[28] Tempest was aware of the three recent cases in New Mexico

as well as one from the previous November in Arizona. Health officials in Arizona informed him of another recent case, so on May 17, Malone and Tempest notified the New Mexico Department of Health of their concerns.^{[12][28]} State officials notified the [Centers for Disease Control and Prevention](#) (CDC) on May 18 and began an investigation with the [Indian Health Service](#) (IHS) and the Navajo Nation's health department. They examined the homes of the deceased and interviewed their families and the physicians who had cared for them.^{[12][29]} On May 24, New Mexico state officials sent a letter to clinicians in the Four Corners states that described the illness and situation and asked for any similar cases to be reported to them immediately, which identified several potential cases.^{[12][28]}

After learning of the situation, the press reported on May 27^{[12][30]} that an unknown disease was killing young tribal members in the Four Corners, which caused great anxiety in the public. Navajo and Hopi people were ostracized from the rest of society, and politicians faced pressure to respond to the situation.^[28] On the same day,^[31] New Mexico state officials contacted the CDC and asked for assistance. On May 28, a team of investigators was created and Jay Butler, an [epidemiologist](#) at the CDC's [Epidemic Intelligence Service](#), was made the leader of the team.^{[28][32]} Less than a day later, the group arrived at Albuquerque and was transported to the University of New Mexico. There, they were joined by members of the UNM medical faculty, IHS physicians, infectious disease and toxicology experts, physicians who had treated the deceased, and various state and national health officials.^{[12][28]} [Robert Breiman](#), a respiratory disease expert, was selected to lead the field investigation, while [C. J. Peters](#), the head of the CDC's Special Pathogens Branch, was put in charge of the laboratory work being done at the CDC in [Atlanta, Georgia](#).^[33]

In a meeting that took place from May 29 to May 31,^[27] the task force agreed to evaluate any person in the area from January 1, 1993, onward who had **radiological imaging that showed evidence of unexplained excess substances in both lungs (bilateral infiltrates) with low levels of oxygen in the blood (hypoxemia) as well as any death accompanied with unexplained pulmonary edema**. The group received clinical information about more than 30 suspected cases and considered various causes of illness. [Plague](#), [tularemia](#), and [anthrax](#), among other diseases, were eliminated from consideration due to lack of evidence. The team believed the outbreak to be caused by **either a new, aggressive form of influenza, an environmental toxin, or a previously unrecognized pathogen**.^{[27][28]}

Hantavirus suspected

Authorities captured rodents to identify the [natural reservoir](#) of the virus causing the outbreak. The western deer mouse was the most commonly captured species and was later confirmed to host the virus.^[note 1]

The investigative team started reviewing medical records on June 1 and obtained tissue samples from suspected cases. Meanwhile, epidemiologists interviewed patient and control families and inspected their homes and workplaces.^[28] After testing at a local laboratory continually yielded negative results,^[12] samples were sent to the CDC in Atlanta for immediate analysis. By June 4, **scientists at the CDC's Special Pathogens Branch had tested IgM antibodies from nine people with 25 different virus samples. Antibodies from every person reacted to three hantavirus species and none of the other viruses: [Hantaan virus](#), [Puumala virus](#), and [Seoul virus](#), each of which can cause HFRS. The antibody samples were then shown to be reactive to [Prospect Hill virus](#), a hantavirus discovered in [eastern meadow voles](#) in [Maryland](#) that had never been associated with human disease or isolated from human tissue**.^{[12][37][38]}

Several investigators had experience with and knowledge of HFRS.^[10] A distinctive feature of the disease is a **significant increase in the vascular permeability of capillary endothelial cells, mainly in the kidneys,**^{[10][39]} which causes massive loss of **intravascular fluid into the space behind the lining of the abdominal cavity.**^{[10][40]} **The loss of intravascular fluid causes the density of blood cells in blood to increase, a condition called hemoconcentration.**^{[10][41]} High levels of hemoconcentration were observed in several potential cases in the ongoing outbreak and, combined with the CDC's findings^[10] and the discovery of mouse feces at a home of the deceased,^[42] a hantavirus was suspected of causing the outbreak.^[10]

Before the outbreak, hantaviruses identified in the Western Hemisphere were only known to infect rodents, with no instances of human disease caused by them observed.^{[10][note 2]} There were also no known **hemorrhagic fevers** native to North America,^[note 3] and none of the infected had traveled abroad or come into contact with foreigners before falling ill.^[12] Furthermore, **unlike with HFRS, the disease had little kidney involvement; in all instances, the main organs affected were the lungs. Nonetheless, an unknown hantavirus that specifically infected pulmonary capillary endothelial cells** was suspected by some investigators.^[10] Acting on the information gathered so far, the CDC dispatched a rodent trapping team to New Mexico, which proceeded to capture around 1,700 rodents from June 7 to mid-August at patient and control sites. The most commonly captured species was the **western deer mouse.**^{[10][12][49]}

New viral disease

Transmission electron micrograph of Sin Nombre virus, the virus responsible for the outbreak. The spherical particles are extracellular virus bodies (**virions**).

At the same time as the rodent trapping operation, scientists at the CDC's Special Pathogens Branch worked to identify the virus. On June 10, **reverse transcription polymerase chain reaction (RT-PCR) was used to obtain a DNA sequence 139 base pairs in length from one segment of the virus's genome from samples taken from two people who had died from the disease.**^{[10][27]} Additionally, hantaviral **antigens** were identified in samples of tissues, such as the endothelium of the pulmonary capillary bed, by the CDC's Viral Pathology Laboratory. On June 16, the same team identified an identical viral base pair sequence and hantavirus antibodies in western deer mice captured on site, which conclusively identified the virus and its natural reservoir.^[10] By late June, testing had shown that about 30% of trapped western deer mice^{[12][49]} and smaller percentages of rodents of other species had been infected by the virus.^{[49][50]} **Late that summer,**^[51] **researchers confirmed that the virus does not spread between people.**^[52]

The virus was first **cultured** in November 1993 by teams at the CDC, which used tissue from a deer mouse trapped near the home of an infected person in New Mexico, and the **US Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick in Frederick, Maryland,**^{[10][49]} which used samples taken from a mouse trapped in California and tissue of an infected person in New Mexico.^{[49][53]} Initially, the virus was named *Four Corners virus* before being rejected because of the negative association with the region.^{[9][54][55]} The CDC and USAMRIID then, in January 1994,^[56] gave the virus the name *Muerto Canyon virus* after a location near where the disease was first observed,^{[10][55]} as it is customary to name hantaviruses after where they are discovered.^{[57][58]} The Navajo, however, strongly opposed any further association with the virus because of the **racial discrimination** that it had triggered against them.^[10] Moreover, the name was problematic given that Muerto Canyon was named after the massacre of 115 Navajo by Spanish troops in 1805,^{[59][60]} so the **Navajo**

[Nation Council](#) unanimously voted to request the CDC to find an alternative name for the virus.^{[61][62]} The name *Convict Creek virus* was proposed, as the virus was cultured from a mouse captured there, but the CDC rejected this name because USAMRIID, not the CDC, had used the mouse to culture the virus.^[59] Ultimately, the CDC officially named the virus *Sin Nombre virus* (SNV), Spanish for *virus without name*.^{[10][62][63]}

The CDC started referring to the disease as ***hantavirus pulmonary syndrome (HPS)*** on August 5, 1993,^[64] and made it the official name in October that year.^{[65][note 4]} The Hantavirus Study Group, formed to study the clinical course of the disease, published their findings in the April 7, 1994, edition of *The New England Journal of Medicine*. They reported 18 people who had either **serologic or PCR evidence of infection**, most of them young adults. Physical examination of these people showed **fever, rapid and shallow breathing (tachypnea), an abnormally fast heart rate (tachycardia), and low blood pressure (hypotension)**. Severe pulmonary edema occurred in nearly all cases. Laboratory findings included hypoxemia, hemoconcentration, higher than normal white blood cell count in the blood (**leukocytosis**), abnormally low platelet levels in the blood (**thrombocytopenia**), and increased time needed for the liver to produce **prothrombin and for blood to clot**.^[10] According to the CDC, early signs of illness included fever, muscle pain, headache, variable **respiratory symptoms** such as coughing, and **gastrointestinal symptoms** such as abdominal pain, nausea, and vomiting. The early stage of the disease was then followed by sudden respiratory distress. Bilateral pulmonary infiltrates developed within two days of hospitalization, and fever, low oxygen levels (**hypoxia**), and hypotension were present during hospitalization. People who recovered from HPS during the outbreak did not experience any **long-term complications**.^[69] **Death was the result of pulmonary edema or heart failure.**^[70]

Government response

Window Rock, Arizona, where Navajo medicine men met to discuss the outbreak, is the capital of the Navajo Nation. Pictured is the [Navajo Nation Council Chamber](#) building in Window Rock.

Fifty [Navajo medicine men](#) met in [Window Rock, Arizona](#),^[note 5] to discuss the outbreak and told people to be wary of deer mice and [prairie dogs](#).^{[42][71]} Navajo elders were aware of the danger of mouse feces and urine, so they recommended burning contaminated clothing and keeping food away from mice.^[71] At the same time, Navajo medicine men performed blessings and purification ceremonies at locations involved in the outbreak, such as places where people fell ill.^[72] The Navajo Nation's government responded to the outbreak by declaring a public health emergency and establishing an Incident Management Team and Inter-Agency Working Group. They also implemented rodent control and public health education programs, providing rat traps to residents and informing them about HPS and ways to reduce their risk of exposure to infected mice.^{[73][74]}

The government opened a toll-free telephone hotline on June 3 to provide updated information about unexplained respiratory illness and to receive calls about suspected HPS throughout the country.^[75] Public health officials advised people to prevent rodents from entering their homes, avoid leaving out food that could attract them, and trap and dispose of rodents while wearing rubber gloves and surgical masks. To deal with rodent excretions, health officials recommended soaking them in a chlorine [bleach](#) solution and then wrapping them in double plastic bags before disposing of them. People were warned to avoid inhaling dust in places infested with mice because the dust could have [aerosols](#) that contain the virus. **Health officials did not recommend poisoning mice since they could die somewhere inaccessible and still spread the virus.**^{[76][77]}

Medical care provided during the outbreak included preventing secondary infections and supporting the body's functions during recovery.^[78] **Many of the infected were placed on ventilators, often while sedated.**^[79] Most rural physicians attempted to stabilize people suspected to have HPS and transport them to other facilities such as the UNM medical center in Albuquerque.^[78] Large regional hospitals, particularly the one at UNM, had higher survival rates due to easier access to equipment and expertise.^[79] On June 4, **the antiviral drug ribavirin was made available for treatment, and intravenous ribavirin stocks were provided to healthcare facilities** in the Four Corners region. Intravenous administration of ribavirin had effectively treated severe Hantaan virus infections when provided early during illness, so it was tested experimentally on suspected cases during the outbreak.^{[80][81]} The CDC considered removing the possibility of infection by trapping and poisoning deer mice, but this was rejected as infeasible given the large geographic area and undesirable since **mice are an important part of the ecosystem.**^[82]

Social and economic impact

During the outbreak, national media were not respectful of the traditional four-day mourning period in Navajo culture.^{[12][83]} The local community was inundated with media who took pictures of funerals, published the names of the deceased, and attempted to interview families of the deceased.^[12] Sometimes, the media incorrectly reported the names of the deceased and communities.^[84] According to Stumpff, media coverage often caused people to view Navajo culture negatively and associate the disease with the Four Corners,^[85] and the disease was publicly referred to as various names related to the area, including Navajo Flu, Navajo Illness, and Four Corners Illness.^[62] In many instances, residents posted anti-media signs along roads.^{[12][86]} Some people felt so much resentment that they refused to assist investigators,^[12] who also failed to respect mourning practices as they continuously asked for information about recent deaths.^[62] Within a month of the outbreak's discovery, it was apparent that HPS was not restricted to the Navajo or the Four Corners region. By that point, however, the Navajo were left to deal with the stigma created by the media, which moved on to other news.^{[12][note 6]}

Before the disease's transmission method was confirmed, there was widespread fear that it was contagious. This contributed to discrimination and racism against the Navajo. For example, some restaurants refused to serve Navajo people, while in others staff wore gloves when serving them^[12] or threw away their used plates instead of re-using them.^[42] People's fears were intensified by the high case fatality rate of HPS even though there was no evidence for transmission between people.^[62] Because of these fears, local restaurants saw a significant decline in business, many people stopped going to the movies, and hardly any people attended the annual Gallup Inter-Tribal Indian Ceremonial that was held that year. Some people wore surgical masks when leaving the house. In general, though, people in the area only went outside when necessary.^[42] In response to news reports, numerous people canceled vacations to the area, and revenue from tourism declined.^[85]

[Peterson Zah](#), the [president of the Navajo Nation](#), was a vocal critic of the news coverage of the outbreak and the stigmatization of the Navajo. He said: "The story of hantavirus is a perfect example of an intercultural setting and the friction that lies just beneath the surface, and which explodes when unknowing outsiders trample on age-old customs. Deaths and the unknown nature of the illness served only to reinforce stereotypes ... [and] the view of Indians as second-class citizens was further supported."^[62] During the outbreak, Zah appealed to the media to respect the privacy of people who lost family members^[83] and urged tribal members to assist medical investigators.^[88] **Before the cause of the outbreak was identified, many Navajo**

speculated that the disease was brought to the reservation by tourists or that [Fort Wingate](#), located 20 miles (32 km) south of the reservation, had stored a [biological](#) or [chemical weapon](#) that escaped, because the [US Army](#) was closing its depot there at the time of the outbreak.^{[12][42]} Later on, some Navajo expressed skepticism toward the connection to mice. One chapter president instead blamed toxic wastes or [radioactivity](#) for causing the outbreak.^{[86][note 7]}

Historical analysis

El Niño increases wetness in the southern United States during winter.

A group of UNM biologists studying deer mice near the Four Corners region at the time^[10] noticed that their population significantly grew from May 1992 to May 1993.^{[49][90]} Working with environmental scientists,^[91] they demonstrated that the conditions of the 1991–1992 El Niño caused a relatively warm 1992–1993 winter and a rainy 1993 spring in the Four Corners region.^[92] The area had been experiencing drought for a few years,^{[49][93]} but with more [snowmelt](#) and rainfall came a relative abundance of springtime vegetation in the region.^{[91][93]} This provided more shelter and food for local animals, which led to rapid growth of the rodent population and, in turn, increased the number of interactions between humans and rodents.^{[91][94][95]} Furthermore, with a higher population density of mice, SNV was able to spread more easily among them.^{[96][97]}

According to traditional Navajo beliefs, mice inhabit the nocturnal and outdoor world and humans the daytime and indoor world. The two should not mix or sickness and death may occur. When mice enter a house and find a disorderly environment with food lying about, they become angry at the mess and may strike down a family member, usually someone young and healthy.^{[27][71]} **Navajo oral tradition spoke of past outbreaks in 1918, 1933, and 1934,^[92] which they attributed to excess caused by disharmony.** Every year in which an outbreak occurred had excess rain and snowfall, which led to increased rodent food supply and consequently greater rodent populations and more human-rodent interactions.^[98]

Genetic analysis of SNV has indicated that it has existed in its natural reservoir since long before the outbreak.^[63] Biologists believe that people probably died from hantavirus infection before the outbreak but that their cause of death was unknown.^[12] Tempest, when recollecting on people he had treated in the years before the outbreak, said: "I will never be able to know for sure but I believe they were also Hantavirus victims."^[42] Serum samples collected in 1991 and 1992 as part of the Navajo Health and Nutrition Survey were tested in June 1993 and showed that **three people out of 270 had antibodies to hantaviruses, indicative of past infection.^{[99][100]} By examining tissue samples from people who died from unexplained [acute respiratory distress syndrome](#) (ARDS), a 38-year-old man who died in Utah in 1959 became the earliest confirmed instance of HPS.^{[49][93]}**

HPS since the outbreak

Tent cabins in [Curry Village](#) in [Yosemite National Park](#), California. **A small outbreak of HPS occurred in the park in 2012, mainly at Curry Village, during which ten visitors were infected and three died.^{[101][102]}**

Following the outbreak, the medical community in the US was asked to report HPS-like illnesses with unexplained causes. **Other hantaviruses responsible for HPS were subsequently found, including [Bayou virus](#), [Black Creek Canal virus](#), and [New York virus](#).^[49]** The disease has since been found to also occur in Canada, Panama, and most of South America.^[103] In the Navajo Nation, the government has implemented long-term prevention and control strategies to address HPS, including rodent control and surveillance programs and

public health education,^[104] and the [CDC Foundation](#) has worked with the Navajo community to implement rodent control measures and educate people about HPS.^[105]

SNV is the most common cause of HPS in North America.^[106] It is primarily associated with one rodent species, and other hantaviruses discovered in North America follow the same pattern.^{[6][91]} Infections are usually contracted by inhaling aerosols of rodent feces, urine, or saliva.^{[107][108]} A few dozen cases occur each year,^[106] most from April to August in rural areas in western states and provinces.^{[111][109]} In South America, [Andes virus](#) is the most common cause of HPS and is transmitted primarily by the [long-tailed pygmy rice rat](#).^{[106][110]} More than 200 cases occur every year, mostly in Argentina, Brazil, and Chile.^[103]

Although HPS was feared by many to be contagious during the 1993 outbreak,^[12] transmission of SNV between people has never been confirmed,^[52] and there is little evidence of human-to-human transmission of hantaviruses in general.^{[111][112]} Because of the health risks imposed by hantaviruses, however, rodents and other small [mammals](#) are routinely surveilled to monitor hantavirus circulation.^{[113][114]} Environmental factors influence the rodent population, which can make HPS more or less frequent. For example, harsher wet winters are associated with a smaller deer mouse population,^[115] while rainfall is beneficial to their population by increasing food availability.^{[115][116]} Consequently, lower winter temperatures are associated with lower HPS incidence, and greater rainfall is associated with higher HPS incidence.^[117]

Treatment of HPS is supportive and includes cardiac monitoring, [mechanical ventilation](#), and [extracorporeal membrane oxygenation](#).^[118] Despite these measures, the disease still has a high case fatality rate, ranging from about 12% to 45%, varying by virus.^[103] Experimental testing of ribavirin during the outbreak did not show a significant benefit to its use,^[119] and research has since shown that it is ineffective if administered after the early stage of HPS.^{[120][121]} As a result, the **CDC does not recommend ribavirin as a treatment for the disease**.^[118] Additionally, there are no approved vaccines to protect against New World hantavirus infections.^{[122][123]} To prevent infection, the CDC advises people to avoid contact with rodents, prevent them from entering one's home, keep one's home clear of food that may attract them, and safely clean up after them.^{[124][125]}

See also

- [Hantavirus pulmonary syndrome](#)
- [Yosemite National Park](#)
- [Sin Nombre orthohantavirus](#)
- [2012 Yosemite hantavirus outbreak](#)
- [MV Hondius hantavirus outbreak](#)

Notes

1. Many sources, including those from 1993, identify the natural reservoir of Sin **Nombre virus** as the species *Peromyscus maniculatus*. In fact, the natural reservoir of the virus is the species *Peromyscus sonoriensis*. The reason for this discrepancy is because the two species were previously classified as one, both under the scientific name *Peromyscus maniculatus*. This species was reorganized in the late 2010s and split into multiple species, including *P. maniculatus* and *P. sonoriensis*. The "old" *P. maniculatus* had a range extending across most of North America, whereas the "new" *P. maniculatus* is limited to southeastern Canada and the northeastern parts of the US east of the [Mississippi River](#). *P. sonoriensis*, on the other hand, is found in most

of the US west of the Mississippi River, including in the Four Corners region, and in most of southwestern Canada, which corresponds to where Sin Nombre virus infections usually occur.^{[34][35][36]}

2. **Seoul virus**, a pathogenic *Old World* hantavirus, was detected in the Western Hemisphere before 1993. As such, the 1993 outbreak represents the discovery of pathogenic *New World* hantaviruses in the Western Hemisphere.^[43]
3. Apart from hantaviral disease, the only other hemorrhagic fever native to North America is caused by [Whitewater Arroyo virus](#),^[44] which was first described in 1996^[45] and connected to human disease in 1999–2000.^[46] [Dengue virus](#), the cause of [Dengue fever](#), exists in southern North America, but it is not native and was introduced into the Americas in [early modern times](#).^{[47][48]}
4. Before *hantavirus pulmonary syndrome*, the CDC called HPS *Navajo flu* during their initial response to the outbreak.^[66] Throughout 1993, the CDC also referred to it variously as *hantavirus-associated respiratory disease*,^[15] *acute hantavirus-associated respiratory disease*,^[16] *hantavirus-associated respiratory illness*,^[67] and *acute hantavirus respiratory illness*.^[18] In the press, the disease was also called *hantavirus-associated ARDS*.^[68]
5. Sources differ on when the meeting of 50 Navajo medicine men took place. Stumpff says this meeting occurred "by May,"^[71] Donovan on May 25,^[42] and Sternberg on June 1.^[27]
6. According to Duane Beyal, the executive press officer of the Navajo Nation, local media tended to report on the outbreak better than national outlets. He did, however, praise national media such as [Reuters](#) for responding well to criticism.^[87]
7. In the Navajo Nation, Chapters are the local form of government, and the Chapter President is an elected official.^[89]

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- Peters CJ, Olshaker M (April 13, 1998). *Virus Hunter: Thirty Years of Battling Hot Viruses Around the World*. Anchor Books. ISBN [978-0-385-48558-6](#). — contains a firsthand account of the outbreak from the perspective of C. J. Peters, the head of the CDC's Special Pathogens Branch

External links

- [Viruses portal](#)
- [The CDC's index page for information about hantaviruses and hantaviral disease](#)
- [ViralZone's article about the molecular biology of orthohantaviruses](#)
- [The Bacterial and Viral Bioinformatics Resource Center's overview page for bioinformatic information about hantaviruses](#)

Hantavirus hemorrhagic fever with renal syndrome

Bottom of Form

From Wikipedia, the free encyclopedia

Hemorrhagic fever with renal syndrome

Specialty [Infectious diseases](#), [nephrology](#)

Symptoms Headache, lower back pain, nausea, vomiting, diarrhea, bloody stool, petechiae

Complications Renal failure

Causes [Hantaviruses](#) spread by rodents

Prevention Rodent control

Treatment Supportive, including intravenous hydration, electrolyte therapy, and platelet transfusions

Medication None

Prognosis Usually good, **case fatality rate of <1%–15%**

Hantavirus hemorrhagic fever with renal syndrome (HFRS) is a [hemorrhagic fever](#) caused by [hantaviruses](#). Signs and symptoms usually occur 2 weeks after exposure to the virus and come in five distinct clinical stages: **febrile (toxic), hypotensive, low urine production (oliguric), high urine production (diuretic), and recovery**. Early symptoms include headache, lower back pain, nausea, vomiting, diarrhea, bloody stool, the appearance of spots on the skin, bleeding in the respiratory tract, and renal symptoms such as kidney swelling, [proteinuria](#), and [hematuria](#). During the hypotensive phase, blood pressure lowers due to microvascular leakage. Renal failure then causes the oliguric phase, before recovering and increasing urine production as disease progression improves. The severity of symptoms varies depending on which virus causes HFRS and ranges from mild illness to severe. The case fatality rate likewise varies by virus, from less than 1% up to 15%.

HFRS is caused mainly by four viruses in Asia and Europe: [Hantaan virus](#), [Seoul virus](#), [Puumala virus](#), and [Dobrava-Belgrade virus](#). In East Asia, the Hantaan virus is the most common cause of HFRS, causes a severe form of HFRS, and is spread by [striped field mice](#). Seoul virus accounts for about a quarter of HFRS cases, causes a moderate form of the disease, and is found worldwide due to the global distribution of its natural reservoir, the [brown rat](#). Puumala virus is the most common cause of HFRS in Russia and northern and central Europe, usually causes a mild form of HFRS, and is transmitted by the [bank vole](#). Dobrava-Belgrade virus is the most common cause of HFRS in southern Europe, and varies in disease severity and natural reservoir depending on its genotype. A mild form of HFRS often called **nephropathia epidemica (NE)** is caused by the Puumala virus and the Dobrava-Belgrade virus. Transmission occurs mainly through inhalation of aerosols that contain rodent saliva, urine, or feces, but can also occur through contaminated food, bites, and scratches. **Vascular [endothelial cells](#) and [macrophages](#) are the primary cells infected by hantaviruses, and infection causes abnormalities with [blood clotting](#), all of which result in fluid leakage responsible for the more severe symptoms**. Recovery from infection likely confers lifelong protection.

The main way to prevent HFRS is to avoid or minimize contact with rodents that carry hantaviruses. Removing sources of food for rodents, safely cleaning up after them, and preventing them from entering one's house are all important means of protection. People who are at risk of interacting with infected rodents can wear masks to protect themselves. **Bivalent vaccines that protect against the Hantaan virus and the Seoul virus are in use in China and South Korea.** Initial diagnosis of infection can be made based on epidemiological information and symptoms. **Confirmation of infection can be done by testing for hantavirus nucleic acid, proteins, or hantavirus-specific antibodies.** Treatment of HFRS is supportive and depends on the phase of the disease and clinical presentation. **Intravenous hydration, electrolyte therapy, and platelet transfusions may be performed, as well as intermittent hemodialysis for renal failure and continuous renal replacement therapy in critical cases. No specific antiviral drugs exist for hantavirus infection.**

More than 100,000 cases of HFRS occur each year. China is the most affected country in Asia, while Finland is the most affected country in Europe. More than 10,000 cases of NE are diagnosed annually. The distribution of viruses that cause HFRS is directly tied to the distribution of their [natural reservoirs](#). Transmission is also greatly influenced by environmental factors such as rainfall, temperature, and humidity, which affect the rodent population and virus transmissibility. **Outbreaks of HFRS have occurred throughout history, especially among soldiers during wartime who live in poor conditions.** During the [Korean War](#) in the 1950s, an epidemic of HFRS occurred among United Nations soldiers stationed near the [Hantan river](#). The outbreak was determined in the 1970s and 1980s to be caused by the Hantaan virus, which was named after the river and which was the first hantavirus discovered. **Other HFRS epidemics include an outbreak in Finland in [World War Two](#) among German and Finnish soldiers, caused by Puumala virus, and an outbreak in Croatia during the [Balkan Wars](#), caused by Puumala virus and Dobrava-Belgrade virus.**

Signs and symptoms

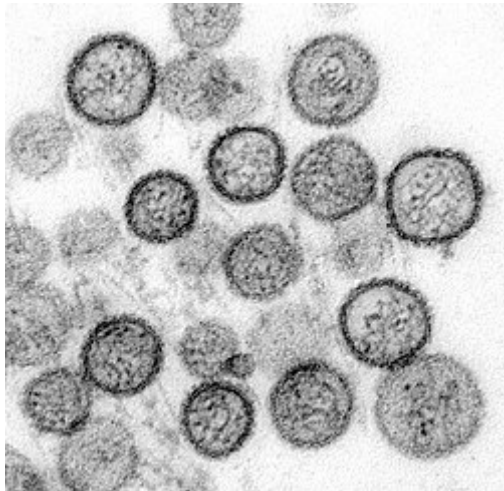
Hantavirus hemorrhagic fever with renal syndrome (HFRS) is characterized by five phases: febrile, hypotensive, low urine production (oliguria), high urine production (polyuria or diuretic), and recovery. Symptoms usually occur 12–16 days after exposure to the virus, but may appear as early as 5 days or as late as 42 days after exposure.^[1] A hallmark of HFRS is acute kidney disease with kidney swelling, excess protein in urine (proteinuria), and blood in urine (hematuria). **Other symptoms include headache, lower back pain, impaired vision, nausea, vomiting, diarrhea, and bloody stool.^[2] These early symptoms last 3–7 days.^{[3][4]} Hemorrhagic symptoms include the appearance of red, purple, or brown spots on the skin (petechiae) and mucosa within 3–4 days after the onset of symptoms,^[4] coughing up blood or blood-stain mucus or airway bleeding ([hemoptysis](#)), congestion of the [conjunctiva](#) in the eye, gastrointestinal bleeding, and intracranial bleeding.** In severe cases, excess blood clotting throughout the body, called **disseminated intravascular coagulation (DIC)**, can occur.^[2] The severity of symptoms varies depending on the virus: Hantaan virus causes severe HFRS; Seoul virus moderate HFRS; Puumala virus mild HFRS;^[5] and Dobrava-Belgrade varies depending on genotype.^[6]

During the hypotensive phase, which lasts 1–3 days,^[7] there is a sudden onset of lower blood pressure and shock due to microvascular leakage, which can result in sudden death.^[2] Urine production and platelet count decrease, white blood cell count in blood increases, and hemorrhaging begins during the hypotensive phase.^[8] The oliguric or diuretic phase, which lasts 2–6 days,^[7] is caused by renal failure with oliguria and proteinuria. During the polyuria phase, which lasts about 1–2 weeks,^[5] renal functions gradually recover, which leads to increased urine

production.^[2] Complete renal function can be restored after a long recovery process, about 2–6 months,^[8] but chronic renal failure, endocrine dysfunction, and hypertension may occur.^[8] **Extra-renal complications include [acute respiratory distress syndrome](#) (ARDS), pituitary gland injury or [insufficient pituitary gland hormone production](#),^[9] and [inflammation of the gallbladder \(cholecystitis\)](#), the pericardium (pericarditis), the brain (encephalitis),^[2] and the pancreas (pancreatitis).**^[10]

Infection with Puumala virus or Dobrava-Belgrade virus often causes a mild form of HFRS known as nephropathia epidemica (NE).^[11] For pregnant women and fetuses, symptoms are more severe,^[1] whereas for children symptoms are milder with greater frequency of abdominal symptoms.^[3] **Serological surveys suggest that many HFRS infections go unnoticed, either as asymptomatic infections or as a mild flu-like illness with symptoms such as high fever, malaise, and muscle pain.**^{[11][12]} In more mild cases, the different phases of illness may be hard to distinguish,^[13] or some phases may be absent, while in more severe cases, the phases may overlap.^[5] **While HFRS is typically associated with renal disease, symptoms sometimes include cardiopulmonary symptoms associated with [hantavirus pulmonary syndrome](#) (HPS).**^{[3][14]} **Some symptoms are associated with specific hantaviruses: Puumala virus often causes ocular symptoms such as blurry vision and nearsightedness,^{[8][15][16]} Hantaan virus can affect the pituitary gland and cause [empty sella syndrome](#),^[17] and Dobrava-Belgrade virus commonly causes ARDS.^[3] Repeated infections of hantaviruses have not been observed, so recovering from infection likely grants life-long immunity.**^{[18][19]}

Virology



Transmission electron micrograph of [Sin Nombre virus](#), a hantavirus

Genome and structure

The genome of hantaviruses is segmented into three parts: the large (L), medium (M), and small (S) segments. Each part is a [single-stranded negative-sense RNA](#) strand, consisting of 10,000–15,000 nucleotides in total.^[20] The segments form into circles via non-covalent bonding of the ends of the genome.^[21] The L segment is about 6.6 kilobases (kb) in length^[22] and encodes [RNA-dependent RNA polymerase](#) (RdRp), which mediates [transcription](#) and replication of viral RNA. The M segment, about 3.7 kb in length,^[22] encodes a glycoprotein precursor that is co-translated and cleaved into Gn and Gc. Gn and Gc bind to cell receptors, regulate immune responses, and induce protective antibodies. The S segment is around 2.1 kb in length^[22] and encodes the N protein, which binds to and protects viral RNA. An [open reading frame](#) in the N

gene on the S segment^[23] of some hantaviruses also encodes the non-structural protein NS that inhibits interferon production in host cells. The untranslated regions at the ends of the genome are highly conserved and participate in the replication and transcription of the genome.^{[2][5][20]}

Individual hantavirus particles (virions) are usually spherical, but may be oval, pleomorphic,^[24] or tubular.^[20] The diameter of the virion is 70–350 nanometers (nm).^[22] The [lipid envelope](#) is about 5 nm thick. **Embedded in the envelope are the surface spike glycoproteins Gn and Gc,**^[2] which are arranged in a lattice pattern.^[22] Each surface spike is composed of a tetramer of Gn and Gc (four units each) that has four-fold rotational symmetry, extending about 10 nm out from the envelope.^[22] Gn forms the stalk of the spike and Gc the head.^[20] Inside the envelope are helical nucleocapsids made of many copies of the nucleocapsid protein N, which interact with the virus's genome and RdRp.^[2] Hantaviruses do not encode matrix proteins to assist with structuring the virion, so how surface proteins organize into a sphere with a symmetrical lattice is not yet known.^[25]

Life cycle

Vascular endothelial cells and macrophages are the primary cells infected by hantaviruses.^[7] [Podocytes](#), tubular cells, [dendritic cells](#), and [lymphocytes](#) can also be infected.^{[2][3]} Attachment and entry into the host cell is mediated by the binding of the viral glycoprotein spikes to host cell receptors, particularly $\beta 1$ and $\beta 3$ [integrins](#).^[7] Decay acceleration factors and complement receptors have also been proposed to be involved in attachment.^{[3][25]} After attachment, hantaviruses rely on several ways to enter a cell, including micropinocytosis, [clathrin](#)-independent receptor-mediated [endocytosis](#) and [cholesterol](#)- or [caveolae](#)-dependent endocytosis.^{[2][3][20]} Old World hantaviruses use clathrin-dependent endocytosis while New World hantaviruses use clathrin-independent endocytosis.^{[3][26][27]}

After entering a cell, virions form vesicles that are transported to early [endosomes](#), then late endosomes and lysosomal compartments. A decrease in pH then causes the viral envelope to fuse with the endosome or [lysosome](#).^{[22][26][27]} This fusion releases viral ribonucleoprotein complexes into the cell cytoplasm, initiating transcription and replication by RdRp.^{[2][3][22]} RdRp transcribes viral -ssRNA into complementary positive-sense strands, then [snatches](#) 5' ("five prime") ends of host [messenger RNA](#) (mRNA) to prepare mRNA for translation by host ribosomes to produce viral proteins.^{[20][22]} Complementary RNA strands are also used to produce copies of the genome, which are encapsulated by N proteins to form RNPs.^{[2][3][22]}

During virion assembly, the glycoprotein precursor is cleaved in the endoplasmic reticulum into the Gn and Gc glycoproteins by host cell signal peptidases.^{[2][20]} Gn and Gc are modified by N-glycan chains, which stabilize the spike structure and assist in assembly in the Golgi apparatus for Old World hantaviruses^[2] or at the cell membrane for New World hantaviruses.^[3] Old World hantaviruses obtain their viral envelope from the [Golgi apparatus](#) and are then transported to the cell membrane in vesicles to leave the cell via [exocytosis](#). On the other hand, New World hantavirus RNPs are transported to the cell membrane, where they bud from the cell surface to obtain their envelope and leave the cell.^{[3][22][27]}

Evolution

The most common form of evolution for hantaviruses is [mutations](#) through single nucleotide substitutions, insertions, and deletions.^[2] Hantaviruses are usually restricted to individual [natural reservoir](#) species and evolve alongside their hosts,^[2] but this one-species-one-hantavirus relationship is not true for all hantaviruses. The exact evolutionary history of hantaviruses is likely obscured by many instances of genome [reassortment](#), host spillover, and

host-switching.^[28] Because hantaviruses have segmented genomes, they are capable of [genetic recombination](#) and reassortment in which segments from different viruses can combine to form new viruses. This occurs often in nature and facilitates the adaptation of hantaviruses to multiple hosts and ecosystems. Within species, geography has also affected the evolution of hantaviruses. For example, Hantaan virus and Seoul virus have both formed multiple lineages corresponding to their geographic distribution.^[2]

Mechanism



The striped field mouse, the natural reservoir of Hantaan virus and the Dobrava-Belgrade virus genotypes Kurkino virus and Saaremaa virus



The [yellow-necked mouse](#), the natural reservoir of Dobrava-Belgrade virus genotype Dobrava virus



The bank vole, the natural reservoir of Puumala virus

The brown rat, a natural reservoir of Seoul virus

The [black rat](#), a natural reservoir of Seoul virus

Transmission

Rodents transmit hantaviruses that cause illness in humans. **In rodents, hantaviruses usually cause an asymptomatic, persistent infection.** Infected animals can spread the virus to uninfected animals through aerosols or droplets from their feces, urine, saliva,^[5] and

blood,^[29] through consumption of contaminated food, from virus particles shed from skin or fur,^[22] via grooming,^[20] or through biting and scratching. Hantaviruses can also spread through the fecal-oral route and across the placenta during pregnancy **from mother to child**. They can survive for **10 days at room temperature,**^[2] **15 days in a temperate environment,**^[11] **and more than 18 days at 4 degrees Celsius,** which aids in viral transmission.^[2] Environmental conditions favorable to the reproduction and spread of rodents are known to increase disease transmission.^[30] **Living in a rural environment, in unhygienic settings, and interacting with environments shared with hosts are the biggest risk factors for infection, especially people who are hikers,**^[5] **farmers and forestry workers,**^[11] **as well as those in mining, the military,**^{[22][31]} **and zoology.**^[3]

Rodents can transmit hantaviruses to humans through aerosols or droplets from the excretions and through the consumption of contaminated food. Rodent bites and scratches can also transmit hantaviruses to humans. **The prevalence of hantavirus among rodent breeders and rodent pet owners is up to 80%.** In one outbreak in North America in 2017, Seoul virus infected 31 people through contact with pet rats. **Andes virus** has often been claimed by researchers to be the only hantavirus known to be spread from person to person, usually after coming into close contact with an infected person. It can also reportedly spread through human saliva, airborne droplets from coughing and sneezing, and to newborns through breast milk and the placenta.^[2] A 2021 systematic review, however, found **human-to-human transmission of the Andes virus to be poorly supported by evidence but possible in limited circumstances, especially between close household contacts such as sexual partners.**^{[12][30]} Puumala virus may be transmissible from person to person through blood and platelet transfusions.^[27]

Hantaviruses that cause HFRS can be transmitted through the bites of mites and ticks.^[32] Research has also shown that pigs can be infected with Hantaan virus without severe symptoms and sows can transmit the virus to offspring through the placenta. Pig-to-human transmission may also be possible, as one swine breeder was infected with hantavirus with no contact with rodents or mites. **Hantaan virus and Puumala virus have been detected in cattle, deer, and rabbits, and antibodies to Seoul virus have been detected in cats and dogs.** The role of these hosts for hantaviruses is unknown.^[2] Infection in these other animals can potentially facilitate the evolution of hantaviruses by genome reassortment.^[3] **In addition to rodents, some hantaviruses are found in small insectivorous mammals, such as shrews and bats.**^{[3][7]} **Hantavirus antigen has also been detected in a variety of bird species, indicative of infection.**^[32]

Man-made built environments are important in hantavirus transmission. **Deforestation and excessive agriculture may destroy rodents' natural habitat.**^[3] **The expansion of agricultural land is associated with a decline in predator populations, which enables hantavirus host species to use farm monocultures as nesting and foraging sites.** Agricultural sites built in proximity to rodents' natural habitats can facilitate the proliferation of rodents as they may be attracted to animal feed.^{[29][33]} **Sewers and stormwater drainage systems may be inhabited by rodents, especially in areas with poor solid waste management. Maritime trade and travel have also been implicated in the spread of hantaviruses.**^[29] Research results are inconsistent on whether urban living increases or decreases hantavirus incidence.^[33] Seroprevalence, showing past infection to hantavirus, is consistently higher in occupations and areas that have greater exposure to rodents.^[12] **Poor living conditions on battlefields, in military camps, and in refugee camps make soldiers and refugees at great risk of exposure as well.**^[31]

Pathophysiology

The main cause of illness is increased vascular permeability, decreased platelet count, and overreaction by the immune system.^{[2][3][4]} The increased vascular permeability appears to be the result of infected cells producing [vascular endothelial growth factor](#) (VEGF), which activate VEGFR2 receptors on endothelial cells, which increases paracellular permeability.^{[3][34]} Oxygenation problems and [bradykinin](#) are also thought to play a role in increased vascular permeability during infection. Coagulation abnormalities may also occur. Virus particles cluster on the surface of endothelial cells, which causes a misallocation of platelets to infected endothelial cells. Disseminated coagulating without signs of hemorrhaging, major blood clots, and damage to vascular endothelial cells during infection may negatively affect coagulation and platelet levels and promote further vascular leaking and hemorrhaging.^{[3][14]}

Infection begins with the interaction of the viral glycoproteins Gn and Gc and β -integrin receptors on target cell membranes. Immature [dendritic cells](#) near endothelial cells transport virions from lymphatic vessels to local lymph nodes to infect more endothelial cells. These cells produce antigens to induce an immune response, especially those of macrophages and [CD8+ T lymphocytes](#). After activation of the immune system, cytotoxic T lymphocytes produce pro-inflammatory cytokines that can damage infected endothelial cells, which can lead to increased vascular permeability and inflammatory reactions. These cytokines include interferon (IFN), [interleukins](#) (IL-1, IL-6, and IL-10), and [tumor necrosis factor](#)- α (TNF- α). Elevated IL-6 levels are associated with low platelet count and renal failure.^{[2][3][14]}

HFRS mainly affects the kidneys and blood vessels, though other parts of the body, such as the nervous system, spleen, and liver, can also be affected.^[2] While most major organs become infected, organ failure does not occur in most, as pathology is different from organ to organ. In the tubular epithelium of the kidneys, tight junction proteins are redistributed, and tubular necrosis occurs, which impairs the kidney tubules and causes **proteinuria and hematuria**. Glomerular endothelium infection in the kidneys causes decreased function of glomerular ZO-1 expression, which reduces the function of the glomerulus as a molecular filter by increasing glomerular permeability, which causes proteinuria and hematuria. Liver infection does not lead to significant dysfunction since hepatic blood vessels are already relatively permeable. In the spleen, infection of immune cells can cause over-activation of immature lymphocytes elsewhere and facilitate prolonged spread of the virus throughout the body.^[14]

Immunology

The innate immune system recognizes hantavirus infection by the detection of viral RNA. This triggers production of interferons, immune cytokines, and [chemokines](#) and activation of [signaling pathways](#) to respond to viral infection.^{[22][26]} [Monocytes](#) respond to infection by using [phagocytosis](#) to consume virus particles.^[1] [IgM](#) antibodies to the viral surface glycoproteins are created to bind to and disable virus particles. During infection, the anti-Gc IgM response is stronger than the anti-Gn IgM response. Long term, the anti-Gc [IgG](#) response is stronger than the anti-Gn IgG response. Anti-N antibodies are produced during infection but are not involved in neutralizing virions.^[23] Long non-coding RNA and [microRNA](#) are involved in inhibiting hantavirus infection.^[1]

Pathogenic hantaviruses can modify the immune response and evade interferon-mediated antiviral signaling pathways in various ways, including by inhibiting interferon activation, inhibiting the activation of [transcription factors](#), and inhibiting downstream [JAK/STAT](#)

[signaling](#).^{[1][22]} They can also regulate cell death to aid in completing their life cycle through [autophagy](#), [apoptosis](#), and [pyroptosis](#). Hantaan virus infection and NP and GP protein expression have been shown to promote the production of microRNAs that reduce the expression of pro-inflammatory cytokines. Furthermore, hantaviruses appear to induce cell stress via endoplasmic reticulum stress while inhibiting the [cellular response to stress](#), which helps the virus escape host stress signaling.^[1]

Prevention

Reducing the risk of exposure to rodents at home, one's workplace, and when camping^[20] prevents hantavirus infection. Rodent control methods such as [rodenticides](#), traps, and cats have been proposed as ways to control the rodent population. Cleaning and disinfecting human living spaces by removing rodent food sources can prevent the contamination of food and other items with hantaviruses from rodent excretions and secretions.^[2] Preventing rodents from entering one's house, removing potential nesting sites around one's house,^[34] sweeping areas likely inhabited by rodents,^[3] covering trash cans, cutting grass, spraying water to prevent dust before activities, and installing public warning signs in endemic areas can help to reduce contact with rodents.^{[5][35]}

People at high risk of infection, including pest exterminators,^[36] **people who work in agriculture, forestry, and animal husbandry** can take preventive measures such as wearing masks to prevent exposure to hantaviruses.^[2] In high risk groups, vaccines may be necessary. Ventilation of rooms before entering, using rubber gloves and disinfectants, and using respirators to avoid inhaling contaminated particles while cleaning up rodent-infested areas reduce risk of hantavirus infections.^[34] Hantaviruses can be inactivated by heating at 60 degrees Celsius for 30 minutes, or with organic [solvents](#), [hypochlorite](#) solvents, and [ultraviolet light](#).^{[2][22]}

[Vaccines against hantavirus](#) infection has been approved in South Korea and China. In South Korea, an inactivated [whole virus vaccine](#) called Hantavax has been marketed since 1990 to protect against HFRS caused by the Hantaan virus and Seoul virus. The vaccine has not shown to prevent infection^[37] but is associated with reduced disease severity.^{[35][38]} Due to a diminishing vaccine-induced antibody response, frequent booster doses are required.^[3] A similar vaccine was approved for use in China in 2005, which provides immunity for up to 33 months.^{[2][38]} Other vaccines have been researched in animal models such as recombinant vaccines, DNA vaccines,^[2] virus-like particle (VLP) vaccines, recombinant vector vaccines,^{[20][34]} and [subunit vaccines](#). These vaccines have shown varying degrees of effectiveness.^{[4][7][22][37][38]}

Diagnosis

Initial diagnosis of hantavirus infection can be made based on epidemiological information and clinical symptoms. **Confirmation of infection also includes detection of hantavirus nucleic acid, proteins, or hantavirus-specific antibodies.**^[2] **Key findings of laboratory findings include thrombocytopenia, leukocytosis, hemoconcentration, elevated serum [creatinine](#) levels, hematuria, and proteinuria.** Hantavirus-specific IgM and IgG antibodies are usually present at the onset of symptoms. IgM is detectable in the acute phase of infection but declines over a period of 2–6 months.^[3] The response of IgG antibodies is low during infection but grows over time^[23] and lasts for one's lifetime.^[3]

Neutralization tests, immunofluorescent assays (IFAs), and [enzyme-linked immunosorbent assays](#) (ELISAs) can be used to detect antibodies to hantavirus infection in blood, usually anti-N or anti-Gc antibodies.^{[3][23]} ELISA is inexpensive and can be used at any

point during the illness,^[5] but results may need to be confirmed by other methods. Rapid immunochromatographic IgM antibody tests can also be used for diagnosis^[3] as they are simple to carry out and inexpensive.^[5] Western blotting can detect hantavirus antigen in tissue samples,^[20] but is costly and time consuming.^[5]

Both traditional and real-time **polymerase chain reaction** (PCR) tests of blood, saliva, **BAL** fluids, and tissue samples can be used. There is a possibility of false negatives with PCR if there are low levels of virus in the blood, and PCR testing is prone to cross-contamination, **but when performed during the onset of infection, it may predict disease severity**. PCR can also be used for postmortem diagnosis and for analysis of organ involvement, and it can be used to sequence the virus's genome to identify which specific virus is causing illness.^{[3][5]}

Management

Treatment of HFRS is supportive in nature. The specific form of treatment depends on the phase of the disease and clinical presentation. Intravenous hydration and electrolyte therapy are essential to maintain blood pressure and electrolyte balance. Platelet transfusions can be used to reduce mortality in cases of severe thrombocytopenia and disseminated intravascular coagulation to control bleeding. If acute kidney injury occurs, then intermittent hemodialysis is used as the first option, and continuous renal replacement therapy in critical HFRS cases.^{[2][4][7][38]} No specific antiviral drugs exist for hantavirus infection, but **ribavirin and favipiravir have shown varying efficacy and safety**.^[2]

Prophylactic use of ribavirin and favipiravir in early infection or post-exposure shows some efficacy, and both have shown some anti-hantavirus activity in vivo and in vitro. Ribavirin is effective in the early treatment of HFRS with some limitations, such as toxicity at high doses and the potential to cause hemolytic anemia.^[2] Anemia is reversible upon completion of ribavirin treatment. In some instances, ribavirin may cause excess bilirubin in the blood (hyperbilirubinemia), abnormally slow heartbeat (sinus bradycardia), and rashes.^[34] Administering ribavirin after the onset of the cardiopulmonary phase of HPS is not an effective treatment,^[22] and currently there is no recommendation for the use of ribavirin to treat HFRS or HPS.^{[3][20]}

Favipiravir has greater efficacy than ribavirin, without anemia as a side effect. In hamster models, oral administration of favipiravir twice per day of 100 mg/kg significantly reduced viral load in the blood and antigen load in the lungs. Oral administration before viremia prevented HPS, but not after this.^{[2][20][22][34]} Several other approaches have been researched as potential anti-hantavirus treatments, including small-molecule compounds that target the virus or host, peptides, **alligator weed**,^[24] antibodies, and classical antiviral drugs, tested mainly to block hantavirus entry into cells or restrain virus replication. Host-targeting medicines are designed to improve vascular function or rebuild homeostasis.^{[5][7][38]}

Prognosis

Prognosis is good in most cases. The case fatality rate ranges from less than 1% to 15%,^{[2][20][30][35]} depending on the virus and location. **In China, where most cases are caused by the Hantaan virus and Seoul virus,^[7] the case fatality rate is about 2.89%.^[39] In South Korea, the case fatality rate is 1–2%.^[2] The global case fatality rate for Seoul virus is around 1%.** Pathogenicity of Dobrava-Belgrade virus varies by genotype: infection with the deadlier genotypes results in death for 10–15% of the infected, while for the milder genotypes, the case fatality rate is 0.3–0.9%. Puumala virus infection has a case fatality rate of

0.1–0.4%.^[2] Post-infection [Guillain–Barré Syndrome](#) has been reported on rare occasions, indicated by acute limb weakness.^[9] Weakness and fatigue are common during recovery.^[7]

People who are over 60 years of age are at an increased likelihood of death, as are tobacco smokers, people who have diabetes, or high blood pressure (hypertension). Deaths typically involve the development of severe complications, and death is more common among those who experience septic shock, ARDS, heart failure, irregular heartbeat, and pancreatitis.^{[10][40][41]} Death is also associated with lower platelet count, elevated white blood cell count, and higher aspartate aminotransferase and alanine aminotransferase.^[41]

The antibody response to hantavirus infection is strong and long-lasting. Early production of neutralizing antibodies (nAbs) that target the surface glycoproteins is directly associated with increased likelihood of survival.^{[25][37]} **High nAb counts can be detected as long as ten years after infection.**^[23] Higher levels of IL-6, in contrast, are associated with more severe disease, and deceased individuals have higher IL-6 levels than survivors.^[37] Genetic susceptibility to severe illness is related to one's human leukocyte antigen (HLA) type, which also depends on the hantavirus, as increased susceptibility to different hantaviruses is associated with different HLA haplogroups.^{[2][3]}

Epidemiology

Most cases of HFRS are caused by just four viruses: Hantaan virus, Seoul virus, Puumala virus, and Dobrava-Belgrade virus.^{[7][42]} The geographic distribution of individual hantaviruses is directly tied to the geographic distribution of their natural reservoir.^[3] The Seoul virus is found worldwide due to the global distribution of its hosts, the [brown rat](#), but mainly circulates in China and South Korea and accounts for about a quarter of all HFRS cases.^[2] In Europe, Dobrava-Belgrade virus and Puumala virus spread,^[2] the latter of which is more common. Infections in Europe are most common in Germany, Finland, and Russia.^[40] The number of cases in Europe has gradually increased over time. In China and Korea, the number of cases has declined significantly.^[38]

More than 100,000 cases of HFRS are reported each year.^[33] **From 1950 to 2007, more than 1.5 million cases and more than 45,000 deaths were recorded in China,**^[34] where 70–90%^[33] of HFRS cases are reported, most of which are caused by the Hantaan virus and Seoul virus.^[7] These cases are distributed throughout China but are more common in the east,^[38] and spike during winter and spring.^[18] Since 2010, HFRS incidence in China has declined significantly, from 0.99 per 100,000 population in 2010 to 0.31 per 100,000 in 2024, while the case fatality rate fell from 1.27% to 0.28% over the same period.^[43] In South Korea, 400–600 cases occur each year.^[2] **Finland is the most affected country in Europe, with 1,000–3,000 cases every year.**^[44] More than 10,000 cases of NE are diagnosed annually.^[25] Infection is more common in men.^[41]

Environment

Further information: [Effects of climate change on hantavirus](#)

Rodent species that carry hantaviruses inhabit a diverse range of habitats, including desert-like biomes, equatorial and tropical forests, swamps, savannas, fields, and salt marshes.^[29] **The seroprevalence of hantaviruses in their host species has been observed to range from 5.9% to 38% in the Americas, and 3% to about 19% worldwide, depending on testing method and location.**^{[22][45]} In some places, such as South Korea, routine trapping of wild rodents is performed to surveil hantavirus circulation.^[35] High humidity can benefit rodent

populations in warm climates, where it may positively impact plant growth and thus food availability.^[29] Increased forest coverage is associated with increased hantavirus incidence, particularly in Europe.^[33]

Rainfall is consistently associated with hantavirus incidence patterns. Heavy rainfall is a risk factor for outbreaks in the following months,^[18] but may negatively affect incidence by flooding rodent burrows and nests.^[46] Infections are more common in the wet season than the dry season.^[29] Low rainfall and drought are associated with decreased incidence since such conditions result in a smaller rodent population,^[46] but displacement of rodent populations via drought or flood can lead to an increase in rodent-human interactions and infections.^[29] In Europe, however, no association between rainfall and incidence has been observed.^[46]

Temperature has varying effects on hantavirus transmission. Higher temperatures create unfavorable environments for virus survival, but it can cause rodents to seek shelter from heat in human settings and are beneficial for aerosol production.^{[3][29]} Lower temperature can prolong virus survival outside a host.^[29] Higher average winter temperature is associated with reduced survival of bank voles, the natural reservoir of Puumala virus, but increased survival of striped field mice in China, the natural reservoirs of Hantaan virus.^[46] Extreme temperatures, whether hot or cold, are associated with lower disease incidence.^[18]

History

Hantavirus hemorrhagic disease was likely first described in the [Yellow Emperor's Internal Canon](#) in Imperial China during the [Warring States Period](#) of 475–221 BCE.^[28] Hantaviruses have been suggested as a cause of "trench nephritis" in soldiers during the [US Civil War](#) and in British soldiers in Flanders, Belgium^[28] during the [First World War](#). The disease was also mentioned in East Asia, where it was probably endemic, and was first described scientifically in [Vladivostok](#) in 1913–1914.^[31] During the [Second World War](#) in 1942, an outbreak of disease with symptoms characteristic of hantavirus infection occurred in [Salla](#), Eastern Lapland, Finland, among German and Finnish soldiers. This outbreak was later reported in 1980 to be caused by a virus transmitted by bank voles and was named the Puumala virus.^[31] Also during the war, around 10,000 Japanese soldiers stationed in [Manchuria](#) developed HFRS.^[5]

HFRS was common amongst United Nations soldiers stationed near the Hantan river^[25] during the Korean War, where it was first identified in 1951^[2] and named "Korean hemorrhagic fever" and "epidemic hemorrhagic fever".^[28] About 3,200 cases occurred from 1951 to 1954.^[31] After the war, in 1976 in South Korea, trapped striped field mice were tested, and antigens in their lungs were shown to react to antibodies in sera from survivors of Korean hemorrhagic fever. A specific agent could not be isolated in cell cultures, but the disease was shown to be caused by an infectious agent, and other known causes of hemorrhagic fever were ruled out.^[28] **In 1978, the virus was isolated for the first time from the lung tissue of a striped field mouse and named the Hantaan virus.**^[4] Retrospective analysis on sera from war veterans later confirmed that the Hantaan virus was responsible for the epidemic during the Korean War.^[31]

The first successful culturing of the virus was in 1981, in which a hantavirus extracted from naturally infected rodents trapped near Songnaeri, South Korea, was transmitted through mice with no history of infection four times. Originally named "KHF strain 76-118", it was renamed to "Hantaan virus, strain 76-118" after the Hantan River and is now commonly called Hantaan virus. Initially thought to be related to arenaviruses, which are also transmitted by rodents, analysis of the structure of hantaviruses suggested it instead belonged to the bunyavirus family, which previously were only known to be transmitted by arthropods.^[28] By 1980, studies confirmed that other viruses related to the Hantaan virus caused long-known

diseases throughout Eurasia. These diseases had a variety of names, so in 1982, the World Health Organization agreed to name the disease "**hemorrhagic fever with renal syndrome (HFRS)**".^{[5][28]} Further analysis of Hantaan virus showed that it possessed the characteristics of bunyaviruses but did not serologically cross-react with other known bunyaviruses, so a new genus, *Hantavirus*, was proposed to accommodate Hantaan virus and related viruses.^[28] In 1985, this group of viruses were given the name "hantaviruses",^[24] and in 1987, the genus was recognized by [International Committee on Taxonomy of Viruses](#).^[47]

See also

- [Hantavirus pulmonary syndrome](#)
- [MV Hondius hantavirus outbreak](#)
- [1993 Four Corners hantavirus outbreak](#)
- [2012 Yosemite hantavirus outbreak](#)

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Hantavirus pulmonary syndrome



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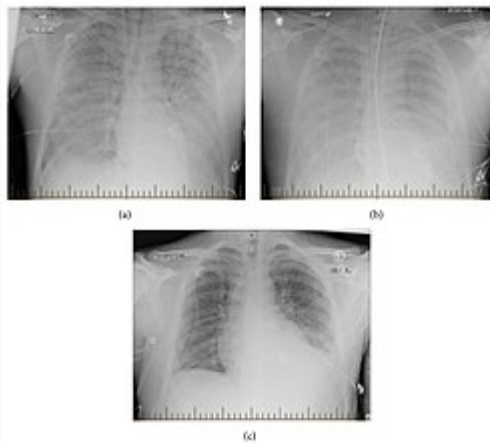
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Hantavirus pulmonary syndrome



Progression of hantavirus pulmonary syndrome

[Specialty](#)

[Pulmonology](#)

[Symptoms](#)

Fever, cough, shortness of breath, headaches, muscle pains, lethargy, nausea, diarrhea

[Complications](#)

Respiratory failure, cardiac failure

[Causes](#)

[Hantaviruses](#) spread by rodents

Prevention	Rodent control
Treatment	Supportive, including mechanical ventilation
<u>Medication</u>	None
<u>Prognosis</u>	Poor, 30–60% case fatality rate

Hantavirus pulmonary syndrome (HPS), also called **hantavirus cardiopulmonary syndrome (HCPS)**, is a severe respiratory disease caused by [hantaviruses](#). The main features of illness are **microvascular leakage** and **acute respiratory distress syndrome**. **Symptoms occur anywhere from one to eight weeks after exposure to the virus and come in three distinct phases.** First, there is an early phase with **flu-like symptoms** such as fever, muscle aches, headache, and shortness of breath, as well as low **platelet** count. Second, there is a **cardiopulmonary** phase during which people experience elevated or irregular heart rate, **cardiogenic shock**, and pulmonary **capillary leakage**, which can lead to respiratory failure, low blood pressure, and buildup of fluid in the lungs and chest cavity. The final phase is recovery, which typically takes months, but **difficulties with breathing can persist for up to two years.** The disease has a case fatality rate of 30 to 60 percent. Death usually occurs suddenly during the cardiopulmonary phase.

HPS is caused mainly by infection with New World hantaviruses in the Americas. In North America, [Sin Nombre virus](#) is the most common cause of HPS and is transmitted by the [western deer mouse](#). In South America, [Andes virus](#) is the most common cause of HPS and is transmitted mainly by the [long-tailed pygmy rice rat](#). In their rodent hosts, these hantaviruses cause a persistent, asymptomatic infection. **Transmission occurs mainly through inhalation of aerosols that contain rodent saliva, urine, or feces, but can also occur through contaminated food, bites, and scratches.** Vascular [endothelial cells](#) and [macrophages](#) are the primary cells infected by hantaviruses, **and infection causes abnormalities with blood clotting**, all of which result in fluid leakage responsible for the more severe symptoms. Recovery from infection likely confers lifelong protection.

The main way to prevent infection is to avoid or minimize contact with rodents that carry hantaviruses. Removing sources of food for rodents, safely cleaning up after them, and preventing them from entering one's house are all important means of protection. People who are at risk of interacting with infected rodents can wear masks to protect themselves. No vaccines exist that protect against HPS. Initial diagnosis of infection can be made based on [epidemiological](#) information and symptoms. Confirmation of infection can be done by testing for hantavirus nucleic acid, proteins, or hantavirus-specific antibodies. Supportive treatment is always performed for HPS and entails continual cardiac monitoring and respiratory support, including [mechanical ventilation](#), [extracorporeal membrane oxygenation](#) (ECMO), and [hemofiltration](#). No specific antiviral drugs exist for hantavirus infection.

In North America, dozens of HPS cases occur each year, while in South America, more than 100 cases occur every year. Isolated cases and small outbreaks have occurred in

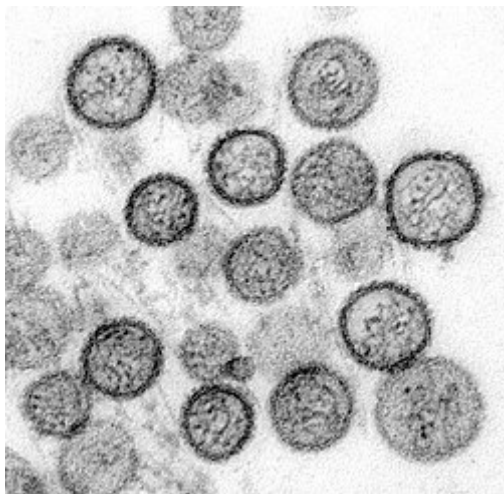
Europe and Turkey. The distribution of viruses that cause HPS is directly tied to the distribution of their natural reservoir. Transmission is also greatly influenced by environmental factors such as rainfall, temperature, and humidity, which affect the rodent population and virus transmissibility. The discovery of HPS came in 1993 during [an outbreak in the Four Corners region](#) of the United States, which was indirectly caused by the [El Niño climate pattern](#). Sin Nombre virus was found to be responsible for the outbreak, and since then, numerous other hantaviruses that cause HPS have been identified throughout the Americas.

Signs and symptoms

HPS symptoms occur about 1–8 weeks after exposure to the virus. The main features of the illness are microvascular leakage and acute respiratory distress syndrome (ARDS). **The disease has three phases: early (prodromal), cardiopulmonary, and recovery. Prodromal symptoms last for 1–5 days^[1] and include flu-like symptoms such as fever, headache, muscle pain (myalgia), nausea, vomiting, dizziness, chills, coughing, and shortness of breath (dyspnea), as well as low platelet count in the blood (thrombocytopenia).**^{[2][3][4]} Within 10 days, the cardiopulmonary phase begins^[5] and lasts for several days. It is marked by elevated heart rate ([tachycardia](#)), irregular heartbeats ([arrhythmias](#)), and cardiogenic shock, a condition in which the heart is unable to pump enough blood for the body. Pulmonary capillary leakage can lead to respiratory failure, buildup of fluids in the lungs ([pulmonary edema](#)), low blood pressure ([hypotension](#)), and buildup of fluid in the chest cavity between the lungs and chest wall ([pleural effusion](#)).[2][3][4]

While HPS is typically associated with cardiopulmonary symptoms, it may include renal symptoms typically associated with [hemorrhagic fever with renal syndrome](#) (HFRS),^{[3][6]} namely acute kidney injury and excess protein in urine ([proteinuria](#)), which sometimes occur during the cardiopulmonary phase.^{[2][3]} During the recovery phase, increased urination ([polyuria](#)) occurs as renal function returns.^[3] Repeated infections of hantaviruses have not been observed, so recovering from infection likely grants life-long immunity.^{[7][8]}

Virology



Transmission electron micrograph of Sin Nombre virus

Genome and structure

The genome of hantaviruses is segmented into three parts: the large (L), medium (M), and small (S) segments. Each part is a [single-stranded negative-sense RNA](#) strand, consisting of

10,000–15,000 nucleotides in total.^[4] The segments form into circles via non-covalent bonding of the ends of the genome.^[9] The L segment is about 6.6 kilobases (kb) in length^[10] and encodes [RNA-dependent RNA polymerase](#) (RdRp), which mediates [transcription](#) and replication of viral RNA. The M segment, about 3.7 kb in length,^[10] encodes a glycoprotein precursor that is co-translated and cleaved into Gn and Gc. Gn and Gc bind to cell receptors, regulate immune responses, and induce protective antibodies. The S segment is around 2.1 kb in length^[10] and encodes the N protein, which binds to and protects viral RNA. An open reading frame in the N gene on the S segment^[11] of some hantaviruses also encodes the non-structural protein NS that inhibits [interferon](#) production in host cells. The untranslated regions at the ends of the genome are highly conserved and participate in the replication and transcription of the genome.^{[2][4][12]}

Individual hantavirus particles (virions) are usually spherical, but may be oval, pleomorphic,^[13] or tubular.^[4] The diameter of the virion is 70–350 nanometers (nm).^[10] The [lipid envelope](#) is about 5 nm thick. Embedded in the envelope are the surface spike glycoproteins Gn and Gc,^[2] which are arranged in a lattice pattern.^[10] Each surface spike is composed of a tetramer of Gn and Gc (four units each) that has four-fold rotational symmetry and extends about 10 nm out from the envelope.^[10] Gn forms the stalk of the spike and Gc the head.^[4] Inside the envelope are helical nucleocapsids made of many copies of the nucleocapsid protein N, which interact with the virus's genome and RdRp.^[2] **Hantaviruses do not encode matrix proteins to assist with structuring the virion, so how surface proteins organize into a sphere with a symmetrical lattice is not yet known.**^[14]

Life cycle

Vascular endothelial cells and macrophages are the primary cells infected by hantaviruses.^[1] [Podocytes](#), tubular cells, [dendritic cells](#), and [lymphocytes](#) can also be infected.^{[2][3]} Attachment and entry into the host cell is mediated by the binding of the viral glycoprotein spikes to host cell receptors, particularly $\beta 1$ and $\beta 3$ [integrins](#).^[1] Decay acceleration factors, complement receptors, and, for New World hantaviruses, protocadherin-1 have also been proposed to be involved in attachment.^{[3][14]} After attachment, hantaviruses rely on several ways to enter a cell, including micropinocytosis, [clathrin](#)-independent receptor-mediated [endocytosis](#) and [cholesterol](#)- or [caveolae](#)-dependent endocytosis.^{[2][3][4]} Old World hantaviruses use clathrin-dependent endocytosis while New World hantaviruses use clathrin-independent endocytosis.^{[3][15][16]}

After entering a cell, virions form vesicles that are transported to early [endosomes](#), then late endosomes and lysosomal compartments. A decrease in pH then causes the viral envelope to fuse with the endosome or [lysosome](#).^{[10][15][16]} This fusion releases viral ribonucleoprotein complexes into the cell cytoplasm, initiating transcription and replication by RdRp.^{[2][3][10]} RdRp transcribes viral -ssRNA into complementary positive-sense strands, then [snatches](#) 5' ("five prime") ends of host [messenger RNA](#) (mRNA) to prepare mRNA for translation by host ribosomes to produce viral proteins.^{[10][4]} Complementary RNA strands are also used to produce copies of the genome, which are encapsulated by N proteins to form RNPs.^{[2][3][10]}

During virion assembly, the glycoprotein precursor is cleaved in the endoplasmic reticulum into the Gn and Gc glycoproteins by host cell signal peptidases.^{[2][4]} Gn and Gc are modified by N-glycan chains, which stabilize the spike structure and assist in assembly in the [Golgi apparatus](#) for Old World hantaviruses^[2] or at the cell membrane for New World hantaviruses.^[3] Old World hantaviruses obtain their viral envelope from the Golgi apparatus and are then transported to the cell membrane in vesicles to leave the cell via [exocytosis](#). On the

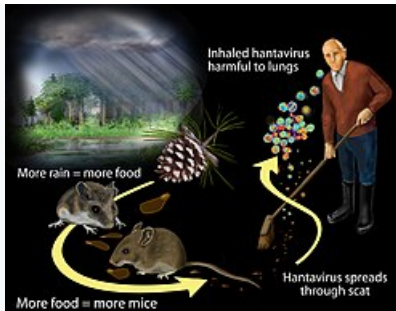
other hand, New World hantavirus RNPs are transported to the cell membrane, where they bud from the surface of the cell to obtain their envelope and leave the cell.^{[3][10][16]}

Evolution

The most common form of evolution for hantaviruses is [mutations](#) through single nucleotide substitutions, insertions, and deletions.^[2] Hantaviruses are usually restricted to individual [natural reservoir](#) species and evolve alongside their hosts,^[2] but this one-species-one-hantavirus relationship is not true for all hantaviruses. The exact evolutionary history of hantaviruses is likely obscured by many instances of genome [reassortment](#), host spillover, and host-switching.^[17] Because hantaviruses have segmented genomes, they are capable of [genetic recombination](#) and reassortment in which segments from different viruses can combine to form new viruses. This occurs often in nature and facilitates the adaptation of hantaviruses to multiple hosts and ecosystems. In particular, reassortment in NWHVs of the S and M segments has been observed in rodents.^[2] Diploid progeny are also possible, in which virions may possess two of the same segment from two parent viruses.^[18]

Mechanism

Transmission



Hantavirus spread

The [long-tailed pygmy rice rat](#), the primary reservoir of Andes virus

The [western deer mouse](#), the natural reservoir of Sin Nombre virus^[note 1]

Rodents transmit hantaviruses that cause illness in humans. In rodents, hantaviruses usually cause an asymptomatic, persistent infection. Infected animals can spread the virus to uninfected animals through aerosols or droplets from their feces, urine, saliva,^[12] and blood,^[22] through consumption of contaminated food, from virus particles shed from skin or fur,^[10] via grooming,^[4] or through biting and scratching. Hantaviruses can also spread through the fecal-oral route and across the placenta during pregnancy [from mother to child](#). They can survive for 10 days at room temperature,^[2] 15 days in a temperate environment,^[23] and more than 18 days at 4 °C (39 °F), which aids in the transmission of the virus.^[2] Environmental conditions favorable to the reproduction and spread of rodents are known to increase disease transmission.^[24] **Living in a rural environment, or in unhygienic settings, and interacting with environments shared with hosts are the biggest risk factors for infection, especially people who are hikers,^[12] farmers and forestry workers,^[23] as well as those in mining, the military,^{[10][25]} and [zoology](#).**^[3]

Rodents can transmit hantaviruses to humans through aerosols or droplets from their excretions and through the consumption of contaminated food. Rodent bites and

scratches can also transmit hantaviruses to humans. Researchers often claim that the Andes virus is the only hantavirus that can spread from person to person, usually after coming into close contact with an infected person. It can also reportedly spread through human saliva, airborne droplets, and to newborns through breast milk and the placenta.^[2] A systematic review of research, however, found the claims of human-to-human transmission not to be supported by sufficient evidence.^[24]

Man-made built environments can facilitate hantavirus transmission. Deforestation and excessive agriculture may destroy rodents' natural habitat.^[3] The expansion of agricultural land is associated with a decline in predator populations, which enables hantavirus host species to use farm monocultures as nesting and foraging sites. **Agricultural sites built in proximity to rodents' natural habitats can facilitate the proliferation of rodents as they may be attracted to animal feed.**^{[22][26]} **Sewers and stormwater drainage systems may be inhabited by rodents, especially in areas with poor solid waste management.** Maritime trade and travel have also been implicated in the spread of hantaviruses.^[22] Research results are inconsistent on whether urban living increases or decreases hantavirus incidence.^[26] Seroprevalence, which shows past infection to hantavirus, is consistently higher in occupations and areas that have greater exposure to rodents.^[27] Poor living conditions on battlefields, in military camps, and in refugee camps make soldiers and refugees at great risk of exposure as well.^[25]

Pathophysiology

Infection begins with the interaction of the viral glycoproteins Gn and Gc with [β₃-integrin](#) receptors on target cell membranes.^[6] The main causes of illness are increased vascular permeability, decreased platelet count, and overreaction by the immune system.^{[2][3]} The virus mainly targets endothelial cells and macrophages. Clusters of virions also cause erroneous platelet aggregation and activation via β₃-integrin.^[6]

The increased vascular permeability appears to be the result of infected cells producing [vascular endothelial growth factor](#) (VEGF), which activate VEGFR2 receptors on endothelial cells, which increases paracellular permeability.^[28] Oxygenation problems and [bradykinin](#) are also thought to play a role in increased vascular permeability during infection.^{[3][6]}

Coagulation abnormalities may also occur. Virus particles cluster on the surface of endothelial cells, which causes a misallocation of platelets to infected endothelial cells. Disseminated coagulating without signs of hemorrhaging, major blood clots, and damage to vascular endothelial cells during infection may negatively affect coagulation and platelet levels and promote further vascular leaking and hemorrhaging.^{[3][6]}

Immature dendritic cells near endothelial cells transport virions from lymphatic vessels to local lymph nodes to infect more endothelial cells. These cells produce antigens to induce an immune response, especially those of macrophages and [CD8+ T lymphocytes](#). After activation of the immune system, cytotoxic T lymphocytes produce pro-inflammatory [cytokines](#) that can damage infected endothelial cells, which can lead to increased vascular permeability and inflammatory reactions. These cytokines include interferon (IFN), [interleukins](#) (IL-1, IL-6, and IL-10), and [tumor necrosis factor-α](#) (TNF-α). Elevated IL-6 levels are associated with low platelet count and renal failure.^{[2][3][6]}

HPS mainly affects the heart and lungs, but other parts of the body, such as the nervous system, spleen, and liver, can also be affected.^[2] **While most major organs become**

infected, organ failure does not occur in most, as pathology is different from organ to organ. Infected lungs experience inflammation and fluid buildup due to immune cell infiltration and endothelial cell activation. For the same reason, infection of the heart leads to interstitial fluid buildup that contributes to myocardial dysfunction and cardiogenic shock. Liver infection does not lead to significant dysfunction since hepatic blood vessels are already relatively permeable. In the spleen, infection of immune cells can cause over-activation of immature lymphocytes elsewhere and facilitate prolonged spread of the virus throughout the body.^[6]

Immunology

The innate immune system recognizes hantavirus infection by the detection of viral RNA. This triggers production of interferons, immune cytokines, and [chemokines](#) and activation of [signaling pathways](#) to respond to viral infection.^{[10][15]} [Monocytes](#) respond to infection by using [phagocytosis](#) to consume virus particles.^[29] [IgM](#) antibodies to the viral surface glycoproteins are created to bind to and disable virus particles. During infection, the anti-Gc IgM response is stronger than the anti-Gn IgM response. Long term, the anti-Gc [IgG](#) response is stronger than the anti-Gn IgG response. Anti-N antibodies are produced during infection but are not involved in neutralizing virions.^[11] Long non-coding RNA and [microRNA](#) are involved in inhibiting hantavirus infection.^[29]

As described above, transport of virions in the lymphatic system exposes more endothelial cells to the virus and overreaction of the immune system is part of the pathology.^{[2][3][6]}

Pathogenic hantaviruses can modify the immune response and evade interferon-mediated antiviral signaling pathways in various ways, including by inhibiting interferon activation, inhibiting the activation of [transcription factors](#), and inhibiting downstream [JAK/STAT signaling](#).^{[10][29]} They can also regulate cell death to aid in completing their life cycle through [autophagy](#), [apoptosis](#), and [pyroptosis](#). Hantaan virus infection and NP and GP protein expression have been shown to promote the production of microRNAs that reduce the expression of pro-inflammatory cytokines. Furthermore, **hantaviruses appear to induce cell stress** via endoplasmic reticulum stress while inhibiting the [cellular response to stress](#), which helps the virus escape host stress signaling.^[29]

Prevention

Reducing the risk of exposure to rodents at home, one's workplace, and when camping^[4] prevents hantavirus infection. **Rodent control methods such as [rodenticides](#), traps, and cats have been proposed as ways to control the rodent population.** Preventing rodents from entering one's house, removing potential nesting sites around one's house,^[28] covering trash cans, cutting grass, and installing public warning signs in endemic areas can help to reduce contact with rodents and their excretions.^{[12][30]} In addition, spraying water before activities can help reduce the generation of dust.^[30]

Cleaning and disinfecting human living spaces by removing rodent food sources can prevent the contamination of food and other items with hantaviruses from rodent excretions and secretions.^[2] **Hantaviruses can be inactivated by heating them at 60 °C (140 °F) for 30 minutes, or by exposing them to organic [solvents](#), [hypochlorite](#) (bleach) solutions, household disinfectant,^[31] or [ultraviolet light](#) (including sunlight).**^{[2][10]} Sweeping and vacuuming should be avoided as there is a risk of aerosolizing the excretions.^[31]

People at high risk of infection, including pest exterminators^[32] and people who work in agriculture, forestry, and animal husbandry can take preventive measures to prevent exposure to hantaviruses.^[2] Rubber or plastic gloves should be worn during cleanup and disinfection of wild rodent excretions and corpses.^[31] It is also advised to ventilate the room before entering and to wear a [respirator](#).^[28] **Heavy infestations should be handled wearing more complete [personal protective equipment](#): disposable coveralls (if possible), rubber boots or disposable shoe covers, rubber/latex/vinyl gloves, protective goggles, and a HEPA respirator (either the negative-pressure/air-purifying half-mask or the powered respirator).**^[31]

Pet rodents should be kept away from wild rodents. New pets should be tested for hantavirus.^[32] Pet rodent items should be cleaned as often as human items; gloving is not required if the rodent is not infected.^[33]

Diagnosis

Initial diagnosis of hantavirus infection can be made based on epidemiological information and clinical symptoms. **Infection can be confirmed through the detection of hantavirus nucleic acid, proteins, or hantavirus-specific antibodies.**^[2] **Key laboratory findings include thrombocytopenia, leukocytosis, hemoconcentration, elevated serum [creatinine](#) levels, hematuria, and proteinuria. Hantavirus-specific IgM and IgG antibodies are usually present at the onset of symptoms.** IgM is detectable in the acute phase of infection but declines over a period of 2–6 months.^[3] The response of IgG antibodies is low during infection but grows over time^[11] and lasts for one's lifetime.^[3]

Neutralization tests, immunofluorescent assays (IFAs), and [enzyme-linked immunosorbent assays](#) (ELISAs) can be used to detect antibodies to hantavirus infection in blood, usually anti-N or anti-Gc antibodies.^{[3][11]} ELISA is inexpensive and can be used at any point during the illness,^[12] but results may need to be confirmed by other methods. **Rapid immunochromatographic IgM antibody tests can also be used for diagnosis^[3] as they are simple to carry out and inexpensive.**^[12] Western blotting can detect hantavirus antigen in tissue samples,^[4] but is costly and time-consuming.^[12]

Both traditional and real-time [polymerase chain reaction](#) (PCR) tests of blood, saliva, [BAL](#) fluids, and tissue samples can be used. There is a possibility of false negatives with PCR if there are low levels of virus particles in the blood, and PCR testing is prone to cross-contamination. When performed during the onset of infection, PCR may predict disease severity. PCR can be used for postmortem diagnosis and for analysis of organ involvement, and it can be used to sequence the virus's genome to identify which specific virus is causing illness.^{[3][12]}

Management

Supportive treatment is always performed for HPS. The specific treatment depends on the disease phase and clinical presentation. Treatment entails continual cardiac monitoring and respiratory support, including mechanical ventilation, [extracorporeal membrane oxygenation](#) (ECMO), and hemofiltration.^{[1][2][34]} If HPS is suspected, then a person may be preemptively prepared for ECMO upon hospital arrival.^[35] Since high nAb titers are associated with favorable outcomes, fresh frozen plasma and sera from recovered individuals has been used to treat HPS and lower the case fatality rate.^{[36][37]} No specific antiviral drugs exist for hantavirus infection, but ribavirin and favipiravir have shown varying efficacy and safety.^[2]

Prophylactic use of [ribavirin](#) and [favipiravir](#) in early infection or post-exposure shows some efficacy, and both have shown some anti-hantavirus activity in vivo and in vitro. Ribavirin is effective in the early treatment of HFRS with some limitations, such as toxicity at high doses and the potential to cause hemolytic anemia.^[2] Anemia is reversible upon completion of ribavirin treatment. In some instances, ribavirin may cause excess bilirubin in the blood (hyperbilirubinemia), abnormally slow heartbeat (sinus bradycardia), and rashes.^[28] The administration of ribavirin after the onset of the cardiopulmonary phase of HPS has not been shown to be an effective treatment^[10] and currently there is no recommendation for the use of ribavirin to treat HFRS or HPS.^{[3][4]}

Favipiravir, in comparison to ribavirin, has shown greater efficacy without anemia as a side effect. In hamster models, oral administration of favipiravir twice per day of 100 mg/kg significantly reduced viral load in the blood and antigen load in the lungs. Oral administration before [viremia](#) prevented HPS, but not after this.^{[2][4][10][28]} Several other approaches have been researched as potential anti-hantavirus treatments, including small-molecule compounds that target the virus or host, peptides, [alligator weed](#),^[13] antibodies, and classical antiviral drugs, tested mainly to block hantavirus entry into cells or restrain virus replication. Host-targeting medicines are designed to improve vascular function or rebuild homeostasis.^{[1][12][34]}

Prognosis

The prognosis for HPS is often poor. The case fatality rate of HPS ranges from 30% to 60%.^{[2][4][24][30]} Death usually occurs 2–10 days after the onset of illness^[10] and occurs suddenly during the cardiopulmonary phase of illness.^{[2][3]} Andes virus infection has a case fatality rate of about 40%, and Sin Nombre virus a case fatality rate of 30–35%.^[2] It typically takes a few months to recover from illness fully.^[3] Difficulties with breathing, however, can persist for up to two years.^[1]

The antibody response to hantavirus infection is strong and long-lasting. Early production of neutralizing antibodies (nAbs) that target the surface glycoproteins is directly associated with increased likelihood of survival.^{[14][36]} High nAb counts can be detected as long as ten years after infection.^[11] Higher levels of IL-6, in contrast, are associated with more severe disease, and deceased individuals have higher IL-6 levels than survivors.^[36] Genetic susceptibility to severe illness is related to one's [human leukocyte antigen](#) (HLA) type, which also depends on the hantavirus, as increased susceptibility to different hantaviruses is associated with different HLA haplogroups.^{[2][3]}

Epidemiology

Most cases of HPS are caused by just two viruses: the Andes virus and the Sin Nombre virus.^[37] The Andes virus is carried primarily by the long-tailed pygmy rice rat (*Oligoryzomys longicaudatus*) and the Sin Nombre virus by the western deer mouse (*Peromyscus sonoriensis*).^{[2][4]} **The Andes virus is mainly found in Argentina, Brazil, and Chile, where it causes more than one hundred cases annually.**^[1] In North America, Sin Nombre virus causes dozens of cases each year.^[2] Overall, there are a few hundred cases of HPS every year.^[37] The geographic distribution of individual hantaviruses is directly tied to the geographic distribution of their natural reservoir.^[3] In the US and Canada, most cases occur in the west.^[38] Individual cases and small clusters of HPS have been reported in Europe^[34] and Turkey.^[39]

Environment

Further information: [Effects of climate change on hantavirus](#)

El Niño's effect on local climates

Rodent species that carry hantaviruses inhabit a diverse range of habitats, including desert-like biomes, equatorial and tropical forests, swamps, savannas, fields, and salt marshes.^[22] The [seroprevalence](#) of hantaviruses in their host species has been observed to range from 5.9% to 38% in the Americas, and 3% to about 19% worldwide, depending on testing method and location.^{[10][40]} In some places, such as South Korea, routine trapping of wild rodents is performed to surveil hantavirus circulation.^[30]

[Climate change](#) and environmental degradation increase contact areas between rodent hosts and humans, which increases potential exposure to hantaviruses. An example of this was the [1993 Four Corners outbreak in the United States](#), which was immediately preceded by elevated rainfall from the 1992–1993 [El Niño](#) warming period. This caused a substantial growth in the food supply for rodents, which led to rapid growth in their population and facilitated greater spread of the hantavirus that caused that outbreak.^{[10][22][41]}

Rainfall is consistently associated with hantavirus incidence in various patterns. Heavy rainfall is a risk factor for outbreaks in the following months,^[7] but may negatively affect incidence by flooding rodent burrows and nests.^[41] In places that have wet and dry seasons, infections are more common in the wet season than in the dry season.^[22] Low rainfall and drought are associated with decreased incidence since such conditions result in a smaller rodent population,^[41] but displacement of rodent populations via drought or flood can lead to an increase in rodent-human interactions and infections.^[22]

Temperature has varying effects on hantavirus transmission. Higher temperatures create unfavorable environments for virus survival and decrease activity levels of [Neotropic](#) rodents, but can cause rodents to seek shelter from heat in human settings, and are beneficial for aerosol production.^{[3][22]} Lower temperatures can prolong virus survival outside a host.^[22] Extreme temperatures, whether hot or cold, are associated with lower disease incidence.^[7] High humidity can benefit rodent populations in warm climates, where it may positively impact plant growth and thus food availability for rodents.^[22]

History

In 1993, an outbreak of highly lethal ARDS occurred in the [Four Corners](#) region of the United States. [This outbreak](#) was determined to be caused by a hantavirus, now named Sin Nombre virus, and represented the first confirmed instance of hantaviruses endemic to the Americas that could cause disease, as well as the discovery of a new type of disease caused by hantaviruses. Following the outbreak, the new disease was named "hantavirus pulmonary syndrome". During subsequent years, many additional hantaviruses that cause HPS were discovered in the Americas.^{[4][17][35]} Andes virus was identified in 1995.^{[1][2][17]} Human-to-human transmission of Andes virus was first reported in an outbreak in 1996 in El Bolsón, Argentina. Since then, sporadic outbreaks with reported person-to-person transmission have occurred.^[42] In 2026, Andes virus was responsible for [an outbreak aboard the MV Hondius](#) while the ship was at sea.^{[43][44]}

Notable cases

- [1993 Four Corners hantavirus outbreak](#)
- [2012 Yosemite hantavirus outbreak](#)
- February 2025, [Betsy Arakawa](#), the wife of actor [Gene Hackman](#), died from the illness.^[45]
- 2026 [MV Hondius hantavirus outbreak](#)

See also

- [Viruses portal](#)

- [Hantavirus hemorrhagic fever with renal syndrome](#)

Notes

1. Many sources identify the natural reservoir of Sin Nombre virus as the species *Peromyscus maniculatus*. In fact, the natural reservoir of the virus is the species *Peromyscus sonoriensis*. The reason for this discrepancy is that the two species previously were classified as one, both under the scientific name *Peromyscus maniculatus*. This species was reorganized in the late 2010s and split into multiple species, including *P. maniculatus* and *P. sonoriensis*. The "old" *P. maniculatus* had a range extending across most of North America, whereas the "new" *P. maniculatus* is limited to the northeastern parts of the United States east of the Mississippi River and southeastern Canada. *P. sonoriensis*, on the other hand, is found in most of the United States west of the Mississippi River and in most of southwestern Canada, which corresponds to where Sin Nombre virus infections usually occur.^{[19][20][21]}

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Hantavirus vaccine

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Transmission electron micrograph of Hantavirus by the [Centers for Disease Control and Prevention](#).

A **hantavirus vaccine** is a vaccine intended to protect against infection by viruses of the genus [Orthohantavirus](#), which can cause [hemorrhagic fever with renal syndrome](#) (HFRS) or [hantavirus pulmonary syndrome](#) (HPS). Vaccine development has included inactivated vaccines, DNA vaccine candidates, viral-vector and recombinant approaches, and early [mRNA vaccine](#) research.

The best-known licensed or locally used vaccine is **Hantavax**, an inactivated vaccine used in South Korea against HFRS caused mainly by [Hantaan virus](#). Hantavirus vaccine development is considered important because hantavirus infections cause substantial morbidity and mortality worldwide. It has been estimated that **about 1.5 million cases and 46,000 deaths occurred in China from 1950 to 2007**. The number of cases was estimated at 32,000 in Finland from 2005 to 2010 and 90,000 in Russia from 1996 to 2006.^[1]

As of 2026, no hantavirus vaccine had been approved for use in the United States, Europe or Latin America, and vaccine candidates for New World hantaviruses associated with HPS remained investigational.^[2]

Inactivated vaccines

The first hantavirus vaccine was developed in 1990, initially for use against [Hantaan virus](#), which causes one of the more severe forms of hemorrhagic fever with renal syndrome.^[3] Hantavax, a rodent-brain-derived inactivated vaccine, has been used in South Korea. In China, rodent-brain-derived and cell-culture-derived inactivated vaccines have also been used, and it has been estimated that about two million doses of such vaccines were administered annually. The wide use of these vaccines may have contributed to the decline of HFRS cases in China to fewer than 20,000 by 2007.^[1]

Other hantaviruses for which inactivated vaccines have been used or studied include [Seoul virus](#). However, available inactivated vaccines are not considered effective against all hantaviruses. **Existing Hantaan-virus-based vaccines are thought to have limited activity against European hantaviruses such as [Puumala virus](#) and [Dobrava-Belgrade virus](#), and do not address New World hantaviruses such as [Andes virus](#).**^{[1][2]}

DNA vaccine candidates

Several experimental hantavirus vaccines have used plasmid [DNA vaccine](#) platforms. These candidates generally encode hantavirus envelope glycoproteins, such as Gn and Gc, with the aim of inducing neutralizing antibody responses.

A phase 2a clinical study has evaluated a **Hantaan/Puumala virus DNA vaccine for prevention of hemorrhagic fever with renal syndrome**.^[4] Earlier phase 1 studies of Hantaan

and Puumala DNA vaccines induced neutralizing antibodies in a proportion of recipients, but development has not led to a generally licensed vaccine in the United States or Europe.^[1]

A first-in-human phase 1 trial of an Andes virus DNA vaccine evaluated safety, [reactogenicity](#) and [immunogenicity](#) in healthy adults. The vaccine encoded the Andes virus Gn and Gc envelope glycoproteins and was administered by PharmaJet's Stratis needle-free jet injection.^[5] Published results reported that the candidate vaccine was safe and induced a durable immune response in the trial population.^[6]

mRNA vaccine research

Research on [mRNA vaccines](#) for hantaviruses has accelerated after the development of mRNA vaccines for [COVID-19](#). **In 2024, researchers at the University of Texas Medical Branch reported that mRNA vaccine candidates against Andes virus protected animals in a lethal challenge model.** The university described Andes virus as a South American hantavirus with human fatality rates up to 30 percent and noted that no approved vaccine existed for the virus.^[7]

In 2026, Moderna confirmed that it was researching mRNA vaccines against hantaviruses in collaboration with the Vaccine Innovation Center of Korea University College of Medicine.^[8] Reporting on the program stated that the collaboration began in 2023, before the 2026 MV Hondius outbreak, and that the work remained preclinical, with no finished vaccine expected in the near term.^[2] Moderna's mRNA Access program states that it offers researchers use of Moderna's mRNA technology to target priority pathogens identified by organizations such as the [World Health Organization](#), the [Coalition for Epidemic Preparedness Innovations](#) and the [National Institute of Allergy and Infectious Diseases](#).^[9]

The Moderna–Korea University work has been described as an effort to develop broader mRNA-based protection against multiple hantavirus strains. According to reporting, the Korean team provides hantavirus antigen sequence information and Moderna supplies corresponding mRNA material for preclinical antigen-expression studies.^[2] Because hantaviruses are diverse and regionally variable, a broadly protective vaccine remains a technical challenge.^[2]

Other vaccine approaches

Other vaccine candidates have included recombinant, viral-vector and virus-derived approaches. Three additional candidates had entered phase I or phase II clinical trials by the early 2010s, including a recombinant vaccine and vaccines derived from Hantaan and Puumala viruses, but their prospects remained unclear.^[1]

Public-health status

No hantavirus vaccine is approved for routine use in the United States or Europe. Public-health guidance therefore continues to emphasize prevention of rodent exposure, safe cleanup of rodent-contaminated areas, early recognition of illness and supportive medical care.^[10]

The vaccine-development landscape differs by hantavirus species and clinical syndrome. Old World hantaviruses such as Hantaan and Puumala viruses are associated mainly with hemorrhagic fever with renal syndrome, while New World hantaviruses such as Andes virus and Sin Nombre virus are associated with hantavirus pulmonary syndrome. A vaccine effective against one hantavirus may not provide broad protection against all medically important hantaviruses.^{[1][2]}

In 2026, scientists at the [University of Bath](#) were reported to be working on a hantavirus vaccine against the Hantaan virus strain.^[11]

See also

- [Gou virus](#)
- [List of vaccine topics](#)
- [Seoul virus](#)
- [Vaccine-naïve](#)

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