

4. EPIDEMIOLOGY OF HUMAN DISEASE

These guidelines focus on the epidemiology of hantavirus pulmonary syndrome (HPS), a disease thus far reported only in the Western Hemisphere. No cases are known to have occurred in Mexico, Central America, or the Caribbean. HPS has been linked to at least six different viruses, with modest clinical differences noted between cases infected with differing viral species. This paper formulates the control and treatment of HPS as a single disease entity until sufficient evidence exists to discriminate it further.

4.1 NORTH AMERICA

As of 9 October 1998, 221 cases of HPS had been confirmed in 29 U.S. states and 3 Canadian provinces (Table 3). Cases have been predominantly from rural areas in the western half of the continent, on either side of the Rocky Mountains. While no cases have been confirmed in Mexico, the range of the primary North American rodent host, *P. maniculatus*, covers the northern half of that country. In addition, four HPS cases in the United States have occurred in areas near the border with Mexico.

In North America, at least four distinct hantaviruses have been associated with HPS. Although the majority

of cases are thought to have been the result of Sin Nombre virus infection (15), New York (16), Bayou (17), and Black Creek Canal (18) viruses are known to have caused six cases of HPS in the eastern and southeastern United States. The deer mouse, *Peromyscus maniculatus*, is recognized as the primary rodent reservoir of SNV (19), while the white-footed mouse (*Peromyscus leucopus*) (20), the rice rat (*Oryzomys palustris*) (21), and the cotton rat (*Sigmodon hispidus*) (22) are believed to be the primary rodent reservoirs for New York, Bayou, and Black Creek Canal viruses, respectively.

4.1.1 United States of America

The initial recognition of HPS in the spring of 1993 stemmed from an epidemic of approximately 27 cases in the southwestern United States. Since then, retrospective analysis of HPS has uncovered cases occurring as far back as 1959. While smaller clusters of two or three cases occurring among co-workers or family members have been reported, the majority of cases since 1993 have occurred sporadically at a rate of 20 to 40 cases per year throughout the United States, suggesting an uncommon yet endemic pattern of occurrence. The common, widespread presence of hantavirus-infected rodents

TABLE 3. Number of hantavirus pulmonary syndrome cases reported in the Americas.

	Number of cases as of 31 December 1997	Most recent data—third quarter, 1998
North America	205	221
United States	181	196
Canada	24	25
South America	208	239
Argentina	133	142
Brazil	6	13
Chile	32	46
Paraguay (52)	35	35
Uruguay	2	3
Total	413	460

contrasts with the less-understood and rare circumstances of transmission to humans.

HPS cases have occurred in all months, but are less frequent during the winter months of December, January, and February. It is unclear if human behavioral or rodent ecological factors play a greater role in the observed seasonal pattern, but it is most likely a combination of both factors.

HPS patients range in age from 11 to 69 years (median = 37) and show a slight male predominance (61%). The disease has been notably rare in young children, with only nine cases (5.2%) in children under 18 years old (23). The racial and ethnic distribution of cases resembles that of the rural western United States. The possible role of genetic factors remains to be elucidated.

Twenty-four diagnosed HPS cases in the United States occurred prior to 1993, and the majority of these were confirmed through analysis of stored autopsy tissue. Of the first 23 cases of HPS occurring in 1993, 15 (65%) died as a result of their illness. The overall case fatality rate of HPS cases in the United States is 44%. However, this has steadily declined since the time of the initial outbreak in 1993; cases with onset of illness after 1 January 1994 had a case fatality rate of approximately 35%. Of those patients with onset of illness during 1997, 3 of 17 (18%) did not survive their illness. The apparent decreasing mortality of HPS can most likely be attributed to improved clinical management rather than changes in the virus or a specific pharmacological therapy. In addition, increased awareness among clinicians and improved diagnostic capabilities have undoubtedly led to the detection of more mild illnesses and improved characterization of the full spectrum of clinical disease.

HPS cases have been associated with activities such as inhabiting dwellings with indoor rodent populations, occupying previously vacant cabins or other dwellings, cleaning barns and other outbuildings, disturbing rodent-infested areas, residing in or visiting areas in which the rodent population has shown a marked increase in density, trapping rodents, and handling live or dead rodents or their excreta (24–26). Activities such as these may have occurred in the context of residential, recreational, or occupational exposures. However, the precise events resulting in human infection are unclear for most cases, since many potential exposures often occur in the weeks leading up to onset of illness.

Serologic testing of household case contacts and persons occupationally at risk for rodent exposure has generally shown less than 1% background seroprevalence of antibody reactive to SNV, supporting the conclusion that asymptomatic infection with HPS-causing hanta-viruses is rare. In addition, there is no evidence of

person-to-person transmission of HPS-causing hanta-viruses in North America. In one study of 266 health care workers with exposure to HPS patients or their body fluids, none tested positive for SNV antibodies (27). Similarly, all reported household or occupational clusters of two or more HPS cases in the United States showed ample evidence of rodent exposure for all cases involved, thus casting doubt on the likelihood that person-to-person transmission was responsible for the observed cluster (28).

4.1.2 Canada

For surveillance purposes, Canada has adopted the HPS case definition of the U.S. Centers for Disease Control and Prevention (CDC) (29). As of 31 December 1997, 24 laboratory-confirmed HPS cases had been reported and, as of 7 March 1998, one additional case had been reported. All 25 cases occurred in the three western-most provinces—British Columbia, Alberta, and Saskatchewan—which represent approximately 25% of the Canadian population (30). The earliest known HPS case occurred in Alberta in 1989 and was identified retrospectively. Since 1994, when HPS was first recognized in Canada, five cases per year, on average, have occurred. More than 40% of cases have occurred during the months of April, May, and June. Alberta, representing approximately 9% of the Canadian population, has reported 64% (16 of 25) of the HPS cases. Overall, cases have ranged in age from 15 to 62 years (mean = 39.5 years); 68% (17 of 25) have been male and 32% (8 of 25) have died. Of those patients with onset of illness since 1 January 1997, one of eight (13%) did not survive the illness. The majority of cases were most likely exposed to SNV during farming and domestic activities in rural areas. Single cases have also been linked to occupational exposures during military exercises, cleanup of a lumber mill, and a wildlife survey. The characteristics of HPS in Canada appear to be similar to those of cases described in the U.S. (30).

Rodent surveys have shown the presence of *Sin Nombre* and *Sin Nombre*-like viruses in deer mice across Canada, with varying seroprevalence. Landscape composition in Canada was found to be a more important predictor of rodent seroprevalence than were such factors as season, viral strain, climate, buildings, or association with human disease (31).

4.2 CENTRAL AMERICA AND THE CARIBBEAN

No cases of HPS are known to have occurred in Central America or the Caribbean. However, the range of

Sigmodon hispidus, the probable host of Black Creek Canal virus, extends from the southeastern United States, through Central America, and into northern South America. In addition, Río Segundo virus has been identified with the harvest mouse, *Reithrodontomys mexicanus*, in Costa Rica but has not been linked to human disease (32). Species that inhabit portions of the Caribbean are more likely to be Old World members of the *Murinae* subfamily of rodents, such as the Norway rat. The absence of HPS in the Caribbean could be the result of the relative infrequency in the region of rodent host species of the *Sigmodontinae* subfamily.

4.3 SOUTH AMERICA

In South America, the presence of hantavirus-infected *Rattus norvegicus* has been known since the 1980s. Various studies conducted during that decade found up to 56% of captured rats seropositive for antibodies reactive to Hantaan virus antigen (33, 34). Other studies conducted near that time provided serologic evidence of past human infection in Brazil, Argentina, Bolivia, and Uruguay (35, 36).

In December 1993, following the outbreak in the United States, HPS was diagnosed in three people in Brazil (37). Active surveillance also led to the detection of several cases in Argentina. Currently, there are several genetically distinguishable viruses associated with HPS in South America and several others not known to cause disease (Tables 1 and 2). By the third quarter of 1998, 239 cases of HPS had been reported from five countries of South America. While cases have occurred throughout the year in an endemic fashion similar to that seen in North America, several clusters account for more than a quarter of all recognized cases on the continent. These clusters have generally occurred from September to January (spring and summer in the Southern Cone) in diverse habitat regions. A country-by-country synopsis of HPS activity will help illustrate the unique epidemiologic features of the disease in each country.

4.3.1 Argentina

As of 7 March 1998, 142 cases had been reported in Argentina. They were principally from Salta and Jujuy provinces in the northwest, Santa Fe and Buenos Aires provinces in the central part of the country, and Río Negro, Chubut, and Neuquén provinces in the south (38, 39). The mean age of HPS cases was 34.7 years, with a

range of 4 to 71 years. Argentina has seen a larger proportion of pediatric cases than the United States (40). The overall case fatality rate of HPS in Argentina is approximately 44%.

Following the 1993 outbreak in North America, active, prospective, and retrospective surveillance was undertaken of patients presenting with fever and unexplained respiratory distress syndrome between 1987 and 1995. In central Argentina, HPS was found during surveillance conducted for suspected cases of leptospirosis and Argentine hemorrhagic fever for which laboratory tests were negative. In northern Argentina, local physicians in Orán, in Salta province, had been reporting case clusters of an acute respiratory distress syndrome of unknown etiology since the 1980s. In the early 1990s, *Leptospira interrogans* was identified as the causative agent of some of these illnesses. However, in 1995, serological studies of cases showed hantavirus as the etiologic agent of disease in some of the remaining undiagnosed cases.

In the south, a cluster of three family members with illness was identified in the province of Río Negro in March 1995. Investigation of this cluster led to the characterization of Andes virus as the etiologic agent in southern Argentina (41). Andes virus was shown to represent a distinct lineage from SNV (41) but to be most closely related to other sigmodontine hantaviruses. It differed from New World hantaviruses of the North American Sin Nombre complex by more than 20% at the amino acid level in the G2 protein region. At least seven viral genotypes associated with different rodent reservoirs have been found circulating in the country, four of which have been linked to HPS (42).

Between September and December 1996, an outbreak of HPS occurred in the same region of Río Negro, affecting at least 18 people. Four of the 18 cases were physicians who lived in the area. Epidemiological, molecular, and ecological data have established person-to-person transmission, particularly when a physician living in a nonendemic region became infected after coming in contact with HPS patients (43, 44, 48). The etiologic agent was again found to be Andes virus, and the putative rodent reservoir, the long-tailed pygmy rice rat, *Oligoryzomys longicaudatus* (42).

4.3.2 Bolivia

While no HPS cases have been reported, both humans and rodents have shown serologic evidence of infection with hantaviruses in Bolivia (35, 45).

4.3.3 Brazil

As of 7 March 1998, six HPS cases had been reported in Brazil, five of which resulted in death. In December 1993, three brothers from Jucitaba, in the São Paulo area, were diagnosed with HPS; two subsequently died of their illness. Lung tissue from one patient yielded evidence of a possibly distinct virus provisionally referred to as Jucitaba virus (4). The brothers lived together in a rural area that showed evidence of rodent infestation. Three of 49 case contacts (6.1%) were positive for antibodies reactive to hantavirus antigen, with no apparent disease (37). Field investigations failed to determine the probable reservoir. Since then, three additional HPS cases have been reported; one case occurred in the state of Mato Grosso in 1995, while the other two were reported from the state of São Paulo.

4.3.4 Chile

HPS was first recognized in Chile in 1995 in a patient from Cochamo, Los Lagos, Region X. As of 25 March 1998, a total of 46 HPS cases had been reported, mainly from Regions IX, X, and XI, in the south of the country. Of these, 28 cases occurred between October 1995 and December 1997, most as a result of an outbreak in Aysén, Region XI, that began in July 1997. The mean age of these 28 HPS patients was 29.7 years (range 2–60 years), and 75% were males; six (21.4%) of the cases were children under 17 years of age. A case fatality rate of 61% was observed. Three clinical outcomes of hantavirus infection were defined in the country: patients with HPS, patients with mild hantaviral disease, and asymptomatic infections. In addition to the 28 cases of HPS, 3 cases with mild febrile hantaviral disease and 1 case with asymptomatic acute infection were identified.

While the clinical description of cases is similar to that in North America, at least three children had petechiae, and all adult cases that had a urinalysis performed had microscopic hematuria and casts (46). Genetic sequencing of tissues from several patients implicated Andes virus as the causative agent (47, 48). Three family clusters occurred in the Aysén region. In one cluster, family members became ill within 1 to 5 days of each other. In another family cluster, illness occurred sequentially, with a period of 16 to 41 days between the index case and illness of the last family member. The third family cluster included a husband, who worked in a rural area, and his wife, who remained in the family home in urban Coyhaique. He developed symptoms suggestive of HPS 12 days after returning to his wife and home, was hospitalized, and died. His wife became ill 22 days after the

initial onset of his symptoms. She had not traveled outside Coyhaique during the previous 12 months and reported no exposure to rodents. The only known exposures for the wife were washing her husband's clothing and caring for him while he was ill.

A serological study of health care workers from the Coyhaique Regional Hospital, where the majority of HPS patients were admitted during the 1997 outbreak, was performed (49). Out of 319 participants (87.9% of those eligible), 12 (3.6%) had IgG antibodies, consistent with the seroprevalence in the community in which the participants lived. Exposure to HPS patients was similar in both antibody-positive and antibody-negative individuals. A population-based, serological survey including individuals from four communities in the Aysén region, one urban and three rural, showed seroprevalence ranging from 2% in the urban area to 13.1% in one of the endemic localities (50).

Ecological studies were carried out in 1997 (51). Overall trap success ranged from 37% to 50%. The most frequently captured rodent was *Oligoryzomys longicaudatus*, with 13% antibody reactivity to Sin Nombre virus.

4.3.5 Paraguay

Thirty-five cases of HPS have been reported in western Paraguay (52). An outbreak of HPS occurred in an agricultural community in the western Chaco region, affecting at least 17 people in the spring and summer of 1995–1996 (52). Six additional cases, retrospectively identified in the region between 1987 and 1994, were serologically confirmed. The case fatality rate during the outbreak period was 12%, but this may have been underestimated due to the relative infrequency of autopsies performed in the region.

The background human seroprevalence was found to be between 7 and 21% among asymptomatic groups and community residents (52). This may indicate a milder illness and a much higher rate of subclinical infection than that observed elsewhere or infection with a less pathogenic, serologically cross-reactive hantavirus. The etiologic agent was named Laguna Negra virus and has been subsequently isolated in cell culture; the vesper mouse, *Calomys laucha*, was found to be the primary rodent reservoir (53).

4.3.6 Peru

There are currently no confirmed reports of hantavirus pulmonary syndrome cases in Peru. However, evidence of hantavirus infection has been found in a number of

rodent species within the country (R. Tesh and D. Watts, personal communication).

4.3.7 Uruguay

At least two cases of HPS have been reported in Uruguay, and previous serologic surveys had detected hantavirus antibodies in the general population (35). Little is known about the etiologic agent or the reservoir.

4.3.8 Venezuela

There are currently no confirmed reports of HPS cases in Venezuela. However, hantavirus antibodies have been detected in three rodents from the Venezuelan llanos, *Oryzomys bicolor*, *Sigmodon alstoni*, and *Zygodontomys brevicauda*. A genetically distinct hantavirus, Caño Delgadito virus, has been isolated from *Sigmodon alstoni*, but so far has not been linked to any human disease (54).