Outbreak of Hantavirus Infection in the Four Corners Region of the United States in the Wake of the 1997–1998 El Niño–Southern Oscillation

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Hantavirus cardiopulmonary syndrome (HCPS), a rodent-borne zoonosis, has been endemic in the Americas for at least several decades. It is hypothesized that the 1991–1992 El Niño–southern oscillation (ENSO) caused increased precipitation that allowed an increase in rodent population densities, thereby increasing the possibility of transmission to humans. The result was a 1993–1994 outbreak of the disease in the Four Corners states of the southwestern United States. A second strong ENSO occurred in 1997–1998, after a period of considerable public education about the risks of hantavirus infection that began during the 1993–1994 outbreak. The caseload of HCPS increased 5-fold above baseline in the Four Corners states in 1998–1999. Regions that had received increased rainfall in 1998 were especially affected. A large majority of the 1998–1999 case patients reported indoor exposure to deer mice. Hantavirus outbreaks can occur in response to abiotic events, even in the face of extensive public education and awareness.

In the spring of 1993, a cluster of patients with an acute cardiopulmonary disease with high mortality was noted in the Four Corners states (New Mexico, Colorado, Utah, and Arizona) of the southwestern United States. The etiologic agent was determined to be a novel hantavirus, now known as Sin Nombre (SN) virus [1]. Hantaviruses, a genus of the family Bunyaviridae, are harbored by murid rodents. Infected reservoir rodents excrete the viruses in their urine, feces, and saliva. The reservoir for SN virus is the deer mouse, *Peromyscus maniculatus* [2]. Transmission to humans occurs through inhalation of virus-contaminated excreta via the aerosol route. Although SN virus infection is not harmful to its rodent host, a severe disease, hantavirus cardiopulmonary syndrome (HCPS), occurs when humans become infected.

HCPS has been endemic in the United States for several decades, with cases recognized from 1959 [3], 1975 [4], and 1978 and later [5]. After the 1993 outbreak, which extended well into 1994 and ultimately affected 52 patients, subsequent cases in the Four Corners region and elsewhere in the United States occurred sporadically. From 1995 through 1997, an average of 4 patients per year received diagnoses of HCPS in the Four Corners states. Despite extensive media attention and public health campaigns during and after the 1993–1994 outbreak, the extent to which the public became informed about ways to avoid exposure to hantaviruses has been little assessed [6, 7].

Materials and Methods

Ascertainment of cases. TriCore Corporation and the University of New Mexico (UNM) School of Medicine offer a rapid diagnostic referral center that processes more samples for hantavirus infection than any other center in North America. In addition, the majority of patients with acute SN virus infection in the Four Corners states are referred to UNM Hospital for treatment. Thus, TriCore/UNM in Albuquerque diagnoses or treats most patients with HCPS in the Four Corners states. The remaining cases were ascertained through the state departments of health. Risk activities and exposure histories were obtained according to standard protocols [8]. Case patients were defined as those whose serum samples exhibited IgM and IgG antibodies reactive with SN virus nucleocapsid antigen and exhibited IgG antibodies to SN virus G1 antigen [9]. Antibody reactivity to the G1 antigen of SN virus is highly specific for SN virus infection and is not seen with related hantaviruses [10]. All of the positive samples were from patients who had compatible clinical illness, characterized by fever, chills, myalgias, thrombocytopenia, headache, nausea, vomiting, and shortness of breath. Four of the case patients did not exhibit cardiopulmo-

nary manifestations and are classified as having had acute SN virus infection but not HCPS.

Hantavirus strip immunoblot assay. The method for our hantavirus strip immunoblot assay used recombinant nucleocapsid and G1 glycoprotein antigens of SN virus [9]. Recombinant SN virus nucleocapsid antigen, ~100 ng/0.16-mm strip, was used [11]. All strips were incubated at room temperature for 4 h in a 1 : 200 dilution of human serum in milk-PBS buffer [9]. After 3 washes in PBS detergent wash solution, the strips were incubated for 15 min in milk buffer solution to block nonspecific binding. The strips were then exposed to a 1 : 1000 dilution of alkaline phosphatase–conjugated goat anti–human IgG or IgM antibody in milk buffer solution for 1 h at room temperature (Roche Diagnostics, Indianapolis). The strips were washed 3 more times and exposed to the alkaline phosphatase substrate nitro blue tetrazolium with 5-bromo-4-chloro-3-indoyl-phosphate. After 10 min at room temperature, the substrate was decanted, and the strips were rinsed twice in deionized water. Band intensities were then recorded on a scale of 0–4+.

El Niño standard departure. The multivariate El Niño–southern oscillation (ENSO) index is used as a measure of the coupled oceanic-atmospheric character of ENSO events. The US National Oceanic and Atmospheric Administration (NOAA) tracks the index, which is designed to predict the likely meteorologic consequences of each ENSO. The index considers the following 6 parameters: sea-level pressure, zonal and meridional components of the surface wind, sea-surface temperature, surface-air temperature, and total-cloudiness fraction of the sky [12]. The ENSO index was downloaded from the NOAA Web site on 30 June 1999.

Precipitation data. Precipitation at case sites was estimated by interpolating reported monthly rainfall data from 310 cooperative weather stations located in the Four Corners region. These data were downloaded from the NOAA Web site. Geographic locations of the weather stations were linked with the associated precipitation information, and the data were stored in a raster-based geographic information system (GIS) with a pixel resolution of 0.01°. Annual precipitation was aggregated from the monthly data, and a 20-year average precipitation pattern was recorded for each station. The procedure was repeated for the total precipitation recorded for 1998.

Precipitation at sites of exposure for patients with acute SN virus infection was estimated by separately interpolating precipitation surfaces for the 20-year average and for 1998, by using surface-generating algorithms residing in the GIS. The geographic locations of case patients were overlaid on the precipitation surfaces for the 20-year average and for 1998, and the estimated precipitation values were extracted. The change in precipitation for 1998, in comparison with the 20-year average, was calculated for each site of exposure.

To test the hypothesis that the local increases in precipitation were associated with HCPS cases, we plotted the distribution of cases in relation to the 1998 deviation from the 20-year average and compared it with 1998 precipitation deviation throughout the entire region. We predicted that if the association of ENSO with HCPS occurred, cases would be more common in areas with above-average precipitation. We compared the cumulative distribution of precipitation for the region with the distribution of precipitation for case sites by the Kolmogorov-Smirnov 2-sample test.

Results

Hantavirus outbreak of 1998–1999. The outbreak of HCPS in 1993 followed a significant ENSO event of 1991–1992, and the outbreak continued into 1994. The lag time between the ENSO event and the increase in caseload was ~1 year (figure 1). After 1994, there were no further ENSO events until winter 1997. Between the years 1992 and 1997, the multivariate ENSO index became >1 only briefly, in 1993 and 1994; this deviation was not considered to be reflective of an El Niño event. Hantavirus cases in the 4 states remained steady at ~4 per year.

In 1997, there was a strong ENSO event that began in mid-year (figure 1). During this ENSO, there was extensive coverage of the event in the press, and public interest in the possibility of a new outbreak of HCPS reached a high level in the Four Corners states. The New Mexico Department of Health (NMDOH) issued press releases advising the public about precautions that should result in decreased exposure to deer mice and their excreta. In May 1998, the NMDOH issued a fax
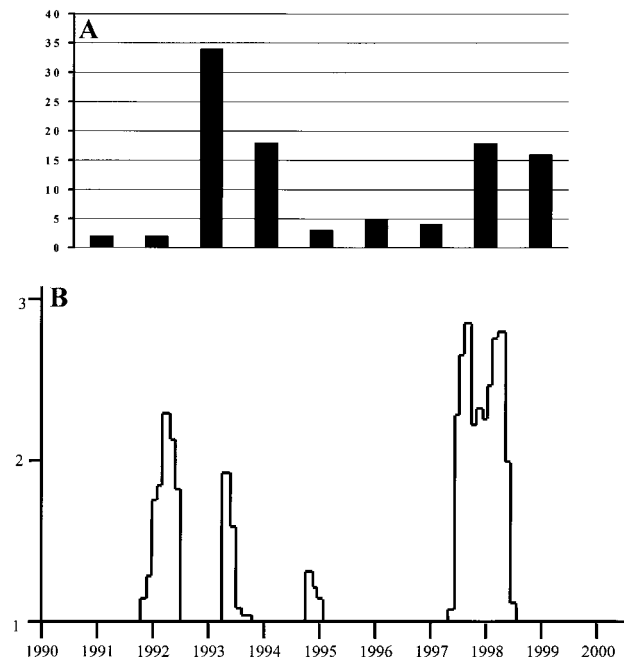
Figure 1. *A,* The number of cases of Sin Nombre hantavirus infection (hantavirus cardiopulmonary syndrome, as well as cases of acute hantavirus disease without cardiopulmonary involvement) in the Four Corners states (New Mexico, Colorado, Utah, and Arizona) for each year during 1991–1999. *B,* Cumulative departure of the multivariate El Niño–southern oscillation (ENSO) index; for simplicity, only those values >1 are shown. The 1999 data for the number of cases of Sin Nombre hantavirus infection span through July. The data for the cumulative departure of the multivariate ENSO index extend through mid-June 1999 and were provided by K. Wolter and M. Timlin of the Climate Diagnostics Center of the US National Oceanic and Atmospheric Administration.

Table 1. Demographic characteristics and clinical severity grade for 42 patients in the 1998–1999 outbreak of hantavirus infection in New Mexico, Colorado, Utah, Arizona, and California.

State, year (no. of patients)	Severity score,[a] no. of patients (no. on ECMO)	Median age, years (range)	Sex
New Mexico, 1998 (6), 1999 (8)	Class 0, 1; class I, 3; class II, 1 (1); class III, 9 (6)	42 (10–75)	8F, 6M
Colorado, 1998 (6), 1999 (4)	Class 0, 1; class I, 1; class II, 4 (1); class III, 4	39 (17–48)	5F, 5M
Arizona, 1998 (3), 1999 (3)	Class 0, 0; class I, 3; class II, 2 (1); class III, 1	43 (28–71)	2F, 4M
Utah, 1998 (3), 1999 (0)	Class 0, 1; class I, 0; class II, 1; class III, 0; unknown (nonfatal), 1	32 (29–37)	1F, 2M
California, 1998 (3), 1999 (6)	Class 0, 2; class I, 2; class II, 3; class III, 2	33 (17–66)	6F, 3M

NOTE. ECMO, extracorporeal membrane oxygenation.

[a] Severity score: class 0, no chest radiographic abnormalities; class I, hantavirus cardiopulmonary syndrome (HCPS) not requiring intubation; class II, HCPS requiring intubation; class III, fatal.

advisory warning all primary care practitioners in the state to be especially alert to the possibility of increased hantavirus activity. A preliminary warning about the increased risk was also published in the medical literature [13].

Despite the warnings and public advisories, hantavirus infections increased in the Four Corners states beginning in the spring of 1998. Between January 1998 and July 1999, the caseload increased to 33, compared with the 6 cases that would have been expected on the basis of the incidence during 1995–1997 (5.5-fold increase; $P < .01$, Fisher's 2-tailed exact test).

The demographic characteristics of patients in the new outbreak were similar to those in the 1993–1994 outbreak (table 1). Including cases from southern California in the analysis, the 42 patients in the 1998–1999 outbreak showed an increased representation of women (22 cases, 52%) and a slightly lower case-fatality ratio (16 fatal cases, 38%) [8]. In comparison with previous outbreaks, the 1998–1999 outbreak showed a higher proportion of patients who did not manifest pulmonary edema and thus did not meet the case definition for HCPS [14]. Furthermore, 9 patients with HCPS who manifested cardiopulmonary derangements that were considered highly predictive of death (e.g., cardiac index of <2.0) were given extracorporeal membrane oxygenation support [15].

Figure 2 shows the approximate geographic location of exposure sites for patients with diagnoses of acute SN virus infection in 1998–1999. California cases are included in this figure, because the climatologic effects of ENSO on southern California are similar to those on the Four Corners states. The cases occurred in clusters, with especially prominent clustering in western New Mexico and in southern California, in the foothills of the Sierra Nevada Mountains. Northern Utah and Col-

orado were less affected in 1999 than in 1998; in fact, no cases of hantavirus infection had been detected in Utah through July 1999. No cases were reported in the southern portions of New Mexico and Arizona, perhaps because the density of the deer mouse population is relatively low there.

Precipitation data showed substantial areas throughout the region with annual precipitation that was at or above the previous 20-year average (figure 3). These areas were primarily concentrated in northwestern New Mexico, northeastern Arizona, and southwestern Colorado. Despite the general tendency of ENSO to increase precipitation in the southwestern United States, there were several areas with precipitation substantially below the average. Below-average precipitation occurred in a belt through most of Utah and northeastern Arizona. Sites experiencing HCPS cases differed from the remainder of the region in the changes in their precipitation patterns in 1998, compared with those of the 20 previous years ($P < .05$). Cases were more likely to occur in areas where precipitation was in the upper 75th percentile of deviations from annual precipitation than would occur by chance alone.

Risk factors for infection.   Patients or their surrogates were questioned in an attempt to ascertain what risk activities may have led to infection. In deciding the most probable site of a patient's exposure, we favored known exposure at sites where live rodents had been seen, trapped, or handled or at sites where rodent infestation was clearly evident. Such exposures were common among patients affected by the 1998–1999 outbreak. As in previous investigations, we found that most exposures occurred in or around the home (table 2) [8]. Three patients also had exposure to automobiles with visible rodent infestation. A previous study suggested that inhalation of recirculated air in an automobile could result in infection [16]. We noted that the overwhelming majority of case patients for whom ex-
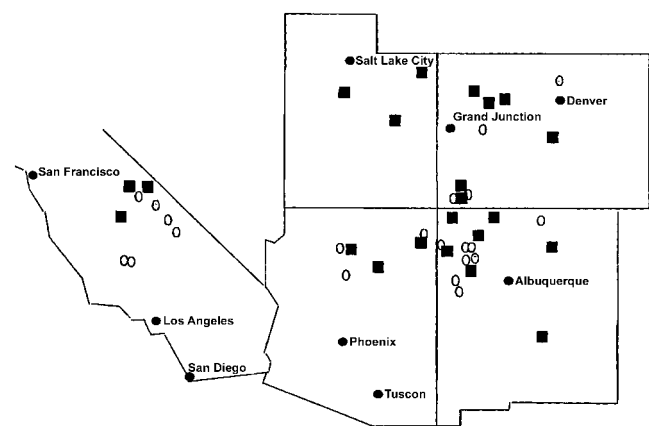
Figure 2.   The most probable location of exposure of each of the 33 patients with acute Sin Nombre virus infection from the Four Corners states (New Mexico, Colorado, Utah, and Arizona) and the 9 cases from California. ■, 1999 cases; ●, locations of major urban centers; 0, 1998 cases.
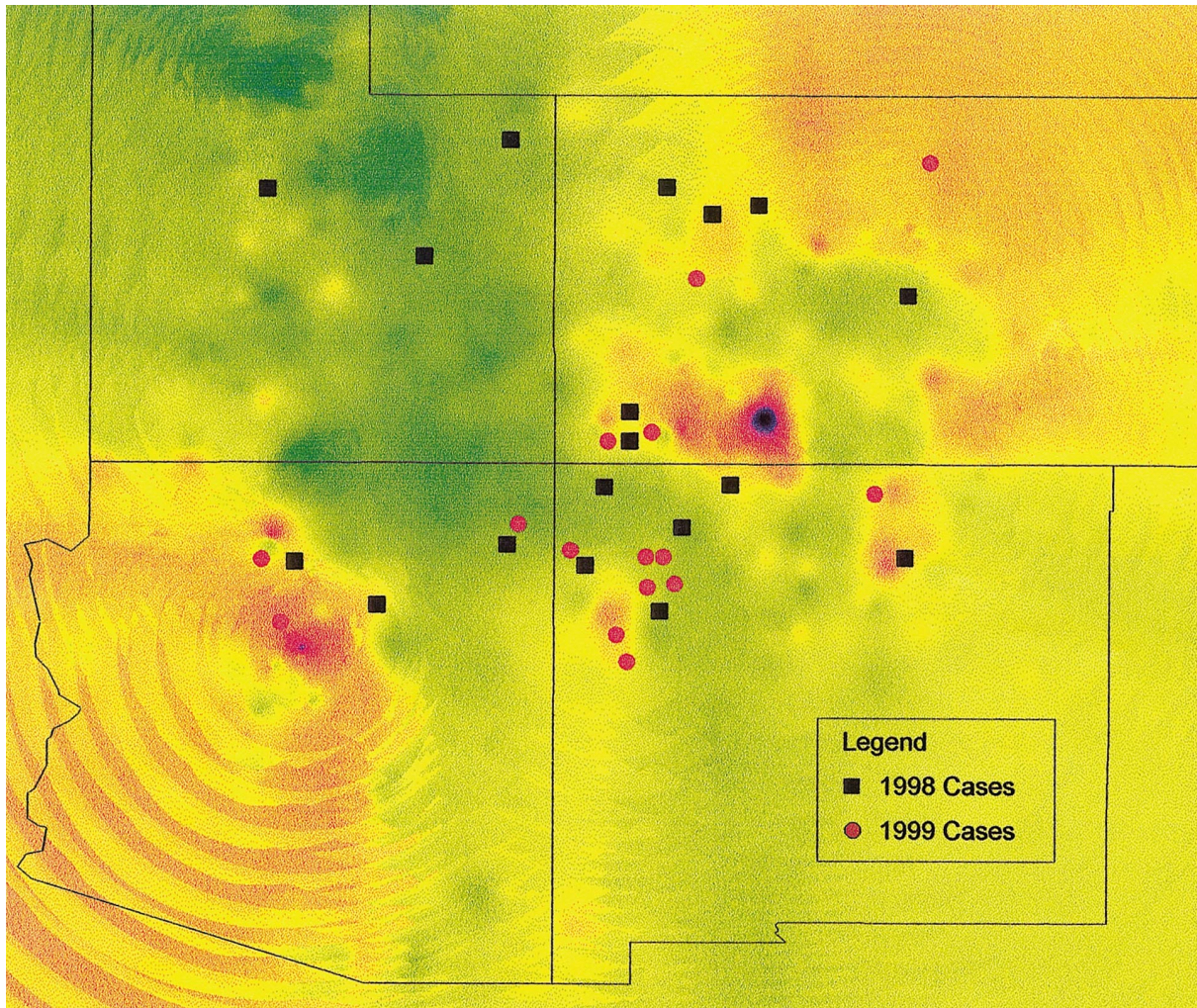
Figure 3. Deviation of annual precipitation in 1998 from the previous 20-year average in the Four Corners states (New Mexico, Colorado, Utah, and Arizona). Approximate locations of exposure are shown. Precipitation relative to the 20-year average ranges from low to high as follows: green to yellow to red to blue. Light green represents approximate equivalence between 1998 precipitation levels and the 20-year average. The banding patterns observed most prominently in southern Arizona are artifactual. They are caused by light coverage of weather stations in those regions that result in inadequate data for interpolation of the precipitation data.

posure data could be obtained were exposed in indoor environments. In rare cases, plausible exposures that occurred <4 days before the onset of illness were excluded, because the incubation period for HCPS appears to be ≥8 days [16] (B.H., unpublished data).

A single case patient provided a history that seemed to offer compelling evidence of an outdoor exposure. This patient, a contractor, had removed insulation from the side of a building and had noted that the insulation was extensively contaminated with rodent droppings. He stood in close proximity to the insulation and felt that he had inhaled particles of the aerosolized insulation; this event occurred ~3 weeks before the onset of his symptoms.

Discussion

We have shown that the ENSO event of 1997–1998 was followed by an outbreak of infection with SN hantavirus in 1998–1999. Although the outbreak was widely feared and was predicted in the press and by public health authorities, the expectation that it could be held in check by a continuous and extensive public education campaign led some to believe that an outbreak would not occur. It is impossible to know with certainty that the ENSO actually caused the increased incidence of SN virus infection. Increased awareness of the disease surrounding the ENSO event in 1997 could have influenced clinical recognition of the syndrome by health care providers. However,

Table 2. Characteristics of likely exposure of 42 patients with acute Sin Nombre virus infection.

Exposure	No. of patients
Site	
Indoor	34[a]
Outdoor	2
Mixed	1
Unknown	5
Situation	
Peridomestic	27
Occupational	7
Recreational	2
Mixed	3
Unknown	3

[a] Includes 3 patients who also had exposure to rodents in private automobiles or vans.

when the outbreak is considered in the context of the previous experience with the 1993–1994 outbreak and the low incidence of HCPS in 1995–1997, ENSO events should be seriously considered as precipitating factors in such outbreaks [17]. The relationship between ENSO and the increased caseload is further supported by the precipitation data. Although we are unable to consider the size of at-risk populations in our analysis, it is of some interest that only 3 cases were recorded in Utah, a state with a population of 2 million. Utah had a lower precipitation in 1998 than its 20-year average.

The risks of exposure in rarely used buildings, such as those used to store food, have been highlighted elsewhere, but specific efforts to determine whether exposures occur indoors or outdoors have been very limited [18]. Our experience suggests that exposure to rodents in such confined spaces may account for a much higher percentage of exposures than the previous literature would suggest. We believe that public health advisories should specifically target reduction of indoor exposure to infested buildings and should place less emphasis on outdoor activities such as gardening, hand-plowing, and weeding.

Acknowledgments

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