A Case-Control Study of Hantavirus Pulmonary Syndrome during an Outbreak in the Southwestern United States


In May 1993, an outbreak of hantavirus pulmonary syndrome (HPS) occurred in the southwestern United States. A case-control study determined risk factors for HPS. Seventeen case-patients were compared with 3 groups of controls: members of case-patient households (household controls), members of neighboring households (near controls), and members of randomly selected neighborhoods (far controls). Investigators trapped more small rodents at case households than at near (P < .05) or far control households (P < .02). After the number of small rodents was controlled for, case-patients were more likely than household controls to hand plow (odds ratio [OR], 12.3; 95% confidence interval [CI], 1.1-143.0) or to clean feed storage areas (OR, 33.4; 95% CI, 1.7-666.0). Case-patients were more likely than near controls to plant (OR, 6.2; 95% CI, 1.1-34.0) and more likely than far controls to clean animal sheds (OR, 11.9; 95% CI, 1.4-103.0). Peridomestic cleaning, agricultural activities, and an increased number of small rodents at the household were associated with HPS.

Hantaviruses are unsegmented, single-stranded RNA viruses of the family Bunyaviridae [1-7]. Five hantaviruses with distinct clinical and epidemiologic features have been characterized: Hantaan, Seoul, Puumala, Dobrava, and Prospect Hill. Each has a single rodent species as its primary reservoir. Hantaviruses are primarily transmitted to humans by inhalation of aerosolized rodent urine, feces, or saliva or particulates contaminated by rodent excreta [4, 5]. Respiratory infection from rodent bites or scratches has been reported [6]. The incubation period of known hantavirus illnesses ranges from 4 to 42 days (average, 12-16) [1-3]. Person-to-person transmission has not been documented with any hantavirus.

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Informed consent was obtained from all participants in this investigation.
The use of trade names is for identification only and does not imply endorsement by the US Public Health Service or by the US Department of Health and Human Services. The opinions expressed herein are those of the author and do not represent the views of the Indian Health Service or of the US Public Health Service.

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In May 1993, an outbreak of hantavirus pulmonary syndrome was characterized by a prodrome of fever and myalgia followed by abrupt onset of respiratory distress and subsequently termed hantavirus pulm onary syndrome (HPS) was identified in the southwestern United States [7, 8]. Virtually identical sequence patterns were amplified from hantavirus-specific RNA extracted from tissues of case-patients and rodents (Peromyscus maniculatus) captured at their households, providing direct evidence that a previously unrecognized hantavirus was the etiology of HPS. During the epidemic period, an interagency team conducted a case-control study to identify risk factors for HPS to assist in formulating prevention strategies and to develop hypotheses for future investigation.

Subjects and Methods

Case definition. Suspected case of HPS were solicited from clinicians, medical examiners, and infection control practitioners through facsimiles, mailing, newsletters, and the media and were reported to county and state health departments, the Indian Health Service, and the Centers for Disease Control and Prevention. A case of HPS was defined as clinical findings of unexplained adult respiratory distress syndrome, unexplained bilateral pulmonary interstitial infiltrates on chest radiograph, and oxygen saturation <90% on room air, on autopsy results compatible with noncardiogenic pulmonary edema with multiple identifiable cause of death in a resident of New Mexico, Arizona, Utah, or Colorado, with onset of symptoms during 1 January to 19 July 1993 and laboratory confirmation of a recent hantavirus infection.
Laboratory evidence of a recent hantavirus infection in humans was established by one or more of the following: positive serology (presence of hantavirus-specific IgM, 2-4-fold rise in IgG titer, or both) as measured by ELISA, positive reverse transcription-polymerase chain reaction for hantavirus RNA, and immunohistochemistry reactive for hantavirus antigen using methods previously described [9-11].

Case-control study: Case-patients were matched with persons ≥10 years old in each of 3 control groups: noninfected members of the case household (household controls; n = 98), noninfected members of the household closest to the case household to whom no relatedness (near controls; n = 70), and noninfected members of a randomly selected household ≥24 km (1.6 km in urban areas) from the case household (far controls; n = 84). Control households were matched with case households by location (urban or rural and on or off an American Indian reservation). Each control subject was asked to submit a blood sample to be tested for evidence of hantavirus infection.

A standard questionnaire was used to collect data during personal interviews with case-patients and controls. Interviews were done during June and July 1993 to obtain information about activities during the 6 weeks before illness onset for case-patients and for the same period for matched controls. Interveners were conducted with a close family member for case-patients who had died. Interviews were in the subjects' primary language (English, Spanish, or an American Indian language). Interveners were not blinded to the case status of interviewees. During June through August 1993, rodents were trapped in and around case and control households and tested for serologic evidence of hantavirus infection using methods previously described [12]. The number of small rodents captured at each household was adjusted for trapping effort and the number of traps lost or sprung without capturing a rodent using the following formula: number of small rodents trapped = number of traps set - (number of sprung traps • 0.51) - number of traps missing.

Statistical analysis. Univariate odds ratios and 95% confidence intervals were calculated by using a separate conditional logistic regression model for each independent variable. Exposure variables with P < .25 in the univariate analysis were included as candidate variables in multivariate conditional logistic regression models. For each of the 3 control groups, models were constructed to test the association between HPS and each of the following: rodent-human contact, agricultural activities, peridomestic cleaning activities, occupation, and host factors. Models controlling for the number of small rodents were constructed for the near and far control comparisons. A backward stepwise procedure was used (removal criteria, P < .15; reentry criteria, P < .10). Variables retained in any of these models were combined into single stepwise models for each control group. The final logistic regression models were rerun to include records with missing values on variables not retained in the stepwise model. The Wilcoxon signed-rank test was used to compare differences between the number of small rodents trapped and the seroprevalence of cross-reactive hantavirus antibodies in Peromyscus species at matched case and control households. Data were entered into Epi-Info (version 5.01; CDC, Atlanta) and analyzed by STATA (release 3.0; Computing Resource Center, Santa Monica, CA).

Table 1. Demographic characteristics of HPS case-patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Case-patients</th>
<th>Household controls</th>
<th>Near controls</th>
<th>Far controls</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (59)</td>
<td>48 (49)</td>
<td>42 (66)</td>
<td>44 (55)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (41)</td>
<td>50 (51)</td>
<td>28 (40)</td>
<td>36 (45)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>11 (65)</td>
<td>79 (81)</td>
<td>50 (71)</td>
<td>67 (84)</td>
</tr>
<tr>
<td>White</td>
<td>5 (29)</td>
<td>13 (13)</td>
<td>13 (19)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (6)</td>
<td>3 (3)</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>—</td>
<td>3 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>35</td>
<td>33</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Range</td>
<td>13-68</td>
<td>10-99</td>
<td>10-88</td>
<td>11-87</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>98</td>
<td>70</td>
<td>80</td>
</tr>
</tbody>
</table>

NOTE. Data are number (%) unless stated otherwise.

Results

Of 21 eligible case-patients, 17 case-patients or their surrogates agreed to participate. The clinical course of 13 of the 17 case-patients has been previously described [8]. The median age of the case-patients was 35 years (range, 13-68). One to 4 cases occurred in each 2-week period from mid-March to mid-July. Ten case-patients (59%) were female, and 11 (65%) were American Indian. Sixteen case-patients (96%) lived in a rural area, and 1 lived in a small town (population <35,000) [13] but visited a rural area each weekend. Ten case-patients (59%) resided on American Indian reservations; of these, 5 (50%) were female. Thirteen (76%) case-patients died and surrogate interviews were conducted.

Four additional case-patients who resided in a single house- hold declined to be interviewed. They were 20-27 years old, were American Indian, and had onset of symptoms during April and May 1993. Two of these patients died of HPS. This was the only instance of clustering of ≥2 patients within a household.

Case-control study. Of 282 eligible controls, 251 (89%) agreed to participate. Of participating controls, 236 (95%) tested negative for a recent hantavirus infection; 12 controls (5%) were not tested. Two near controls and 1 far control (1.3% of all controls tested) had a detectable IgG antibody, suggesting past infection, and were excluded from the analysis. None showed serologic evidence of a recent hantavirus infection. Controls were similar to case-patients with respect to sex, race, and age (table 1).

Univariate analysis identified 22 exposure variables with P < .1 when cases were compared with ≥1 of the control groups (table 2). Age and sex were not associated with HPS. Case-patients were more likely than any control group to trap rodents in or around their household and to have handled dead mice; they were more likely than near and far controls to observe mice around the exterior of the home. Of the 60 persons who attempted rodent trapping, 35 reported
<table>
<thead>
<tr>
<th></th>
<th>Cases controls</th>
<th>Households controls</th>
<th>Near controls</th>
<th>Far controls</th>
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<tbody>
<tr>
<td></td>
<td>N=total (%)</td>
<td>OR 95% CI P</td>
<td>N=total (%)</td>
<td>OR 95% CI P</td>
</tr>
<tr>
<td>Rodent-human contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats in human contact</td>
<td>19(175)</td>
<td>27(73)</td>
<td>5.3 1.3-21.6</td>
<td>.02</td>
</tr>
<tr>
<td>Households mouse</td>
<td>15(160)</td>
<td>26(91)</td>
<td>5.2 1.2-22.6</td>
<td>.03</td>
</tr>
<tr>
<td>Observe mice around house</td>
<td>10(175)</td>
<td>21(59)</td>
<td>2.4 0.6-10.3</td>
<td>.28</td>
</tr>
<tr>
<td>Observe mice elsewhere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observe mice around home</td>
<td>10(175)</td>
<td>21(59)</td>
<td>2.8 0.5-14.5</td>
<td>.23</td>
</tr>
<tr>
<td>Observe mice elsewhere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observe rodents droppings</td>
<td>11(175)</td>
<td>31(95)</td>
<td>0.9 0.2-3.6</td>
<td>.9</td>
</tr>
<tr>
<td>Observe rodents droppings</td>
<td>11(175)</td>
<td>31(95)</td>
<td>1.2 0.4-4.4</td>
<td>.8</td>
</tr>
<tr>
<td>Parasite activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean food storage areas</td>
<td>11(164)</td>
<td>17(95)</td>
<td>1.4 0.4-5.1</td>
<td>.6</td>
</tr>
<tr>
<td>Clean food storage areas</td>
<td>11(164)</td>
<td>17(95)</td>
<td>1.0 0.7-1.5</td>
<td>.01</td>
</tr>
<tr>
<td>Clean living areas</td>
<td>11(164)</td>
<td>17(95)</td>
<td>2.5 0.2-28.0</td>
<td>.02</td>
</tr>
<tr>
<td>Host factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholera medical problem</td>
<td>9(175)</td>
<td>19(95)</td>
<td>4.3 1.3-14.0</td>
<td>.02</td>
</tr>
<tr>
<td>Cholera medical problem</td>
<td>9(175)</td>
<td>19(95)</td>
<td>5.6 0.4-77.0</td>
<td>.2</td>
</tr>
<tr>
<td>Agricultural activities</td>
<td>4(164)</td>
<td>9(95)</td>
<td>4.8 0.8-28.0</td>
<td>.09</td>
</tr>
<tr>
<td>Host plow</td>
<td>5(179)</td>
<td>9(95)</td>
<td>13.5 2.4-75.0</td>
<td>.003</td>
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<tr>
<td>Mechanical fasting</td>
<td>2(177)</td>
<td>2(95)</td>
<td>13.5 2.4-75.0</td>
<td>.003</td>
</tr>
<tr>
<td>Plant a domestic garden</td>
<td>8(167)</td>
<td>12(95)</td>
<td>6.4 1.2-35.9</td>
<td>.02</td>
</tr>
<tr>
<td>Animal droppings in home</td>
<td>1(166)</td>
<td>2(95)</td>
<td>14.9 1.5-129.1</td>
<td>.002</td>
</tr>
<tr>
<td>Animal droppings in stool</td>
<td>3(167)</td>
<td>6(95)</td>
<td>3.6 1.0-11.7</td>
<td>.05</td>
</tr>
<tr>
<td>Newborn animals sleep in</td>
<td>6(175)</td>
<td>11(95)</td>
<td>2.5 0.7-8.4</td>
<td>.2</td>
</tr>
<tr>
<td>Occupation</td>
<td>4(164)</td>
<td>9(95)</td>
<td>27.8 2.8-376.0</td>
<td>.005</td>
</tr>
<tr>
<td>Gender</td>
<td>4(164)</td>
<td>9(95)</td>
<td>27.8 2.8-376.0</td>
<td>.005</td>
</tr>
<tr>
<td>Jewelry maker</td>
<td>4(164)</td>
<td>9(95)</td>
<td>15.1 1.5-157.0</td>
<td>.02</td>
</tr>
<tr>
<td>Aged</td>
<td>4(164)</td>
<td>9(95)</td>
<td>11.4 0.7-183.0</td>
<td>.09</td>
</tr>
</tbody>
</table>

**NOTE:** Und. = undefined.

* a.g., allergies, vomiting, physial disease, hypen allergenicus, cystoadenoma, unspaintated arthritis.
success. Human contact with other types of domestic or wild animals, whether alive or dead (rats, chipmunks, opossums, raccoons, cats, dogs), was not associated with HPS. Case-patients were more likely than household and near controls to report their occupation as herder. However, herding activities were not associated with HPS. Each of the 4 case-patients who reported herder occupation as herder were American Indian. Occupation as a rancher, farmer, or construction worker was not associated with HPS. Twelve case-patients (71%) did hand-painting or plumbing or reported their occupation as herder.

Case-patients were more likely than near or far controls to clean nests used for food storage in the household. Within case households, case-patients were more likely than household controls to clean adjacent structures (outbuildings) where food, grain, hay, or straw were stored or to clean adjacent structures where animals are kept. Seven case-patients (43%) reported cleaning either type of structure. No associations were found with clearing or straightening woodpiles, trash piles, or compost heaps. HPS case-patients were more likely to assist in animal births than were far controls.

Case-patients were more likely than household and near controls to report a nonmedical chronic medical problem and were more likely than near controls to report an autoimmune or hypersensitivity disorder, such as allergies or asthma. Exposure to insects or ectoparasites (flies, ticks, mosquitoes, nites, gnats, lice) was not associated with HPS. There was no association between HPS and consumption of specific food (piston nuts, unpasteurized milk, home-buttered meat, commodity foods). Recreational activities (running, hiking, hunting, fishing), domestic or occupational activities (weaving, wood gathering, hay haulage), group activities, traditional ceremonies, and travel were not associated with HPS.

Among all participants, female subjects (67%) were more likely than male subjects (33%) to clean food storage areas in the house, and males (61%) were more likely than females (39%) to handle a dead mouse. No other associations were found between subjects' sex and the risk activities identified. There were no associations between underlying chronic medical condition and risk activities.

Rodent trapping. More small rodents were trapped at case households that at near control (P = 0.03) or far control (P = 0.02) households (figure 1A). The seroprevalence of hantavirus antibodies in P. leucopus animals was not significantly different between case and control households (figure 1B). P. maniculatus (deer mouse; P. truei, pine mouse; P. leucopus, brush mouse) were the most commonly captured (80%, 1139/1687) and had the highest seroprevalence of hantavirus (27%, 304/1139) [12]. Seropositive P. leucopus animals were trapped in and around the household of the 4 persons who declined to be interviewed.

Multivariate analysis. Results of analysis of variables retained in the final multivariate model for households included the final multivariate models controlling for the number of small rodents trapped at near and far control households are shown in table 3. Case-patients were more likely than household controls to hand paw and to clean feed storage areas in adjacent structures. Case-patients were more likely than near controls to plant a domestic crop and more likely than far controls to be a herder or to clean animal sheds.

Discussion

This study is the first to identify specific risk factors for HPS. This is the first epidemiologic investigation of any hantavirus.
Table 3. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for factors associated with HPS in multivariate analysis controlling for the number of small rodents trapped at rear and front control households.

<table>
<thead>
<tr>
<th>Household controls</th>
<th>Near controls</th>
<th>Far controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Hand prey</td>
<td>1.3</td>
<td>1.1-1.43</td>
</tr>
<tr>
<td>Place a domestic coop</td>
<td>10.1</td>
<td>0.4-26.305</td>
</tr>
<tr>
<td>Occupation as herder</td>
<td>1.4</td>
<td>1.7-666</td>
</tr>
<tr>
<td>Jewelry maker</td>
<td>12.4</td>
<td>0.7-44</td>
</tr>
<tr>
<td>Clean inside storage area in adjoining structures</td>
<td>12.4</td>
<td>0.7-44</td>
</tr>
<tr>
<td>Smoke dirty charcoal</td>
<td>12.4</td>
<td>0.7-44</td>
</tr>
</tbody>
</table>

*Household companions controlled for number of small rodents by study design.

The associations between nondisabling chronic medical conditions and HPS, including the association between a hyperimmune or autoimmune disorder and HPS in the univariate analysis, suggest that host factors may affect the development of HPS in some patients. An aberrant immune response could be part of an immunopathophysiologic mechanism of HPS in patients with a preexisting autoimmune or hyperimmune disorder, as is seen with lymphocytic choriomeningitis virus [16]. Most reported HPS patients have been 20-50 years of age, which is the same age group predominately affected by other hantaviruses [17]. Lack of patients who are very young may reflect the role of the immune response in the pathophysiology of HPS.

Alternatively, the absence of cases among the very young and the elderly may reflect age-specific peridomestic or occupational activities associated with exposure. Many of the risk activities identified are common household chores that are not sex-specific, a finding supported by the nearly even number of male and female case-patients and the relatively few associations between sex and the risk activities identified. This is a distinct epidemiologic characteristic of newly recognized hantavirus-associated HPS in the southwestern United States, since other known hantaviruses predominantly affect males, presumably because of occupational risk activities [1-3, 17].

The occurrence of the first recognized outbreak of HPS during spring and summer may be due in part to an increased likelihood of certain activities during these months. However, an unusual population increase of P. monticola during the spring of 1993 may be the most important factor for this outbreak [18]. Increased Puumala virus infection is seen in Scandinavia during years when the natural host (bank vole, Clethrionomys glareolus) is abundant [14, 19]. Only 1.3% of eligible controls had detectable levels of hantavirus IgM antibodies and none had IgG, suggesting that subclinical hantavirus infection in the Southwest is not common. This finding is consistent with a study of >400 persons.
who sought health care for mild illness during the 1993 out-
break, which showed an IgG seropositivity rate of 1.0% [20]. In
addition, serum samples collected in 1991 and 1992 from per-
sons living in the outbreak area as part of a nutritional sur-
vey had an IgG seropositivity rate of 1.1% [21]. These results
suggest that infection with the newly recognized hantavirus has a very high likelihood of causing HPS. The prevalence of hantavirus antibodies in the Southwestern U.S. is remark-
able similar to the seroprevalence of 1.2% in persons living in areas where wild rat-associated hantavirus has been
epidemic in China [22].

Differences in the risk factors identified in the compar-
sions with each of the 3 control groups in the univariate and multivariate analyses may be due to the small number of cases, the variable number of controls, or the hetero-
geneity nature of disease transmission. Case-patients and household controls lived in the same household; therefore, these comparisons allowed evaluation of the association be-
 tween HPS and various exposures with the same potential for
domestic rodent exposure. Comparisons between the case-
patients and the controls allowed assessment of associa-
tions between HPS and the same activities with different levels of rodent population density.

Limitations of this study may include an ascertainment bias in the retrospective identification of cases, because ap-
tapologies are not routinely done in persons living in the area.
A withdrawal bias may have been caused by the refusal of 4 case-patients to be interviewed. An interview bias may have been caused by the lack of biasing of interviewers to the case or control status of subjects. Recall bias from infor-
gation-gathering or from the widespread media coverage of the outbreak may have overestimated or underestimated the odds ratios.

The findings from this study suggest that eliminating rodents from homes environments is the basis for prevention. Spec-
cific measures to reduce risk for hantavirus transmission include prevention of rodents entry into buildings, eradication of rodents from buildings, and removal of potential food sources and rodent testing sites [23]. Cleaning and agricul-
tural activities in rodent-infested areas should be done after ventilation and disinfection procedures have been followed. Heightened precautions, including the use of masks with high-efficiency particulate air filters, may be needed in heavily infested environments. Additional studies are needed to define the potential risk of activities in open versus closed spaces and the potential for household versus occupa-
tional exposures. These recommendations are most applic-
able for persons living in rural areas, as most HPS case-
patients lived in or visited rural areas during their presumed incubation period. Sporadic cases of HPS caused by newly recog-
nized hantaviruses continue to be identified in a wide area of the United States [24, 25]. Reduction of human ex-
posure to rodents, rodent excreta, and contaminated particu-
lates should decrease hantavirus-associated morbidity and mortality.

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tead, T. Michael Fink, Ralph fulghum, Maggie Gallagher, Peter Goon, Richard Hackins, Sasser John, Norbert Kalachuk, Ali Khan, Clark Kooi, Rima Khabaz, Craig Levy, Harvey Lip-
man, Pat McCornick, Bermece Milane-Baza, Bea Montilla, Ron Moore, Raymond Reed, Lula Riggs, Isaac Romero, Lawrence Sandis, Herman Shorty, David Tibbs, Chuck Viek, Gregory Waunaka, Memie Yazzie, and all the community health representatives, epidemiologist, laboratory workers, physicians, public health nurses, nurses, and others for their time and effort in the investigation.

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