THE INCUBATION PERIOD OF HANTAVIRUS PULMONARY SYNDROME


Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; Epidemiologic Services, Kansas Department of Health and Environment, Topeka, Kansas; Epidemiology Service, Oklahoma State Department of Health, Oklahoma City, Oklahoma; Division of Communicable Disease Epidemiology, Pennsylvania Department of Health, Harrisburg, Pennsylvania; Department of Biology, Indiana University of Pennsylvania, Indiana, Pennsylvania; Division of Communicable Disease Control, California Department of Health Services, Sacramento, California

Abstract. In 1993 Sin Nombre virus was recognized as the cause of hantavirus pulmonary syndrome (HPS) and the deer mouse (Peromyscus maniculatus) was identified as the reservoir host. Surveillance by the Centers for Disease Control and Prevention and state health departments includes investigation to determine the likely site(s) and activities that led to infection, an environmental assessment of the home and workplace, and possibly rodent trappings at these sites. As of December 31, 1998, there were 200 confirmed cases from 30 states (43% case-fatality ratio). The national HPS case registry was examined to determine the incubation period of HPS. Review of 11 case-patients with well-defined and isolated exposure to rodents suggests that the incubation period of HPS is 9 to 33 days, with a median of 14–17 days. Case investigations allow a better understanding of the incubation time of HPS and may define high-risk behaviors that can be targeted for intervention.

INTRODUCTION

Hantavirus pulmonary syndrome (HPS) is an acute, often fatal, febrile illness characterized by bilateral interstitial pulmonary infiltrates and cardiorespiratory compromise, clinically resembling acute respiratory distress syndrome. Fever, chills, muscle aches, headaches, and gastrointestinal symptoms are present in most confirmed cases. As of December 31, 1998, the Centers for Disease Control and Prevention (CDC) had confirmed 200 cases of HPS in 30 states, with a case-fatality proportion of 43%. Some of these cases were discovered retrospectively; the earliest identified case had onset of illness in 1959. In the United States, Sin Nombre virus (SNV) is the hantavirus most frequently associated with HPS. The primary reservoir of SNV is the deer mouse (Peromyscus maniculatus). Other pathogenic hantaviruses in the United States include Bayou virus (BV), Black Creek Canal virus (BCCV), and New York (NY) virus. Their primary reservoirs are the rice rat (Oryzomys palustris), cotton rat (Sigmodon hispidus), and the white-footed mouse (Peromyscus leucopus), respectively. The Centers for Disease Control and Prevention have confirmed 3 cases of HPS caused by BV, 1 case due to BCCV, and 2 cases attributed to NY virus.

Hantaviruses are believed to be transmitted primarily from rodent to human via inhalation when the virus, which is found in rodent urine or saliva, becomes aerosolized. Peridomestic, occupational, or recreational exposure to rodents, rodent excrement, and nests are considered risks for HPS, and precautions should be taken to rodent-proof homes, workplaces, and recreational areas. Caution is also advised when entering or cleaning rarely used structures where rodents may reside.

The incubation period for disease caused by SNV and other North American hantaviruses is not well established. However, on the basis of data from patients with hemorrhagic fever with renal syndrome (HFRS), another disease caused by hantaviruses, the incubation period of hantiviral infection has been estimated to be from 1–6 weeks.

Whenever possible, investigations of HPS patients are conducted to determine exposure to the reservoir host. A better understanding of the incubation period may help to determine when the virus was contracted and suggest behaviors that can be targeted for intervention. It may also help physicians to consider HPS in the differential diagnosis.

MATERIALS AND METHODS

The Centers for Disease Control and Prevention maintains a registry of confirmed HPS cases that occur in the United States. Confirmation of a case is based on serologic, genetic, or immunohistochemical results and clinical history of illness. The registry includes the case-patient’s medical chart and investigation forms and reports. This registry was reviewed to determine if there were cases where patients were exposed to rodents or their excreta, which appeared to be limited to a discrete episode. These investigations focused on the patient’s activities in the two months prior to onset of illness. Any rodent exposure during this period was considered potentially useful in determining how the patient was infected. If available, results from polymerase chain reaction (PCR) tests were also used to help determine where the exposure may have occurred.

RESULTS

For all 200 cases, the probable exposure site for each case-patient was determined to be either peridomestic, occupational, or recreational. Most of the cases in which exposure was well-defined were found to have peridomestic rodent contact. About 5% had known recreational exposure (e.g., camping, hiking) within 2 months prior to illness, while 8% were occupationally exposed (e.g., farming, trapping rodents) (Figure 1).

This review of the registry revealed that over half of the cases had multiple episodes of/for constant rodent exposure. Nine, 6 of whom died, had rodent exposure for a discrete time period which allowed for an estimate of an incubation period. Two other cases had known exposure sites, but the period in which they could have contracted the virus could
only help define a minimum value for the incubation period because they were at that site for a prolonged time before leaving. In these 11 cases, exposure occurred in the state of residence, unless otherwise noted.

Case A was a 29-year-old man from Washington with onset of illness on May 21, 1993 (estimated incubation period 0–11 days). He arrived in New Mexico on May 11, 1992 and moved into the trailer home of his sister, who had recently died of HPS. Eight of 27 rodents trapped at the home were hantavirus seropositive.

Case B was a 23-year-old woman from Idaho with onset of illness on June 14, 1994 (estimated incubation period 0–13 days). She had moved into a rodent-infested, abandoned house in Idaho 2 weeks prior to her illness and had done extensive cleaning.

Case C was a 45-year-old man from California with onset of illness on June 4, 1995 (estimated incubation period >8 days). He had thoroughly cleaned his cabin in California and then traveled to New Mexico on May 26, 1995. Neither of the 2 *P. maniculatus* captured at this possible New Mexico exposure site was positive, but 6 of the 11 *P. maniculatus* captured at his cabin in California were seropositive for SNV antibodies. The sequence of the virus from the patient was closely related to that of rodents captured in his home county in California and distinct from genetic material amplified from other sites in New Mexico, indicating that exposure probably occurred in the cabin in California.

Case D was a 32-year-old woman from Idaho with onset of illness on August 12, 1992 (estimated incubation period 10–18 days); her illness was identified retrospectively by serology. She had traveled to an Arizona town where she stayed from July 25 to August 2, 1992. During that vacation period, she had cleaned the rodent-infested houseboat in which she was staying.

Case E was a 31-year-old male from Colorado with onset of illness on May 12, 1993 (estimated incubation period of >10 days). He had been staying in Arizona for 11 days before onset of illness. Viral sequencing from one of the *P. maniculatus* captured near his home in Colorado identically matched the viral sequence from this patient, whereas the sequence from rodents at the Arizona site were quite different.

Case F was a 41-year-old man from Kansas with onset of illness on March 12, 1997 (estimated incubation period 12–19 days). For about a week beginning February 21, 1997, his duties included working in a basement with old paper records where he encountered rodents and handled rodent droppings without using gloves or disinfectant. He denies having contact with rodents at his home.

Case G was a 26-year-old man from Oklahoma with onset of illness on October 19, 1996 (estimated incubation period 16 days). Investigation of his homesite showed no evidence of rodents. Traps that had been set at his home for 2 years failed to catch any mice. However, on October 3, 1996, he had visited a salvage yard behind his worksite to remove a CB radio from an old abandoned truck. This truck showed evidence of rodent infestation (e.g., an abundance of rodent feces and a strong smell of rodents). The salvage yard was next to a field where excess grain was discarded, providing an excellent habitat for rodents.

Case H was a 40-year-old man from Pennsylvania with onset of illness on November 11, 1997 (estimated incubation period 16–18 days). Between October 24 and October 26, 1997, he and other hunters slept in a cabin loft that had rodent droppings and where they had stored their sleeping gear. A mattress was placed on the floor and a desiccated *P. leucopus* was in a trap within one foot of the mattress. Three of the 7 *P. leucopus* caught in and around the cabin were seropositive for hantaviral antibodies. The viral sequence from one mouse was nearly identical to the sequence obtained from virus found in tissues of Case H. He had no other known exposure to rodents.

Case I was a 55-year-old man from California with onset of illness on August 27, 1995 (estimated incubation period 16–22 days). While camping in the Sierra Nevada Mountains between August 5 and August 11, 1995, he crawled under...
a recreation vehicle parked on the campground; he also ate at a camp store where there was evidence of rodents. Two of 28 P. maniculatus trapped at the campground were positive for SNV antibodies. The viral sequence from one P. maniculatus was identical to the viral sequence from the patient. His home was rodent-free and he had no apparent exposure to rodents in his workplace.

Case J was a 22-year-old man from Rhode Island with onset of illness on January 17, 1994 (estimated incubation period 21–25 days). He traveled to New York during the Christmas holidays where he reportedly stayed at a vacation home for 3 days. A conservative estimate would put him at this home sometime between December 23 and December 27, 1993. A viral sequence of the New York-1 virus was obtained from one of 4 white-footed mice trapped at this vacation home and was nearly identical to the sequence obtained from virus in the tissues of Case J.

Case K was a 42-year-old woman from California with onset of illness on March 24, 1994 (estimated incubation period 25–33 days). During an 8-day visit (February 18–27, 1994) to New Mexico, the patient cleaned out a home where, the investigation report notes, she was exposed to rodents and had contact with rodent droppings while cleaning out the garage. PCR results showed that viral sequence from Case K matched that of rodents from New Mexico. All 39 P. maniculatus collected from her California home were negative for SNV.

When the upper limit for Cases C and E is excluded because it cannot be clearly defined, the possible range of the incubation period for these cases is 0–33 days. The mean is approximately 15 days and the median is 14–17 days. Eight of the cases had an incubation period consistent with 9–25 days (Figure 2).

**DISCUSSION**

The incubation period of HFRS has been estimated to be from 1 to 6 weeks. In a Russian laboratory outbreak of HFRS in 1962, the incubation period of HFRS ranged from 14 to 32 days. United Nations forces stationed in Korea developed HFRS as early as 7 days after arrival and as late as 46 days after departure. In the 1940s, Russian scientists injected serum and/or urine from HFRS cases intravenously or intramuscularly into human volunteers who developed HFRS 11 to 23 days later.

In the United States, it is often difficult to determine when and where the case-patient contracted the virus. In about half of the cases, exposure to rodents or rodent-infested areas was not noted. And in those who reported exposure to rodents that may have carried hantavirus, most had multiple or continuous exposure, especially in rural areas.

Limited recall, a high case-fatality ratio, and continuous exposure to rodents, whether at home, work, or in a recreational setting, limit the information available to help determine the incubation period of HPS. Because of well-defined exposures, the histories of the 11 cases presented provide an estimate of the incubation period of HPS in the United States. Review of these 11 cases, along with previous studies of HFRS case-patients, suggests that the incubation period of HPS can be regarded as 1 to 5 weeks. Understanding the incubation period of HPS is an important tool in the investigation of HPS cases, especially given the recent suggestion of person-to-person transmission of a South American hantavirus, Andes virus, that also causes HPS, although there is no evidence of person-to-person transmission in the United States.

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Authors’ Addresses: Joni C. Young, Ali S. Khan, Thomas G. Ksiazek, and Clarence J. Peters, Special Pathogens Branch, MS A26, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, Georgia 30329-4018. Gail R. Hansen, Kansas Department of Health and Environment, Bureau of Epidemiology and Disease Prevention, Landon State Office Building, 900 SW Jackson, Room 1051 South, Topeka, Kansas 66612-1290. Tim K. Graves, Oklahoma State Department of Health, Epidemiology Service, 1000 NE 10th Street, Room 605, Oklahoma City, Oklahoma 73117-1290.
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