AN INTERSTATE OUTBREAK OF TICK-BORNE RELAPSING FEVER AMONG VACATIONERS AT A ROCKY MOUNTAIN CABIN

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Abstract. In July 1995, an outbreak of acute febrile illness affected 11 (48%) of 23 family members from Nebraska and Kansas who had vacationed at a Colorado cabin in June. Similar symptoms were identified among five (17%) of 30 additional persons from Nebraska, Kansas, Florida, and Texas who had vacationed at the same cabin. Symptoms suggested tick-borne relapsing fever (TBRF). Although no spirochetes were detected in available blood smears from five case-patients, *Borrelia hermsii* was cultured from the blood of one case-patient and two chipmunks trapped near the cabin. Case-patients were more likely than non-ill cabin visitors to have slept on the floor (odds ratio [OR] = 28.0, 95% confidence interval [CI] = 3.0–258) or in the top bunk bed (OR = 5.2, 95% CI = 1.1–25.1). Tick-borne relapsing fever should be considered in the differential diagnosis of fever in patients who have stayed overnight in mountain cabins in the western United States.

Tick-borne relapsing fever (TBRF) is caused by infection with spirochetes of the genus *Borrelia* transmitted by soft ticks of the genus *Ornithodoros*. In the United States, TBRF is endemic in the western states, where the identified agents and their associated tick vectors are *Borrelia hermsii* and *Ornithodoros hermsi*, *B. turicatae* and *O. turicata*, and possibly *B. parkeri* and *O. parkeri*.

*Ornithodoros* ticks are nocturnal, transient feeders, and most patients are unaware of being bitten. Following an incubation period of about seven days (range = 4–18 days), infected persons experience an abrupt onset of fever, shaking chills, headache, myalgias, and arthralgias. The duration of the primary febrile attack averages three days (range = 12 hr to 17 days), followed by defervescence, usually accompanied by shaking chills. The afebrile interval averages seven days (range = 1–3 days) and without appropriate antibiotic therapy, is followed by an average of three relapses (range = 0–13).

In late July 1995, Nebraska Department of Health officials were notified that 11 (48%) of 23 members of a family from Nebraska and Kansas had become ill following overnight stays in late June at a mountain rental cabin in Estes Park, Colorado (elevation = 7,800 feet). Features of the illness, including relapsing episodes of fever to 105°F, headache, and chills, were compatible with TBRF. Centers for Disease Control and Prevention (CDC) and Colorado Department of Health officials were notified and an investigation was conducted with the following objectives: 1) document and confirm the source of the outbreak among index family members by obtaining clinical specimens for testing and by conducting interviews to obtain information on exposure and course of illness; 2) determine if there were other cases resulting from residence in the same cabin; 3) conduct an on-site environmental assessment of the cabin and its immediate surroundings; and 4) contact physicians in the local community to alert them of the illness cluster and determine if there had been other TBRF cases diagnosed in the community that season.

MATERIALS AND METHODS

Case-patient identification. Case-patients were identified as persons with onset of illness occurring within 18 days of remaining overnight in the identified cabin during the rental season (May 28–August 20, 1995) and who met one of the following laboratory or clinical criteria: 1) confirmed cases: spirochetes visualized on a Wright- or Giemsa-stained blood smear, *B. hermsii* isolated from whole blood using Barbour-Stoenner-Kelly II (BSK II) medium, or positive for antibodies to *B. hermsii* by a combined IgG and IgM enzyme immunoassay (EIA) and a history of a recurrent illness, which included two of these five characteristic symptoms: fever, chills, sweats, myalgias, and headache; 2) probable cases: a history of a recurrent illness, which included two of the five characteristic symptoms; or 3) suspected cases: a history of a nonrecurrent illness, which included three of the five characteristic symptoms. The CDC policies with regard to human subjects review during investigation of an acute health problem in a community were adhered to.

To identify potential case-patients among other renters of the cabin, rental records for the 1995 season were obtained. Active surveillance for additional TBRF cases in the community was conducted among the five health-care centers in the area. On August 18, a letter/questionnaire was telefaxed to alert health-care workers to the cluster of suspected TBRF cases and to request assistance in the identification of additional suspected cases. Those who did not respond by either telefax or mail within three weeks were contacted by telephone.

Data collection. Standardized telephone interviews were conducted with at least one representative of each family that had vacationed at the cabin. Information was obtained on illness history and potential risk factors for illness for all persons who had stayed at the cabin during that rental season. In light of the nocturnal feeding habits of the tick vector, sleeping location was examined as a possible risk factor. Descriptive data analysis was performed using Epi Info version 6.02 (CDC, Atlanta, GA) software. StatXact version 2.05 software (Cytel Software Corp., Cambridge, MA) was used to compute odds ratios and their 95% confidence intervals for potential risk factors among ill versus non-ill persons.

Specimen collection. Clotted blood specimens, Giemsa-
stained thin-smears, or both were obtained from recently or currently symptomatic persons by primary health-care providers or state health laboratories and forwarded to CDC. Serum specimens were obtained in the same manner by CDC from all available convalescent case-patients and non-ill persons for testing for antibodies to *B. hermsii*.

**Culture.** Clotted blood specimens were triturated in an equal volume of sterile saline and 0.1 ml was diluted into 15 ml of BSK II medium (Sigma, St. Louis, MO). Cultures were maintained at 33°C and monitored weekly by dark-field microscopy for evidence of spirochetal growth. Spirochete isolates were identified on the basis of morphology and Western immunoblotting with a monoclonal antibody (H9826) specific for *B. hermsii*.

**Serologic testing.** Polystyrene plates (Immulon II; Dynex Technologies, Chantilly, VA) were coated with 0.1 μg of *B. hermsii* (strain HS 1, low-passage) lysate in 100 μl of 0.1 M NaCO₃ buffer (pH 9.6) at 4°C overnight. Wells were washed five times with 20 mM Tris, pH 7.4, 0.14 M NaCl, 2.7 mM KCI, 0.05% (v/v) Tween 20 (TBS-T), blocked with 300 μl/well of EIA block (3% fetal bovine serum in TBS-T) for 30 min at 37°C, and washed five times with TBS-T. Test serum samples were diluted 1:500 in EIA block and added to duplicate wells (100 μl/well). Six negative control serum samples were also tested at a 1:50 dilution on each plate. Plates were incubated at 37°C for 1 hr and washed as above. Bound antibody was detected with goat anti-human IgG plus IgM (heavy and light chain) conjugated with alkaline phosphatase (Jackson Immunoresearch Laboratories Inc., West Grove, PA). The conjugate (diluted 1:10,000 in TBS-T) was added (100 μl/well) and incubated at 37°C for 1.5 hr. Wells were washed as above and incubated for 0.5 hr with p-nitrophenyl phosphate (2 mg/ml, 100 μl/well) in 0.05 M carbonate buffer (pH 9.8) with 1 mM MgCl₂. Color development was stopped with 5 N NaOH (100 μl/well). Optical densities (ODs) were measured at 405 nm. Negative, equivocal, and positive cut-off values were determined for each plate. Samples with ODs less than the mean of the six negative controls plus one standard deviation were considered to be negative. Samples with ODs greater than the mean of the six negative controls plus three standard deviations were considered to be positive. Samples with ODs between the negative and positive cut-off values were considered to be equivocal.

**Environmental assessment.** On August 7, 1995, five weeks after the index family’s stay at the rental cabin, the interior of the cabin was inspected for evidence of rodent infestation and cracks or crevices that would allow soft ticks or rodents access to the interior, and rodent burrows were flagged in an attempt to collect ticks. Additional environmental investigations on August 21 included placement of CO₂ traps in the crawl space under the house in an attempt to collect ticks, and two nights of small-mammal trapping on the property immediately surrounding the cabin within a radius of approximately 100 yards. Trapped mammals were anesthetized, and whole blood collected for culture in BSK II medium. Recovered rodent-nesting material was processed for ticks by using a Berlese funnel.

**RESULTS**

**Case-patient assessment.** Eleven (47.8%) of the 23 index family members from Nebraska and Kansas reported symptoms compatible with TBRF. In addition to the index family, five families from Nebraska, Kansas, Texas, and Florida that had vacationed at the cabin that season were identified. Through telephone interviews with these five families, 30 other lodgers of this cabin where identified; five (17%) reported symptoms compatible with TBRF. Of the 16 total persons reporting symptoms compatible with TBRF, the median age was 11.5 years (range = 2–66), and nine (56.3%) were male. Other than the 16 persons associated with this particular cabin, no other persons reporting symptoms compatible with TBRF were identified in the community.

Giemsa-stained thin-blood smears and clotted blood specimens collected during febrile episodes were available from four case-patients. Of these, one was collected during the initial febrile episode and three during the third or greater episode. Three of the four case-patients had not been treated with antibiotics prior to specimen collection; the fourth case-patient had taken a three-day course of amoxicillin during the initial febrile episode, but went on to have three relapses. A blood smear and clotted blood specimen were also obtained from a fifth case-patient who was afebrile at the time of specimen collection and had experienced the last febrile episode two weeks earlier. All five thin blood smears were microscopically negative for spirochetes. Although spirochetes were not visually detected in a thin blood smear collected from the case-patient during the initial febrile episode, *B. hermsii* was cultured from blood from the same case-patient. Identification of this *Borrelia* isolate was confirmed by Western immunoblotting with species-specific monoclonal antibody.

Serum specimens were obtained from 13 convalescent case-patients, and from 11 persons with no history of illness. The EIA showed results that were positive for three (23%) of 13 case-patients, equivocal for eight (62%), and negative for two (15%). Of the 11 non-ill persons, results were equivocal for three (27%) and negative for eight (73%).

Fever, myalgia, and chills were the symptoms most commonly reported by case-patients (Table 1). Based on clinical and laboratory data, four (25%) case-patients met the definition of a confirmed case, nine (56%) of a probable case, and three (19%) of a suspected case. Dates of onset ranged from June 5 to August 24. The majority of cases (75%) occurred in June, corresponding with the index family’s visit to the cabin (Figure 1). During the two-week period that the index family rented the cabin, there was one night when up to 21 persons remained overnight in the cabin. Case-patients

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Fever</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Chills</td>
<td>14 (88)</td>
</tr>
<tr>
<td>Sweats</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (19)</td>
</tr>
</tbody>
</table>

**TABLE 1**

Reported symptoms among confirmed, probable, and suspected cases (n = 16)
were significantly more likely to have slept on the floor or in the top bunk bed, but they were no more likely to have reported a history of tick or insect bites than non-ill persons (Table 2).

Twelve (75%) of 16 case-patients reported experiencing one or more relapses. Case-patients experienced a mean of 2.8 febrile relapses (range = 1–5) prior to receiving antibiotic therapy. Of those experiencing relapses, the mean length of the initial febrile episode and the subsequent afebrile episode was 3.5 days (range = 1–7) and 7.4 days (2–12), respectively. One family member was hospitalized for a period of four days during one of the relapses and recovered following a course of treatment with doxycycline. Twelve (75%) of the 16 case-patients were eventually treated with antibiotics; five (41.7%) with doxycycline, five (41.7%) with amoxicillin, one (8.3%) with erythromycin, and one (8.3%) with tetracycline. All of the case-patients eventually recovered, regardless of whether or not they were treated with antibiotics. One case-patient reported symptoms compatible with a Jarisch-Herxheimer reaction (a sudden, transient, febrile reaction observed after administration of antibiotics) following antibiotic treatment.

Environmental assessment. Several cracks and crevices that would permit entry of both rodents and ticks were observed inside the cabin, in the crawl space under the house, and outside along the foundation. Evidence of rodent infestation of the cabin included recovery of carcasses of a chipmunk and a mouse, along with rodent nesting material, from the crawl space under the house, and observation of chipmunk feces in the attic. One adult *O. hermsi* was recovered from the nesting material. An attempt to recover *Borrelia* from this tick by allowing it to feed on a laboratory mouse was unsuccessful. Attempts to collect ticks by flagging rodent burrows and by placement of CO₂ traps in the crawl space under the house were also unsuccessful. No attempts to collect ticks were made after August 22, when the site was visited by a pest control company, which treated indoor and outdoor cracks and crevices with a pyrethrin-based acaricide. The owners and property manager of the cabin were advised at the onset of the investigation to inform all current and subsequent inhabitants of the cabin of the illness cluster and of the potential for transmission of TBRF while remaining in the cabin.

Small mammal trapping yielded the following: 17 Uinta chipmunks (*Tamias umbrinus*), 10 golden-mantled ground squirrels (*Spermophilus lateralis*), three deer mice (*Peromyscus maniculatus*), and one long-tailed vole (*Microtus longicaudus*). Whole blood specimens obtained from each rodent were cultured in BSK II medium; two Uinta chipmunks were culture-positive for *B. hermsii*.

**Discussion**

This outbreak is consistent with previous reports of TBRF in the Rocky Mountains. Although TBRF typically occurs sporadically, outbreaks associated with persons remaining overnight in rustic cabins in the coniferous highlands of California, Arizona, and Washington have been reported. The true incidence of TBRF is unknown because it frequently goes undiagnosed and reporting is incomplete. The disease is currently reportable only in the states of California, Colorado, Idaho, Texas, and Washington. Two-hundred eighty-five cases were reported in these states and in Arizona, New Mexico, Nevada, Oregon, Utah, and Wyoming during 1985–1996 (CDC, unpublished data).

The classic symptomatology of TBRF, which includes the characteristic course of recurrent febrile episodes, eventually resulted in suspicion of TBRF as the cause of the outbreak. For many of these case-patients, onset of symptoms occurred after they returned to their respective states of Nebraska, Kansas, Texas, and Florida. Diagnosis of TBRF can be particularly challenging when onset occurs in a state in which TBRF does not occur (peripatetic cases). This highlights the importance of obtaining a detailed travel history from febrile patients. Tick-borne relapsing fever was not initially considered in the differential diagnosis by attending physicians of any of the case-patients in the outbreak, resulting in missed opportunities for identification of spirochetes on blood smears from case-patients early in the course of illness and prompt treatment with an appropriate antibiotic. *Borrelia* are highly susceptible to a variety of antimicrobials, including penicillins, tetracycline, chloramphenicol, and erythromycin. Once the illness cluster was identified as a suspected TBRF outbreak, immediate action was taken to obtain specimens for blood smears, culture, and serology, and recently or currently symptomatic case-patients were treated with antibiotics.

Direct observation of spirochetes in blood smears is the simplest and most rapid method of laboratory diagnosis of TBRF. During febrile episodes of the illness, spirochetes can be observed in stained peripheral blood smears in approximately 70% of cases. However, the number of circulating spirochetes diminishes with each successive relapse and spirochetes are rarely observed in blood smears collected during afebrile periods. Increased sensitivity of the microscopic method may be achieved by monitoring dehemoglobinized
thick blood smears. This type of sample was not available in the current study. The inability to visually confirm spirochetes in the thin smears from five case-patients is likely due to inappropriate timing of collection. In the current investigation, a culture was successfully initiated from a blood clot collected during the initial febrile episode of one case-patient, despite being held for four days at ambient temperature prior to its arrival at the reference laboratory.

*Borrelia hermsii* can be cultured in BSK II medium, especially from blood of acutely febrile patients. Although BSK II medium is commercially available, it is not routinely offered through most clinical laboratories for culturing of blood specimens. Spirochetes can be cultured from whole blood that has been allowed to clot and held at 4°C until inoculation into BSK II medium is possible.

Although EIA and immunofluorescent assays have been used for the detection of antibodies against relapsing fever borreliae, these methods are not standardized or widely used. Development and standardization of these tests are complicated by antigenic variability of relapsing fever spirochetes and antigenic conservation among relapsing fever spirochetes and *B. burgdorferi* sensu lato, which may lead to false-negative or false-positive results, respectively. Four case-patients in this investigation were either positive or equivocal by EIA for both *B. burgdorferi*, the causative agent of Lyme disease, and *B. hermsii*, emphasizing the problem of serologic cross-reactivity between *B. burgdorferi* and *B. hermsii*. Western immunoblotting has been used in an attempt to identify seroconversion to antigens with greater diagnostic specificity. A recent study indicated that antibody reactivity to a specific protein, GlpQ, may enable discrimination between TBRF and the Lyme disease exposure. Both of these approaches require further development and standardization before they will be generally useful in a clinical diagnostic setting.

Both *Ornithodoros* ticks and wild rodents serve as reservoir hosts of TBRF spirochetes. In the western United States, dwellings such as cabins, log houses, or sheds can serve as harborage and nesting sites for ticks and rodents. In the current investigation, the ecologic studies in the vicinity of the cabin showed an abundance of rodents: two, both Uinta chipmunks, had active infections with *B. hermsii*. Chipmunks (*Tamius* spp.) have been previously described as important reservoirs of *B. hermsii*. In the current investigation, evidence that rodents had become established in the cabin in question included the presence of rodent-nesting material in the crawl space under the cabin, carcasses of a chipmunk and mouse in the crawl space, and rodent feces in the attic. The recovery of only one *O. hermsi* tick from the cabin is not unexpected since areas where ticks may reside, such as behind walls, are frequently inaccessible and trapping methods often have a low yield.

A possible predisposing factor in this outbreak was the high density of persons in the cabin during a two-week period in June, when on one night, up to 21 members of the index family remained overnight in the cabin. The highest incidence rates of infection occurred during this interval. The cabin was equipped to sleep nine persons on a combination of beds, a bunk bed, a sofa, and a sleeper sofa. As a result of overcrowding, some persons slept on the floor, which may have increased their risk of being bitten by ticks. However, sleeping on the floor was not a requirement for illness, since nine (56%) case-patients reported not having slept on the floor. It is unclear why ill persons were more likely to have reported sleeping in the upper bunk. It is possible that a gap in the paneling next to the upper bunk or rodent infestation of the attic may have allowed ticks to gain entry at that level. Eliciting an accurate history of persons’ sleeping locations in the cabin was difficult. Because of the large number of occupants, it was not uncommon for persons to have slept in more than one location during their stay. The painless, nocturnal, and transient feeding of *Ornithodoros* probably explains why so few persons reported a history of a tick or insect bite.

This epidemic highlights the need for increased awareness among persons at risk of acquiring TBRF through recreational exposures in disease-endemic areas such as the Rocky Mountains. In such areas, efforts should focus on education. The public should be informed about the importance of vector-reduction activities such as removal of rodent nesting materials, periodic fumigation of dwellings, and rodent-proofing of summer cabins to prevent rodent access to foundations or attics. Clinicians should be informed on the importance of a detailed travel history and inclusion of TBRF in the differential diagnosis of febrile illness occurring during the spring and summer months in patients staying overnight in mountain cabins in such areas.

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