

EHRlichiosis IN A GOLF-ORIENTED RETIREMENT COMMUNITY

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Abstract Background. Ehrlichiosis due to *Ehrlichia chaffeensis* usually occurs sporadically or in small clusters, with an annual incidence estimated at 3 to 5 cases per 100,000 population in areas of endemic disease. The putative principal vector is the Lone Star tick (*Amblyomma americanum*). We investigated an outbreak of ehrlichiosis that occurred in June 1993 among members of a golf-oriented retirement community (community A) in Tennessee. The community is densely wooded and borders a wildlife-management area where deer are numerous.

Methods. We conducted a case-control study, using medical-history reviews, serologic testing, and testing with the polymerase chain reaction for *E. chaffeensis* infection. We also surveyed a sample of 10 percent of the households in community A and in another golf-oriented community (community B) more than 20 miles (32 km) from the wildlife-management area. Survey participants completed a questionnaire and provided specimens for serologic testing. In both communities, searches for ticks were undertaken.

HUMAN ehrlichiosis was first described in the United States in 1987.¹ Of more than 400 cases that have been reported since that time, most have occurred in small groups, or sporadically in isolated cases, usually after exposure to ticks.²⁻¹¹ Annual incidence rates of 3 to 5 cases per 100,000 population have been estimated in areas of endemic disease, but few population-based studies have been conducted.^{5,6} The severity of illness varies greatly,¹² but asymptomatic infection with *Ehrlichia chaffeensis* has been reported only infrequently.^{5,13} *Amblyomma americanum* (the Lone Star tick) has been implicated as a vector.¹⁴ We report an outbreak of ehrlichiosis in humans and the subsequent investigation, the results of which broaden our understanding of the epidemiologic features of this emerging infectious disease.

METHODS

Background

During one week in June 1993, four men, all of whom lived in a golf-oriented retirement community in eastern Tennessee, were hospitalized with an illness characterized by severe headache, vomiting, abdominal pain, and fever. Laboratory studies indicated leukopenia,

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Results. Eleven cases of symptomatic ehrlichiosis were identified in the case-control study, 10 of which were in community A (attack rate, 330 per 100,000). Of 311 surveyed residents of community A, 12.5 percent had serologic evidence of past *E. chaffeensis* infection, as compared with 3.3 percent of 92 in community B (relative risk in community A as compared with community B, 3.9; 95 percent confidence interval, 1.2 to 12.2). The risk of infection was associated with tick bites, exposure to wildlife, golfing, and among golfers, retrieving lost golf balls from the rough. Persons who never used insect repellent were more likely to have had infection than persons who did. In community A, thousands of Lone Star ticks were found; in community B, only three ticks were found.

Conclusions. The high rate of *E. chaffeensis* infection in community A resulted from its proximity to a wildlife reserve. When outdoor recreational activities are common and concentrations of ticks are high, outbreaks of arthropod-borne zoonoses can be anticipated. (N Engl J Med 1995;333:420-5.)

thrombocytopenia, and mild hepatitis. Although two of the men responded promptly to doxycycline, the other two required prolonged intensive care. The most severely ill man had acute renal and respiratory failure followed by coma. All four survived.

Investigation of the Outbreak

A working diagnosis of acute ehrlichiosis was confirmed by the presence of elevated levels of IgG antibody to *E. chaffeensis* in serum specimens from two men (reciprocal titers, 256 and 1024; the other two did not have detectable antibody) and positive polymerase-chain-reaction (PCR) tests of blood specimens from all four (Table 1).

The four men lived in the same community (community A), a golf-oriented retirement resort located on 15,000 acres (6073 hectares) of densely wooded land. Each reported a recent tick bite in community A; three were golfers. This community shared a fenceless northern border with an 80,000-acre (32,389-hectare) wildlife-management area, and wildlife (particularly deer) were commonly encountered on all four of the community's golf courses and around dwellings. Community A (which has 3000 permanent residents) was located 10 miles (16 km) north of Crossville, Tennessee, the largest town in Cumberland County (population, 35,000) (Fig. 1). This town contained all the physicians' offices and the single hospital in the county and thus provided medical care for virtually the entire county population.

Another golf-oriented retirement community in Cumberland County (community B, with 1000 permanent residents) was located 10 miles (16 km) south of the town on 5000 acres (2024 hectares). Community B had less wildlife because of its surroundings, primarily open farmland with little cover, and a six-lane highway separated it from the wildlife-management area.

Identification of Cases

A retrospective search for additional cases of ehrlichiosis focused on patients who had febrile illnesses between March 1 and June 30, 1993. We reviewed the medical records of any patients of the primary care physicians who had fever and no specific diagnosis, as well as those of all patients who had leukopenia, thrombocytopenia, or hepatitis or who had been tested for either Rocky Mountain spotted fever or Lyme disease at the hospital laboratory. Patients who had had fever and whose history in the medical records was compatible with ehrlichiosis were interviewed with a standard questionnaire, and a serum specimen was obtained during the convalescent phase. A second convalescent-phase serum specimen was obtained approximately

Table 1. Results of Nested PCR of Peripheral Blood and Immunofluorescent-Antibody Tests of Serum for Antibodies to *Ehrlichia chaffeensis*.*

PATIENT No.	METHOD OF CASE IDENTIFICATION	DATE OF ONSET OF SYMPTOMS	DAYS BETWEEN ONSET AND COLLECTION OF SPECIMEN	PCR RESULTS, SPECIMEN 1	RECIPROCAL ANTIBODY TITER		DAYS BETWEEN SPECIMEN COLLECTIONS
					SPECIMEN 1	SPECIMEN 2	
1	Retrospective	June 1	44	ND	4096	2048	27
2	Retrospective	June 5	27	ND	512	512	34
3	Retrospective	June 5	40	ND	512	512	27
4	Retrospective	June 13	29	ND	1024	512	31
5	Index case	June 19	12	+	1024	256	36
6	Index case	June 21	11	+	256	128	38
7	Index case	June 23	9	+	<16	<16†	38
8	Index case	June 25	7	+	<16	256	39
9	Prospective	July 15	16	ND	<16	512	45
10	Prospective	July 17	2	+	<16	<16†	23
11	Prospective	August 16	3	ND	<16	128	43

*ND denotes not detected; plus signs indicate positive tests. The limit of detection of antibody to *E. chaffeensis* is a reciprocal titer of 16.

†A third reciprocal antibody titer of less than 16 was measured 75 days after the onset of illness.

four weeks later from the patients who had serologic evidence of infection in the initial specimen.

In addition, a prospective search for cases extended from July 1 through September 1, 1993. All hospital and clinic patients of the primary care providers were screened for fever (temperature $>37.8^{\circ}\text{C}$). Patients with fever were excluded from further study if chest radiographs, bacterial cultures, or surgical procedures during the first 24 hours of evaluation explained the fever. For each patient identified in the prospective search, an acute-phase serum specimen was obtained, and a convalescent-phase serum specimen was obtained approximately four weeks later. In addition, whole-blood specimens were collected in tubes containing EDTA for PCR testing when feasible. All patients were interviewed with a standard questionnaire, and their medical records were reviewed.

Patients were classified as having a confirmed case of acute ehrlichiosis if their serum specimens had an elevated initial level of antibody to *E. chaffeensis* (reciprocal titer ≥ 64) for retrospective cases or, for prospectively ascertained cases, an increase of fourfold or more in the titer or a positive nested-PCR test of blood.^{6,9,13}

Informed consent was obtained from the participants. This investigation was conducted according to the guidelines for human experimentation of the Department of Health and Human Services.

Case-Control Study

The controls in this study were patients identified in the prospective search who provided both acute- and convalescent-phase serum specimens and who did not meet the case definition. Basic demographic characteristics, clinical data, and variables related to exposure were compared between cases and controls.

Household Serosurveys

In mid-August 1993, a 10 percent random sample of all households in both community A and community B was selected from a roster of current residents' addresses. Members of the selected households were invited by telephone to participate in the survey. All participants completed a standard questionnaire and provided a serum sample. The questionnaire covered basic demographic characteristics, variables related to exposure, and the medical history. In the community survey, participants with a reciprocal antibody titer of 64 or higher were considered to have evidence of past infection.

Laboratory Studies

All specimens were tested at the Centers for Disease Control and Prevention (CDC). The indirect fluorescent-antibody test used to quantify antibodies reactive to *E. chaffeensis* was performed as described previously.¹⁵ The serum specimens were also tested for anti-

bodies to *Rickettsia rickettsii*, *R. typhi*, and *Coxiella burnetii* by an indirect fluorescent-antibody test. A nested PCR for the 16S ribosomal RNA of *E. chaffeensis* was performed on all whole-blood specimens. The primers ECB (5'CGTATTACCGCGGCTGCTGGC-A3') and ECC (5'AGAACGAACGCTGGC-GGCAAGCC3'), which amplify all known ehrlichia species, were used in the initial amplification step.¹⁶ For the nested PCR, each product was amplified in two separate reaction mixtures. The first mixture contained the primers ECA (5'AACACATGCAAGTC-GAACGGA3') and HE3 (5'TATAGGTAC-CGTCATTATCTCCCTAT3'), which amplify all known ehrlichia species. The second mixture contained the *E. chaffeensis*-specific primer HE1 (5'CAATGCTTATAACCTTT-TGGTTATAAAT3') and HE3.¹⁷ These primers were used to verify that all possible amplified products were *E. chaffeensis*.

Collection of Ticks

In August 1993, ticks were collected by standardized techniques along the edges of the fairways in both community A and community B. In addition, 16 white-tailed deer (*Odocoileus virginianus*) and 20 medium-sized mammals were collected in and around community A and examined for ticks; these mammals were 12 rac-

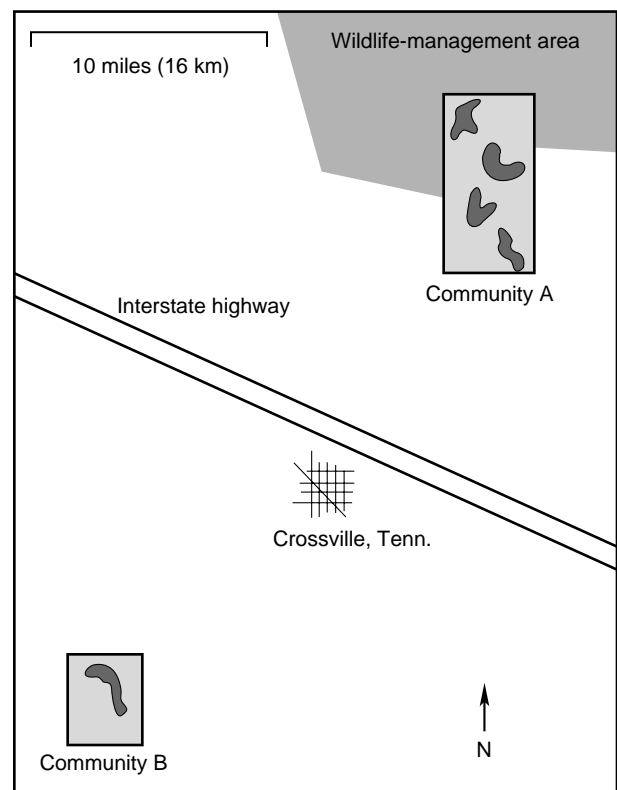


Figure 1. Schematic Map of Crossville, Tennessee, and the Two Retirement Communities.

Community A has four golf courses; community B has one (shaded areas within rectangles). The area between the interstate highway and community A is primarily uninhabited woodland, whereas rural farmland stretches south of the highway to community B.

coons (*Procyon lotor*), 4 opossums (*Didelphis virginiana*), 2 red foxes (*Vulpes vulpes*), 1 skunk (*Mephitis mephitis*), and 1 groundhog (*Marmota monax*). Despite numerous attempts to collect rodents, none were found. The ticks were identified according to standard morphologic criteria.

Statistical Analysis

Significance tests in the case-control study were performed by using the Mann-Whitney test for continuous variables and Fisher's exact test for dichotomous variables. The 95 percent confidence intervals for all relative risks in the serosurvey were calculated by the method of Greenland and Robins. All analyses were performed with Epi Info, a software package provided by the CDC.¹⁸

RESULTS

Eleven cases of symptomatic, acute ehrlichiosis occurred during the six-month period covered by the study (Table 1): the four index cases, four cases identified retrospectively, and three cases identified by the prospective search. Based on a referral-area population of 35,000, the rate of symptomatic ehrlichiosis during the six-month study period was 31 cases per 100,000 population (annual rate, 62 per 100,000). Ten of the case patients lived in community A; therefore, the rate of symptomatic infection in that community was 330 cases per 100,000. No infections with *R. rickettsii*, *R. typhi*, or *C. burnetii* were detected.

Identification of Cases

The retrospective search involved an initial review of the medical records of 76 patients. Sixty-one (80 percent) were identified because they had leukopenia, thrombocytopenia, or hepatitis or had been tested for Rocky Mountain spotted fever or Lyme disease. A large proportion of these patients were afebrile or had easily identifiable medical conditions that were responsible for the abnormal laboratory values (e.g., chronic liver disease, lymphoreticular cancer, or recent chemotherapy); therefore, these patients were excluded. Twenty-one patients were interviewed and tested serologically; four had elevated levels of antibody to *E. chaffeensis* (Patients 1, 2, 3, and 4 in Table 1).

Of the 34 patients identified as eligible for the prospective study, 10 declined to participate. Of the remaining 24 patients, 3 met the case definition (Patients 9, 10, and 11 in Table 1).

Case-Control Study

Twenty-one patients identified in the prospective search did not have an increase in antibodies. Blood specimens were obtained from six for PCR testing; all were negative. These 21 patients served as the controls for the 11 case patients. All the control patients' illnesses resolved, but a definitive clinical diagnosis was determined for only two, who had cellulitis and sinusitis. Of the 21 control patients, 18 (86 percent) received antibiotic treatment, 14 (67 percent) with a tetracycline analogue.

Of the 11 case patients, 2 never had detectable antibodies to *E. chaffeensis*, but the results of the nested PCR were positive (Patients 7 and 10 in Table 1). Both these patients had received doxycycline during the first 24 hours after the onset of fever. The remaining nine

Table 2. Demographic Characteristics and Symptoms of Case Patients and Controls.*

VARIABLE	CASE PATIENTS (N = 11)	CONTROLS (N = 21)	P VALUE
Demographic characteristic			
Median age (range) — yr	66 (60–71)	60 (6–75)	0.25
	% (no.)		
Male sex	91 (10)	48 (10)	0.02
Resident of community A	91 (10)	43 (9)	0.01
Hospitalized	64 (7)	29 (6)	0.07
Activity near wooded area	91 (10)	86 (18)	1.00
Tick bite	82 (9)	43 (9)	0.06
Golfer	73 (8)	33 (7)	0.06
Symptom			
Fever	100 (11)	100 (21)	—
Nausea	73 (8)	43 (9)	0.11
Headache	64 (7)	62 (13)	1.00
Myalgia	64 (7)	48 (10)	0.60
Abdominal pain	55 (6)	19 (4)	0.05
Vomiting	36 (4)	24 (5)	0.70
Arthralgia	9 (1)	10 (2)	1.00
Rash	0	0	—

*Case patients had evidence on serologic or PCR testing of recent infection with *E. chaffeensis*; controls had no such evidence.

had detectable antibodies within 11 to 45 days of the onset of illness (range of reciprocal titers, 128 to 4096).

The median age of the case patients was not significantly different from that of the controls (Table 2), although the range of ages differed greatly in the two groups. The narrow age range of the case patients was reflected in their place of residence; 91 percent lived in community A, a retirement community, as compared with fewer than half the controls. Case patients were more likely to be male, to have played golf, and to recall a tick bite or the attachment of a tick within 14 days of the onset of illness.

The symptoms of case patients and controls were similar (Table 2); no one in either group had a rash. However, the case patients were more likely than the controls to have thrombocytopenia and had lower peripheral leukocyte counts (Table 3). At least 75 percent of case patients whose hepatic aminotransferase and serum creatinine levels were measured had elevated levels during their illness, as compared with none of the control patients.

Household Serosurveys

Of 190 households invited to participate in community A and 67 in community B, 179 (94 percent, or 311 persons) and 57 (85 percent, or 92 persons), respectively, participated in the serosurvey. The proportion of persons tested who had evidence of past infection with *E. chaffeensis* was significantly higher in community A (39 of 311, or 12.5 percent) than in community B (3 of 92, or 3.3 percent; relative risk in community A as compared with community B, 3.9; 95 percent confidence interval, 1.2 to 12.2). The proportion of these persons who reported a recent symptomatic infection was low in both communities (3 of 39 vs. 0 of 3).

Among the residents of community A, the risk of previous ehrlichial infection did not differ significantly according to sex or age. The duration of residence (Table

Table 3. Results of Laboratory Studies during Illness of Case Patients and Controls.

VARIABLE	CASE PATIENTS (N = 11)	CONTROLS (N = 21)	P VALUE
Platelets			
Median minimal value — per mm ³	59,000	216,000	0.006
Range	42,000–265,000	65,000–368,000	
Abnormal count (<150,000/mm ³) — % (no./no. tested)	80 (8/10)	27 (4/15)	0.02
Leukocytes			
Median minimal value — per mm ³	3600	6200	0.003
Range	1700–7600	3400–27,700	
Abnormal count (<4000/mm ³) — % (no./no. tested)	73 (8/11)	11 (2/19)	0.001
Hematocrit			
Median minimal value — %	36.3	40.2	0.38
Range	18–49	29–49	0.07
Abnormal for age and sex — % (no./no. tested)	45 (5/11)	11 (2/18)	
Aspartate aminotransferase			
Median minimal value — IU/liter	127	28	<0.001
Range	34–614	9–47	0.001
Abnormal value (>40 IU/liter) — % (no./no. tested)	75 (6/8)	0 (0/11)	
Alanine aminotransferase			
Median minimal value — IU/liter	280	26	0.007
Range	30–309	13–40	0.01
Abnormal value (>40 IU/liter) — % (no./no. tested)	80 (4/5)	0 (0/7)	
Creatinine			
Median minimal value — mg/dl	1.5	0.9	<0.001
Range	1.2–10.3	0.7–1.1	0.001
Abnormal for age — % (no./no. tested)	86 (6/7)	0 (0/9)	

*To convert values for creatinine to micromoles per liter, multiply by 88.4.

4), the location of the home, and the proximity of the home to the woods were also unrelated to the risk of infection. Although people with pets were not more likely to have had an infection, those who reported that they frequently saw deer in their gardens had a frequency of ehrlichial antibodies nearly double that of those who did not encounter deer (relative risk, 1.7; 95 percent confidence interval, 1.0 to 3.3). Persons who reported several tick bites (four or more in 1993) had twice the risk of ehrlichiosis of those who could recall no more than three tick bites or none. There was a significantly lower risk of infection among those who always used insect repellent (Table 4).

Golfing was a principal outdoor activity for residents of community A; 63 percent of the respondents reported playing golf in the previous 12 months, and these persons were nearly twice as likely to have evidence of past infection as nongolfers. Among men who golfed, the risk of infection was significantly greater for players who reported higher golf scores — that is, poorer golfers. Rates of past infection in community A did not differ according to the golf course used most frequently. Although the attack rate increased as the amount of golf played per week increased, this trend was not significant. The golfing practice that was most strongly associated with infection was retrieving a golf ball that was hit off the course instead of using a new ball (relative risk, 3.7; 95 percent confidence interval, 1.2 to 11.6).

The protective effect of insect repellent was evident when the risk of infection was stratified according to golfing activity. Golfers who routinely retrieved lost balls from the woods and did not use insect repellent had the highest rate of past infection (29 percent) of

all survey participants, followed by golfers who retrieved lost balls but used insect repellent regularly (16 percent). Similar decreases in infection rates according to the use of insect repellent were found among golfers who never retrieved lost balls (14 percent among those who did not use insect repellent and 2 percent among those who did) and among nongolfers (12 percent and 6 percent, respectively).

Collection of Ticks

Ten separate attempts to collect ticks systematically were conducted around the golf courses and at other sites in each community. Ticks were found on all these occasions in community A; on nine occasions more than 1000 ticks were counted. More than 100 ticks were counted on each of the deer and on the majority of the medium-sized mammals; one raccoon and the groundhog had no detectable ticks. *A. americanum* was the only tick found in community A, both on the animals and free-living.

Only 1 of the 10 collection attempts in community B yielded any ticks (a total of three): two *A. americanum* and one *Dermacentor variabilis* (the American dog tick). Animals were not collected in community B.

DISCUSSION

This outbreak of human ehrlichiosis due to *E. chaffeensis* is large in terms of both the total number of cases and the community attack rate. The rate of symptomatic infection in the small retirement community (community A) was 330 cases per 100,000 (annual rate, 660 per 100,000), at least 200 times higher than previous estimates from local, state, or national sources.⁵⁻⁷ Although some geographic clustering of human ehrlichiosis and other arthropod-borne infections has been reported,^{6,11,13,19} the focal concentration of the infections in and around community A was striking. This community had been built recently in a dense forest directly adjacent to the wildlife-management area. Community B, in contrast, was located 20 miles (32 km) from the wildlife-management area, across an interstate highway, and was surrounded by cleared farmland. Deer and other wildlife were regular visitors to community A but were rarely encountered in community B. Although many people in community B also played golf, there were no cases of clinical ehrlichiosis during the summer outbreak, and residents had a significantly lower prevalence of antibodies to *E. chaffeensis* than the residents of community A.

Although golf is generally viewed as a low-risk activity, Topping postulated in a 1947 review of Rocky Mountain spotted fever that less skillful golfers might be at increased risk.²⁰ He suggested that a golfer's skill

Table 4. Evidence of Past Infection with *Ehrlichia chaffeensis* among Residents of Community A and Relative Risk of Such Infection, According to Demographic, Household, and Behavioral Characteristics.

CHARACTERISTIC	EVIDENCE OF PAST INFECTION (%)	RR (95% CI)*
	no./total no. (%)	
Length of residence in community		
<2 yr	2/19 (10.5)	1.0 (—)†
2–5 yr	16/113 (14.2)	1.4 (0.3–5.4)
6–10 yr	15/135 (11.1)	1.1 (0.3–4.3)
>10 yr	6/44 (13.6)	1.3 (0.3–5.9)
Pets at home		
Yes	10/87 (11.5)	1.0 (—)†
No	29/224 (12.9)	1.2 (0.6–2.3)
Deer frequently seen in yard or garden		
No	27/249 (10.8)	1.0 (—)†
Yes	12/62 (19.4)	1.7 (1.0–3.3)
Frequency of activities near woods (including golf)		
Never	0/19	—
<1 day/wk	8/84 (9.5)	1.0 (—)†
1–3 days/wk	17/119 (14.3)	1.5 (0.7–3.2)
≥4 days/wk	14/89 (15.7)	1.6 (0.7–3.6)
No. of tick bites in 1993		
0	19/170 (11.2)	1.0 (—)†
1	6/53 (11.3)	1.0 (0.4–2.4)
2–3	6/56 (10.7)	1.0 (0.4–2.3)
≥4	8/32 (25.0)	2.2 (1.1–4.7)
Use of insect repellent		
Always	5/98 (5.1)	1.0 (—)†
Sometimes	16/120 (13.3)	2.6 (1.0–6.9)
Never	18/93 (19.4)	3.8 (1.5–9.8)
Golfer		
No	9/114 (7.9)	1.0 (—)†
Yes	30/197 (15.2)	1.9 (1.0–3.9)
Average score/18 holes		
Men		
<100	8/75 (10.7)	1.0 (—)†
≥100	9/35 (25.7)	2.4 (1.1–5.6)
Women‡		
<100	4/13 (30.8)	1.0 (—)†
≥100	6/54 (11.1)	0.4 (0.1–1.1)
No. of holes played/wk		
≤18	8/60 (13.3)	1.0 (—)†
19–36	8/63 (12.7)	0.9 (0.4–2.4)
37–54	7/45 (15.6)	1.2 (0.5–3.0)
≥55	7/29 (24.1)	1.8 (0.7–4.5)
Strategy for lost balls		
Use new ball	3/57 (5.3)	1.0 (—)†
Retrieve ball	27/140 (19.3)	3.7 (1.2–11.6)

*RR denotes relative risk, and CI confidence interval.

†Reference category.

‡Data were missing for 20 women golfers.

correlated inversely with the likelihood of exposure to the rough, and thus to tick bites and infection. In community A, the golf-related characteristic that was most highly correlated with evidence of *E. chaffeensis* infection was the golfer's strategy regarding lost balls. Those who regularly left the fairway to search in the woods were at significantly higher risk than those who simply used a new ball. This association reinforced the likelihood of transmission from an arthropod vector. The hypothesis was strengthened further by the strong protection afforded by the regular use of insect repellent, an effect that was consistently observed in all the subgroups we analyzed. Protection by the use of insect repellent has been previously reported for Lyme disease, another tick-borne zoonosis.²¹

The wildlife and environmental surveys around community A yielded numerous ticks; *A. americanum* was the only species recovered. This species has been impli-

cated as the principal vector of *E. chaffeensis*; it is abundant in areas of endemic disease,^{7,12,13} and *E. chaffeensis* has been identified by PCR in pooled samples of *A. americanum*.¹⁴ The abundance of wildlife, especially deer, in community A was consistent with increased exposure to *A. americanum*, since deer and livestock are the preferred animal hosts of this species.²² The number of cases of ehrlichiosis peaked in late June and decreased dramatically after mid-July, a pattern that is consistent with the host-seeking activity of *A. americanum*.²² In addition to declines in the questing tick population after mid-July, a heightened awareness of ticks in community A prompted by an education campaign that began in early July may have helped reduce exposure.

The majority of people in both communities who had serologic evidence of past ehrlichial infection did not have a febrile illness during the five months before the study. Asymptomatic infection is known to occur,^{5,11,13}; the only other population-based serologic survey found that 67 percent of acute infections were asymptomatic.¹³

E. chaffeensis has been recovered from clinical specimens only rarely¹⁵; thus, PCR testing was instrumental in the timely recognition of this outbreak. This testing is particularly useful early in the infection, when antibodies are not yet detectable.^{9,17,23} Indeed, all the case patients in our study who were tested promptly after the onset of symptoms had positive PCR tests. Two never had serologic responses, even when tested more than 75 days after the specimen was obtained; however, both had been treated with doxycycline within 24 hours of the onset of fever. Whether prompt antibiotic therapy effectively aborts a detectable antibody response is unknown, but serologic responses are lacking in a substantial number of patients.⁹ Therefore, alternative, more direct methods of diagnosis, such as PCR testing, are invaluable.

Although the selection of the control patients for the case-control study had limitations, this method was similar to that used by others,⁶ and it allowed us to make use of a conveniently available population during the height of the outbreak. However, misclassification of some persons with exposure may have resulted solely from the lack of antibody response, a phenomenon that was unknown at the time this outbreak was being investigated. Among the 15 control patients who were not tested by PCR, some may have had undetected infections with *E. chaffeensis*. Indeed, 11 (73 percent) had received a tetracycline-like antibiotic that could have affected the serologic response. Nonetheless, this potential misclassification would have tended to eliminate differences between case patients and controls, yet we found several such differences.

Human ehrlichiosis due to *E. chaffeensis* is one of several emerging infections that have been characterized recently.^{24–26} This outbreak reflects a more global phenomenon brought about when humans have disrupted a local habitat. It is probable that the increased encroachment of susceptible humans into wildlife environments has led to focal increases in the incidence of the disease. When outdoor recreational activities are popular and the concentration of ticks is high, outbreaks of arthropod-borne zoonoses are likely.

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