

Research Paper

Serologic Evidence for Exposure to *Rickettsia rickettsii* in Eastern Arizona and Recent Emergence of Rocky Mountain Spotted Fever in This Region

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ABSTRACT

During 2002 through 2004, 15 patients with Rocky Mountain spotted fever (RMSF) were identified in a rural community in Arizona where the disease had not been previously reported. The outbreak was associated with *Rickettsia rickettsii* in an unexpected tick vector, the brown dog tick (*Rhipicephalus sanguineus*), which had not been previously associated with RMSF transmission in the United States. We investigated the extent of exposure to *R. rickettsii* in the local area through serologic evaluations of children and dogs in 2003–2004, and in canine sera from 1996. Antibodies to *R. rickettsii* at titers ≥ 32 were detected in 10% of children and 70% of dogs in the outbreak community and 16% of children and 57% of dogs in a neighboring community. In comparison, only 5% of canine samples from 1996 had anti-*R. rickettsii* antibodies at titers ≥ 32 . These results suggest that exposures to RMSF have increased over the past 9 years, and that RMSF may now be endemic in this region. **Key Words:** *Rickettsia rickettsii*—Rocky Mountain Spotted fever—Seroprevalence—Brown dog tick—*Rhipicephalus sanguineus*. Vector-Borne Zoonotic Dis. 6, 423–429.

INTRODUCTION

ROCKY MOUNTAIN SPOTTED FEVER (RMSF) is a severe and sometimes fatal disease caused by infection with the tickborne pathogen *Rickettsia rickettsii*. Clinical illness follows a bite from an infected tick, and is characterized by fever, rash, and possible complications, including encephalitis, respiratory disorders, and coagulopathy; case-fatality in untreated pa-

tients may be as high as 30% (Dalton et al. 1995). RMSF may also cause a similarly severe or fatal illness in dogs, and dogs may serve as sentinels for risk of disease in humans (Gordon et al. 1984, Hinrichsen et al. 2001, Keenan et al. 1977a, Keenan et al. 1977b, Magnarelli et al. 1982, Norment and Burgdorfer 1984, Sexton et al. 1976). RMSF is widely distributed throughout the eastern, south-central, and mid-western United States, corresponding to the distribu-

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tion of the American dog tick (*Dermacentor variabilis*) and the Rocky Mountain wood tick (*Dermacentor andersoni*), the expected tick vectors (Comer 1991). In endemic regions where the highest incidence of human disease is reported, prevalence of antibodies to *R. rickettsii* in humans and dogs has been reported as high as 21% and 63%, respectively (Kelly et al. 1982, Wilfert et al. 1985).

Historically, RMSF has been rarely reported in Arizona, where climatic conditions are generally unfavorable to support survival of *D. variabilis* or *D. andersoni*. However, during 2002–2004, we investigated an outbreak of RMSF involving fifteen patients from a rural community in eastern Arizona (Demma et al. 2005). The findings from this investigation indicated a novel transmission cycle for RMSF in the United States, involving the brown dog tick (*Rhipicephalus sanguineus*). Although *Rh. sanguineus* is known to harbor other spotted fever group rickettsiae (SFGR), this tick had not been previously associated with transmission of *R. rickettsii* in the United States. The investigation indicated that the outbreak of human RMSF in the affected community was associated with extremely high numbers of *Rh. sanguineus* ticks, and close human interaction with free-roaming community dogs heavily parasitized by these ticks (Demma et al. 2005).

The sudden emergence of an outbreak of RMSF in this community where cases had not been previously reported raised concerns over establishment of a new endemic disease cycle in the region. Interestingly, no cases of human RMSF had been reported from a nearby community to the south, despite similar environmental circumstances. We investigated the extent of RMSF endemicity in the region by determining the presence of anti-*R. rickettsii* antibodies in serum samples collected from children and dogs from the affected community (Community 1) and the nearby community (Community 2) in 2003–2004. In addition, we assessed the historical time frame for exposures to RMSF by using a comparison of results from canine sera collected from dogs in Community 1 in 1996 (Nicholson et al. 2006). The findings of these investigations provided some insight into the emergence of RMSF in this unique ecological setting.

METHODS

Setting

Community 1, the site of a 2002–2004 outbreak of RMSF, covers 2600 square miles in eastern Arizona. The community has a population of ~20,000 people. Altitude ranges from 5000 to 7000 ft (1500–2100 m), and the climate is hot and dry (during May–September the average summer high is 30°C [86°F], and the average annual rainfall is only 45 mm). The region is predominantly composed of piñon-juniper woodlands and semi-arid grasslands.

Community 2 (where no human cases were reported at the time of this study) is located 60 miles directly south of Community 1. The communities are separated by a large canyon, nine miles wide, with a river of widely varying depth depending on season. Community 2 spans 2800 square miles and the total population is ~12,500 people. The altitude of this community is lower than that of Community 1 at 2500 ft (762m) elevation. Climatic conditions are similar to those in Community 1, but are slightly warmer and less dry (May–September high temperature is 35.5°C [96°F], average annual rainfall 52.8 mm). The region consists of semi-arid grasslands and desert environments. Community 2 is very similar to Community 1 in its predominant housing structures, number of feral dogs, and high levels of *Rh. sanguineus* infestation that have been described elsewhere for Community 1 (Demma et al. 2005).

Human serosurvey

A prospective serosurvey was initiated at two regional hospitals, each serving one of the two communities. Serum samples were collected at random from children (pediatric patients < 18 years) having blood drawn for any reason during inpatient or outpatient visits. Duplicate samples were removed, patient identifiers were removed, and all samples were coded for testing; housing area of residence was recorded for patients in Community 1. Specimens were collected from Community 1 during November 2003 to January 2004, and from Community 2 during August 2004. Specimens were tested at the Centers for Disease Control and Prevention (CDC) by an indirect

immunofluorescence antibody assay (IFA) against *R. rickettsii* modified from Philip et al. (1976). Immunoglobulin G (IgG) levels were determined by endpoint titration of the serum samples; antibody titers were expressed as the reciprocal of the highest dilution at which distinct antibodies were present. A seropositive specimen was defined for this survey as presence of anti-*R. rickettsii* IgG antibodies at a titer ≥ 32 . Geometric mean titers (GMTs) of IgG antibody titers for each community were calculated for all seropositive specimens with an antibody titer ≥ 32 using log-transformed data and compared between groups by using non-parametric tests. Patient serum samples with anti-*R. rickettsii* titers were also tested for IgG antibodies reactive with *Rickettsia rhipicephali*, a related SFGR found in *Rh. sanguineus* ticks that may result in immunologic stimulation and potential serologic cross-reactivity with *R. rickettsii* (Gage and Jerrells 1992).

Canine serosurvey

Canine serum was obtained from dogs presenting at no-cost rabies clinics held in the two communities in June 2004. Serum specimens were examined for serologic reactivity to *R. rickettsii* by IFA as described for human samples above, utilizing canine IgG specific conjugate. A seropositive specimen was defined as presence of anti-*R. rickettsii* IgG antibodies at a titer ≥ 32 . Endpoint IgG levels were determined by serial twofold titration of the serum samples. Serologic reactivity to *R. rhipicephali* was also determined by using an IFA.

To provide a retrospective analysis of anti-SFGR seroprevalence in this area, we compared these results to those from canine specimens that had been collected from Community 1 during a rabies clinic in the summer of 1996 for the purposes of a *Yersinia pestis* (plague) serosurvey. Canine whole blood had previously been

collected and initially stored on Nobuto filter paper strips. Antibodies from these specimens were eluted into a borate buffer and the eluate was stored frozen at -70°C as 1/32 dilutions. In 2004, endpoint IgG antibody titers to both *R. rickettsii* and *R. rhipicephali* were determined on these eluted specimens using the IFA assays (Nicholson et al. 2006). A seropositive case was defined as presence of anti-*R. rickettsii* IgG antibodies at a titer ≥ 32 .

RESULTS

Human serosurvey, 2003–2004

One hundred eighty-four serum specimens were collected from children presenting to have blood drawn at the hospital serving Community 1 between November 2003 and January 2004. Of these, 18 children (10%) had anti-*R. rickettsii* IgG antibodies present at titers ≥ 32 . Nine children (5%) had high levels of IgG antibody at titers ≥ 128 (Table 1). Positive patient samples were found throughout Community 1, and did not appear restricted to certain housing areas. Thirty-one serum specimens were collected from children from Community 2 during August 2004 (Table 1). Five children (16%) had anti-*R. rickettsii* antibody titers ≥ 32 , including one child (3%) with a titer ≥ 128 . Geometric mean anti-*R. rickettsii* titers for Community 1 and Community 2 were 106 and 51, respectively. There was no statistically significant difference in GMT between communities, nor greater association between community and the number of specimens with anti-*R. rickettsii* IgG titers ≥ 32 .

To assess the role of possible immunologic cross-reactivity with *R. rhipicephali*, *R. rickettsii*-positive specimens were also evaluated for the presence of anti-*R. rhipicephali* antibodies. For Communities 1 and 2, three of 18 (17%)

TABLE 1. ANTI-*RICKETTSIA RICKETTSII* IGG ANTIBODY TITER RESULTS OBTAINED FROM CROSS-SECTIONAL, ANONYMOUS SEROSURVEY OF PEDIATRIC PATIENTS IN TWO COMMUNITIES IN ARIZONA, 2003–2004

Community	Date sampled	Titer ≥ 32 (% total)	Titer ≥ 128 (% total)	Range of endpoint titers	Geometric mean titer
1	November 2003 to January 2004	18 (9.8)	9 (4.9)	<16 to 512	106
2	August 2004	5 (16.1)	1 (3.2)	<16 to 256	51

and three of 5 (60%) *R. rickettsii*-positive specimens, respectively, tested positive for anti-*R. rhipicephali* antibodies at titers ≥ 32 . *R. rhipicephali* titers were fourfold lower than the corresponding anti-*R. rickettsii* titer for all patients in Community 1, but titers were more similar in Community 2, ranging from twofold higher to twofold lower *R. rickettsii* compared to *R. rhipicephali* titers.

Canine serosurvey

During the no-cost rabies vaccine clinic held in June 2004, serum samples were collected from 97 dogs from Community 1 and 14 dogs from Community 2. The number of dogs with anti-*R. rickettsii* and anti-*R. rhipicephali* antibodies at titers ≥ 32 , and the range of positive titers, is shown in Table 2 for each community. In Community 1, 78 (70%) dogs sampled were positive for anti-*R. rickettsii* antibodies at titers ≥ 32 (GMT 7976, range 64–262,144), and 65 (59%) dogs were positive for anti-*R. rhipicephali* at titers ≥ 32 (GMT 6105, range 64–8192). In Community 2, eight (57%) of 14 dogs were positive for anti-*R. rickettsii*, and four (29%) were positive for anti-*R. rhipicephali* antibodies. For individual dogs, there was no consistent relationship between anti-*R. rickettsii* and anti-*R. rhipicephali* antibody titers; for some dogs, anti-*R. rickettsii* antibodies were significantly lower than anti-*R. rhipicephali* antibodies, but in other dogs, the results were reversed. Dogs in all housing areas of community 1 showed high levels of antibodies. The canine seroprevalence within individual community housing areas ranged from 38% to 100% for *R. rickettsii* and 29% to 100% for *R. rhipicephali*. There was no apparent association between the locations of the human cases associated with recently reported RMSF outbreak

(Demma et al. 2005) and seroprevalence of *R. rickettsii* in dogs.

Of 329 dog blood samples collected from Community 1 during 1996 and analyzed by IFA, 17 (5%) were positive for only anti-*R. rickettsii* IgG antibodies at titers ≥ 32 (GMT = 38) and 12 (4%) dogs were positive only for IgG antibodies to *R. rhipicephali* at titers ≥ 32 (GMT = 32) (Nicholson et al. 2006). In contrast with the contemporary results, no samples were positive for antibodies reactive with both organisms.

DISCUSSION

We assessed the prevalence of antibodies to *R. rickettsii* in dogs and humans from a region of Eastern Arizona that had recently experienced an unusual outbreak of RMSF (Demma et al. 2005). Evidence of antibodies was considered a marker of prior infection with *R. rickettsii*. We found evidence of exposure to *R. rickettsii* in both children and dogs from Community 1 and Community 2, suggesting that the pathogen was widely distributed throughout the region. Prevalence of antibodies to *R. rickettsii* in both humans and dogs from the region was as high as that seen in areas of the United States where RMSF is endemic (Carpenter et al. 1999, Breitschwerdt et al. 1987; Hoskins et al. 1988, Kelly et al. 1982, Marshall et al. 2003, Wilfert et al. 1985). The pediatric serosurveys in the two communities were conducted in different years and seasons and our results may have been influenced by seasonal differences in tick activity. Unfortunately, information on community of residence was unavailable for patients in Community 2, so we cannot estimate the geographic range of pediatric exposures.

TABLE 2. RESULTS FROM A SEROSURVEY OF DOGS IN TWO COMMUNITIES IN ARIZONA, 2004

Neighborhood	Total no. serum	Anti- <i>R. rickettsii</i> GMT (total no. positive; range)	Anti- <i>R. rhipicephali</i> GMT (total no. positive; range)
Community 2—Housing Area A	14	512 (8; 64–16,384)	512 (4; 64–8, 192)
Community 1—Housing Area A with no RMSF	351	10,736 (38; 64–131,072)	4,648 (32; 256–131,072)
Community 1—Housing Area B with reported human RMSF cases	461	21,073 (32; 64–262,144)	14,864 (29; 128–262,144)
Totals	111	7,976 (78; 64–262,144)	6,105 (65; 64–262,144)

Although a medical chart review at the hospital serving Community 1 and an informal discussion with community residents in 2004 did not reveal any past reports of RMSF-like illness in this population, it is possible that cases had occurred without recognition, or that subclinical infections had occurred. Since completion of our serosurvey, RMSF infection was confirmed in nine residents (two fatal cases) from Community 2 in 2005, providing further evidence of presence of *R. rickettsii* in the region.

All patients with anti-*R. rickettsii* antibody titers ≥ 64 had titers that were at least fourfold lower to *R. rhipicephali*, suggesting that the infections were due to *R. rickettsii*. There is no evidence that *R. rhipicephali* is pathogenic for humans, and PCR confirmation of *R. rickettsii* in four patients during the 2003–2004 seasons (Demma et al. 2005) supports our assumption that anti-SFGR antibodies observed in this study are likely due to *R. rickettsii* exposure. However, we cannot dismiss the idea that the serologic response might result from exposure to another SFGR species not evaluated.

Sera collected from dogs in 1996 had evidence of antibodies to *R. rickettsii*, although at lower proportions, suggesting that this current intense focus of RMSF may be a relatively recent occurrence (Nicholson et al. 2006). Moreover, lack of dually reactive samples and lower prevalence to *R. rickettsii* and *R. rhipicephali* in 1996 suggests that the brown dog tick may have been present at lower densities and the recent emergence of RMSF in the region may be due to entry of *R. rickettsii* into an expanding tick vector population.

The current serologic prevalence in dogs could be confounded by exposure to other SFGR known or expected to exist in this area. We explored this possibility by assaying the serum samples for antibodies reactive with *R. rhipicephali*, another SFGR identified from ticks in this area. *R. rhipicephali* is related to, but distinct from *R. rickettsii* as shown by serologic responses in mice, guinea pigs, and dogs (Burgdorfer 1975, Gage and Jerrells 1992, Philip et al. 1978). Dogs exposed to *R. rhipicephali* developed moderate homologous antibody titers to *R. rhipicephali* antigen, but did not develop antibodies to *R. rickettsii* antigen (Burgdorfer et

al. 1978). Conversely, dogs exposed to *R. rickettsii* developed high antibody titers to the homologous antigen, and considerably lower titers against *R. rhipicephali* (Burgdorfer et al. 1978, Breitschwerdt et al. 1988). Studies in guinea pigs have characterized their crossreactive response as appearing late in the infection and due to lipopolysaccharide and rOmpB antigens (Gage and Jerrells 1992). A significant correlation ($p < 0.01$, Pearson's chi-square test) between the two SFGR antibody titers was observed in sera collected from both humans and dogs in 2003 and 2004, which may indicate that some cross-reactivity did occur in this analysis.

With the large populations of *Rh. sanguineus* present at these sites, we must assume that the measured canine antibodies are a mixture of homologous immune reactions to each agent, as well as the anamnestic responses to shared antigens by heterologous challenge. This complex mix of immune responses may not be possible to sort out and future studies should focus on establishing which species are circulating in the bloodstreams of the local dogs. Only one attempt was made to examine dog bloods by PCR and all 24 randomly chosen dogs were PCR-negative at the time of sampling (data not shown).

R. rhipicephali exhibits varying degrees of pathogenicity in experimental hosts ranging from occasional deaths in immunosuppressed voles to unapparent infection in dogs; dogs exposed to *R. rhipicephali* by needle inoculation or tick bite did not show clinical signs of infection, develop fever, or detectable rickettsemia (Burgdorfer et al. 1978, Norment and Burgdorfer 1984). When dogs previously exposed to *R. rhipicephali* were challenged with virulent *R. rickettsii*, rickettsemia of *R. rickettsii* was shortened in two dogs and eliminated in another (Burgdorfer et al. 1978). This suggests that prior infection by *R. rhipicephali* may influence and even protect dogs against *R. rickettsii* challenge.

Dogs have long been associated with RMSF cases in other endemic areas. In these areas, close association of dogs harboring large tick populations are known to increase the risk for the occurrence of human infection. The brown dog tick has long been known to be an efficient tick vector of experimental *R. rickettsii* infection, but had not been recognized as a signifi-

cant natural vector of the pathogen to humans in the United States (Parker et al. 1933). *Rh. sanguineus* has a worldwide distribution, and can be a vector of *R. rickettsii* in Mexico and *R. conorii* in the Mediterranean region (Bustamante and Varela 1947, Bustamante et al. 1946, Gilot et al. 1990).

Currently, the source of *R. rickettsii* introduction into this region is not known. The pathogen may have been introduced to the region by the translocation or immigration of rickettsemic dogs or wildlife from an endemic area such as central Mexico or regions outside of Arizona. There have been anecdotal reports of recent increases in deer and elk herds in northern Arizona and anecdotal reports of increases in local stray dogs that preceded the recent increase in human cases in Community 1. Another hypothesis is that a transient expansion of *D. variabilis* or *D. andersoni* ticks into the region may have introduced *R. rickettsii* into the local canine population and infected the *Rh. sanguineus* population through co-feeding. Presence of the expected vector ticks does not appear to be needed to maintain *R. rickettsii* in the communities, as a previous entomologic investigation conducted during the 2002–2004 outbreak investigation revealed no evidence of *Dermacentor* spp. ticks collected from dogs and the domestic environment in Community 1 (Demma et al. 2005).

The documentation of the emergence and endemic status of RMSF in this region is important to direct ongoing treatment, prevention, control efforts, and education to prevent human illness and death. These serologic findings demonstrate that *R. rickettsii* is likely present and indicate a potential risk for human infection in these particular communities. Expanded serologic surveys of dogs, which may act as sentinels for RMSF, may be helpful to further define the geographic boundaries of RMSF in the state. The documented presence of *R. rickettsii* antibodies in dogs and humans in Community 2 in 2004, followed by confirmation of human infection in this community in 2005, suggests that serologic evidence of exposure may be useful to predict areas of human risk for infection. Serosurveys and active surveillance for RMSF should be initiated in other communities in eastern Arizona with similar ecological conditions resulting in frequent hu-

man, dog, and tick interactions in order to ascertain risk for human exposure.

The broad distribution of *Rh. sanguineus* in the Western Hemisphere and its ecological differences from known *Dermacentor* tick vectors raises concerns over the introduction of RMSF into other areas of the United States previously considered unlikely to support transmission. Thus, physicians, health educators, and other community public health partners should maintain a heightened awareness of the clinical signs and symptoms and community awareness of RMSF regardless of the geographic region in which they practice, due to the potential for unexpected emerging disease patterns.

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