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Ying Bai

U.S. Centers for Disease Control and Prevention

Charles H. Calisher

College of Veterinary Medicine and Biomedical Sciences

Michael Y. Kosoy

U.S. Centers for Disease Control and Prevention

J. Jeffrey Root

College of Veterinary Medicine and Biomedical Sciences

Jeffrey B. Doty

College of Veterinary Medicine and Biomedical Sciences

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## Persistent Infection or Successive Reinfection of Deer Mice with Bartonella vinsonii subsp. arupensis<sup>∇</sup>

Ying Bai, 1\* Charles H. Calisher, 2 Michael Y. Kosoy, J. Jeffrey Root, 2† and Jeffrey B. Doty 2

Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, U.S. Centers for Disease Control and Prevention, Fort Collins, Colorado 80521, and Arthropod-Borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology and Pathology,

College of Veterinary Medicine and Biomedical Sciences, Colorado State University,

Fort Collins, Colorado 80523<sup>2</sup>

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Bartonella infections are common in rodents. From 1994 to 2006, longitudinal studies of a rodent community, consisting mainly of deer mice ( $Peromyscus\ maniculatus$ ), were conducted in southwestern Colorado to study hantaviruses. Blood samples from deer mice captured one or more times during the period 2003 to 2006 (n=737) were selected to study bartonellae in deer mice. Bartonellae were found to be widely distributed in that population, with an overall prevalence of 82.4% (607/737 mice). No correlation was found between bartonella prevalence and deer mouse weight or sex. Persistent or successive infections with bartonellae were observed in deer mice captured repeatedly, with a prevalence of 83.9% (297/354), and the infection appeared to last for more than 1 year in some of them. Persistent infection with bartonellae may explain the high prevalence of these bacteria in deer mice at this site and, perhaps, elsewhere. Genetic analysis demonstrated that deer mouse-borne bartonella isolates at this site belong to the same species,  $B.\ vinsonii$  subsp. arupensis, demonstrating a specific relationship between  $B.\ vinsonii$  subsp. arupensis and deer mice.

Bacteria of the genus *Bartonella* include a variety of genetically and phenotypically related hemotropic, facultative, intracellular, Gram-negative bacteria. Numerous investigations have demonstrated well that infections caused by these microorganisms are widespread in mammals of many species. Notably, bartonellae have been extensively studied in rodents from various regions of the world (4, 6, 9, 16, 19, 22, 28, 30, 35).

Whereas bartonella infections are prevalent in rodents, studies have shown that prevalences may vary among rodents of different species (3). For example, bartonella prevalence was 23% in black-tailed prairie dogs (*Cynomys ludovicianus*) (2) and >70% in Northern grasshopper mice (*Onychomys leucogaster*) (1). It is not clear how bartonella prevalence is maintained at such high levels in rodent communities. Previous studies have reported that increasing rodent age is inversely associated with bartonella prevalence (2, 13, 20) and that there is a continuous turnover of *Bartonella* genotypes in individual rodents during the infection period (5, 13, 20, 25, 32, 33).

Further, rodent-associated *Bartonella* species are very diverse genetically, having differing relationships with their hosts; investigations from North America and Asia suggested cospeciation of bartonellae with their rodent hosts (9, 20, 22, 35), whereas multiple rodent species may share the same *Bartonella* species in the United Kingdom (4). Although pathogenic effects of bartonellae are not commonly observed in rodents, some rodent-borne *Bartonella* species have been as-

To better understand the ecology of bartonellae and their rodent hosts, we selected a rodent community which consists primarily of deer mice (*Peromyscus maniculatus*) to conduct mark-release-recapture sampling and to study bartonella infection in the deer mice at this specific site. We determined the prevalence of bartonellae in the population by culturing the bacterium from deer mouse blood, evaluated the diversity of bartonella strains by comparing partial sequences of the citrate synthase gene (*gltA*), a marker commonly used for differentiating *Bartonella* species, and estimated successive bartonella infections in individual deer mice.

#### MATERIALS AND METHODS

Study site, trapping, and animal processing. Investigators at Colorado State University conducted longitudinal studies of Sin Nombre virus infections in deer mice at a site near Fort Lewis (37°13′31″N, 109°10′51″W) in southwestern Colorado from June 1994 to September 2006. More than 3,200 blood samples were taken from deer mice at the site during that >12-year study.

For logistical reasons, only samples collected from October 2003 to June 2006 were used in this study. The vegetation at this site is dominated by montane shrubland superimposed on intrusive igneous rocks forming laccoliths (14). A summary of the trapping details and of the results of trapping and testing of deer mice captured at this site was published for data collected from 1994 to 1997 (8).

Two trapping webs were established and trapping sessions conducted every 6 weeks, as weather and logistics permitted. Trapping was not done during the winter and early spring months (December to April), resulting in a total of 12 trapping sessions from October 2003 to June 2006. Rodents were trapped for

sociated with human infections, such as *B. elizabethae* in rats (11), *B. vinsonii* subsp. *arupensis* in deer mice (18, 34), *B. washoensis* in ground squirrels (24), and *B. grahamii* in voles (21). The mechanism of transmission of bartonella is not yet clear. Many believe blood-feeding arthropods, such as fleas, may play an important role in this process (7, 10, 15, 17, 29, 31). However, isolation of bartonellae from embryos and neonates of naturally infected rodents also suggests the likelihood of vertical transmission (23).

<sup>\*</sup> Corresponding author. Mailing address: Bacterial Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, 3150 Rampart Road, Fort Collins, CO 80521. Phone: (970) 266-3555. Fax: (970) 225-4257. E-mail: YBai1@cdc.gov.

<sup>†</sup> Present address: U.S. Department of Agriculture, Wildlife Services, National Wildlife Research Center, Fort Collins, CO 80521.

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three consecutive nights on each trapping occasion. Detailed trapping methods were published elsewhere (8). The rodent community consisted mainly of deer mice, with rodents of other species accounting for a small portion of the community. The present study was restricted to analysis of deer mouse samples.

Deer mice were processed by following safety procedures published by the U.S. Centers for Disease Control and Prevention (27). Details were published elsewhere (8). The species of mice were recorded, their sex and reproductive status determined, and their weight and other standard measurements taken. Capture status (first capture, recapture [different trapping sessions], or repeater [within the same trapping session]) was noted. Blood samples were collected from the retro-orbital plexus of new captures and recaptures. New captures were marked with uniquely numbered ear tags.

Bartonella culturing. Whole blood was diluted 1:4 in brain heart infusion broth supplemented with 5% amphotericin B to reduce the likelihood that bacterial and fungal contaminants would overgrow slow-growing bartonella bacteria, and then  $100~\mu l$  of diluted blood was plated on heart infusion agar containing 5% rabbit blood and incubated in an aerobic atmosphere with 5% carbon dioxide at  $35^{\circ}$ C for 4 weeks. Bacterial growth was monitored at the end of each week. Bacterial colonies were presumptively identified as bartonellae based on their morphology. Morphologically distinct colony types from each sample were identified individually. Subcultures of bartonella colonies from the original agar plate were streaked onto secondary agar plates, also supplemented with 5% rabbit blood, and incubated under the same conditions until sufficient growth was observed. Pure cultures were harvested and stored in 10% glycerol.

Verification of bartonellae by amplification of the citrate synthase gene (gltA). Bartonella isolates were verified by PCR amplification of a specific region in the citrate synthase gene (gltA) of bartonellae using primers BhCS781.p (5'-GGG ACCAGCTCATGGTGG-3') and BhCS1137.n (5'-AATGCAAAAAGAACAG TAAACA-3') to generate a 379-bp amplicon of the bartonella gltA gene. Genomic DNA was prepared by heating a suspension of microorganisms for 10 min at 95°C, followed by centrifugation of the lysed cells for 1 min at 6,000  $\times$  g. The supernatant was then transferred to a clean centrifuge tube to be used as the template DNA. PCR amplifications were performed in a PTC 200 Peltier thermal cycler (MJ Research, Inc., Taunton, MA). Positive and negative controls were included within each PCR assay to evaluate the presence of appropriately sized amplicons and contaminants, respectively. PCR products were separated and visualized by 1.5% agarose gel electrophoresis with ethidium bromide staining.

Sequencing and phylogenetic analysis of DNA. PCR products of appropriate size were purified with the QIAquick PCR purification kit (Qiagen, Valencia, CA) and sequenced in both directions using an Applied Biosystems model 3130 genetic analyzer (Applied Biosystems, Foster City, CA). Sequencing reactions were carried out in a PTC 200 Peltier thermal cycler using the same primers as in the initial PCR assay at a concentration of  $1.6~\mu M$ .

Sequences were analyzed using Lasergene (DNASTAR, Madison, WI) sequence analysis software to determine the consensus of sequences for the amplified region of the gltA gene. The Clustal V program within MegAlign was used to align and compare bartonella gltA sequences obtained from deer mouse samples in the present study with sequences from other Bartonella genotypes available from the public domain to determine homology. A genetic variant was defined when at least one nucleotide difference was present between sequences.

**Statistical analysis.** Chi-square analyses were performed using the SAS program (Statistical Analysis System, version 9.1; SAS Institute Inc., Cary, NC) to determine whether bartonella prevalences differed between sexes and weight groups.

#### RESULTS

**Trapping summary.** A total of 1,419 individuals, consisting of 1,275 deer mice (89.9%) and 144 other rodents (10.1%), were captured. Of the 1,275 deer mice, 737 were randomly selected for the present study; they consisted of 365 females and 372 males. Weights of the deer mice ranged from 6 g to 34 g. Deer mouse samples were separated into five mass classes at 4-g increments; there were 204 mice of  $\leq$ 14 g, 220 of 15 to 18 g, 229 of 19 to 22 g, 71 of 23 to 26 g, and 13 of  $\geq$ 27 g.

During the trapping period, most deer mice were captured once. However, 133 individuals were repeatedly captured. These included 75 mice captured twice; in addition, 36, 16, 4, and 2 mice were captured 3, 4, 5, and 6 times, respectively,

TABLE 1. Pattern of bartonella infection in 36 deer mice<sup>a</sup>

Bartonella infection at wk <sup>b</sup> :									
0	6	12	18	24	30	36	42	48	Total
+	+	+							15
+	+		+						2
+				+	+				4
+	+					+			2
+					+	+			1
+				+			+		1
+	+	_							1
_	+	+							1
_	+						+		1
+	_	+							3
+	_	_							1
_	_	+							2
+				_	_				1
+							_	_	1

 $<sup>^</sup>a$  Each mouse was captured three different times in Fort Lewis, CO, from October 2003 to June 2006.

resulting in a total of 354 capture times. The interval between any two captures ranged from 6 to 60 weeks (Tables 1 and 2).

Bartonella prevalence and temporal pattern by mass class. Bartonellae were cultured from 607 of 737 deer mice, giving an overall prevalence of 82.4%. Male and female deer mice were infected with bartonellae at about the same rate, 80.6% (300/372 mice) versus 84.1% (307/365 mice) ( $\chi^2 = 1.52$ , P = 0.22), respectively.

Among weight groups, bartonella prevalence was 79.9% (163/204), 86.8% (191/220), 79.9% (183/229), 81.7% (58/71), and 92.3% (12/13) for mice of  $\leq$ 14 g, 15 to 18 g, 19 to 22 g, 23 to 26 g, and  $\geq$ 27 g, respectively. There was no apparent difference in bartonella prevalence between weight (age) groups ( $\chi^2 = 5.7$ , P = 0.22).

Genetic similarity of bartonella isolates from the deer mice. gltA sequences were obtained from 221 bartonella isolates from 84 deer mice that had been captured at least twice. Sequencing analyses revealed six closely related genetic variants with similarities of 99.1 to 99.7% between themselves. These variants are 98.2 to 99.5% similar to B. vinsonii subsp. arupensis (GenBank accession no. AF214557), suggesting that all six variants identified in the present study belong to B. vinsonii subsp. arupensis, according to the species definition of La Scola et al. (26). The most common variant (named A) contained 192 of the 221 sequences and was identical to a bartonella isolate from a deer mouse in Nevada (GenBank accession no. AY064535). Five other variants named B, C, D, E, and F contained 11, 8, 4, 4, and 2 of the 221 sequences, respectively, and were identical to bartonella isolates previously obtained from deer mice in Arizona, Colorado, and Nevada, with GenBank accession no. AF489536, AY064533, AY589568, AF489538, and AF489537, respectively.

Successive infection with bartonella organisms and changes of *Bartonella* genotypes in recaptured deer mice. The overall prevalence of bartonella infection in repeatedly captured deer mice was 83.9% (297/354 mice). Of the 75 mice captured twice, 55 were positive for bartonella at both captures. Thirty-six mice that were captured three times were infected with bartonella at

 $<sup>^{</sup>b}$  +, infected with bartonella; -, uninfected with bartonella. Week 0 is the week of first capture.

<sup>&</sup>lt;sup>c</sup> Total, number of individuals exhibiting the pattern.

1730 BAI ET AL. APPL ENVIRON, MICROBIOL.

Mouse	No. of captures		Genetic variant <sup>b</sup> at indicated wk of capture										
		0	6	12	18	24	30	36	42	48	54	60	
1	4	A	A	A	A								
2	4	A	A	A	A								
3	4	A		A	A	A							
4	4	A		A	A	A							
5	4	A					A		A	A			
6	4	E					A	A		A			
7	4	A	A	В						В			
8	4	A	В						A	A			
9	4	A	A	A							A		
10	4	A		A	A	_							
11	4	A	_	A	A								
12	4	C	A	_	C								
13	4	A					_	A	A				
14	4	F					A	_	A				
15	4	A					A	_	A				
16	4	_	_	A	+								
17	5	A	A	A	A	A							
18	5	A					A	A	A	A			
19	5	A					_	_	_	A			
20	5	_	В	A							_	_	
21	6	A					A	A	A	_	A		
22	6	F					A	_	_	A	A		

TABLE 2. Status of bartonella infection and changes of Bartonella genotypes in deer mice<sup>a</sup>

1 to 3 captures, 16 mice captured four times were infected with bartonella at 2 to 4 captures, 4 mice captured five times were infected with bartonella at 2 or 5 captures, and 2 mice captured six times were infected at 4 or 5 captures (one mouse each). Bartonella infection in these mice was either consecutive or nonconsecutive. Infection may last as long as 60 weeks in some mice (Tables 1 and 2).

Bartonella gltA sequences were available for 79 mice that were captured multiple times and infected with bartonellae at at least at two captures. Of these, 57 remained infected with the same genetic variant, variant A, during the entire period of observation; the other 22 mice showed different variants at different capture occasions, and the results for 6 of them are shown in Table 2.

#### DISCUSSION

The present study reported bartonella infection in deer mice at a high prevalence (>80%). The results are in accordance with reports from other studies (4, 9, 19, 22, 35). Genetic analysis demonstrated that all bartonella isolates from deer mice were of *B. vinsonii* subsp. *arupensis*, with six genetic variants identified. Our findings support the fact that there is specificity of *Bartonella* spp. for their rodent hosts, at least in North America and some other regions (22, 35).

How bartonella infections are maintained at such high prevalences in rodent populations is puzzling. Our longitudinal study provides an explanation for such an observation. In this study, bartonellae were successively detected by mark-recapture techniques in repeatedly captured deer mice, consecutively or intermittently, for more than 1 year. Although deer mice can live up to 5 years in captivity, they survive for only a mean of about a year in the wild due to predation by foxes,

coyotes, snakes, and birds of many species. As a consequence of successive infections, most deer mice likely become infected during their lifetimes. Over time, a very high prevalence of infection develops in the population of surviving deer mice. Nonconsecutive infection may suggest that a mouse could clear the infection, perhaps through an immune mechanism. Nevertheless, it looks like the immunity does not last long, as many mice later became infected again, even with bartonellae of the same genotype.

Similar observations were reported earlier. Cotton rats can be infected with a bartonella strain that is different from the bartonella strain with which it had been infected, perhaps due to poor cross-protection against the related organism (25). This does not explain the findings from the present study. Although Bartonella variants may replace other variants, all Bartonella variants that we found in deer mice were of the same species and had very high similarities. In fact, an intermittent bartonella infection in deer mice may not be the case at all. It is possible that many mice have chronic, persistent infections, from which bartonellae were never completely cleared. A plausible explanation is that the deer mice were not free of infection but that their bacteremia levels were too low to be cultured and may be detected only by a more sensitive approach, such as PCR. An alternative explanation is that these bacteria can persist in a "hidden niche" in their latent form and can be reactivated and amplified from sequestration under specific conditions, such as sudden changes in surroundings. The ages of rodents, often assessed by their weights, have been found to be an important factor in assessing infection rates in a population. An inverse correlation of bartonella prevalence and ages of the rodent hosts has been reported in several studies (2, 13, 20, 25). Acquiring immunity was hypoth-

<sup>&</sup>lt;sup>a</sup> Mice were captured 4 to 6 times during a 60-week longitudinal study at 6-week intervals in Fort Lewis, CO, from October 2003 to June 2006.

<sup>&</sup>lt;sup>b</sup> The letters A to F represent the six bartonella genetic variants identified in deer mice. +, infected with bartonella, but no sequencing data are available; -, uninfected with bartonella.

esized to explain such a correlation (2). In the present study, we were not able to detect bartonella prevalence differences between age groups, and we did not observe a weight-dependent prevalence pattern. This might explain why deer mice may be found to be infected with bartonellae on different capture occasions, regardless of age. Moreover, the same very high prevalence of bartonellae in very young deer mice may suggest that vertical transmission of bartonellae has occurred. However, it is possible that the mice were quickly infected postpartum due to intimate contact with infected mice and by sharing bartonella-infected arthropods. Deer mice are well known to be involved in the natural cycles of Borrelia burgdorferi and other borreliae causing Lyme disease, as well as in the transmission of Sin Nombre virus, an etiologic agent of hantavirus pulmonary syndrome. The present study suggests that deer mice are the, or a, primary reservoir of Bartonella vinsonii subsp. arupensis, a species that has been associated with human bartonellosis (12, 34). The work reported here extends our understanding of the epidemiologic significance of deer mice and their public health importance as reservoirs of pathogenic agents.

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