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ASSOCIATION BETWEEN MOVEMENT AND SIN NOMBRE VIRUS (*BUNYAVIRIDAE*: *HANTAVIRUS*) INFECTION IN NORTH AMERICAN DEERMICE (*PEROMYSCUS MANICULATUS*) IN COLORADO

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ABSTRACT: Capture data from long-term, mark-recapture studies were used to evaluate movements of North American deermice (*Peromyscus maniculatus*) on mark-recapture webs in Colorado with respect to Sin Nombre virus (SNV) infection status, age, sex, and trapping site. Latitude and longitude coordinates for each capture during the approximately 12-yr study were used to produce an individual minimum convex polygon (MCP) area representing the movements (not home range) of an individual mouse over time. These MCP areas were compared by SNV infection status (as determined by the presence of antibody), age, and sex. Antibody-negative deermice had significantly larger mean MCP areas than did antibody-positive mice. No differences in MCP area were found between male and female mice (either positive or negative). The smaller MCP areas of antibody-positive mice correspond to decreased movement by SNV-infected deermice on the trapping webs. These findings may indicate that SNV has a negative effect on movement, perhaps by reducing the health of infected deermice.

Key words: Deermouse, fitness, hantavirus, mark-recapture, minimum convex polygon, movement, *Peromyscus maniculatus*, Sin Nombre virus.

INTRODUCTION

Hantavirus pulmonary syndrome (HPS) is a severe, acute respiratory disease endemic to the Americas (Bausch and Ksiazek, 2002), which was first identified after an outbreak in the southwestern United States in 1993 (Nichol et al., 1993). Investigations following the outbreak led to isolation of the etiologic agent, Sin Nombre virus (SNV), and the identification of the reservoir host, the North American deermouse (*Peromyscus maniculatus*; hereafter referred to as deermice; Childs et al., 1994). Sin Nombre virus (*Bunyaviridae*, *Hantavirus*) is one of more than 40 recognized hantavirus genotypes in the New World, 17 of which occur in North America (Mills et al., 2010). Six of these North American viruses are known to cause HPS in humans (Ksiazek et al., 1995). Among these, SNV has caused the greatest number of recognized infections in humans. Since the initial outbreak in 1993, 580 HPS cases have been reported in 34 states with a case-fatality ratio of 36% (CDC, 2012).

The 1993 outbreak prompted the initiation of long-term ecologic studies in several states in the western United States. (Mills et al., 1999; Douglass et al., 2001); studies were undertaken to monitor hantavirus infection in rodent populations and to investigate the ecologic dynamics of virus infection in rodent host populations. This research has resulted in a greatly improved understanding of the ecology of the rodent host and the prevalence of the

antibody against SNV and other hantaviruses in rodent populations throughout the western United States (Douglass et al., 1996, 2001, 2007; Mills et al., 1997, 1998, 1999; Abbott et al., 1999; Calisher et al., 1999a, 2001, 2007). Specifically, this research has shown that 1) gender and age biases exist within populations of deermice with respect to infection with SNV (Calisher et al., 1999a, 2007; Douglass et al., 2001, 2007); 2) recently infected Montana deermice were more likely to be males in breeding condition (Douglass et al., 2007); and 3) transmission of SNV in deermice may occur through seasonal interactions, possibly behaviors associated with breeding (Root et al., 2005; Bagamian et al., 2012), and intraspecific aggressive encounters (Calisher et al., 1999a; Douglass et al., 2001). Despite this knowledge, many questions remain regarding the basic biological relationships between rodent reservoir hosts and hantaviruses. Two aspects of these relationships that have received recent attention are the effects of hantavirus infection on hosts (Douglass et al., 2001, 2007; Kallio et al., 2007) and the identification of behavioral characteristics (Klein et al., 2004) that predispose hosts for infection. For example, the relative extent of movement by individual hosts has been used as a measure of host health (Mills et al., 1991) as well as a factor contributing to the hosts' risk of exposure to SNV and other hantaviruses (Mills et al., 1999; Root et al., 1999; Calisher et al., 2001).

Several studies have addressed movement of rodents in their natural habitat (Wolff, 1985; Douglass, 1989; Ribble and Millar 1996; Calisher et al., 1999b; Ribble et al., 2002; Sommaro et al., 2010). There also has been consideration of rodent movement with respect to potential infection with SNV. Because males typically have larger home ranges than do females (Wilson and Ruff, 1999), it has been hypothesized that a higher prevalence of SNV infection in males may be because their larger home ranges contribute to their being involved in additional aggressive encounters (Calisher et al., 2001; Mills and Childs, 2001). Root et al. (1999) reported a positive association between SNV antibody prevalence and distance moved for certain age groups of Colorado deermice; however, in that study, movement may have been influenced by differences in the type and amount of vegetative cover.

Several additional studies have been undertaken to better understand associations between mouse mobility and SNV infection. Movements of sylvan and peridomestic deermice have been studied to help explain recognized differences in antibody prevalence between these two populations (Douglass et al., 2006). Lonner et al. (2008) investigated SNV antibody prevalence in dispersing deermice, and Waltee et al. (2009) examined seasonal dispersal and timing of seroconversions. None of these studies, however, directly compared nondispersal movements between infected (antibody-positive) and uninfected (antibody-negative) mice.

Our objectives were to analyze movements of deermice on Colorado trapping webs using a minimum convex polygon (MCP; Mohr, 1947) measurement as well as a minimum-linear-distance-moved measurement and to examine the relationship between infection with SNV and movement as defined by these measures. Our intent was not to estimate home range of deermice but to examine differences in movements on the scale of a trapping array. To control for potential confounders known to be associated with the prevalence of SNV infection in deermice (i.e., sex, age, and site-specific differences) we employed a multiple-regression model that considered all of these variables simultaneously.

MATERIALS AND METHODS

Rodents were sampled on trapping webs located in southwest Colorado, La Plata County (Hesperus, 37°13′30.9″N, 108°10′51.1″W, altitude 2,438 m), and in west central Colorado, Mesa County (Molina, 39°09′45.8″N,

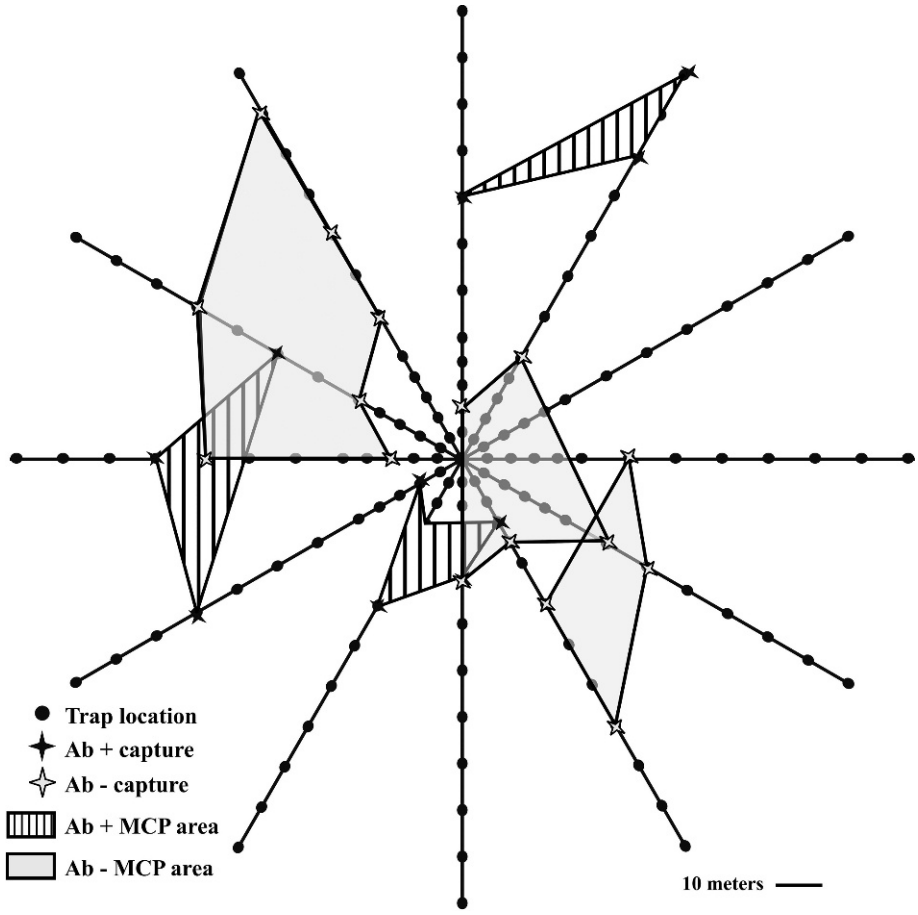

FIGURE 1. An illustration of minimum convex polygons (MCP) on a web-based trapping array for individual deermice comprising three or more trap locations (captures) over time. Ab^+ = antibody-positive for Sin Nombre virus (SNV), Ab^- = antibody negative for SNV, cross-hatched areas represent an MCP area of an individual Ab^+ North American deermouse (*Peromyscus maniculatus*) with three or more captures over time, and shaded areas represent an MCP area of an individual Ab^- deermouse with three or more captures over time.

108°03′18.4″W, altitude 1,951 m). For approximately 12 yr (June 1994 to October 2006), two webs at each site were trapped for three consecutive nights every 6 wk, with the exception of winter months (November–March) when the webs were inaccessible. Each web contained 145 live traps (7.6×8.9× 22.9 cm; H .B. Sherman Traps, Inc. Tallahassee, Florida, USA) baited with a mixture of cracked corn, rolled oats, and peanut butter. Traps were arrayed in 12 transects of 100 m, radiating outward at 30° increments from a single trap placed in the center (Fig. 1). Twelve traps were placed along each transect with the first three traps placed at 5-m intervals, and the eight remaining traps placed at 10-m intervals.

Captured rodents were transported to a central processing area where standard measurements and weights were recorded; processing followed biosafety guidelines published by the Centers for Disease Control and Prevention (CDC; Mills et al., 1995). Each rodent was classified to sex, based on physical inspection of external genitalia, and reproductive condition and was marked with a stainless steel ear tag stamped with a unique identification number (Mills et al., 1999). Blood samples were collected from the retro-orbital sinus of anesthetized rodents using heparinized capillary tubes. After blood samples were taken, rodents were returned to traps and allowed to fully recover from the anesthesia before being released at the exact site of

capture. Antibody assays were conducted using enzyme-linked immunosorbent assay (ELISA; Feldmann et al., 1993) to detect immunoglobulin G (IgG) antibodies to SNV in blood samples of each rodent. The assays were conducted at Colorado State University and confirmed at the CDC (Atlanta, Georgia, USA). As has been demonstrated for numerous hantaviruses (e.g., Lee et al., 1981; Yanagihara et al., 1985; Hutchinson et al., 1998), deermice with antibodies reactive to Sin Nombre virus are considered chronically infected and persistently shedding. All procedural protocols were approved by the CDC Institutional Animal Care and Use Committee.

Capture data were used to create MCPs from which movement area could be calculated. Juveniles (mice weighing <14 g; Calisher et al., 2007) were excluded from the analyses because antibody in juveniles can represent passively acquired maternal antibody (Mills et al., 1997; Glass et al., 1998). Including juveniles with passively acquired SNV antibodies could have negatively biased the estimated movement area of antibody-positive adult mice with established territories. Excluding juveniles, a distinction was made between younger and older mice using the mean body weight of 21 g for all mice as a point of separation—"younger" mice were defined as those weighing 14–20 g; those ≥21 g were considered "older."

To estimate movement for a particular rodent, an MCP was generated using the Geospatial Modeling Environment (GME; formerly Hawth's Tools, http://www.spatialecology.com/gme), an extension for the ArcGIS 9.3.1 (ESRI, Redlands, California, USA) geographic information system software, in combination with the open-source statistical software R (R Core Development Team, v. 2.12.0; R Foundation for Statistical Computing, Wien, Austria). The MCP is a polygon that encompasses the locations of all points, thereby creating a convex polygon "hull," which, for our study, represents the spatial extent of mouse movement. Universal Transverse Mercator (UTM) coordinates were recorded for every trapping station within the web using a global positioning system. We compiled a list of all trapping stations where an individual rodent was captured and used the UTM coordinates as the input data for generating each MCP. Because at least three nonlinear points are required to define a polygon, an MCP was generated for a rodent only if at least three nonlinear captures at different trap stations, in one or more sessions, were recorded throughout the capture history of that rodent (Fig. 1).

We developed a multiple linear regression model to identify the effects of SNV antibody status, sex, age, and trapping site on mouse movement as defined by MCP area. To meet the assumptions of linear regression, we normalized the polygon area using a natural log transformation. Because actual home range is larger than the area used on a trapping web (Douglass, 1989), the area of the polygon would be expected to increase with an increasing number of capture points over time. To control for number of captures as a possible confounder, the log-transformed polygon area for each rodent was adjusted by dividing by the number of trapping sessions (defined as any session during which the rodent could have been captured [i.e., was known to be alive], even if the rodent was not captured) between the first and last capture of that rodent. We developed interaction terms to assess the independence of effects of SNV antibody status, sex, age, and site on MCP area. Visual examination of a normal probability plot confirmed a normal distribution of residuals about the regression line for the final model. Criteria used for inclusion in the model were set at $\alpha=0.05$ and exclusion at $\alpha=0.01$. Nightly and monthly linear movements were also examined using the Mann-Whitney *U*-test. Statistical analyses were completed using PASW Statistics Release version 18.0.0 (SPSS Statistics, Rel. 18.0.0. SPSS Inc., Chicago, Illinois, USA).

RESULTS

The data presented herein represent a portion of a much larger effort: more than 102,000 trap nights and more than 3,400 deermouse captures (which include recaptures) at the two Colorado sites throughout the 12-yr study. Of these mice, 537 had detectable antibody to SNV, for an overall combined period prevalence of 17.2% (Table 1). The overall antibody prevalence at the Hesperus, Colorado, USA, site (20.7%) was significantly greater than it was that at the Molina, Colorado, USA (10.6%; $\chi^2=61.229$, df=2, $P<0.001$). A total of 542 individual deermice were captured three or more times. Of these 542 mice, 154 (102 males; 52 females) had antibodies to SNV and were eligible for determining MCP area (Table 2). Given that it takes a deermouse about 2 wk or longer to develop a detectable IgG antibody response, we considered mice that

TABLE 1. Trapping summary and prevalences of antibody to Sin Nombre virus (SNV$^+$) in North American deermice (*Peromyscus maniculatus*) at Hesperus and Molina, Colorado, USA, 1994–2006 (includes juvenile mice).

Web[a]	Duration[b]	TN[c]	Captures	No. tested	SNV$^+$			Prevalence[d]
					Total	Male	Female	
Hesperus								
ha	12 (4)	27,115	1,076	1,055	186	128	58	17.6
hb	12 (4)	27,260	1,132	990	238	149	89	24.0
Total		54,375	2,208	2,045	424	277	147	20.7
Molina								
ma	12 (0)	23,925	613	606	52	28	24	8.5
mb	12 (0)	23,780	585	464	61	37	24	13.1
Total		47,705	1,198	1,070	113	65	48	10.5
Total all sites		102,080	3,406	3,115	537	342	195	17.2

[a] ha = Hesperus grid A; hb = Hesperus grid B; ma = Molina grid A; mb = Molina grid B.

[b] Duration = yr (mo).

[c] TN = trap nights (*number of traps*×*number of nights set*).

[d] Prevalence = *number SNV antibody-positive/number tested.*

seroconverted between captures as antibody-positive and that they were infected for a sufficiently long period that the infection would have affected their movement. This assumption almost certainly would have meant that we assigned some movements by antibody-negative mice to antibody-positive mice. This error would have decreased the power of our analyses in finding significant differences in MCP area between infected and uninfected deermice. Had we not made this assumption, however, the sample size of the antibody-positive MCPs would have been too small to allow analysis at all.

One-way analysis of variance (ANOVA) demonstrated statistically significant differences in MCP area among sites, ages, and SNV status, for minimums of three, four, and five or more captures over two or more trapping sessions (Table 3). There were no significant differences in MCP area between sexes. Mean MCP areas for three or more captures over one or more trapping sessions (Table 4) are expressed as adjusted means where $\bar{X}_{\text{adjusted}}$ is the mean of the normalized and time-controlled data. To examine potential confounding factors by interaction of these variables on MCP area, a stepwise multiple linear regression using data from one or more capture sessions and three or more captures was performed. The stepwise linear regression produced a model in which site, SNV infection, and age were all highly significant indicators of MCP area (F=47.416; df=3, P=<0.001). Infection with SNV (β=−0.163; P<0.001) and

TABLE 2. Numbers of adult deermice (>14 g; *Peromyscus maniculatus*) and numbers of Sin Nombre virus (SNV) antibody-positive North American deermice captured three or more times during one or more trapping sessions at two Colorado, USA, sites, by sex and age class, 1994–2006. Younger mice are those less than the overall mean weight (21 g); older mice are those heavier than or equal to the mean.

Site	Deermice	Male	Female	SNV$^+$			Age	
				Total	Male	Female	Younger	Older
Hesperus	340	178	162	125	87	38	170	170
Molina	202	110	92	29	15	14	116	86
Totals	542	288	254	154	102	52	286	256

TABLE 3. Results for one-way analysis of variance (ANOVA) performed on minimum convex polygon (MCP) area generated by three, four, and five or more captures of North American deermice (*Peromyscus maniculatus*) over two or more trapping sessions in Colorado, USA, 1994–2006. df=1 (between groups), $n=2$ (within groups).

		MCP-site		MCP-age		MCP-SNV$^+$		MCP-sex	
	n	F_{stat}	P	F_{stat}	P	F_{stat}	P	F_{stat}	P
3+ captures	481	67.215	<0.05	9.575	<0.05	40.773	<0.05	2.931	0.088
4+ captures	380	70.216	<0.05	8.466	<0.05	29.918	<0.05	0.801	0.371
5+ captures	264	65.468	<0.05	10.736	<0.05	22.793	<0.05	0.787	0.376

age ($\beta=-0.152$; $P<0.001$) were negatively associated with MCP area, and site was positively associated with MCP area ($\beta=0.917$; $P<0.001$; Table 5). No other variables, including interaction terms, had significant effects and, therefore, did not enter the model. A stepwise linear regression was also performed on a truncated data set from two or more capture sessions (three or more captures separated by 6 wk, $n=481$) with the same results as the data from one or more capture sessions (three or more captures within a single capture session, $n=542$).

A three-way ANOVA was also performed in an attempt to identify different variables that may have entered the model when all variables were included, but the results were identical to the stepwise linear regression. We chose to present the results of the stepwise linear regression to demonstrate the absence of confounding variables.

We also examined the effect SNV infection had on day-to-day and month-to-month linear movements. Because the data did not meet the normality assumption of ANOVA, we used a Mann-Whitney *U*-test to analyze the linear movements. For the day-to-day movements of deermice at the two sites, no statistically significant difference in minimum distance moved was observed between mice with antibody to SNV ($\bar{X}=22.47$ m, median=15.86 m, SD=22.01) and mice without antibody ($\bar{X}=22.19$ m, median=15.52 m, SD=22.76; $P=0.601$). Zero values (mice captured in the same trap on two nights) were included in the analysis. Similarly, no significant difference in minimum distance moved on a month-to-month basis was found between mice with antibody to SNV ($\bar{X}=33.19$ m, median=30.0 m, SD=21.93) and mice without antibody ($\bar{X}=35.62$ m, median=30.0 m, SD=24.81; $P=0.710$).

DISCUSSION

Although we primarily focused on the relationship between infection with SNV and MCP area, age and site also had significant effects on MCP area independent of infection with SNV. Average MCP area was greater for younger mice than it was for older mice. This supports the

TABLE 4. Mean minimum convex polygon (MCP) areas for deermice (*Peromyscus maniculatus*) in Colorado, USA, are expressed as adjusted means, where $\bar{X}_{adjusted}$ is the mean of the normalized and time-controlled data (see "Materials and Methods").

	SNV infection		Age		Site		Sex	
	Negative	Positive	Younger	Older	Hesperus	Molina	Female	Male
MCP[a]	2.75	1.99	2.77	2.27	2.14	3.19	2.49	2.57
SD	1.31	1.04	1.37	1.21	1.01	1.43	1.08	1.44
n	388	154	286	256	340	202	254	288

[a] MCP = $\bar{X}_{adjusted}$ minimum convex polygon area in square meters.

TABLE 5. Results of a multiple linear regression analysis for minimum convex polygon (MCP) area occupied by North American deermice (*Peromyscus maniculatus*) in Colorado, USA, 1994–2006. Combines Hesperus and Molina, Colorado, USA, trapping sites. Predictor variables were constant: site, Sin Nombre virus (SNV) antibody status, and age; dependent variable was MCP area.

	Unstandardized coefficients		Standardized coefficients		
Model[a]	*B*	SE	*B*	*t*	*P*
Constant	2.514	0.087		28.767	0.000
Site	0.917	0.105	0.344	80.713	0.000
SNV	−0.466	0.113	−0.163	−40.112	0.000
Age	−0.391	0.100	−0.152	−30.920	0.000

[a] Site = Hesperus and Molina, Colorado, USA; SNV = antibody to Sin Nombre virus vs. no antibody to Sin Nombre virus; Age = above vs. below 21-g mean body weight.

findings of Root et al. (1999) that younger male rodents at the same Colorado, USA, trapping sites examined in this study moved greater linear distances between trapping occasions than did older rodents of either gender. Waltee et al., (2009) found that more adult deermice dispersed on two large trapping grids in Montana, USA, than did subadults. These seemingly contrasting findings, however, may be because these studies measured two different variables. Although Waltee et al., (2009) measured dispersal (usually considered as one-way directional movement) on the scale of hundreds of meters, our study and that of Root et al. (1999) measured movements by resident animals on the scale of a single trapping web. In our study, most of the MCP areas were calculated using long-term cumulative movement, usually over a period of several months.

Despite previous findings that male deermice typically have larger home ranges than do females (Blair 1940; Williams 1955; Merritt and Merritt 1980; Wilson and Ruff 1999), we found no significant differences in MCP area between sexes. Previous trap-based studies were conducted on grids (not webs) and were conducted for more than three nights. Both of these factors might have allowed for more captures and more data points for calculating movement, perhaps providing more accuracy or, at least, greater variability in measures of movement. Root et al. (1999) also found no difference between adult males and adult females at these sites but demonstrated that movement of subadult males was greater than movement of adult females. These findings are consistent with our data, which indicate that male and female deermice in Colorado, USA, had similar long-term movement patterns on trapping webs. The Root et al. (1999) findings, as well as ours, represent movement by deermice while on a trapping web and, as with all trap-based studies, are influenced by the presence of traps filled with food. We found that MCP area differed among sites (Hesperus, Colorado, USA, vs. Molina, Colorado, USA), which have different vegetation features: the vegetative cover was dense at Molina and relatively sparse at Hesperus. Root et al. (1999) hypothesized that differences in vegetative cover at these same two Colorado sites contributed to differences in distances deermice moved there—smaller linear movements occurred in dense cover (Molina, Colorado, USA) than in sparse cover (Hesperus, Colorado, USA). However, our data indicate the opposite. The mean MCP area at the sparse vegetative cover site of Hesperus ($\bar{X}_{\text{adjusted}}$=2.14 m^2, SD=1.01) was smaller than at the dense vegetative cover site, Molina ($\bar{X}_{\text{adjusted}}$=3.19 m^2, SD=1.43). Given that mice with antibody to SNV had smaller MCP areas, it is tempting to explain this difference in MCP area based on the higher number of antibody-positive mice at Hesperus relative to the number of positive

mice at Molina ($n=110$ and 44, respectively; Table 2), Colorado, USA. The larger number of positive mice with smaller MCP areas at Hesperus, Colorado, USA, resulted in a smaller average MCP area for the site as a whole. However, the lack of a significant interaction term between site and SNV infection with respect to MCP area ($P=0.451$) indicates that this explanation likely is incorrect.

The observed differences in MCP areas may be related to predation risk. Open microhabitat presents a greater risk of predation by raptors and other visually oriented predators. Deermice are extremely vulnerable to owl predation for example (Longland and Price, 1991), and, as noted by Pierce et al. (1992), deermice routinely climbed into the brush canopy to avoid predation by rattlesnakes. The dense vegetative cover at Molina, Colorado, USA, could have provided a means of predator avoidance as well as created a safer environment for the mice, thereby resulting in increased movement.

Our primary goal was to determine whether there were differences in movement between deermice infected with SNV and those that were not infected. We found that SNV antibody-positive mice had significantly smaller MCP areas than did antibody-negative mice. Older animals are much more likely to be antibody-positive (Calisher et al., 2001), and, as evidenced by our study and that of Root et al. (1999), older animals move lesser distances than do younger animals (perhaps because they establish territories in higher-quality microhabitats, among other reasons). Thus, it could be hypothesized that our finding of lesser movement by antibody-positive deermice might be associated with age. A second logical hypothesis is that the antibody-positive mice move less because most of them were found at the Hesperus, Colorado, USA, site, where cover was lower. However, these explanations are not supported by our statistical analysis, which indicated that the significant effect of SNV antibody status on MCP area was independent of both site and age.

After consideration of all alternatives, we believe that the most plausible explanation for the smaller MCP areas is that SNV infection in deermice causes a reduction in health and a subsequent decrease in movement. Prior research investigating the effects of hantavirus infection on rodents has yielded conflicting results. Hantavirus infection in rodent hosts has typically been thought to be asymptomatic, resulting in no overt morbidity (Meyer and Schmaljohn, 2000) or pathology (Botten et al., 2001, 2003). However, Netski (1999) reported that deermice infected with SNV had similar disease pathology to that found in humans infected with SNV. Further, other recent field studies have suggested that deermice naturally infected with SNV experience detrimental effects. Douglass et al. (2007) found that recently infected, male deermice gained less weight during a 1-mo period than did uninfected, male deermice. Two other field studies reported a significantly lower survivorship (measured by residence time on the study site) in juvenile and subadult Montana deermice that had antibodies reactive against SNV (Douglass et al., 2001) and among male deermice as well as adults in breeding condition (Luis et al., 2012), suggesting a reduction in fitness after SNV infection.

Botten et al. (2003) reported a transition from acute infection to persistent infection in laboratory-infected deermice between 60 and 90 days postinoculation. In our study, SNV infection status is based on solely the presence or absence of antibodies to SNV in mice examined at 6-wk intervals. Therefore, most mice represented herein would have been in the persistent (postacute) phase of infection for at least some, if not most, of their capture history. Under these assumptions, the finding that SNV infection is the best variable to explain the effects on deermouse movements on the webs suggests that SNV infection may cause a chronic health effect (illness) in deermice.

Changes in mouse behavior or physical condition following infection (e.g., decreased movement, increased aggression, decreased weight gain) are difficult to confirm using typical longitudinal field studies because sampling is infrequent and the precise time of infection is unknown. These changes might more effectively be studied using laboratory experiments (e.g., Klein et al.) or newly developed techniques, such as frequent sampling (and perhaps positional monitoring) of small numbers of mice in seminatural outdoor enclosures (Bagamian et al., 2012).

The suggestion that SNV infection causes decreased fitness in infected deermice warrants additional research on home range and movement at other trapping arrays in the western United States. We hope that these studies will lead to a better understanding of the cause and effect relationships between pathogen transmission and movement patterns for hantaviruses and their rodent hosts as well as other host pathogen systems.

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