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NATURAL HISTORY OF SIN NOMBRE VIRUS INFECTION IN DEER MICE IN URBAN PARKS IN OREGON

Laurie Dizney,[1,4] Philip D. Jones,[2] and Luis A. Ruedas[2,3]

[1] Department of Biology, University of Utah, 257 South 1400 East, Salt Lake City, Utah 84112-0840, USA
[2] Department of Biology, Portland State University, PO Box 751, Portland, Oregon 97207-0751, USA
[3] Museum of Vertebrate Biology, Portland State University, PO Box 751, Portland, Oregon 97207–0751, USA
[4] Corresponding author (email: l.dizney@utah.edu)

ABSTRACT: Sin Nombre virus (SNV), one of at least 45 hantaviruses described worldwide, is hosted by the deer mouse, *Peromyscus maniculatus*, a common species throughout most of North America. Herein, we describe general life-history characteristics of deer mice and the ways in which these factors relate to the incidence of SNV infections among populations of this host species in and around Portland, Oregon. In total, 3,175 deer mice were captured from October 2002 to September 2005. Transmission of SNV appears to be associated with male breeding behaviors, as more males and adults were infected than expected by capture rate; spring and summer had the highest infection prevalence, as well as scrotal male captures. Wounding rates between infected and uninfected deer mice were not different in any age or sex class. Capture rates were significantly and positively related to the interaction of temperature departure from normal, total precipitation, and number of clear days from two seasons previous ($P=0.029$), while infection prevalence was significantly and negatively related to the capture rate of juveniles from two seasons previous ($P=0.029$).

Key words: Deer mouse, infection prevalence, *Peromyscus maniculatus*, Sin Nombre virus, zoonotic disease.

INTRODUCTION

In recent years, there has been a surge of newly described zoonotic diseases (Kruse et al., 2004; Jones et al., 2008). Hantaviruses present a model system to explore host-parasite ecology (Yates et al., 2002), not only to understand hantavirus transmission dynamics, but also to elucidate the mechanisms of disease emergence. Sin Nombre virus (SNV) is the hantavirus of greatest public health concern in the US (Monroe et al., 1999; Fulhorst et al., 2007), and deer mice (*Peromyscus maniculatus*) have been identified as its primary rodent reservoir (Childs et al., 1994). Because of the broad geographic distribution of the host, and because the virus is thought to be environmentally transmitted to humans through aerosolized deer mouse excreta (Doyle et al., 1998), SNV potentially poses a large risk to human health. Notwithstanding, many aspects of the host's ecology remain elusive (Yates et al., 2002), and in the absence of a treatment or cure, a more complete understanding of host-virus population dynamics is required in order to predict and prevent future outbreaks of this potentially fatal human disease.

Portland, Oregon, has a metropolitan area population of 1.8 million people and a park system totaling over 5,100 ha. Most of these parks are natural areas with trails that are in relatively close proximity to habitations, thus increasing the opportunity for direct and indirect contact between deer mice and humans. Despite this disease potential, most research into the ecology of SNV transmission to date has occurred either at confirmed hantavirus pulmonary syndrome (HPS) case sites or in rural areas. Urban parks have not been investigated, but these may constitute areas with great potential for pathogen transmission to humans. Transmission of SNV within reservoir populations appears to be horizontal, occurring primarily due to bites during aggressive intraspecific encounters (Mills et al., 1999). Aggression increases in males during the breeding season and in females when defending their young (Wolff, 1989), suggesting SNV

transmission could vary seasonally. Climatic factors may also affect SNV prevalence in host populations (Parmenter and Vigil, 1993; Abbott et al., 1999; Engelthaler et al., 1999; Douglass et al., 2001; Yates et al., 2002). The rainy, relatively mild climate of western Oregon presents a set of environmental conditions that have yet to be assessed in relation to SNV–deer mouse interactions, despite confirmed human cases of HPS (eight in Oregon, 39 in Washington since 1994). The aim of this study was to examine host-virus population dynamics in urban parks in the Portland, Oregon, area and the ecologic factors associated with variation within this system.

MATERIALS AND METHODS

Study sites

Five forested sites were sampled in the Portland, Oregon, area from October 2002 to September 2005: Forest Park (45.5916°N, 122.7983°W); Tryon Creek State Park (45.4337°N, 122.6690°W); Powell Butte Park (45.4837°N, 122.5059°W); Oxbow Regional Park (45.4879°N, 122.2970°W); and Tualatin River National Wildlife Refuge (TRNWR; 45.3957°N, 122.8305°W). Four of the sites were secondary forest sites, and Oxbow was the only old-growth site. The predominant native tree at all sites is Douglas fir (*Pseudotsuga menziesii*), and each site has varying amounts of western hemlock (*Tsuga heterophylla*), western red cedar (*Thuja plicata*), and Oregon big-leaf maple (*Acer macrophyllum*). A detailed description of the study sites is provided elsewhere (Dizney et al., 2008).

Trapping and processing

One trapping web (Parmenter et al., 2003) was established in each of the five parks and used from October 2002 to September 2005. To trap as many animals as possible, three different trap types were used. One folding aluminum Sherman® and one similar-sized wire-mesh live-trap modeled after O'Farrell et al. (1994) were placed at each trap station, except for the center of the web, where two Sherman live-traps and two wire-mesh traps were placed 90° apart. Additionally, 19-l (30-cm-diameter, 36-cm-height buckets) pitfalls were placed at the 20-, 50-, and 100-m trap station of each line. Each trapping event lasted four consecutive nights; traps were checked once daily in the morning. Each study site was trapped 19 times over 3 yr (six–seven times per year spaced approximately 8 wk apart) for a total of 124,640 trap nights. Traps were baited with peanut butter and rolled oats, and polyester batting was added to reduce cold-induced mortalities. This research was conducted under the auspices of federal, state, and city permits, and complied with the Animal Care and Use Guidelines of the American Society of Mammalogists (Gannon et al., 2007).

All captures were treated as if infected with SNV (Mills et al., 1995a). Animals were identified to species, and weight, sex, age, reproductive condition, and scarring were recorded (Mills et al., 1995b). Blood was taken from the retro-orbital sinus and tested for immunoglobin G (IgG) antibodies to SNV by enzyme-linked immunosorbent assay (ELISA; Feldmann et al., 1993). During the first 2 yr of the study, deer mice were euthanized using a chloroform chamber (Mills et al., 1995b) for use in a companion study. During the last year of the study, deer mice were marked with an ear-tag and released at the location of capture. Animals that died were deposited at the Museum of Vertebrate Biology at Portland State University.

Data analysis

Since the trapping protocol changed for the third year of the study, a *t*-test was used to ensure that data from the three years could be combined. The first two years involved removal sampling, where captures were euthanized and were therefore no longer part of the population, whereas during the third year, captured animals were released. To determine whether removal affected subsequent capture rates within the same trapping period, differences between number of captures on the first and last day of the trapping period were calculated, averaged, and compared between removal and replacement sampling; there was no significant difference between the first two years and the third year of the study ($t=0.50$, $P=0.63$). For subsequent analyses, all years were therefore treated jointly.

Four age categories of deer mice were used. Juveniles were defined by their pelage. Non-juvenile deer mice were assigned to three different mass categories to approximate age: subadults if <16 g, young adults (≤ 1 yr) from 16 to 20 g, and old adults (>1 year) if >20 g. For statistical analyses, deer mice were counted only once per trapping period. SNV infection prevalence was inferred from antibody prevalence, and in order to compare all

TABLE 1. The number of deer mice captures within each category and the frequency that number represents within the given age or sex category. *Indicates significantly more and + indicates significantly fewer deer mice infected or wounded compared to the expected number based on capture rates. Significance was based on a test for homogeneity of proportions with Yates' continuity correction when only two proportions were evaluated, or a Fisher's exact test for count data when one or more expected frequencies were less than five.

	Captures	Frequency	Infected	Frequency
Males	1620	0.51	97	0.68*
Females	1555	0.49	45	0.32+
Juveniles	170	0.06	1	0.01+
Subadults	1050	0.34	22	0.15+
Young adults	1446	0.47	91	0.64*
Old adults	432	0.14	28	0.20
Wounded males	109	0.68*	8	0.61
Wounded females	52	0.32+	5	0.39
Wounded juveniles	2	0.01+	0	0.00
Wounded subadults	38	0.24	3	0.23
Wounded young adults	82	0.51	7	0.54
Wounded old adults	39	0.24*	3	0.23

three years of the study, infected deer mice were counted one time only, during the first capture. Data for the five parks were combined even though one site (Forest Park) accounted for the majority of infected deer mice. This was done because all parks showed similar trends in infection but had too few infected individuals during a given season or year to be separately analyzed with confidence. To standardize numbers of deer mice captures due to occasional unequal sampling effort among seasons and years, data are presented as capture rates (number of captures/total number of trap nights during a given time period). Infection prevalence was calculated as the number of infected deer mice divided by the total number of deer mice captured for a given time period. Deer mouse densities (deer mice per ha) were calculated for each park using the DISTANCE program, following Parmenter et al. (2003). For the purposes of this study, winter was defined as January through March, spring was April–June, summer was July–September, and fall was October–December.

Statistical analyses were undertaken using R (R Development Core Team, 2006). Significance levels were set at 0.05. Proportions (infection prevalence, capture rates) were compared with a test for heterogeneity of proportions (Zar, 1999). When only two proportions were compared, Yates' continuity correction was applied (Brower et al., 2002). Fisher's exact test for count data was used when one or more expected frequencies were less than five (Crawley, 2002). Linear regression was applied to test the relationships between climatic factors and capture rates, as well as the relationship between deer mice density, capture rate, and juvenile capture rate and infection prevalence, for the same season, for the previous season, and for two seasons previous (Crawley, 2002). Climate data were obtained from the Oregon Climate Services archives (http://www.ocs.oregonstate.edu/index.html) for the station nearest to all study sites (45°35′N, 122°36′W; Multnomah County Oregon). Climatic variables considered were: average temperature, average temperature departure from normal (DFN), total precipitation, average precipitation DFN, number of days with more than 0.25 mm, 2.5 mm, and 13 mm of rainfall, number of days with a minimum temperature of less than 0 C, number of days with the maximum temperature above 32 C, number of clear days, number of partly cloudy days, and number of cloudy days. All climatic variables were analyzed singly and in combination with all other variables.

RESULTS

Captures

In total, 3,175 deer mice were captured over 3 yr (Table 1). Most of the animals captured were young adults, followed by subadults, old adults, and juveniles. Males were wounded significantly more often than expected by capture rates ($\chi^2=4.64$, $P=0.03$), and females were wounded significantly less than expected ($\chi^2=6.27$,

TABLE 2. Seasonal capture data of deer mice. The number of total captures for each category is given. To standardize captures, total capture value for each season was divided by the trap effort for that season. The resulting capture rates were compared with a test for homogeneity of proportions with Yates' continuity correction. *Indicates significantly more and + indicates significantly fewer captures compared to other seasons.

	Captures	Winter	Spring	Summer	Fall
Total	3,175	0.0252	0.0272	0.0242+	0.0253
Scrotal	850	0.0042	0.010*	0.0091*	0.0037
Pregnant	127	0.0012	0.0011	0.0013	0.0005+
Subadult	1,004	0.0095*	0.0072	0.0068	0.0087*
Juveniles	181	0.0009	0.0009	0.0018*	0.0020*

$P=0.01$). Wounds were observed on 82 young adults, followed by 39 old adults, 38 subadults, and two juveniles. However, when viewed as the proportion of wounded mice within each age class, wounding increased with age: 0.01 for juveniles, 0.04 for subadults, 0.06 for young adults, and 0.09 for old adults. Only old adults were wounded significantly more than expected by capture rates ($\chi^2=9.21$, $P=0.002$), while juveniles were wounded significantly less ($\chi^2=4.16$, $P=0.04$), and subadults were wounded marginally less ($\chi^2=3.09$, $P=0.078$).

More deer mice were captured in spring than other seasons (Table 2), although the pairwise difference was only significant between spring and summer ($\chi^2=5.2$, $P=0.022$). Breeding preparedness showed a seasonal bias: Scrotal males were significantly more abundant in spring and summer versus fall and winter ($\chi^2=151.81$, $P<0.001$). Fewer pregnant females were captured in fall than any other season (winter: $\chi^2=7.96$, $P=0.005$; spring: $\chi^2=5.69$, $P=0.017$; summer: $\chi^2=10.08$, $P=0.001$). The second winter (W2) had unusually high numbers of deer mice, including pregnant females. In that winter, 33 pregnant females (26% of captured adult females) were captured, compared to zero and two (0% and 6% of captured adult females) during the other winters. When W2, with its unusually high numbers of pregnant females, was taken out of the analysis, winter captures of pregnant deer mice were significantly lower than any other season (spring: $\chi^2=16.38$, $P<0.001$; summer: $\chi^2=20.93$, $P<0.001$; fall: $\chi^2=5.34$, $P=0.02$). More juveniles were caught in summer and fall than winter and spring ($\chi^2=20.07$, $P<0.001$), and more subadults were caught in fall and winter than spring and summer ($\chi^2=15.58$, $P<0.001$). The regression analysis showed a significant and positive relationship between an interaction of temperature departure from normal, total precipitation, and number of clear days and the capture rate two seasons later ($R^2=62.28$, $P=0.029$).

The number of deer mice caught varied substantially among years (Table 3); capture rate in year two (Y2) was highest, followed by Y3 and Y1 ($\chi^2=174.4$, $P<0.001$). Many of the annual differences in this study can be attributed to the winter of Y2 (W2: Table 3). More adult, old adult male, and pregnant deer mice were caught in W2 than either W1 or W3 (all $\chi^2>44.77$, all $P<0.001$). More juveniles were captured in W2 than W3 ($\chi^2=5.19$, $P=0.022$).

Infection prevalence

In total, 142 deer mice with antibody to SNV were caught over the 3-yr study: 45 females and 97 males (Table 1). Young adults had the greatest number of infections (91), followed by old adults (28), and subadults (22). Young adults were infected significantly more often than would be expected based on their overall capture rate ($\chi^2=5.86$, $P=0.016$), subadults and

TABLE 3. Annual differences in deer mouse captures. The top number gives the number of captures. The bottom number is the number of captures divided by trap nights during the given time period, giving a standardized capture rate. *Indicates a significance difference between years according to a test of homogeneity of proportions with Yates' continuity correction.

	Year 1	Year 2	Year 3	Winter 1	Winter 2	Winter 3
Total captures	669	1,522	984	137	385	204
	0.019*	0.033*	0.023*	0.021	0.037*	0.017
All adults	355	966	669	50	251	123
	0.010*	0.021*	0.015*	0.008	0.024*	0.010
Old adult males	34	97	58	1	32	2
	0.0009	0.0021*	0.0013	0.0002	0.0030*	0.0002
Pregnant	12	77	38	0	33	2
	0.0003*	0.0017*	0.0009*	0.0000	0.0031*	0.0002
Juveniles	72	76	33	7	15	5
	0.0020	0.0017	0.0008*	0.001	0.0014*	0.0004*

juveniles were infected significantly less than expected ($\chi^2=10.58$ and 4.75, $P=0.001$ and $P=0.029$, respectively), and old adults were infected more than expected, though not significantly so ($P=0.10$). Males made up a significantly larger proportion of the infected animals ($\chi^2=4.39$, $P=0.036$) compared to noninfected animals, and thus females made up significantly less ($\chi^2=5.97$, $P=0.015$).

There were no differences in the frequency of wounding in infected versus uninfected deer mice by age class or sex (Fisher's exact test, $P>0.97$ for all; Table 1) or in infection prevalence between wounded and unwounded deer mice ($P>0.83$ for all; Table 1).

Infected deer mice were captured in all seasons (Fig. 1), but the highest prevalence occurred in summer, followed by spring, fall, and winter. Summer infection prevalence was significantly greater than fall and winter (summer vs. fall $\chi^2=8023$, $P=0.004$; summer vs. winter $\chi^2=26.17$, $P<0.001$) and marginally greater than spring (summer vs. spring $\chi^2=3.70$, $P=0.054$). Thirteen infected deer mice were captured in Y1, 76 in Y2, and 53 in Y3, but when viewed as prevalence, Y3 had the highest levels of infection, although not significantly more than Y2 ($P=0.75$). Y1 prevalence was less than either Y2 or Y3 ($\chi^2=9.60$, $P=0.002$ and $\chi^2=10.59$, $P=0.001$ respectively).

The linear regression revealed that the only significant relationship between SNV infection in deer mice and deer mice density, capture rate, and juvenile capture rate (Table 4) was a negative one between infection prevalence and the juvenile capture rate two seasons previous ($F=7.087$, $R^2=0.40$, $P=0.029$; Fig. 2).

DISCUSSION

The frequency of captures in different age classes indicates the active population is primarily constituted by young adults, followed by subadults, old adults, and juveniles. Only 14% of the captures in this

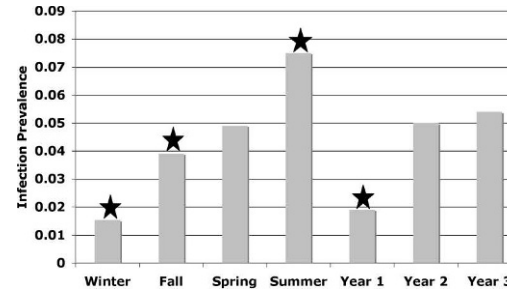

FIGURE 1. The seasonal and annual frequency of Sin Nombre virus (SNV) infection in deer mice. ★ indicates significance for a test of homogeneity of proportions with Yates' continuity correction utilized when two proportions were compared. All pairwise comparisons between seasons were significantly different from one other except for fall and spring. Year one had significantly lower infection prevalence than either year two or three.

TABLE 4. Deer mouse infection prevalence, overall capture rate, juvenile capture rate, and density across the 12 seasons of this study.

	Fall	Winter	Spring	Summer
Year 1				
Infection prevalence	0.018	0.007	0.006	0.045
Capture rate	0.029	0.019	0.017	0.026
Juvenile capture rate	0.0041	0.0010	0.0010	0.0020
Density (per ha)	14.29	6.52	5.92	14.01
Year 2				
Infection prevalence	0.031	0.013	0.066	0.075
Capture rate	0.019	0.042	0.048	0.036
Juvenile capture rate	0.0013	0.0013	0.0017	0.0018
Density (per ha)	10.19	28.87	27.78	17.14
Year 3				
Infection prevalence	0.053	0.029	0.045	0.124
Capture rate	0.035	0.020	0.027	0.019
Juvenile capture rate	0.0013	0.0004	0.0000	0.0011
Density (per ha)	13.42	9.95	11.83	8.53

study were in the largest weight class, suggesting that most deer mice do not usually live beyond 1 yr in the wild, particularly not surviving the winters (Table 3). Wounds were present among individuals of all ages, and prevalence of wounds increased with age, suggesting aggressive behavior starts young and continues throughout life. The primary seasons for mating among deer mice in Oregon appear to be spring and summer, as evidenced by the capture of more scrotal males and pregnant females during those seasons, and more juveniles captured in the summer and fall. There were at least some scrotal males, pregnant females, and juveniles during all four seasons, suggesting some breeding year-round.

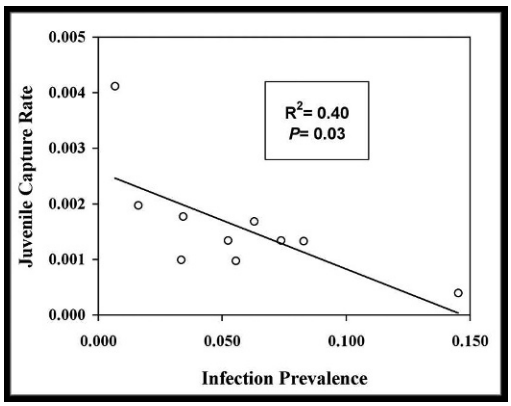

FIGURE 2. The relationship between deer mice infection prevalence and juvenile capture rate two seasons previous using linear regression (R^2=0.40, P=0.029).

Deer mouse abundance varied significantly among years. Similar annual fluctuations have been shown in other seasonal climates (Calisher et al., 2000; Douglass et al., 2001; Bowman et al., 2008) and desert biomes (Mills et al., 1999), and are hypothesized to be associated with food availability (Gashwiler, 1979; Parmenter and Vigil, 1993; Yates et al., 2002). After good seed crop years, Falls et al. (2007) found that deer mouse populations peaked, more adults overwintered, and breeding started earlier. Although not measured during this study, our data suggest that the wetter, warmer spring of Y2 led to high seed production in the fall, as evidenced by the significantly higher frequency of adults that survived the winter and capture rates of juveniles and pregnant females during W2.

SNV infection was more frequent in adults and males than expected by capture rate, and less frequent in juveniles,

subadults, and females, and the highest infection prevalence was in summer, followed by spring. These findings are consistent with the hypothesis that aggressive behaviors among males are an important means of SNV transmission (Mills et al., 1999) and are likely due to breeding. The male bias in infection could be due to males moving more than females, and thus being more likely to encounter other deer mice (Wolff, 1989). However, the similar capture rates between males and females found in this study do not support this hypothesis. One juvenile had antibodies to SNV, likely due to transient maternal antibodies (Botten et al., 2000).

Several studies have suggested that wounding is related to infection with SNV (Glass et al., 1988; Mills et al., 1998; Calisher et al., 1999); our data do not support those findings. The higher frequency of infected subadults with wounds found in this study, although not significant, suggests that dispersal may be a particularly efficient time in life for SNV transmission. However, the low overall numbers of infected and wounded deer mice make any conclusions difficult.

Some studies that suggest deer mouse density (Biggs et al., 2000) and capture rate (Calisher et al., 2007) are positively correlated to infection prevalence; others, including ours, have found no such relationship (Douglass et al., 2001). Our findings showed that the third summer had the highest infection prevalence of the study, although capture rates and densities were among the lowest. The high infection prevalence of Y3, and particularly the third summer, is likely explained by the low number of juveniles that were added to the population. Juveniles dilute infection prevalence, as seen in the previous years. The linear regression revealed that juvenile capture rate negatively affected infection prevalence two seasons later. Thus, following juvenile capture rates, at least in this study, was a better indicator of infection prevalence than either overall capture rate or density. Presumably, and as evidenced from the increased juvenile capture rate of the third summer, the incidence of infection would decrease to Y1 levels by spring or summer of the following year (Adler et al., 2007).

Removal sampling during the first 2 yr of the study theoretically could have affected subsequent captures or infection transmission. We believe this to be highly unlikely because: 1) all parks, regardless of deer mouse density or capture rates, showed similar trends, suggesting population dynamics were not disrupted, 2) the first and third years of the study (the second year had such large numbers of deer mice that a comparison seems inappropriate) showed no difference in the number of subadult deer mice ($\chi^2=0.25$, $P=0.62$), the age class we would expect to catch in greater numbers if a significant number of territories had been freed by removal sampling and taken over by dispersers, and 3) we assume that removal sampling would have taken a sample proportional to the population structure of the entire population, thus not changing, but possibly instead leading to underestimation of, both population numbers and infection prevalence.

The Pacific Northwest offers a unique set of climatic factors that undoubtedly affect the population of deer mice and the transmission of SNV. This study demonstrates that deer mouse populations in Oregon vary annually, and that this variation might be tied to food resources, supporting a bottom-up regulatory force. Long-term studies in differing environments can elucidate the factors underlying SNV–deer mice dynamics in order to build models that can predict times of high SNV prevalence, thus protecting the public from this zoonosis.

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