The Role of Heterogeneity in the Persistence and Prevalence of Sin Nombre Virus in Deer Mice

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ABSTRACT: Many diseases persist at a relatively low prevalence, seemingly close to extinction. For a chronic disease in a homogeneous population, reducing the transmission rate by a fraction proportional to the prevalence would be sufficient to eradicate the disease. This study examines how higher prevalence of the Sin Nombre virus in male deer mice (*Peromyscus maniculatus*) might contribute to disease persistence. Analyzing data from over 2,000 individual mice captured in 19 sites over 4 years, we found prevalences of 18.5% in males and 8.8% in females. By examining recaptures, we determined that males are more likely to contract the infection because of higher susceptibility or higher encounter rates. Comparing across 86 sampling periods, we found a higher proportion of males when population densities were low. A capture-recapture analysis indicates that males live longer than females. A mathematical model based on the measured parameters and population size trajectories suggests that the combined heterogeneity in encounters, susceptibility, and mortality may buffer the disease from extinction by concentrating disease in the subgroup most likely to transmit the disease. This buffering effect is not significantly stronger in a fluctuating population, indicating that these forms of heterogeneity might not be the key for disease persistence through host population bottlenecks.

Keywords: hantavirus, Sin Nombre virus, sex-biased transmission.

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For an infectious disease to persist, it must have hosts to infect and a sufficiently high rate of infecting those hosts (Lloyd-Smith et al. 2005*a*). When hosts become rare, diseases are at risk of local extinction because of reduced transmission (Swinton et al. 2002) or stochastic die-off (Begon et al. 2003; Conlan and Grenfell 2007) or when other environmental factors reduce disease persistence within hosts, host contact rates, or probability of transmission. Diseases at low prevalence, like other rare species, would seem most prone to extinction due to small changes in host densities or environmental factors.

In a homogeneous population, the equilibrium prevalence p^* of a disease without acquired immunity or vertical transmission from parent to offspring is related to the basic reproductive number R_0, the number of new infections caused by the first infected individual (Anderson and May 1992), according to

$$p^* = 1 - \frac{1}{R_0}, \text{ or}$$

$$R_0 = \frac{1}{1 - p^*} \quad (1)$$

(app. A in the online edition of the *American Naturalist*). In this simple case, a reduction of R_0 by a fraction p^* reduces R_0 below 1 and leads to disease extinction. For example, 20% prevalence corresponds to $R_0 = 1.25$. In directly transmitted diseases, R_0 is proportional to the transmission rate between individuals. A chronic disease with 20% prevalence would thus be eradicated by a long-term 20% decrease in the transmission rate. In rodents, which experience large changes in host population size and possibly in contact rates over a range of timescales (Fryxell et al. 1998; Mills et al. 1999), reductions in R_0 below 1 could persist for long enough to drive the disease to extinction.

For diseases with recovery and acquired immunity, the reduction in transmission required for disease eradication is much larger. In measles, which has rapid recovery and lifelong immunity, a tiny value of p^* (far less than 1%)

corresponds to a value of R_0 greater than 10 (Anderson and May 1992; app. A).

Acquired immunity creates one type of heterogeneity in a host population. Other forms of heterogeneity, including host encounter rates, infectiousness, and susceptibility, can affect the relationship between prevalence and persistence. Theory developed in the context of sexually transmitted diseases has focused on heterogeneity in encounter rates. Because these rates appear nonlinearly in the expression for R_0, a heterogeneous population has a higher value of R_0 than a homogeneous population with the same average rate of encounters between individuals (Lajmanovich and Yorke 1976; Castillo-Chavez et al. 1989; Adler 1992). In contrast, infectiousness and susceptibility both appear linearly, and the value of R_0 depends only on their respective means (Galvani and May 2005), although they can interact to alter R_0 when their covariance is nonzero (Becker and Marschner 1990).

Other studies suggest that heterogeneity of infection risk is an important parameter to include in disease models. For example, heterogeneity in contacts in a model of bovine tuberculosis (*Mycobacterium bovis*) in possums (*Trichosurus vulpecula*) decreases the population level impact of the disease and increases the difficulty of disease elimination (Barlow 2000). Similarly, sexually mature male yellow-necked mice (*Apodemus flavicollis*) with large body size garner a large proportion of ticks (Perkins et al. 2003), and treatment or removal of these hosts would have a disproportionate effect on the prevalence of the encephalitis the ticks carry.

In contrast, studies that normalize the value of R_0 rather than the underlying properties of individual hosts find that heterogeneity in infectiousness can increase the probability of extinction in the initial stages of an epidemic. In this case, the first infected individuals are unlikely to be the so-called superspreaders that contribute disproportionately to R_0 (Galvani and May 2005; Lloyd-Smith et al. 2005*b*).

Disease persistence is also closely tied to the total host population size itself (Ostfeld et al. 1996). If the hosts that are most likely to carry and transmit the infection are the hosts that survive population crashes, the disease is more likely to persist through bottlenecks. If those same hosts instead were the hosts most likely to die during periods of decline, the bottleneck acts much like a targeted control measure and effectively eliminates the disease (Barlow 2000; Perkins et al. 2003).

For directly transmitted diseases, the interaction between host heterogeneity and population size fluctuations depends on how contact rates vary with host density. Models range from a constant-contact (or frequency-dependent) model, where the contact rate is independent of population size, to a mass-action (or density-dependent) model, where the contact rate is proportional to population size (McCallum et al. 2001). With a mass-action model, fluctuations in the host population have larger effects on persistence because contact rates decrease when the population size becomes small.

The Sin Nombre virus (SNV) provides a well-studied example of long-term persistence at relatively low prevalence (summarized in Adler et al. 2008). This pathogen, primarily of deer mice (*Peromyscus maniculatus*), has received extensive attention since the first large human outbreak in the southwestern United States in 1993–1994 (Schmaljohn and Hjelle 1997; Engelthaler et al. 1999). Deer mice remain infected for life (Mills et al. 1999; Kuenzi et al. 2005). There is no vertical transmission from parents to offspring, but offspring of infected mothers can carry protective maternal antibodies for a time (Borucki et al. 2000). The most likely route of transmission is through direct contact of deer mice during aggressive encounters (Botten et al. 2002). Scarring has been used as a measure of aggressive interaction (Botten et al. 2002), and several studies have found scarring to be positively correlated with seropositivity (Calisher et al. 1999, 2007; Douglass et al. 2001).

Many studies have identified associations between SNV infection and host characteristics. Most prominently, there is a widespread finding of higher prevalence in males (Mills et al. 1997; Boone et al. 1998; Douglass et al. 2001; Calisher et al. 2005, 2007; Allen et al. 2006). A recent study identified this pattern in adults but found no such effect in juveniles and subadults (Calisher et al. 2007), perhaps due to the presence of maternal antibodies (Borucki et al. 2000).

Several studies have found higher prevalence in individuals with higher mass (Mills et al. 1997; Escutenaire et al. 2000; Douglass et al. 2001; Calisher et al. 2007). Because mass generally increases with age in mice, this is to be expected in a chronic pathogen. A steeper slope of the relationship between prevalence and mass in males than in females may indicate more rapid acquisition by older males (Calisher et al. 2007) but could also be due to more rapid weight gain in females. A recent study directly examined seroconversion (from seronegative to seropositive status) and found higher rates in adult males in breeding condition (Douglass et al. 2007).

This study uses an extensive data set collected from more than 2,000 deer mice captured over the course of 4 years in the west desert of Utah for an investigation of the causes and consequences of higher prevalence in males. We use logistic regression to identify factors associated with seropositivity in the population of animals at their initial capture and parametric survivorship models to study seroconversion in the smaller number of animals that were recaptured in multiple seasons. In addition, we look at factors leading to observed patterns of sex-ratio bias, focusing on the role of differential survivorship in the two sexes.

We hypothesize that three types of heterogeneity may

be important in this disease: higher susceptibility, higher encounter rates, and higher survivorship in males. We construct and parameterize a mathematical model to examine the importance of these factors for disease persistence and prevalence. Specifically, we predict (1) heterogeneity in encounter rates will contribute to disease persistence in a stable population, (2) heterogeneity in mortality will magnify this effect in a fluctuating population, and (3) heterogeneity in susceptibility will have little effect on prevalence in either stable or fluctuating populations.

Methods

Field Data

Deer mice were nondestructively sampled from 19 different sites near the West Tintic Mountains in the Great Basin Desert of central Utah (Juab and Utah counties; Lehmer et al. 2007). A total of 2,032 deer mice were captured at least once, with 166 recaptured in a subsequent season and 1,658 recaptured within the same season (a total of 3,856 captures). Captures took place over 19 sites using a 3.14-ha trapping web (Mills et al. 1999) during each spring (May and June) and fall (August–October) in the years 2002–2005. Each site was trapped for 3–7 nights during a season. Mouse densities per hectare were computed as the number captured divided by 3.14. Not all sites were trapped in each of the eight possible season and year combinations, leading to a total of 86 such combinations.

Animals were identified to species, weighed and sexed, and given uniquely numbered ear tags (Lehmer et al. 2007). Mice had reproductive status determined by visual estimation of external reproductive condition (recorded as positive for lactating or perforate females and scrotal males; Botten et al. 2002; Calisher et al. 2005) and scarring (present or absent) recorded by visual examination. On their first capture in any given season, mice were tested for SNV exposure with enzyme-linked immunosorbent assays for antibodies (immunoglobulin G) against SNV in blood in a laboratory (biosafety level 3) at the University of Nevada, Reno (Otteson et al. 1996). To correct for differences in technique, season, and year, a mass z score was computed as the number of standard deviations from the mean mass for that sex, season, and year. Juveniles were not excluded because mass z score, often used to identify young animals, was included in the analyses.

Statistics

All statistical analyses were done in R, version 2.4.0 (R Development Core Team 2007). To analyze the probability of seroconversion (transition from seronegative to seropositive status) in mice recaptured in a later season, we used maximum likelihood to fit models of the form

$$\Pr(\text{mouse } i \text{ seropositive}) = 1 - e^{-[\alpha_0(1+\Sigma\alpha_j X_{ij})]T_i}, \quad (2)$$

where X_{ij} is the value of covariate j in mouse i, α_j is the coefficient, and T_i is the time between captures of mouse i. Covariates considered were scarring, mass z score, sex, and season. For a given model, the maximum likelihood was found using the "optim" function in R. Covariates were included in the final model if they increased the log likelihood by more than 2.0. Confidence limits were estimated by computing where the log likelihood decreased by 2.0 (Edwards 1972; Hilborn and Mangel 1997) using the "uniroot" function in R.

We used logistic regression ("glm" in R with the binomial family; Hosmer and Lemeshow 2000) to analyze the factors associated with seropositivity in the initial captures. We first tested the effects of season, year, sex, scars, reproductive status, mass z score, and population size in a univariate analysis. We then included those in a full model without interactions and used backward selection (with a $P = .1$ cutoff) to remove insignificant terms. We tested for interactions between male sex and the other covariates using forward selection (adding terms with $P < .05$). We also used logistic regression to test for factors associated with the proportion of males. In each case, we report the results on the final multivariate model.

To estimate the probability of capture and apparent survivorship, we extracted a series of events for each mouse starting on its date of first capture, using the Cormack-Jolly-Seber model with a constant survival probability per unit time (Brownie et al. 1986; Nichols 2005). For each subsequent trapping night at that site, the mouse was recorded as either trapped or not trapped. For each mouse, the log likelihood of a given record is

$$\ln(L) = -\delta(t_l - t_f) + c\ln(p) + m\ln(1-p) + \ln\left[1 - p\sum_{t_j > t_l}(1-p)^{j-1}e^{-\delta(t_j - t_l)}\right],$$

where δ is the estimated probability of disappearance during 1 day, p is the probability of capture conditional on presence, t_l is the last day that mouse was seen, t_f is the first, c is the number of times captured between the first and last nights, m is the number of times missed between the first and last nights, and t_j is the jth date after t_l for trapping at that site. The total log likelihood was found by summing over all mice. There were 2,039 mouse/date combinations when a mouse known to be alive could have

been recaptured and was not, and there were 15,917 mouse/date combinations after the last sighting.

To test for effects of sex and seropositivity, models were built with different parameters (values of δ and p) for each subgroup, parameters that were optimized with the "optim" function in R, and improvement in model fit was tested with the likelihood ratio test (Hilborn and Mangel 1997). We tested for the effects of mass z score by setting $\delta = \delta_0 + \delta_1 z$ and testing whether δ_1 differs significantly from 0.

Empirical Results

The populations at the 19 sites fluctuated around a mean of 7.98 mice/ha (fig. 1*A*). The infection prevalence averaged 13.2% across sites (fig. 1*B*) and was uncorrelated with the current population density but was significantly correlated with the density 1 year earlier.

Sex-Biased Prevalence and Population Sex-Ratio Bias

Of the 2,157 initial captures in any season with a recorded sex, 81 out of 915 females (8.8%) and 230 out of 1,242 males (18.5%) were seropositive ($\chi^2 = 39.1$, $P < .0001$). Overall prevalence was 14.4% in individuals. Of the 86 combinations of site, season, and year, 69 had at least one seropositive individual, meaning that the infection was absent in 17, or nearly 20%, of samples. Of these 69, 54 had male prevalence greater than female prevalence, one

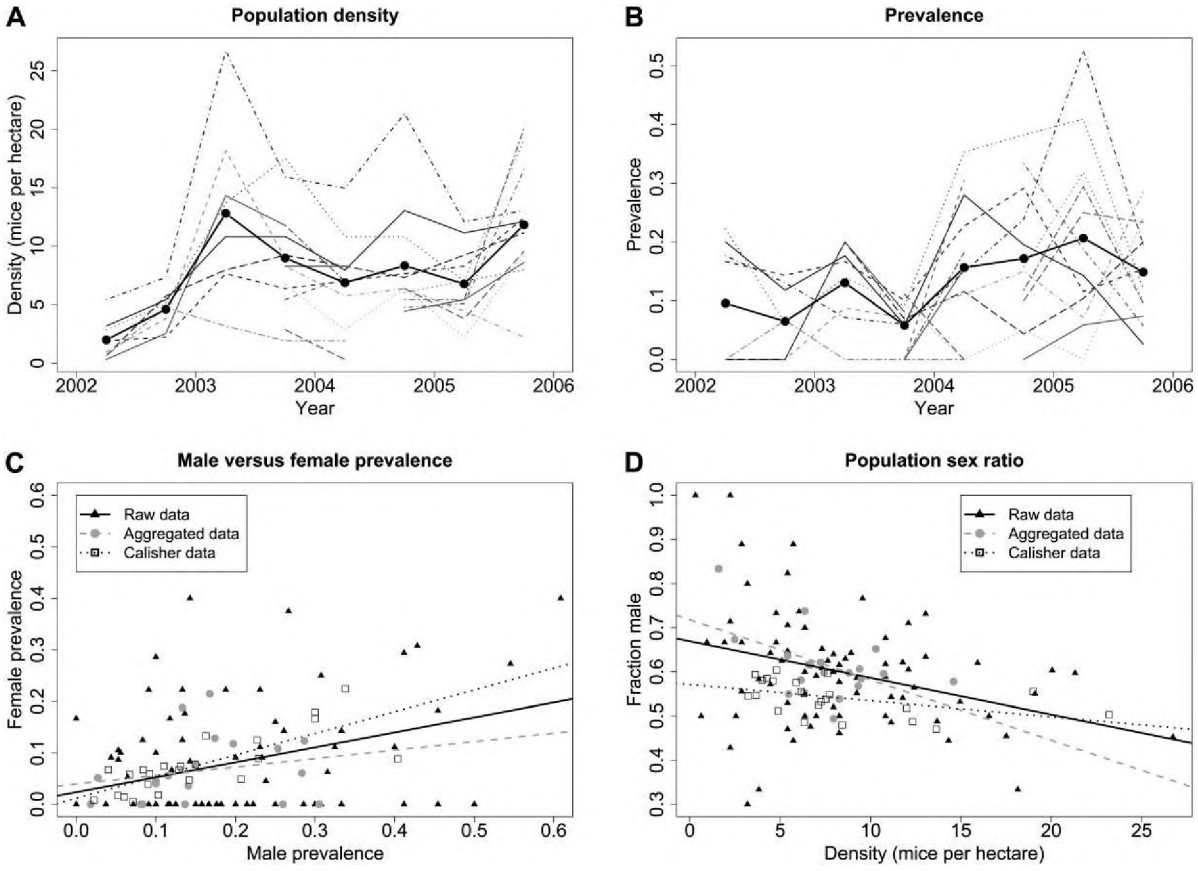

Figure 1: Summary of empirical data. *A*, Trajectories of population density at the 19 sites (*gray lines*) and the average population density (*solid black line*) over the course of the study. *B*, Trajectories of prevalence at the 19 sites (*gray lines*) and the average prevalence (*solid black line*). *C*, Relationship of male and female prevalence at the full set of 86 measurements (*triangles*), the measurements aggregated by site (*circles*) and data from the 23 sites reported by Calisher et al. (2007; *squares*). Linear regression lines are included for illustration. Male and female prevalence are significantly correlated with the raw data (Kendall's $\tau = 0.26$, $P < .01$) and the Calisher data (Kendall's $\tau = 0.63$, $P < .0001$) but not for the aggregated data (Kendall's $\tau = 0.25$, $P = .14$). *D*, Relationship of the proportion of males with the total mouse density for the full set of 86 measurements (*triangles*), the measurements aggregated by site (*circles*) and data from the 23 sites reported by Calisher et al. (2007; *squares*). Linear regression lines are included for illustration. The population sex ratio and density are significantly correlated with the raw data (Kendall's $\tau = -0.20$, $P < .01$) and the Calisher data (Kendall's $\tau = -0.39$, $P < .01$) but only marginally so with the aggregated data (Kendall's $\tau = -0.32$, $P = .06$).

had equal prevalence, and 14 had male prevalence lower than female prevalence (fig. 1*C*). The relationship between male and female prevalence is similar to that in a recent study of the same two species (Calisher et al. 2007), where reported results pooled measurements in sites over several seasons. For more direct comparison, figure 1*C* also shows male and female prevalence after combining over seasons and years, giving 19 data points of which 17 show male-biased prevalence.

The fraction 0.568 of males, based on the 1,146 males and 871 females captured at least once, differs significantly from 0.5 ($\chi^2 = 37.49$, $P < .0001$). However, this difference is due at least in part to the higher probability of trapping males (see below). The observed fraction of males depends on the population density, with more male-biased populations in sites with lower density (Kendall's $\tau = 0.20$, $P < .01$; fig. 1*D*). Again, the recently published data of Calisher et al. (2007) show a similar, if weaker, trend than found in our data aggregated by site.

Sex-Biased Prevalence

We looked in two ways for factors leading to higher male prevalence: (1) using maximum likelihood to identify factors associated with seroconversion in mice that were captured in multiple seasons and (2) using logistic regression to identify factors associated with seropositivity for each mouse at its initial capture. Of the 166 individuals recorded as recaptured in a different season, 123 were seronegative on their initial capture and had consistently recorded data on sex, mass, and scars. Of these, 22 out of 82 males seroconverted, as did five out of 41 females. Using a parametric survival model (eq. [2]), maximum likelihood identified two factors associated with seroconversion, male sex, and mass *z* score (table 1). The interaction between these factors was not significant. Averaging over all mice gives an estimated mean rate of seroconversion of 0.00170/day for males and 0.00072/day for females, with a ratio of 2.37.

We tested the effects of season (spring or fall), year (2002, 2003, 2004, or 2005 recorded as factors), sex, scarring, reproductive status, mass *z* score, and population density, using the 1,877 individuals (out of 2,032) with complete data at their initial capture. Logistic regression identified several factors and interactions associated with seropositivity (table 2). Males were more likely to be seropositive, as were individuals with scars. Although males are more likely to have scars, both factors are significant in the multiple regression, while their interaction is not. Seropositivity was higher in spring and higher in the last 2 years of the study (2004 and 2005), after population sizes had recovered from the effects of the 2002 drought. The roughly 1-year delay between increased population size and increased prevalence is consistent with the results found at other sites (Adler et al. 2008). Male sex interacted with season, creating a smaller (but still positive) increase in male seropositivity in the spring. Males with higher mass had a higher probability of seropositivity. The coefficients and significance of the covariates were robust to removal of year from the model. Reproductive status and current population density had no significant effect on the probability of seropositivity.

Table 1: Factors associated with seroconversion

Factor	Coefficient	Lower CL	Upper CL
Baseline rate	.001100	.0000736	.00171
Male sex	9.1314	4.2269	18.080
Mass *z* score	6.6051	2.518	11.924

Note: CL = confidence limit.

Table 2: Factors associated with seropositivity

Factor	Coefficient	SE	*P*
Intercept	−3.86514	.37667	<.0001
Male sex	1.03009	.25889	<.0001
Scars	.63560	.15489	<.0001
Mass *z* score	.25162	.13066	.054
Spring	1.19153	.27306	<.0001
Spring: male sex	−.69476	.32381	.03
z score: male sex	.55329	.16040	<.0001
Year 2003	.08414	.33246	.8
Year 2004	.92934	.32436	<.0001
Year 2005	.92505	.32175	<.0001

We looked at characteristics of the site in the previous season to attempt to identify the source or mode of transmission. Starting from the model in table 2, we used forward selection to test for effects of the densities of males and females, the densities of infected males and females, the summed mass *z* scores of all males and females, and the summed mass *z* scores of infected males and females. These analyses excluded 336 individuals lacking data for the previous season (for a total of 1,696).

All variables with the exception of the summed mass *z* score of infected females were significant when added to the model in table 2. However, backward selection removed all but two: the summed mass *z* score of infected males (coefficient 0.05847, SE 0.02853, $P = .04$) and the summed mass *z* score of all females (coefficient 0.04242, SE 0.01708, $P = .013$). Inclusion of these variables produced only small changes in the coefficients of the basic model (app. B in the online edition of the *American Naturalist*). The effect of summed infected male mass *z* score indicates that transmission may occur largely from heavy infected males. The effect of summed female mass *z* score could be due to a higher probability of subsequent infection by large territorial females. However, due to the high degree of collinearity among these variables, these results

must be treated with caution. Bootstrapping analysis found that these terms were retained in a majority of samples, although other terms were often retained in the final model (app. B).

Population Sex Ratio Bias

We used logistic regression on all initial captures to identify factors that correlate with a higher proportion of males (table 3). The negative coefficient for density supports the finding that males are more common when population density is low, and the negative coefficient for spring indicates that males are less common in spring.

The correlation of the population sex ratio bias with density could be due to at least three causes: alteration of birth sex ratio as a function of conditions, differential male and female survivorship, or density- and sex-dependent dispersal. We have insufficient data on juvenile mice to test the birth sex ratio, and we cannot effectively distinguish dispersal from mortality (of the 166 mice recaptured, only four can be unequivocally identified as having moved between sites).

We used a parametric survivorship mark-recapture model to examine the effects of gender and seropositivity on the probability of recapture ("Methods"). Males are slightly more likely to be captured than females, independent of their infection status (table 4). Because we did not implement a full Jolly-Seber model due to the complex structure of this data set, we cannot accurately estimate the true fraction of males in the population. However, a substantial portion of the observed sex-ratio bias is probably due to this difference.

Overall male apparent mortality is about 20% lower than that of females. Interpreting apparent mortality as true mortality, we estimate a mean life span of 90 days for uninfected males and 69 days for uninfected females. In addition, we find that the apparent mortality of infected individuals is approximately 28% higher than that of uninfected individuals for both sexes, with no support for different effects of infection on the two sexes. We found no effect of mass z score on survivorship in either sex, but we cannot rule out that some other covariate that is correlated with infection underlies the observed difference. The estimated values correspond to a mean life span of 71 days for infected males and 54 days for infected females. Because our model does not incorporate differences in the probability of capture among individuals and seasons (Nichols 2005), these results should be treated as hypotheses subject to improved estimation using more flexible methods, such as Bayesian models that can treat individuals as random effects (Clark 2007; Zheng et al. 2007).

Table 3: Factors associated with a high proportion of males

Factor	Coefficient	SE	P
Intercept	.765285	.104378	<.0001
Spring	−.327917	.088343	<.001
Density	−.028343	.007564	<.001

Table 4: Analysis of recapture data

Factor	Coefficient	Lower CL	Upper CL
Male catchability	.345	.327	.362
Female catchability	.306	.285	.326
Uninfected male apparent mortality	.0110	.0100	.0122
Uninfected female apparent mortality	.0144	.0128	.0164
Disease-induced mortality	1.276	1.047	1.611

Note: CL = confidence limit.

Model and Parameter Estimates

Model Derivation

The data analysis identified three possible forms of heterogeneity: (1) males have lower apparent mortality, (2) males are more likely to become infected (higher susceptibility), and (3) males may have higher encounter rates. Our data cannot distinguish the last two possibilities, so we study them and their interaction with mortality separately. The effects of mass z score and season will be modeled in future work.

Our model is a two-sex version of the SI model of susceptible and infected individuals (Anderson and May 1992; Diekmann and Heesterbeek 2000) tracking the densities of susceptible males and females (S_m and S_f, respectively) and infected males and females (I_m and I_f, respectively; Allen et al. 2006). For convenience, we also use the male and female prevalences p_m and p_f and the total populations N_m and N_f (variables and parameters are summarized in table 5):

$$\frac{dS_m}{dt} = -v_m^2\sigma_m g_{mm} p_m S_m - v_m v_f \sigma_m g_{mf} p_f S_m - \delta_m S_m + bN_f, \quad (3)$$

$$\frac{dS_f}{dt} = -v_m v_f \sigma_f g_{fm} p_m S_f - v_f^2 \sigma_f g_{ff} p_f S_f - \delta_f S_f + bN_f, \quad (4)$$

Table 5: Variables and parameters in the model

Symbol	Description
N_m, N_f	Densities of male and female mice
I_m, I_f	Densities of male and female infected mice
S_m, S_f	Densities of male and female susceptible mice
p_m, p_f	Prevalence of infection in male and female mice
δ_m, δ_f	Daily mortality probability for susceptible males and females
k	Proportional increase in mortality due to infection
σ_m, σ_f	Susceptibility of males and females
b	Production of female offspring per females per day
v_m, v_f	Encounter parameters for males and females
g_{mm}, g_{fm}, ...	Density dependence of contacts between males, males and females, etc.
N_d	Normalizing population density for the mass-action model

$$\frac{dI_m}{dt} = v_m^2\sigma_m g_{mm} p_m S_m + v_m v_f \sigma_m g_{mf} p_f S_m - k\delta_m I_m, \quad (5)$$

$$\frac{dI_f}{dt} = v_m v_f \sigma_f g_{fm} p_m S_f + v_f^2 \sigma_f g_{ff} p_f S_f - k\delta_f I_f. \quad (6)$$

We assume proportionate mixing between the sexes (Castillo-Chavez et al. 1989) as described by the encounter parameters v_m and v_f, potentially different male and female susceptibilities of σ_m and σ_f, a per-female birth rate of $2b$, and a sex ratio of 0.5 at birth. The uninfected mortality rates for males and females are δ_m and δ_f, increased by a factor of k in infected individuals.

The terms g_{mm}, g_{mf}, g_{fm}, and g_{ff} describe the density dependence of encounters. For simplicity, we compare two extreme cases (McCallum et al. 2001). In the constant-contact model (or frequency-dependent model), each g is equal to 1. In the mass-action (or density-dependent) model, the contact rate is proportional to population density, and $g_{mm} = g_{fm} = 2N_m/N_d$ and $g_{mf} = g_{ff} = 2N_f/N_d$, where N_d normalizes the models to match when the total population is equal to N_d with an even sex ratio. Thus, the rate at which males are infected by females, for example, is proportional to the product of the number of infected females and the number of susceptible males.

To model a fluctuating population, we created a population trajectory using the 86 measured population sizes (the numbers measured in each 3.14-ha site, shown as per-hectare densities in fig. 1*A*). We embedded these values in a single time series by linearly interpolating, with lognormally distributed noise (with mean = 1 and SD = 0.8), between the last value in one site and the first value in the next, creating on average nine new data points between each pair. The new time series has a total of 245 points. Sites are concatenated in a random order, and results were not sensitive to the order chosen or the details of interpolation.

We solve for the birth rate $b(t)$ that produces a given trajectory of the total population $N(t)$. In the absence of disease-induced mortality (where $k = 1$), the equations for the total populations N_m and N_f are linear, and we can solve for $b(t)$ directly (Adler et al. 2008). When $k \neq 1$, this method does not work (because the disease affects the population dynamics). We instead adjusted the birth rate in each interval so that the population size matches the given population time series.

The differential equations are deterministic, and they give trajectories of population size of infected and uninfected males and females in a region of 3.14 ha. The populations studied here are embedded in a much larger and relatively homogeneous population throughout the west desert of Utah and are thus samples rather than isolated sites with their own dynamics (Keeling and Grenfell 2002). To compare with empirical data, we sampled from the results in a way to mimic the field observations at each of the 86 times corresponding to populations chosen from the field data (excluding the interpolating values). First, we chose a Poisson-distributed number of males with mean given by the model output for N_m. We chose a Poisson-distributed number of females with mean given N_f but reduced by a factor estimating the lower probability of catching a female over an average of three nights of sampling (a factor of $0.926 = \{1 - [1 - 0.306]^3\}/\{1 - [1 - 0.345]^3\}$). The numbers of infected males and females were chosen as binomial random variables with probabilities given by the model output of p_m and p_f.

As an alternative to comparing samples from the simulation with the empirical data, we treated the measured male and female prevalences in each site as random effects and used empirical Bayes methods to estimate the underlying distribution from which these prevalences were drawn (Cassella 1985; Clark 2007). If these values closely match the deterministic results of the simulation, the re-

sults are consistent with heterogeneity created solely by population fluctuations because the model has no other form of heterogeneity among sites.

Model Parameterization

The mortality rates are estimated from the model in table 4 and simplified to $\delta_f = 0.0145$ and $\delta_m = 0.8\delta_f$. We use $k = 1.276$ as the estimate of the increase in mortality due to the disease. The results on seroconversion (table 1) suggest that males are roughly twice as likely to become infected. We thus set either $v_m = 2v_f$ (heterogeneity in encounters) or $\sigma_m = 2\sigma_f$ (heterogeneity in susceptibility).

We compute the average values of the mortality rate, susceptibility, and encounter rates as the average weighted by the fractions of males and females in the population at equilibrium. The fraction of males will approach $\delta_f/(\delta_m + \delta_f)$. We choose the mean encounter rate so that the mean prevalence across sites matches the measured average of 13%. Mean susceptibility is fixed at 1, and the mean death rate is fixed at 0.0129 (the measured mean). The normalizing density N_d is set to the mean population density of 8.0 mice/ha observed in this study.

Comparison of Model with Data

The models with constant contact, whether with higher encounter parameter or higher susceptibility in males, accurately predict the ratio of male to female prevalence and capture the distribution of male and female prevalence (fig. 2). The distribution of samples from the simulation and the empirical data match well ($P > .3$ for both males and females using the Kolmogorov-Smirnov test "ks.test" in R). The distribution of empirical Bayes estimates of the prevalence and the deterministic simulation results largely overlap, sharing 88% of area for males and 81% of area for females. This concordance indicates that the simulations, which include only population fluctuation as a source of variation, capture the extent of the observed variation without appealing to other forms of heterogeneity. With mass action, the simulation predicts a large proportion of sites with unrealistically high and low prevalence (results not shown).

The model produces a significantly lower fraction of males when the population density is higher, but it is with a slope significantly less than that in the data (fig. 3*A*). Samples from the simulation generally show no significant relationship. The empirical Bayes estimates of the distribution of the proportion of males across sites have a wider distribution than those in the simulation, indicating that another source of heterogeneity, probably seasonality (table 3), plays an important role (fig. 3*B*). That the simulation nonetheless closely fits the empirical prevalence data

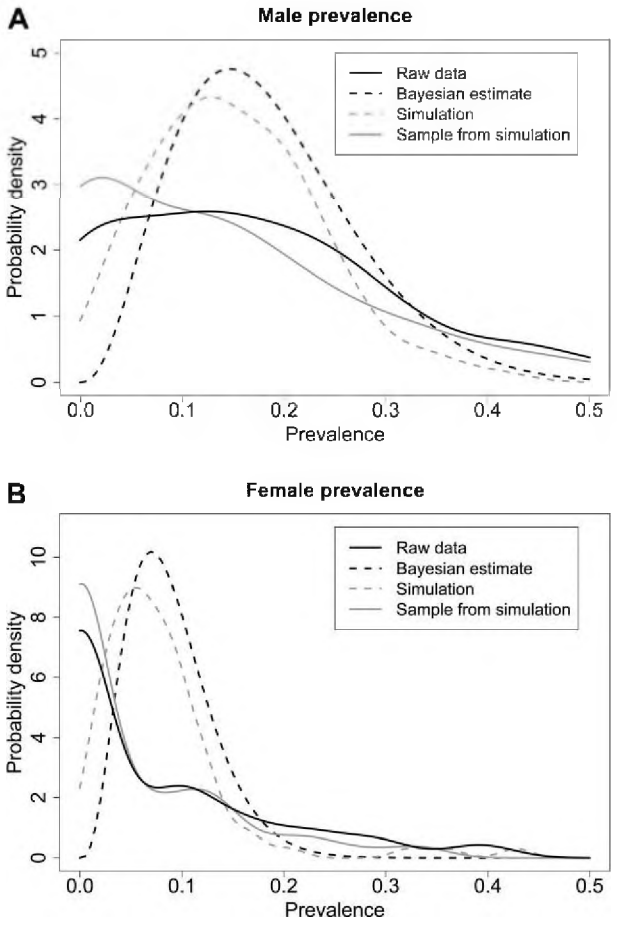

Figure 2: Smoothed distribution of prevalences for males (*A*) and females (*B*) across 86 measurements using the raw data (*solid black line*), the deterministic simulation with heterogeneity in encounters and mortality (*dashed gray line*), samples from the deterministic simulation (*solid gray line*), and empirical Bayes estimates based on the measured values (*dashed black line*). Parameter values are $k = 1.276$, $v_f = 0.0615$, $v_m = 0.123$, $\bar{v} = 0.0956$, $\sigma_f = \sigma_m = 1$, $\delta_f = 0.0145$, and $\delta_m = 0.0116$, assuming constant contact. Results with heterogeneity in susceptibility and mortality are similar.

suggests that sex ratio variation has only a small effect on the dynamics of prevalence.

Effects of Heterogeneity on Prevalence

We use the simulations to study how heterogeneity affects the prevalence of the disease by comparing mean prevalence over a range of parameters with and without the three forms of heterogeneity (encounter, susceptibility, and mortality). Figure 4*A* uses a baseline with heterogeneity in encounters and mortality but none in susceptibility, and figure 4*B* uses a baseline with heterogeneity in susceptibility and mortality but none in encounters. Removing

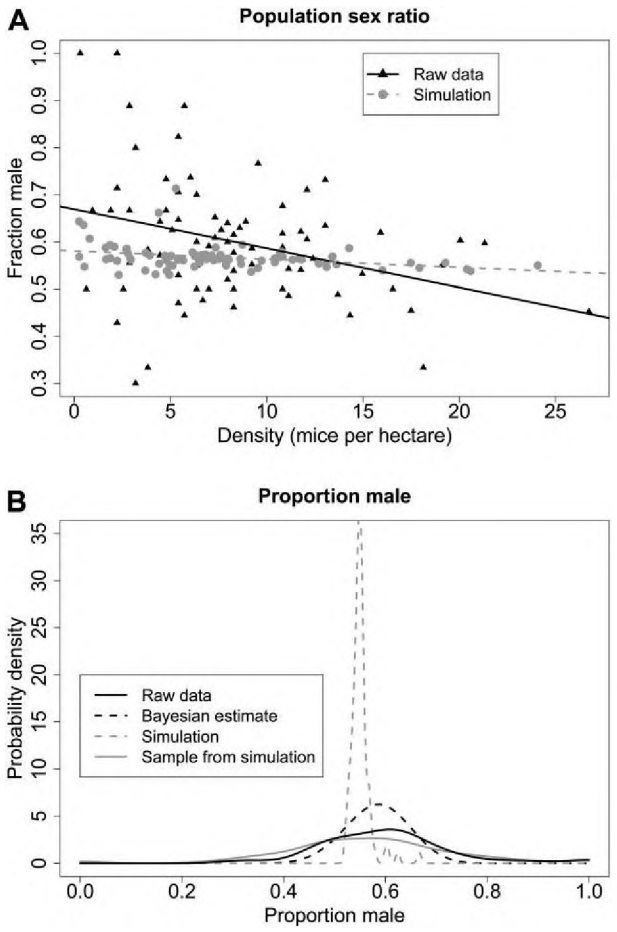

Figure 3: *A*, Relationship of the proportion of males with mouse density in the raw data (*triangles*) and the simulation (*circles*). Parameter values as in figure 2; linear regression lines are included for illustration. The values are significantly correlated in the simulation results (Kendall's $\tau = -0.22$, $P < .01$). *B*, Smoothed distribution of the proportion male using the same parameter values and symbols as in figure 2.

heterogeneity in encounter rates (while keeping the mean rate the same) lowers both male and overall prevalence (cf. points *B* and *M* in fig. 4*A*). However, removing heterogeneity in mortality (point *E* in fig. 4*A* and point *S* in fig. 4*B*) or in susceptibility (point *M* in fig. 4*B*) leads to overall increases in prevalence. The prevalence with neither form of heterogeneity is similar to that with mortality heterogeneity only (point *N* in fig. 4). Removing the fluctuations in population size leads to an increase in prevalence (point *C* in fig. 4).

We can directly solve for the equilibria in the absence of fluctuations (app. C in the online edition of the *American Naturalist*). Contrary to our prediction, removing heterogeneity has nearly identical effects on prevalence in the presence or absence of fluctuations (cf. *black arrows* and *dashed gray arrows* in fig. 4). In particular, we expected to see the largest effect of combined heterogeneity in encounters and mortality in the presence of fluctuations. Their removal leads to a 35% reduction in overall prev-

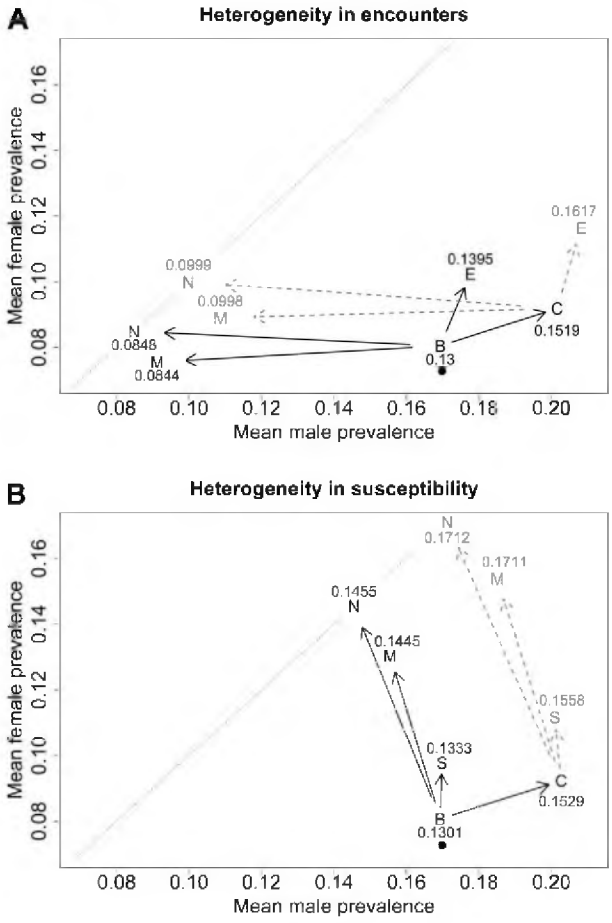

Figure 4: Effects of removing different factors on the mean male and female prevalence generated by the simulation while maintaining the mean value. Numbers below or above the letters give the overall prevalence, and the large dot indicates the empirical result. The thin dotted line is the line of equal male and female prevalence, achieved only in the absence of heterogeneity. *A*, Fluctuations and heterogeneity in encounters and mortality (*point B*), fluctuations and heterogeneity in mortality (*M*), fluctuations and heterogeneity in encounters (*E*), fluctuations only (*N*), constant population with heterogeneity in encounters and mortality (*C*), constant population with heterogeneity in mortality (*gray M*), constant population with heterogeneity in encounters (*gray E*), and constant population with no heterogeneity (*gray N*). Parameter values as in figure 2. *B*, Fluctuations and heterogeneity in susceptibility and mortality (*point B*), fluctuations and heterogeneity in mortality (*M*), fluctuations and heterogeneity in susceptibility (*S*), fluctuations only (*N*), constant population with heterogeneity in susceptibility and mortality (*C*), constant population with heterogeneity in mortality (*gray M*), constant population with heterogeneity in susceptibility (*gray S*), and constant population with no heterogeneity (*gray N*). Parameter values as in figure 2, except $v_f = v_m = \bar{v} = 0.0996$ and $\sigma_f = 0.6429$, $\sigma_m = 1.286$.

alence whether or not fluctuations are included (cf. points *B* and *N* in fig. 4*A*).

How Heterogeneity Changes Equilibrium Prevalence and R_0

This study addresses an apparent paradox: if a population were homogeneous, chronic diseases with low prevalence would have values of the basic reproductive number R_0 dangerously close to the extinction threshold at $R_0 = 1$. We hypothesize that heterogeneity associates a larger value of R_0 with a particular prevalence than is given by equation (1). In a heterogeneous population, computing R_0 is facilitated by finding the next-generation operator, which tabulates the number of male infections created by a male, the number of male infections created by a female, and so forth. The basic reproductive number R_0 is the leading eigenvalue of this matrix (Diekmann et al. 1990). Detailed calculations are given in appendix D in the online edition of the *American Naturalist*.

Figure 5 compares the case with no heterogeneity with various forms of heterogeneity. As always, the population-wide average encounter parameter, susceptibility, and death rate are normalized to ensure that observed effects are due to heterogeneity itself. We see that a particular prevalence is associated with a larger R_0 in the presence of heterogeneity and that this effect is enhanced when fluctuations are included. The computation of R_0 does not explicitly include fluctuations, and an extension of the theory in periodically forced populations might be necessary (Bacaer and Guernaoui 2006). Although the absolute effects are not large, the R_0 associated with a prevalence of 0.13 changes from 1.15 in the absence of all heterogeneity to 1.22 with fluctuations and heterogeneity in encounters and mortality. This value is 50% farther from the extinction threshold.

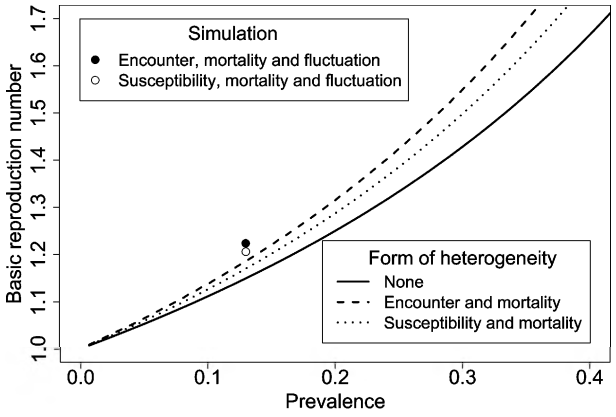

Figure 5: Effects of heterogeneity on the relationship between equilibrium mean prevalence and R_0, comparing cases with no heterogeneity (*solid curve*), heterogeneity in susceptibility and mortality (*dotted curve*), and heterogeneity in encounters and mortality (*dashed curve*). The solid dot plots the R_0 associated with heterogeneity in encounters and mortality, using the baseline parameter values from figure 1 against the prevalence found in the simulation with these parameter values and fluctuations. The open dot plots the R_0 associated with heterogeneity in susceptibility and mortality using the baseline parameter values from figure 2 against the prevalence found in the simulation with these parameter values and fluctuations.

Discussion

We hypothesized that SNV persists at low prevalence in deer mouse populations due in part to various forms of heterogeneity and focused here on heterogeneity between the sexes. Our data analysis identified three forms of heterogeneity in this population. The higher prevalence and seroconversion rate in males indicates roughly doubled susceptibility or encounter rates. Without more detailed time series, we are unable to distinguish between these two mechanisms. A bias in the population sex ratio at times of low density is consistent with our direct estimate of a 20% lower mortality rate in males.

Our preliminary capture-recapture analysis found a significant increase of 28% in the mortality rate in infected animals and could not distinguish the extent of this effect in males and females. This disease-induced mortality would require the disease to have substantially higher transmission in order to survive, but it has little interaction with heterogeneity. These results contrast with an earlier finding that antibody-positive *Peromyscus boylii* had higher apparent survival (Abbott et al. 1999). More complete analysis of this complex data set is required to verify this result, in particular to deal with heterogeneities among individuals and differences among sites and seasons.

We used these data to parameterize a system of differential equations tracking infected and susceptible males and females. A mass-action model fit the distribution of prevalences poorly, and we focus on a constant-contact model (McCallum et al. 2001; Adler et al. 2008), although the reality could be a more complex contact process (Ryder et al. 2007). In combination, the estimated higher male susceptibility or encounter rates along with lower male mortality are sufficient to explain higher male prevalence and part of the bias in the sex ratio. The simulations capture much of the observed variation in prevalence (fig. 2), arguing that this variation might be largely the result of population size changes rather than intrinsic differences among sites and years, as found in other wildlife diseases (Smith 2006). However, the simulations capture only a portion of the observed sex ratio bias (fig. 3), implying that another factor, quite possibly seasonality, needs to be included (Altizer et al. 2006).

In fluctuating populations, removing heterogeneity in encounter rates decreases prevalence substantially (fig. 4*A*), while removing heterogeneity in susceptibility increases prevalence (fig. 4*B*), consistent with results showing that the final size of an epidemic decreases with higher variance in susceptibility (Dwyer et al. 2000). Removing heterogeneity in mortality increases prevalence slightly and has little interaction with the other forms of heterogeneity, contrary to our original prediction. The relative effects of heterogeneity on prevalence are nearly identical with and without fluctuations, again contrary to prediction.

The value of R_0 associated with the observed prevalence is increased both by heterogeneity and by population fluctuations (fig. 5). If R_0 is a measure of the sensitivity of the disease to global extinction, these populations are as much as 50% farther from the threshold at $R_0 = 1$ than would be expected if they were constant and homogeneous. Extremely large values of R_0, in combination with disease-induced mortality, could create unstable dynamics that could drive the disease to extinction, but this is unlikely with the low values estimated here.

To the best of our knowledge, only one study has documented a difference between male and female survival in rodents, finding that females survived longer than males in the Norway rat (McGuire et al. 2006). If the differences we estimated are consistent across years and are due to survival rather than dispersal, population fluctuations do not eliminate the core group crucial for infection (males) but rather the individuals least important for transmission (females). Our results using a deterministic model with a particular pattern of population size find that the persistence of long-lived males through population bottlenecks may not be critical to SNV persistence, but stochastic models with longer and deeper bottlenecks would provide a more critical test of this hypothesis.

Seasonal differences, large body mass, and scarring were also significantly correlated with seropositivity. Modeling seasonality would require developing models with temporally varying parameters. In mice, mass serves as a surrogate for age. The heterogeneity created by higher susceptibility or encounter rates in older mice may be at least as important as that created by males, and their interaction may accentuate the importance of heterogeneity for disease persistence through bottlenecks. Models including age structure are substantially more complex to parameterize and analyze (Diekmann and Heesterbeek 2000) than the ordinary differential equations presented here and will be a focus of future work. In either case, more detailed data analysis would be required to quantify seasonal and mass-based effects, and the loss of power due to subdivision of the data may limit our ability to do so.

At least five other factors could also play major roles in SNV persistence. First, newly infected individuals have been found to be most infectious (Douglass et al. 2001; Botten et al. 2002). In the extreme case where individuals become entirely noninfectious after a short period but continue to be scored as infected based on serology, the system becomes equivalent to one with lifelong immunity, which can greatly enhance persistence at low prevalence (app. A).

Second, temporary maternal antibody protection (Borucki et al. 2000) also creates an immune class which increases the value of R_0 associated with low prevalence. Preliminary analysis of this case indicates that the effect of maternal antibodies can exceed that of the forms of heterogeneity studied here if antibodies persist for as much as 20% of life.

Third, the infection may alter behavior. Increased aggression has been observed in Norway rats infected with Seoul virus, another member of the hantavirus family (Klein et al. 2004). A recent study of SNV in deer mice found no effect of wounds (including recently acquired wounds) on acquisition of infection and suggests that infection may in fact cause wounds due to behavioral changes (Douglass et al. 2007).

Fourth, dispersal almost certainly plays a substantial role in disease persistence (Hagenaars et al. 2004). Movement of infected animals is common (Root et al. 2003), and one study of Puumala virus, a hantavirus of bank voles, found that mobile animals have higher prevalence (Escutenaire et al. 2000). Such differences could greatly alter how the disease persists in spatial refugia during periods of low host population size and prevalence (Mills et al. 1999). Small-scale variation in weather and habitat may lead to desynchronized dynamics over small spatial scales (Engelthaler et al. 1999; Glass et al. 2000), increasing the importance of dispersal (Adler 1993).

Finally, local disease die-off in small populations is a stochastic process. Heterogeneity in infectiousness can increase the probability of extinction due to stochastic effects (Lloyd-Smith et al. 2005*b*). Stochastic models of hantavirus show substantial contribution to variation (Allen et al. 2006), and coupling with population and spatial dynamics will be crucial to understanding how this disease persists.

Hantaviruses have coevolved with their rodent hosts for millions of host generations (Yates et al. 2002), with strong concordance of phylogenies at the genus level (Herbreteau et al. 2006). SNV has many subtle interactions with its host, including sex-biased prevalence, production of maternal antibodies, and, possibly, disease-induced mortality and behavioral changes. Although a highly coevolved virus might still face the classical trade-off between virulence and transmission (Bull 1994), it may tune the expression of that virulence far more precisely than a virus with only a brief history in its host and affect only a subset of hosts in specific ways. Understanding the detailed interactions

between a virus and a host in a real ecological setting provides a window into the long-term course of host-pathogen coevolution.

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