

Sin Nombre hantavirus decreases survival of male deer mice

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Abstract How pathogens affect their hosts is a key question in infectious disease ecology, and it can have important influences on the spread and persistence of the pathogen. Sin Nombre virus (SNV) is the etiological agent of hantavirus pulmonary syndrome (HPS) in humans. A better understanding of SNV in its reservoir host, the deer mouse, could lead to improved predictions of the circulation and persistence of the virus in the mouse reservoir, and

could help identify the factors that lead to increased human risk of HPS. Using mark–recapture statistical modeling on longitudinal data collected over 15 years, we found a 13.4% decrease in the survival of male deer mice with antibodies to SNV compared to uninfected mice (both male and female). There was also an additive effect of breeding condition, with a 21.3% decrease in survival for infected mice in breeding condition compared to uninfected, non-breeding mice. The data identified that transmission was consistent with density-dependent transmission, implying that there may be a critical host density below which SNV cannot persist. The notion of a critical host density coupled with the previously overlooked disease-induced mortality reported here contribute to a better understanding of why SNV often goes extinct locally and only seems to persist at the metapopulation scale, and why human spillover is episodic and hard to predict.

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Introduction

The effects of a pathogen on its reservoir host can have important consequences on the transmission and persistence of the pathogen. Historically, the conventional wisdom was that “well-adapted” pathogens should be relatively harmless to their hosts, although evolutionary tradeoff theory shows that an intermediate level of virulence can often be the optimal strategy for directly transmitted pathogens in terms of maximizing their fitness (Antia et al. 1994; Frank 1996). More virulent pathogens may have a shorter infectious period because they may kill

the host or induce a strong immune response. However, they are often more transmissible, since increased parasite reproduction and shedding are often correlated to virulence (Antia et al. 1994). At the population level, acute pathogens may be more likely to invade, but experience wider fluctuations in prevalence, have a higher critical community size or higher critical host density, and as a consequence are more likely to go extinct because of epidemic (King et al. 2009) or endemic (Lloyd-Smith et al. 2005) fadeouts, respectively. Although theory can provide important insights into expected patterns and processes, empirical evidence of how chronic infections affect reservoir hosts of zoonotic diseases in nature is rare (Kallio et al. 2007). We examine the effect of Sin Nombre virus (SNV) on the reservoir host, the deer mouse (*Peromyscus maniculatus*), using mark–recapture statistical modeling and long-term field data.

Although SNV is the etiologic agent of hantavirus pulmonary syndrome (HPS), an acute infection with an overall mortality rate of 35% in humans, it is generally thought to cause a chronic, avirulent infection in the deer mouse reservoir host (LeDuc 1987; Mills et al. 1999). Both laboratory and field studies have revealed that the virus is horizontally and directly transmitted in the deer mouse reservoir (Botten et al. 2002; Mills et al. 1999). The virus is shed in infected rodents' urine, feces and saliva, and transmission occurs through inhalation of the aerosolized virus or through aggressive encounters among mice (Mills et al. 1999). Infection appears to be lifelong, although recent studies reveal that infected mice may move from an acute phase, in which the virus is readily isolated from blood and tissues, to a chronic phase, in which the virus is only detected intermittently (Botten et al. 2003; Kuenzi et al. 2005), and infected mice may be most infectious in the first few months after infection (Botten et al. 2000).

Authors of published studies generally assume or claim that there is no effect of SNV on the deer mouse reservoir host (i.e., Botten et al. 2000; Calisher et al. 1999; Easterbrook and Klein 2008). Indeed, there has been a long-standing belief that hantaviruses have experienced a long coevolutionary history with their rodent hosts, possibly dating back to the divergence of higher muroid taxa (i.e., Plyusnin and Morzunov 2001; Yates et al. 2002). It has been postulated that during this long coevolutionary history, the rodent hosts may have evolved adaptations to mitigate detrimental effects of infection (Easterbrook and Klein 2008). However, this may be an overly simplistic view in the face of the trade-off theory (Frank 1996). Furthermore, recent phylogenetic analyses suggest there may not have been a long coevolutionary history. The time to the most recent common ancestor of hantaviruses in the subfamily Sigmodontinae may be only approximately 200 years (Ramsden et al. 2009). Finally, mathematical

theory broadly predicts that chronic, avirulent pathogens should exhibit a pattern of stable endemicity akin to logistic growth within the host population, eventually coming to an equilibrium (Haggett 2000). This seems at odds with the empirical pattern of sporadic disappearance of the virus and recurrent epidemics seen in the deer mouse reservoir (Douglass et al. 2001). However, local conditions (e.g., climate, population structure, and density) that potentially affect viral transmission rates or host density may intermittently lower the basic reproductive ratio below the threshold for local persistence (e.g., Anderson and May 1981), and could also lead to the observed dynamics.

Evidence is slowly mounting that SNV infection in its deer mouse host is not as asymptomatic as previously supposed. Netski et al. (1999) documented changes in lung morphology in infected deer mice similar to those seen in humans with HPS. However, Botten et al. (2000) reported no histopathologic changes, even when the RNA load was high. Douglass et al. (2007) found a decrease in weight gain for newly infected males and a decrease in persistence at the study site for antibody-positive juveniles and subadults (Douglass et al. 2001). However, probability of capture was not taken into account in the previous studies. It therefore remains to be determined if antibody-positive mice are less likely to be recaptured or less likely to survive.

Another issue that remains to be addressed for SNV is the appropriate formulation of the force of infection; that is, the per capita rate or probability of becoming infected per unit time (McCallum et al. 2001). The two most commonly used formulations for the force of infection are density-dependent transmission, where transmission is proportional to the density of infected individuals, and frequency-dependent transmission, where transmission is proportional to the frequency (or proportion) of infected individuals. This empirical quantity is estimated by following susceptible individuals and determining if they have become infected after a short amount of time. When this is done at several host densities it is possible to deduce the contact structure (McCallum et al. 2001). This question is of great applied interest because important dynamic properties relating to persistence and circulation of the pathogen depend critically on how transmission scales with population size (Ferrari et al. 2011).

Using capture–mark–recapture analyses on 15 years of longitudinal data, we examine the null hypothesis that survival of deer mice is not affected by SNV infection. We also contrast the competing hypotheses that SNV is transmitted in a density-dependent versus frequency-dependent fashion by investigating which model for the force of infection is best supported by the data. A greater understanding of SNV in its reservoir host, including patterns of transmission and possible disease-induced mortality, would

lead to a better understanding of emergence and persistence of the virus in the mouse reservoir and human risk. This is particularly important for this deadly zoonotic pathogen, since there is no effective vaccine or cure; currently, the main public health approach is preventative in terms of minimizing exposure.

Methods

Field site and animal processing

Long-term studies of deer mice have been conducted in Cascade County, central Montana, since June of 1994. The study site is agricultural grassland, where deer mice typically account for over 85% of the small mammal assemblage (Douglass et al. 2001). Live trapping was conducted for three consecutive nights every month on two grids (approximately 1 km apart) from June 1994 through December 2008. Grids consisted of 100 trap stations equally spaced (10 m apart) in a square of 1 ha, with one Sherman live trap per station. Each captured mouse was tagged with a uniquely numbered ear-tag, its breeding status, body mass and presence of scars noted, and a blood sample taken. Since SNV infection is life-long, we can use antibodies as a marker of infection. Whole blood samples were tested for IgG antibodies against SNV using an enzyme-linked immunosorbent assay (ELISA) at the Montana Department of Health and Human Services or at Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia. For a detailed description of the field methods, see Douglass et al. (2001).

Capture–mark–recapture analysis

We analyzed the capture histories using capture–mark–recapture (CMR) statistical modeling (Lebreton et al. 1992), as implemented in Program MARK (White and Burnham 1999), using multistrata models (Nichols et al. 1992). We collapsed the three consecutive nightly trapping occasions into one primary trapping occasion, and goodness of fit (GOF) tests were performed on the multistrata capture histories (Pradel et al. 2005) using U-CARE (Choquet et al. 2005). These data were used in two separate analyses.

First, we used the full dataset (both trapping grids, 175 monthly trapping occasions) to estimate probability of recapture (p), survival (S), and force of infection (Ψ , probability of becoming infected over the one-month trapping interval, given survival over that interval). There is evidence that survival and recapture rates may vary between the sexes, by infection status, by breeding status, seasonally, or at other temporal scales (Douglass et al. 2001, 2007; Kuenzi et al. 2007). Therefore, the covariates

we explored were sex, antibody status (positive or negative), month, year, and time. Since the mouse abundances on the two grids were significantly correlated [Pearson's product moment correlation test on minimum number alive (MNA); $R = 0.77$, $p < 0.001$], we analyzed the capture histories from the two grids jointly. For this mark–recapture analysis, there were two strata (SNV antibody positive and SNV antibody negative) and two groups (male and female). Eleven juveniles (based on their weight, <14 g, Fairbairn 1977) tested antibody positive. Seven were retrapped and were antibody negative the following month. No juvenile was positive for the antibody after its first trapping occasion. Rather than being due to infection, the antibodies were likely maternally derived, so we considered them uninfected (in the antibody-negative class) in our analyses.

We were interested in testing for the two most commonly used formulations for the force of infection. Therefore, in addition to sex, month, and year (Calisher et al. 2002; Douglass et al. 2001, 2007), the covariates that we used for the transition probabilities (the probability of becoming antibody positive given survival over the one-month interval) were I_{t-1}/N_{t-1} (the proportion of infected individuals during the previous month; the frequency-dependent formulation) and I_{t-1} (the density of infected individuals during the previous month; density-dependent formulation). For the population estimates, we used POPAN models in Program MARK (see the Electronic supplemental material, ESM, Table S3).

We have previously shown that survival does not differ between juvenile and adult age classes (Luis et al. 2010). However, these age classes were defined based on weight, not reproductive status. Therefore, as a secondary analysis, we explored the possible effects of breeding or interactions between infection and breeding on survival. Males were considered to be in breeding condition if their testes were descended, and females to be in breeding condition if they were perforate, pregnant, or lactating. In this analysis, there were four strata (non-breeding antibody negative, non-breeding antibody positive, breeding antibody negative, and breeding antibody positive) as well as two groups (male and female). However, for this second analysis, due to computing constraints, we used only a subset of the data—the last 105 months of one trapping grid. Unfortunately, this was necessary due to the nature of the long-term dataset; the analysis with the full data set and two strata pushed our computers to the limits of their memory and processing power, while four strata overwhelmed the program and required more memory than our modern computers possessed (8 GB). See ESM Table S2 for the full set of models we ran and their statistics.

We evaluated the appropriateness of including the covariates using Akaike's information criterion (AICc).

Covariates were included in the models by altering the design matrix using RMark (Laake 2007), a package for the R software environment (R Development Core Team 2005). Probabilities of recapture, survival, and force of infection were essentially modeled as a function of these covariates, assuming multinomial errors within a generalized linear framework (McCullagh and Nelder 1989). The link function was logit for all three parameters. In the capture-history data, deaths are confounded with emigration, so the parameter estimated here is “apparent survival;” simply called “survival” hereafter.

Results

Over the 15-year study period, there were 5,930 captures of 2,770 different mice, 229 of which tested SNV antibody positive. GOF tests revealed the most general model fitted the data (GOF for the JMV model; males $\chi^2 = 324.7$, $df = 316$, $p = 0.356$; females $\chi^2 = 192.8$, $df = 270$, $p = 1.00$). Past encounter history was not a significant factor (test 3G males $\chi^2 = 247.5$, $df = 271$, $p = 0.85$; females $\chi^2 = 151.9$, $df = 245$, $p = 1.00$), although trap dependence was observed (“trap-happy” or “-shy” animals; test M males $\chi^2 = 77.2$, $df = 45$, $p = 0.002$; females $\chi^2 = 40.9$, $df = 25$, $p = 0.024$). See ESM Fig. S1 for the time series of captures split by antibody status and sex.

The best model (lowest AICc value) for probability of recapture included antibody status and time (a different value for each of the 174 months; Table 1). Antibody-positive individuals were more likely to be recaptured than antibody-negative individuals [mean probability of recapture: 0.70 (SE 0.09) vs. 0.59 (SE 0.10)]. Both sex and antibody status, as well as month and year, were important for the probability of monthly survival. Antibody-positive males had lower survival (0.58, SE 0.06) than antibody-negative males (0.66, SE 0.06), antibody-negative females (0.68, SE 0.04), and antibody-positive females (0.70, SE 0.04) (Fig. 1). Therefore, as an ad hoc analysis, we ran a model that contained a dummy variable for the interaction between sex and antibody status, in which survival for infected males (0.58, SE 0.06) was estimated separately from females and uninfected males (0.67, SE 0.04). This model showing a 13.4% decrease in survival for antibody-positive males was found to be the best model by AICc (Table 2).

Since infected mice tend to be older animals in breeding condition (Douglass et al. 2007), an alternative hypothesis is that the observed reduced survival is solely a consequence of breeding. Therefore, we ran the second analysis on the subset of the data, which revealed that in addition to infection, breeding status affected recapture and survival (Table 3, ESM Table S2). Average values for monthly

Table 1 Mark–recapture models for probability of recapture (p) using the following models for survival and force of infection: $S(\sim$ antibody status), $\Psi(\sim$ antibody status)

Model	No. param.	AICc	Weight
$p(\sim$ antibody status + time)	179	12,602.27	0.680
$p(\sim$ sex + antibody status + time)	180	12,604.09	0.274
$p(\sim$ time)	178	12,608.44	0.031
$p(\sim$ antibody status + year \times month)	184	12,612.93	0.003
$p(\sim$ antibody status + year + month)	31	13,276.68	0.000
$p(\sim$ month)	16	13,363.39	0.000
$p(\sim$ antibody status)	6	13,672.59	0.000

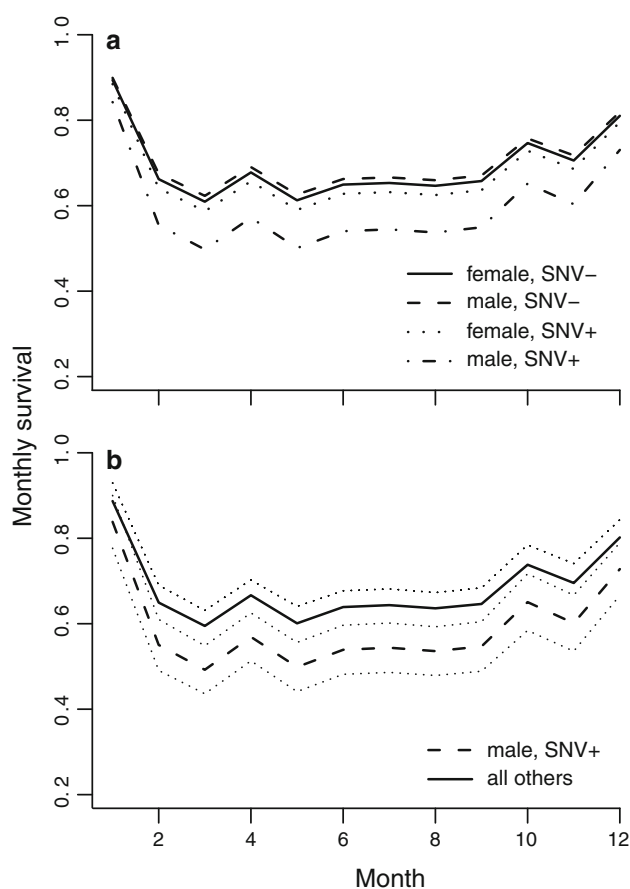


Fig. 1 Monthly probability of deer mouse survival **a** for the model $S(\sim$ sex \times antibody status + month + year) $p(\sim$ antibody status + time) $\Psi(\sim I_{t-1})$ for an average year (1998), which shows that infected males had the lowest survival. **b** The best model in which survival for infected males was estimated separately from the others (uninfected males, uninfected females, and infected females). Light dotted lines show \pm SE (for other years, the pattern may shift up or down by approximately 0.1)

survival for this reduced dataset were: non-breeding SNV negative 0.81 (SE 0.05), breeding SNV negative 0.75 (SE 0.07), non-breeding SNV positive 0.70 (SE 0.08), breeding

SNV positive 0.59 (SE 0.09) (Fig. 2). Likely due to the reduced sample size for this second analysis, August survival could not be estimated. Moreover, the standard errors overlapped between the groups, and the best model did not include sex. However, the second- and third-ranked models did include sex and had a significant amount of the model weight (Table 3). (See ESM Table S2 for the full set of models.)

We investigated two types of models for the force of infection: the density-dependent model, for which the force of infection is a function of the density of infected individuals in the previous month (I_{t-1}), and the frequency-dependent model, for which the force of infection is a

function of the prevalence of infection in the previous month (I_{t-1}/N_{t-1}). The best model for the force of infection was the density-dependent formulation. There was, however, some AICc weight for the frequency-dependent formulation and sex dependence in transmission (Table 2).

Discussion

Although some recent studies have suggested that SNV infection in deer mice may be symptomatic and influence the survival of deer mice, this question has not been addressed directly from demographic field data. We

Table 2 Mark-recapture models for survival (S) and force of infection (Ψ) using the best model for recapture $p(\sim$ antibody status + time), accounting for 175 parameters

Model	No. param.	AICc	Weight
$S(\sim$ dummy + month + year) $\Psi(\sim I_{t-1})$	205	12,437.04	0.250
$S(\sim$ dummy + month + year) $\Psi(\text{sex} + I_{t-1})$	206	12,437.26	0.224
$S(\sim$ dummy + month + year) $\Psi(\sim I_{t-1}/N_{t-1})$	205	12,437.62	0.187
$S(\sim$ sex + antibody status + month + year) $\Psi(\sim I_{t-1})$	206	12,438.05	0.151
$S(\sim$ sex * antibody status + month + year) $\Psi(\sim I_{t-1})$	207	12,438.08	0.150
$S(\sim$ month + year) $\Psi(\sim I_{t-1})$	204	12,440.75	0.039
$S(\sim$ sex * antibody status + month + year) $\Psi(\sim)$	206	12,449.46	0.001
$S(\sim$ sex * antibody status + month) $\Psi(\sim I_{t-1})$	193	12,481.88	0.000
$S(\sim$ antibody status + month) $\Psi(\sim I_{t-1})$	191	12,482.04	0.000
$S(\sim$ sex + month) $\Psi(\sim I_{t-1})$	191	12,483.98	0.000
$S(\sim$ sex * antibody status + month) $\Psi(\sim$ year + $I_{t-1})$	207	12,487.55	0.000
$S(\sim$ sex * antibody status + year) $\Psi(\sim I_{t-1})$	196	12,526.51	0.000
$S(\sim$ antibody status) $\Psi(\sim I_{t-1})$	180	12,591.05	0.000
$S(\sim$ sex) $\Psi(\sim I_{t-1})$	180	12,599.42	0.000

See Table S1 for the full set of models we ran

I_{t-1} refers to the number of infected individuals last month (density-dependent formulation)

I_{t-1}/N_{t-1} refers to the proportion of infected individuals last month (frequency-dependent formulation)

Dummy denotes a dummy variable indicating two values—a value for infected males and a value for all others

* Interaction of the two terms in the model in addition to their individual effects

Table 3 Rankings of mark-recapture models for secondary analysis including breeding status, in which survival (S) was estimated, using the best model for recapture, $p(\sim$ time + stratum), and force of infection, $\Psi(\sim$ stratum), accounting for 111 parameters

Model	No. param.	AICc	Weight
$S(\sim$ month + breeding status + antibody status)	125	6,718.5	0.353
$S(\sim$ month + sex * breeding status + antibody status)	127	6,719.5	0.214
$S(\sim$ month + sex + breeding status + antibody status)	126	6,720.1	0.158
$S(\sim$ month + breeding status * antibody status)	126	6,720.9	0.106
$S(\sim$ month + sex + breeding status)	125	6,721.3	0.087
$S(\sim$ month + breeding status)	124	6,722.0	0.061
$S(\sim$ month)	123	6,724.2	0.020
$S(\sim$ breeding status + antibody status)	114	6,755.9	0.000

See ESM Table 2 for the full set of models we ran

Here, stratum is breeding status * antibody status

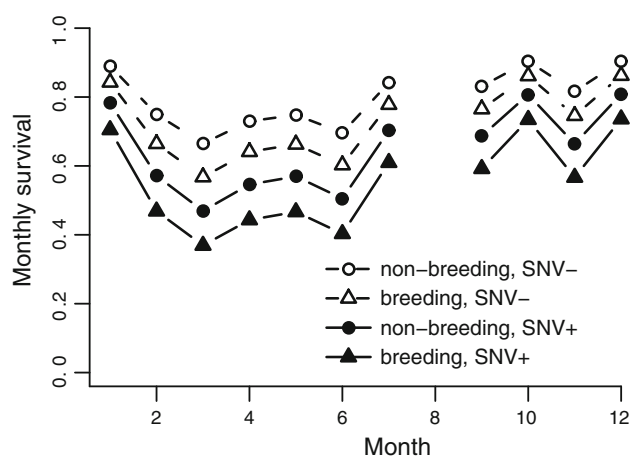


Fig. 2 Monthly probability of deer mouse survival from the secondary analysis $S(\sim \text{month} + \text{breeding status} + \text{antibody status})$. Circles represent non-breeding, triangles breeding, open symbols SNV negative, and solid symbols SNV positive (with the reduced dataset, August survival could not be estimated)

addressed this issue by comparing the survivals of antibody-positive and antibody-negative mice and found a decrease in the survival of infected deer mice. In the first analysis with the larger sample size, this 13.4% decrease in survival was seen only in infected males. The secondary analysis revealed that there is also an important interaction with breeding status. Uninfected mice in breeding condition had on average a 7.4% decrease in survival compared to non-breeding uninfected mice; infected mice in breeding condition had on average a 15.7% decrease in survival compared to non-breeding infected mice. Non-breeding infected mice had on average a 13.6% decrease in survival compared to non-breeding uninfected mice, and breeding infected mice had a 21.3% decrease in survival compared to breeding uninfected mice.

We believe the 13–21% disease-induced reduction in survival is likely to be an underestimate, since we do not know how long after initial infection animals are likely to experience the most acute disease-induced mortality. We speculate that the length of the incubation period (time between infection and onset of any disease) would be 2–4 weeks, since substantial RNA levels can be detected at one week and peak at three weeks post-infection (Botten et al. 2000; Hardestam et al. 2008). Unfortunately, we also do not know precisely when many infected individuals acquired the infection. Using the presence of antibodies to the virus as a marker of infection means that we cannot detect infected individuals until after they develop detectable antibodies, which also appears to take approximately 2–4 weeks (Botten et al. 2000). Infected mice that experience disease-induced mortality would only be detected if their incubation period is longer than their time to seroconversion. Inter-trapping intervals longer than the time to

seroconversion would also decrease the detection of infected individuals. If the incubation period is shorter than the one-month inter-trapping interval, we may therefore only detect a subset of the animals that experience disease-induced mortality, depending on when they became infected in relation to the trapping occasions. In addition to a higher disease-induced mortality, the true prevalence and incidence in the reservoir population may also be higher than the longitudinal data suggest.

Previous research has established that, in mammals, males (particularly those in breeding condition) tend to have greater prevalence and intensity of many micro- and macroparasitic infections than females, through increased exposure, increased susceptibility mediated through immunocompromising sex hormones such as testosterone (Klein 2000; Poulin 1996), or sexual size dimorphism (Moore and Wilson 2002). Males often have larger home ranges, disperse more, and have more aggressive contacts than females (Klein 2000), which would increase their exposure. Male Norway rats infected with Seoul hantavirus tended to have higher circulating testosterone and neurotransmitters, which may contribute to aggression and increase the likelihood of transmission through bites (Easterbrook et al. 2007). *Peromyscus spp.* have also been shown to increase social contacts with an increase in testosterone (Gear et al. 2009). Testosterone has been shown to decrease both humoral and cell-mediated immune responses (Ahmed et al. 1985; Klein 2000), and castration of males can increase protection against both micro- and macroparasites relative to that of females (Ahmed et al. 1985). Another possible mechanism for sex-biased parasitism is sexual size dimorphism; the larger sex may experience an energetic tradeoff between somatic growth and immune function (Moore and Wilson 2002). Male-biased mortality is common and has been correlated to male-biased parasitism (i.e., Grobler et al. 1995; Moore and Wilson 2002). Had we not included SNV data in our analysis, we would have seen a male bias in overall mortality, although it would be weak. With the additional data on SNV antibody status, we showed that this male-biased mortality is associated with infection.

The secondary analysis, examining the effect of breeding, indicated that in addition to infection, being reproductively active also decreases apparent survival. Thus, the mice with the lowest apparent survival were those that were both infected and in breeding condition (a 27.2% decrease in survival compared to non-breeding, uninfected mice). Reproduction may decrease the survival of male deer mice for many of the same reasons listed above; for example, the high energetic costs of having larger home range and increased aggression. In this secondary analysis, the best model did not include sex, indicating that females may also pay the cost of reproduction. Pregnancy and

lactation are extremely energetically expensive; increasing litter size has been shown to decrease the survival of female rodents (Koivula et al. 2003). However, since the top-ranked model with the larger sample size as well as other highly ranked models in this analysis included sex, males may pay a higher price for reproduction than females. This additive effect of SNV infection on breeding mice may be a result of immunocompromising effects of sex hormones and the energetic demands of both being reproductively active and fighting infection.

With these analyses, we are unable to separate mortality and permanent emigration or dispersal. Therefore, an alternative hypothesis is that rather than decrease survival, SNV and/or breeding may make mice more likely to emigrate. However, a previous study of dispersal in this mouse population revealed no significant correlation between dispersal and being antibody positive for SNV (Lonner et al. 2008). Therefore it appears more likely that infection is causing a decrease in survival. Although there was not a significant correlation between dispersal and antibody status, the dispersers were more likely to be adult males with scars—the subpopulation more likely to be infected (Lonner et al. 2008). If, in fact, infected mice are more likely to emigrate, this could be important for the spread and metapopulation persistence of the virus. Although the previous dispersal study revealed that dispersing animals were not more likely to be antibody positive, they were more likely to be in breeding condition (Lonner et al. 2008). Therefore, the decrease in apparent survival that we saw for mice in breeding condition could be an increase in emigration; we found that mice in breeding condition had a lower recapture rate, which could mean that these mice were more likely to come and go from the study grid. Another possibility is that the decrease in apparent survival was a combination of survival and emigration; for instance, it is possible that breeding mice may be both more sensitive to infection and more likely to emigrate.

Older males are more likely to be infected with SNV than the rest of the population (Douglass et al. 2001). Therefore, one hypothesis is that infected individuals have a lower survival just because they are old and senescent. However, in previous analyses on deer mouse population dynamics, in which we did not consider the infection, we showed that juvenile and adult deer mouse survival were not significantly different in this population (Luis et al. 2010). Furthermore, we also tested a subset of the CMR data used here, including age class in the analysis, and again, models including age class were not significantly better than those without (A. Luis, unpubl. data). This suggests that the decrease in survival is not a reflection of senescence.

In our analyses, we saw 11 juveniles that were positive for maternal antibodies (see ESM Table S3 for time series

of mice by age class). Maternal antibodies can have important effects on both individuals and populations (Kallio et al. 2006, 2010). However, since we were interested in the effect of infection on survival and these individuals were not infected, we chose to ignore the maternal antibodies and consider them as antibody negative. Another important question to examine would be the effects of maternal antibodies on survival, but with the small sample size we are unable to examine this currently.

Our results suggest that transmission of the virus is density dependent, rather than frequency dependent. This is a common assumption for directly transmitted pathogens (McCallum et al. 2001), although empirical evidence is equivocal (Smith et al. 2009). Aggressive encounters are thought to be an important transmission mechanism, and fights over mates or territory can increase with increased density (Wolff 1989). These results may also help shed light on the sporadic disappearance of the virus from the population. For pathogens with density-dependent transmission, there is a critical host density necessary for disease invasion and persistence. We have previously shown that environmental conditions have a strong impact on the population dynamics of the deer mouse (Luis et al. 2010). If the environmental carrying capacity drops below the critical host density, the pathogen cannot persist and will fade out, providing a possible explanation for the sporadic SNV incidence. Although the best statistical model had density-dependent transmission, there was a significant amount of AICc weighting on the frequency-dependent model. Splitting the data by study grid could potentially help tease apart this issue, but an additional partitioning of the data (in addition to the splits by infection status and sex) would decrease the power of the analysis, and is not feasible at this time. More detailed analysis and modeling of the disease dynamics may help to definitively resolve this issue.

Previous literature has suggested that SNV affects deer mice (Douglass et al. 2007, 2001) and that Puumala hantavirus decreases survival in bank voles (Kallio et al. 2007). Our results, in addition to these studies, should cause us to question the previously held belief that hantaviruses cause chronic, avirulent disease in their reservoir hosts. It seems more likely that SNV is a moderately virulent virus with both an acute and a chronic stage. For diseases that cause a reduction in host survival, the infectious period is effectively shortened, which could decrease the spread of the infection and local persistence of the virus. Perhaps the overlooked fatality in infected deer mice along with density-dependent transmission can help explain how SNV often goes extinct locally and only seems to persist at the metapopulation scale (Douglass et al. 2001; Kuenzi et al. 1999; Mills et al. 1999). A quantitative model for the SNV–deer mouse system including disease-induced mortality would be useful for exploring this possibility further.

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