

ENDEMIC HANTAVIRUS INFECTION IMPAIRS THE WINTER SURVIVAL OF ITS RODENT HOST

EVA R. KALLIO,^{1,2,3,6} LIINA VOUTILAINEN,² OLLI VAPALAHTI,^{3,4,5} ANTTI VAHERI,^{4,5} HEIKKI HENTTONEN,²
ESA KOSKELA,¹ AND TAPIO MAPPES¹

¹Department of Biological and Environmental Science, P.O. Box 35, FIN-40014, University of Jyväskylä, Finland

²Vantaa Research Unit, Finnish Forest Research Institute, P.O. Box 18, Vantaa FIN-01301 Finland

³Department of Basic Veterinary Sciences, Faculty of Veterinary Medicine, University of Helsinki, P.O. Box 66, FIN-00014 University of Helsinki, Finland

⁴Department of Virology, Haartman Institute, P.O. Box 21, FIN-00014 University of Helsinki, Finland

⁵HUCH Laboratory Diagnostics, P.O. Box 403, Helsinki FIN-00029 HUS Finland

Abstract. The influence of pathogens on host fitness is one of the key questions in infection ecology. Hantaviruses have coevolved with their hosts and are generally thought to have little or no effect on host survival or reproduction. We examined the effect of Puumala virus (PUUV) infection on the winter survival of bank voles (*Myodes glareolus*), the host of this virus. The data were collected by monitoring 22 islands over three consecutive winters (a total of 55 island populations) in an endemic area of central Finland. We show that PUUV infected bank voles had a significantly lower overwinter survival probability than antibody negative bank voles. Antibody negative female bank voles from low-density populations living on large islands had the highest survival. The results were similar at the population level as the spring population size and density were negatively correlated with PUUV prevalence in the autumn. Our results provide the first evidence for a significant effect of PUUV on host survival suggesting that hantaviruses, and endemic pathogens in general, deserve even more attention in studies of host population dynamics.

Key words: bank vole; endemic pathogen; infection; mortality factor; *Myodes glareolus*; population dynamics; Puumala hantavirus; survival.

INTRODUCTION

The effect of parasite infection on the host population is one of the major questions in infectious disease ecology (Anderson and May 1979, Dobson and Hudson 1995). In wildlife, a parasite's impact on its host population may also affect the parasite's own persistence, and furthermore, the infection risk to other species, including humans. Endemic parasites tend to persist for long times in host populations with rather stable prevalence. They do not usually induce severe pathogenicity or obvious decreases in survival or reproduction of their hosts (Anderson and May 1979, Grenfell and Dobson 1995). Yet, they may induce deleterious effects, and thus, decrease the fitness of the hosts. These effects may be difficult to separate from other factors that influence fitness of wildlife populations (Dobson and Hudson 1995, Feore et al. 1997, Telfer et al. 2002, 2005).

For population-level regulation, the parasite must influence the host reproduction or survival in a density-dependent manner (Gulland 1995, Tompkins and Begon

1999). Although host regulation by parasitism is best demonstrated by experimental studies, evidence for parasites regulating their hosts is still rare. All information on the influence of parasitism on host fitness, both at individual and population levels, is valuable in evaluating the role of parasites in host population dynamics (Hudson et al. 1998, Tompkins and Begon 1999, Telfer et al. 2002, 2005 Cavanagh et al. 2004, Burthe et al. 2006).

Puumala virus (PUUV) is a member of the genus *Hantavirus*, each of which is carried by a specific rodent host species; the host of PUUV is the bank vole (*Myodes* [earlier, *Clethrionomys*] *glareolus*). Hantavirus infection in the rodent host is chronic, i.e., the immune response of the host does not clear the infection and virus replication is persistent. Consequently, the host may be infectious for the duration of life (Meyer and Schmaljohn 2000) and transmission of hantavirus is horizontal (Gavrilovskaya et al. 1990, Kallio et al. 2006a). Despite some evidence of cellular-level effects, hantavirus infections have been thought to be asymptomatic in their rodent hosts because of long coevolution between them. No clinical illness, increased mortality, or reduced fecundity caused by hantaviruses have been reported in rodent hosts (e.g., Gavrilovskaya et al. 1990, Bernshtein et al. 1999, Netski et al. 1999, Compton et al. 2004, Kallio et al. 2006b). An exception was reported by Calisher et al. (2005), who observed lower survival in Sin

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⁶ Present address: Finnish Food Safety Authority, Mustialankatu 3, Helsinki FIN-00790 Finland.
E-mail: eva.kallio@evira.fi

Nombre virus seropositive deer mice. However, as the authors pointed out, the results may also be caused by the older age of the infected mice. In humans, PUUV causes a mild form of hemorrhagic fever with renal syndrome; in Europe thousands of cases are diagnosed annually (Vapalahti et al. 2003).

We studied the overwinter survival of bank voles in relation to PUUV infection status over three consecutive winters in a total of 55 island populations. The survival of free-living voles was monitored by live-trapping the populations in October and in May and analysed by simultaneously measuring the individuals' sex and age, and population density.

METHODS

Study species

Bank voles are characterized by a mean life expectancy of only a few months, as only a fraction of individuals survive over one winter (Prévot-Julliard et al. 1999). In central Finland, reproduction occurs from May until mid-September (Koivula et al. 2003). Successful overwintering is crucial for fitness of late summer cohorts, as they usually delay breeding until the following summer (Prévot-Julliard et al. 1999). Bank vole populations show seasonal and multi-annual fluctuations in abundance in most of Fennoscandia and in our study area as well (Hansson and Henttonen 1985, Hanski et al. 1991).

Study site and design

The study was conducted on 55 island populations of bank voles. A total of 22 islands were sampled over three consecutive winters (21, 12, and 22 islands in 2002, 2003, and 2004, respectively) in Lake Konnevesi, in central Finland (62°37' N, 26°20' E). The sizes of the islands varied from 0.24 to 3.20 ha and the minimum distance from the mainland was 180 m. The islands were covered by boreal forests (Hakkarainen et al. 2007), the natural habitat for bank voles. As a part of a separate long-term study examining the life histories of voles on islands (*unpublished data*), new bank vole populations were established on the islands each year in early June. For the purposes of the current study, the island populations were live trapped just before winter in late October for three consecutive years. The trapping was conducted using Ugglan Special live traps (Grahnb AB, Sweden) baited with sunflower seeds and potatoes. The trap density was 25 traps/ha spaced about 20 m from each other. Prebaited traps were left on the islands for two nights, after which they were set and checked over the three consecutive days. The effectiveness of this trapping procedure in catching the bank voles on small island populations was separately studied by trapping 27 island populations for several days (E. Kallio et al., *unpublished data*). In that study, out of a total of 284 trapped bank voles, 82% (233 individuals) were trapped during the first night, 17% (48) on the second and only three new individuals (1%) on the third night.

The voles trapped in October were transferred into the laboratory, where they were individually marked, sexed, and weighed to the nearest 0.1 g. The ages of the voles were determined on the basis of the fur coat and whether they were previously marked: marked individuals were those trapped as adults the previous spring and thus were more than a year old. A blood sample was taken from each individual's retro-orbital sinus with 18 μ L capillary tubes (Hemacrit tube, Hirschmann Laborgeräte, Germany). Infection status was determined by detecting the PUUV-specific IgG-antibodies using immunofluorescence assay (IFA; Vapalahti et al. 1995). Because of the chronic nature of hantavirus infection, the presence of IgG antibodies indicates a current infection (Meyer and Schmaljohn 2000). Within a few days of these procedures, the voles were returned to their respective islands of capture.

The populations were re-monitored each spring (in May) using similar trapping protocols as in the autumn. All trapped individuals were taken to the laboratory where they were identified and blood samples were taken. Then they were either kept in the laboratory for other studies or released back to the islands as part of the summer studies.

Statistical analyses

Our sampling design may have resulted in a degree of correlation between observations because groups of samples were taken from the same islands during the same winters. To control these potential sources of pseudoreplication, we used generalized linear mixed models (GLMM; Paterson and Lello 2003), which take the potential spatial and temporal correlations of the observations into account. The survival of bank voles from October to May was analysed with GLMM with a logit link function and binomial errors (as the survival of each individual was a binary measure), and the parameters were estimated using restricted maximum-likelihood procedures (REML). PUUV infection status (PUUV- or PUUV+), sex (female or male) and age (<1 year or >1 year old) were used as categorical fixed factors. Body mass, bank vole population density (number of individuals per hectare) in October, and the size of the island (ha) were used as continuous fixed factors. Island identity and year were included in the models as random factors. In addition, the following population-level analyses were conducted: (1) the extinction of bank vole populations during winter (no voles vs. at least one vole in the population, binary population-level outcome), (2) PUUV persistence until spring (presence or absence of PUUV infected individuals in the spring in the population, binary population-level outcome), (3) bank vole population size (number of bank voles on an island) in the spring, and (4) density (number of bank voles per the size of the island [ha]) in the spring (continuous response variables). Year was included in these models as a random effect. The explanatory variables were the host population size

TABLE 1. Bank voles surviving from October to May in relation to PUUV (Puumala virus) infection status, sex, and age in autumn.

Category	PUUV- voles		PUUV+ voles	
	No. in autumn	Surviving (%)	No. in autumn	Surviving (%)
Sex				
Females	308	22.4	89	4.5
Males	285	11.2	64	3.1
Age				
>1 year old	15	20	30	3.3
<1 year old	578	17	123	4.1

(number of individuals per island), the host population density on the islands, the size of the islands, and PUUV prevalence in the host population in the autumn. Moreover, the PUUV prevalence in the spring (individual-level binary outcome, logit link function, and binomial error) was studied using the island and year as random factors.

The multicollinearity among the explanatory variables in the full models was assessed by variance inflation factors and tolerance values. In the case of collinearity, variables were omitted based on biological meaning and consequently the largest variance inflation factor was 1.42 and the lowest tolerance value 0.7, suggesting no bias in the standard errors of regression coefficients among the variables used in the models. In the absence of model selection criteria, such as the Akaike Information Criterion as standard method for comparing GLMMs (Burnham and Anderson 2002, Johnson and Omland 2004) we followed a step-down procedure to select the final models. We started from the full models including all variables that did not violate the collinearity assumptions as main effects and two-way interactions of the biologically meaningful possibilities. We then simplified the model by removing the interaction terms first and followed by nonsignificant variables (at 5% significance level) one by one. The fit statistics for the

models with binary outcomes were performed and the outcome of generalized chi-square values divided by the degrees of freedom was always ≤ 1 . This indicated that no overdispersion was detected in our models. The analyses were performed using SAS v. 9.1 statistical software (SAS Institute 2002).

RESULTS

In total, 751 bank voles were released on the islands in October during the three years of the study. Out of these, 153 (20.5%) were PUUV+, of which 89 (58.2%) were females and 64 (41.8%) were males. A total of 107 individuals (14.3%) survived over the winter (Table 1). Only five individuals (PUUV+, one case; PUUV-, four cases) were found to have moved to another island between trapping sessions. Because the exact time of the dispersal could not be determined, these individuals were included in the analyses of the islands where they were originally released in the autumn.

PUUV-infected bank voles had a significantly lower overwinter survival than noninfected individuals. In addition, survival was influenced by sex, population density in autumn, and island size (Table 2, Fig. 1). The age and body mass of individuals did not affect the survival probability. Thus, the survival was highest in non-infected females that inhabited large islands with low bank vole density.

Out of a total of 55 island populations monitored for overwintering survival, 38 populations survived until the following spring. None of the predictor variables (bank vole population density in autumn, PUUV prevalence in autumn, island size) were related to extinction probability of the vole population during winter ($P > 0.1$ for all of the effects). However, in the 38 surviving populations, PUUV prevalence in the autumn was related to lower bank vole population density and size in spring (Table 3).

PUUV-infected individuals were present in 34 populations in the autumn and in 15 populations in the spring. The persistence of PUUV in the populations during the spring in the 38 populations that survived was

TABLE 2. Parameter estimates (logit scale) for a model of bank vole overwinter survival, including the covariance parameter estimates for the random factors.

Source of variation	Standard estimate	Error	df	<i>t</i>	<i>P</i>
Individual-level covariates					
Intercept	0.01269	1.4137			
PUUV	-1.4332	0.4541	1, 739	-3.16	<0.002
Sex	-1.0552	0.2429	1, 739	-4.35	<0.001
Age	0.1775	0.6855	1, 739	0.26	0.796
Body mass	-0.05296	0.05467	1, 739	-0.97	0.333
Population-level covariates					
Density in autumn	-0.07032	0.01660	1, 105	-4.24	<0.001
Island size	0.4169	0.1864	1, 18.9	2.24	0.038
Random factors					
Island	0.06293	0.1135			
Year	0.2719	0.3206			

Note: Intercept represents a young female not infected with PUUV.

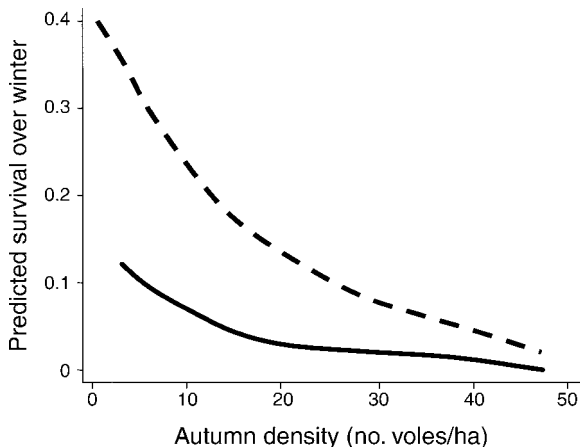


FIG. 1. Predicted survival of bank voles over winter in relation to PUUV (Puumala virus) infection and population density: dashed line, PUUV- individuals; solid line, PUUV+ individuals.

positively related to autumn prevalence ($F_{1,34} = 7.79$, $P = 0.009$) and population density in the spring ($F_{1,34} = 8.28$, $P = 0.007$). A spring blood sample was available from 103 out of the 107 individuals that survived, of which 34 were infected. In spring the individual-level infection probability was not predicted by any of the individual or population-level variables (see Table 2; $P > 0.1$ for all of the effects).

DISCUSSION

This study suggests that Puumala virus infection significantly decreased the overwinter survival of its rodent hosts in natural populations, despite the expectation that hantaviruses have become well adapted to their rodent hosts during the millions of years of co-evolution (Nemirov et al. 2004). Therefore, despite some cell-level pathological alterations (e.g., Gavrilovskaya et al. 1990, Netski et al. 1999, Compton et al. 2004), hantavirus infections have traditionally been considered asymptomatic in their rodent hosts. No clinical illness or decreases in fecundity and survival have been found to be caused by hantavirus infections (Childs et al. 1989, Gavrilovskaya et al. 1990, Bernshtein et al. 1999, Netski et al. 1999, Compton et al. 2004, Kallio et al. 2006b). An exception is from Calisher et al. (2005), who observed lower survival in Sin Nombre virus seropositive deer mice (*Peromyscus maniculatus*). As the authors pointed out, however, the result may have been caused by the greater age of infected mice, as old individuals are more often infected than young ones. In our study, age did not influence the survival of the bank voles (Table 2). We cannot say much about dispersal differences between infected and non-infected voles, but in general dispersal seemed to be very low. This suggests that dispersal would not explain the observed results.

Our novel results on the negative influence of hantavirus infection on the rodent host may arise for

several reasons. We worked on relatively small islands over periods of five to six months of frost and snow, so that harsh environmental conditions, together with a relatively large sample size in our study, may have revealed the deleterious effects of PUUV infection. During winters some parts of the islands may become deprived of food and chronically infected voles may not be able to compensate for the energetic costs induced by the persistent elevation of the immune response (Telfer et al. 2002). Compton et al. (2004) assumed that insulinitis and hyperglycemia in hantavirus-infected rodents may cause a diabetes-like condition in the host. This, together with the chronic replication of PUUV in the bank voles (particularly in the lungs) and persistent antibody production (Meyer and Schmaljohn 2000) may cause the deleterious consequences observed here (e.g., Sheldon and Verhulst 1996, Lochmiller and Deerenberg 2000, Norris and Evans 2000). In addition, the metabolic rate of the infected individuals may be higher than in the non-infected individuals, which could be especially detrimental for successful overwintering. Still another explanation for the observed effect may be that infection increases the vulnerability of the infected hosts to predation (e.g., Hudson et al. 1992, Skorpung and Högstedt 2001). Although least weasels (*Mustela nivalis nivalis* (L.)) and birds of prey were observed on the study islands, the significance of this possible mechanism for poorer survival of PUUV-infected voles currently remains unexplored.

That high PUUV prevalence in autumn is related to lower the bank vole density and population size in the spring further supports the conclusion that PUUV infection decreases bank vole survival, even though the probability of population extinction was not predicted by PUUV prevalence. Although PUUV infection seemed to regulate bank vole populations, the role of PUUV in the cyclic vole fluctuations could not be evaluated in this study. It is important to bear in mind that the most characteristic feature of Fennoscandian vole cycles is the synchronous crash of all sympatric species (Hansson and Henttonen 1988). An endemic

TABLE 3. Effects of the significant explanatory variables on the bank vole population density (no. individuals/ha) and the bank vole population size (no. individuals per island) in spring.

Source of variation	<i>F</i>	<i>df</i>	<i>P</i>
Population density in spring			
PUUV prevalence in autumn	4.31	1, 35	0.045
Population density in autumn	10.12	1, 35	0.003
Population size in spring			
PUUV prevalence in autumn	5.72	1, 32.7	0.023
Population size in autumn	18.22	1, 30.8	0.001
Island size	10.71	1, 34	0.003

Note: Year was used as a random factor in both of the linear mixed models (covariance parameter estimates of year, 0 and <0.02 , for the models of population density and size, respectively).

pathogen should, therefore, be able to infect and regulate all local vole species in a similar manner. Thus, vole population cycles in northern Fennoscandia, which are mostly attributed to predation by specialist predators (reviewed, e.g., by Hansson and Henttonen 1988, Hanski et al. 1991, Korpimäki et al. 2003), cannot be driven only by PUUV because it is a bank vole specific pathogen. However, as earlier suggested, microparasites could modify vole dynamics (Soveri et al. 2000, Cavanagh et al. 2004).

Low host population size and density are unfavorable for the long-term persistence of directly transmitted parasites, and therefore the lower overwintering success of infected individuals should be disadvantageous from the virus' point of view (e.g., Tompkins et al. 2002, Begon et al. 2003, Sauvage et al. 2003). Although PUUV survives outside of the host for a prolonged period of time, especially in winter-like conditions (Kallio et al. 2006a), the virus faded out from 22 of 34 island populations during the winter. Not surprisingly, the higher the autumn PUUV prevalence and spring population sizes were, the higher the persistence probability was. However, in populations where PUUV persisted over winter, the spring prevalence was not explained by any of the measured population-level variables.

To summarize, our study strongly suggests that PUUV infection can decrease survival of its free-ranging host, the bank vole. PUUV infection in bank voles should be further studied to clarify the mechanisms causing the negative effects observed here. Moreover, the role of endemic pathogens as mortality factors deserves attention in theoretical and empirical studies on host-parasite dynamics.

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