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THE DYNAMICS OF MURID GAMMAHERPESVIRUS 4 WITHIN WILD, SYMPATRIC POPULATIONS OF BANK VOLES AND WOOD MICE

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ABSTRACT: Murid gammaherpesvirus 4 (MuHV-4) is widely used as a small animal model for understanding gammaherpesvirus infections in man. However, there have been no epidemiological studies of the virus in wild populations of small mammals. As MuHV-4 both infects cells associated with the respiratory and immune systems and attempts to evade immune control via various molecular mechanisms, infection may reduce immunocompetence with potentially serious fitness consequences for individuals. Here we report a longitudinal study of antibody to MuHV-4 in a mixed assemblage of bank voles (*Clethrionomys glareolus*) and wood mice (*Apodemus sylvaticus*) in the UK. The study was conducted between April 2001 and March 2004. Seroprevalence was higher in wood mice than bank voles, supporting earlier work that suggested wood mice were the major host even though the virus was originally isolated from a bank vole. Analyses of both the probability of having antibodies and the probability of initial seroconversion indicated no clear seasonal pattern or relationship with host density. Instead, infection risk was most closely associated with individual characteristics, with heavier males having the highest risk. This may reflect individual variation in susceptibility, potentially related to variability in the ability to mount an effective immune response.

Key words: *Apodemus sylvaticus*, bank vole, *Clethrionomys glareolus*, endemic infection, host-pathogen dynamics, MHV-68, sympatric hosts, wood mouse.

INTRODUCTION

Gammaherpesviruses have been isolated from a wide range of mammals and appear to be relatively host specific (Nash et al., 2001). Murid gammaherpesvirus 4 (MuHV-4) has been extensively used as a small animal model for understanding gammaherpes virus infections in man and domestic animals (Nash and Sunilchandra, 1994; Simas and Efstathiou, 1998). Despite the large number of laboratory studies using the MuHV-4 strain MHV-68, studies of infection in wild populations have been restricted to surveys, and little is known about the dynamics of infection in wild populations. Moreover, there is no evidence in the literature of natural transmission amongst laboratory mice.

Strain MHV-68 was originally isolated from a bank vole (*Clethrionomys glareolus*) in Slovakia (Blaskovic et al., 1980). Related isolates have been obtained from bank voles, wood mice (*Apodemus sylvaticus*) (Blaskovic et al., 1980), and a shrew (*Crocidura russula*) (Chastel et al., 1994), and the group of viruses is thought to be geographically widespread and occur in a range of small mammal species (Nash et al., 2001). In a preliminary study of bank voles and wood mice in the UK, we found a higher prevalence of both antibody to MuHV-4 and viral DNA in wood mice, potentially indicating that wood mice, and not bank voles as originally believed, may be the major hosts (Blasdell et al., 2003).

The natural route of infection of MuHV-4 is unknown, although it is likely to be through the respiratory route. In artificially infected laboratory mice, initial infection occurs in the lungs, followed by a spread to the spleen and the establishment of latent infections in B lymphocytes, lung epithelial cells, dendritic cells, and macrophages (Nash et al., 2001). The virus can also down-regulate major histocompatibility complex class I expression (Stevenson et al., 2000) and restrict inflammatory cell responses (Van Berkel et al., 2000; Stevenson and Efstathiou, 2005). Thus, infection may affect host immunocompetence, both by directly infecting cells related to immune system and influencing immune responses. Typically,

innate and adaptive immunity limit viral infection. However, approximately 10% of infected laboratory mice develop lymphoproliferative disease (Nash et al., 2001) and laboratory mice lacking some parts of the immune system can develop lymphomas (Tarakanova et al., 2005) and experience lethal infections (Ehtisham et al., 1993; Stevenson et al., 1999). Interestingly, there is some evidence that the pathogenesis of experimentally infected, laboratory-bred wood mice is different from lab mice (D. Hughes, pers. comm.) and studies of natural infections in wild rodents are likely to make significant contributions to our understanding of this disease.

Wild animals are obviously exposed to more potential stressors than laboratory mice, and infection may influence individual fitness and even population dynamics. Such effects may occur directly by MuHV-4–induced reductions in survival or reproductive rates or indirectly by lowering immunocompetence and facilitating infections by other, more pathogenic disease organisms. To date, however, no study of MuHV-4 epidemiology in wild populations has been conducted. Here we follow up our preliminary study of bank voles and wood mice with a longitudinal study. We investigate temporal patterns in antibody prevalence and whether infection risk reflects seasonal patterns, variation in host density, or individual host characteristics. Such information is important for determining the potential of the disease to influence host population ecology.

METHODS

As part of a long-term project investigating host-pathogen dynamics, bank voles and wood mice were trapped from April 2001 to May 2003 within a 1 ha plot of mixed woodland in northwest England (N 53°19′ W 03°03′). A 10 × 10 grid was marked out with 100 trap stations, permanently situated at 10 m intervals. Two Longworth traps (Penlon Ltd., Oxfordshire, UK) were placed at each trap station. Trapping occurred approximately monthly (primary trap sessions) for a period of 2–3 days, with traps checked daily and twice daily during winter and summer respectively. All bedding material and obvious waste was removed from traps containing animals and they were cleaned with 70% ethanol prior to being reset. Traps were sterilized in an autoclave between primary trapping sessions. All animals captured were tagged using subcutaneous passive integrated transponder tags (Labtrac by AVID plc, East Sussex, UK). Few tag losses were observed during the study. On first capture within a monthly trapping session sex, reproductive condition, and weight were recorded and a 20–40 μl blood sample was taken from the tip of the tail. Males and females were defined as mature if they had, or had previously been recorded with, scrotal testes or a perforate vagina, respectively. The site was also trapped in September 2003, December 2003, and March 2004. Trapping was essentially the same during these three trapping sessions, except traps were set for five nights and checked daily and animals were not tagged. However, a fur clipping system was used that enabled the capture history of each individual over the five days to be monitored.

Sera were separated from blood samples and the presence of IgG antibody to MuHV-4 determined by immunofluorescence assay (IFA), essentially as described for cowpox antibody (Crouch et al., 1995) except using MHV-68–infected Vero cells as antigen. Briefly, Vero cell monolayers in 96-well plates were inoculated with 5–10 plaque-forming units of the MHV-68 strain of MuHV-4, fixed with ethanol after 48 hr incubation, and stored until needed at 4 C. Immunofluorescence assays were done by rehydrating the cells in PBS, and then serial incubations with serum (diluted 1:20 and 1:40) and anti-mouse fluorescein isothiocyanate (FITC), separated by washing in phosphate-buffered saline (PBS), before viewing under UV illumination. The assay was previously optimized using sera from experimentally infected rodents and a sera sample from an experimentally infected rodent was used as a positive control. Antibodies to MuHV-4 are not known to cross-react with other viruses, and previous PCR and isolation studies in these and other populations (Blasdell et al., 2003) have only detected MuHV-4 in wood mice and bank voles. The IFA was conducted on all blood samples collected between January 2002 and March 2004 and on wood mouse blood samples collected between April 2001 and December 2001. Some wood mouse blood samples from 2001 were not available for testing as they were too

small to separate and had been used in other diagnostic tests.

Statistical analyses

Two Generalized Linear Mixed Modelling (GLMM) analyses (described below) were conducted using the glmmPQL procedure (Venables and Ripley, 2002) in the R software package available under the GNU General Public License at http://www.r-project.org. Both analyses used a logit link with binomial errors and models were fitted using restricted maximum likelihood.

In the first analysis, we investigated what factors influenced the probability that an animal was seropositive. The dependent variable was a binary measure, with seropositive and seronegative blood samples classified as 1 and 0, respectively. To allow us to use the data collected between September 2003 and March 2004 (when trapping was not monthly), we only used data from some primary trap sessions, selecting sessions that were separated by 3–4 mo (range of interval=83–125 days). A total of 11 primary trapping sessions were used in this analysis.

In the second analysis, we examined what factors influenced the probability that an animal seroconverted between trap sessions t_{t-1} and t_t. Individuals were classified as 1 or 0 at trap session t_t, according to whether the individual seroconverted from being antibody negative to antibody positive, or remained antibody negative between trap sessions t_{t-1} and t_t. Individuals were only included in the analysis if they were caught in both trap sessions concerned, and seropositive captures subsequent to the initial seropositive result were discarded. As this analysis required longitudinal data, only data collected between April 2001 and May 2003 were used.

Both the above analyses were conducted in two stages. We first investigated whether there was any seasonal pattern in the dependent variable, considering whether seasonal categories or a sinusoidal curve fitted the data best. Random effects (see below) were not included in this stage to enable us to use the Akaike Information Criterion (AIC) to select between nonnested models. In the second stage, we investigated the effect of host density (considering current population density and population density at a lag of 3 and 6 mo), sex, mass (used as a proxy for age), maturity, and two-way interactions between sex and mass and sex and maturity. Between April 2001 and April 2003, population size estimates were calculated using the Jolly Seber method for open populations (see review of methods by Schwarz and Seber, 1999). To estimate population size from May 2003 onwards, we used a closed capture model that allowed individual heterogeneity in capture probabilities (Mh in program CAPTURE, Rexstad and Burnham, 1992). These estimates of abundance equate to an estimation of density per hectare. All density and mass covariates were log-transformed. Following a step down procedure, eliminating interactions first, we retained only those variables significant at the 5% significance level.

As individuals are sampled from the same site at the same time, individual observations are not independent and in both analyses trap session was included as a random effect. Individual animals could also be sampled during more than one trap session and, consequently, it could be argued that "individual" should also have been included as a random effect. However, in the first analysis the length of the time interval between included trap sessions reduced this problem of pseudoreplication. Examination of the data set indicated that those animals that were tagged ($n=158$) only appeared an average of 1.4 times. In the second analysis, the variance component due to individual effect was not estimable. This is probably due to the relatively low number of captures included for each animal (average=2.7, $n=171$). Thus, individual was not included as a random effect.

RESULTS

The density of both host species showed seasonal and annual variation (Fig. 1). The bank vole population increased over the course of the study with an autumn peak of approximately 100/ha and 130/ha in 2002 and 2003, respectively. The wood mouse population peaked at approximately 120/ha, 70/ha, and 100/ha in 2001, 2002, and 2003, respectively.

Between April 2001 and May 2003, a total of 1,060 blood samples from 346 individual wood mice were tested for antibodies to MuHV-4. Each individual had between one and 16 blood samples tested (mean=3.05, SE=0.14). Between January 2002 and May 2003, 868 blood samples from 258 bank voles were tested, with each individual tested between one and 12 times (mean=3.26, SE=0.16). Antibodies to MuHV-4 were more preva-

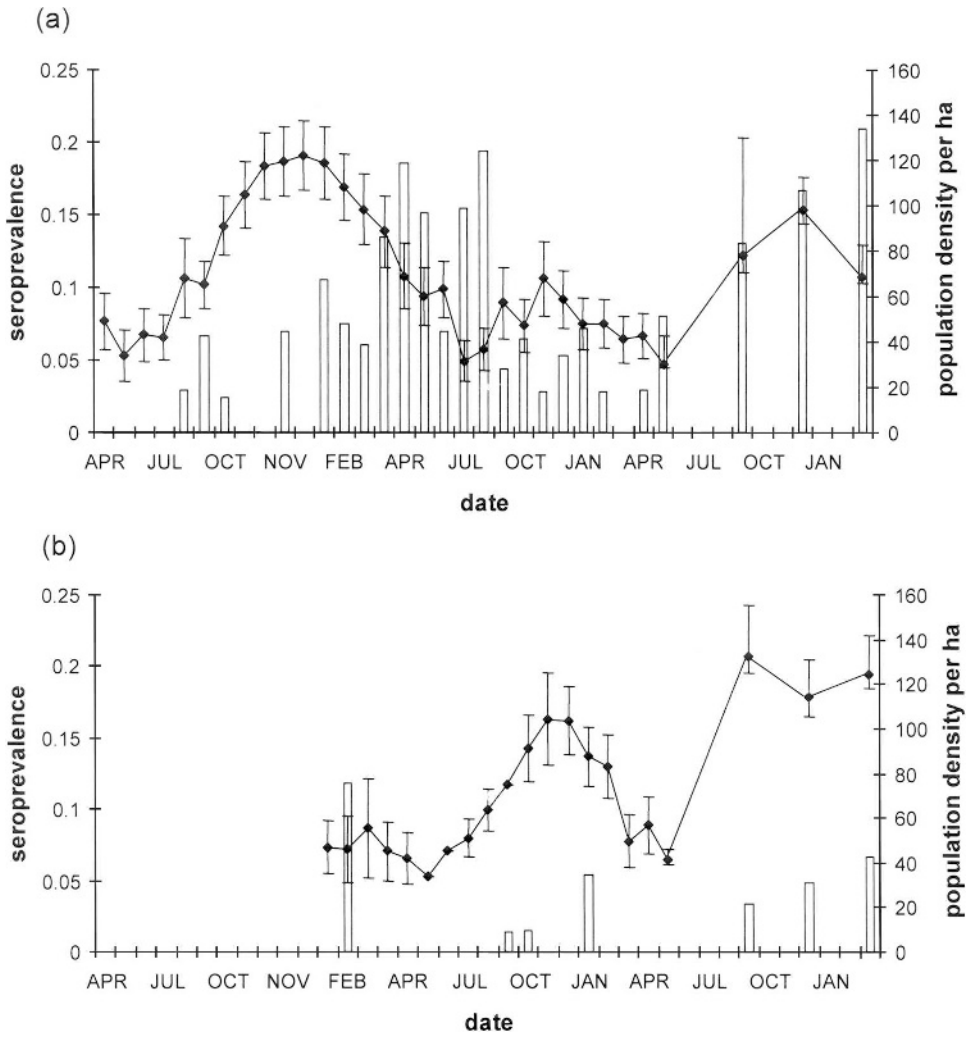

FIGURE 1. The estimated population density (line) and the proportion of sampled animals that tested positive for the presence of antibodies to murid gammaherpesvirus 4 (MuHV-4) (bars) for (a) wood mice and (b) bank voles. The 95% confidence intervals for population density estimates are also shown. Bank vole blood samples were only tested from January 2002 onwards and so only data from those months are presented.

lent in wood mice than bank voles, with 37 wood mice (11%) and eight bank voles (3%) testing positive at least once. There were 73 and eight positive blood samples from wood mice and bank voles, respectively. Thus, all eight bank voles that were recorded as positive had only a single positive capture, with four animals never being caught again and four animals testing negative on later captures. In contrast, wood mice were frequently seropositive on more than one capture, with 18 of the 26 wood mice caught subsequent to their first positive capture testing positive on at least one other occasion. Despite this, antibodies in wood mice may decline or disappear over time, as 17 of these 26 wood mice tested negative on at least one occasion after a positive test result. Time between first and last positive result for wood mice ranged from 28 to 195 days. There was no evidence of any sex-difference in the maintenance of antibody, with 30% and

33% of males ($n=20$) and females ($n=6$), respectively, having only a single positive capture followed by at least one negative capture.

Of the blood samples collected during the three trap sessions from September 2003 to March 2004, a further 35 wood mouse blood samples (17.8%, $n=209$) and 17 bank vole blood samples (5.0%, $n=341$) tested positive. As the animals were not tagged, it was not possible to tell how many individual animals this represented.

There was little discernible temporal pattern in the prevalence of seropositive bank voles (Fig. 1b). However, the seroprevalence in wood mice appeared to show two peaks, one during the summer of 2002 and one during the winter of 2003–2004 at the end of the study (Fig. 1a). There is no obvious seasonal pattern to these outbreaks, although examination of the graphs appears to suggest they occur just after periods of high wood mouse density.

Due to the low number of positive bank vole blood samples, further investigations and analyses were restricted to the wood mouse data. Blood samples from male wood mice appeared more likely to be seropositive than samples from females (males: 12%, $n=721$; females: 4%, $n=600$). Blood samples from older, heavier individuals were also more likely to be seropositive (animals <17.5 g: 0.7%, $n=293$; 18–25 g: 6%, $n=700$; >25 g: 17%, $n=296$). These patterns are investigated more fully using the GLMM described below.

Risk factors associated with seropositive mice

The data set used in the analysis to investigate what factors influence the probability that a wood mouse was seropositive included 490 observations, of which 49 were positive. There was no evidence of any seasonal pattern or effect of wood mouse abundance on the probability of being seropositive. The final model included an interaction between sex and mass (Table 1), such that males with the largest mass were the most likely to be seropositive. The predicted risk of being seropositive for the heaviest males was approximately 10%, compared to only 3% for the heaviest females (Fig. 2).

TABLE 1. Parameter estimates (logit scale) for a model of the risk of an individual wood mouse being seropositive. Standard errors (SE), *t*-values, degrees of freedom (df), and probabilities that a coefficient differs from 0 are also presented.

Covariate	Coefficient (SE)	*t*-value (df)	*P*
Intercept	−9.30 (4.73)	−1.96 (476)	0.05
Male	−19.90 (6.23)	−3.20 (476)	0.002
Mass	4.19 (3.61)	1.16 (476)	0.25
Male*mass	15.31 (4.65)	3.29 (476)	0.001

Risk factors associated with seroconversion

The data set used to investigate what factors influence the probability that a wood mouse will seroconvert included 459 observations and 14 seroconversions. Care needs to be taken when interpreting the results due to the small number of seroconversions, but the results are of interest primarily as a comparison with the analysis of seropositivity. Again there was no evidence of a seasonal pattern or an effect of density. There were two potential final models: in one, males were more

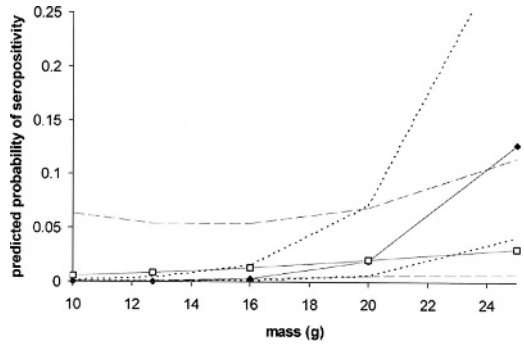

FIGURE 2. The relationship between mass and the predicted probability that an animal is seropositive for males (filled symbols) and females (open symbols). Short dotted lines show the 95% confidence interval for males and long dotted lines show the 95% confidence interval for females.

likely to seroconvert than females ($t=2.35$, df=432, $P=0.02$; coefficient for males on log-scale =1.80, SE=0.76); whilst in the other the probability of seroconversion increased with increasing mass ($t=2.59$, df=432, $P=0.01$; coefficient on log-scale =10.39, SE=4.01). When both these covariates were included in a model, both covariates were marginally nonsignificant (sex: $t=1.84$, df=431, $P=0.07$; mass: $t=1.85$, df=431, $P=0.06$), indicating that both factors may have some effect.

DISCUSSION

The results provide further evidence that wood mice rather than bank voles are the major host for MuHV-4 in wild populations of small mammals. This supports our previous preliminary study at the same site (Blasdell et al., 2003). Antibody prevalence was much lower in bank voles than wood mice, and there were several months where no positive bank voles were found. Although some caution in interpretation is required due to the relatively short (2 yr) length of the study, this suggests that the virus may not be able to persist within the bank vole population, but that spill-over infections occur from the sympatric wood mouse population.

Although examination of temporal patterns in seroprevalence indicated that infection in wood mice may peak following high population density, the GLMM showed no such relationships when individual factors were taken into account. Rather, analyses revealed that both the probability of a wood mouse having antibodies and the probability of initial seroconversion depended on sex and mass. Older males were more likely to be seropositive than any other category of animal. Similarly, heavier males are the most likely to seroconvert. The interaction between sex and mass in the analysis of seropositivity indicated that the probability of a female having antibodies showed no increase with weight. Although no such interaction was found in the analysis of seroconversion, this may have reflected a lack of power in the dataset.

Thus, the risk of infection appears to be related more to the sex and age of an animal than population level characteristics such as host density. The results may reflect behaviors associated with risk or variation in susceptibility. Other studies of viral infections in wild rodent populations have also shown a male bias in infection rates for hantavirus (Abbott et al., 1999) and cowpox (Hazel et al., 2000) and attributed such differences to the higher territorial aggression and travel distances in males. However, if the risk of infection with MuHV-4 was related to such factors, one might have also expected a strong seasonality as is seen in cowpox (Hazel et al., 2000), with infection more likely during the breeding season when males are encountering more conspecifics as a consequence of breeding behavior and territorial disputes. No such seasonality was detected, rather there appeared to be one outbreak that started early in 2002 and declined in autumn 2002, and a further outbreak occurred in late 2003. The sex bias may therefore reflect differences in susceptibility, potentially related to variation in the ability to mount an effective immune response. Increased levels of testosterone are known to depress both cell- and humoral-mediated immune responses in reproductively active males (Klein, 2000; Saino et al., 2000), while stress-related corticosteroids are known to confound the production of antibodies (Khansari et al., 1990). This may explain why it is older males that are most at risk.

The findings here contrast with our results for cowpox virus in the same study system. Cowpox virus is more prevalent among bank voles than wood mice and exhibits clear seasonal peaks in seroconversion (Hazel et al., 2000). Despite the lower prevalence in wood mice, cowpox appears to successfully transmit and persist within the wood mouse population with little evidence of transmission be-

tween the two host species (Begon et al., 1999; Carslake et al., in press). Moreover, the proportion of animals infected with cowpox increases with host density (Telfer et al., 2005). Thus, the dynamics of MuHV-4 and cowpox differ considerably within this multihost population. Cowpox dynamics are consistent with a seasonal flush of susceptible animals during the breeding season and some density dependence in transmission rates (Begon et al., 1998). In contrast, MuHV-4 dynamics show no strong seasonal or density-dependent patterns and infections appear to be more concentrated within one section of the population (old males). Consequently, MuHV-4 is not strongly influenced by either the influx of young animals during the breeding season or overall population density. If transmission in such infections is density-dependent, infection risk is likely to be related to the density of the high-risk group, rather than overall population density (Begon et al., 2002).

Examination of the longitudinal data indicate that animals may not maintain detectable levels of antibody postinfection, with all bank voles and many wood mice reverting to negative after one or more positive results. However, antibodies may be again detected later in a capture sequence. Seven of the 11 wood mice that reverted to negative after their initial positive result(s) and were caught again were subsequently detected with antibodies. This could reflect a lack of sensitivity in the diagnostic tests. However, it may also indicate reactivation of a latent infection, reinfection, or the disappearance of maternal antibodies followed by infection. As antibodies were only detected in two animals weighing less than 17.5 g, this last explanation can be discounted.

This study is the first to investigate the epidemiology of MuHV-4 in wild populations and the results provide an interesting contrast with another directly transmitted virus in the same study system. Unlike cowpox, where season and host density play an important role in determining infection risk, individual characteristics such as sex and age appear to be the predominate risk factors for MuHV-4. Future analyses aim to examine interactions between microparasites (viruses and bacteria) in this system, investigating the hypothesis that infection by MuHV-4 facilitates infection by other pathogens.

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