PROCEEDINGS OF THE ROYAL SOCIETY B

Proc. R. Soc. B (2005) **272**, 1163–1169
doi:10.1098/rspb.2004.3050
Published online 2 June 2005

Peak shift and epidemiology in a seasonal host–nematode system

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Insight into the dynamics of parasite–host relationships of higher vertebrates requires an understanding of two important features: the nature of transmission and the development of acquired immunity in the host. A dominant hypothesis proposes that acquired immunity develops with the cumulative exposure to infection, and consequently predicts a negative relationship between peak intensity of infection and host age at this peak. Although previous studies have found evidence to support this hypothesis through between-population comparisons, these results are confounded by spatial effects. In this study, we examined the dynamics of infection of the nematode *Trichostrongylus retortaeformis* within a natural population of rabbits sampled monthly for 26 years. The rabbit age structure was reconstructed using body mass as a proxy for age, and the host age–parasite intensity relationship was examined for each rabbit cohort born from February to August. The age–intensity curves exhibited a typical concave shape, and a significant negative relationship was found between peak intensity of infection and host age at this peak. Adult females showed a distinct periparturient rise in *T. retortaeformis* infection, with higher intensities in breeding adult females than adult males and non-breeding females. These findings are consistent with the hypothesis of an acquired immune response of the host to a parasite infection, supporting the principle that acquired immunity can be modelled using the cumulative exposure to infection. These findings also show that seasonality can be an important driver of host–parasite interactions.

Keywords: age–intensity relationship; peak shift; periparturient rise; seasonality

1. INTRODUCTION

The interaction between parasite and host is a dynamic process, in which the parasite exploits the host's nutrient-rich environment and attempts to avoid detection, while the host reacts through a range of immunological responses to reduce the parasite's recruitment and survival. Selection should favour those parasites that can successfully take advantage of the immunologically naive hosts to produce abundant and successful infective stages before the environment becomes hostile. Since the majority of higher vertebrates exhibit highly seasonal birth production, the immunologically naive hosts are only available during the breeding season, and for much of the remaining year, the host population consists of individuals with experience of prior infection. Thus, if we are to examine how parasites persist through time, we must consider not only the seasonal change in the environmental conditions that influence transmission, but also how the host age structure and the population immunity varies.

Models of the host age–parasite intensity relationship often assume that acquired immunity develops as a function of the cumulative exposure to parasites (Anderson & May 1985; Woolhouse 1992, 1998). When transmission rates are high, the parasite intensity will rise rapidly, reaching a peak in relatively young individuals. This peak will be followed by a reduction in intensity whenever acquired immunity enhances parasite mortality or inhibits recruitment. By contrast, when the rate of transmission is low, the intensity rises more slowly and peaks, with lower intensity, in older-age individuals. The cumulative exposure at the point of turnover will be roughly the same, but the age-at-peak depends on the force of infection. This pattern has become known as the 'peak shift' (Woolhouse 1998), and predicts a negative correlation between the peak of infection and the age at which the peak occurs. To date, evidence for the peak shift comes from a comparison of age–intensity curves obtained from different, endemically infected populations (reviewed in Woolhouse 1998; Wilson *et al.* 2002). Although suggestive, this evidence may be confounded by spatial variations in susceptibility or genetic variations in parasites between host populations.

Identification of a peak shift not only provides support for the hypothesis that acquired immunity is a function of the cumulative exposure to the parasite, but also refutes alternative explanations such that self-cure immunity is age dependent or a function of age-related exposure, or indeed is a function of the current intensity of infection or seasonal changes in exposure. Nevertheless, other

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Received 29 November 2004
Accepted 21 December 2004

demographic factors may interfere with the age-related immunological response and modify the peak shift pattern. Seasonal breeding coupled with a seasonal environment, where transmission is restricted to a few months of the year, will select for parasites with long-lived infective stages, which survive from one breeding season to the next, or favour the evolution of mechanisms that permit the long-term persistence of worms in a population (e.g. Fenton & Hudson 2002; Fenton *et al.* 2004). For instance, arrested development or delays in parasite recruitment effectively increase parasite survival through periods when transmission is limited. Similarly, the periparturient rise (which is probably a more effective mechanism for increasing parasite fitness in a seasonal environment) results in an increase in worms and egg production in immunocompromised breeding females. This phenomenon occurs as a consequence of relaxation of immunity, mainly associated with hormonal changes during late pregnancy and lactation, and leads to a pulse of infective stages on the pasture just as the seasonal production of immunonaive juvenile hosts start grazing.

In this paper, we examine the dynamics of *Trichostrongylus retortaeformis* in a population of wild rabbits sampled monthly for 26 years. This population of rabbits exhibits seasonal breeding that lasts from late winter to late summer. This long breeding season allows us to investigate the development of infection in rabbit cohorts born in different months and to distinguish the monthly variations in parasite intensity from confounding seasonal conditions that influence transmission. Specifically, we aimed to identify whether there is evidence of a shift in the peak of infection between cohorts of rabbits born in different months. First, we examined whether the host age–parasite intensity relationships of each cohort conformed to the profile predicted from the models of acquired immunity. Second, we investigated whether the seasonality in the force of infection resulted in a peak shift between cohorts. Third, we looked for evidence of a seasonal periparturient rise in female rabbits. Our objective is to obtain insight into the development of the host self-cure response and the related seasonal timing of the infectious events.

2. METHODS

(a) *The data*

Parasite intensity of *T. retortaeformis* was recorded each month from a sample of wild rabbits shot from a multi-warren population in central Scotland between 1977 and 2002 (Boag *et al.* 2001). Rabbits were randomly sampled (min. = 1, max. = 64 individuals per month) from warrens in a 400 ha area located at the interface of heather moorland and arable farmland. For every individual sampled, we recorded body mass, sex, breeding conditions (nursing females, pregnant females) and parasite intensity (Boag *et al.* 2001).

The age structure of the rabbit population was reconstructed using individual body mass as a proxy for age (Cowan 1983). We first classified the rabbits into eight age–mass classes that corresponded to three major age categories: kittens (class 1: 100–200 g, class 2: 201–480 g, class 3: 481–750 g); juveniles (class 4: 751–1030 g, class 5: 1031–1300 g); and adults (class 6: 1301–1580 g, class 7: 1581–1860 g, class 8: 1861 g or more). Each age class was calculated based on an individual average monthly growth of 280 g, as predicted from a daily average growth rate of 9 g (Dunnet 1956; Parer & Libke 1991). Second, from this age classification, we estimated the month of birth for each individual. Third, we used the parasite intensity data to produce a host age–parasite intensity curve for each monthly cohort throughout the breeding season. The estimation of age may have induced additional uncertainty in our analysis owing to secondary factors that may have influenced body mass, especially in older individuals, and could have led to some misclassification (Dudzinski & Mykytowycz 1960; Parer 1977). Since we used a large sample size (a total of 2804 individuals) over 26 years, possible biases owing to significant annual variation in body growth should be largely averaged out. Indeed, rabbit body mass was relatively constant across the 26 years of sampling (coefficient of variation: mean = 44.05, s.e. = $\pm$1.18), and the year-to-year variations appeared to be caused by differences in the percentage of individuals sampled in each age class within each year (generalized linear model with Poisson error distribution: body mass versus age class, year and their interaction for all $p < 0.05$). We also verified the predictability of body mass using two other body measures that are correlated with age, foot length and body length, from a subsample of 287 rabbits. Body mass increased linearly with both foot and body length in young and immature age classes, but the relationships reached an asymptote in adult rabbits. The point of flex of the mass–body size relationship corresponded to age class 5 for both foot and body length. Therefore, since we used relatively broad age–mass classes, which should be robust to minor variations in body mass, then individuals weakened by parasites or other factors are unlikely to change categories. Overall, our age–mass classification proved a reasonable method for distinguishing between age cohorts.

Trichostrongylus retortaeformis is a directly transmitted gastrointestinal nematode commonly found in wild rabbits, its principal host species (Anderson 2000). Like most trichostrongylid nematodes, the survival of free-living stages is sensitive to climatic conditions and, because they require moist and warm environment for development and transmission, we can expect seasonal variability in abundance of infective stages (Soulsby 1982). Eggs of trichsotrongylids commence development when temperature exceeds 10 °C, and migration of larvae onto vegetation ceases below a temperature of 2.7 °C (Crofton 1946*a*,*b*). The parasitic adult stage inhabits the small intestine and experimental infections of 3- to 4-month-old rabbits found no pathology when infected with a single dose of 5000–7000 larvae, but diarrhoea and loss of mass with larger infections of 10 000 larvae (Haupt 1975). There was also evidence that *T. retortaeformis* reduces birth mass and the number of offspring in captive rabbits (Dunsmore 1980). With a challenge of 10 000 larvae, only a small proportion of third and fourth infective-stage larvae failed to develop into sexually mature *T. retortaeformis* (Haupt 1975).

An inspection of our rabbit dataset found no evidence of infection in the youngest individuals (age class 1), probably because these small kittens are still suckling and have yet to be exposed to the contaminated pasture. Infection was first detected in individuals of age class 2, which should have just emerged from the nesting burrows and were experiencing the contaminated pasture as parasite-naive hosts. Therefore, this initial infectious load probably reflects the environmental force of infection once it has been weighted by the

age/size-dependent food intake. Since temperature in winter is below 10 °C, when free-living parasite stages are not active, and considering that we did not sample individuals belonging to age class 1 between October and January, we restricted our analyses to the cohorts of rabbits born between February and August. No young age classes were collected in cohorts of rabbits born in September and October so we excluded these two cohorts. We analysed our data with and without these two cohorts and this exclusion made no difference to the conclusions. During post-mortem analysis, we recorded the presence of myxoma lesions and, because we have previously identified an interaction between myxoma and nematodes (Boag *et al.* 2001), we based our analysis on myxomatosis-free individuals.

We also obtained monthly climatic data on temperature (minimum grass temperature and minimum soil temperature within 10 cm depth) and total rainfall from 1980 to 1999 from Mylnefield (or Invergowrie) climatic station, 7 km from the study site. Weather is important for the development of the free-living stages of the parasite, and monthly changes in temperature and rainfall were compared with the seasonal changes in parasite intensity in rabbits of age class 2, which probably reflects the relative environmental force of infection.

(b) *Analyses*

Prior to analyses, we classified the rabbits sampled during the 26 year period according to their age and cohort. In the analysis, each cohort is denoted by the month of birth (between February and August). A main objective of our analysis is to describe the shape and reveal the mechanisms that generate the age–intensity curves. As such, we fitted cubic splines (Hastie & Tibshirani 1990) to the age–intensity relationship, because such splines can describe a wide variety of shapes. Specifically, for each cohort born between February and August, a smooth spline curve (4 d.f.) was fitted to the log-mean parasite intensity [$\log(x+1)$] by host age. To enhance precision in the spline regressions, each mean intensity was weighted by the corresponding number of rabbits sampled. We also undertook this analysis for each sex separately to search for evidence of changes in immunity by sexes and periparturient rise in reproductive females. In this case, the spline curve was fitted to the log-mean parasite intensity [$\log(x+1)$] by age of rabbits sampled every month, from February to August. A generalized linear model with negative binomial errors was undertaken between intensity in age classes 6–8, and a series of population and environmental variables that may be important in affecting the periparturient rise.

A key variable in the theory of immune-mediated interactions and peak shift is the mean age at peak of infection. Calculation of this quantity requires us to know how the parasite burden of a cohort is distributed across the hosts' age classes—the mean age at peak of infection is the expectation of this distribution. Explicitly, to examine the distribution of parasites in the host we need to use a probability distribution and somewhat arbitrarily choose the flexible two-parameter Weibull probability density distribution (McCullagh & Nelder 1989):

$$f(x) = \frac{\gamma}{\alpha}\left(\frac{x}{\alpha}\right)^{(\gamma-1)} \mathrm{e}^{-(x/\alpha)^{\gamma}} \quad x \geq 0;\ \ \gamma,\ \ \alpha > 0, \tag{3.1}$$

where x is the age of the host for each parasite recorded in a cohort, γ is the shape parameter set to 2 and α represents the scale parameter set to 2. We estimated the parameters by maximum likelihood. The Weibull distribution describes a variety of distributional shapes, and should consequently result in relatively robust estimates.

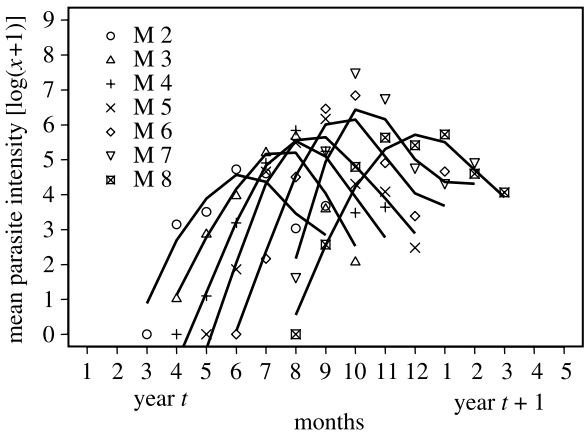

Figure 1. Host age–parasite intensity profiles for each cohort of individuals born from February (M 2) to August (M 8). The smooth profiles represent a cubic spline curve fitted to the relationship between geometric mean of parasite intensity and host cohorts, averaged over 26 years of data (symbols).

We visualized the estimated distributions by scaling each one by the total parasite burden of each cohort. We subsequently estimated the mean age at peak of infection for each cohort, according to the expectation of the estimated Weibull distributions:

$$\bar{x} = \alpha\Gamma\left(\frac{1}{\gamma} + 1\right), \tag{3.2}$$

where Γ represents the gamma function. We investigated the relationship between the total parasite burden of each cohort and the mean age at peak of infection to look for evidence of peak shift.

To identify the climatic variable that accounted for the seasonal variation in the force of infection we performed a generalized linear model, with negative binomial errors, between parasite intensity in rabbits of age class 2, as response, and the monthly value of climatic variables (minimum grass temperature, minimum temperature in 10 cm depth soil and total rainfall), from February to August across the 26 years. This analysis is based on the assumption that rabbits in age class 2 probably reflect the relative environmental force of infection and that this is a relative measure since foraging rates will increase with increasing size and age.

3. RESULTS

For each cohort (named by the month of birth), the age–intensity relationship exhibited a typical self-cure profile with two dominating patterns (figure 1). First, the shape of the smoothed curves was relatively similar between cohorts, with all curves reaching peak intensity in the juveniles and decreasing in the older age classes. Second, the peak intensity of infection increased exponentially with the month of birth for cohorts born between February and July, and decreased for cohorts born in August.

The age–intensity profiles for rabbits of each sex sampled every month were clearly different during the breeding months (figure 2). In the main breeding season (April–July), adult females carried a significantly greater intensity of infection than adult males (table 1*a*). The hypothesis that

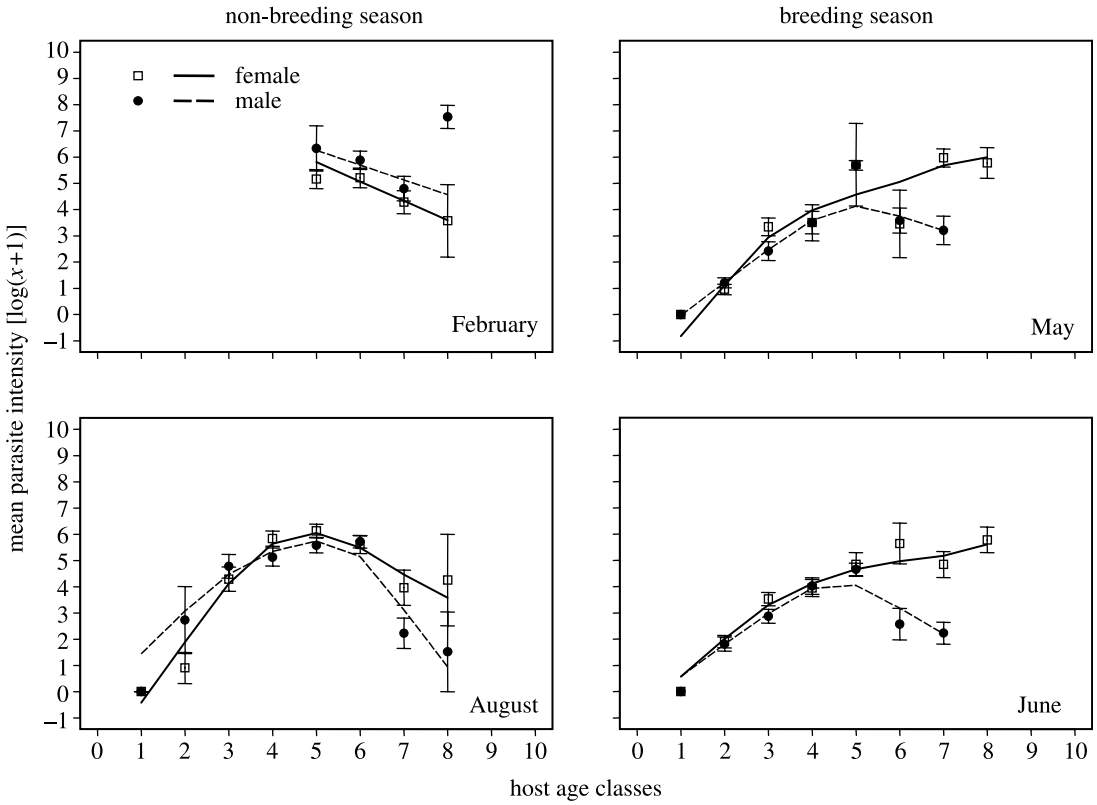

Figure 2. Host age–parasite intensity profiles by sex for rabbits sampled every month. Each profile represents a cubic spline curve fitted to the relationship between geometric mean of parasite intensity and host age classes, averaged over 26 years of data (symbols). The standard error bars of the mean intensity are reported. For simplicity, snap shots for February, May, June and August are presented.

Table 1. Generalized linear model between *T. retortaeformis* intensity in adult rabbits (cohorts 6–8) in the main breeding season (from April to July) and (*a*) sex, age and month; parameter of aggregation $k=0.24$ (± 0.01); (*b*) nursing, age and month; parameter of aggregation $k=0.35$ (± 0.03). Generalized linear model weighted by number of rabbits.

significant variables	slope	$F_{\text{d.f.}}$	p
(*a*)			
sex	5.65	29.48_{498}	0.001
age	0.98	13.10_{499}	0.001
sex×age	−0.73	6.35_{496}	0.01
month×sex	−0.36	6.13_{497}	0.01
(*b*)			
month×nursing×age	−0.60	4.43_{255}	0.04

this difference was a consequence of a periparturient rise in immunosuppressed breeding females was supported further by the observation that parasite intensity was affected by monthly changes (modelled as continuous variable in the analysis) in adult nursing females (table 1*b*).

The estimated age–parasite intensity curves for each month of birth showed that the peak parasite intensity increased with the month of birth from spring to summer. The rabbit cohort born in July had the highest level of infection at the peak, whereas the cohort born in February had the lowest values (figure 3*a*). We found a significant negative relationship between the total intensity of infection and the estimated mean age at peak of infection (figure 3*b*; $y=-1973x+13878$, $p<0.05$) in line with the predictions of the peak shift hypothesis.

The threshold of minimum grass temperature of 2.7 °C, when infective larvae are expected to migrate onto the vegetation, was exceeded in all months from May (mean ± s.e. = 3.05 ± 0.151) to September (mean ± s.e. = 5.32 ± 0.163), with a peak in the minimum temperature in the month of July (mean ± s.e. = 8.15 ± 0.134). The generalized linear model between mean parasite intensity in rabbits of age class 2 and weather variables (from March to August over 26 years) identified a significant effect of minimum grass temperature (slope = 0.40, d.f. = 76, $p<0.01$), but no apparent influence of minimum temperature in 10 cm depth soil or total rainfall.

4. DISCUSSION

In this study of *T. retortaeformis* dynamics in an age-structured population of wild rabbits, we provide strong empirical evidence of parasite regulation through acquired immunity to the nematode infection. The monthly age–intensity curves exhibited a characteristic concave type 3 relationship (Hudson & Dobson 1995), and the parsimonious explanation is that this pattern was generated by the development of acquired immunity in the rabbit cohorts, moulded by seasonality in both transmission and host reproduction. This finding is supported by two pieces of evidence: first, a significant peak shift result from the seasonality in the force of infection and second, a clear periparturient rise in the intensity of infection in adult females during the breeding season. The shift in the peak of infection with host age is consistent with the model of acquired immunity developing in relation to the cumulative exposure to parasites. A refined analysis will be needed

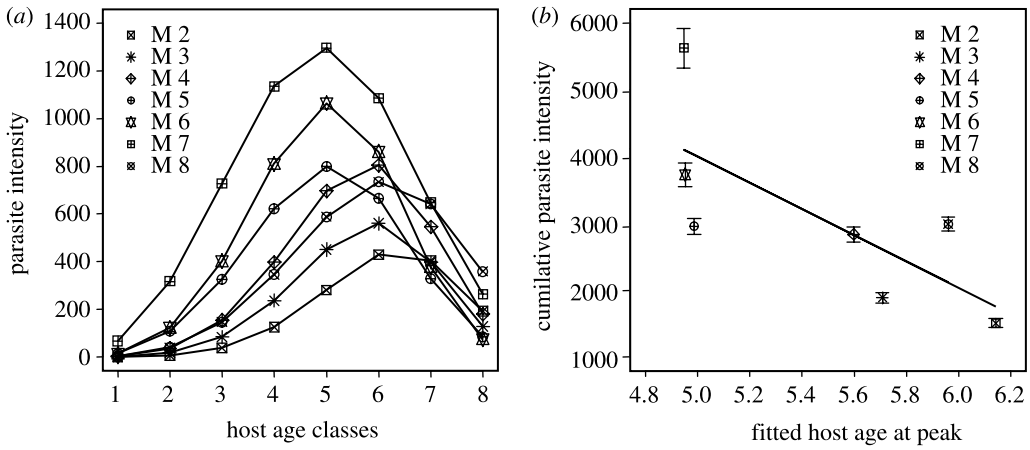

Figure 3. (*a*) Parasite density profiles by host cohort in each month of birth, from February (M 2) to August (M 8), estimated using the Weibull probability density distribution. We have rescaled the curves, multiplying each one by the parasite intensity in each age class of every month. (*b*) Relationship between cumulative (±s.e.) parasite intensity and estimated mean host age at peak from February (M 2) to August (M 8) months of birth.

to discern whether there are additional influences of host age, season or current levels of infection. However, acquired immunity through past exposures appears to be the dominating regulatory mechanism for the within-host dynamics in this system.

Had the turnover in the age–intensity curve been primarily driven by age-dependent immunity, we would expect the intensity of infection to peak at the same host age in every cohort. If the turnover was a function of current intensity influencing immunity, then the curves should have turned over at the same peak intensity and not at the same level of accumulated exposure. However, both of these immune-mediated hypotheses work on the principle that the turnover arises from decreasing worm survival; the alternative is that there may have been a seasonal or age-related change in exposure. If this was driven simply by the seasonal force of infection, we would have seen all the age–intensity curves peak in the same month, which we did not. Age-related changes in exposure could also have occurred if the rabbits had changed their diet as they became older. We did not examine diet, but the evidence is that rabbits feed on the same diet irrespective of age. Therefore, age-related change in exposure seems unlikely, and can be refuted when we consider the findings of the intensity-dependent rise in infection during the periparturient rise. As such, these data imply that the age–intensity relationship was determined primarily by immune response of the host.

We have identified a peak shift between cohorts of hosts from a single, naturally occurring population, and have avoided the spatially confounding effects between host populations observed in other studies (e.g. Woolhouse 1998). The greater parasite intensity in adult breeding females than in adult males and not pregnant females provided good evidence of a periparturient rise during the spring to summer period. We have also presented additional evidence that adult females exhibit acquired immunity to parasites, which became relaxed when they were pregnant. In addition, the occurrence of both a periparturient rise and the peak shift suggests that it is unlikely that the age–intensity profiles' turnover was a consequence of parasite-induced host mortality. One other explanation was that the turnover in the age–intensity curves may have been caused by frailty in the data. Since parasites are usually aggregated within their host population, a fall in sample size with host age can reduce the chance of sampling heavily infected individuals (Pacala & Dobson 1988), and thus lead to an apparent turnover in the age–intensity curve (Gregory & Woolhouse 1993). We were able to reject this explanation for the age–intensity patterns observed here because we were careful to weight our analysis by sample size, such that the age–intensity curves indicate a true turnover.

The intensity of *T. retortaeformis* infection rose rapidly in the young rabbit age classes with evidence of an efficient acquired immune response developing within just four months. Since parasites are available on the pasture in a seasonal pulse that coincides with the reproduction of the host, the force of infection varied seasonally between rabbit cohorts. In July, when transmission rate was greatest (as identified by an examination of the increase in infection in the rabbit cohort born in this month and the recorded grass temperature), both infection and immunity built up rapidly. In early spring, rabbit density was low, birth rate was low and transmission rate was also low. Therefore, parasite intensity increased slowly with age and peaked when rabbits were relatively old. Since parasite transmission is low during winter months, the relatively low parasite intensity found in the older rabbits sampled in the late winter to early spring period was probably the result of exposure in the previous year. We suspect that parasites ingested in earlier months may have entered arrested development during winter and re-emerged the following spring—particularly in the immunocompromised adult females as they started breeding. There is evidence that in seasonal environments the relative abundance of arrested trichostrongylid larvae that overwinter within the host can range between 50 and 90%, depending on the adversity of the environmental conditions and the level of host immunity (Soulsby 1982). Laboratory studies with domestic rabbits have found evidence of arrested development and a periparturient rise for *T. retortaeformis* (Michel 1952). Our findings provide good evidence that these patterns

also occur in wild rabbit populations living in a seasonal environment.

We suspect that the parasites recruited into the adult parasite population, as a consequence of the periparturient rise, added to the seasonal pulse of infective larvae on the pasture, and contributed significantly to the exponential increase in the intensity of infection observed across the cohorts born from late spring to summer. We found that parasite intensity was strongly related to grass temperature, although this was insufficient to explain the seasonal shift in the peak age of infection.

We based our analyses on rabbit age classes reconstructed from body mass data. This could be a limitation of this study because seasonal variation as well as annual changes in body mass may have affected our classification. However, we have used discrete age classes, rather than a continuous variable for age, and tested these age classes with other measures of body size, which all indicate that mass is a good measure for distinguishing between cohorts. In this respect, the distinct periparturient rise among the adult females during the breeding season, where females did not lose mass but did gain parasites within their age class, provided reasonable evidence that individuals did not change age categories as infection varied. As such, we felt confident of having described the general age–intensity pattern of this rabbit population. Another limitation of this study is that we have considered only one parasite species even though we know that there are four other gastrointestinal helminths that infect this host population, which exhibit a series of complex interspecific interactions (Lello *et al.* 2004). We cannot exclude the possibility that other parasites may interact with *T. retortaeformis*, or indeed the immune response of the host and may shape the age–intensity curve. Preliminary analyses indicate that this is not a strong effect, although we are currently examining these patterns and interactions in more detail and aim to capture the age–intensity pattern observed with a mathematical model.

In conclusion, theoretical models predict that acquired immunity can generate a shift in the peak of infection with host age. There is now growing evidence that such patterns may be relatively common in animal populations (Gregory *et al.* 1992; Quinnell 1992; Müller-Graf *et al.* 1997). Our study provides new evidence that this does occur within a natural free-ranging population owing to seasonal variability in infection rate and host reproduction. Furthermore, we have identified that acquired immunity is a dominant force shaping the population dynamics of a parasitic nematode of rabbits, and we found negligible support for any alternative explanations for the turnover in the age–intensity curve.

I.M.C and B.B. were funded by the Leverhulme Trust and S.J.C. by the Wellcome Trust. This study was conducted as part of the 'seasonality in infectious diseases' working group supported by NCEAS-UCSB and the State of California.

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As this paper exceeds the maximum length normally permitted, the authors have agreed to contribute to production costs.