Appendix A: Details of the mathematical modeling

Our model of the development and effect of immunity is similar to a standard model for gastrointestinal nematodes in ruminants (Roberts & Grenfell 1991). Acquired immunity builds in response to the host's history of parasite exposure, therefore *cumulative exposure* is a central quantity in the host-parasite interaction (Anderson & May 1985). Generally, exposure is assumed to be affected by the environmental force of infection and host age according to $\phi(a)F(t)$, where *F(t)* is the abundance of infectious larvae per unit weight of comestible herbage (possibly seasonally varying – *t* represents the time of the year) and *a* is the rabbit's age. The variate $\phi(a)$ represents the age-specific monthly feeding rate. The product of *F* and ϕ is the season- and age-specific force of infection. Based on the above considerations, the general model for the host cumulative exposure to parasite infective stages, *E*, is:

$$\frac{dE(a,t)}{dt} = \phi(a)F(t). \qquad (1)$$

The host's acquired ability to mount a response to the parasite, *I*, will be proportional to *E*, according to $I(a,t,c) = \beta(a,t,c)E(a,t)$, but where the constant of proportionality β (*viz*. 'immunocompetence'), may depend on age, season, and cohort *c*(=*t*-*a*, i.e. month of birth). Immunity may wane, but since this happens at a slow rate (e.g. 0.01 yr^{-1} according to Kao *et al*. (2000)) we neglect this since we consider rabbits no older than one year.

If we assume that acquired immunity *I(a,t,c)* at time *t* of a cohort born in month *c* acts to inhibit (in an exponential fashion) the establishment of ingested parasites, then the infection rate is

$$R(a,t,c) = \phi(a)F(t)\exp(-I(a,t,c)).$$

We further assume that mature parasites have a constant mortality rate μ, independent of hosts' immunity or intra-parasite density dependence. Consequently, the mean number of parasites at time *t* in the rabbit cohort born in month *c* will obey the following differential equation:

$$\frac{dP(a,t,c)}{dt} = \phi(a)F(t)\exp(-I(a,t,c)) - \mu P(a,t,c). \qquad (2)$$

Equations (1)-(2) represent our general model of parasite exposure and establishment. For model fitting and data analysis, however, we need to specify the functional forms of the various components of the model. In particular, we need to define candidate models for (i) how the force of infection varies through the year, *F(t)*, (ii) how feeding rates depends on age, $\phi(a)$, and (iii) how immunocompetence varies among individuals, $\beta(a,t,c)$. A definition of the model parameters is reported in table 1 of the MS, and the meaning of the letters used to denote different components of the models is summarised in table 2.

The force of infection, *F*, will itself depend on the history of reproductive adult parasites present in the host population. Since we do not have available data on host density or a reliable measure of parasite fecundity (which will depend on the hosts immunity as well as the adults intestinal density), we are unable to model or estimate the force of infection independently. We therefore use a generic mathematical expression that encompasses three scenarios for the force of infection:

$$F(t) = [1 + f_1 \sin(\omega\{t - \theta_1 + 3\} + f_p \sin[\omega\{t - \vartheta_p + 3\}]) + f_2 \sin(2\omega\{t - \theta_2 + 3\})]$$

where *t* is the time in months and $\omega = \pi/6$ month^{-1} is the angular frequency corresponding to annual variation (there is no multiplicative constant in the expression for *F* as this would be indistinguishable from a constant in the feeding rate).

This elaborate expression for the force of infection has the following three possible scenarios:

(i) *Sinusoidal*: where $p=f_2=0$, and the parameters f_1 and θ_1 are estimated through model fitting. This is denoted as model 'F', and θ_1 represents the month where *F* is maximal.

(ii) *Sinusoidal plus second harmonic* (denoted as model 'FH'): where $p=0$, and the parameters f_1, f_2, θ_1 and θ_2 are estimated with model fitting.

(iii) *Sinusoidal phase modulation* (denoted as model 'FP'): where $f_1=0$, and the parameters f_1, p, θ_1 and θ_p are estimated with model fitting. Models FH and FP are used to assess whether there is any significant non-sinusoidality in the force of infection, *F* .

Though the feeding rate ϕ varies with rabbit age *a*, we can only infer individuals' age indirectly from their body mass. While this adds some additional uncertainty to the analysis (discussed in some detail in Cattadori *et al*., 2005) we believe our results are robust enough to describe patterns of feeding rate and parasite infection with age. We use the age/body mass calibration of Cattadori *et al*. (2005) to obtain the following allometric model for feeding rate:

$$\phi = \phi_0 \left(200 + 275a \big/ 3340 \right)^{\gamma}$$

where ϕ_0 and γ are constants. The constant γ is allowed to be nonzero if the age-dependent feeding rate G is present in the model; the parameter ϕ_0 needs to be fitted whatever the model.

Our previous study on the *T. retortaeformis*-rabbit interaction highlighted the occurrence of heterogeneities (mainly related to season, age and sex) in infection intensity (Cattadori *et al*. 2005), so here we consider various scenarios for how immunocompetence varies among individuals:

Age-dependence (A): where $\beta_A = \beta_0 + \beta_1 a$. This allows older rabbits to have a higher immunocompetence than younger individuals. We denote by 'I' models where $\beta_0 \neq 0$ and by 'A' models where $\beta_1 \neq 0$.

Season-dependent condition (T): where $\beta_T = (1 + \beta_{1T} \sin(\omega(t - \psi_T + 3)))$, ψ_T being the month in which immunocompetence is maximal. We denote by `S' models where $\beta_{1T} \neq 0$.

Cohort-dependent immunity (C): where $\beta_C = 1 + \beta_{1C} \sin(\omega(b - \psi_C + 3))$, ψ_C being the month in which the most immuno-competent rabbits were born.

In total, these components combine to form 72 possible models. We have not tested all combinations, but the nested structure imposes bounds on the likelihoods that enable us to reject some of simpler models without explicit fitting.

Statistical procedure

Equation (2) may be interpreted as the first moment of a linear stochastic immigration-death process, in which case the parasite burdens would be distributed among hosts as a Poisson distribution with mean *P*. However, our data, in common with many macroparasite systems, display aggregated distributions among hosts

(Boag *et al*. 2001), so when fitting the data we shall assume a negative-binomial distribution among hosts (Grenfell *et al*. 1995).

To estimate model parameters, we pick initial values for all parameters and integrate the differential equations (1) and (2) to give predicted mean infection levels for rabbits in different age and birth classes. The differential equations are well behaved, and may be robustly solved using fixed-step numerical integration. The likelihood of the model is then calculated by assuming that each rabbit's parasite burden is drawn from a negative binomial with the predicted mean (appropriate to its age and cohort) and a shape parameter *k*. We then use standard multidimensional optimisation routines (Nelder-Mead Simplex and Conjugate Gradient (Press *et al*. 1992)) to update the values for the parameters and find the model parameters for which the likelihood is maximised. The Akaike Information Criterion (AIC=-2(log likelihood)+2(number of parameters)) was calculated for each model and the degree, ΔAIC, by which a model differs from the model with the lowest (best) AIC is used to evaluate the relative accuracy of these models (Burnham & Anderson 1998). The standard rule of thumb is that models with ΔAIC values of 0-2 well predict the pattern observed in the raw data (`good support'), models with values of 4-7 poorly describe the pattern of the raw data (`some support'), and models with values of 10+ are not reliable (`no support').

References

Anderson, R.M. & May, R.M. (1985) Herd immunity to helminth infection and implications for parasite control. *Nature,* 315, 493–496.

Boag, B., Lello, J., Fenton, A., Tompkins, D.M. & Hudson, P.J. (2001) Patterns of parasite aggregation in the wild european rabbit (*Oryctolagus cuniculus*). *Int J Parasitol,* 31, 1421–1428.

Burnham, K.P. & Anderson, D.A. (1998) *Model Selection and Inference: a Practical Information Theoretic Approach.* Springer-Verlag, New York.

Cattadori, I.M., Boag, B., Bjørnstad, O.N., Cornell, S.J. & Hudson, P.J. 2005 Immuno-epidemiology and peak shift in a seasonal host-nematode system. *Proc Roy Soc London B* 272, 1167-1169.

Grenfell, B.T., Wilson, K., Isham, V.S., Boyd, H.E.G. & Dietz, K. (1995) *Parasitology*, 111, S135–S151.

Kao, R.R., Leathwick, D.M., Roberts, M.G. & Sutherland, I.A. (2000) Nematode parasites of ruminants: a survey of epidemiological parameters and their application in a simple model. *Parasitology*, 121, 85–103.

Press, W.H., Teukolsky, S.A., Vetterling, W.T. & Flannery, B.P. (1992) *Numerical Recipes in Fortran: the Art of Scientific Computing*, 2nd. Edition, Cambridge University Press, New York.

Roberts, M.G. & Grenfell, B.T. (1991) The population dynamics of nematode infections of ruminants: periodic perturbations as a model for management. *IMA J Math Appl Med Biol.* 8, 83–93.