The Immunoepidemiology of Parasites of Farmed Animals*

M.G.Roberts
AgResearch, Wallaceville Animal Research Centre,
P.O.Box 40063, Upper Hutt, New Zealand

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Abstract

The population dynamics of farmed animals are controlled by humans, and often encourage higher parasite burdens than would be usual in wild animals. As a result, the immunity to reinfection acquired by the host is an important determinant of parasite population dynamics. For example, lambs are highly susceptible to gastrointestinal nematodes as they begin to graze, but develop an immunity that accounts for observed within-year variation in parasite load and pasture contamination. In the longer term, control measures are compromised by the development of parasite strains resistant to chemotherapy, focusing attention on the development of "natural" measures including antiparasite vaccines. The immunoepidemiology of parasites of farmed animals must therefore be considered on three levels: the interaction between the parasite and the host's immune system determining the individual's level of protection; the development of acquired immunity determining the within-year parasite population dynamics; and the long-term effects of control measures on the between-year parasite population dynamics.

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1. Introduction

Considerable progress has been made towards establishing mathematical descriptions of the epidemiology of diseases of humans (Isham & Medley, 1996) and wild animals (Grenfell & Dobson, 1995), but less attention has been paid to models for the spread of diseases in farmed animals. The mathematical theory of immunology is in its infancy, has concentrated on the development of models relevant to the human immune system, and has mimicked conventional models of population dynamics and competition, using differential equations to represent the interactions between invading parasite (antigen) and host response (for example, antibody). Whereas the population dynamics of macroparasites of farmed animals depend critically on protective acquired immunity (Roberts, 1995), the responses observed in the animal may have little to do with protection and may occur at some cost to the host animal. The challenge is to bridge the gap between within-host immunology and between-host epidemiology. One way to facilitate this would be to use mathematical models to generate testable hypotheses concerning mechanisms of protection. These would aid in the development of vaccines and vaccination strategies, and an enhanced understanding of some of the immunological mechanisms involved in host protection. In this paper we review some recent results as they apply to the immunoepidemiology of helminth parasites of farmed animals.

2. The Epidemiology of Immunity

It has long been established that the coevolution of parasites and their hosts has not necessarily led to avirulent parasite strains (see May & Anderson, 1990; Mitchell, 1991). However, the breeding of domestic animals and their husbandry, including parasite control and grazing management, has left little opportunity for free "coevolution" within this system. The "evolution" of the host has been by selective breeding, which may include breeding for resistance or resilience to parasite challenge (Bisset & Morris, 1996). The evolution of the parasite has been constrained by the widespread use of anthelmintics, which has introduced a strong selection pressure for strains resistant to chemotherapy (Dobson et al., 1996). A major feature of the epidemiology of macroparasites of farmed animals is that the hosts are maintained at a greater population density that would be usual for wild animals, and constraints on their movement make it more difficult to avoid infection from free-living stages of parasites. This results in higher levels of parasite challenge than encountered by wild animals, and a greater stimulus for the acquisition of immunity to re-infection (Roberts, 1995).

Acquired immunity to helminths may be stimulated by antigen derived from larvae, adult parasites, and/or parasite eggs; and its target may be larvae, adults and/or eggs, depending on the species of parasite. Woolhouse (1994) noted that for schistosomes of humans it is possible to distinguish between some of these nine possible combinations from age-intensity curves, but for other combinations more than one mechanism can lead to identical epidemiological consequences. In this paper we will discuss models with acquired immunity being stimulated by incoming larval challenge, or by the presence of adult parasites, and acting to reduce one or more of: the probability of establishment of further parasites; the rate of development of parasites; the fecundity of parasites; and the survival of parasites (see Lloyd, 1995).

The effect of acquired immunity on parasite epidemiology and control can be dramatic. For example, Fig.1 shows the relationship between the mean number of larvae and the age of the host for two species of cestode[1] parasites of sheep. The data are consistent with acquired immunity having little or no effect on the establishment of *E.granulosus*, but severely limiting the establishment of *T.hydatigena* in older animals. A higher level of acquired immunity implies a higher basic reproduction ratio (R_0), and this was confirmed by the different levels of success in controlling these parasites in New Zealand (Roberts & Gemmell, 1994).

Acquired immunity can have a considerable effect on the within year dynamics of parasites of farmed animals. New-born animals are, by definition, immunologically naive (although there exists some maternally-derived immunity against some species of parasite), and first experience challenge by free-living parasite stages when they begin to graze contaminated pasture. The development of acquired immunity proceeds with the ageing of the animal, and usually with changes in the weather and other environmental factors, so when analysing data there is inevitably some confounding of effects. However, parasite burdens in grazing ruminants typically show an initial sharp increase with time, followed by an exponential decay. Roberts & Grenfell (1991; 1992) showed that this was more consistent with parasite transmission being limited by acquired immunity than by seasonal factors (see Fig.2). Similar patterns have been generated by a model for the dynamics of nematode parasites of feral sheep, that incorporates immunity acquired by the host (Grenfell et al., 1995).

[1]Cestodes have a two-host life cycle. The adult tapeworm lives in the intestines of a carnivore (definitive host) and passes eggs with the host's faeces. Eggs ingested by a herbivore (intermediate host) develop into larvae (cysts) within muscle tissue or organs, and the life-cycle is completed when the carnivore ingests a larva. Important cestodes of farmed animals are *Echinococcus granulosus*, the cause of hydatid disease, *Taenia ovis* (sheep measles), *T.hydatigena* (false hydatids), *T.saginata* (beef tapeworm) and *T.solium* (pig tapeworm) (Roberts, 1994).

3. The Population Dynamics of Immunity

Roberts & Grenfell (1991) modelled the dynamics of nematode parasites (directly transmitted roundworms) of farmed ruminants using the system of differential equations:

$$\begin{aligned}\frac{dL}{dt} &= -(\rho+\beta)L + q\lambda(r)I \\ \frac{dI}{dt} &= \beta p(r)L - \mu(r)I \\ \frac{dr}{dt} &= \beta L - \sigma r\end{aligned} \tag{3.1}$$

where L is the density of larvae on pasture, I is the mean number of parasites per host and r is the mean herd level of acquired immunity. Other parameters are: ρ, the loss rate of larvae from pasture; β the rate at which larvae are eaten by host animals; q the probability that a parasite egg develops into an infective larva; and σ, the rate of fade of acquired immunity. Immunity regulates the parasite population via the non-increasing functions $\lambda(r)$, the average rate of egg production per adult parasite; and $p(r)$, the probability that an ingested larva develops into an adult parasite; and the non-decreasing function $\mu(r)$, the death rate of adult parasites. A full discussion of these equations may be found in Roberts & Heesterbeek (1995). They have a unique non-trivial steady state solution if

$$Q_0 = \frac{q\lambda(0)\beta p(0)}{(\rho+\beta)\mu(0)} > 1 \tag{3.2}$$

and the zero solution is globally stable if $Q_0 < 1$.

In equations (3.1) immunity is modelled as the cumulative experience of larval challenge, discounted over time. Woolhouse (1992) investigated the consequences of more complicated relationships for r, including the stimulation of immunity by adult parasites. One deficiency with all of these formulations is that r has no direct biological meaning. Another problem is that nematode parasites are so ubiquitous in farmed systems that the suggestion of fading immunity is often met with a puzzled expression by the field scientist.

Despite the difficulty encountered in measuring σ, the concept of fading immunity has a great deal of appeal as setting $\sigma = 0$ would imply that equations (3.1) had no steady state. However, Figure 2 shows that steady state analysis is inappropriate for these systems, as they are typically far from equilibrium. In fact, equations (3.1) are appropriate for describing the within-year dynamics, but the annual introduction of new-born animals onto infected pasture requires the periodic resetting of I and r to zero, while keeping L continuous.

A simple model that captures the essence of nematode systems within a year is

$$\begin{aligned}\frac{dx}{dt} &= \kappa x\left(Q(z)-1\right) \\ \frac{dz}{dt} &= x\end{aligned}\tag{3.3}$$

for $t \in (0,1)$, with $x(0) = X, z(0) = 0$. Here x is pasture parasite density, which is assumed to be closely followed by host parasite burden $\left(\frac{dI}{dt} \to 0 \text{ quickly in } (3.1)\right)$. It is also assumed that the rate of fade of acquired immunity is negligible ($\sigma \to 0$). We require $Q'(z) \leq 0$ and $Q(0) > 1$. An example function is

$$Q(z) = \begin{cases} Q_0 > 1 & \text{for } z < 1 \\ 1 & \text{for } z = 1 \\ 0 & \text{for } z > 1 \end{cases}$$

for which the within-year solution is

$$x(t) = \begin{cases} Xe^{\kappa(Q_0-1)t} & \text{for } t < t_1 \\ Xe^{-\kappa t}\left(1+\frac{\kappa(Q_0-1)}{X}\right)^{\frac{Q_0}{Q_0-1}} & \text{for } t > t_1 \end{cases}\tag{3.4}$$

where

$$t_1 = \frac{\log\left(1+\kappa\left(Q_0-1\right)/X\right)}{\kappa\left(Q_0-1\right)}$$

i.e. $z(t_1) = 1$. The solution (3.4) represents an exponential increase in parasite burden until acquired immunity takes effect, followed by an exponential decrease. The between-year dynamics of the system are obtained by defining $\phi(X) = x(1)$, i.e.

$$\phi(X) = \begin{cases} Xe^{\kappa(Q_0-1)} & \text{for } X < X^{\#} = \frac{\kappa(Q_0-1)}{e^{\kappa(Q_0-1)}-1} \\ Xe^{-\kappa}\left(1+\frac{\kappa(Q_0-1)}{X}\right)^{\frac{Q_0}{Q_0-1}} & \text{for } X > X^{\#} \end{cases}\tag{3.5}$$

and iterating on ϕ. A fixed point exists for $Q_0 > 1$ and is defined by

$$\phi(X^*) = X^* = \frac{\kappa\left(Q_0-1\right)}{e^{\kappa(Q_0-1)/Q_0}-1}$$

The fixed point is always stable if $Q_0 > 2$, but is unstable for $Q_0 < 2$ and

$$\kappa > \frac{Q_0}{Q_0-1}\log\frac{Q_0}{2-Q_0}$$

Repeated iterations of ϕ for five different values of κ are shown in Fig.3. The principle that is demonstrated by Fig.3 is that the long-term dynamics of solutions of equations (3.3) can be quite complicated, and depend critically on the values of system parameters. Equations (3.3) are a simple limiting case of equations (3.1) , which in turn are representative of more complicated models of nematode parasite dynamics (see Barnes et al. 1995, Grenfell et al. 1987, Leathwick et al. 1992, Smith & Grenfell, 1994). Parasite control measures that change the system parameters could therefore have quite dramatic effects on the qualitative dynamics of any of these models. The source of this complicated behaviour is the function representing the effects of acquired immunity on parasite growth and transmission, $Q(z)$, which we have given the very simple form of a step function. A major challenge is to develop improved representations of the within-host dynamics of acquired immunity, which can provide better estimates of functions such as $Q(z)$ and improve our understanding of the immunoepidemiology of parasites.

4. Parasite Control

We have seen that parasite control measures could dramatically change the long-term dynamics of parasite populations. Considering equations (3.3) on $(0,1)$, the effects of control may be measured by the change in $\|x\|$. The mean parasite burden is then the L_1 norm, and the maximum parasite burden the L_∞ norm.

To date, parasite control has been almost exclusively by chemotherapy and grazing management (Barger, 1996), but the development of strains resistant to drugs (see Dobson et al., 1996) has led to the call for more "natural" animal remedies. Vaccines are regarded as natural because they act to stimulate the host's immune system, and do not lead to a chemical residue problem (Lightowlers, 1994). It is a simple matter to model the epidemiological effects of a vaccine. For example, if all host animals are treated with a vaccine whose permanent effect is to multiply the probability that an ingested larva develops into an adult parasite by an amount less than $1/Q_0$, then the parasite population will be eradicated over time (see equation (3.2)). One could conclude that in order to develop methods of manipulating an animal's immune system one would seek a better understanding of it, and that the development of logical models would be a useful adjunct. An impediment to this is that the immune system is regarded as too complicated to model by many immunologists, despite substantial evidence to the contrary (see, for example Bell et al., 1978; DeLisi, 1976; Marchuk, 1983). For a brief and accessible review of some immunological principles see Novotny & Nicholls (1995).

It appears that T helper cells (notably Th-2) are activated in response to parasite infection, and this response is mediated by cytokines (Grencis, 1996; Miller, 1996). Morris (1995) states "it is impossible to provide precise definitions of what a cytokine is: the best that can be done is to build up an idea of what they are by describing their properties." and then "all generalisations about their properties are subject to exception.". In addition, Miller (1996) lists 15 potential sources of cytokines in the nematode-infected gastro-intestinal tract. However, when regarded in equivalent detail, epidemiological processes must seem just as complicated, and it has been necessary to make simplifications in order to facilitate progress and understanding. Some recent progress of this nature in modelling acquired immunity is reviewed in the next section.

While the reduction of parasite numbers has been considered to be the objective of control, farmers are concerned with animal production rather than parasite populations. Hence there is an interest in animals that are resilient to parasites (Bisset & Morris, 1996), that is, animals that grow despite being infected. Disadvantages with this approach include infected animals serving as reservoir hosts for those that are less resilient, and its inappropriateness for parasite species that directly affect the quality of animal products (for example intermediate stages of cestodes that inhabit muscle). However, there is a cost to the host animal in producing a response to a parasite, and if this cost is less than the damage caused by the parasite it is in the host's interest to tolerate the infection.

The fact that a substance is produced in response to parasite challenge or presence does not in itself indicate that this substance is involved in protection against further infection, or the suppression of existing infection. For example, the presence of antibodies to nematodes in sheep is taken as an indication of resistance to infection (Stear & Murray, 1994), and hence a desirable trait; whereas cattle with antibodies to tuberculosis are regarded as potential sources of infection and culled from the herd (Griffin et al., 1995).

5. Models for Immunity

One approach to modelling the dynamics of acquired immunity is to represent interactions between "antigen" and "antibody" using techniques from the population dynamics literature. The simplest way to represent this competition is with two differential equations, one for the number (intensity) of parasites in the host animal (I) and the other for the density of T cells (T). Following Austin & Anderson (1996) we have

$$\begin{aligned} \frac{dI}{dt} &= \Lambda(t) - (\mu + hT)\, I \\ \frac{dT}{dt} &= cIT - \sigma T \end{aligned} \tag{5.1}$$

where the host is acquiring new parasites at rate $\Lambda(t)$, T cells proliferate at rate cI in response to the presence of parasite, and kill parasites at rate hT. The mean life expectancies of parasite and T cell within the host are $1/\mu$ and $1/\sigma$ respectively.

The qualitative dynamics of equation (5.1) become easier to determine when they are rewritten in non-dimensional terms. In particular, we show that the immune system remains inactivated while Λ remains below a critical value, defined by $\Lambda_{\text{crit}} = \mu\sigma/c$. Rescaling $I \leftarrow cI/\sigma$, $T \leftarrow hT/\mu$, $t \leftarrow \mu t$, and $\Lambda \leftarrow \Lambda/\Lambda_{\text{crit}}$, we obtain

$$\begin{aligned} \frac{dI}{dt} &= \Lambda(t) - (1+T)\,I \\ \frac{dT}{dt} &= \alpha\,(I-1)\,T \end{aligned} \tag{5.2}$$

Note that this non-dimensionalisation differs from that employed by Austin & Anderson (1996).

When Λ is constant equations (5.2) have two possible steady states. If $\Lambda \leq 1$ then the immune system is not activated, and as $t \to \infty$, $(I,T) \to (\Lambda, 0)$. If $\Lambda > 1$ then the immune system is activated, and $(I,T) \to (1, \Lambda - 1)$. If this relationship is viewed in evolutionary terms, it is hardly surprising that the parasite's best strategy is to maintain Λ just below one, and hence achieve the highest intensity of infection possible while failing to activate the immune system. If the host's objective is to minimise its parasite burden, then its optimum strategy is to proliferate T cells as rapidly as possible, i.e. maximise c (Austin & Anderson, 1996). This simplistic view assumes that the cost to the host of producing a response is negligible.

The model (5.1) is a simplification of earlier work that took separate account of naive and activated T cells (Schweitzer & Anderson, 1991) or explicitly included the regulation of T cell proliferation by cytokine (Schweitzer & Anderson, 1992). Other relevant work here is that of McLean (1994) that modelled the response of naive, activated and memory T cells, and the cytokine IL-2, to a replicating virus. Austin & Anderson (1996) generalised equations (5.1) to include density-dependent T cell proliferation, multiple T cell clones reacting to different antigenic epitopes, and genetic diversity in the parasite population. These last two extensions are briefly (and individually) discussed below.

Consider a parasite whose antigen bears multiple epitopes[2] recognised by the host's immune system. Without loss of generality, let epitope-1 be the epitope for which c_i/σ_i is maximised, i.e. the immunodominant epitope. We will show that the critical level of parasite challenge for this system is $\Lambda_{\text{crit}} = \mu\sigma_1/c_1$. Rescaling $I \leftarrow c_1 I/\sigma_1$, $\Lambda \leftarrow \Lambda/\Lambda_{\text{crit}}$, $T \leftarrow h_i T_i/\mu$ for the population of T cells activated at

[2]Antigenic epitope is an operational definition of a surface area, on an antigenic molecule, either directly responsible for, or intimately involved in, specific antibody interaction (synonymous with an "antigenic determinant"). Definition from Novotny & Nicholls (1995).

epitope-i for n epitopes, and $t \leftarrow \mu t$ as before, we obtain

$$\begin{aligned} \frac{dI}{dt} &= \Lambda(t) - \left(1 + \sum_{i=1}^{n} T_i\right) I \\ \frac{dT_i}{dt} &= \alpha_i \left(\Omega_i I - 1\right) T_i \end{aligned} \tag{5.3}$$

where $\alpha_i = \sigma_i/\mu$ and $\Omega_i = c_i\sigma_1/\left(c_1\sigma_i\right) \leq 1$; with $\Omega_1 = 1$.

When Λ is constant, the system (5.3) has $n+1$ steady states: $I = \Lambda$, $T_i = 0 \forall i$; and n steady states with $I = 1/\Omega_j$, $T_j = \Lambda\Omega_j - 1$ and $T_i = 0$ for $i \neq j$. If all $\Omega_i \leq 1$ the first is stable, otherwise the steady state $\left\{I = 1, T_1 = \Lambda - 1, T_i = 0 \quad \text{for} \quad i > 1\right\}$, is stable. The other steady states are always unstable. Hence the immune system reacts to the parasite by cloning T cells associated with the immunodominant epitope. Equations (5.2) and (5.3) have at least the same static behaviour if the correct T cell clone is chosen in (5.2), lending some hope that simple models could give insights into the behaviour of more complex systems.

Finally, Austin & Anderson (1996) investigated a system where the parasite shows genetic diversity, and found that this could lead to a threshold higher than $\Lambda = \Lambda_{\text{crit}}$ for the activation of T cells. They concluded that the best strategy for a parasite is to "generate variability at immunogenic sites on antigens of key importance to survival and transmission". This diversity could have significant effects on the epidemiology of the parasite. For malaria it has been suggested that instead of a single parasite with a high basic reproduction ratio (R_0), there exist multiple strains each having more moderate values of R_0. The requirement for a vaccine would then be to have moderate efficacy against all strains, rather than high efficacy against a single parasite (Gupta & Day, 1994). Similar principles could also apply to the immunoepidemiology of macroparasites of farmed animals.

6. Conclusions

We have seen that the immunoepidemiology of macroparasites of farmed animals must be considered on three levels: within year, between year, and within host. The within year dynamics are determined largely by the interaction between the parasite and the host, via acquired immunity. Each new birth cohort of host animals encounters an environment contaminated by the previous generations, hence determining the between year dynamics. These long-term dynamics are important when evaluating control strategies. Parasite control to date has relied on the use of chemotherapy, which has led to the development of parasite strains resistant to anthelmintic treatment. This, combined with an international perception of a need for "clean green" products, has stimulated a search for new alternative control methods. One response to the need for more natural parasite control is to develop methods of manipulating the hosts' immune system. To do this will require an improved understanding of the mechanisms of immunity to macroparasites, and this will require the development of mathematical descriptions of the system.

We have seen how simplified models of host-parasite interactions can lead to results similar to those obtained from more complicated models, how even simple models can lead to complicated dynamics, and how parasite heterogeneity can modify the nature of host-parasite interactions. We now have to develop models that generate hypotheses that are testable by simple experiments. By doing so we will be able to:

- determine which aspects of the host-parasite interaction are the most important in determining the dynamics of the parasite population;
- determine which aspects of the host-parasite interaction are the most important in determining the dynamics of host immunity;
- convince experimental parasitologists of the benefit of applying mathematical models to epidemiology and immunology; and
- design better anti-parasite vaccines and control strategies.

7. References

1. Austin DJ, Anderson RM. Immunodominance, competition and evolution in immunological responses to helminth parasite antigens. Parasitology 1996;113:157-172.

2. Barger IA. Prospects for integration of novel parasite control options into grazing systems. International Journal for Parasitology 1996;26:1001-1007.

3. Barnes EH, Dobson RJ, Barger IA. Worm control and anthelmintic resistance: adventures with a model. Parasitology Today 1995;11:56-63.

4. Bell GI, Perelson AS, Pimbley GHJ, eds. Theoretical Immunology. New York: Marcel Dekker, 1978.

5. Bisset SA, Morris CA. Feasibility and implications of breeding sheep for resilience to nematode challenge. International Journal for Parasitology 1996;26:857-868.

6. DeLisi C. Antigen antibody interactions. Berlin: Springer, 1976. Lecture Notes in Biomathematics; vol. 8.

7. Dobson RJ, le Jambre L, Gill JH. Management of anthelmintic resistance: inheritance of resistance and selection with persistent drugs. International Journal for Parasitology 1996;26:993-1000.

8. Grencis RK. T cell and cytokine basis of host variability in response to intestinal nematode infections. Parasitology 1996;112:S31-S37.

9. Grenfell BT, Smith G, Anderson RM. A mathematical model of the population biology of *Ostertagia ostertagi* in calves and yearlings. Parasitology 1987;95:389-406.

10. Grenfell BT, Wilson K, Isham VS, Boyd HEG, Dietz K. Modelling patterns of parasite aggregation in natural populations: trichostrongylid nematode-ruminant interactions as a case study. Parasitology 1995;111:S135-S151.

11. Grenfell BT, Dobson AP, eds. Ecology of infectious diseases in natural populations. Cambridge: Cambridge University Press, 1995.

12. Griffin JFT, Mackintosh CG, Buchan GS. Animal models of protective immunity in tuberculosis to evaluate candidate vaccines. Trends in Microbiology 1995;3:418-424.

13. Gupta S, Day KP. A strain theory of malaria transmission. Parasitology Today 1994;10:476-481.

14. Isham VS, Medley GF, eds. Models for infectious human diseases: their structure and relation to data. Cambridge: Cambridge University Press, 1996.

15. Leathwick DM, Barlow ND, Vlassoff A. A model for nematodiasis in New Zealand lambs. International Journal for Parasitology 1992;22:789-799.

16. Lightowlers MW. Vaccination against animal parasites. Veterinary Parasitology 1994;54:177-204.

17. Lloyd S. Environmental influences on host immunity. In: Grenfell BT, Dobson AP, eds. Ecology of Infectious Diseases in Natural Populations. Cambridge: Cambridge University Press, 1995:327-361.

18. Marchuk GI. Mathematical models in immunology. New York: Optimization Software Inc., 1976.

19. May RM, Anderson RM. Parasite-host coevolution. Parasitology 1990;100:S89-S101.

20. McLean AR. Modelling T cell memory. Journal of Theoretical Biology 1994;170:63-74.

21. Miller HRP. Prospects for the immunological control of ruminant gastrointestinal nematodes: natural immunity, can it be harnessed? International Journal for Parasitology 1996;26:801-811.

22. Mitchell GF. Co-evolution of parasites and adaptive immune responses. In: Ash C, Gallagher RB, eds. Immunoparasitology Today. Cambridge: Elsevier Trends Journals, 1991:A2-A5.

23. Morris AG. Cytokines. In: Meyers RA, ed. Molecular Biology and Biotechnology: a comprehensive desk reference. New York: VCH Publishers, 1995:200-204.

24. Novotny J, Nicholls A. Immunology. In: Meyers RA, ed. Molecular Biology and Biotechnology: a comprehensive desk reference. New York: VCH Publishers, 1995:449-457.

25. Roberts MG, Lawson JR, Gemmell MA. Population dynamics in echinococcosis and cysticercosis: Mathematical model of the life cycles of *Taenia hydatigena* and *T.ovis*. Parasitology 1987;94:181-197.

26. Roberts MG, Grenfell BT. The population dynamics of nematode infections of ruminants: Periodic perturbations as a model for management. IMA Journal of Mathematics Applied in Medicine and Biology 1991;8:83-93.

27. Roberts MG, Grenfell BT. The population dynamics of nematode infections of ruminants: The effect of seasonality in the free-living stages. IMA Journal of Mathematics Applied in Medicine and Biology 1992;9:29-41.

28. Roberts MG. Modelling of parasitic populations: Cestodes. Veterinary Parasitology 1994;54:145-160.

29. Roberts MG, Gemmell MA. Echinococcosis. In: Scott ME, Smith G, eds. Parasitic and Infectious Diseases: Epidemiology and Ecology. San Diego: Academic Press, 1994:249-262.

30. Roberts MG, Heesterbeek JAP. The dynamics of nematode infections of farmed ruminants. Parasitology 1995;110:493-502.

31. Roberts MG. A pocket guide to host-parasite models. Parasitology Today 1995;11:172-177.

32. Schweitzer N, Anderson RM. Helminths, immunology and equations. In: Ash C, Gallagher RB, eds. Immunoparasitology Today. Cambridge: Elsevier Trends Journals, 1991:A76-A81.

33. Schweitzer AN, Anderson RM. Dynamic interaction between CD4+ T cells and parasitic helminths : mathematical models of heterogeneity in outcome. Parasitology 1992;105:513-522.

34. Smith G, Grenfell BT. Modelling of parasite populations: gastrointestinal nematode models. Veterinary Parasitology 1994;54:127-143.

35. Stear MJ, Murray M. Genetic resistance to parasitic disease: Particularly of resistance in ruminants to gastrointestinal nematodes. Veterinary Parasitology 1994;54:161-176.

36. Woolhouse MEJ. A theoretical framework for the immunoepidemiology of helminth infection. Parasite Immunology 1992;14:563-578.

37. Woolhouse MEJ. Immunoepidemiology of human schistosomes: taking the theory into the field. Parasitology Today 1994;10:196-202.

8. List of Figures

1. The mean numbers of larvae in *Echinococcus granulosus* ($\blacksquare, \square$) and *Taenia hydatigena* ($\blacklozenge, \lozenge$) in male and female sheep, respectively, at different ages in New Zealand in 1958. Figure adapted from Roberts et al. (1987).

2. The pasture larval density (L), mean adult parasite burden (I), and level of acquired immunity (r) throughout a one year cycle; as predicted by equations (3.1); with (a) $L(0) = L(1)$, $I(0) = r(0) = 0$; (b) limit cycle obtained with q replaced with $\overline{q}\,(1 + \sin 2\pi t)$; (c) with $L(0) = L(1)$, $I(0) = r(0) = 0$ and q replaced with $\overline{q}\,(1 + \sin 2\pi t)$. Figure adapted from Roberts & Grenfell (1991,1992).

3. The result of 200 iterations of the function $\phi(X)$ as defined by equation (3.5), with $Q_0 = 1.35$ and different values of κ. (a) $\kappa = 1$, the solution tends to a steady state; (b) $\kappa = 3$, the solution tends to a period-2 limit cycle; (c) $\kappa = 5$, the solution exhibits an irregular pattern; (d) $\kappa = 9$, the solution tends to a period-3 limit cycle; and (e) $\kappa = 12$, the solution exhibits an irregular pattern.