The dynamics of nematode infections of farmed ruminants

M. G. ROBERTS[1] *and* J. A. P. HEESTERBEEK[2]

[1] *AgResearch, Wallaceville Animal Research Centre, P.O. Box 40063, Upper Hutt, New Zealand*
[2] *Agricultural Mathematics Group (GLW-DLO), P.O. Box 100, 6700 AC Wageningen, The Netherlands*

(*Received 16 June 1994; revised 29 September 1994; accepted 29 September 1994*)

SUMMARY

In this paper the dynamics and control of nematode parasites of farmed ruminants are discussed via a qualitative analysis of a differential equation model. To achieve this a quantity, 'the basic reproduction quotient' (Q_0), whose definition coincides with previous definitions of R_0 for macroparasites, but extends to models with periodic time-varying transition rates between parasite stages or management interventions, is introduced. This quantity has the usual threshold property: if Q_0 is less than one the parasite population cannot maintain itself in the host population, and in the long term becomes extinct; but if Q_0 is greater than one the parasite can invade the host population. An alternative quantity, $\mathscr{R}(E)$, that is often easier to calculate is also introduced, and shown to have the same threshold property. The use of these two quantities in analysing models for the dynamics of nematodes in complex situations is then demonstrated, with reference to the dynamics of mixed parasite species in one host; the effects of breeding host animals for resistance to parasitism; and the development of parasite strains that are resistant to chemotherapy. Five examples are discussed using parameters for the dynamics of nematode infections in sheep, and some statements on control policies are derived.

Key words: host–parasite models, macroparasites, nematodes, ruminants.

INTRODUCTION

The concept of the basic reproduction ratio (R_0, also known as the basic reproductive rate) is central in understanding the dynamics of infectious diseases caused by directly reproducing microparasites (Anderson, 1982; Anderson & May, 1982, 1991; Diekmann, Heesterbeek & Metz, 1990). R_0 was defined by Diekmann *et al.* (1990) as the expected number of secondary cases produced in a completely susceptible population, by a typical infected individual during its entire period of infectiousness. The other references cited above contain essentially the same definition (see also Dobson & Grenfell, 1994; Mollison, 1994; Scott & Smith, 1994). A disease can invade and maintain itself in the host population only if $R_0 > 1$. If $R_0 < 1$ the disease cannot maintain itself and in the long run becomes extinct. This is the threshold theorem of Kermack and McKendrick (Kermack & McKendrick, 1927; Diekmann *et al.* 1994), and its use in determining long-term disease dynamics is readily apparent.

The concept of R_0 for macroparasitic infections, leading to an analogous threshold theorem, has also been introduced (for example Anderson & May, 1991; Roberts, Lawson & Gemmell, 1987; Roberts & Grenfell, 1991; Roberts, Smith & Grenfell, 1994). Individual hosts may be classified as infected with a microparasite or not, due to the rapid proliferation of the infectious agent once established, but the number of macroparasites that constitutes an infection is important, and the threshold theorem must be formulated in terms of the dynamics of the parasite population. Anderson & May (1991, page 436) for example, define R_0 for a macroparasite as 'the average number of offspring (or female offspring in the case of a dioecious species) produced throughout the reproductive life-span of a mature parasite that themselves survive to reproductive maturity in the absence of density-dependent constraints on population growth'. It is obvious from this statement that the quantity so defined has the required threshold property for macroparasitic infections.

The definition of R_0 for infectious diseases contains the word *typical*, and the difficulty of specifying the typical individual led Diekmann *et al.* (1990) to examine the concept in a rigorous mathematical setting. These authors were able to define R_0 as the dominant eigenvalue of an operator (a matrix in many applications) that relates the number of infected hosts in the current generation to the number of hosts in the 'next generation'. The dominant eigenvalue provides a measure of the increase in the number of infected hosts from one generation to the next, after many generations have passed. This mode of definition provides a framework within which R_0 may be defined and calculated in many complicated situations, including those where contact patterns are heterogeneous or host behaviour is age-structured (for details see also Heesterbeek, 1992).

The dynamics of nematode infections of farmed ruminants have been studied by Roberts & Grenfell (1991, 1992) using a simple three-equation model.

Important questions relate to the influence of heterogeneity on the dynamics of these infections, for example: the dynamics of mixed parasite species in one host; the effects of breeding host animals for resistance to parasitism; and the development of parasite strains that are resistant to chemotherapy. To investigate these it is necessary to have a formal definition of a threshold quantity for macroparasites that has analogous properties to those of R_0 for microparasitic infections. A recent paper by Heesterbeek & Roberts (1994) has developed such a quantity, which has been tentatively called Q_0, and which one could call the basic reproduction quotient. The change in terminology is to avoid a fruitless debate on whether this is in fact 'R_0 for macroparasites' (Roberts, 1994*a*). What matters is that Q_0 has the useful threshold property: $Q_0 > 1$ implies that the parasite can invade the host population, and $Q_0 < 1$ implies that the parasite population cannot persist. In fact Heesterbeek & Roberts (1994) presented three related quantities with this property, resulting from mathematical, biological or practical considerations respectively.

In the present paper the logic leading to the definition of Q_0 is reviewed in biological terms. The model of Roberts & Grenfell (1991) is developed to include heterogeneity in the host and parasite populations, and the assembled methodology is used to make statements about the control of parasite populations in ruminants, and the development of parasite strains that are resistant to chemotherapy.

THE MODEL

A simple model comprising three differential equations was used to describe the dynamics of nematode parasites of ruminants by Roberts & Grenfell (1991). Two state variables were used: L to represent the density of infective larvae on the pasture, and A to represent the mean number of adult parasites per host.

The rate of change of L was described by an equation similar to

$$\frac{dL}{dt} = -(\rho+\beta H)L + q\lambda(r)HA, \tag{1}$$

where ρ is the rate at which the density of pasture larvae would decrease in the absence of ruminants, β is the rate at which larvae are eaten by ruminants, $\lambda(r)$ is the mean rate at which a single adult parasite produces eggs, q is the probability that an egg develops to become an infective larva and H is the number of host animals/unit area.

The difference between equation (1) and that analysed by Roberts & Grenfell (1991) is that in the earlier paper L was used for the number of larvae on an area that supports one host animal. In the present paper L has been rescaled by a factor H, and β by a factor $1/H$, relative to their values in the earlier paper.

The rate of change of A, the mean number of adult parasites/host, was described by the differential equation

$$\frac{dA}{dt} = \beta p(r)L - \mu(r)A, \tag{2}$$

where β is as defined above, $p(r)$ is the probability that a larva, once eaten, develops into an adult parasite, and $\mu(r)$ is the rate of mortality of adult parasites.

The factors λ, p, and μ, in equations (1) and (2) have been written as functions of r, which is used as a measure of the average level of acquired immunity in the host population. This is defined by the equation

$$\frac{dr}{dt} = \beta L - \sigma r \tag{3}$$

and is therefore the average discounted (over time) cumulative larval challenge experienced by the host population. The parameter σ is the rate at which r would decrease in the absence of new larval challenge. The rescaling of L and β relative to their usage by Roberts & Grenfell (1991) does not affect equations (2) and (3).

In the model of Roberts & Grenfell (1991), λ and p may decrease as r increases, and μ may increase. Our desired threshold quantity, however, is defined in the absence of acquired immunity, that is when $r = 0$. There is an inherent contradiction in this, as by equation (3) if a host has experienced infection then r cannot be zero. The threshold is, nevertheless, a limiting quantity that determines the response of a previously parasite-free host–parasite system to the first introduction of the parasite. The level of immunity that has been acquired by the host is, at this time, so small that its effect on the dynamics is negligible.

The rate of production of infective larvae by an adult parasite in the absence of acquired immunity is $q\lambda(0)$, and the average life-span of the adult is $1/\mu(0)$ years. Hence the average number of larvae due to one adult parasite over its entire life would be $q\lambda(0)/\mu(0)$. Using a similar argument, the average number of adult parasites *per host* produced by one infective larva in the absence of acquired immunity would be $\beta p(0)/(\rho+\beta H)$. Putting these formulae together, the number of adult parasites that would be produced in the next generation by A adult parasites in the present generation is $Q_0 A$, where

$$Q_0 = \frac{q\lambda(0)}{\mu(0)}\frac{\beta p(0)}{(\rho+\beta H)}H.$$

A quantity equal to Q_0 (recall our rescaling of β) was described by Roberts & Grenfell (1991) as the basic reproductive rate of infection (= the basic repro-

duction ratio of the parasite population). Those authors showed that if $Q_0 > 1$ then equations (1)–(3) have a unique non-zero steady-state solution for L, A and r, whereas if $Q_0 < 1$ all three variables tend to zero with time, corresponding to the parasite population becoming extinct.

The argument leading to the definition of Q_0 could have been formulated differently, as follows. One adult parasite would, over the course of a year, give rise to $q\lambda(0)$ larvae, each with a life-expectancy of $1/(\rho+\beta H)$ years; in other words $q\lambda(0)/(\rho+\beta H)$ larva-years. Similarly, each larva-year would, in the absence of acquired immunity give rise to $\beta Hp(0)/\mu(0)$ adult parasite-years. Therefore, over the course of the life-cycle each adult parasite-year results in Q_0 adult parasite-years in the next generation, where

$$Q_0 = \frac{q\lambda(0)}{(\rho+\beta H)}\frac{\beta H p(0)}{\mu(0)}. \tag{4}$$

Both definitions of Q_0 are, of course, the same formula. This arises because equations (1)–(3) form an autonomous model, that is, one for which rates of transition between the stages in the life-cycle are independent of time. For nematode parasites transition rates between free-living stages often depend on the weather, and may be regarded as seasonal. Also, management interventions in farmed populations may cause discontinuous changes in parasite burdens. When time (t) appears explicitly in the expressions for development rates, or parasite life-expectancy changes with time, then it is not so simple to define Q_0 in terms of the system parameters. The latter definition (in terms of parasite-years) leads directly, in time-dependent cases, to a quantity with the correct threshold property. It may also be argued that the former is correct, but for non-autonomous systems a method of 'averaging' the number of parasites of the next stage produced over the year is required in order to provide a *typical* value. Correct averaging takes account of parasite life-expectancies, and once again the two definitions agree. This has been explained in more detail by Heesterbeek & Roberts (1994).

The definition of Q_0 in terms of the changes in size of discrete generations recalls similar uses in ecology where, for example R_0 has been used as the net reproductive rate of a population (Southwood, 1978). This usage is consistent with ours only in the absence of density-dependent effects on population demography.

The expression for Q_0 defined by equation (4) is not unique in having the required threshold property, in fact Q_0 raised to any positive power also has the property. In the theory developed by Heesterbeek & Roberts (1994), one of the ways to define and calculate Q_0 is to introduce a matrix K, derived directly from the model's equations in a simple way, and then to define Q_0 in terms of $\mathcal{R}(K)$, the dominant eigenvalue of K. More precisely, $\mathcal{R}(K)$ is the spectral radius of K, but for models of infectious diseases this is usually equal to the dominant eigenvalue (Diekmann *et al.* 1990). For the model defined by equations (1)–(3)

$$K = \begin{pmatrix} 0 & \dfrac{q\lambda(0)H}{\rho+\beta H} \\ \dfrac{\beta p(0)}{\mu(0)} & 0 \end{pmatrix},$$

and the definition $Q_0 = \mathcal{R}(K)^2$ leads directly back to equation (4). Any integer power of $\mathcal{R}(K)$ has the same threshold property. To justify our choice of $Q_0 = \mathcal{R}(K)^2$ we point out that equations (1)–(3) are a simplification of a more complex system. For example, Grenfell, Smith & Anderson (1987) presented a model for the population dynamics of *Ostertagia ostertagi* that consisted of 10 equations, 1 for egg production, 3 for the different larval stages on the herbage and 6 for the parasitic stages within the host. Equations (1 and 2) may be recovered by combining the first 4 and the last 6 respectively, and making some mathematical approximations based on time-scale arguments. If we had defined $Q_0 = \mathcal{R}(K)$ then different values of Q_0 would be obtained for the 10-equation model and our 2-equation model. It would be unfortunate if a biologically defined quantity changed in value according to the degree of simplification of a mathematical model. Our definition, which is $Q_0 = \mathcal{R}(K)^k$ where k is the number of stages in the model life-cycle, overcomes this difficulty (see Heesterbeek & Roberts, 1994).

In many situations the transition rates between different parts of the life-cycle are not independent of time. Roberts & Grenfell (1991) investigated a scenario where farm management strategies were modelled by a periodic resetting of one or more state variables, and Roberts & Grenfell (1992) analysed a model where the dynamics of the larval phase were seasonal and therefore time-dependent. The second situation requires equations (1) and (2) to be replaced with

$$\begin{aligned} \frac{dL}{dt} &= -(\rho(t)+\beta(t)H)L + q(t)\lambda(r)HA \\ \frac{dA}{dt} &= \beta(t)p(r)L - \mu(r)A, \end{aligned} \tag{5}$$

where ρ, β and q are now functions of time t. A simple expression for Q_0 such as equation (4) can no longer be obtained. The number of parasites produced in the next stage as a result of a single parasite in the present stage is now a time-dependent quantity, and some mechanism is required to relate this to a *typical* parasite. With the realistic assumption that these time dependencies are periodic, Heesterbeek & Roberts (1994) developed a scheme

Table 1. Parameter values used in the examples

Parameter	Value	Function	Definition
$p(0)$	0·65	$p(r) = p(0)\exp(-10^{-5}r)$	Probability that an ingested larva develops into an adult parasite
$q(=q_0)$	0·5	$q(t) = q_0(1+\sin 2\pi t)$	Probability that an egg develops into an infective larva
H	0·0015 m^{-2}		Host population density
β	23733 yr^{-1}	Constant	Rate at which larvae are eaten by host animals
$\lambda(0)$	1678 yr^{-1}	Constant	Mean rate at which an adult parasite produces eggs
$\mu(0)$	6·4 yr^{-1}	Constant	Mortality rate of adult parasites
ρ	356 yr^{-1}	Constant	Rate at which larvae are lost from the pasture, for reasons other than being eaten by host animals
σ	0·01 yr^{-1}	Constant	Rate at which acquired immunity would decline in the absence of larval challenge

whereby the matrix equivalent to K (containing the instantaneous parasite-years in the next stage resulting from a single parasite-year in the present stage), could be averaged over a whole period, resulting in a matrix, $\mathscr{K}$, with $Q_0 = \mathscr{R}(\mathscr{K})^k$. A similar argument formalizes the definition of Q_0 when state variables are periodically reset to model management practices. Although the construction of $\mathscr{K}$, and hence the definition of Q_0, make sound biological sense, they can no longer be calculated explicitly in terms of the system parameters, and must be found by numerical solution of the model.

Heesterbeek & Roberts (1994) presented an alternative threshold quantity for the time-dependent problem that makes good pragmatic sense and is easier to calculate than Q_0. The procedure is as follows. First of all, solve equations (5) numerically over a single period (1 year) with initial conditions $L(0) = 1$, $A(0) = 0$. The resulting values of the variables at the end of the period are L_1 and A_1 say. Now repeat the procedure, with initial conditions $L(0) = 0$, $A(0) = 1$, obtaining L_2 and A_2 say. We have in effect defined a mapping $I \to E$, from the initial parasite population to the end-point population, where

$$I = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \quad \text{and} \quad E = \begin{pmatrix} L_1 & L_2 \\ A_1 & A_2 \end{pmatrix}.$$

The first and second columns of E are the numbers of parasites in each stage after one period, resulting from a single initial larva and a single initial adult respectively. In Heesterbeek & Roberts (1994) it is proved that $\mathscr{R}(E) < 1$ if and only if $Q_0 < 1$, and hence $\mathscr{R}(E)$ may be used as a threshold quantity for non-autonomous (periodic) macroparasite models. It must be stressed that $\mathscr{R}(E)$ does not equal Q_0.

The numerical examples used throughout this paper are based on the parameters used by Roberts (1994*b*) to model the dynamics of *Trichostrongylus colubriformis* in lambs in New Zealand. The parameter values are given in Table 1. For these parameter values $Q_0 = 7{\cdot}75$ for the autonomous model (parameters as in Table 1, with $q = q_0$) as calculated from equation (4). A control measure based on chemotherapy may be modelled by replacing $\mu(0)$ with $\mu(0)+c$ (c is the increase in the rate of mortality due to control), and to use this mechanism to reduce Q_0 to 1 would require $c = 43{\cdot}2$. For the autonomous model $\mathscr{R}(E) = 6{\cdot}52 \times 10^{16}$, and replacing $\mu(0)$ with $\mu(0)+c$ (as above) reduces this to 1. Clearly, the entries in the matrix E can get very large, but $\mathscr{R}(E)$ still has the correct threshold property. Note that c is approximately equal to the number of successful treatments/year, so for these parameter values it is not practical to achieve eradication of the parasite population by chemotherapy.

For the seasonal model (parameters as in Table 1, with $q = q_0(1+\sin 2\pi t)$) similar values of $\mathscr{R}(E)$ and c were obtained (see Table 2). Roberts & Grenfell (1991) modelled the annual replacement of stock on infected pasture by resetting A (in equations 1 and 2, or 5) and r (in equation 3) to zero every year. When this was incorporated in the model small reductions in $\mathscr{R}(E)$ and c were again observed (see Table 2). Although resetting (i.e. stock replacement) dramatically changes the temporal pattern of parasite abundance, it does little to affect the control effort required to eradicate the parasite population. This is because the direct effect of resetting on Q_0 is through the removal of 1-year-old host animals, and hence their parasites. At this time the animals have lost the majority of their parasite burdens, and have acquired an immunity to reinfection.

The values of Q_0 for the seasonal models, and those with resetting, that are presented in Table 2 have been estimated from $\mathscr{R}(E)$ and c. This is because direct computation of Q_0 involves the inversion of a matrix, which for these parameter values is nearly singular, causing the numerical procedure to become unstable. Q_0 has therefore been approximated by $(\mu+c)/\mu$, where c is the value that reduces $\mathscr{R}(E)$, and consequently Q_0, to 1. It is therefore Q_0 for an equivalent (in some sense) autonomous model.

Table 2. Values of the threshold parameters (Q_0 and $\mathscr{R}(E)$) and the level of control effort (c) required to reduce these to 1, for the autonomous (equations 1–3) and seasonal (equations 3 and 5) models, with and without annual stock replacement

(Parameter values are as in Table 1. * Indicates that Q_0 could not be evaluated numerically, but has been estimated from $\mathscr{R}(E)$ and c. See text for further explanation.)

Model	Q_0	$\mathscr{R}(E)$	c
Autonomous	7·75	$6{\cdot}52\times10^{16}$	43·2
Seasonal	7·35*	$1{\cdot}07\times10^{16}$	40·6
Autonomous with replacement	6·36*	$6{\cdot}19\times10^{15}$	40·7
Seasonal with replacement	5·97*	$1{\cdot}00\times10^{15}$	38·2

MULTIPLE HOST TYPES

Consider first the situation where there are two different types of host. We are thinking here of different age-classes sharing the same grazing, different breeds or the introduction (to a flock or herd) of animals that have been selected for nematode resistance. Equations (1–3) are replaced with

$$\begin{aligned}
\frac{dL}{dt} &= -(\rho+\beta_1 H_1+\beta_2 H_2)\\
&\quad\times L+q(\lambda_1(r_1)H_1A_1+\lambda_2(r_2)H_2A_2)\\
\frac{dA_1}{dt} &= \beta_1 p_1(r_1)L-\mu_1(r_1)A_1\\
\frac{dA_2}{dt} &= \beta_2 p_2(r_2)L-\mu_2(r_2)A_2\\
\frac{dr_1}{dt} &= \beta_1 L-\sigma_1 r_1\\
\frac{dr_2}{dt} &= \beta_2 L-\sigma_2 r_2,
\end{aligned}\qquad (6)$$

where the subscripts 1 and 2 refer to host types 1 and 2 respectively. The matrix K is now defined by

$$K=\begin{pmatrix} 0 & \dfrac{q\lambda_1(0)H_1}{\rho+\beta_1H_1+\beta_2H_2} & \dfrac{q\lambda_2(0)H_2}{\rho+\beta_1H_1+\beta_2H_2}\\ \dfrac{\beta_1p_1(0)}{\mu_1(0)} & 0 & 0\\ \dfrac{\beta_2p_2(0)}{\mu_2(0)} & 0 & 0\end{pmatrix}$$

The entries in K are determined as follows. The rate of production of stage-1 parasites (larvae) by stage-2 parasites (adults in host type 1) is $q\lambda_1(0)H_1$ per year, and their life-expectancy is $1/(\rho+\beta_1H_1+\beta_2H_2)$ years. Hence K_{12} is the number of stage-1 years due to a stage-2 year. The other entries are calculated in a similar manner.

By definition $Q_0=\mathscr{R}(K)^2=a_1Q_0^{(1)}+a_2Q_0^{(2)}$, where $Q_0^{(1)}$ and $Q_0^{(2)}$ are the values of Q_0 that would hold for host types 1 and 2 respectively if the other host type were absent (equation 4 with appropriate indexing). The factors $a_1=(\rho+\beta_1H_1)/(\rho+\beta_1H_1+\beta_2H_2)<1$ (similarly a_2) account for the reduced amount of larvae ingested by host type 1 due to competition by host type 2.

Example 1 : lambs and ewes

As an example of two different host types grazing together, consider a mixed flock of lambs and ewes (types 1 and 2 respectively). Although some component of the resistance of ewes to infection will be due to their past experience, we will model their increased resistance by taking $p_2(0)=0{\cdot}2$ (arbitrarily), with all other parameters the same for both types (see Table 1). Assuming the stock density for each host type to be 7·5 animals per hectare (to preserve 15 ha^{-1} overall) we obtain $Q_0^{(1)}=4{\cdot}06$ and $Q_0^{(2)}=1{\cdot}25$. Hence $Q_0=5{\cdot}07$, a reduction from 7·75 due to the replacement of half the flock with more resistant animals.

If chemotherapy were applied to host types 1 and 2 at rate c_1 and c_2 respectively, resulting in a basic reproduction quotient Q_c for the parasite population under control, then

$$Q_c=\frac{a_1\mu_1(0)}{\mu_1(0)+c_1}Q_0^{(1)}+\frac{a_2\mu_2(0)}{\mu_2(0)+c_2}Q_0^{(2)}.$$

For example, if $c_1=c_2=4$ (4 effective treatments/year for all host animals) then $Q_c=3{\cdot}12$. For a given total number of treatments (c_1+c_2 fixed) the minimum value of Q_c is obtained when

$$\frac{a_1\mu_1(0)}{(\mu_1(0)+c_1)^2}Q_0^{(1)}=\frac{a_2\mu_2(0)}{(\mu_2(0)+c_2)^2}Q_0^{(2)}.$$

With our parameters, and the restriction $c_1+c_2=8$, this is achieved when $c_1=7$ and $c_2=1$, leading to $Q_c=2{\cdot}88$. The optimum strategy is therefore to apply the majority of treatments to the hosts that would, on their own, lead to the highest value of Q_0. The optimum values of c_1 and c_2 that result in $Q_c=1$, and hence lead to eradication of the parasite population are given in Table 3, together with a summary of threshold parameters for seasonal models and models with replacement (and two hosts).

When the dynamics of the parasite populations under chemotherapy are examined separately for each host type, it is found that $a_1\mu_1Q_0^{(1)}/(\mu_1+c_1)=2{\cdot}38$ and $a_2\mu_2Q_0^{(2)}/(\mu_2+c_2)=0{\cdot}73$ when $c_1=c_2=4$. Hence the parasite population could not maintain itself in the ewe population at this host density and level of treatment, and the lamb population acts as a reservoir. However, when $c_1=7$ and $c_2=1$ the corresponding figures are 1·85 and 1·03 respectively, and the parasite population can just maintain itself within the ewe population.

Table 3. Values of the threshold parameters (Q_0 and $\mathcal{R}(E)$) and the level of control effort (c) required to reduce these to 1, for Example 1

		Q_0	$\mathcal{R}(E)$	c
Autonomous	Lambs	4·06		32·14
	Ewes	1·25		14·98
	Overall	5·07	$3{\cdot}03 \times 10^{10}$	
Seasonal			$1{\cdot}21 \times 10^{10}$	
Autonomous with replacement			$2{\cdot}07 \times 10^{9}$	
Seasonal with replacement			$8{\cdot}15 \times 10^{8}$	

Example 2 : breeding for resistance

Suppose parasite control were to be achieved by replacing a proportion of the host population with resistant animals. If, initially, we have Q_0 as defined by equation (4), and a proportion s of the hosts were replaced with animals having a different value of $p(0)$, (hence $p_1(0)$ and $p_2(0)$ for host types 1 and 2 respectively) and all other parameters identical, then

$$Q_c = \left(1 - s + s\frac{p_2(0)}{p_1(0)}\right) Q_0.$$

Using our example parameters (Table 1) for host type 1, and assuming arbitrarily $p_2(0)/p_1(0) = 0{\cdot}1$, then the smallest value of s that renders the parasite population no longer viable ($Q_c < 1$) is 0·97. This demonstrates that a minority of susceptible host animals can act as a reservoir of parasites for a majority of resistant animals. Even if $p_2(0)$ were equal to zero, we would have $s = 1 - 1/Q_0$, and the proportion of the flock that has to be replaced tends to 1 for large Q_0.

When stock replacement is included in the model, we find numerically that $Q_c = 1$ when $s = 0{\cdot}88$, which corresponds to 88 % of the host animals being required to be resistant to achieve eradication of the parasite population, or ensure that the parasite population is no longer viable. The critical s values for the corresponding seasonal model are equal to those of the autonomous model, to the nearest percentage point.

MULTIPLE PARASITE TYPES

In many ruminant grazing systems animals are infected not with a single nematode species, but with a community of them. This led Leathwick, Barlow & Vlassoff (1992) to develop a model for nematodiasis in New Zealand lambs, rather than a model for a single parasite species. In the present paper we investigate the establishment threshold for a second parasite type (type is used to indicate either species or strain within a species) in the presence of a first, where there is some reciprocity in the immunity acquired by the host against the two types.

We assign subscripts 1 and 2 to the variables L, A, and r, parameters q, ρ, β, and σ, and functions p, λ and μ in the obvious way, but p, λ and μ may now depend on r_1 and r_2. The equations for the dynamics of the two parasite types are

$$\begin{aligned}
\frac{dL_1}{dt} &= -(\rho_1 + \beta_1 H) L_1 + q_1 \lambda_1(r_1, r_2) H A_1 \\
\frac{dA_1}{dt} &= \beta_1 p_1(r_1, r_2) L_1 - \mu_1(r_1, r_2) A_1 \qquad (7) \\
\frac{dr_1}{dt} &= \beta_1 L_1 - \sigma_1 r_1
\end{aligned}$$

with similar equations for type 2. Assume now that type 1 is established, and in a (dynamic) equilibrium in the host population, and consider the threshold problem for type 2. The small amplitude equations for parasite type 2 are

$$\begin{aligned}
\frac{dL_2}{dt} &= -(\rho_2 + \beta_2 H) L_2 + q_1 \lambda_2(r_1, 0) H A_2 \qquad (8) \\
\frac{dA_2}{dt} &= \beta_2 p_2(r_1, 0) L_2 - \mu_2(r_1, 0) A_2
\end{aligned}$$

where r_1 is calculated from equations (7) with $r_2 = 0$, or alternatively equations (1)–(3) with appropriate parameters for type 1; i.e. the solution of the equations for the dynamics of parasite type 1 with type 2 absent. If parasite type 1 is in a steady equilibrium, then we can write down Q_0 for type 2 directly,

$$Q_0^{(2)} = \frac{q_2 \lambda_2(r_1, 0) \beta_2 H p_2(r_1, 0)}{(\rho_2 + \beta_2 H) \mu_2(r_1, 0)},$$

and parasite type 2 can invade if $Q_0^{(2)} > 1$. Observe that replacing the parameter and function subscripts 2 with subscript 1 in the definition of $Q_0^{(2)}$ gives, not the formula for $Q_0^{(1)}$ (Q_0 for parasite type 1), which requires $r_1 = 0$, but an effective reproduction quotient for parasite type 1 ($Q^{(1)}$ say). As we have assumed this type to be in equilibrium, $Q^{(1)} = 1$, which demonstrates that for parasite type 2 to invade it must have some fitness advantage over the established parasite population (of type 1), at the prevailing levels of acquired immunity (r_1) in the host population. This assumes, of course, that parasite type 2 occupies exactly the same niche in the host population as parasite type 1.

If we have annual stock replacement leading to periodic resetting, or seasonal development rates, equations (7) and (8) define a non-autonomous threshold problem that must be solved numerically. This may be done by solving equations (7) with $r_2 = 0$ for parasite type 1, and then using r_1 so obtained in equations (8) to calculate $\mathcal{R}(E)$, the dominant eigenvalue of the matrix E.

Example 3 : two parasite types with reciprocal immunity

Suppose that a chemotherapy programme were to

reduce the abundance of parasite type 1, and hence reduce r_1 to r_c. There is a concurrent change in the value of Q_0 for parasite type 2 to $Q_c^{(2)}$, where

$$Q_c^{(2)} = \left(\frac{\lambda_2(r_c,0)}{\lambda_2(r_1,0)}\right)\left(\frac{p_2(r_c,0)}{p_2(r_1,0)}\right)\left(\frac{\mu_2(r_1,0)}{\mu_2(r_c,0)+c_2}\right)Q_0^{(2)}.$$

The first two factors in the definition of $Q_c^{(2)}$ are greater than or equal to one, and $\mu_2(r_1,0) \geqslant \mu_2(r_c,0)$. If c_2 were small the effect of chemotherapy on parasite type 2 would be to increase Q_0, and the ability of that type to invade the host population. Note that if all parameter values for parasite types 1 and 2 are identical, $Q_c^{(2)} = 1$, and parasite type 2 has no advantage over type 1. This example will be discussed in the context of the development of parasite strains that are resistant to chemotherapy in the next section.

THE INCORPORATION OF GENETICS IN THE MODEL

Consider a nematode population with three genotypes (two homozygous and one heterozygous), arising from a simple genetical system. We label the two alleles R and S, and subdivide the parasite population into RR, RS and SS strains. The equations for the dynamics of larvae of the RR strain on pasture and adult parasites of the RR strain within the host are

$$\frac{dL_{RR}}{dt} = -(\rho+\beta H)L_{RR} + q\lambda(r)H\Lambda_{RR}(A_{RR} + A_{RS} + A_{SS})$$

$$\frac{dA_{RR}}{dt} = \beta p(r)L_{RR} - \mu(r)A_{RR}, \tag{9}$$

with similar equations for the RS and SS strains. The equation for acquired immunity is

$$\frac{dr}{dt} = \beta(L_{RR}+L_{RS}+L_{SS}) - \sigma r.$$

The functions Λ_{RR}, Λ_{RS} and Λ_{SS} are the proportions of eggs of each particular strain that are produced, as functions of the numbers of adult parasites of each strain present in the population. Hence

$$\Lambda_{RR} = \frac{A_{RR}^2 + A_{RR}A_{RS} + A_{RS}^2/4}{(A_{RR}+A_{RS}+A_{SS})^2}$$

$$\Lambda_{SS} = \frac{A_{SS}^2 + A_{SS}A_{RS} + A_{RS}^2/4}{(A_{RR}+A_{RS}+A_{SS})^2}$$

and

$$\Lambda_{RS} = \frac{2A_{RR}A_{SS} + A_{RR}A_{RS} + A_{RS}A_{SS} + A_{RS}^2/2}{(A_{RR}+A_{RS}+A_{SS})^2}.$$

In deriving these relationships it has been assumed that parasite numbers are always sufficient for each female parasite to be able to find a mate. A similar development for the dynamics of nematode populations of humans may be found in Anderson, May & Gupta (1989), together with a discussion of the necessary corrections at low parasite density when this assumption is not satisfied.

Assume now that the parasite population is in a (dynamic) equilibrium with the 'R-gene' absent. Then (L_{SS}, A_{SS}, r) obey equations (1)–(3), and we denote this solution by (L, A, r). We construct the threshold property for the invasion of the 'R-gene' by considering small fluctuations in parasite population density about (L, A, r). The equations for L_{RR} and A_{RR} are therefore

$$\frac{dL_{RR}}{dt} = -(\rho+\beta H)L_{RR}$$

$$\frac{dA_{RR}}{dt} = \beta p(r)L_{RR} - \mu(r)A_{RR}.$$

In deriving these equations it has been recognized that A_{RR} and A_{RS} are both small quantities, and hence Λ_{RR} is the sum of products of small quantities, and may be neglected. The solutions for L_{RR} and A_{RR} tend to zero over time, therefore the ability of the R-gene to invade the parasite population is determined by the dynamics of the heterozygous parasite population. The equations for L_{RS} and A_{RS} are (neglecting A_{RR}, which tends to zero)

$$\frac{dL_{RS}}{dt} = -(\rho+\beta H)L_{RS} + q\lambda(r)HA_{RS}$$

$$\frac{dA_{RS}}{dt} = \beta p(r)L_{RS} - \mu(r)A_{RS}, \tag{10}$$

which are equivalent to equations (8). The problem of whether the RS strain can establish when the SS strain is present may therefore be addressed in an identical manner to the analysis already presented for two parasite types. The relevant threshold quantity is

$$Q_0^{(R)} = \frac{q\lambda(r)\beta H p(r)}{(\rho+\beta H)\mu(r)}.$$

Once again we see that if the RS strain has no advantage over the SS strain, then by definition $Q_0^{(R)} = 1$.

Example 4 : the development of parasite strains resistant to chemotherapy

Consider a parasite population in which the 'S-gene' predominates. If chemotherapy has been introduced, and the parasite population has attained a new equilibrium, then

$$\frac{q\lambda(r_c)\beta H p(r_c)}{(\rho+\beta H)(\mu(r_c)+c)} = 1$$

where c is the increase in parasite mortality due to chemotherapy, and r_c is the value of r under chemotherapy. Suppose now that the chemotherapy

increases the mortality of the heterozygous *RS* strain by an amount c_R, less than or equal to c. It is then immediate that

$$Q_0^{(R)} = \frac{q\lambda(r_c)\beta H p(r_c)}{(\rho+\beta H)(\mu(r_c)+c_R)} = \frac{\mu(r_c)+c}{\mu(r_c)+c_R}.$$

This expression is analogous to that for $Q_c^{(2)}$ in Example 3, and provides a measure of the ability of the *R*-gene to establish. Using the parameters in Table 1, and letting $c = 4$ and $c_R = 0$ for example, we obtain $Q_0^{(R)} = 1{\cdot}63$. Alternatively, solving equations (1)–(3) with μ replaced with $\mu + c$ for the *SS* strain, and using the value of r so obtained in the solution of equation (10) leads to $\mathscr{R}(E) = 49{\cdot}3$ in the absence of annual host replacement, and $\mathscr{R}(E) = 49{\cdot}2$ with host replacement. Note that Q_0 for the *SS* strain during chemotherapy is, for this example, $Q_c = 4{\cdot}77$. The control measure is, therefore, insufficient to eradicate the *SS* strain ($Q_c > 1$), but confers an advantage on the resistant strains ($Q_0^{(R)} > 1$).

Example 5 : resistance to chemotherapy with two host types

The equations for the dynamics of a parasite population with two host types (equations 6), have a steady state solution when $Q_0 = a_1 Q_0^{(1)} + a_2 Q_0^{(2)} > 1$, where a_1 and a_2 are as defined previously. The steady state values of r_1 and r_2 may be determined from $a_1 Q^{(1)}(r_1) + a_2 Q^{(2)}(r_2) = 1$, where

$$Q^{(1)}(r_1) = \frac{q\lambda_1(r_1)\beta_1 H_1 p_1(r_1)}{(\rho+\beta_1 H_1)\mu_1(r_1)}$$

with a similar expression for $Q^{(2)}(r_2)$. If a chemotherapy programme that consists of increasing the mortality of parasites in host types one and two by c_1 and c_2 respectively, reduces r_1 to r_c at steady state, then r_c may be determined from

$$\frac{a_1\mu_1(r_c)}{\mu_1(r_c)+c_1} Q^{(1)}(r_c) + \frac{a_2\mu_2(r_c')}{\mu_2(r_2')+c_2} Q^{(2)}(r_c') = 1$$

$$r_c' = \frac{\beta_2\sigma_1}{\beta_1\sigma_2} r_c.$$

Similar reasoning to that in Example 4 yields

$$Q_0^{(R)} = \frac{a_1\mu_1(r_c)}{\mu_1(r_c)+c_{R1}} Q^{(1)}(r_c) + \frac{a_2\mu_2(r_c')}{\mu_2(r_c')+c_{R2}} Q^{(2)}(r_c')$$

In Example 1 it was assumed that the epidemiological parameters of both parasites were as in Table 1 (particularly $\mu_1 = \mu_2 = \mu$), apart from $p_1(0) = 0{\cdot}65$ and $p_2(0) = 0{\cdot}2$. In Example 5 c_R was assumed to be zero. Repeating these assumptions, and using $c_1 = c_2 = c$ and $H_1 = H_2 = H/2$ (hence $a_1 = a_2$) leads to $r_c = r_c'$, $a\mu(Q^{(1)} + Q^{(2)})/(\mu + c) = 1$ and therefore $Q_0^{(R)} = (\mu + c)/\mu$, as in Example 4. Furthermore, $Q^{(1)}(r)/p_1(0) = Q^{(2)}(r)/p_2(0)$ for all r and μ is independent of r, so similar arguments to those used in Example 1 show that when a fixed number of treatments $(c_1 + c_2)$ are available $Q_0^{(R)}$ is minimized when

$$\frac{a_1\mu_1 p_1(0)}{(\mu_1+c_1)^2} = \frac{a_2\mu_2 p_2(0)}{(\mu_2+c_2)^2}.$$

As in Example 1, when the total number of treatments is fixed at 8 the optimum strategy with our parameters is $c_1 = 7$, $c_2 = 1$. The strategy to minimize the development of resistance in nematodes is the same as the strategy to optimally control the nematode population: apply the majority of treatments to the most susceptible host type.

DISCUSSION

The basic reproduction ratio has been the cornerstone of models for infectious diseases since the Dahlem conference in 1982 (Anderson & May, 1982). During this time the concept has been borrowed frequently for application to models of helminth parasites (for example Anderson & May (1991) and other references cited earlier). These uses were not incorrect, but when parasite life-cycles with transmission or mortality rates that vary with time (leading to seasonal models), or production systems incorporating regular farmer intervention (leading to models with resetting) are considered, more formal definitions are required (Heesterbeek & Roberts, 1994). We have seen in this paper how a formal definition aids in the clarification of concepts in parasite control when heterogeneity in either host or parasite complicate the life-cycle.

Two distinct threshold quantities have been discussed. The tentatively named basic reproduction quotient (Q_0) for parasite populations has two alternative definitions, which coincide for autonomous models. The definitions, in terms of either parasites or parasite-years in the next generation are equal if the former is correctly averaged over a time period. The value of Q_0 is easy to calculate for an autonomous model, and may be explicitly expressed for autonomous models with resetting. However, in the latter case numerical instability prevented its calculation when our example parameter values were incorporated. For seasonal models Q_0 must be calculated numerically, and similar difficulties may occur. For the examples in the present paper it was found that the easily calculated value of Q_0 for the autonomous system without resetting gave a useful guide to its values for more complicated models.

The quantity $\mathscr{R}(E)$ has a precise mathematical definition, and is easier to calculate than Q_0 for all but the autonomous model with no resetting, but has less biological meaning. In fact, the use of $\mathscr{R}(E)$ as a threshold quantity has a circular feeling to it, along the lines 'if a population increases in size, then it increases in size'. We have confirmed that, in all our examples, model control interventions that reduced Q_0 to one also reduced $\mathscr{R}(E)$ to one. Despite its lack

of intuitive appeal, $\mathscr{R}(E)$ is often a useful quantity for determining the long-term dynamics of parasite populations.

Even though these threshold quantities must often be calculated numerically, their use offers considerable advantage over the determination of long-term parasite population dynamics by carrying out a series of simulations. Apart from the usual arguments concerning the generality of qualitative results in opposition to the specificity of results from simulations (see Mollison, Isham & Grenfell, 1994), Q_0 and $\mathscr{R}(E)$ are calculated from the linearization of the model equations. This means that for many examples the non-linearities (i.e. the precise nature of the dynamics of acquired immunity) need not be determined, and the amount of data required to analyse the model is reduced. It is acknowledged that the model used to illustrate these threshold quantities is highly simplified. It does, however, contain the main features of the nematode life-cycle in farmed ruminants and could therefore be applied to problems involving parasites in sheep, cattle or goats. Simulation models must be tailored to a particular system and invariably contain many more parameters (see for example Grenfell *et al.* (1987); Barnes & Dobson (1990) and Smith & Grenfell (1994) and references therein). The simple model used here has been shown to display dynamical behaviour that is qualitatively correct (Roberts, 1994*b*; Roberts & Grenfell, 1991; 1992).

Equations (6) were used to model the influence of two distinct types of host on parasite population dynamics, and the method could easily be extended to more than two. By different host types we mean distinct groups of animals that have different interactions with the parasite population, but are both able to be infected by it. It was found that Q_0 for the parasite population could be expressed as a linear combination of the two values of Q_0 that would apply if each host type were present in isolation. It was also found that if chemotherapy were to be applied as a control or eradication strategy, it should be directed for preference to the host type with the largest Q_0. In Example 1, if a total of 8 treatments were available then 7 should be applied to the lambs and one to the ewes. In Example 2 the replacement of host animals with others more resistant to infection by parasites was investigated. It was found that a high proportion of host animals need to be replaced for this to be an effective parasite eradication strategy in the absence of other control measures.

The dynamics of more than one parasite type in a farmed host population has been discussed. This problem has previously been examined in wild animal populations (Dobson, 1985; Roberts & Dobson, 1994), and experimentally for farmed animals where there may be a shared acquired immunity between two parasite species (for example, prior infection of lambs with *O. circumcincta* may provide protection against subsequent infection with *T. colubriformis* (Dobson, Barnes & Windon, 1992)). The model demonstrates that for a second species of parasite to invade where a first is already established it must have some advantage, and that the advantage may be a direct consequence of a control intervention. These ideas were built upon with reference to the development of parasite strains resistant to chemotherapy.

A model for the dynamics of a parasite population with an emerging gene for resistance was proposed. It was found that the criterion for the development of resistance is determined by the transmission and mortality parameters of the susceptible strain and the heterozygous strain. This is because for small densities of the '*R*-gene' the probability that a parasite with the gene is able to find one of the opposite sex with the same gene is low, and the *RR* strain cannot invade until the *RS* strain has established. It was shown in Example 4 how the use of chemotherapy as a control measure gives the *RS* strain the advantage required to invade the population. In Example 5 the use of chemotherapy where there are two host types and a gene for enhanced parasite resistance to chemotherapy was discussed. It was found that $Q_0^{(R)}$, the threshold quantity for the development of resistance, is minimized when chemotherapy is applied in preference to the host type with greatest individual Q_0.

Finally, in all of these examples the use of chemotherapy has been modelled by increasing parasite mortality by a value c. Although approximately true when a large number of treatments are applied, this would be more appropriate for a sustained release capsule. Individual treatments could be modelled by the resetting of state variables, in a similar manner to that used for farm management practice above (but without changing the value of r). The timing of interventions would then be important in determining the threshold criteria. This will be discussed in a future paper.

This work was conceived while the authors took part in the programme on epidemic models at the Isaac Newton Institute for Mathematical Sciences, University of Cambridge. The authors are grateful to the organizers of the programme, and to the institute, for the opportunity to participate. M.G.R. also received financial assistance from a Trimble Agricultural Research Fellowship and MSD-AgVet Ltd. and an extended period of leave from the New Zealand Pastoral Agriculture Research Institute Ltd, J.A.P.H. was financially supported by the Netherlands Organization for Scientific Research, NWO; the Royal Society and SERC Grant GR G59981. Stewart Bisset made many helpful comments on an earlier draft of the paper.

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