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How will public and animal health interventions drive life-history evolution in parasitic nematodes?

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SUMMARY

Infection caused by parasitic nematodes of humans and livestock can have significant health and economic costs. Treatments aimed at alleviating these costs, such as chemotherapy and vaccination, alter parasite survival and reproduction, the main selective pressures shaping life-history traits such as age to maturity, size and fecundity. Most authors have argued that the life-history evolution prompted by animal and public health programmes would be clinically beneficial, generating smaller, less fecund worms, and several mathematical models support this view. However, using mathematical models of long-lasting interventions, such as vaccination, and regularly repeated short interventions, such as drenching, we show here that the expected outcome actually depends on how mortality rates vary as a function of worm size and developmental status. Interventions which change mortality functions can exert selection pressure to either shorten or extend the time to maturity, and thus increase or decrease worm fecundity and size. The evolutionary trajectory depends critically on the details of the mortality functions with and without the intervention. Earlier optimism that health interventions would always prompt the evolution of smaller, less fecund and hence clinically less damaging worms is premature.

Key words: mortality rates, health interventions, maturation time, vaccination, chemotherapy, anthelmintic.

INTRODUCTION

Infections by parasitic nematodes have a large impact on the health of humans and domestic livestock. Two key life-history traits, fecundity and body size, are important determinants of nematode infectiousness and host damage (Skorping, Read and Keymer, 1991; Stear, Strain and Bishop, 1999). Both are a consequence of the age at which nematodes mature. All other things being equal, it takes longer to get bigger, and nematode growth stops or rapidly declines after reproduction begins. Moreover, bigger worms can produce more eggs (Skorping *et al.* 1991; Morand, 1996; Gemmill, Skorping and Read, 1999; Leignel and Cabaret, 2001; Sorci *et al.* 2003). Consequently, age at maturity must be subject to intense natural selection. Here we ask how health interventions, such as widespread vaccination and chemotherapy, might alter nematode life history evolution. Most previous work has shown that smaller, less fecund worms are the likely outcome (Medley, 1994; Poulin, 1998; but see Skorping and Read, 1998; Gemmill *et al.* 1999). In this paper we show that a variety of evolutionary outcomes is

possible, including the evolution of larger and hence more fecund and damaging worms.

Previous theoretical work on the evolution of parasitic nematode life-histories has followed standard life history theory (Roff, 1992; Stearns, 1992) and assumed that mortality schedules are the major determinants of selection (Skorping *et al.* 1991; Morand and Sorci, 1998; Gemmill *et al.* 1999; Morand and Poulin, 2000; Sorci *et al.* 2003). Where chances of survival are high, nematodes should delay maturity to gain the fecundity benefits of large size. However, when chances of survival are low, worms should mature early in order to achieve some reproduction before death, even if this means they mature at small size and hence have low fecundity. Thus, where daily survival rates are high, one might expect a life history like that of *Ascaris lumbricoides*, for example, which reaches up to 30 cm in length and produces 25 million eggs over a lifetime. In contrast, where chances of survival are low, natural selection should favour a life-history like that of the pin worm, *Enterobius vermicularis*, which has a maximum length of 1 cm and produces no more than 20 000 eggs. A formal model of this idea, together with experimental data on survival rates, explains about 50 percent of the cross-species variation in age to maturity of parasitic nematodes of mammals (Gemmill *et al.* 1999).

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The aim of animal and human health programmes like chemotherapy and vaccination is to reduce worm survival. Thus, nematode life-histories could evolve in response to public and animal health programmes (Medley, 1994; Read and Skorpung, 1995; Poulin, 1998; Skorpung and Read, 1998; Leignel and Cabaret, 2001). This evolution may in principle occur in parallel with, or instead of, the evolution of drug or vaccine resistance. There is no direct evidence yet of such evolution, but it has not to our knowledge been looked for (for indirect evidence, see Leignel and Cabaret, 2001). In other contexts, where it has been looked for, life-history evolution in response to anthropogenic alterations in mortality schedules has been demonstrated. For instance, size-selective harvesting of populations of Atlantic silverside (*Menidia menidia*) changed size-dependent mortality schedules, and produced rapid evolution of slow growing, smaller fish in large-harvested populations and fast-growing, larger fish in small-harvested populations (Conover *et al.* 2005).

Most previous theoretical work on the evolution of nematode age in response to medical and veterinary intervention has suggested that the resulting life-history evolution would be beneficial from a disease control standpoint. The argument is that intervention-induced increases in mortality will mean that natural selection will always favour earlier maturation and thus result in smaller and less fecund worms (Medley, 1994; Poulin, 1998; Gemmill *et al.* 1999). However, existing formal models of this make fairly restrictive assumptions about the nature of nematode mortality patterns, in particular assuming that mortality rates are unaffected by age at maturity. Here we formally analyse earlier verbal suggestions (Read and Skorpung, 1995; Skorpung and Read, 1998; Gemmill *et al.* 1999) that some types of stage- or size-specific mortality might generate clinically-detrimental life history evolution.

It seems highly likely that mortality rates will vary with worm size. Larger nematodes presumably provide more stimulus to the immune system, all else being equal, because they will secrete more antigens and have a larger surface area, and may do more damage. Alternatively, smaller nematodes may be more vulnerable to immune attack if they are less able to withstand damage from a given number of effector molecules. The host immune response can also alter worm fecundity directly and indirectly via its effects on worm size (Wilkes *et al.* 2004; Viney, Steer and Wilkes, 2006). Moreover, immunity can differentially affect the survival of different developmental stages of parasites. For example, in *Strongyloides ratti* different mortality rates were observed for larval and adult stages which are in different host tissues (Bell, Adams and Gerb, 1981). Here we consider the effects of chemotherapy and vaccination allowing for these sort of more complex mortality schedules. We also consider the effects

both of changes in mortality schedules which might be continuous (e.g. vaccination or, in the case of farm animals, artificially-selected resistant hosts) or those which would be pulsed (e.g. many chemotherapeutic regimes used in an agricultural context). We show that optimism emerging from previous models may be misplaced: in some circumstances, animal and public health interventions may select for increased time to maturity, which would result in larger and more fecund worms.

MODELS

Here we consider the size-independent mortality model (henceforward ‘‘SIM’’ model) developed by Gemmill *et al.* (1999), and introduce our new model, which incorporates size-dependent mortality (henceforward ‘‘SDM’’ model). We then use these models to study the effect of public and animal health interventions on worm life-history evolution. In a subsequent section, we develop a model to study the effect of size-dependent mortality when there are pulsed interventions like regular drenching of farm animals with anthelmintics (henceforward ‘‘SDMP’’ model). All models assume that worm births are steady over time and the population is in equilibrium, hence lifetime reproductive success (measured as lifetime egg production) is an appropriate measure of fitness. Anderson and May (1985) provide evidence supporting this assumption. Analysis of the epidemic situation, where other fitness measures are more appropriate, is beyond the scope of this paper.

Throughout, symbols are as given in Table 1, and all mortality rates are instantaneous mortality rates – the probability of death at any particular point in time.

Size independent mortality model

The assumptions of this model are as follows (Gemmill *et al.* 1999): (1). Worms grow throughout development, but growth ceases at maturity. (2). Per unit time fecundity increases with worm size and hence with maturation time α , according to the relationship fecundity = $c\alpha^\beta$. (3). Within the host, parasites experience a constant juvenile mortality rate, M_j , until maturation. (4). After the onset of reproduction, parasites experience a constant adult mortality rate, M_a .

The probability of survival to maturation at time α is derived by treating the occurrence of death as a random variable with distribution Poisson(λ) where λ is the mortality rate, M_j . Thus, the average lifetime fecundity for individuals maturing at α is given by

$$\omega = c\alpha^\beta e^{-M_j\alpha} \frac{1}{M_a} \quad (1)$$

Table 1. Variables and Parameters for SIM, SDM and SDMP models. Note all ages are measured from first infection of the mammalian host

α	Age at maturity
$\omega(\alpha)$	Fitness of worms maturing at α
c	Constant relating age at maturity to worm fecundity
β	Exponent of allometric relationship relating age at maturity to fecundity
M_j	Within-host mortality rate for juvenile parasites
M_a	Within-host mortality rate for adult parasites
$m(z)$	Mortality rate experienced by juvenile parasites at age z
$d(\alpha)$	Mortality rate experienced by adult parasites which matured at age α
$\omega_h(\alpha)$	Fitness of worms maturing at α in hosts experiencing a health intervention
β_h	Allometric exponent relating fecundity to age at maturity in hosts experiencing a health intervention acting to reduce rate of increase of fecundity with age
$m_h(z)$	Mortality rate experienced by juvenile parasites at age z in hosts experiencing a health intervention acting to increase juvenile parasite mortality
$d_h(\alpha)$	Mortality rate experienced by adult parasites which matured at age α in hosts experiencing a health intervention acting to increase adult parasite mortality
$s_h(\alpha^*)$	Selection gradient at α^* under an intervention
I	Time interval between doses; ($I > \alpha$)
H	Proportion of hosts dosed during dosing events
D_j	Probability of juvenile parasites dying as a result of dosing event, if in dosed host
D_m	Probability of adult worms dying as a result of dosing event, if in dosed host
t	Time from start of interval between dosing events; ($0 < t < I$)
$\omega_p(\alpha)$	Overall average fitness of parasites maturing at age α under pulsed dosing

The model comprises three elements: $c\alpha^\beta$, the daily fecundity following maturity at α , $e^{-M_j\alpha}$ the probability of survival to maturity with pre-patent period α , and $\frac{1}{M_a}$ the life expectancy post-maturity (assuming survival times are exponentially distributed).

The age at maturity favoured by natural selection, α^* , corresponds to the maximum of $\omega(\alpha)$, at which the derivative $\omega'(\alpha^*)=0$, namely

$$\alpha^* = \frac{\beta}{M_j} \tag{2}$$

The same result can be derived from an explicitly epidemiological framework (Appendix A).

Size-dependent mortality model

We now extend the size-independent model (equation (1)) to include size-dependent mortality before and after maturation. In the next section, we use this framework to explore the effects of health interventions on optimum time to maturity.

To incorporate size-dependent mortality, we replace assumptions (3) and (4) above with the following: (5). Pre-maturity mortality rate is determined by size, and so changes during larval development. It is given by the function $m(z)$, where z is the time (age) from arrival in host. (6). Adult parasites experience constant mortality, determined by the size at which they matured, and given by the function $d(\alpha)$.

The size-dependent mortality model has a mortality rate which varies with time, and so the occurrence of death is a non-homogeneous Poisson process with distribution $Poisson(m(z))$. Thus, the

probability that death will not occur before age z is given by

$$1 - F(z) = e^{-\mu(z)}$$

where

$$\mu(z) = \int_0^z m(u)du \quad (z > 0)$$

Fitness is therefore given by

$$\omega(\alpha) = c\alpha^\beta e^{-\mu(\alpha)} \frac{1}{d(\alpha)} \tag{3}$$

which reduces to equation (1) for constant mortality rates $m(z) = M_j$ and $d(\alpha) = M_a$.

The optimal value, α^* , is again determined by the condition $\omega'(\alpha^*)=0$. Thus,

$$0 = \frac{\beta}{\alpha^*} - \frac{d'(\alpha^*)}{d(\alpha^*)} - m(\alpha^*) \tag{4}$$

with the additional requirement that, to ensure $\omega(\alpha)$ is maximal at $\alpha = \alpha^*$, the second derivative must be negative.

As illustrated in Appendix B, multiple solutions may be possible for some combinations of mortality functions so that the theoretical global optimum may not always be the value selected for.

THE EVOLUTIONARY CONSEQUENCES OF PUBLIC AND ANIMAL HEALTH PROGRAMMES ON NEMATODE AGE AT MATURITY

Interventions like chemotherapy, vaccination and, in the case of animal diseases, enhanced host resistance

through selective breeding could affect many of the key functions and variables which shape the selection pressures on nematode age to maturity. For instance, enhanced host resistance or subcurative chemotherapy can reduce c , the absolute worm fecundity (e.g. Crook and Viney, 2005; Viney *et al.* 2006). It follows from equations (2) and (4) that this has no effect on the evolution of age to maturity whether or not there is size-dependent mortality. Similarly, if the adult mortality rate does not vary with age at maturity, then equation (4) reduces to equation (2) and changes to the absolute value of the adult mortality rate will also have no effect on selection for age at maturity. Otherwise, however, interventions which alter the juvenile mortality rate at a given age, $m(z)$, the adult mortality rate for worms maturing at a given age, $d(\alpha)$ or the rate at which fecundity increases with age at maturity, β , will prompt evolutionary change in age to maturity. For instance, host immunity reduces the fecundity of *S. ratti*, by both reducing worm size and by reducing the fecundity of worms of a given size (Viney *et al.* 2006). It follows from (4) that where such effects occur, disease control interventions like mass vaccination which affect the immune environment experienced by a worm population will impose selection for altered age to maturity.

To understand the direction of this new selection, we consider two types of intervention. The first is where the entire natural life-span of the worms can be expected to fall within a period where the intervention is having an effect, as would be the case for immunisation or enhanced resistance by selective breeding; for simplicity we consider this under the general heading of ‘sustained interventions’. The second is where the intervention acts as series of brief, regularly spaced, discrete events against the background of the underlying mortality rates, as occurs with chemotherapy in an agricultural context, where animals are routinely drenched at particular intervals. We refer to this as ‘pulsed interventions’. These two situations need to be modelled in different ways, so we consider each in turn.

The effects of sustained interventions on optimum time to maturity

With size-dependent mortality, there is no generalised equation for α^* analogous to equation (2). However, an indication of the immediate direction of selection on age to maturity under an intervention can be determined by the sign of the selection gradient, the derivative of the fitness function under the intervention, in the vicinity of the pre-intervention value of α^* . This corresponds to the sign of $s_h(\alpha^*)$ where

$$s_h(\alpha^*) = \frac{\beta_h}{\alpha^*} - \frac{d_h'(\alpha^*)}{d_h(\alpha^*)} - m_h(\alpha^*) \quad (5)$$

with one or more of β_h , $d_h(\alpha^*)$ and $m_h(\alpha^*)$ affected by an intervention. When equation (5) is positive, the intervention is creating selection pressures that favour worms which grow for longer before reproduction; when equation (5) is negative, natural selection favours shorter maturation periods. Note that this selection gradient approach applies only in the immediate region of the pre-intervention α^* . Where multiple solutions are possible (e.g. Appendix B), the overall direction of evolutionary change may be different.

Inspection of equations (5) and (4) reveals the following. All else being equal, a health intervention which changes the pre-maturity mortality function to $m_h(z)$, with greater mortality for a given size ($m_h(z) > m(z)$, for all relevant values of z) will always favour reduced time to maturity. This is also true for size-independent mortality (equation (2); Gemmill *et al.* 1999). In both cases, this is because greater prematurational mortality selects for earlier reproduction, despite the fecundity costs, to ensure that worms survive to reproduce at all. Similarly, an intervention which changes the rate of increase of fecundity with size, so that worms are less fecund for a given size (i.e β to β_h such that $\beta_h < \beta$), will make $s_h(\alpha^*) < 0$, so that initial selection pressure will always favour a reduced time to maturity. This too is true for size independent mortality (equation (2); Gemmill *et al.* 1999), and is because the intervention is reducing the fecundity gains which accrue through delayed reproduction. Thus, interventions which increase juvenile mortality or decrease the rate of increase of fecundity with worm size will favour the evolution of an earlier age at maturity which will result in smaller and less fecund worms, whether or not mortality rates are size-dependent. These effects are illustrated in Fig. 1.

An intervention which affects mortality rates of mature worms has more complex effects on the optimal age to maturity. Inspection of equations (5) and (4) shows that the direction of selection under the intervention depends upon the difference between $d'(\alpha^*)/d(\alpha^*)$ and $d_h'(\alpha^*)/d_h(\alpha^*)$, the proportionate rates of change in mortality with size before and after imposing the intervention. This difference depends in turn upon the detail of each function around α^* . If the difference is positive, then the initial selection pressure will favour earlier maturing worms (Fig. 2a–c). If the difference is negative, as is always the case if the slope of $d_h(\alpha)$ is less than or equal to that of $d(\alpha)$, then interventions to increase adult mortality will always favour worms which delay maturation (Fig. 2d–f and g–i). If age to maturity does not affect adult mortality, then the slopes of $d(\alpha)$ and $d_h(\alpha)$ will be zero, and the adult mortality rate imposes no selection on age to maturity (Gemmill *et al.* 1999).

To understand how changes in adult mortality can have these contrasting effects on age to maturity, it is

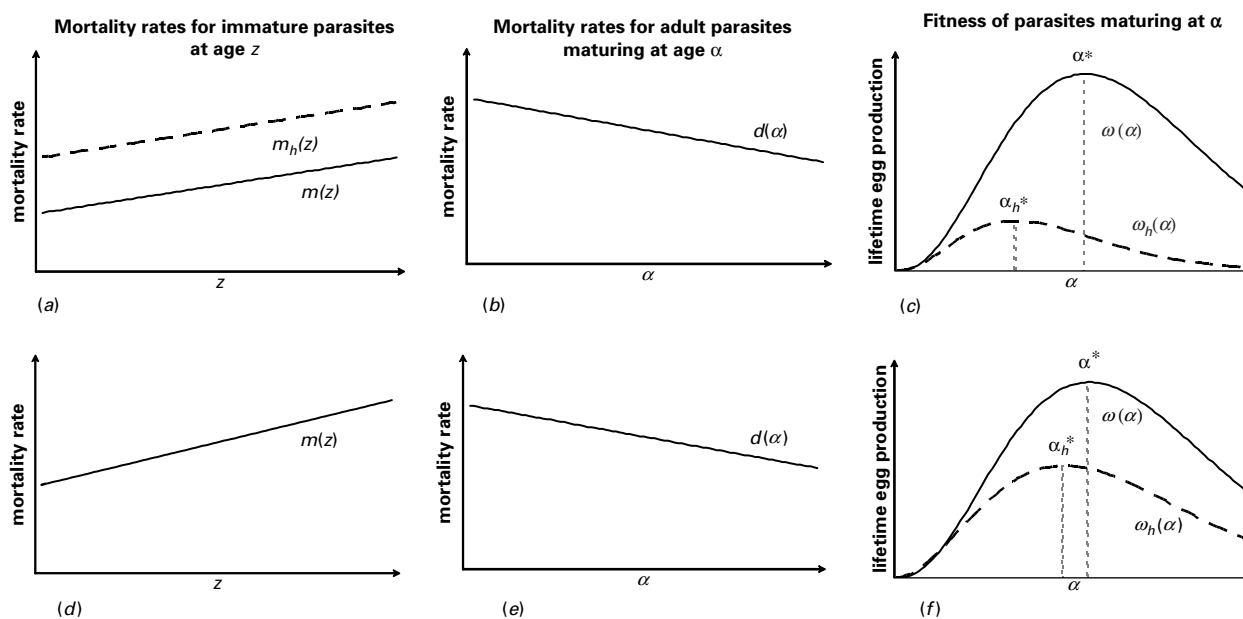


Fig. 1. Illustration of the effects of interventions which increase juvenile mortality or reduce fecundity. Panels (a) to (c) illustrate the effects on fitness of an intervention which increases the juvenile mortality rate from $m(z)$ to $m_h(z)$, and panels (d) to (f) show the effect of an intervention which leaves the mortality rates unchanged but reduces the rate at which fecundity increases with age at maturity. In both cases the fitness function under the intervention reaches its maximum with a shorter time to maturity (α_h^*) than that without the intervention (α^*). Continuous lines show functions without the intervention, dashed lines with the intervention.

helpful to consider the situation before the intervention is imposed. At the optimum age to maturity, α^* , there is the highest possible product from the three components of fitness: (i) chance of surviving to maturity, (ii) fecundity and (iii) duration of reproduction (adult life expectancy). By definition, worms maturing earlier or later than the optimum age will not have maximum fitness, so any associated improvement in one or more of the fitness components must be proportionately more than offset by a reduction in the other component(s). For example, worms beginning reproduction after the optimum age will have a relative fitness benefit from increased fecundity, but this benefit must be outweighed by a proportionately greater reduction in the product of their chance of surviving to maturity and their duration of reproduction.

Now consider an intervention which changes adult mortality rates and hence duration of reproduction, whilst the other two components of fitness remain unchanged. The proportionate rate of change in the duration of reproduction with increasing age to maturity may (i) remain unchanged, (ii) increase (adult life expectancy increasing more quickly, or decreasing more slowly with size than without the intervention), or (iii) reduce (increasing more slowly or decreasing more rapidly with size than without the intervention). In case (i), the proportionate change in fitness costs and benefits for worms maturing before or after α^* will be

unchanged and the optimum age at maturity will be unaffected by the intervention. In case (ii), worms maturing after α^* will enjoy a greater proportionate improvement in reproductive life than was the case with no intervention. Since the other components of fitness are unchanged, this means that increased fitness will now be achieved by worms maturing some time after α^* , and such worms will be favoured by selection. In case (iii), the reverse occurs and selection will therefore favour earlier maturing worms.

As an example, consider parasites evolved to mature at the optimum age in hosts whose immune response increases in effectiveness with the size of adult worms. An intervention increasing adult mortality consistently for adult worms of all sizes would decrease the proportionate reduction in life expectancy for later maturing worms, whilst leaving unchanged the proportionate increase in fecundity, and reduction in chance of reaching maturity. This sort of intervention would favour worms with longer times to maturity.

The situation is further complicated because the direction of initial selection pressure as given by the sign of equation (5) need not indicate the overall direction of selection in cases where multiple local optima exist for the fitness function under an intervention, $\omega_h(\alpha)$. In such cases, one of which is illustrated in Fig. 3, the slope of $\omega_h(\alpha)$ close to the original α^* may not correspond to the change in α

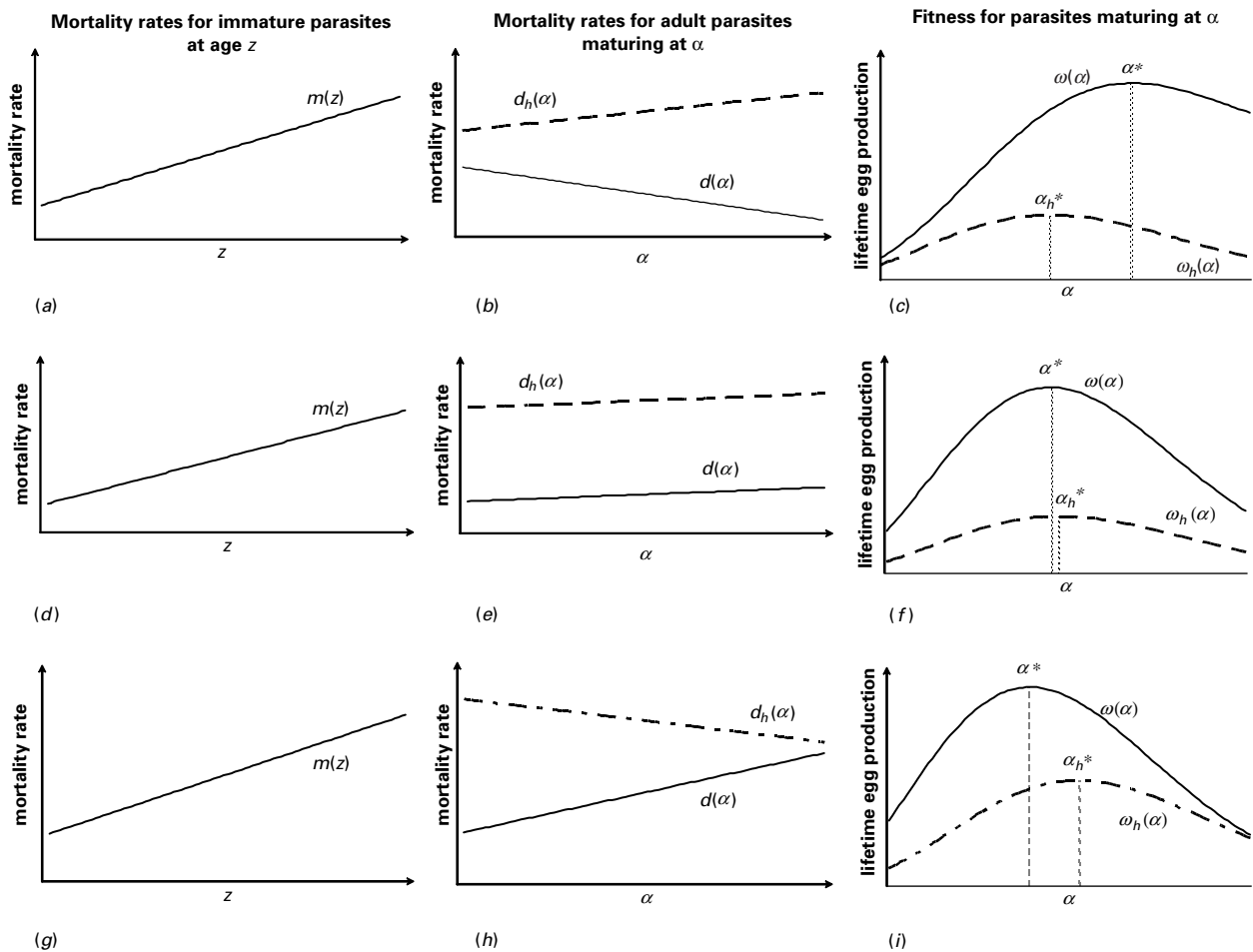


Fig. 2. Illustration of the effects of interventions increasing the adult mortality rate for parasites maturing at age α . Panels (a) to (c) show an intervention which increases the proportionate rate at which adult mortality rate changes with age at maturity, resulting in a reduction in optimum time to maturity. Panels (d) to (f) show an intervention which keeps the same rate of increase in mortality rate, so that, with higher absolute mortality, there is a reduced proportionate rate of increase and hence an increased optimum time to maturity. Panels (g) to (i) show an intervention with reduced rate of increase in mortality rate, and also reduced proportionate rate of increase in mortality, as might result if an intervention more easily resisted by larger worms outweighed the effects of an immune response more easily evaded by smaller worms, giving an increased optimum time to maturity. Continuous lines show functions without the intervention, and dashed lines with the intervention.

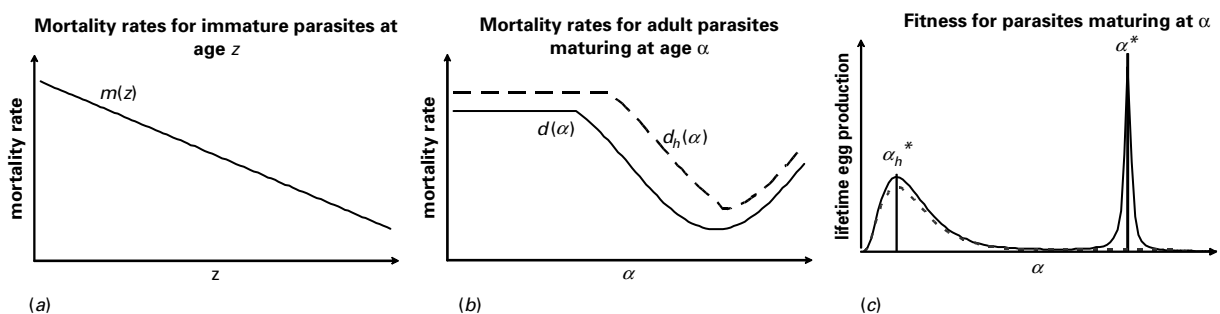


Fig. 3. Illustration of the effects of an intervention changing adult mortality in an example with multiple optima for the fitness function. Panel (a) shows the assumed pre-maturity mortality function, panel (b) shows the assumed post maturity mortality functions with and without intervention, and panel (c) shows the fitness functions with and without the intervention. The slope of the post maturity mortality function under the intervention is always less than or equal to that without the intervention, so initial selection pressure will favour increased time to maturity. However, the overall optimum now falls on a different peak of the fitness function and selection will in fact favour a lower value of α . Continuous lines show functions without the intervention, and dashed lines with the intervention.

required to give the maximum achievable fitness. Outcomes in such cases will be unpredictable, depending upon specifics of starting conditions and the details of the functions involved.

Size-dependent mortality function with pulsed interventions

Drug treatments can arise as brief periodic events rather than on-going changes to mortality functions or fecundity parameters. Vaccine boosts (and some natural immunity processes) conceivably could do the same thing. The following assumptions and revised equations incorporate pulsed interventions, or interventions conferring transient changes in mortality, within the SDM model: (7) Dosing is periodic at a fixed interval, I . (8) Parasites are assumed to infect hosts randomly at a constant rate, and are thus equally likely to arrive at any time point during the interval between dosing events. (9) The proportion of parasites experiencing a second dose is assumed to be zero or very small for convenience of analysis. (Parameter values must be consistent with this assumption.). (10) The effect of the intervention on any given parasite is assumed to vary only according to whether the parasite is immature or adult, irrespective of size or age. (11) Between dosing events, mortality rates are in accordance with those given by $m(z)$ and $d(\alpha)$.

Worms infecting a host during interval I can be divided into the following four groups. (A) Worms which die before the dosing event, without reaching maturity. These worms have zero fitness and thus do not contribute to the overall fitness function. (B) Worms which die before the dosing event, having reached maturity. These have fitness in accordance with the assumptions of the SDM model, but the post-maturity life expectancy must be the average for worms dying before I , not the overall post-maturity life expectancy. Fitness for worms in this category, arriving in the host at time t , is modelled by function $f(t)$. (C) Worms which survive until the dosing event, and are mature at the time of the dosing event. These worms will reproduce from maturity to age $I - t$, and then will either die in the dosing event, or will survive the dosing event and subsequently die according to the post-maturity mortality function. Fitness for worms in this category, arriving in the host at time t , is modelled by function $g(t)$. (D) Worms which survive until the dosing event and are immature at the time of the dosing event. These worms will either die in the dosing event before reproducing, or will survive to mature and reproduce in accordance with the SIM and SDM models. Fitness for worms in this category arriving in the host at time t , is modelled by function $h(t)$.

Using the symbols given in Table 1, the average fitness for worms in all categories arriving at

time t is given by

$$\omega_p(\alpha) = \frac{\int_0^{I-\alpha} f(t)dt + \int_0^{I-\alpha} g(t)dt + \int_{I-\alpha}^I h(t)dt}{I} = \frac{c\alpha^\beta e^{-\mu(\alpha)}}{d(\alpha)} \left(1 - \frac{H}{I} \left(D_m \frac{1 - e^{-d(\alpha)(I-\alpha)}}{d(\alpha)} + \alpha D_j \right) \right) \tag{6}$$

The derivation of this expression is given in Appendix B.

In order to find the optimum value of α under the pulsed intervention, α_p^* , we require $\omega_p'(\alpha_p^*) = 0$, which, since $\frac{c\alpha_p^\beta e^{-\mu(\alpha_p^*)}}{d(\alpha_p^*)}$ is non-zero, is equivalent to

$$0 = \left(\frac{\beta}{\alpha_p^*} - \frac{d'(\alpha_p^*)}{d(\alpha_p^*)} - m(\alpha_p^*) \right) \times \left(1 + \frac{H}{I} \left(\frac{D_m(e^{-d(\alpha_p^*)(I-\alpha_p^*)} - 1)}{d(\alpha_p^*)} - \alpha_p^* D_j \right) \right) + \frac{H}{I} \times \left(D_m \left(e^{-d(\alpha_p^*)(I-\alpha_p^*)} \left(1 + \frac{d'(\alpha_p^*)}{d(\alpha_p^*)} \left(\alpha_p^* - I - \frac{1}{d(\alpha_p^*)} \right) \right) + \frac{d'(\alpha_p^*)}{d(\alpha_p^*)^2} \right) - D_j \right) \tag{7}$$

From this equation it is evident that, in addition to the detail of the underlying mortality functions $m(z)$ and $d(\alpha)$, all the parameters associated with the pulsed intervention – the effectiveness of the treatment (D_m, D_j), the proportion of the host population treated (H) and the interval between doses (I) – have the potential to affect the evolution of time to maturity.

As for the SDM model, it is not possible to derive an explicit solution for α_p^* for the SDMP model. However, again, the direction of the slope of the fitness function at α^* , the optimum value of α without the intervention, will give the direction of the initial selection pressure acting on time to maturity under the intervention. Since, from equation (4), $\frac{\beta}{\alpha^*} - \frac{d'(\alpha^*)}{d(\alpha^*)} - m(\alpha^*) = 0$, and since $\frac{H}{I} \geq 0$, the sign of the selection gradient at α^* corresponds to the sign of $s_p(\alpha^*)$, where

$$s_p(\alpha^*) = D_m \left(e^{-d(\alpha^*)(I-\alpha^*)} \left(1 + \frac{d'(\alpha^*)}{d(\alpha^*)} \left(\alpha^* - I - \frac{1}{d(\alpha^*)} \right) \right) + \frac{d'(\alpha^*)}{d(\alpha^*)^2} \right) - D_j \tag{8}$$

It is clear that the sign of $s_p(\alpha^*)$ will depend upon the detail of the mortality functions and the parameters of the pulsed intervention and hence that selection pressure may favour increased or decreased α according to the specifics of $m(z)$ and $d(\alpha)$, and the values for the intervention parameters, D_j, D_m

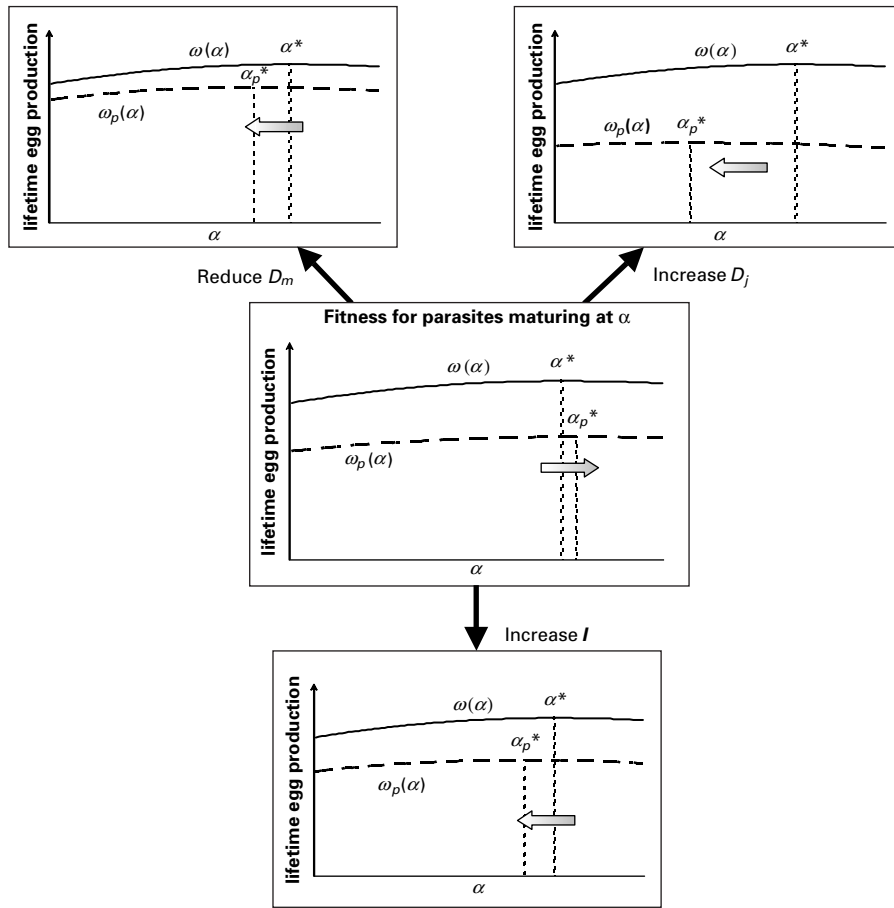


Fig. 4. Illustration of the effects of values for pulsed-dose model parameters on optimum time to maturity. From a given set of starting values, the direction of initial selection, for longer or shorter time to maturity can be changed by adjusting any of the three parameters, dosing interval, I , treatment mortality in immature parasites, D_j , and in mature parasites, D_m . Simple linear functions are assumed for $m(z)$ and $d(\alpha)$, with negative slope for $d(\alpha)$. Continuous lines show the fitness function without intervention, $\omega(\alpha)$, dashed lines show the fitness function under pulsed intervention, $\omega_p(\alpha)$.

and I . Given this, it is also clear that increasing the pre-maturity mortality D_j will always act to reduce the strength of selection for increased time to maturity when $s_p(\alpha^*) > 0$, and to increase the strength of selection for reduced time to maturity when $s_p(\alpha^*) < 0$.

For example, Fig. 4 illustrates that the optimum age to maturity under a pulsed intervention may be either longer or shorter than that without intervention, depending upon the relative and absolute values of the parameters D_j , D_m and I . Thus, within a given range of values for any two of these parameters, the direction of initial selection can be determined by the value of the third parameter. For instance, within a suitable range of values for I and D_m , changing the parameter D_j alone can change the direction of initial selection pressure. In each case, a limit may exist beyond which given values for one or more of these parameters fixes the direction of initial selection irrespective of the value of the others.

The proportion of hosts dosed, H , does not influence the direction of initial selection pressure. However, it does help to determine the size of the change from α^* to α_p^* , and can contribute to the

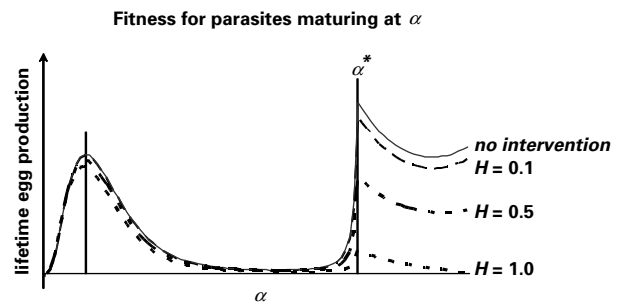


Fig. 5. Effect of H , proportion hosts dosed, on selection for time to maturity. In this example with multiple optima for the fitness function, although the selection gradient around α^* is positive and initial selection favours increased time to maturity, increasing the value of H moves the global optimum to the earlier peak, giving overall selection in favour of a reduced time to maturity.

overall direction of selection pressure in cases with multiple solutions as illustrated in Fig. 5, where increasing H for a particular intervention produces very small changes in the values of α at which the peaks of the fitness function fall, but ultimately causes the optimum value of α to move from the

second to the first peak. In practice, the outcome of such a change would depend *inter alia* upon there being sufficient variation in α within the parasite population to allow the transition between the two optima, given that most intervening values of α would be selected against.

DISCUSSION

Nematode life history traits respond readily to selection (e.g. Paterson and Barber, 2007). Consequently, animal and human health programmes which alter nematode mortality schedules (almost always the aim of such programmes) can drive life-history evolution. For nematode age at maturity, a key life-history trait with important fitness consequences, we found that the resulting evolution could have variable outcomes. In some cases clinically beneficial evolution giving smaller, less fecund worms is likely. But in some cases, evolution prompted by animal and human health programmes could generate nematode life-histories which would be clinically detrimental: larger worms producing more eggs.

The simplest trade-off model of nematode age to maturity (Gemmill *et al.* 1999; Morand and Poulin, 2000), assumes size-independent mortality (SIM model above), and predicts that selection on age at maturity is primarily driven by juvenile mortality rates. Consequently, selection will always favour earlier maturity under interventions which increase mortality or reduce the fecundity gains associated with increased size. However, the models developed here show that when adult mortality rate changes with parasite size, then both adult and juvenile mortality rates influence the evolution of age at maturity. Critically, and unlike juvenile mortality, the effect of adult mortality on optimal age to maturity is not unidirectional. Analysis of equations (4), and (5) shows that enhanced adult mortality can select for earlier or later age to maturity. Thus it is possible for animal or public health interventions like immunisation programmes or widespread chemotherapy to promote either smaller less fecund worms or larger more fecund worms.

Which of these possible outcomes occurs will depend upon the biology of the parasite, the biology of the interactions between parasite and host immune system, and on the specifics of the health intervention applied. Predicting the outcome for any particular case requires knowledge of the pre- and post-maturity mortality functions, with and without the intervention. These are currently not known for any worm, and indeed they would be difficult to determine even where direct experimentation is possible. Furthermore, for pulsed interventions, the interval between doses, the proportion of hosts dosed, and juvenile and adult parasite mortality rates resulting from the treatment all also help to determine whether

selection will favour earlier or later maturing worms under the intervention. There are no simple generalities and indeed, given current levels of understanding, it is not even easy to speculate on which evolutionary outcomes are more likely.

Nonetheless, the complexity of this issue does not make it go away. Human interventions which change mortality schedules will exert selection pressure. In many cases, the resulting evolution in life-history traits will have little clinical significance, or will result in increased animal or public health. However, where, for example, the larval stage is much more pathogenic than the adult parasite, prolonging the time taken to reach adulthood may have undesirable clinical consequences. In such instances it would be important to take account of whether a given intervention strategy might be expected to select for a longer duration of larval stage, and plan accordingly.

In some instances, it may even be possible to avoid undesirable evolution. Often the selection pressures imposed by an intervention cannot be readily adjusted as, for example, with vaccine-induced immunity, although even here, the likely effects of stage or tissue-specific immunity could be investigated where there are several vaccine candidates being evaluated. For pulsed interventions, some elements, such as the time interval between doses, can readily be adjusted. Where such control is possible, rather than simply ameliorating selection for unwanted changes, it might be possible to specify an intervention to intentionally exert selection pressure in favour of a desirable change.

Detailed models developed to analyse specific cases could extend our models in a number of ways. For example, contrary to our assumption 11, worms which survive a dosing event may be damaged in some way and experience higher mortality rates, or have lower fecundity, than would otherwise be the case. This and other circumstances, such as seasonal life-cycles and dosing patterns might mean that worms are more likely to enter hosts early or late in the dosing cycle, contrary to our assumption 8. Certain combinations of dosing strategy and life-history may mean that a significant proportion of worms survive more than one dosing event, violating our assumption 9. Alternatively, density effects may mean that worms surviving a dosing event, or arriving in a host shortly after a dosing event, may experience lower mortality or higher fecundity than would otherwise be the case. We doubt that such complexities would alter our general conclusion that some interventions can select for clinically-detrimental worm evolution, but they might nonetheless be important considerations for evaluating the magnitudes of any such evolution in particular cases.

The relationship between mortality rate and age at maturity suggests that in an environment where

mortality rate showed variation, as would be expected within a normal host population, there would be benefits to the parasite in adjusting the age of maturity according to the mortality rate actually experienced or predicted in its individual host, provided the benefits of such flexibility outweighed the costs of achieving it. Such flexibility has been demonstrated experimentally for at least two nematode species (Guinnee *et al.* 2003). This may provide a means of testing our conclusions, by examining whether the changes flexibly adopted by worms under different mortality schedules, a system which should have evolved to maximise worm fitness, are consistent with the responses predicted by the models.

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Table 2. Equivalence of parameters used in the models discussed in Appendix A. A and M is from Anderson and May (1985), M and P, Morand and Poulin (2000) and SIM is the model of Gemmill *et al.* (1999) described in the current paper

A and M	Parameter Description	M and P	SIM
k	Parameter summarising aggregation of parasites within host population	not explicitly included	n/a
s	Proportion of females in parasite population	not explicitly included	n/a
Φ	Mating function	not explicitly included	n/a
β	Transmission co-efficient between host and infective stages	β	n/a
d_1	Proportion of parasites entering host which survive to maturity	not explicitly included	n/a
d_2	Proportion of output transmission stages surviving to infective stage	assumed immediately infective	n/a
N	Host density	H	n/a
μ	In-host parasite mortality rate arising from host death	b	part of M_j and M_a
μ_1	In-host parasite mortality rate arising from other causes	immature μ_L mature μ_p	part of M_j part of M_a
μ_2	Free-living parasite mortality rate	μ_w	n/a
λ	Fecundity/eggs per day	$\lambda = \alpha^a c$	$c\alpha^\beta$

APPENDIX A: MORAND AND POULIN MODEL

Morand and Poulin (2000) derived an alternative model for the relationship between parasite mortality rate and optimal time to maturity using R_0 , the basic reproductive rate, based on explicit epidemiology, as follows;

$$R_0 = \frac{(\alpha^a)^c \beta H}{\alpha(\mu_w + \beta H)(\frac{1}{\alpha} + b + \mu_L)(b + \mu_p)} \tag{9}$$

giving

$$\alpha^* = \frac{-ca}{(ca-1)(\mu_L + b)} \tag{10}$$

with symbols as in Table 2. Equation (10) differs from equation (2). However, we show here that the two models give an equivalent solution for optimal age to maturity.

The derivation of equation (9) is based on a model by Anderson and May (1985),

$$R_0 = \frac{ks\Phi\beta d_1 d_2 N \lambda}{(\mu + \mu_1)(\mu_2 + \beta N)}$$

which separates the parasite mortality rate into two components, mortality of parasites within a living host, and parasite mortality through host death. The Anderson and May model also reflects a period of larval development outside the host prior to infectiousness, and a subsequent period of viability in the environment during which infective larvae may contact and infect hosts. Morand and Poulin (2000) ignored aggregation and implicitly assumed that all worms are hermaphrodite, so the parameters k , s , and Φ in the Anderson and May model can be ignored.

Morand and Poulin (2000) give the proportion of larvae infecting hosts which ultimately become adults within the host as $\frac{1}{\alpha} \frac{1}{(\mu_L + b + \frac{1}{\alpha})}$. This seems to be replicating the Anderson and May formula for the proportion of eggs produced which ultimately infect hosts, given by the probability of survival to infective stage \times life expectancy of infective larvae in the environment \times *per diem* transmission rate. However, this is not an appropriate representation of the process of in-host maturity where the transition from juvenile to adult occurs at age α for all larvae surviving to age α , not randomly at a given rate after age α has been reached. In addition, the use of $1/\alpha$ as the rate at which immature parasites become mature is inappropriate, since maturation does not happen randomly across all ages of immature parasites, but only to the proportion which have survived to age α , and this would only be $1/\alpha$ in the case where the in-host mortality rate among immature parasites was zero.

Using the parameters of the Morand and Poulin model, the amended formula for the proportion of immature parasites which survive a period of α days from arrival in-host to reach maturity is $e^{-(\mu_L + b)\alpha}$.

Incorporating this means that equation (9) becomes

$$R_0 = \frac{\alpha^a c \beta H}{(\mu_w + \beta H)(b + \mu_p)} e^{-(b + \mu_L)\alpha} \tag{11}$$

giving

$$\alpha^* = \frac{-ca}{(\mu_L + b)} \tag{12}$$

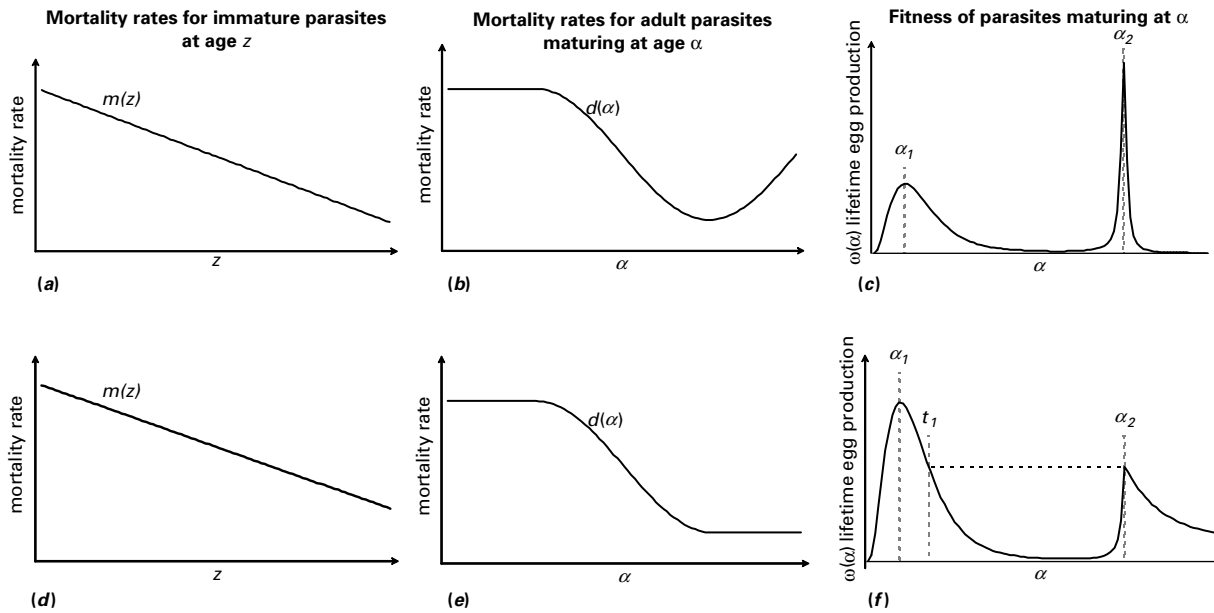


Fig. 6. Illustrations of multiple maxima for the fitness function (equation (3)). Mortality rates as a function of age for juveniles (left panels) and of age at maturity for adults (middle panels) generate the fitness functions shown in the right hand panels. The adult mortality function shown could arise if, for example, bigger worms are harder to kill and smaller worms are harder to detect. For (c), multiple local optima are found, with the global optimum falling on the later peak at α_2 . In (e), there are also multiple local optima, but the global optimum falls at α_1 , on the first peak. In this case, in the absence of lower limits on the time needed to physically achieve maturity, selection would favour maturity at α_1 . If minimum achievable time to maturity is between α_1 and t_1 , selection will favour maturity at the minimum achievable age, and if the minimum achievable time to maturity is greater than t_1 , then selection will favour maturity at α_2 .

Since $(\mu_L + b)$ is the total mortality rate for immature parasites, equivalent to M_j in the SIM model, and ca is equivalent to β in the SIM model, equations (12) and (2) are equivalent.

APPENDIX B: ILLUSTRATION OF MULTIPLE MAXIMA FOR FITNESS FUNCTION

Fig. 6 gives examples of situations in which there can be more than one age to maturity associated with fitness maxima.

APPENDIX C: DERIVATION OF PULSED INTERVENTION MODEL

In this Appendix we derive expressions for the functions $f(t)$, $g(t)$ and $h(t)$ introduced in section 3.2, and hence show that fitness is given by equation (6). For $0 < t \leq (I - \alpha)$, we have

$$\begin{aligned}
 f(t) = & \text{probability of survival from } t \text{ to } t + \alpha \\
 & \times (1 - \text{probability of survival from } t + \alpha \text{ to } I) \\
 & \times \text{average life expectancy for worms} \\
 & \quad \text{dying between } t + \alpha \text{ and } I \\
 & \times \text{fecundity for worms maturing at age } \alpha
 \end{aligned}$$

The average life expectancy post-maturity for worms born at time t which survive to time $t + \alpha$

and die before time I , can be calculated from the definite integral on age q , measured from maturity, from 0 to $(I - t - \alpha)$ of the proportion of such worms surviving to age q less the proportion which will survive to I .

Thus the average life expectancy post maturity, for worms born at time t which die between $t + \alpha$ and I is

$$\begin{aligned}
 & \frac{1}{1 - e^{-d(\alpha)(I-t-\alpha)}} \\
 & \times \left(\int_0^{I-t-\alpha} e^{-d(\alpha)q} dq - (I-t-\alpha)e^{-d(\alpha)(I-t-\alpha)} \right) \\
 & = \frac{1}{d(\alpha)} - \frac{(I-t-\alpha)e^{-d(\alpha)(I-t-\alpha)}}{1 - e^{-d(\alpha)(I-t-\alpha)}}
 \end{aligned}$$

So

$$\begin{aligned}
 f(t) = & c\alpha^\beta e^{-\mu(\alpha)} (1 - e^{-d(\alpha)(I-t-\alpha)}) \\
 & \times \left(\frac{1}{d(\alpha)} - \frac{(I-t-\alpha)e^{-d(\alpha)(I-t-\alpha)}}{1 - e^{-d(\alpha)(I-t-\alpha)}} \right) \\
 = & c\alpha^\beta e^{-\mu(\alpha)} \\
 & \times \left(\frac{1 - e^{-d(\alpha)(I-t-\alpha)}}{d(\alpha)} - (I-t-\alpha)e^{-d(\alpha)(I-t-\alpha)} \right)
 \end{aligned}$$

For $g(t)$, we obtain, for $0 < t \leq (I - \alpha)$

$g(t)$ = probability of survival from t to I
 × ((probability in undosed host + probability in dosed host but survives)
 × (average life expectancy from I) + $I - \alpha - t$)
 × fecundity for worms maturing at age α

giving

$$g(t) = c\alpha^\beta e^{-\mu(\alpha)} e^{-d(\alpha)(I-\alpha-t)} \times \left(I - t - \alpha + \frac{1 - H + H(1 - D_m)}{d(\alpha)} \right)$$

For the function $h(t)$ we find, with $(I - \alpha) < t < I$

$h(t)$ = probability of survival from t to α
 × (probability in undosed host + probability in dosed host but survives)
 × average life expectancy from α
 × fecundity for worms maturing at age α

which yields

$$h(t) = \frac{c\alpha^\beta e^{-\mu(\alpha)}}{d(\alpha)} (1 - H + H(1 - D_j))$$

The definite integrals of these functions over the relevant ranges for t give the following;

$$\int_0^{I-\alpha} f(t) dt = \frac{c\alpha^\beta e^{-\mu(\alpha)}}{d(\alpha)^2} \left((d(\alpha)(I - \alpha) + 2) e^{-d(\alpha)(I - \alpha)} - 2 + d(\alpha)(I - \alpha) \right)$$

$$\int_0^{I-\alpha} g(t) dt = \frac{c\alpha^\beta e^{-\mu(\alpha)}}{d(\alpha)^2} \left((2 - HD_m) + (d(\alpha)(\alpha - I) + HD_m - 2) e^{-d(\alpha)(I - \alpha)} \right)$$

$$\int_{I-\alpha}^I h(t) dt = \frac{c\alpha^{\beta+1} e^{-\mu(\alpha)} (1 - HD_j)}{d(\alpha)}$$

These functions are then combined to give the overall fitness function

$$\omega_p(\alpha) = \frac{1}{I} \left(\frac{c\alpha^\beta e^{-\mu(\alpha)}}{d(\alpha)^2} \left((d(\alpha)(I - \alpha) + 2) e^{-d(\alpha)(I - \alpha)} - 2 + d(\alpha)(I - \alpha) \right) + \frac{c\alpha^\beta e^{-\mu(\alpha)}}{d(\alpha)^2} (2 - HD_m) + (d(\alpha)(\alpha - I) + HD_m - 2) e^{-d(\alpha)(I - \alpha)} + \frac{c\alpha^{\beta+1} e^{-\mu(\alpha)} (1 - HD_j)}{d(\alpha)} \right) \tag{13}$$

This can be rearranged to give

$$\omega_p(\alpha) = \frac{c\alpha^\beta e^{-\mu(\alpha)}}{d(\alpha)} \times \left(1 - \frac{H}{I} \left(D_m \frac{1 - e^{-d(\alpha)(I - \alpha)}}{d(\alpha)} + \alpha D_j \right) \right)$$

which is equation (6).