Density dependence and the control of helminth parasites

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ABSTRACT: The transient dynamics and stability of a population is determined by the interplay between species density, its distribution and the regulating processes facilitating and constraining population growth. Using the host-helminth parasite system as an example, we propose that the point in the parasite’s lifecycle upon which these regulatory mechanisms operate will influence the rate of host reinfection following anthelmintic chemotherapy, and the likely success of control programmes. A parasite species whose population size is down-regulated by processes acting upon ‘mating and/or early’ life-stages (e.g. density-dependent fecundity), will reinfect a host population at a slower rate than a species for which such regulation operates upon ‘late’ life-stages (e.g. density-dependent parasite mortality). Under-representing the nature and magnitude of density-dependent mechanisms, and in particular those operating upon ‘late’ life-stages, may cause the resilience of the parasite population to a control perturbation to be underestimated. The importance of facilitating and constraining regulatory processes on metapopulation dynamics is discussed.
Introduction

Density-dependent processes are ubiquitous in nature and recognition of their role in regulating population abundance is an integral part of current ecological theory. Negative density-dependent processes operating upon intra- and/or interspecific interactions restrict growth rates at high population densities and help stabilize natural communities. When population numbers fall, restrictions tend to be relaxed, with the ensuing increase in per capita rates of survival and/or reproduction contributing to population persistence and resilience. There is also a growing realization of the importance of positive (facilitating) density-dependence in ecological theory (Bruno et al. 2003). Host-parasite associations provide a unique opportunity to explore the influence of negative and positive feedback mechanisms on population dynamics (Anderson and May 1978; Adler and Kretzschmar, 1992; Rosà and Pugliese, 2002), and importantly, to address a central issue for population ecology, namely, why species extinction is a rare phenomenon (Murdoch et al. 2003).

This paper investigates the influence of regulatory processes on the transient dynamics of helminth parasites. A number of large-scale, chemotherapy-based programs for the control of helminth parasites of humans are presently in operation, with the goal of either eliminating the parasites, or their associated disease burden (Sékétéli et al. 2002; Molyneux and Zagaria 2002; Fenwick et al. 2003). However, there is considerable uncertainty as to how long these programs should be maintained for in order to achieve their intended goals. Mathematical models can provide valuable insights into the dynamics of parasite populations undergoing perturbations due to chemotherapy and can help optimize treatment strategies to achieve program objectives (Winnen et al. 2002; Stolk et al. 2003). However, these models should be rigorously validated against data from treated populations,
as on some occasions they have underestimated the rates of parasite reinfection following relaxation of control efforts (Borsboom et al. 2003).

The rate at which parasites will reinfect a host population following a round of incomplete chemotherapy (i.e., with < 100% therapeutic coverage) will be influenced by the different density-dependent mechanisms that operate within the helminth’s lifecycle.

Reducing parasite density through chemotherapy will lessen the impact of processes restricting parasite population size, increasing the per capita probability that an individual worm will complete its lifecycle and thus enhancing reinfection rates.

The basic reproduction ratio, denoted $R_0$, of a helminth parasite is the average number of offspring (or of female offspring in the case of dioecious species) produced throughout the reproductive lifespan of a mature (or female) parasite that themselves survive to reproductive maturity in the absence of density-dependent constraints (Anderson and May 1992; for a mathematical definition see Diekmann et al. 1990). However, for parasites with obligatory sexual reproduction, this definition, though useful, is somewhat incomplete. Since reproduction is itself a density-dependent process (a host must harbor at least one mated female for transmission to occur) both positive (up-regulating) and negative (down-regulating) density-dependent processes must be considered in formulations of reproduction ratios for these parasites (Nåssell 1976; May 1977).

Regulatory mechanisms can act upon any stage of the parasite’s lifecycle. In this paper we refer to two categories of density dependence; processes that operate upon ‘mating and/or early’ life-stages (defining ‘mating and/or early’ as those parasite stages that mate and reproduce up until the arrival of infective progeny in the definitive host), and those acting upon ‘late’ life-stages (defining ‘late’ as those stages in the definitive host prior to adult worm mating). (Notice, however, that parasite mortality is considered to operate upon

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1 The concept of $R_0$ has been extended to incorporate environmental variability and re-named as the basic reproductive quotient, $Q_0$ (Roberts & Heesterbeek 1995).
‘late’ life-stages, either upon incoming, or established parasites which may have already mated. Therefore, in addition to the parasite standpoint, we shall also consider the status of the host as producing transmission stages, or receiving infective stages, as we now proceed to describe.)

Processes which act upon ‘mating and/or early’ life-stages encompass all density-dependent mechanisms that occur between a female worm being fertilized and the ensuing transmission stages becoming infective and gaining access to a new host (e.g. density-dependent fecundity). These processes are conditional on the worm burden of the host contributing transmission stages to the next generation. Density-dependent mechanisms which act upon ‘late’ life-stages include all processes affecting the development of incoming parasites, as well as the survival of established parasites. We assume that these processes are conditional on the number of worms already established in the host exposed to and receiving these infective stages (from the transmitting host). We propose that the rate of parasite reinfection will be influenced by whether density dependence is acting upon ‘mating and/or early’, or ‘late’ life-stages, i.e. whether the process in question is conditional on, respectively, the number of worms harbored by either the transmitting, or the receiving host. For example, in Onchocerca volvulus (the causal agent of river blindness), the impact of regulatory mechanisms operating within the insect vector, such as density-dependent microfilarial uptake or larval development (Basáñez et al. 1995; Soumbev-Alley et al. 2004) and parasite-induced vector mortality (Basáñez et al. 1996) will be determined by the intensity of infection of the host contributing transmission stages (microfilariae).

Conversely, mechanisms such as density-dependent parasite establishment may be regulated by the number of worms already inhabiting the host receiving the infection (Duerr et al. 2003). For a graphical representation see figure 1.
The interactions between regulatory processes and the parasite’s (overdispersed) distribution make the relationship between worm burden and its contribution to transmission strongly nonlinear (Churcher et al. 2005). We use simple models, motivated by experimental and observational data, to highlight the influence of different density-dependent mechanisms on the rate of parasite reinfection following chemotherapy. We use a variety of examples in order to illustrate the applicability of our theoretical results both within parasitology and in a broader ecological context, as parallels can be drawn between helminth reinfection following chemotherapy and the colonization of fragmented habitats following environmental change.

Model Development

Anderson and May (1992) discuss how $R_0$, and hence the intrinsic growth rate of a helminth infection, relates to the mean worm burden at endemic equilibrium, the severity of density-dependent constraints, and the degree of parasite aggregation within the host population (as measured by the overdispersion parameter $k$ of the negative binomial distribution). This relationship is further explored here in order to describe the parasite population dynamics at non-equilibrium scenarios (i.e., when the parasite population is perturbed by a control intervention).

The term ‘effective reproduction ratio’, denoted $R_e$, is used to describe the average number of adult progeny produced during the reproductive life-span of an adult worm inhabiting a host population harboring a given mean intensity of infection, and therefore subject to density-dependent mechanisms. Unlike $R_0$, $R_e$ is a function of the number of parasites per host at a given time $t$, reaching unity at endemic equilibrium (when each female parasite replaces herself and the parasite population size remains constant over time).
The host immune system is thought to play an important role in mediating many types of
density-dependent mechanisms (Tallis and Leyton 1966; Woolhouse 1992; Stear et al. 1995;
Paterson and Viney 2002). For the purposes of this paper, however, we shall assume that all
regulation is determined by the current worm load, and not influenced by a host’s history of
infection.

The distribution of helminth parasites among hosts tends to be highly aggregated
(Crofton 1971; Shaw and Dobson 1995). To incorporate the effect of parasite distribution,
regulation is modeled within each individual host and then averaged across all possible host
infection states (May 1977; Churcher et al. 2005). We shall assume the helminth population
to be dioecious, to have a 1:1 sex ratio, to be completely polygamous, and to have a highly
overdispersed distribution among hosts adequately described by the negative binominal
distribution. In addition we assume that there is no latency, i.e. infective stages, once
acquired, develop instantly into new adult worms.

More generally, helminth populations will be regulated by multiple density-
dependent mechanisms, conditional on both the mean worm burden within the host
contributing transmission stages and that within the host receiving infective stages (Basañez
and Boussinesq 1999; Norman et al. 2000). For the sake of simplicity, the dynamic
consequences of either category of density dependence will be explored separately at first,
and jointly later.

*Down-regulation acting upon ‘mating and/or early’ life-stages*

We will initially assume that the parasite population is regulated solely by the restrictions
imposed by single-sex infection and constraints on worm fecundity. The human intestinal
nematode *Ascaris lumbricoides* is an example of a dioecious parasite regulated by density-
dependent fecundity (Hall and Holland 2000). Churcher et al. (2005) introduce the term ‘effective transmission contribution’, to describe the net number of transmission stages (eggs per gram of faeces) contributed to the environment by a given worm burden in the presence of facilitating (the mating probability) and constraining density dependence. In the case of parasite species in which the only down-regulating process is density-dependent fecundity, the expression for the effective transmission contribution, denoted \( \Theta(W, k) \) is given by the equation

\[
\Theta(W, k) = \frac{\lambda_0}{c_F} \left\{ 1 - \left[ 1 + \frac{W}{2k} \right]^k \right\} ^{-k} + \left[ 1 + \frac{W(2 - \exp(-c_F))}{2k} \right]^{-k} - \left[ 1 + \frac{W(1 - \exp(-c_F))}{2k} \right]^{-k},
\]

(1)

where \( W \) is the mean worm burden, \( \lambda_0 \) is the maximum number of eggs produced per adult female worm per gram of feces, \( c_F \) is a measure of the severity of density-dependent constraints on worm fecundity, and \( k \) the overdispersion parameter of the negative binomial distribution. Density-dependent fecundity has been assumed to be a negative exponential function of worm burden (Anderson and May 1992; Churcher et al. 2005). The effective reproduction ratio, \( R_e \), is given by

\[
R_e = \frac{\Theta(W, k) K}{W \left[ \mu_w + \mu_H \right]},
\]

(2)

where \( \frac{1}{\mu_w} \) is the life expectancy of the adult worm and \( \frac{1}{\mu_H} \) the life expectancy of the host. Density-independent processes in the parasite’s lifecycle have been amassed into a single term, kappa (\( K \)). For the hypothetical parasite under discussion, where parasite
mating and fecundity are the only processes subject to density-dependent regulation in the parasite’s lifecycle, $K$ can be thought of as the proportion of eggs which reach reproductive maturity per year. (As $\Theta$ estimates the mean number of eggs per gram of feces, $K$ must incorporate an annual rate of fecal excretion.) At endemic equilibrium (i.e., in a stable parasite population before the initiation of any control intervention), $R_e$ will be equal to one and therefore $K$ can be estimated by,

$$K = \frac{W^* \left[ \mu_W + \mu_H \right]}{\Theta(W^*, k)},$$

where $W^*$ denotes the endemic adult worm burden. In principle, $W^*$ can be estimated from long-term field data and indirect measures of $K$ can thus be obtained (the composite processes included in $K$ are difficult to measure directly). Equations (1)–(3) permit a crude investigation of the rates of parasite reinfection following chemotherapy for a host population with a given endemic intensity of infection. For a parasite to be (locally) eliminated, the mean worm burden must be lowered to such an extent that $R_e$ remains consistently below one. (The ability of the parasite to persist, however, will depend on the distribution of the individual parasite’s reproduction numbers being about one (Antia et al. 2003).) For a list of definitions, parameter values, and functions see table 1.

*Down-regulation acting upon ‘late’ life-stages*

The epidemiological significance of density-dependent mechanisms regulating parasite establishment and survival within the definitive host is widely recognized (Tallis and Leyton
1966; Woolhouse 1992), although quantifying their magnitude and effect in humans and large vertebrate hosts is understandably difficult. Insight has been gained from experimental evidence gathered in animal models of human parasites (Denham et al. 1972; Denham and McGreevy 1977; Trees et al. 1992; Paterson and Viney 2002); helminths of veterinary importance (Stear et al. 1995); quantification of immunological responses (Haswell-Elkins et al. 1992; Pritchard et al. 1990; Stear et al. 1995), and through the use of mathematical models (Grenfell et al. 1987; Michael and Bundy 1989; Basáñez et al. 2002; Duerr et al. 2003). Here we assume that the parasite is regulated solely by the restrictions imposed by single-sex infection and by density-dependent parasite mortality in the definitive host.

We explore two possible functional forms for the relationship between the number of worms, \( N \), and the parasite’s probability of survival in the presence of density-dependent mortality, \( S_i(N) \). Two functional forms are differentiated by suffix \( i \). \( S_1(N) \) (fig. 2A) describes a survivorship that decreases exponentially with increasing worm burden, illustrated by \textit{Trichuris muris} in the mouse host (Michael and Bundy 1989); \textit{Strongyloides ratti} in the rat host (Paterson and Viney 2002), and \textit{Ostertagia circumcincta} (=ostertagi) in sheep (Grenfell et al. 1987). \( S_2(N) \) (fig. 2B) describes a survivorship that is maximal and approximately constant for initial worm burdens decaying at an accelerating rate afterwards (a reverse sigmoid survivorship (Bellows 1981)), as recorded in the \textit{Hymenolepis diminuta}–rodent system (Hesselberg and Andreassen 1975). Density-dependent parasite establishment can also be described as a form of density-dependent mortality, specifically occurring in ‘late’ larval stages: assessing precisely at which life-stages density-dependent mortality occurs is difficult from experimental infections. In the absence of this information we assume that larvae and adult stages are equally affected, and that figs. 2A and 2B represent adequately the shape of two possible density-dependent mortality functions.
(instead of referring only to density-dependent parasite establishment as a function of infective inoculum).

The mathematical expression chosen to represent the exponential survivorship is

\[ S_1(N) = s_0 \exp[-c_M(N - 1)], \]

where \( N \geq 1 \), \( c_M \) is the severity of density-dependent parasite mortality, and \( s_0 \) is the probability of survival of a single worm, which will be incorporated within the density-independent section \( (K) \) of the helminth’s lifecycle (fig. 2A).

The expression corresponding to the reverse sigmoid survivorship is

\[ S_2(N) = s_0 \exp[-c_M(N - 1)] \left[ 1 + \frac{c_M(N - 1)}{\sigma} \right]^\sigma, \]

where \( \sigma \) is a shape parameter (fig. 2B). In the limit when \( \sigma \to 0 \), \( S_2(N) \) approaches the exponential function \( S_1(N) \). We explore the population dynamics of two hypothetical parasite species exhibiting each of these types of survivorship respectively.

The biological mechanisms generating helminth aggregation among hosts will influence parasite regulation and the rate of reinfection following chemotherapy (Anderson and May 1978; Anderson and Medley 1985; Quinnell et al. 1990). The interplay between variability in host susceptibility (Quinnell 2003), heterogeneity in exposure (Shaw et al. 1998), aggregated infection events (Quinnell et al. 1995) and density-dependent mechanisms (Anderson and Gordon 1982; Quinnell et al. 1990; Galvani 2003) have all been implicated in the generation of the observed (overdispersed) distributions. For simplicity, we assume that the causes of parasite overdispersion are independent of density-dependent
mortality, and that the degree of aggregation (as measured by the negative binomial $k$
parameter) remains constant throughout the reinfection process. The ‘effective
survivorship’, $\Omega_i(W,k)$, is the average probability that a parasite will survive in the presence
of density-dependent worm mortality, where suffix $i$ indicates the particular function, $S_i(N)$,
described earlier. The effective probability of survival is

$$\Omega_i(W,k) = \frac{\sum_{n=1}^{\infty} P(N) N S_i(N)}{W},$$

(6)

where $P(N)$ is the probability that a host contains $N$ adult worms and $W$ is the mean worm
burden (see appendix A for its derivation). Equation (6) evaluates the survival probability
of a parasite inhabiting a host with a given worm burden and averages across all parasite
loads in the host population. Assuming that $P(N)$ follows a negative binomial distribution,
closed forms of equation (6) can be derived for $\Omega_1$ and $\Omega_2$ (appendix A). At endemic
equilibrium, ($W = W^*$), the average survivorship $\Omega_i(W^*,k)$, must counterbalance the rate
of parasite acquisition so as to ensure that $R_e$ remains equal to unity. The more highly
aggregated the parasite population, the greater the influence that heavily infected hosts will
have over parasite population regulation. The effective reproduction ratio for a parasite
regulated solely by the restrictions imposed by mating and density-dependent parasite
mortality in the definitive host is

$$R_e = \frac{\Theta_0(W,k)K \Omega_i(W,k)}{W[\mu_W + \mu_H]},$$

(7)
where $\Theta_0(W, k)$ is the effective transmission contribution when there is no density-

dependent fecundity, i.e. $\Theta_0(W, k) = \lim_{c_F \to 0} \Theta(W, k)$.

Down-regulation acting upon both ‘mating and/or early’ and ‘later’ life-stages

In reality, most parasite populations will be constrained by multiple down-regulating

mechanisms, operating throughout their lifecycle. For a parasite exhibiting both density-
dependent fecundity and density-dependent mortality, $R_e$ can be calculated from equation

(7) by allowing both $c_F$ and $c_M$ to be greater than zero. Note that $K$, the term encompassing

all the remaining density-independent processes must be recalculated using an extension of

equation (3), $K = \frac{W^* [\mu_W + \mu_H]}{\Theta(W^*, k) \Omega_i(W^*, k)}$.

Estimation of the rate of parasite reinfection

To highlight the difference between the two categories of down-regulation (acting upon

‘mating and/or early’ or ‘late’ life-stages), deterministic models are constructed to estimate

parasite reinfection following incomplete mass chemotherapy (typically, mass treatment

programs of human populations achieve, at best, therapeutic coverage levels between 60 and

80% of the total population). The following infection/reinfection scenarios are explored: (1)

The negative exponential function is adopted either for density-dependent fecundity or

density-dependent mortality. The two types of parasite under comparison will thus have

identical pre-control $R_e$ profiles, though they will behave differently following incomplete

mass chemotherapy. (2) The parasites are regulated solely by the restrictions imposed by
single-sex infection and density-dependent mortality but differ in their survivorship functions \((S_1(N) vs. S_2(N))\). (3) The parasites are regulated by either constraints on fecundity or mortality or both, with processes affecting fecundity as described in equation (1) and mortality following equation (5).

In all three situations we assume that the parasite population is at endemic equilibrium prior to treatment and that chemotherapy instantaneously kills all worms inhabiting a treated individual whilst allowing immediate parasite reinfection (i.e., drug efficacy is 100% and it has very short half-life within the host). Contact rates with infective stages are approximated by mass action across both treated and untreated sections of the host population. The full models are described in appendix B.

**Results**

The relationship between the effective reproduction ratio \(R_0\) and the mean number of worms per host is depicted in figure 3 for a hypothetical species regulated solely by density-dependent fecundity and mating. In particular, the intensity of infection \(W_{MAX}\) at which worms reproduce at their fastest per head rate \(R_{eMAX}\) is represented. The hypothetical parasite’s \(R_0\) value of approximately 4.1 (calculated from equation (2) when \(c_F \to 0\), i.e. \(\frac{\lambda_0 K}{2[\mu_w + \mu_H]}\), using \(K = 7.02\times10^{-4} \text{year}^{-1}\) with parameters from table 1, is markedly higher than the corresponding \(R_{eMAX}\) estimate obtained of 2.61 (fig. 3(b)), reflecting the importance of single-sex infections in restricting population growth at low worm densities. The choice of the exponential decay in fecundity with increasing worm burden accentuates the discrepancy between \(R_0\) and \(R_{eMAX}\), as the fastest reduction in the rate of egg production
occurs at low intensities of infection. Other crude methods of calculating $R_0$ (Anderson and May 1992), which omit the influence of single-sex infections, considerably overestimate the maximum growth rate of the parasite population, depending on the degree of parasite overdispersion and the severity of the regulatory constraints.

All $R_e$ profiles cross unity at two intensities of infection; the endemic mean worm burden (the stable equilibrium when $R_0 > 1$), and the breakpoint density (the unstable equilibrium), below which the parasite population will tend towards local extinction (Macdonald 1965; Anderson and May 1992). For a given level of endemicity, parasites with stronger down-regulation will reinfect a host population faster than those belonging to a species with weaker regulatory constraints (the density-independent contribution to the growth rate will have to be higher to compensate for stronger regulatory constraints if the same endemic equilibrium value is to be achieved). Parasites with more severe down-regulating density dependence and/or highly overdispersed distribution will also have a lower $W_{MAX}$ and breakpoint densities, making them harder to eliminate (Duerr et al. 2005).

Reinfection scenario (1): density-dependent processes acting upon ‘mating and/or early’ vs. ‘late’ parasite life-stages

The rate of parasite reinfection will depend on the relaxation of the mechanisms down-regulating transmission, and specifically, on the life-stage whose regulation is being relaxed. Following incomplete mass chemotherapy, a parasite transmitted from an untreated to a treated host will experience very little density-dependent restriction if the down-regulating processes operate upon ‘late’ life-stages. A female worm in an untreated, heavily infected host will have a high chance of mating and her offspring will have a high probability of completing their life-cycle if transmitted to a treated host where density-dependent constraints on parasite survival will be minimal. Conversely, if down-regulation
operates upon ‘mating and/or early’ life-stages, a parasite transmitted from a heavily
infected untreated host to a treated host would still have the same probability of completing
its lifecycle as it would have before treatment.

Therefore, with everything else being equal, a species with negative density
dependence acting upon establishing life-stages will reinfect the treated section of the host
population at a faster rate than a species with density dependence operating upon the
production of transmission stages (and hence still acting within those untreated hosts who
will constitute the main source of reinfection) (fig. 4). This delay in reinfection is
accentuated by mating restrictions imposed by single-sex infections, as female worms
infecting treated hosts may initially find themselves without access to males. Sufficiently
high reinfection rates will eventually enable the worms in the treated host population to
exceed their breakpoint density and contribute to transmission.

As mentioned earlier, the model presented here assumes that juvenile parasites reach
reproductive maturity immediately after entering the host. Incorporating a prepatent period
would accentuate the difference in reinfection rates by delaying the production of
transmission stages by the treated host population. During reinfection, the treated host
population will produce a higher proportion of new infections if down-regulation acts upon
‘mating and/or early’ life-stages. For a species down-regulated at ‘late’ life-stages, treated
hosts will have a lower relative contribution to the overall number of new infections (as
untreated hosts continue to produce offspring unimpeded by density dependence), making
reinfection less dependent on young worms (whose reproduction would be restricted by a
delay in reproductive maturity).

The disparity in growth rates displayed by parasite populations regulated by either
category of density dependence results from the different parasite densities harbored by
treated and untreated hosts. If the totality of host population were treated (100% coverage),
no difference between the two hypothetical parasites would be observed (the two $R_e$ profiles
are identical as illustrated in fig. 4). Table 2 summarizes, for the two parasite types, the
impact of positive and negative density dependence on parasite reinfection rates.

Infection scenario (2): both parasite species regulated by density-dependent mortality but
differing in survivorship functions

The discrepancies in the $R_e$ profiles for the different functional forms will depend on
the distribution of worms among hosts. $\Omega_1(W,k)$, and $\Omega_2(W,k)$ differ the most at low
degrees of parasite overdispersion (results not shown). This is because a higher proportion
of worms are inhabiting hosts that have a low mean worm burden, the parasite density at
which $S_1(N)$ and $S_2(N)$ differ most dramatically (fig. 5A). The interaction between the
positive and negative regulatory mechanisms ensures that $W_{MAX}$ is higher with the $S_2(N)$
functional form. It should be noted that a relatively small difference in the shape of the
density-dependent function (fig. 5A) results in widely differing reinfection rates and
equilibrium values.

The type of functional form describing density-dependent parasite survival, $S_i(N)$,
will influence the population dynamics of a helminth infection. The interplay between
parasite distribution and the shape of this functional form makes the relationship between
effective survivorship, $\Omega_i(W,k)$, and mean worm burden highly nonlinear (fig. 5B). Two
different cases are depicted. The first assumes that the endemic mean worm burden for the
helminth infection in question is known or can be measured. By also measuring the severity
of density-dependent mortality, the magnitude of the density-independent section of the
lifecycle, $K$, can be estimated (using a function akin to equation 3 or its extension). To
enable the two hypothetical parasites to have the same endemic mean worm burden, another
process in the helminth’s lifecycle must be more efficient to compensate for the lower survival probability of the species with the $S_1(N)$ (exponential) relationship. This more efficient lifecycle results in a faster rate of reinfection and higher $R_{eMAX}$ for the parasite with the $S_1(N)$ function (figs. 5C and 5E). The second case assumes that the endemic intensity of infection is unknown but that the two hypothetical parasites have the same value for $K$. In this case the parasite with the $S_2(N)$ function has the higher $R_{eMAX}$, reinfection rate, and endemic mean worm burden (figs. 5D and 5F).

Reinfection scenario (3): parasites regulated by either constraints on fecundity or mortality, or both.

The incorporation of multiple negative density-dependent mechanisms into the parasite’s lifecycle increases the rate of reinfection (fig. 6). The combined restriction imposed by density-dependent fecundity and density-dependent mortality forces the density-independent sections of the lifecycle to be highly efficient (high $K$ value) if the same endemic worm burdens are to be achieved. Quantification of the various regulatory processes operating upon parasite populations will enable the likely success of parasite elimination campaigns to be investigated (fig 6B).
Discussion and Conclusions

Population stability is associated with the stage of the lifecycle upon which density dependence operates. Using the host-helminth parasite system as an example, we have shown that a species whose population size is restricted by processes acting upon ‘late’ life-stages (e.g. adult worm survival), will be more resilient to control efforts than a species with density dependence operating upon ‘mating and/or early’ life-stages in the lifecycle, (e.g. upon the production of transmission stages). In addition, the severity and shape of the relationship governing down-regulation as a function of worm burden will influence the likely success of parasite control or elimination. The interplay between the multiple opposing density-dependent mechanisms makes the relationship between mean worm burden and transmission highly nonlinear and somewhat counterintuitive. Although the operation of down-regulating processes would dictate that nearly unconstrained parasite population growth would take place at low worm burdens, the presence of facilitating density-dependent mechanisms shifts $W_{MAX}$ to intermediate mean worm burdens. In support of our theoretical results, a similar hump-shaped relationship between population density and survival has been shown experimentally in drosophilid flies (Rohlfs and Hoffmeister 2003).

Published estimates of $R_0$ for gastrointestinal helminths and schistosome parasites tend to be low (compared to those of viral infections), typically in the range of 1 to 5 (Anderson and May 1992). This would indicate that they should be relatively easy to eliminate, though practical experience indicates this is clearly not the case (Woolhouse et al. 1996). Failure to quantify both the up- and down-regulating processes governing parasite population dynamics could go some way towards explaining this discrepancy.
There is a growing recognition of the importance of intraspecific facilitating density-dependent mechanisms in helminth population dynamics (Duerr et al. 2005). Helminths are highly effective at down-modulating the host immune response to maximize their survival and reproductive output (Maizels and Yazdanbakhsh 2003), with (reverse) dose-dependent immunological responsiveness being observed in a number of parasites (King et al. 2001; Brattig et al. 2002; Maizels et al. 2004). Other examples of facilitating mechanisms include longer survival of *Heligmosomoides polygyrus* in highly infected hosts (Dobson et al. 1985; Robinson et al. 1989) and greater survival of *O. volvulus* with increasing intake by certain vector species (Basáñez et al. 1995). Interspecific density-dependent interactions should also be considered (Allen and MacDonald 1998; Lello et al. 2004; Bottomley et al. 2005).

All throughout this paper it has been assumed that density dependence is determined by the current worm load, and not influenced by a host’s history of infection. Experimental evidence from animal models indicates that some density-dependent mechanisms may be immunologically driven (Stear et al. 1995; Paterson and Viney 2002). Prior exposure to infection has been shown to reduce parasite establishment and survivorship in *S. ratti*, although no effect was detected in the level of density-dependent fecundity, despite regulation being immunologically-driven (Paterson and Viney 2002). Genetic epidemiological analysis has indicated that host predisposition to infection may have a genetic determinant in *A. lumbricoides* (Williams-Blangero et al. 1999) and *Schistosoma mansoni* (Marquet et al. 1996). If host genetics influence the shape of the relationship between density dependence and worm burden, a single (average) shape function, $S_i(N)$, may not adequately predict the rate of parasite reinfection. Likewise, if heterogeneity in exposure is a major contributor to the generation of helminth overdispersion, models would be required to average across exposure events. More complex models will also be needed to investigate scenarios where density dependence interacts with processes generating
overdispersion, when the degree of overdispersion changes under control interventions (Anderson and Medley 1985; Quinnell et al. 1990), or when rates of parasite reinfection (and their associated uncertainty) need to be reliably estimated.

Most existing models investigating the impact of chemotherapy on helminth infections have been developed by fitting equilibrium data and subsequently predicting the impact of the intervention (but see Subramanian et al. 2004; Michael et al. 2004). At endemic equilibrium, density dependence maintains a constant level of infection over time, irrespective of where in the lifecycle down-regulating processes act. Although a model (underlined by specific structural and parameter assumptions) may be robust enough to predict the intensity of infection at equilibrium, the crucial regulatory mechanisms may be miss-placed within the parasite’s lifecycle for lack of experimental or observational evidence, or the shape of the true relationship miss-represented. Due to the difficulty in obtaining experimental data on the nature and magnitude of density-dependent mechanisms operating upon ‘late’ life-stages (as they occur within definitive, vertebrate, hosts), these processes may have been systematically under-represented, causing the resilience of the parasite population to control efforts to be underestimated or at least not adequately quantified. Ideally, the worldwide helminth control programs now in operation should systematically collect parasite reinfection and abundance data under the pressures exerted during the intervention. This would greatly help the development and validation of non-equilibrium models for epidemiological surveillance, and the prompt detection of anthelminthic resistance.

The concepts outlined above can be considered in a broader ecological context. The rate of invasion and colonization of fragmented habitats within a metapopulation will depend on the nature of the inter- and intraspecific density-dependent interactions regulating a species population size. A species whose negative density-dependent mechanisms occur
in ‘late’ life-stages, and are therefore relaxed following migration to a sparsely populated patch, will have higher patch connectivity. High inter-patch migration increases the chance of colonization events and will enhance patch persistence. Interestingly, early sucessional plants (r-strategists) tend to be down-regulated by interspecific competition acting upon these ‘late’ life-stages. Conversely, a species whose down-regulation acts upon ‘mating and/or early’ life-stages (i.e. conditional on the population density of the transmitting patch), will have lower patch connectivity and be less likely to support a viable metapopulation (Ovaskainen and Hanski, 2003). Further analogies can be made between parasite population dynamics and the behavior of metapopulations, specifically since patch population densities are typically overdispersed (Rosewell et al. 1990) and that there is a growing realization of the importance of intraspecific facilitation (not only via the Allee effect) in a variety of environments (Bertness and Leonard 1997; Bruno et al. 2003; Rohlfs and Hoffmeister 2003). Ecological models which fail to distinguish the stage of the lifecycle upon which density dependence operates will fail to recreate accurately a population’s transient dynamics and stability.

Acknowledgments

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Appendices

Appendix A: Derivation of $\Omega_i(W,k)$

This appendix shows the derivation of expressions for the effective survivorship $\Omega_i(W,k)$ used in figures 5 and 6, corresponding to exponential and reverse sigmoid survival probabilities of a worm inhabiting a host with $N$ worms: $S_1(N) = \exp[-c_M(N-1)]$ (equation 4) and $S_2(N) = \exp[-c_M(N-1)] \left(1 + \frac{c_M(N-1)}{\sigma}\right)^\sigma$ (equation 5), where $c_M$ and $\sigma$ are $> 0$ (and $s_0 = 1$). We first consider $S_2(N)$, since $S_1(N) = \lim_{\sigma \to 0} S_2(N)$. The effective survivorship is the average probability of worm survival over the host population (equation 6). Assuming that the distribution of adult worms among hosts is negative binomial

$$P(N) = \frac{\Gamma(N+k)}{\Gamma(k)N!} \alpha^N (1-\alpha)^k,$$  \hspace{1cm} (A1)

with mean and aggregation parameters $W$ and $k$, and $\alpha = \frac{W}{W+k}$. Substituting $P(N)$ and $S_2(N)$ into equation (6) and rearranging, gives

$$\Omega_i(W,k) = \frac{1}{A} (1-\alpha)^k \sum_{N=0}^{\infty} \frac{\Gamma(N+k)}{\Gamma(k)N!} (\alpha A)^N N \left(1 + \frac{c_M(N-1)}{\sigma}\right)^\sigma, \hspace{1cm} (A2)$$

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where $A = \exp(-c_M)$. For a given integer value of $\sigma$, we expand the binomial term on the right hand side of (A2), write appropriate powers of $N$ as derivatives with respect to $\alpha A$, and make use of the normalization of $P(N)$, to obtain closed expressions. For $\sigma \to 0$,

$$\Omega_1(W, k) = \left( \frac{1-\alpha}{1-A\alpha} \right)^{-k} \frac{k}{k + (1-A)W}, \quad \text{(A3)}$$

and, for $\sigma = 2$,

$$\Omega_2(W, k) = \left( \frac{1-\alpha}{1-A\alpha} \right)^{-k} \frac{k}{k + (1-A)W} \left[ (1-B)^2 + \left( \frac{c_M}{2} + \frac{B}{k+1} \right)B \right], \quad \text{(A4)}$$

where $B = \frac{c_M}{2} (k+1) \frac{\alpha A}{1-\alpha A}$.

Appendix B: Models of parasite reinfection

This appendix outlines the models used to investigate the rate of parasite reinfection following incomplete mass chemotherapy. We first describe the model used in figure 4 to demonstrate the importance of the stage in the parasite’s lifecycle upon which density dependence is operating (i.e. upon ‘mating and/or early’ or ‘late’ life-stages). The effective survivorship (exponential) function $\Omega_i(W, k)$ is incorporated into different sections of the lifecycle to describe either mortality of adult parasites or mortality of transmission stages (i.e. the two categories of down-regulation under investigation). Each host population is
subdivided into treated and untreated sections, whose dynamics are described by the following system of differential equations,

\[
\frac{dW_{cE}}{dt} = \left[ C \Theta_0\left(W_{TE}, k\right) \Omega_1\left(W_{TE}, k\right) + (1 - C) \Theta_0\left(W_{UE}, k\right) \Omega_1\left(W_{UE}, k\right) \right] K - (\mu_w + \mu_H)W_{cE} \tag{B1} \]

\[
\frac{dW_{cL}}{dt} = \left[ C \Theta_0\left(W_{TL}, k\right) + (1 - C) \Theta_0\left(W_{UL}, k\right) \right] K \Omega_1\left(W_{cL}, k\right) - (\mu_w + \mu_H)W_{cL} \tag{B2} \]

where \(W_{cd}\) charts the mean number of worms per host, with suffix \(c\) indicating the treatment category (\(c = T\) or \(c = U\) for worms within, respectively, treated or untreated hosts), and suffix \(d\) specifying whether the density dependence is acting upon ‘mating and/or early’ (\(d = E\)) or ‘late’ (\(d = L\)) life-stages; and \(C\) is the treatment coverage (the proportion of the host population treated at each round), which determines the relative size of each subpopulation and their contribution to transmission. The overall population size is given by \(W_d = CW_{td} + (1 - C)W_{ud}\). Treatment acts to reduce \(W_{td}\) instantaneously by a proportion determined by the drug efficacy (assumed to be 100%). For the generation of figure 5, we use equation (B2) and use \(\Omega_1(W, k)\) or \(\Omega_2(W, k)\).

The full equation used in figure 6, to estimate parasite reinfection when negative density dependence acts upon both ‘mating and/or early’ and ‘late’ life-stages (denoted by suffix \(d = B\)) is

\[
\frac{dW_{cB}}{dt} = \left[ C \Theta\left(W_{TB}, k\right) + (1 - C) \Theta\left(W_{UB}, k\right) \right] K \Omega_1\left(W_{cB}, k\right) - (\mu_w + \mu_H)W_{cB} \tag{B3} \]
where $c_F$ (within $\Theta(W_{cd}, k)$), and $c_M$ (within $\Omega_j(W_{cd}, k)$) are set = 0 or >0 according to the type of hypothetical parasite represented. Solutions were obtained the Berkeley Madonna numerical integration software for Windows, version 8.01 (Macey and Oster 2000) with 4th order Runge-Kutta.
Literature cited


Table 1. Definition and values of parameters and variables used in the model

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition of variables and parameters</th>
<th>Value and units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$W(t)$</td>
<td>mean number of adult worms per host at time $t$</td>
<td>-</td>
</tr>
<tr>
<td>$\Theta(W,k)$</td>
<td>net number of eggs contributed by a given worm burden for a parasite exhibiting density-dependent fecundity ($c_F &gt; 0$)</td>
<td>-</td>
</tr>
<tr>
<td>$\Omega_i(W,k)$</td>
<td>average per worm survivorship in the presence of density-dependent worm mortality; $i$ indicates the survivorship function $S_i(N)$ used; $N$ is the number of parasites (see text)</td>
<td>-</td>
</tr>
<tr>
<td>$k$</td>
<td>overdispersion parameter of the negative binomial</td>
<td>0.1–1.0</td>
</tr>
<tr>
<td>$K$</td>
<td>composite parameter encompassing all density-independent processes in the parasites lifecycle (including rate of fecal excretion)</td>
<td>year$^{-1}$</td>
</tr>
<tr>
<td>$c_F$</td>
<td>severity of density-dependent constraints on worm fecundity</td>
<td>0.01–0.3§ worm$^{-1}$</td>
</tr>
<tr>
<td>$c_M$</td>
<td>severity of density-dependent constraints on worm mortality</td>
<td>0.1¶ worm$^{-1}$</td>
</tr>
<tr>
<td>$\lambda_0$</td>
<td>maximum number of eggs produced per gram of feces per adult female worm for very small $W$ (or when $c_F \to 0$)</td>
<td>3,120§ worm$^{-1}$</td>
</tr>
<tr>
<td>$\mu_W$</td>
<td>per capita death rate of adult worms</td>
<td>0.25† year$^{-1}$</td>
</tr>
<tr>
<td>$\mu_H$</td>
<td>per capita death rate of host</td>
<td>0.02‡ year$^{-1}$</td>
</tr>
</tbody>
</table>

§ From *Ascaris lumbricoides* data presented in Hall and Holland (2000) and estimated by Churcher et al. (2005); nominal value for $c_F = 0.1$ worm$^{-1}$.
¶ This work.
† Equivalent to a life expectancy of 4 years, typical of some parasites of humans as summarized in Anderson and May (1992).
‡ Equivalent to a human life expectancy of 50 years.
Table 2. A summary of the impact of positive (facilitating) and negative (constraining) density dependence on the rate of helminth reinfection following incomplete mass chemotherapy. Examples are included within brackets.

<table>
<thead>
<tr>
<th>Parasite life-stage upon which regulation operates</th>
<th>mating and / or early</th>
<th>late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (facilitating) density dependence</td>
<td>Enhances reinfection</td>
<td>Slows down reinfection</td>
</tr>
<tr>
<td></td>
<td>(mating probability)</td>
<td>(parasite establishment)</td>
</tr>
<tr>
<td>Negative (constraining) density dependence</td>
<td>Slows down reinfection</td>
<td>Enhances reinfection</td>
</tr>
<tr>
<td></td>
<td>(fecundity, mortality of transmission stages)</td>
<td>(mortality of adult parasites)</td>
</tr>
</tbody>
</table>
Figure 1: The location of possible density-dependent mechanisms in the lifecycle of a filarial parasite exemplified by *Onchocerca volvulus*. Density-dependent mechanisms can be categorized as acting upon either ‘mating and/or early’ (dotted line boxes) or ‘late’ (solid line boxes) life-stages. These regulatory processes are conditional on the intensity of infection in either the transmitting (‘mating and/or early’) or the receiving (‘late’) host. Parasite life-stages are shown in italics.
Figure 2: Relationships between the probability of adult worms establishing $S_j(N)$ and the number ($N$) of infective stages administered to the rat host: (A) establishment of *Strongyloides ratti* at 22 days post-infection vs. infective dose. Equation (4) was fitted (solid line) to data (open squares) from Paterson and Viney (2002) with $s_0 = 0.65$ (for $N = 1$) and $c_M = 0.007$ infective larva$^{-1}$; (B) the percentage of *Hymenolepis diminuta* worms recovered 56 days post-infection vs. cysticercoid dose. Equation (5) was fitted (solid line) to data (open squares) from Hesselberg and Andreassen (1975) giving $s_0 = 1$, $\sigma = 2$, and $c_M = 0.089$ cysticercoid$^{-1}$ (note the log scale on the x axis). Graph inserts represent the fitted survivorship functions as the population’s excess worm mortality rate, calculated as $-\log[S(N)]$ (Anderson and May 1978; Bellows 1981). Dividing $-\log[S(N)]$ by the number of worms gives the additional hazard per individual worm (constant for (A) and an increasing function of $N$ for (B)).
Figure 3: The relationship between the effective reproduction ratio of a helminth parasite and the mean worm burden for different severities of density-dependent fecundity ($c_F$). The density-independent stages of the parasite lifecycle, summarized in composite parameter $K$, are adjusted to ensure all hypothetical parasites yield an endemic mean burden of 15 worms per host. Dashed line: $c_F = 0.01$ worm$^{-1}$, $K = 2.43 \times 10^{-4}$ year$^{-1}$ (a); thick solid line: $c_F = 0.1$ worm$^{-1}$, $K = 7.02 \times 10^{-4}$ year$^{-1}$ (b); black dotted line: $c_F = 0.3$ worm$^{-1}$, $K = 1.59 \times 10^{-3}$ year$^{-1}$ (c). Vertical grey dashed lines mark the intensity of infection, $W_{\text{MAX}}$, at which the parasite population will grow at its fastest rate per capita, $R_{e_{\text{MAX}}}$ (horizontal grey dotted lines). Thin solid line corresponds to $R_e = 1$. Note that the effective reproductive ratio crosses the unity line twice; at a lower (breakpoint) density (unstable equilibrium) and at a higher (endemic equilibrium) density. The overdispersion parameter is set at $k = 0.1$. 

$R_{e_{\text{MAX}}} (a)$

$W_{\text{MAX}} (a)$

$R_{e_{\text{MAX}}} (b)$

$W_{\text{MAX}} (b)$

$R_{e_{\text{MAX}}} (c)$

$W_{\text{MAX}} (c)$
Figure 4: The impact of regulatory constraints acting on different parasite life-stages on the rate of parasite reinfection following incomplete mass chemotherapy. The dotted line represents a species down-regulated by processes acting upon ‘mating and/or early’ life-stages (e.g. mortality of transmission stages). The solid thick line represents a species down-regulated by processes operating upon ‘late’ stages of the lifecycle (e.g. adult parasite mortality). Both hypothetical parasites have identical $R_e$ profiles when both the treated and untreated sections of the host population have the same pre-control mean worm burden (see insert). A single treatment is given at year 1 to 80% of the host population. The endemic mean worm burden is 15 worms per host; the severity of the density-dependent constraint, $c_F$ or $c_M = 0.1$ worm$^{-1}$; the density-independent component of the lifecycle, $K = 3.8 \times 10^{-3}$ year$^{-1}$ and overdispersion parameter, $k = 1.0$. 
Figure 5: The impact of two different density-dependent parasite mortality functions on the rate of parasite infection: (A) the two functional forms under investigation, namely, \( S_1(N) \) (dashed line, \( c_M = 0.1 \text{ worm}^{-1} \)) and \( S_2(N) \) (solid line, \( \sigma = 2, c_M = 0.1 \text{ worm}^{-1} \)); (B) the effective survival probability, with dashed line \( \Omega_1(W,k) \) using \( S_1(N) \) and solid line \( \Omega_2(W,k) \) using \( S_2(N) \) with \( k = 1 \); (C), (D) the \( R_e \) profiles for each of the hypothetical parasite types, and (E), (F) the rate of parasite invasion into a naïve host population under different assumptions about density-independent \( K \) (see below) with overdispersion \( k = 1 \). (C) and (E) allow the probability that a parasite will complete the density-independent section of its lifecycle, \( K \), to vary between parasite types so that the endemic intensity is 15 worms per host \( (S_1(N)) \), dashed line, \( K = 1.03 \times 10^{-3} \text{ year}^{-1} \); \( S_2(N) \), solid line, \( K = 3.96 \times 10^{-4} \text{ year}^{-1} \). (E) and (F) illustrate the case when \( K = 3.83 \times 10^{-3} \text{ year}^{-1} \) for both parasites, which differ in their survival function \( S_j(N) \) (lines as above). Parasites invade from an initial mean worm burden of 1 parasite per host.
Figure 6: The synergistic effect of multiple down-regulating mechanisms upon: (A) $R_e$ profiles and (B) the rate of reinfection following chemotherapy (scenario (3)), for parasites regulated entirely by density-dependent fecundity (dotted line, with same functional form as in equation. (4), $c_F = 0.1 \text{ worm}^{-1}, K = 7.02 \times 10^{-4} \text{ year}^{-1}$); entirely regulated by density-dependent mortality (solid line, with $S_2(N)$ as in equation. (5), $c_M = 0.1 \text{ worm}^{-1}, K = 1.43 \times 10^{-3} \text{ year}^{-1}$); or by both fecundity and mortality (dashed line, with functional forms as above, $c_F = c_M = 0.1 \text{ worm}^{-1}, K = 5.78 \times 10^{-3} \text{ year}^{-1}$). Thin solid line represents $R_e = 1$. The transient dynamics of reinfection are investigated for 10 years of annual chemotherapy (the same 80% of the host population is treated each year), with overdispersion $k = 0.1$. 