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# An unlikely partnership: parasites, concomitant immunity and host defence

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Concomitant immunity (CI) against macroparasites describes a state of effective anti-larval immunity coupled with persistent adult infection. Experimental studies indicate that immunologically concealed adult worms might promote anti-larval immunity via the release of cross-reactive antigens, thus creating a barrier against continual infection and restricting burden size within the host. CI offers an important potential benefit to established worms by preventing overcrowding within the host. Thus, CI may be interpreted as akin to vaccination; relatively long-lived adult worms 'vaccinate' their host with larval surface antigens and so benefit from reduced conspecific competition. The shared responsibility for host vaccination among adult worms leads to a problem of collective action. Here, we build on earlier analytical findings about the evolutionary forces that shape cooperation among parasites in order to produce a stochastic simulation model of macroparasite social evolution. First, we theoretically investigate a parasite adaptation hypothesis of CI and demonstrate its plausibility under defined conditions, despite the possibility of evolutionary 'cheats'. Then we derive a set of predictions for testing the hypothesis that CI is partly a host-manipulative parasite adaptation. Evidence in support of this model would present an unusual case of adaptive population regulation.

**Keywords:** schistosomiasis; density-dependent fecundity; host manipulation; cooperation; group behaviour

## 1. INTRODUCTION

Concomitant immunity (CI) is characterized by the ability of a host to mount an effective defence against larval stages whilst being unable to clear a persistent burden of adult worms (Smithers & Terry 1969). From the parasite perspective, the generation of CI may be beneficial as it reduces intraspecific competition within the host. Even if it is beneficial to established parasites, CI may not be a parasite adaptation. It may, alternatively, be an incidental effect of an immunological reaction that is shaped by distinct host and parasite adaptations. Here, we ask if and when CI can be understood as a parasite adaptation and not simply as an incidental effect.

CI has received the most empirical attention in schistosomiasis and, thus, we shall motivate the paper with reference to this disease. The life cycle of schistosomes involves both definite and intermediate hosts. Free-swimming larval stages (cercariae) are produced by the intermediate host (certain aquatic snails) and then penetrate the definitive host (e.g. humans) and pass into the circulation. Passage through the lungs triggers a developmental shift to the schistosomulal stage and a new antigenic surface. Ultimately, mated adult worms relocate to veins that surround the small intestine or the bladder. Eggs, which are the major source of pathology, leave the body via faeces or urine and then, as free-swimming miracidia, they infect new mollusc intermediate hosts.

Smithers & Terry (1967) presented compelling evidence that it is the camouflaged adult worms that are responsible for generating the anti-larval immune response that is integral to schistosome CI. They transferred adult schistosomes (*Schistosoma mansoni*) from infected to uninfected monkeys in a series of surgical transplant experiments and later challenged the recipients with large numbers of cercariae. The recipient monkeys were almost totally resistant to cercarial challenge, despite having no previous experience of larval schistosome stages, yet were unable to reject the implanted adults. Thus, a curious situation is revealed wherein adult worms are exempt from the immune response that they themselves provoke (Smithers & Terry 1969).

Established adult worms constantly excrete and secrete antigens into the blood (both directly via secretory/excretory products and indirectly via products released from migrating eggs), thereby providing a potent stimulus for the immune system. Secretory/excretory products appear to stimulate an effective host response against challenge infection in rhesus monkeys and hamsters (Smithers & Terry 1967), rabbits (Tendler *et al.* 1986) and mice (Cutts & Wilson 1997), thereby providing a plausible immunological basis for CI.

In addition to exposure to the larval antigens released by adults, immunity to the incoming larval stages may accumulate with exposure to larval challenge itself. Larval exposure seems particularly important in rats (Smithers & Terry 1965) and appears to be central to the CI found in lymphatic filariases (Maizels & Lawrence 1991).

Thus, there are two distinct sources of antigen that are acting to strengthen immunity against larval challenge and form the mechanistic basis of CI: larval-triggered and adult-triggered CI. From an evolutionary perspective, the latter is the more enigmatic. Adult-triggered CI

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may be interpreted as akin to vaccination; relatively long-lived adult worms 'vaccinate' their host against subsequent larval challenge and so benefit from reduced conspecific competition.

The vaccination analogy for adult-triggered CI highlights a potential evolutionary trade-off faced by schistosomes. Consider a minimal amount of adult CI operating due to the cross-reactivity of certain excretory products of the adult schistosome with larval antigen. This limited amount of free vaccination may then be enhanced, but at a cost. The vaccine may be delivered amongst the excretory/secretory products of the adult or the egg. The trade-off is between a limited, incidental form of CI ('passive CI') and a stronger, adaptive yet costly form of CI ('adaptive CI'). In other words, passive CI is simply a consequence of adult and larval worm presence, whereas adaptive CI is the product of a specific, evolved adult worm behaviour. Passive CI may be formed by any combination of the larval- or adult-derived mechanisms, whereas adaptive CI would comprise a similar degree of larval-triggered immunity together with increased adult-triggered immunity.

The existence of density-dependent fecundity is crucial to any adaptive theory of CI. Given a crowding effect on egg output, any mechanism acting to limit the adult population per host would in turn increase productivity for established resident worms. Medley & Anderson (1985) fitted a power function linking infrapopulation size to individual fecundity using Cheever's (1968) human autopsy data on *S. mansoni* infections in Brazil. According to the fitted function, an increasing infrapopulation size leads to decreases in individual fecundity, although the rate of decrease is insufficient to cause group fecundity to decline. Autopsy data on *Schistosoma haematobium* infections in Egypt (Cheever *et al*. 1978) are suggestive of an even stronger impact of parasite density on individual fecundity. Here, the mean egg output of heavily infected hosts appeared to be lower than that of hosts with fewer worms. Density-dependent constraints on individual parasite fecundity are assumed to result from the effects of resource competition and/or acquired immune responses to both past and current infection.

Although schistosome CI may form an important aspect of the immunological regulation of worm burdens, immunological regulation (whether innate or acquired) is not the only determining force. Schistosome worms, akin to other organisms dependent on small dispersal stages for their reproductive success (e.g. many intertidal invertebrates and terrestrial plants), are potentially subject to the vagaries of highly stochastic and, hence, potentially limiting recruitment: this is often considered under the banner of 'supply side ecology' (Lewin 1986; Arneberg *et al*. 1998). Here, we investigate a model system that occupies both supply side-limited and supply-saturated dynamics in order to explore the potential interrelation of density dependence, supply side limitation and adaptive population regulation in schistosome worms.

The reasonable assumption of a cost to secretion of additional larval antigen presents a theoretical difficulty in the evolution of adaptive CI. Individual vaccinating worms will pay the cost of antigen secretion, but any benefits will be shared across the adult population within the host. If all members of the group pay the cost, then the group should outperform a group of non-vaccinating individuals. But how can selection ensure that all individuals pay the cost? One cheat benefits from the vaccination cover of its co-inhabitants whilst outperforming them due to its saving on secretion costs.

Brown (1999) analytically addressed the generic problem of cooperation among host-manipulating parasites. In his model, infrapopulation size is a key parameter determining the evolutionarily stable strategy of host manipulation. CI introduces a further complexity as infrapopulation size is determined by the extent of host manipulation on an ecological time-scale, thereby introducing an ecological–evolutionary feedback loop. In order to investigate the effects of this complication, a stochastic simulation model of CI evolution was devised with the aim of generating a predictive model of the extent of adaptive CI in schistosome populations as a function of larval exposure rate, the degree of density-dependent fecundity and the pattern of dispersal.

## 2. A SIMULATION MODEL OF CONCOMITANT IMMUNITY EVOLUTION

### (a) *Ecology of concomitant immunity*

The ecological dimension of the model determines the equilibrium worm burden per host in each generation as a function of the rate of larval exposure $\lambda$ and the antigenic profile of both the challenging larvae and established adult worms of each host. Heterogeneities among the hosts' exposure to cercariae and among the hosts' susceptibility to infection are captured by heterogeneity in the parameter value $\lambda$, with each host experiencing a distinct value $\lambda_h$ that is stochastically drawn from a negative binomial distribution with mean $\lambda$.

Hosts accumulate parasites in each generation until either the rate of larval exposure $\lambda_h$ balances the rate of worm death $b$ or until host exposure to larval antigen (from both adults and larvae) passes a threshold level $v$ (i.e. the 'vaccine' target: exposure to larval antigen in excess of $v$ causes recruitment to stop in the host under consideration). The first scenario is more common when $\lambda_h$ is low, thereby leading to a supply side-limited equilibrium burden $n_h = \lambda_h/b$. The second scenario becomes increasingly common as $\lambda_h$ increases, leading to $n_h$ being limited by the host immune response in a density-dependent manner (at a value below the immigration–death equilibrium of $\lambda_h/b$).

Note that the values of $n$ reflect only a mean equilibrium burden in chronically exposed hosts. Changes in worm burden through the course of the host's exposure to larval challenge are not explicitly modelled. Thus, at sufficiently high forces of infection, the equilibrium burden may be low due to a long history of high exposure to larval antigen. This is not to say that the same host did not suffer high burdens earlier in the course of infection.

In an ecological dimension, the extent of adult-triggered CI is presented as a fixed parameter. In this study, we are interested in understanding the evolutionary dynamics of CI and, thus, we introduce an 'adaptive CI' component of adult CI as an evolutionary variable. The extent of adult and larval CI is quantified using the following parameters: $l$, the constant of larval immunogenicity, quantifies the strength of larval-triggered CI and the combination $a + m$

quantifies the strength of adult-triggered CI, with *a* referring to the passive element and *m* to the adaptive component, which is the evolutionary variable of interest below.

### (b) *Evolution of concomitant immunity*

The ecological dimension of the model dictates the distribution of worms across the host population. The evolutionary dimension of the model is driven by the fitness consequences of being in differing group sizes for individual parasites. Given density-dependent fecundity, parasites in overcrowded hosts will suffer reduced fitness as egg output and/or survival is suppressed. If the consequences of overcrowding are sufficiently severe, it may be in the interests of adult parasites to produce greater amounts of larval antigen (i.e. increase $m$) in order to reduce $n$ and, hence, increase their individual parasite fitnesses.

Given the reasonable assumption of a cost of increasing $m$, the problem of collective action emerges. Individual worms face the cost of contributing to host vaccination, while every member of the infrapopulation feels the benefits, regardless of their cooperative contribution. Adapting Brown's (1999) analytical model, we can construct a fitness function $w$ for adaptive CI in which contributing to host vaccination has a negative fitness impact on the individual and a positive fitness impact on the group (and, hence, indirectly on every individual within the group). Thus, $w$ can be represented as the product of an individual ($I$) and group ($G$) component by

$$w(m, \overline{m}) = I(m)G(n\ \overline{m}). \tag{2.1}$$

Here, $m$ is the adaptive contribution to CI and $w(m, \overline{m})$ is the fitness of an $m$ strategist in a group the average strategy of which is $\overline{m}$. $I(m)$ equals the individual fitness function, which is a declining function of $m$, and $G(n\ \overline{m})$ equals the group fitness function, which is typically a rising function of summed manipulative effort, $n\ \overline{m}$.

As in Brown (1999), the individual fitness function is simply $I(m) = 1 - cm$, where $c$ is the unit cost of larval antigen secretion. The key point of departure from the earlier analytical models arises over the exact nature of the group fitness function $G(n\ \overline{m})$. The relationship between the collective vaccine behaviour of an infrapopulation $n\ \overline{m}$ and the resulting fitness reward to each individual $G(n\ \overline{m})$ consists of two separate steps. In the first step, the individual vaccinating behaviour $m$ of colonizing worms acts to limit the equilibrium infrapopulation size $n$ within each host (see § 2a). The mechanics of this process are detailed below in § 2c. Then, in the second step, the fitness reward to each established worm is determined as a function of its host's infrapopulation size $n$ according to a density-dependent fecundity function based on Medley & Anderson's (1985) empirically derived model. This model links infrapopulation size to individual fecundity $F(n)$ according to the relationship $F(n) = 45.48n^{-0.2887}$. The empirically derived parameter 0.2887 represents a measure of the severity of density dependence and in this study is represented as the key predictive variable $d$.

To summarize, $G(n\ \overline{m})$ can be expressed as $F(n(\overline{m}))$. In other words, the cooperative act (increasing $m$) affects the group size $n$, which in turn has a fitness consequence to each member of the group, as determined by the relationship $F(n) = n^{-d}$. This indirect chain of influence, which reflects the ecological–evolutionary feedback that is centred on the infrapopulation size $n$, makes the analytical techniques introduced in Brown (1999) difficult to apply. Here, instead, we develop a stochastic simulation approach to CI evolution.

### (c) *Simulation structure*

The simulation begins with the creation of a fixed number of hosts, each of which is capable of holding any number of parasites. In each generation, each host in turn accumulates parasites incrementally, thereby allowing the worm burden to be a function of the rate of larval exposure and of the behaviour of the worms already present. When every host has acquired its equilibrium burden $n_h$, the simulation proceeds to the next generation and a new population of naive hosts. The new generation of hosts are infected with the offspring of parasites selected from the previous generation of hosts.

Intermediate hosts are not explicitly modelled, but the dispersal parameter $T$ reflects the extent of mixing during the transmission stages. More specifically, $T$ determines the amount of migration among infrapopulations during infection. Each new parasite is chosen for each host with probability $1-T$ from one specifically chosen host of the previous generation and with probability $T$ from a randomly chosen host.

New parasites inherit the vaccination phenotype ($m$–value) of their parent, with a minority inheriting a different value due to mutation. Selection operates at both the individual and infrapopulation levels. Parasite infrapopulations with greater summed fitness are more likely to contribute to the next generation than less cooperative/overcrowded infrapopulations, with the likelihood of contribution being proportional to the relative summed fitness of the infrapopulation. Conversely, less cooperative individuals are more likely to contribute to the next generation than individuals within the same host who contribute more to immunity manipulation. Here, the likelihood of a contribution of an individual worm is proportionate to its individual fitness relative to other members of the infrapopulation. The conflict between individual (within-host) and group (between-host) interest is thus treated analogously to the analytical models of host manipulation presented in Brown (1999).

## 3. SIMULATION RESULTS

In this section, we begin with an analysis of the invasion dynamics of adaptive CI before then considering the influence of a number of ecological traits on the evolutionary equilibrium of $m$. Finally, we review the empirical predictions that are derived from the simulation results.

### (a) *Invasion dynamics*

Every simulated evolutionary sequence in the following results begins with an ancestral state of non-manipulation $m = 0$. Thus, one can analyse the invasion fate of adaptive CI for a given parameter set by tracing the mean value of $m$ over evolutionary time. Figure 1 illustrates the fate of $m$ (averaged over the population of worms) over 30 000 generations given three different conditions of density

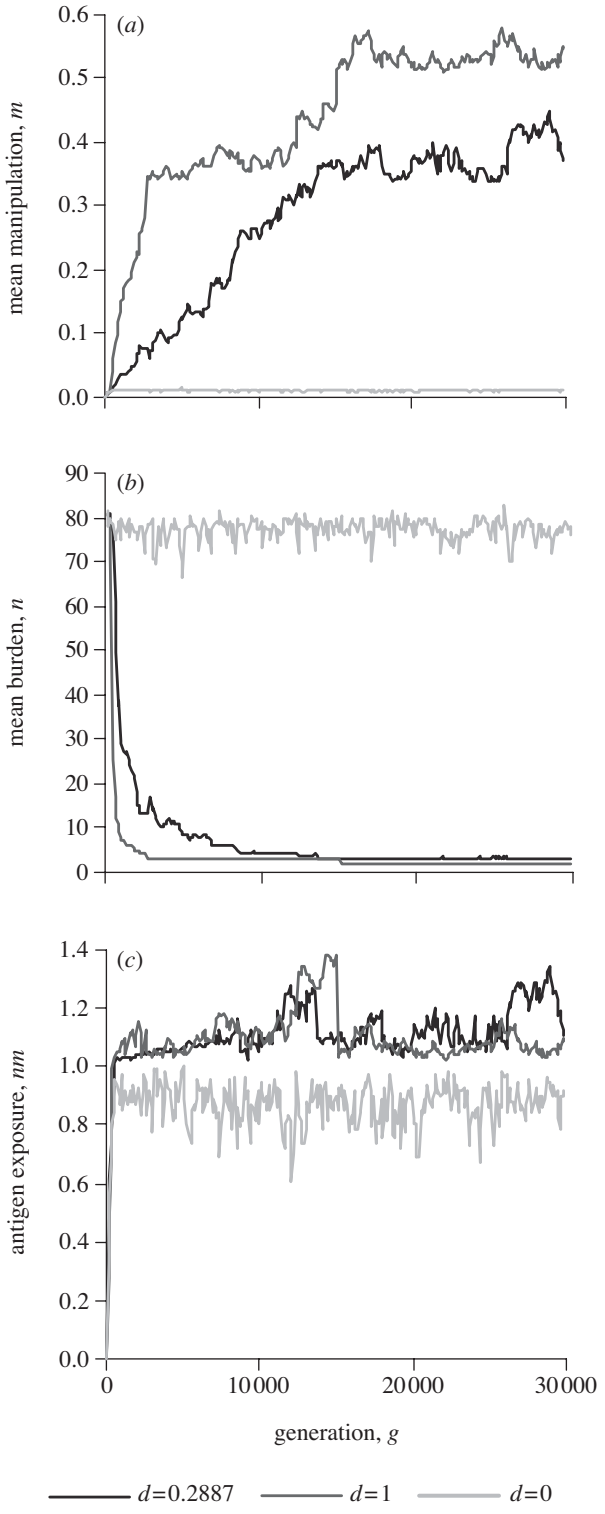


Figure 1. Representative invasion dynamics of adaptive CI under three separate conditions of density dependence ($d=0$, $d=0.2887$ and $d=1$). (*a*) The mean adaptive adult-derived larval antigen $m$, (*b*) the mean chronic worm burden $n$, and (*c*) the mean host exposure to larval antigen $nm$ as a function of the generation number $g$. $\lambda=80$, $T=0.5$, $c=0.01$, $v=1$, $a=l=0$, host number = 100 and mutation rate = mutation distance = 0.01.

dependence $d$. In the absence of density-dependent limitations on fecundity ($d=0$), we see that $m$ is scarcely raised above zero, thereby reflecting the lack of selective benefit to infrapopulation regulation and the cost $c$ of raising $m$. Note that, in the absence of density dependence, $m$ is still marginally greater than zero with the mean value of $m=0.01$ arising due to a mutation–selection balance. We see substantial increases in $m$ over evolutionary time for values of $d$ greater than zero, thereby leading to the establishment of an evolutionary equilibrium at *ca.* 15 000 generations (given the mutation parameters used in this study). The level of this evolutionary equilibrium in turn depends on the strength of the density dependence, with larger values of $d$ being associated with higher average levels of $m$ (see figure 1*a*). Note that values of $m$ in excess of the mutation–selection balance are not inevitable given density-dependent fecundity due to the problem of evolutionary cheats. In particular, raising the dispersal ($T$) and the antigen cost ($c$) promotes cheating, so that cooperative raises in $m$ are undermined (not shown). For a discussion of the role of relatedness (or dispersal) in shaping within-host cooperative strategy see Brown (1999).

Turning to the consequences for the mean infrapopulation size of these three selective conditions ($d=0$, $d=0.2887$ and $d=1$), we see three distinct outcomes (figure 1*b*). When $d=0$, the average infrapopulation size is only minimally depressed below the ancestral condition of 80 (an immigration–death equilibrium with no acquired immunity), thereby reflecting the presence of a minimal level of $m$ (see figure 1*a*). Given a positive value of $d$, the average infrapopulation size rapidly decreases as $m$ increases, up to the establishment of an evolutionary equilibrium after *ca.* 15 000 generations. When $d=0.2887$ the combination of a vaccine target of $v=1$ and an equilibrium value of $m$ of *ca.* 0.35 ensures that three worms are sufficient for effectively immunizing the host against further infection. When $d=1$ the greater equilibrium value of $m$ (*ca.* 0.55) is reflected in a modal equilibrium infrapopulation size of two worms. It is worth reiterating at this point that the values of $n$ quoted above are the mean infrapopulation sizes of chronically infected adult hosts. Thus, a value of $n=2$ does not preclude much higher burdens during the acute phases of infection, nor does it preclude extensive variation around this mean value among chronically infected adults.

Despite taking *ca.* 15 000 generations to reach an evolutionary equilibrium, an ecologically effective level of immuno-manipulation is arrived at much earlier, as illustrated by the rapid arrival (after *ca.* 500 generations) at an infrapopulation production of antigen in excess of $v$ (figure 1*c*). The evolutionary dynamics beyond this point consist of a shift from many parasites vaccinating a little to a few parasites vaccinating a lot, while the total larval antigen production remains near constant throughout at a level marginally greater than $v$.

### (b) *Evolutionary equilibria*

We present further simulation results on the equilibrium properties of $m$ and $n$ as a function of the average cercarial exposure ($\lambda$), density dependence ($d$), passive immunogenicity ($a$ and $l$) and migration ($T$) in electronic Appendix A available on The Royal Society's Publications Web site. These results can be summarized as providing a framework of the constraints within which adaptive evolution for elevated $m$ can operate (see figure 2). As illustrated by figure 1, density-dependent limitations on

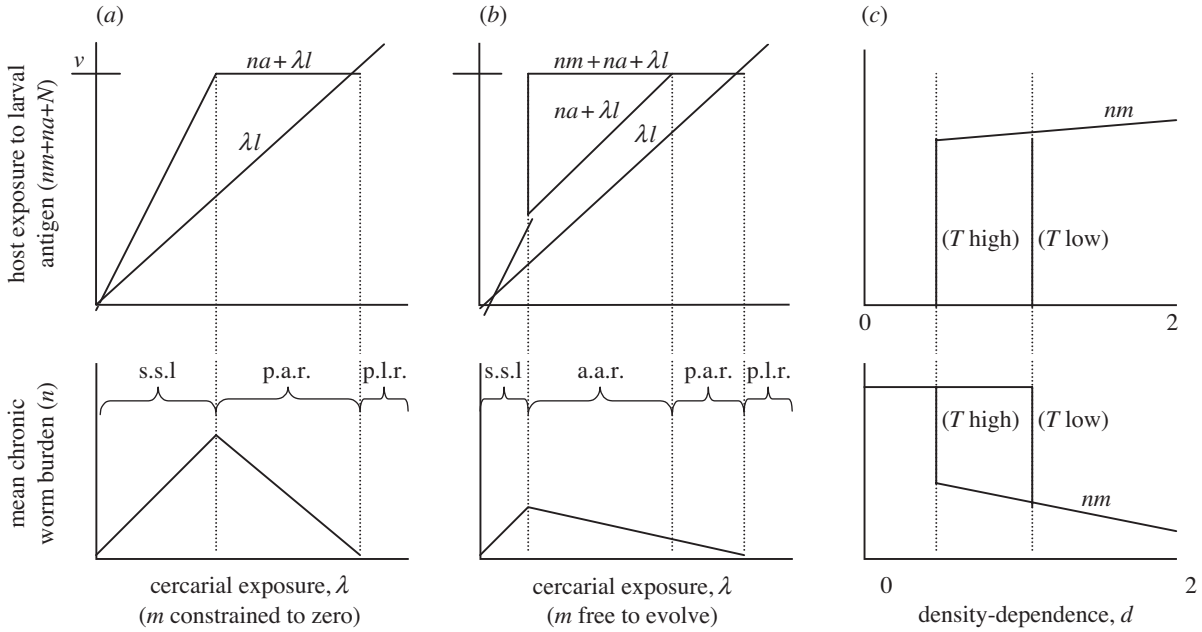


Figure 2. Schematic diagram illustrating host exposure to larval antigen (upper row) and its associated mean chronic worm burden $n$ (lower row), as a function of (*a*) larval exposure $\lambda$ with $m$ constrained to zero, (*b*) larval exposure $\lambda$ with $m$ free to evolve, and (*c*) density dependence $d$. Hosts experience three potential sources of larval antigen: passive larval-derived $\lambda l$, passive adult-derived $na$ and adaptive adult-derived $nm$. Depending on the source and extent of host exposure to larval antigen, four distinct phases of chronic burden limitation are possible: supply side limitation (s.s.l.), passive adult-derived regulation (p.a.r.), adaptive adult-derived regulation (adaptive CI) (a.a.r.) and passive larval-derived regulation (p.l.r.). (*c*) ($T$ low) represents low interhost dispersal of infective stages and ($T$ high) represents high interhost dispersal of infective stages.

fecundity are necessary for increases in adaptive CI. However, they are not in themselves sufficient. For instance, a low $\lambda$-value precludes increases in $m$ due to the dominant role of supply side limitation. Similarly, high levels of passive CI (whether $a$ or $l$) restrict the parameter space in which an elevated $m$ can be favoured (figure 2).

Figure 2*a* illustrates a hypothetical case of host exposure to larval antigen ($nm + na + \lambda l$) and the consequent worm burden ($n$) in the absence of an adaptive evolution of adult-derived larval antigen ($m$ is constrained to zero). The figure illustrates three distinct phases of chronic burden limitation: supply side limitation at low values of $\lambda$ (a total host exposure to larval antigen less than the vaccination threshold $v$), passive adult-derived regulation at intermediate values of $\lambda$ (due to the key contribution of adult worms ($na$) in raising the larval antigen exposure above $v$), and passive larval-derived regulation at high values of $\lambda$ ($\lambda l$ is greater than $v$). In contrast, figure 2*b* illustrates the same schema, but with the additional possibility of an evolved response in the production of adult-derived larval antigen ($m$). Here, we see the introduction of adaptive CI, a fourth distinct phase of burden limitation, which is governed by the adaptive production of adult-derived larval antigen. The surge in $nm$ above a critical level of $\lambda$ leads to a restriction of the supply side limitation region and a consequent drop in the mean chronic worm burden ($n$).

Figure 2*c* schematically illustrates the consequences of changes in the density dependence $d$ and dispersal pattern $T$ on the evolution of $m$. New recruits add to the productivity of the group while reducing the productivity of resident individuals for levels of $d$ between zero and unity. This split between individual and group interests is reflected in the divergent behaviour of strains experiencing strong dispersal (high $T$, i.e. low within-host relatedness) and strains experiencing weak dispersal or high clumping of dispersal stages (low $T$, i.e. high within-host relatedness). If dispersal is high, established worms have little selective 'interest' in the reproductive success of challenge larvae (due to the low likelihood of close parentage) and, thus, are able to vaccinate the host in order to protect their individual productivity, even if $d$ is less than unity. However, if dispersal is low and density dependence is less than unity, newly arrived larvae increase the fitness of established adults by increasing their inclusive fitness. Finally, when density dependence is greater than unity, the conflict between individuals and the group ceases as now all established parasites are selected for limiting recruitment, regardless of the dispersal pattern (figure 2*c*).

### (c) *Predictions*

The signature of adaptive CI is apparent in the changes in $m$ with $\lambda$, $d$ and $T$, as summarized schematically in figure 2 and detailed in electronic Appendix A. Thus, the best hope of testing the adaptive CI hypothesis is to look for differences in the production of specific cross-reactive antigens between foci of infection that are characterized by different levels of these predictive parameters. The null hypothesis of non-adaptive CI predicts that the antigenic content of adult secretory/excretory products will be invariant with respect to these same parameters. The molecular basis of $m$ is clearly restricted by the requirements of larval cross-reactivity.

The existence of adaptive between-lineage differences in $m$ would have both immunological and epidemiological consequences, thereby allowing further tests of the

adaptive CI hypothesis beyond direct examination of differences in parasite phenotype. On an immunological level, the existence of an adaptively raised production of larval antigen by adult worms would lead to an increase in the ratio of anti-larval immunity to anti-egg immunity in infected hosts, thereby allowing a further diagnostic test of the adaptive changes in $m$ outlined in figure 2.

Epidemiological predictions of the adaptive CI hypothesis are more troublesome to generate, as both adaptive and passive models of CI can create qualitatively indistinguishable predictions about the relationship between infrapopulation size and cercarial exposure. The most promising epidemiological test is on foci that have experienced recent changes in $\lambda$ (or other predictive parameters), thereby presenting a natural experiment in CI evolution. Consider a strain ancestrally adapted to a low level of cercarial exposure, thereby leading to a restricted $m$ due to a dominant effect of supply side regulation. If this strain were to experience an increase in the transmission rate, the resulting mean worm burden would be significantly higher than any putative adaptive CI strain occupying a similar ecological condition. A lack of epidemiological difference between newly intensified and historically intense foci of infection would argue against the existence of adaptive CI.

The routine use of human-adapted parasite strains in experimental infections of small animals offers a similar natural experiment. Given the assumption that density-dependent fecundity is more severe in smaller hosts, the adaptive hypothesis predicts that human parasite infections in small mammal hosts will be less tightly immunoregulated (due to a lower $m$) than small mammal specialists in small mammal hosts.

## 4. DISCUSSION

The ecological dimension of this model presents a simple caricature of schistosome biology. The dynamics of worm burdens are reduced to a rapid monotonic approach to an equilibrium value $n_{\mathrm{h}}$ and, hence, the consequences of transient peak burdens are ignored. At the population level, we assume a 'black box' vector function that consistently equals out the supply of cercariae ($\lambda_{\mathrm{h}}$), regardless of the changes in metacercarial output due to changes in CI. The use of an asexual model represents a major simplification, given the dioecious reproductive biology of schistosomes. One consequence of dioecy will be to reduce parasite fitness at very low burden sizes due to the decreased probability of finding a mate (May & Woolhouse 1993). Dioecy may also have more subtle effects on the evolution of adaptive CI. Male schistosomes are generally bigger and more active than females (Basch 1990), which would indicate a higher male mortality rate. Likewise, local mate competition would indicate a female-biased sex ratio (see, for example, West *et al*. 2000). In contrast, male-biased sex ratios predominate, at least for *S. mansoni* in mice (Liberatos 1981). One potential explanation for this sex bias lies in an extension of the adaptive CI model. Adults of one sex may be particularly concerned about larval individuals of the same sex, as they will compete for the same resources: males will compete for females and females will compete for immune-restricted access of eggs to the external environment. If resource competition is stronger among females (due to immune-mediated egg mortality), females may vaccinate more ferociously against females, thus shaping the observed sex bias.

The theory underlying adaptive CI can be placed within the larger framework of adaptive host manipulation, wherein parasites adaptively modify their host's behaviour or physiology in order to promote their persistence and/or transmission (Brown 1999). Although the host manipulation literature has focused on adaptations that promote trophic transmission (see Poulin (2000) and references therein), adaptive CI presents one example among many of potential adaptations that promote macroparasite persistence in the face of the mammalian immune system. Other examples include the production of proteases for neutralizing specific immune components, modulatory products for suppressing or skewing the responsiveness of the immune system and antigens for habituating the host response (see Riffkin *et al*. 1996).

In this paper, we demonstrate the theoretical feasibility of adaptive infrapopulation regulation in macroparasite worms via a mechanism of collective immunomanipulation. The three dimensions of the simulation results give an ecological perspective to three preoccupations in schistosome biomedical research: the relative importance of supply side regulation versus immunoregulation (e.g. Gryseels & De Vlas 1996), the relevance of small mammal models to human infection (e.g. Mclaren & Smithers 1985) and the use of vector control (e.g. Gryseels & De Vlas 1996).

The significance of supply side regulation was investigated through the use of a cercarial exposure parameter, i.e. $\lambda$. The impact of adaptive CI can be seen in a shift away from supply side regulation (contrast figure 2*a*,*b*), as adaptively increasing CI reduces the ratio of parasite vacancies to the supply of cercariae (due to the combination of enhanced host resistance and raised fecundity in the remaining worms).

The density-dependence parameter $d$ introduced an ecological dimension to the assessment of small mammal models of human CI. Experimental lines of human parasite strains are routinely maintained in small mammal hosts for many generations, thereby exerting ecologically distinct selective pressures on the parasite that could potentially select for raised levels of adaptive CI (see figure 1).

Finally, varying the dispersal parameter $T$ indicates that adaptive CI might be sensitive to dispersal ecology, given that the density dependence $d$ lies between zero and unity, in line with human host parameterization (see figure 2*c*). The model indicates that reductions in parasite mixing (for instance due to transmission bottlenecks following imperfect vector control) could lead to a significant reduction in the selective force that maintains adaptive CI, as challenge larvae offer the potential for raising the inclusive fitness of established adult worms.

The testing of the adaptive CI hypothesis will require a careful analysis of interstrain differences in CI, with particular attention paid to the host environment, both recent (i.e. experimental) and historic. For reasons of experimental malleability and ease of strain maintenance, *S. mansoni* in mice has become a near-ubiquitous paradigm of schistosome infection. Here, we join other authors in

calling for a greater diversity of model systems. As Higgins-Opitz & Dettman (1991) noted, interstrain differences, such as the strength of CI, may account for much of the regional variation in morbidity and, hence, are worthy of examination. We argue further that progress in understanding these strain differences can be aided by a careful consideration of their evolutionary and ecological context. In comparison to the complexities of schistosome–host interactions, the current model is a crude simplification. However, it is a first step in synthesizing the ecological and evolutionary dynamics of CI.

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## REFERENCES

Arneberg, P., Skorping, A., Grenfell, B. T. & Read, A. 1998 Host densities as determinants of abundance in parasite communities. *Proc. R. Soc. Lond.* B **265**, 1283–1289.

Basch, P. F. 1990 Why do schistosomes have separate sexes? *Parasitol. Today* **6**, 160–163.

Brown, S. P. 1999 Cooperation and conflict in host-manipulating parasites. *Proc. R. Soc. Lond.* B **266**, 1899–1904.

Cheever, A. W. 1968 A quantitative post-mortem study of *Schistosomiasis mansoni* in man. *Am. J. Trop. Med. Hyg.* **17**, 38–64.

Cheever, A. W., Kamel, I. A., Elwi, A. M., Mosimann, J. E., Danner, K. & Sippel, J. E. 1978 *Schistosoma mansoni* and *Schistosoma haemotobium* infections in Egypt. *Am. J. Trop. Med. Hyg.* **27**, 55–75.

Cutts, L. & Wilson, R. A. 1997 The protein antigens secreted *in vivo* by adult male *Schistosoma mansoni*. *Parasitology* **14**, 245–255.

Gryseels, B. & De Vlas, S. J. 1996 Worm burdens in schistosome infections. *Parasitol. Today* **12**, 115–119.

Higgins-Opitz, S. B. & Dettman, C. D. 1991 The infection characteristics of a South-African isolate of *Schistosoma mansoni*—a comparison with a Puerto-Rican isolate in BALB/c mice and *Mastomys coucha*. *Parasitol. Res.* **77**, 142–151.

Lewin, R. 1986 Supply side ecology. *Science* **234**, 25–27.

Liberatos, J. D. 1981 *Schistosoma mansoni*: male biassed sex ratios in snails and mice. *Exp. Parasitol.* **64**, 165–177.

Maizels, R. M. & Lawrence, R. A. 1991 Immunological tolerance—the key feature in human filariasis. *Parasitol. Today* **7**, 271–276.

May, R. M. & Woolhouse, M. E. J. 1993 Biased sex-ratios and parasite mating probabilities. *Parasitology* **107**, 287–295.

Mclaren, D. J. & Smithers, S. R. 1985 *Schistosoma mansoni*—challenge attrition during the lung phase of migration in vaccinated and serum-protected rats. *Exp. Parasitol.* **60**, 1–9.

Medley, G. & Anderson, R. M. 1985 Density dependent fecundity in *Schistosoma mansoni* infections in man. *Trans. R. Soc. Trop. Med. Hyg.* **79**, 532–534.

Poulin, R. 2000 Manipulation of host behaviour by parasites: a weakening paradigm? *Proc. R. Soc. Lond.* B **267**, 787–792.

Riffkin, M., Seow, H. F., Jackson, D., Brown, L. & Wood, P. 1996 Defence against the immune barage: helminth survival strategies. *Immunol. Cell Biol.* **74**, 564–574.

Smithers, S. R. & Terry, R. J. 1965 The infection of laboratory hosts with cercariae of *Schistosoma mansoni* and the recovery of adult worms. *Parasitology* **55**, 695–700.

Smithers, S. R. & Terry, R. J. 1967 Resistance to experimental infection with *Schistosoma mansoni* in rhesus monkeys induced by the transfer of adult worms. *Trans. R. Soc. Trop. Med. Hyg.* **61**, 517–533.

Smithers, S. R. & Terry, R. J. 1969 Immunity in schistosomiasis. *Ann. NY Acad. Sci.* **160**, 826–840.

Tendler, M., Pinto, R. M., Lima, A. O., Gebara, G. & Katz, N. 1986 *Schistosoma mansoni*—vaccination with adult worm antigens. *Int. J. Parasitol.* **16**, 347–352.

West, S. A., Smith, T. G. & Read, A. F. 2000 Sex allocation and population structure in apicomplexan (protozoa) parasites. *Proc. R. Soc. Lond.* B **267**, 257–263.

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