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DETERMINING THE OPTIMAL DEVELOPMENTAL ROUTE OF *STRONGYLOIDES RATTI*: AN EVOLUTIONARILY STABLE STRATEGY APPROACH

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Abstract.—Understanding the processes that drive parasite evolution is crucial to the development of management programs that sustain long-term, effective control of infectious disease in the face of parasite adaptation. Here we present a novel evolutionarily stable strategy (ESS) model of the developmental decisions of a nematode parasite, *Strongyloides ratti*. The genus *Strongyloides* exhibits an unusual developmental plasticity such that progeny from an individual may either develop via a direct (homogonic) route, where the developing larvae are infective to new hosts, or an indirect (heterogonic) route, where the larvae develop into free-living, dioecious adults that undergo at least one bout of sexual reproduction outside the host, before producing offspring that develop into infective larvae. The model correctly predicts a number of observed features of the parasite's behavior and shows that this plasticity may be adaptive such that pure homogonic development, pure heterogonic development, or a mixed strategy may be optimal depending on the prevailing environmental conditions, both within and outside the host. Importantly, our results depend only on the benefits of an extra round of reproduction in the environment external to the host and not on benefits to sexual reproduction through the purging of deleterious mutation or the generation of novel, favorable genotypes. The ESS framework presented here provides a powerful, general approach to predict how macroparasites, the agents of many of the world's most important infectious diseases, will evolve in response to the various selection pressures imposed by different control regimes in the future.

Key words.—Developmental plasticity, evolutionarily stable strategy model, parasite evolution, sexual reproduction, strain polymorphism.

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Parasitic nematodes are widespread and highly successful parasites, infecting up to one-third of the human population and causing persistent and debilitating infections, especially in the developing world (Anderson and May 1992). More generally, virtually all higher metazoans can be infected by parasitic nematodes and, for this reason, nematode infection is an important feature of the biotic environment of most organisms. A major factor in their success is that parasitic nematodes are remarkably flexible in their life histories, being able to adapt rapidly to changing environments, both within and outside their hosts.

To date, much of the work on parasite life-history traits has focused on parasite virulence, due to its obvious implications for host health. A large number of theoretical models have been developed that have identified a range of mechanisms that may lead to the evolution of higher or lower parasite virulence (May and Anderson 1983; Nowak and May 1994; Frank 1996; Gandon et al. 2001; Boots and Sasaki 2003). However, parasite life cycles comprise a variety of life-history traits, each one crucial to the persistence of the parasite, and each one subject to natural selection. Therefore, it is essential to consider how other aspects of a parasite's life cycle will evolve if we are to predict how parasites may respond to the changing selection regimes imposed by future control strategies. One aspect of parasites' life cycles that has received surprisingly little detailed theoretical interest is the reproductive strategy. Clearly this is central to the ability of a parasite to persist and so may be expected to be under considerable selection pressure. Here we consider one group of parasitic nematodes that exhibit an unusual plasticity in the development of their larvae and ask whether this developmental plasticity is of adaptive significance to maximize the probability of transmission between hosts.

Strongyloides species are parasitic nematodes that infect a range of species, including humans (Grove 1989). The basic life cycle of *Strongyloides* is shown in Figure 1. The parasitic form is female only and reproduces by mitotic parthenogenesis (Viney 1994), passing eggs into the external environment. These eggs can then develop by one of two routes. In the direct, homogonic route, eggs develop through two larval molts into infective third stage larvae (iL3s). In the indirect, heterogonic route, eggs develop through four larval molts into free-living adult males and females. These free-living adults mate and produce eggs by conventional sexual reproduction, which ultimately develop into iL3s as for homogonic development (Viney et al. 1993). The production of free-living adults is potentially advantageous because it allows the final number of infective larvae to be increased. Furthermore, there may be additional advantages to sexual reproduction in parasites, which have been postulated to include avoiding strain-specific host immune responses (Read and Viney 1996; Gemmill et al. 1997). Set against this, however, is the increased development time required to produce the heterogonic infective larvae and the increased potential for mortality during the extra developmental stages. Switching between homogonic, heterogonic, or mixed development may therefore be advantageous to maximize transmission potential in response to prevailing environmental conditions.

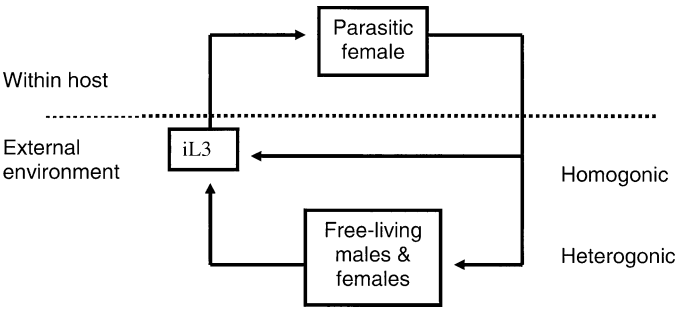

FIG. 1. *Strongyloides* spp. life cycle. iL3 are the infective, third stage larvae.

Most *Strongyloides* species retain both the homogonic and heterogonic routes of development and the control of the switch between these routes has been particularly well studied in *S. ratti*, a natural parasite of rats (Dawkins 1989). Different geographic isolates of *S. ratti* have been observed to vary in their propensity for development by one or other developmental route (Viney et al. 1992); the proportion developing by either route can be altered through selection, indicating a genetic component to the switch between alternate modes of development (Viney 1996). Furthermore, the favored developmental route has also been shown to be affected by environmental conditions, both within the host, where an anti-*Strongyloides* immune response results in a greater propensity for heterogonic development (Gemmill et al. 1997; Harvey et al. 2000), and external to the host, where heterogonic development tends to be favored at higher ambient temperatures (Viney 1996; Harvey et al. 2000).

Two obvious questions arise: Why is variation in life-cycle development maintained in *Strongyloides* species? What, if any, is the adaptive significance of preferential development by one or other route in response to the environment? To answer these questions, we developed a model of the *S. ratti* life cycle and determined how different environmental pressures influence the evolutionarily stable strategy (ESS) of the parasite in terms of the optimal route of development. We begin by describing a simple model from which we obtain an expression for the basic reproductive ratio (R_0) of the parasite, a relative measure of a parasite's fitness, enabling us to highlight which life-history parameters are important in determining the optimal route of development. We then parameterize the model using data from the literature and laboratory experiments and predict which developmental route we would expect the parasite to adopt. Finally, we develop a novel ESS model, which takes into account interactions between parasite strains, and obtain simple criteria defining regions of parameter space where either pure homogonic development, pure heterogonic development, or mixed strategies would be expected.

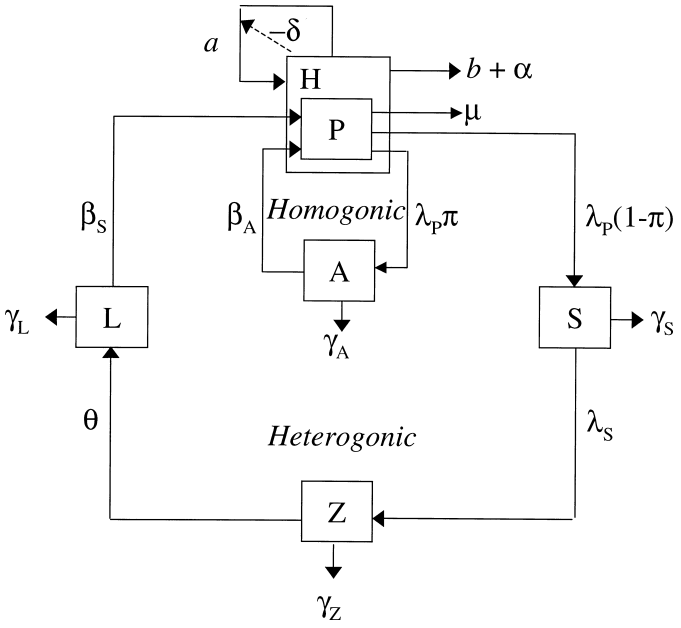

FIG. 2. Schematic diagram of the simple *Strongyloides ratti* model.

MODELING THE *STRONGYLOIDES RATTI* LIFE CYCLE

Model Structure

As described more fully in Appendix 1, we describe the *S. ratti* life cycle by modifying the simple host-macroparasite models of Anderson and May (1978). Hosts (H) are assumed to reproduce at a density-independent rate *a* and die at rate *b*. Adult parasites (P) are distributed among hosts according to a negative binomial distribution with parameter *k* and impose a cost, *c*, on the host by either increasing host mortality at rate α or decreasing host fecundity at rate δ ($c = \alpha + \delta$). For simplicity, it is assumed there are no density-dependent constraints acting on the parasitic females as might occur, for instance, through the action of host immunity. Hence, in the model, adult parasites die at a constant rate μ and produce eggs at a constant rate λ_P, of which a fraction, π, develop by the homogonic route and $(1 - \pi)$ develop by the heterogonic route. The homogonic larvae (denoted A for ''asexual'') either die at rate γ_A or infect at rate β_A. The heterogonic larvae become sexual adults (S), which either die at rate γ_S or produce eggs (Z) at rate λ_S. These eggs either die at rate γ_Z or mature into infective, iL3 larvae (L) at rate θ. Finally, these infective larvae either die at rate γ_L or infect hosts at rate β_S to produce parasitic adult females. The presence of the category Z in the model provides a maturation delay so that the heterogonic route takes $1/\theta$ time units longer than homogonic development; it should be noted that the precise location of this maturation class in the life cycle (i.e., either before or after the sexual adult stage) does not affect the following results. The full model is shown schematically in Figure 2 and all parameters are listed in Table 1.

What Is the Optimal Homogonic Proportion (π_{OPT})?

By describing the complete life cycle in terms of a population model, it is possible to derive an expression for the basic reproductive ratio of a parasite adopting either a pure homogonic strategy ($R_{0,HOM}$), a pure heterogonic strategy ($R_{0,HET}$), or a mixed one ($R_{0,MIXED}$):

TABLE 1. Parameters in the model and estimated values.

Parameter	Comments	Estimate (± SE)
Within-host adult parasite mortality (μ)	nude rats	0.004 day^{-1}
	normal rats	0.210 day^{-1}
Homogonic iL3 mortality (γ_A)	19°C	0.123 ($\pm$0.015) day^{-1}
	25°C	0.173 ($\pm$0.015) day^{-1}
Heterogonic iL3 mortality (γ_L)	19°C	0.172 ($\pm$0.015) day^{-1}
	25°C	0.222 ($\pm$0.015) day^{-1}
Free-living female mortality (γ_S)	19°C	0.282 ($\pm$0.020) day^{-1}
	25°C	0.386 ($\pm$0.018) day^{-1}
Mortality of the pre-iL3, heterogonic stages (γ_Z)		—
Sex ratio of heterogonic adults (M:F)	19°C	1:1
	25°C	1:2
Daily per capita homogonic parasite fecundity ($\lambda_{P,A}$)	includes mortality from egg to iL3	56.5 ($\pm$5.2) day^{-1}
Daily per capita heterogonic parasite fecundity ($\lambda_{P,S}$)	includes mortality from egg to free-living adult	$\lambda_{P,A}$/3.8 ($\pm$0.34)
Per capita lifetime fecundity of heterogonic free-living females	19°C	16 ($\pm$3) eggs
	25°C	34 ($\pm$5) eggs
Daily per capita fecundity of heterogonic free-living females (λ_S)	19°C	0.89 day^{-1}
	25°C	5.67 day^{-1}
Homogonic iL3 transmission (β_A)		—
Heterogonic iL3 transmission (β_S)		—
Parasite-induced host mortality (α)		—
Parasite-induced reduction in host fecundity (δ)		—
Total impact of parasites on host (c)	$\alpha + \delta$	—
Total loss rate of parasitic adults (Γ)	$b + \alpha + \mu$	—
Negative binomial aggregation parameter (k)		0.47
Host reproductive rate (a)		—
Background host mortality rate (b)		—

$$R_{0,HOM} = \frac{\beta_A \lambda_P H}{\Gamma(\gamma_A + \beta_A H)}, \quad (1)$$

$$R_{0,HET} = \frac{\beta_S \lambda_P \lambda_S \theta H}{\Gamma \gamma_S (\gamma_Z + \theta)(\gamma_L + \beta_S H)}, \quad \text{and} \quad (2)$$

$$R_{0,MIXED} = \frac{\beta_A \lambda_P H \pi}{\Gamma(\gamma_A + \beta_A H)} + \frac{\beta_S \lambda_P \lambda_S \theta H (1 - \pi)}{\Gamma \gamma_S (\gamma_Z + \theta)(\gamma_L + \beta_S H)}, \quad (3)$$

where Γ is the total loss rate of the adult parasites ($= b + \alpha + \mu$). These reproductive ratios can be thought of as expressions of the relative fitness of the parasite and so any life-history parameters that increase R_0 will tend to increase fitness and so should be selected for. Hence, from these expressions we can gain some insight into the evolution of each life-history parameter and which strategy we would expect to win out over evolutionary time.

Importantly, the basic reproductive ratio of a parasite playing a mixed strategy ($R_{0,MIXED}$) is simply the sum of the reproductive ratios of parasites playing each pure strategy, weighted by the relative investment in each route (measured by π). From this, the optimal proportion of eggs developing via the homogonic route (π_{OPT}) is the value of π that maximizes $R_{0,MIXED}$. Differentiating $R_{0,MIXED}$ with respect to π, setting equal to zero and solving for π, reveals that π_{OPT} is either one or zero (i.e., a pure strategy), depending on whether $R_{0,HOM} > R_{0,HET}$. Under the conditions of the model, it is never possible for a mixed-strategy parasite to have a basic reproductive ratio greater than both pure strategy parasites.

To illustrate how the different life-history parameters combine to determine which developmental route is ultimately favored, we consider the relative benefit of a strain playing a pure homogonic strategy compared to a strain playing a pure heterogonic strategy. Allowing for the possibility that parasites that develop via the two routes may differ in their reproductive outputs and their within-host survival, the relative benefit of pure homogonic development is given by the expression:

$$\frac{R_{0,HOM}}{R_{0,HET}} = \frac{\beta_A}{\beta_S} \cdot \frac{\lambda_{P,A}}{\lambda_S \cdot \lambda_{P,S}} \cdot \frac{\Gamma_S}{\Gamma_A} \frac{\gamma_S(\gamma_L + \beta_S H)}{\gamma_A + \beta_A H)} \left(\frac{\gamma_Z}{\theta} + 1 \right), \quad (4)$$

where $\lambda_{P,A}$ is the daily fecundity of parasites developing via the homogonic route, $\lambda_{P,S}$ is the fecundity of heterogonic parasites, $\Gamma_A = b + \mu_A + \alpha$ is the net within-host loss rate of parasites developing via the homogonic route, and $\Gamma_S = b + \mu_S + \alpha$ is the net within-host loss rate of parasites developing via the heterogonic route. If the above expression is greater than one, homogonic development is favored, if it is less than one, heterogonic development is favored. Hence, it can be seen that the ultimate outcome of evolution can be considered in terms of parameter combinations, matching like for like between the two developmental routes; if, for instance, heterogonic iL3s have relatively high infectivity ($\beta_S > \beta_A$) or if heterogonic parasites have low within-host mortality rates (μ_S and therefore Γ_S are relatively low), or if the extra reproduction due to the free-living adults (λ_S) is sufficiently high, then heterogonic development will be favored.

PARAMETER ESTIMATION

Basic life-history parameters were estimated either using published values, from reanalysis of existing (published or unpublished) data or from experiments specific to this work and are summarized in Table 1. We concentrated on obtaining

parameter estimates for isofemale lines ED321 (= ED5 in Viney et al. 1992) and ED248, both of which exhibit substantial levels of heterogonic development (Viney et al. 1992; Viney 1996; Gemmill et al. 1997).

Strongyloides ratti Mortality Parameters

Laboratory experiments carried out on isofemale line ED248 (see Supplementary Material 1 available online at http://dx.doi.org/10.1554/03-550.1.s1) produced parameter estimates for the mean temperature-dependent mortality rates of iL3s developing via the homogonic route (γ_A) or heterogonic route (γ_L) of: γ_A, 19°C = 0.123 day^{-1}; γ_A, 25°C = 0.173 day^{-1}; γ_L, 19°C = 0.172 day^{-1}; and γ_L, 25°C = 0.222 day^{-1}.

Analysis of unpublished data (M. P. Gardner, D. Gems, and M. E. Viney, pers. comm.) of infections in both immunologically normal rats and in immunologically deficient (and *S. ratti* susceptible) nude rats by both direct and indirect sampling (Gemmill et al. 1997; Harvey et al. 2000), produced estimates for mean adult parasite mortality of μ_{NUDE} = 0.0036 day^{-1} and μ_{NORMAL} = 0.21 day^{-1}. Analysis of unpublished data (see online Supplementary Material 1) provided estimates for the mean daily mortality rate of the free-living females (γ_S) of 0.282 day^{-1} at 19°C and 0.386 day^{-1} at 25°C.

Strongyloides ratti Reproductive Parameters

Analysis of unpublished data on line ED321 provided daily per capita fecundity estimates for the adult female parasites ($\lambda_{P,A}$) of approximately 56 eggs female^{-1} day^{-1} in nude rats. Reanalysis of data from Paterson and Viney (2003) on line ED248 suggest that there is an increased cost to producing heterogonic eggs relative to homogonic eggs and this cost appears to manifest itself in terms of the number of eggs produced, such that it is approximately 3.8 times more costly to produce heterogonic eggs than homogonic eggs (see online Supplementary Material 1). Hence, we assume $\lambda_{P,S} = \lambda_{P,A}/3.8$. These estimates account for development from egg to either free-living adult or homogonic iL3 and so include mortality of all the early developmental larvae.

Analysis of unpublished data on line ED321 (see online Supplementary Material 1) estimated the total fecundity of the free-living females to be around 16 eggs female^{-1} at 19°C and 34 eggs female^{-1} at 25°C. Hence, the daily rate of production per female is this number divided by the mean longevity of the free-living females ($1/\gamma_S$) at the appropriate temperature. However, this value has to be adjusted to take into account the fact that not all heterogonic adults are female. Data from Harvey et al. (2000) suggest that of those worms that develop by the heterogonic route, the male:female adult sex ratio varies from approximately 1:1 to 1:2 depending on the temperature (with more females produced at higher temperatures). Therefore, at 19°C, the sex ratio is approximately 1:1 and so the daily per capita fecundity of the free-living females in the model is $16 \times 0.111 \times 0.5 = 0.89$ eggs day^{-1} and at 25°C, the sex ratio is approximately 1:2 and so the daily per capita fecundity is $34 \times 0.25 \times 0.67 = 5.67$ eggs day^{-1}.

Other Parameters

Data presented by Harvey et al. (1999) provide an average degree of aggregation of $k = 0.47$. Furthermore, it is observed that the duration of heterogonic development takes approximately 4 days longer than homogonic development at 19°C, and so $\theta_{19} = 0.25$. At 25°C, heterogonic development takes only 3 days longer than homogonic development and so $\theta_{25} = 0.33$. At this stage it is not possible to estimate any of the other parameters in the model. Importantly, we have no information on the transmission rate of the iL3s and, crucially, we do not know if it differs for iL3s that have developed via the homogonic route compared to the heterogonic route. Transmission rates are typically the most difficult parameters to estimate for any host-parasite model. Ideally, to do this, susceptible rats would be released into a natural arena seeded with a known number of iL3s and, after a fixed period of time, the rats would be recaptured and the number of infecting nematodes counted. Such intensive field trials have yet to be conducted for *S. ratti*, and laboratory-based estimates cannot be obtained because iL3s are typically injected into rats, which clearly does not provide a means of estimating transmission potential in natural infections.

Which Developmental Strategy Has the Greatest R_0?

Assuming natural selection acts to maximize the basic reproductive ratio, the above parameter values (with arbitrary values for the unknown parameters, and assuming $\beta_A = \beta_S$) produces estimates of: $R_{0,HOM} = 79$ and $R_{0,HET} = 166$ at 19°C and $R_{0,HOM} = 79$ and $R_{0,HET} = 221$ at 25°C.

This model therefore predicts that these *S. ratti* lines should always develop via the heterogonic route. Furthermore, the model predicts that increasing ambient temperatures favors heterogonic development; at 19°C heterogonic development has an approximately two-fold advantage over homogonic development, whereas at 25°C this advantage increases to nearly three-fold. While these predictions broadly capture the pattern seen for *S. ratti*, in that heterogonic development is increasingly favored as temperature increases (Harvey et al. 2000), they do not suggest that polymorphism is possible. This maximize-R_0 approach only predicts that one or other strategy (heterogonic development under these conditions) should outcompete the other, but not the conditions under which mixed developmental strategies should be maintained. Therefore, to understand the adaptive nature of the observed variations in developmental strategies (Viney et al. 1992), a more sophisticated modeling approach is required.

An Evolutionarily Stable Strategy Model of *Strongyloides ratti*

Model Structure

The maximize-R_0 analysis described above is the traditional method for assessing the evolution of macroparasite life-history strategies (Dobson and Merelender 1991; Morand and Poulin 2000). However, it makes a number of limiting assumptions, ignoring any possible interactions between parasites, leading to an incomplete picture of life-history evolution. Here we develop a more rigorous ESS approach. For this model, it is assumed that there is a resident parasite strain

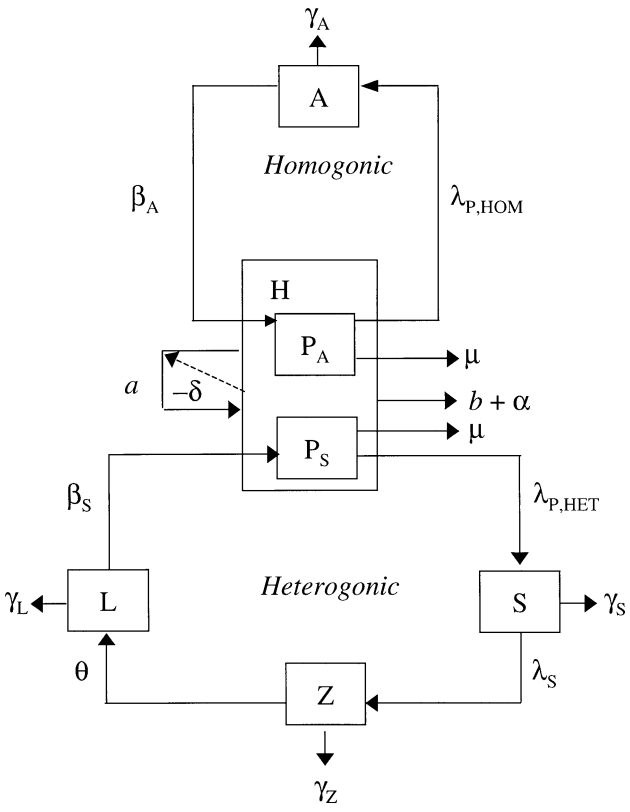

FIG. 3. Schematic diagram of the evolutionarily stable strategy *Strongyloides ratti* model.

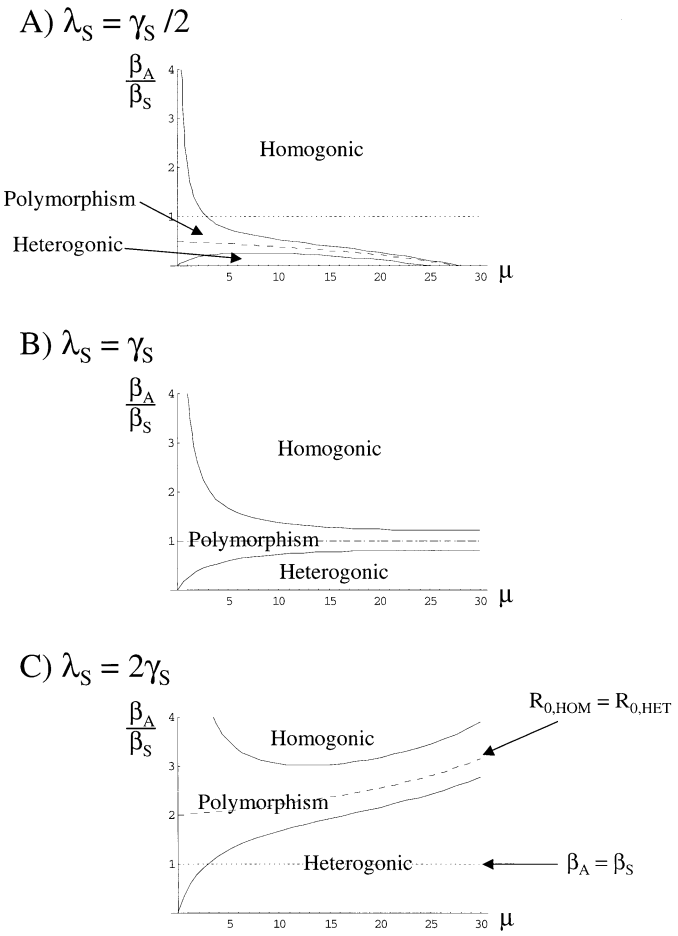

FIG. 4. Relative homogonic transmission rate (β_A/β_S) − μ parameter space for the evolutionarily stable strategy model for different values of daily free-living female fecundity (λ_S), showing regions of either pure heterogonic or pure homogonic development and strain polymorphism. The dotted horizontal line represents where the heterogonic and homogonic transmission rates are equal and the dashed nonlinear curve is the line $R_{0,HOM} = R_{0,HET}$.

playing a pure homogonic strategy and this strain is at endemic equilibrium with the host population. We then assume a mutation occurs, leading to the existence of a mutant, heterogonic strain. We are then interested in whether this mutant strain can invade (and replace) the resident strain and whether it can itself become resident. We then reverse the roles of the two strains and see under what conditions the homogonic strain can invade the heterogonic one. A strain that is resistant to invasion is said to be evolutionarily stable and represents an end point of evolution, whereas if both strains are mutually invasible, strain polymorphism is possible.

The full ESS model (see Fig. 3 and Appendix 2) comprises seven variables, representing the host population (H), the homogonic strain adult parasites (P_A), the heterogonic strain adult parasites (P_S), the homogonic iL3s (A), the free-living, heterogonic adults (S), heterogonic eggs (Z), and the heterogonic iL3s (L). We can make a number of assumptions about the covariance in distributions of the adult parasites within the host and the timing of the maturation stage in the heterogonic life cycle, but these make little difference to the predictions of the model.

Results of the Evolutionarily Stable Strategy Model

General behavior

Because we do not have reliable estimates for all parameters in the model, we initially use arbitrary parameter values to explore the general behavior of the model and to determine which parameters the model is most sensitive to. In the next section, we will consider the specific predictions using the estimated values for isofemale lines ED321 and ED248.

Analysis of the model (see Supplementary Material 2 available online at http://dx.doi.org/10.1554/03-550.1.s1) reveals that evolution does not simply act to maximize R_0 and that some degree of strain polymorphism is possible, indicating that mixed strategies may be viable. This is illustrated in Figure 4 (again, using arbitrary parameter values), where the dashed line represents the line of equal R_0 values. The previous maximize-R_0 analysis would suggest that anything lying above this line would be purely homogonic and anything below the line would be purely heterogonic. However, the ESS analysis reveals there may be a substantial region around this line where both strains can coexist.

The model allows us to explore which parameters are important in influencing which developmental route is favored by evolution. In general, the outcome of evolution depends on the balance of parameters in a manner similar to that seen in the maximize-R_0 analysis described above; if those parameters that increase $R_{0,HOM}$ are greater than the corre-

sponding parameters for heterogonic development (e.g., if $\beta_A > \beta_S$) then homogonic development will tend to be favored (Fig. 4). Importantly, note that the absolute value of each transmission parameter is irrelevant; the model's predictions only depend on the magnitude of their relative values (e.g., β_A/β_S).

While the influence of the development route–specific parameters (i.e., β_A vs. β_S, $\lambda_{P,A}$ vs. $\lambda_{P,S}$, etc.) is fairly intuitive, the role of adult parasite mortality rate, μ, is less so. It has previously been found that heterogonic development tends to be favored when host immunity is high (Gemmill et al. 1997), and it has been hypothesized this may be because the genetic exchange that occurs during sexual reproduction enables the parasite to overcome specific immune responses. Although the model does not include explicit host immunity, the rate of within-host mortality of the adult parasites can be thought of as a surrogate for host immunity; at high levels of μ there is considerable parasite mortality, implying a highly immune host population, and at low levels of μ there is low parasite mortality, implying a highly susceptible host population.

The model predicts that the influence of μ depends crucially on the relative rates of mortality and fecundity of the free-living females (γ_S and λ_S, respectively). If the fecundity of the free-living females (λ_S) is lower than their mortality rate (γ_S), as the environment in the host becomes increasingly harsh (increasing μ), homogonic development becomes increasingly preferable (Fig. 4A). When mortality and fecundity of the free-living females are equal, the optimal developmental route is less sensitive to the degree of parasite mortality within the host and is primarily determined by the transmission rates of the iL3s; if $\beta_S > \beta_A$, then heterogonic development is favored, if $\beta_S < \beta_A$, then homogonic development is favored (Fig. 4B). However, if, as is likely to be the case, the fecundity of the free-living females is greater than their mortality rate, increasing μ leads to heterogonic development being favored, even if $\beta_A > \beta_S$ (Fig. 4C). Assuming within-host parasite mortality in the model does reflect the degree of immunity in the host, this prediction of increasing heterogonic development with increasing μ matches previous empirical observations (Gemmill et al. 1997; Harvey et al. 2000). It should be emphasized that this result is obtained without the need to invoke recombination as a benefit of sex.

As might be expected, the host-specific parameters (host reproductive rate, *a*, or mortality rate, *b*) and also the impact the parasites have on the host (either through increased host mortality, α, or decreased host fecundity, δ) or the degree of aggregation within the host population (as measured by *k*) have no effect on whether heterogonic or homogonic development is favored (Fig. 5). Furthermore, the impact the parasite has on its host (whether it be through increased host mortality, α, or a reduction in host fecundity, δ) also has little effect on the region of strain polymorphism (Fig. 5A, B). However, both the degree of aggregation of the parasites and the reproductive rate of the host have a substantial impact on the region of strain polymorphism (Fig. 5C, D), such that highly aggregated parasites, or those infecting highly fecund hosts, are more likely to show highly mixed strategies. Increased aggregation allows parasites to infect subsets of the host population, reducing the opportunity for direct competition between sexual and asexual strains. Similarly, highly fecund hosts means more hosts are available for infection and the two parasite strains are less likely to occur together in the same host individual. Hence, at the population level, strain coexistence (polymorphism) is more likely.

Specific predictions for Strongyloides ratti

Using the parameter value estimates described earlier, it can be seen that the outcome of evolution is very sensitive to the relative transmission rates, for which we have no estimates (Fig. 6). If the transmission rate of the heterogonic iL3s is the same as the transmission rate of the homogonic iL3s ($\beta_A = \beta_S$), the current estimate of the adult parasite mortality in immunologically compromised (nude) rats ($\mu = 0.0036$ day^{-1}) indicates that at 19°C, strain polymorphism is possible, such that mixed populations of both homogonic and heterogonic development should be found (as marked by 1 in Fig. 6A). However, as adult parasite mortality within the host increases (which may be a proxy for increasing host immunity), homogonic development become increasingly less favored until at the value observed for immunologically normal rats ($\mu = 0.21$ day^{-1}, marked by 2 in Fig. 6A), pure heterogonic development is favored. Therefore, *S. ratti* from host populations with high levels of immunity would be expected to develop predominantly by the heterogonic route. Similar arguments can be applied to development at the individual level; if adult parasite mortality in the model is a proxy for host immunity, it is possible that μ will increase throughout the duration of infection, as the increased exposure to parasites will lead to an increase in the host immune response. Therefore, from Figure 6A we would predict that the proportion of eggs that develop via the heterogonic route should increase throughout the duration of infection, as is empirically observed (Viney et al. 1992; Viney 1996; Gemmill et al. 1997).

Finally, given the observed temperature dependence of the mortality rates (Table 1), it is possible to predict how the optimal strategy depends on environmental conditions. At 25°C (Fig. 6B), the region of parameter space where heterogonic development is favored is much larger than that at 19°C (Fig. 6A) and, assuming that the transmission rates of heterogonic and homogonic derived infective larvae are equivalent, it appears that at no level of adult parasite mortality is anything other than pure heterogonic development predicted. Therefore, the model predicts increased ambient temperatures will substantially increase the likelihood of heterogonic development, as is found with empirical observations (Viney 1996; Harvey et al. 2000).

It is difficult to draw any firm conclusions about the degree of strain polymorphism since, as described above, this is highly dependent on the host-specific parameters. However, using arbitrary values for these remaining parameters, it is possible to construct Figure 7, which shows the expected proportion of the population developing by the heterogonic route. The flat planes of this figure at 0 and 1 represent regions of parameter space where a pure developmental route (homogonic or heterogonic, respectively) is an ESS, whereas the incline represents the region where different degrees of poly-

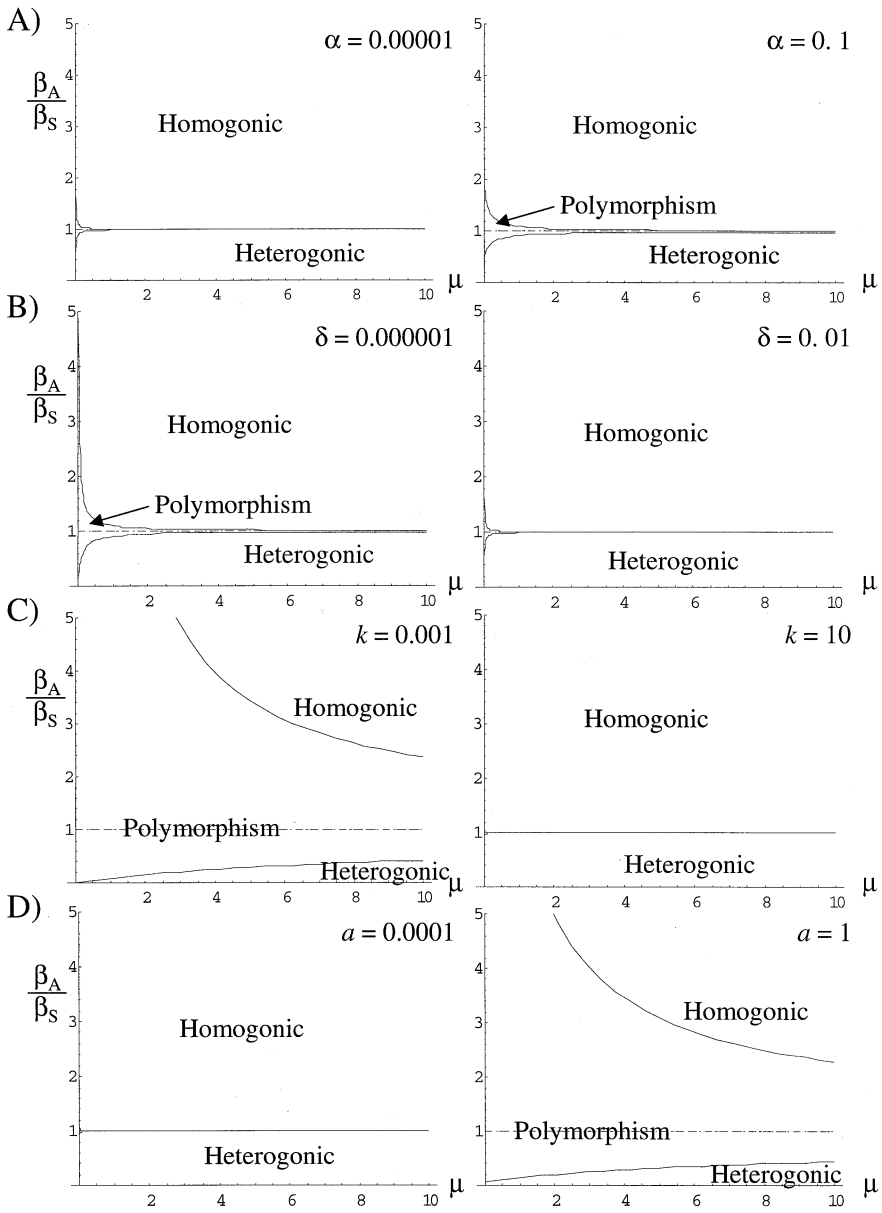

FIG. 5. $(\beta_A/\beta_S) - \mu$ parameter space for the evolutionarily stable strategy model for different values of (A) parasite-induced host mortality, α; (B) parasite-induced reduction of host fecundity, δ; (C) coefficient of aggregation, k; and (D) host reproductive rate, a, showing regions of either pure heterogonic or pure homogonic development and strain polymorphism. The dashed horizontal line represents where the heterogonic and homogonic transmission rates are equal.

morphism may be expected. Once again it can be seen that the higher the temperature, the more likely it is for heterogonic development to be favored (cf. Figs. 7A and 7B); at 25°C heterogonic development is highly favored, unless the transmission rate of the homogonic larvae is substantially higher than that of the heterogonic larvae. At 19°C, and assuming $\beta_A = \beta_S$, the expected proportion of worms developing via the heterogonic route is about 80%, which approximates that observed for lines ED248 and ED321, from which most parameter estimates were taken (Viney et al. 1992; Viney 1996; Gemmill et al. 1997). However, it should be emphasized once again that the gradient of the incline in Figure 7 (although not its location) is dependent on the unknown, host-specific parameters.

DISCUSSION

Understanding the factors that shape the evolution of parasites is crucial if we are to predict how such disease-causing agents will respond to different control strategies directed at different aspects of their life history. Here we present an ESS analysis of the evolution of a crucial aspect of a parasite's life cycle, its reproductive strategy. We used the *S. ratti* system because this parasite exhibits a variety of reproductive

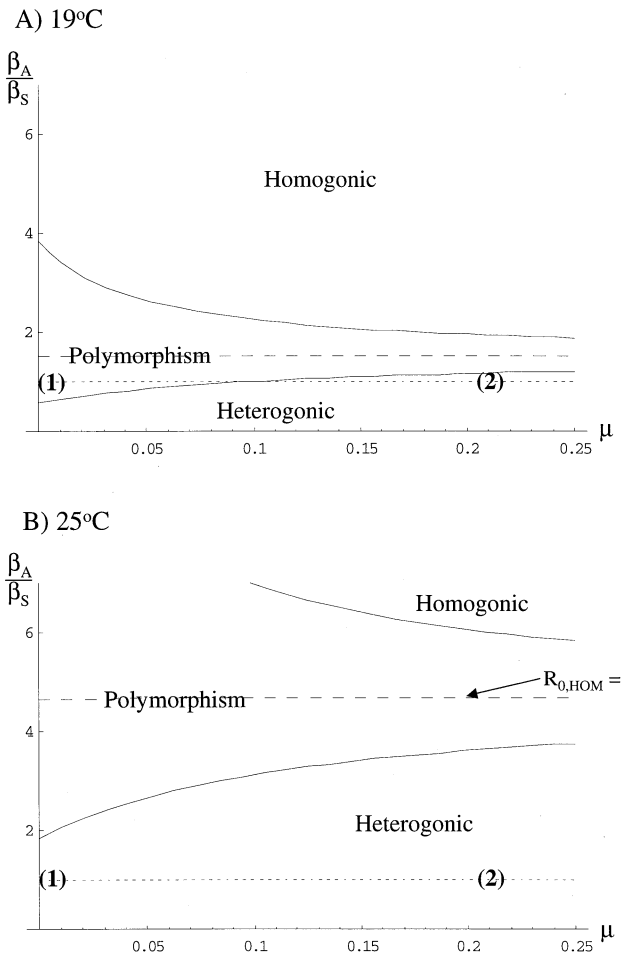

FIG. 6. $(\beta_A/\beta_S) - \mu$ parameter space for the evolutionarily stable strategy model, with all other estimated parameter values from Table 1, showing regions of either pure heterogonic or pure homogonic development and strain polymorphism. The dotted horizontal line represents where the heterogonic and homogonic transmission rates are equal and the dashed line is the line $R_{0,HOM} = R_{0,HET}$. The numbers in parentheses represent the estimated location of isofemale line ED321 in (1) nude (immunologically compromised) rats and (2) immunologically normal rats. (A) using parameter values for 19°C; and (B) using parameter values for 25°C.

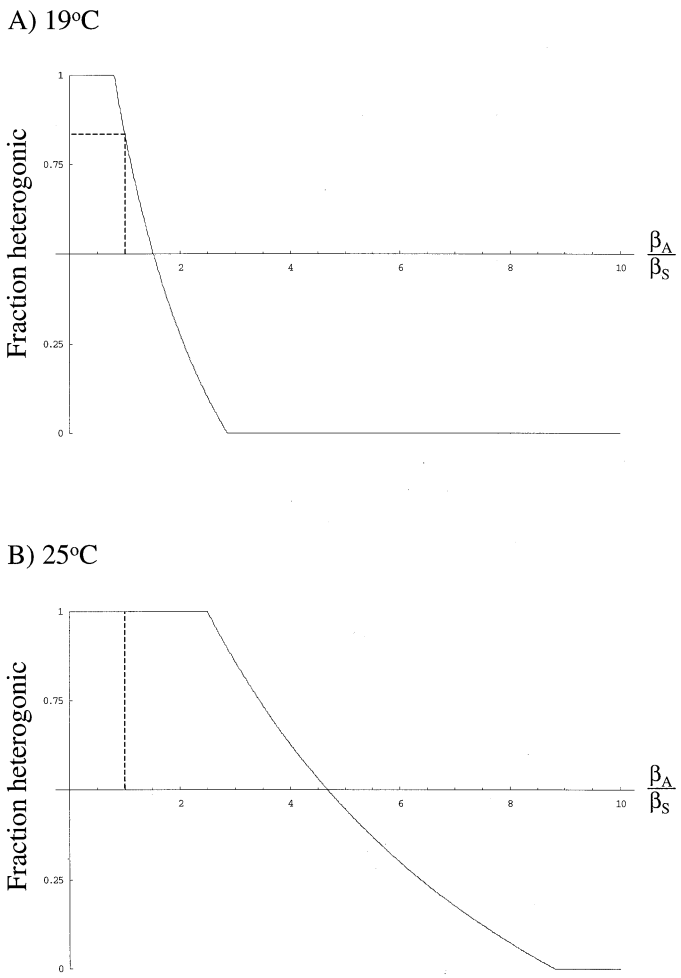

FIG. 7. The expected fraction of nematodes developing via the heterogonic route as a function of the relative homogonic iL3 transmission rate (β_A/β_S), with all other estimated parameter values from Table 1. The upper and lower flat planes represent regions of parameter space where either heterogonic or homogonic development, respectively, are evolutionarily stable strategies, whereas the incline shows different; compositions of the region of strain polymorphism. (A) using parameter values for 19°C; and (B) using parameter values for 25°C. The dotted lines represent $\beta_S = \beta_A$.

strategies, ranging from pure parthenogenetic reproduction through to pure dioecious sexual reproduction, making it an ideal model system with which to explore questions of parasite reproduction strategies.

Our model provides an adaptive explanation of preferential development by either the homogonic or heterogonic route that is consistent with a number of observed responses to the environment. First, *S. ratti* shows preferential development by the heterogonic route as the temperature of the external environment increases (Viney 1996; Harvey et al. 2000). Our ESS model shows that an increase in ambient temperature from 19°C to 25°C leads to a dramatic increase in the occurrence of heterogonic development, primarily through increasing the reproductive output of individuals developing via the heterogonic route. This is achieved by increasing the overall fecundity of the free-living females, skewing the sex ratio to favor the production of females (Harvey et al. 2000), and reducing the extra time taken to complete heterogonic development (Table 1).

Second, our model predicted the presence of polymorphism in development often seen in *Strongyloides* spp. For instance, isofemale line ED321 has previously been noted to predominantly develop by the heterogonic route, but with a significant proportion of individuals developing by the homogonic route, especially early in an infection (Viney et al. 1992; Viney 1996; Gemmill et al. 1997). Based on realistic parameter values, the ESS model presented here predicted the same overall trend, and similar levels of polymorphism at the population level. Furthermore, the model highlighted a number of potential mechanisms that might maintain such polymorphism. Parasitic nematodes are commonly observed to have an aggregated distribution between hosts (Shaw and Dobson 1995), and our results indicate that this aggregation will promote strain polymorphism by reducing the opportunity for

direct competition between sexual and asexual strains. Similarly, high rates of host reproduction will also reduce the potential competition between sexual and asexual strains, as the probability of co-occurrence within the same host will decrease as host reproductive rate increases, and so strain polymorphism at the population level is facilitated.

Clearly, the model presented here is very simple. It is a deterministic, population-level model, ignoring both demographic and environmental stochasticity. Hence, the degree of polymorphism predicted by this model is likely to be a minimum estimate. It is quite possible that inherent variation between individuals (either hosts or parasites) and variations in the environment would lead to increased levels of polymorphism. Furthermore, variation in developmental route within an individual, in the form of bet-hedging, may be an adaptive strategy to overcome uncertainties in the environment (Fenton and Hudson 2002). By producing some offspring that develop via the homogonic route and some that develop via the heterogonic route, a female parasite may maximize the chances that at least some of her genes are present in the next generation, regardless of any uncertainties in the future. Such a possibility would once again widen the observed degrees of polymorphism beyond those predicted by the current model. Nevertheless, we believe the simple framework presented here is sufficient to provide a clear insight into the underlying biological mechanisms that determine the optimal developmental of *S. ratti* populations in the wild.

Taken together, the predictions concerning the roles of temperature and host biology in influencing the optimal developmental route and the degree of polymorphism may go some way to explain the observed variations in developmental behavior of different geographical isolates. Typically, strains isolated from warmer climates tend to develop more by the heterogonic route than those from cooler climates (Viney et al. 1992), which is a prediction of our model. Furthermore, geographical differences in host life history (e.g., life span and reproductive rate) and ecology (affecting the degree of parasite aggregation), over which the parasites may have little control, would alter the optimal degree of investment in either route. Therefore, given the mechanistic understanding provided by our modeling framework, it is possible to explain why different geographic isolates of *S. ratti* differ in terms of their observed developmental behavior.

Following on from this, it would be interesting to extend our analysis to different species of *Strongyloides*, where there is evidence of interspecific variation in the number of free-living, adult generations that can occur. *Strongyloides planiceps* has been shown to have up to nine free-living generations, whereas *S. stercoralis*, like *S. ratti*, had only one (Yamada et al. 1991). Interestingly, it has been suggested that the *Strongyloides* genus is a recent radiation, possibly from an ancestor with multiple free-living generations (Dorris et al. 2002). The adaptive significance of multiple versus single free-living generations remains unclear, although a model framework similar to the one presented here may be the ideal tool with which to address this intriguing question. However, parameter estimation for other species would be more difficult than it has been for *S. ratti*, given the relative lack of data for most of these other species.

Finally, host immune responses, the major cause of mortality of parasitic females (Paterson and Viney 2002), are known to induce increased heterogonic development in *S. ratti* (Gemmill et al. 1997; Harvey et al. 2000). Previous experiments have shown that eggs from immunologically normal hosts are more likely to develop via the heterogonic route than eggs from immunosuppressed hosts (Gemmill et al. 1997; Harvey et al. 2000). Furthermore, the proportion of eggs developing by the heterogonic route increases through the course of an infection in immunologically normal hosts, concurrent with the development of an adaptive immune response and consequent increased mortality of adult parasites (Viney et al. 1992; Viney 1996; Gemmill et al. 1997). This increase in the propensity for heterogonic development with increased adult parasite mortality emerged naturally from our model. As the within-host environment becomes increasingly hostile, the benefits of the extra fecundity provided by the free-living, heterogonic adults quickly outweighs the benefits of rapid, homogonic reproduction.

The evolution of sex has interested evolutionary ecologists for decades, due to the apparent two-fold advantage of asexual reproduction over sexual reproduction (Maynard Smith 1971; Williams 1975). One possible explanation for the maintenance of sexuality is that sexual reproduction is necessary either to avoid mutational meltdown, that is, the catastrophic accumulation of deleterious, synergistic mutations, or to bring together beneficial mutations that have arisen in separate lineages (Otto and Michalakis 1998). However, these mutational explanations do not, without special pleading, explain why such high rates of sexual reproduction are found in some populations of *S. ratti* ($>$ 80% in the United States and Japan) compared to such low rates in others ($<$ 1% in the United Kingdom; Viney et al. 1992).

Alternatively, sexual reproduction may be advantageous when the organism is subjected to frequency-dependent selection (Hamilton 1980; Bell and Smith 1987; Hamilton et al. 1990). The most popular version of this hypothesis, often called the Red Queen hypothesis, states that the genetic recombination that occurs during sexual reproduction could be beneficial to free-living organisms to avoid parasites that target common host genotypes. Similarly, for the parasites themselves, sex should be favored as an evolutionary response to avoid the host's specific immune system targeted against common parasite genotypes (Lythgoe 2000, 2002; Galvani et al. 2003); such arguments have previously been proposed to explain the occurrence of sexual reproduction in *S. ratti* (Lythgoe 2000, 2002; Galvani et al. 2003). However, since the model presented here has no density-dependent, long-lived immunity, the advantage for heterogonic development (at least in this model) was simply due to the relative weight of numbers, through the extra reproduction by the free-living females. Interestingly, a recent series of experiments (Paterson and Viney 2003) found no evidence for any genotype-specific immunity in *S. ratti* infections, suggesting that heterogonic development may, as indicated by the present model, be an adaptive response to increase the production of infective stages under stressful conditions, rather than to generate novel parasite genotypes to avoid any specific host immune response.

A general feature of helminth biology is that they are ex-

posed to very different environments at different points of their life cycle: for example, digeneans sequentially parasitize invertebrate and vertebrate hosts, and geohelminths (such as *Strongyloides* spp.) exhibit both parasitic and free-living stages. A common strategy used by helminths is to couple a developmental transition with the transition from one environment to another, so that different developmental stages can exhibit adaptations appropriate to their specific environment. Given this, there is no a priori reason why the switch between heterogonic and homogonic development should be to gain advantages from sexual reproduction per se. Instead, from our results, it seems more likely that the propensity for sexual reproduction in *Strongyloides* is a facultative response to adopt an alternative developmental strategy depending on environmental cues, allowing it to either infect a new host quickly (homogonic development) or increase the number of infective stages (heterogonic development) as the prevailing environmental conditions dictate. Interestingly, the closely related free-living nematode, *Caenorhabditis elegans*, has a similar developmental choice, switching to a resistant dauer phase under conditions of starvation or environmental stress. The molecular basis of how *C. elegans* senses its environment and how environmental cues result in a switch to dauer development are well characterized (Riddle and Albert 1997; Blaxter 1999; Wang and Kim 2003). By combining this genetic resource with the evolutionary approach outlined here, it may be possible to make rapid progress in characterizing the molecular basis of how parasitic nematodes respond to their environment and the evolution of their life-history strategies.

Although our results predict under which conditions heterogonic development may be favored over homogonic development, they do not explain why reproduction in the free-living stages is sexual rather than parthenogenetic, as found in the parasitic adults. Indeed, the predictions generated by the model would remain the same regardless of the form of reproduction occurring; the advantages for one route of development over the other arise simply through the relative values of the respective life-history parameters. However, it should be emphasized that the model does not dismiss the possibility that sexual reproduction is beneficial in some way. The fact that *Strongyloides* spp. do retain sexual reproduction and, consequently, the opportunity for genetic exchange and recombination, suggests that sex is essential for the long-term viability of *Strongyloides* populations and is at least occasionally favorable for individual parasites. Whatever the correct explanation for the occurrence of sexual reproduction in *S. ratti*, the evolution of sex in parasites has important applied consequences. The model presented here suggests that under conditions of high parasite mortality as would be imposed, for instance, by a vaccination program, *S. ratti* is likely to switch more to a free-living and, hence, sexual strategy. Under these conditions, the parasite benefits not only from a direct increase in numbers compared with homogonic development but also potentially through the creation of novel genotypes, which may reduce the impact of strain-specific vaccines.

The evolutionary approach presented here, embedding epidemiological models within an ESS framework, provides a powerful method to analyze how life-history strategies of parasites are likely to evolve and results in a richer array of evolutionary outcomes than the standard maximize-R_0 analyses often used to explore the evolution of macroparasite life-history strategies (Dobson and Merelender 1991; Gemmill et al. 1999; Morand and Poulin 2000). This model is based on biologically intuitive parameters and accurately predicts the optimal developmental strategy of this parasite in different biotic (via the host's immune system) and abiotic (through the ambient temperature) environments. Using empirical data from specific systems is essential to direct and validate these evolutionary models and, in turn, to make predictions regarding the evolutionary trajectories of specific infectious diseases in response to evolutionary pressures, including novel control measures. Given the activity in infectious disease research, the prospects for gathering appropriate empirical data are good. Macroparasites, including parasitic nematodes, are a major cause of human disease in the developing world and evolutionary theory is of clear relevance to understanding the basic processes of infection and to aid the development of treatment programs against the diseases that they cause.

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Appendix 1

Description of the Simple Strongyloides ratti Model

As described in the main text, we use a modified version of the standard Anderson and May (1978; May and Anderson 1978) macroparasite models. The full model is:

$$\frac{dH}{dt} = rH - cP, \tag{A1}$$

$$\frac{dP}{dt} = H(A\beta_A + L\beta_S) - P\Gamma_P - \frac{P^2\alpha k'}{H}, \tag{A2}$$

$$\frac{dA}{dt} = P\lambda_P\pi - A(\gamma_A + \beta_A H), \tag{A3}$$

$$\frac{dS}{dt} = P\lambda_P(1 - \pi) - S\gamma_S, \tag{A4}$$

$$\frac{dZ}{dt} = \lambda_S S - Z(\theta + \lambda_Z), \quad \text{and} \tag{A5}$$

$$\frac{dL}{dt} = \theta Z - L(\gamma_L + \beta_S H), \tag{A6}$$

where $\Gamma_P = (\alpha + \mu + b)$, $k' = (1 + k)/k$, and all other parameters are defined in Table 1. To simplify the analysis, we first make the assumption that the dynamics of the external phases of the parasite life cycle are fast relative to the host's dynamics and, second, we rephrase the model in terms of the mean parasite burden, M (= P/H), producing the model:

$$\frac{dH}{dt} = rH - cMH \quad \text{and} \tag{A7}$$

$$\frac{dM}{dt} = MH\lambda_P\left[\frac{\beta_A\pi}{\gamma_A + \beta_A H} + \frac{\beta_S\lambda_S\theta(1 - \pi)}{\gamma_S(\theta + \gamma_Z)(\gamma_L + \beta_S H)}\right] - M(\Gamma_M + M\sigma), \tag{A8}$$

where $\Gamma_M = (\alpha + \mu + a)$ and $\sigma = [(\alpha/k) - \delta]$.

Appendix 2

Description of the Evolutionarily Stable Strategy Strongyloides ratti Model

We assume initially that the homogonic and heterogonic parasite strains have the same impact on the host population (i.e., the same α and δ values), although they are allowed to differ in terms of their within-host death rates, such that adult parasites of the homogonic strain (P_A) die at rate μ_A within the host and adult parasites of the heterogonic strain (P_S) die at rate μ_S. Hence, the net rate of loss of the homogonic and heterogonic strains within the host are $\Gamma_{P,A} = (\alpha + b + \mu_A)$ and $\Gamma_{P,S} = (\alpha + b + \mu_S)$, respectively. We also assume the two parasite strains have the same frequency distribution among the host population (as measured by the negative binomial parameter, k), and there is no interaction between the two parasite strains within an individual host, so the covariance of the two distributions is zero. Under these assumptions, the full two-strain ESS model is:

$$\frac{dH}{dt} = rH - c(P_A + P_S), \tag{A9}$$

$$\frac{dP_A}{dt} = HA\beta_A - P_A\Gamma_{P,A} - \frac{P_A\alpha}{H}(P_A k' + P_S), \tag{A10}$$

$$\frac{dP_S}{dt} = HL\beta_S - P_S\Gamma_{P,S} - \frac{P_S\alpha}{H}(P_S k' + P_A), \tag{A11}$$

$$\frac{dA}{dt} = \lambda_{P,A}P_A - A(\gamma_A + \beta_A H), \quad \text{(A12)}$$

$$\frac{dS}{dt} = \lambda_{P,S}P_S - S\gamma_S, \quad \text{(A13)}$$

$$\frac{dZ}{dt} = \lambda_S S - Z(\theta + \lambda_Z), \quad \text{and} \quad \text{(A14)}$$

$$\frac{dL}{dt} = Z\theta - L(\gamma_L + \beta_S H), \quad \text{(A15)}$$

where $k' = (1 + k)/k$. Once again, we rephrase the model in terms of the mean parasite burdens, M_A (= P_A/H) and M_S (= P_S/H) and combine the external phases of the parasite life cycle to produce the final model:

$$\frac{dH}{dt} = rH - cH(M_A + M_S), \quad \text{(A16)}$$

$$\frac{dM_A}{dt} = \frac{\beta_A\lambda_{P,A}M_A H}{\gamma_A + \beta_A H} - M_A(\Gamma_{M,A} + M_A\sigma - M_S\delta), \quad \text{and} \quad \text{(A17)}$$

$$\frac{dM_S}{dt} = \frac{\beta_S\lambda_{P,S}\lambda_S\theta M_S H}{\gamma_S(\theta + \gamma_Z)(\gamma_L + \beta_S H)} - M_S(\Gamma_{M,S} + M_S\sigma - M_A\sigma), \quad \text{(A18)}$$

where $\Gamma_{M,i} = (\alpha + a + \mu_i)$ and $\sigma = (\alpha/k - \delta)$.