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The role of sex in parasite dynamics: Model simulations on transmission of *Heligmosomoides polygyrus* in populations of yellow-necked mice, *Apodemus flavicollis*

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Abstract

We investigated possible mechanisms that could cause sex-biased parasite transmission of the helminth *Heligmosomoides polygyrus* in its rodent host, *Apodemus flavicollis*, using a modelling approach. Two, not mutually exclusive, hypotheses were examined: that sex-biased parasite transmission is caused by differences in immunity that influence the success of free-living stages and/or is caused by sex differences in host behaviour and the dissemination of infective stages. Model simulations were compared with results from a field manipulation experiment of *H. polygyrus* in replicated populations of *A. flavicollis*. Simulations predicted the experimental field results, and both hypotheses explained the pattern observed. Transmission is male-biased if a male immune response increases fertility, hatching or survival of free-living stages. Alternatively, transmission is male-biased if their behavioural characteristics allow them to spread infective larvae in areas more frequently used by females. These results highlight that host sex is not only responsible for differences in parasite susceptibility, but may profoundly influence host–parasite interactions, resulting in a sex bias in parasite transmission.

Keywords: Gastrointestinal nematodes; Sex-biased parasitism; Transmission heterogeneities; Macroparasite dynamics

1. Introduction

Numerous studies have provided evidence that host–parasite systems are characterised by heterogeneities, particularly variations in the susceptibility and exposure to infective agents (Wilson et al., 2002). These heterogeneities result in the well documented observation that parasites exhibit non-random distributions within their host populations (Shaw and Dobson, 1995; Shaw et al., 1998) and from this follows the assumption that individual hosts make an uneven contribution to parasite transmission (Woolhouse et al., 1997). Several factors that contribute to the observed heterogeneities have been identified; one recurring empirical observation is that host sex generates differences in parasite intensities, with males usually exhibiting higher parasite intensities than females (Poulin, 1996; Wilson et al., 2002).

Additional empirical studies on different host–parasite systems have also shown that males may play a greater role than females in maintaining parasite transmission (Skorping and Jensen, 2004), regardless of whether a sex-bias in parasite intensity was observed in the population (Ferrari et al., 2004). In the study by Ferrari et al. (2004), we investigated whether host sex was epidemiologically important to the gastrointestinal parasite *Heligmosomoides polygyrus* in the yellow-necked mouse (*Apodemus flavicollis*). The infection status of each sex was manipulated in a field experiment, and it was found that when *H. polygyrus*

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was removed from male *A. flavicollis*, the parasite load (measured as egg production) significantly decreased in females, while in contrast when *H. polygyrus* was removed from females, there was no apparent effect on the parasite load in males. This sex-bias in transmission was observed in the absence of significant sex-bias in either helminth burden or in the number of parasite eggs expelled in the hosts' faeces. This is an important point that underlines two significant aspects of the dynamics of *H. polygyrus* infection in *A. flavicollis*. First, that transmission is male-biased and secondly that a sex-bias in parasite intensity is not a pre-requisite for sex-biased transmission. In essence, this suggests the pattern is not a consequence of differences between the sexes in terms of the rate of production of infective stages, but that infective stages expelled by males have a greater probability of successfully infecting a host than those expelled by females (Skorping and Jensen, 2004).

To elucidate the mechanisms responsible for sex-biased parasite transmission we sought to distinguish between the processes that make males more successful in expelling parasite eggs with a greater chance of survival, from processes that may lead males to deposit eggs in strategic places, or favourable habitat, leading to subsequently higher transmission rates. In this respect, we investigated two hypotheses to explain sex-biased parasite transmission (Ferrari et al., 2004): (i) male immunity is compromised by testosterone (Folstad and Karter, 1992) and even if this does not influence parasite intensity or the number of eggs produced, it leads to a higher egg hatching rate and free-living larvae survival (Finkelman et al., 1997), and (ii) mouse spatial behaviour (Ims, 1987; de Mendonça, 2003. Aspects of the social ecology of the yellow-necked mouse *A. flavicollis*. Ph.D. Thesis. University of Cambridge, Cambridge; Gromov, 2006) generates sex differences in exposure and/or transmission of infective stages, leading to greater transmission success from males.

To examine the relative contribution of these two non-mutually exclusive hypotheses, we used mathematical models to explore the dynamics of parasite infection for a macroparasite with a direct life cycle. In this paper, we modify a deterministic multi-host model (Tompkins et al., 2000) focusing on a system where one parasite species is shared by the two sexes of one host species. The models are tailored to the population dynamics of *H. polygyrus* in the host *A. flavicollis*, and the parameters are estimated using field data (Ferrari et al., 2004 and unpublished data) and published data on *H. polygyrus* and *A. flavicollis*.

Initially, we examined the *A. flavicollis–H. polygyrus* interaction using a simple model (Model 1) that does not consider host sex. This model provides a baseline against which we compare the subsequent models that examined interactions between the infection processes and host sex. As such, Model 1 was then extended to a multi-sex system where each sex is considered independently (Models 2 and 3). Models 2 and 3 allow for differences in immunity or behavioural characteristics between males and females, respectively. We then used Models 2 and 3 to simulate the experimental removal of parasites (Ferrari et al., 2004), and the model predictions were compared with field results to identify the conditions under which one sex could be responsible for the transmission of the parasite population in the absence of sex-biased parasitism.

2. Materials and methods

2.1. Model descriptions

We used a macroparasite model with direct life-cycle transmission, following Anderson and May (1978). This is a deterministic model that assumes that time is a continuous variable and that processes of reproduction, birth and death occur continuously. These models explore the dynamics of host population size, the adult parasite population size and the abundance of free-living infective stages. In accordance with the observed frequency distribution of *H. polygyrus* in *A. flavicollis* in Trentino (Ferrari et al., 2004), we assumed that adult parasites are distributed among individual hosts following a negative binomial distribution, where the parameter k provides an inverse measure of the extent of parasite aggregation within the host population (Shaw et al., 1998). Due to the high dimensionality of the multi-host models which make complete algebraic analysis difficult (Begon and Bowers, 1995; Greenman and Hudson, 2000) we investigated the two-sex-host–parasite system only through numerical simulations.

2.1.1. Model 1: no sex effect

Initially, we considered the whole population of hosts and parasites. The flow chart of this basic model is shown in Fig. 1A where the various birth, death and transmission processes are summarised.

The resulting model consists of the three coupled differential equations:

$$\frac{dN}{dt} = N[b - d - (b - d)N/K - \alpha X] \quad (1)$$

$$\frac{dX}{dt} = X[-\sigma - b - \alpha(X/k + 1)] + \beta\psi L \quad (2)$$

$$\frac{dL}{dt} = hNX - \delta L - \beta NL \quad (3)$$

A full list of parameters with their biological interpretation is given in Table 1. We prefer to derive the equation for the mean parasite intensity $X(t) = P(t)/N(t)$ rather than the total parasite population $P(t)$, since $X(t)$ is more easily related to field measurements. The host population N, in Eq. (1), increases with birth rate b and decreases with death rate d. We assume linear density dependence in the growth rate of the host population with K being the carrying capacity of *A. flavicollis*. The host population is reduced by the effect of the parasite on host survival (the parameter α represents the parasite-induced host mortality) while the

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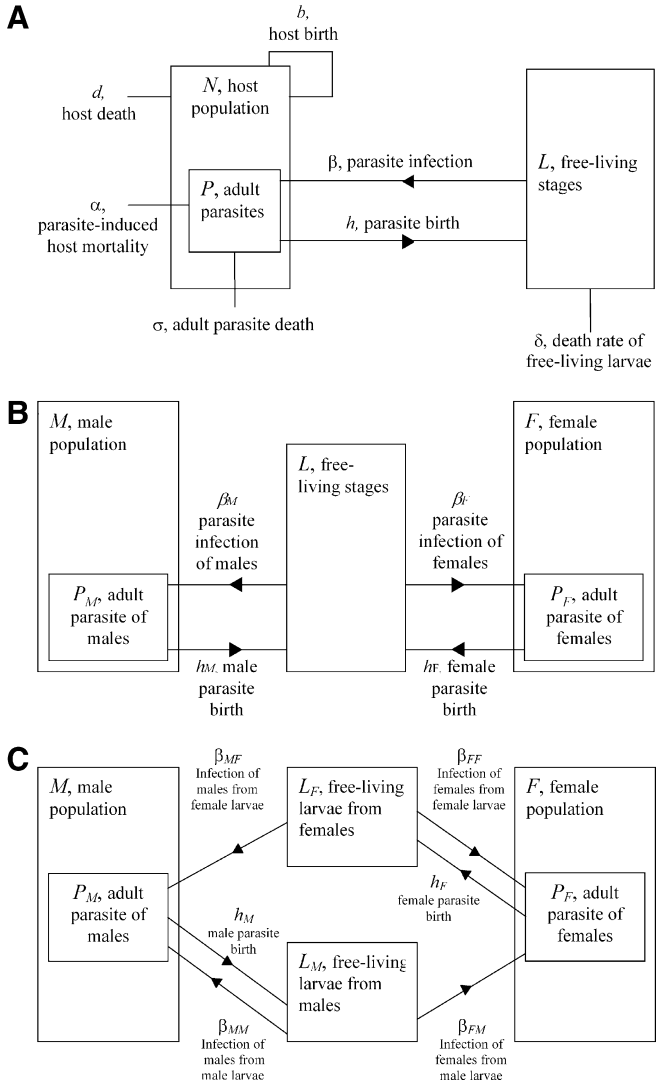

Fig. 1. Schematic representations of *Apodemus flavicollis–Heligmosomoides polygyrus* interactions according to the host compartments considered. Flow chart of the direct life cycle of *H. polygyrus* in the entire *A. flavicollis* population (A). The *A. flavicollis* population is considered to be composed of two-host sexes and a common free-living infective pool (B) and then with two-host sexes and two free-living infective pools (C).

effect by *H. polygyrus* on host fecundity is assumed to be negligible (Scott, 1990). A linear relationship between parasite intensity and parasite-induced host mortality is assumed, such that the total death rate of a host, carrying i parasites, is given by $d + \alpha i$. The mean parasite burden x, in Eq. (2), increases with the rate of larval ingestion β, is reduced by a proportion that fail to develop into an adult stage ψ, and decreases due to the combined effects of parasite death rate σ and host death rate d, both natural and parasite-induced. Infective free-living larvae, in Eq. (3), are produced by adult parasites at rate h (this would be the rate of egg production multiplied by the egg hatching rate and the survival probability from egg to infecting larval stage). Free-living larvae decrease through both natural mortality δ and ingestion by hosts β.

2.1.2. Model 2: two host sexes and a shared free-living infective larvae pool

To examine the effect of host sex on the dynamics of *H. polygyrus*, the dynamics of male and female hosts were investigated, respectively. We did this by splitting the host population compartment of Model 1 into two compartments corresponding to males, M, and females, F. Consequently, the adult parasite pool was also split in two subpopulations: X_M, the adult parasites harboured by males and X_F those harboured by females. However, we assume the males and females share a common free-living infective pool, L. This model allows us to explore the consequences of different parasite dynamics in relation to host sex, such as differences in parasite production of infective larvae (h), and also the consequences of behavioural differences in the exposure of the two sexes to free-living infective stages (β). The life-cycle of the two parasite sub-populations sharing a common free-living infective pool is illustrated in Fig. 1B.

Model 2 is described by the following five coupled differential equations:

$$\frac{dM}{dt} = bF + M[-d_M - (b - d_M)(M + F)/K - \alpha_M X_M] \quad (4)$$

$$\frac{dF}{dt} = F[b - d_F - (b - d_F)(M + F)/K - \alpha_F X_F] \quad (5)$$

$$\frac{dX_M}{dt} = X_M[-\sigma_M - b - \alpha_M(X_M/k_M + 1)] + \beta_M \psi_M L \quad (6)$$

$$\frac{dX_F}{dt} = X_F[-\sigma_F - b - \alpha_F(X_F/k_F + 1)] + \beta_F \psi_F L \quad (7)$$

$$\frac{dL}{dt} = h_M M X_M + h_F F X_F - \delta L - \beta_M M L - \beta_M F L \quad (8)$$

Eqs. (4)–(8) describe the temporal variations in the abundance of male and female hosts, indicated, respectively, with M and F, their mean adult parasite burden, X_M and X_F, and the size of the common free-living infective pool, L. Here, we assume that newborn hosts are proportional only to female abundance, and the sex ratio of the offspring is set at 1:1. While we could consider more complex functions, relating the number of newborns to the abundance of total adults individuals (Iannelli et al., 2005), our choice is more relevant to the parasite system and the problem considered in this study. All other aspects concerning the dynamics of male and female hosts (M and F) and their mean parasites burden (X_M and X_F) are modelled following Model 1 but taking into account the sex-specific parameters. For the common free-living pool the gain terms are estimated as the sum of the production of infective larvae by male and female hosts, h_M and h_F, and losses are due to the ingestion of larvae by both sexes, β_M and β_F. Since we are using the two-host-sexes model, the number of parameters in Model 2 are doubled with respect to Model 1 except for host birth rate and the death rate of common free living larvae (Table 1).

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Table 1
Numerical values and biological interpretation of population parameters for *Apodemus flavicollis* and *Heligmosomoides polygyrus*

Parameter	Value (units)	Description
$N(F, M)$[a]	Variable	Size of host population
X[a]	Variable	Mean adult parasite burden
L[a]	Variable	Number of free living infective larvae
K	50	Host population carrying capacity
d[a]	3.7×10^{-3} (day^{-1})	Instantaneous death rate of host due to all causes except parasite
b	8.21×10^{-3} (day^{-1})	Instantaneous birth rate of hosts
σ[a]	1.3×10^{-2} (day^{-1})	Instantaneous death rate of adult parasite
h[a]	1 (day^{-1})	Instantaneous rate of production of infective parasite larvae
ψ[a]	8×10^{-2}	Proportion of ingested infective larvae that develop to the adult stages
α[a]	2.4×10^{-4} ($worm^{-1}\,day^{-1}$)	Instantaneous death rate of host due to parasite
β[a]	4×10^{-4} ($host^{-1}\,day^{-1}$)	Instantaneous rate of ingestion of free-living infective larvae
k[a]	0.36	Aggregation parameter of the Negative Binomial distribution (for *H. polygyrus* in *A. flavicollis*)
δ[a]	1.6×10^{-2} (day^{-1})	Instantaneous death rate of infective free-living larvae

[a] Subscript M, F in Model 2 and 3 refer to parameter values for specific host sex.

2.1.3. Model 3: two host sex and two free-living infective pools

In the final model, we introduced a further distinction in parasite transmission where we considered two separate compartments of free-living infective larvae which correspond to the larvae produced by adult parasites harboured by males, L_M, and females, L_F, respectively (Fig. 1C).

The resulting model is defined by six coupled differential equations describing the changes in male and female hosts, their mean adult parasite burden, and the free-living stages produced by the hosts of different sexes (L_M, L_F).

$$\frac{dM}{dt} = bF + M[-d_M - (b - d_M)(M + F)/K - \alpha_M X_M] \quad (9)$$

$$\frac{dF}{dt} = F[b - d_F - (b - d_F)(M + F)/K - \alpha_F X_F] \quad (10)$$

$$\frac{dX_M}{dt} = X_M[-\sigma_M - b - \alpha_M(X_M/k_M + 1)] + \beta_{MM}\psi_M L_M + \beta_{MF}\psi_M L_F \quad (11)$$

$$\frac{dX_F}{dt} = X_F[-\sigma_F - b - \alpha_F(X_F/k_F)] + \beta_{FF}\psi_F L_F + \beta_{FM}\psi_F L_M \quad (12)$$

$$\frac{dL_M}{dt} = h_M M X_M - \delta_M L_M - \beta_{MM} M L_M - \beta_{FM} F L_M \quad (13)$$

$$\frac{dL_F}{dt} = h_F F X_F - \delta_F L_F - \beta_{FF} F L_F - \beta_{MF} M L_F \quad (14)$$

The dynamics of male and female hosts were modelled as in Model 2. Mean parasite intensities for each host sex (X_M, X_F) increased according to the sum of ingested larvae from each larval compartment (L_M, L_F). When the ingestion rate of the free-living larvae from the two different infective pools is equal for males and females ($\beta_{MM} = \beta_{FM}$, $\beta_{FF} = \beta_{MF}$), Model 3 behaves exactly as Model 2.

2.2. Parameter estimation

2.2.1. Known biological traits

Most of the parameters for the model simulations are derived from the field experiment by Ferrari et al. (2004) and unpublished data on population dynamics of *A. flavicollis* in Trentino (Italy). The mean lifespan of *A. flavicollis* is taken as 270 days from our unpublished data and mean number of offspring, surviving till weaning, is taken as six per year from our studies (unpublished data) so the daily host mortality d is 0.0037/day and host birth rate b 0.00821/day. The observed sex ratio in the field was close to 1:1 and here we assume it to be 1:1. The carrying capacity K is set to 50 mice per hectare according to the maximum density we observed during the field experiment.

We take the adult *H. polygyrus* life span in *Apodemus* spp. to be 76 days, and the mortality rate (σ) is 0.013/day after Gregory et al. (1990). The lifespan of infecting L_3 larvae is assumed to be 2 months, with a mortality rate (δ) of 0.016/day for trichostrongylid nematodes (Dobson and Hudson, 1992; Fernàndez et al., 2001). Laboratory experiments estimated the parasite-induced mortality by a single parasite on a host (α) to be 0.00024/day (Keymer and Hiorns, 1986). The proportion of infective free-living stages that develop to adult stages (ψ) in laboratory mice varies from 80% to 8%; we selected the lowest values since wild mice show higher resistance to infection (Slater and Keymer, 1988; Enriquez et al., 1988; Gregory et al., 1990). We found that *H. polygyrus* exhibited an aggregated distribution in natural populations of *A. flavicollis* that did not significantly differ from a negative binomial distribution (deviance = 63.5, df = 104, $P = 0.9$, $k = 0.36$) (unpublished data). This aggregated pattern justifies the model assumptions.

2.2.2. Uncertain biological traits

To estimate the unknown parameters of infective free-living larva production (h) and larval ingestion rates (β), we obtained informed estimates through sensitivity analysis with Model 1.

Specifically, according to Model 1 (see Appendix A), the equilibrium density ($\bar{N}$) of the hosts depends only on the carrying capacity (K), the parasite-induced host mortality (α), the maximum host growth rate ($b - d$) and the average parasite load ($\overline{X}$), while indirectly it is affected by the larval ingestion (β) and fecundity rates (h). We then have an

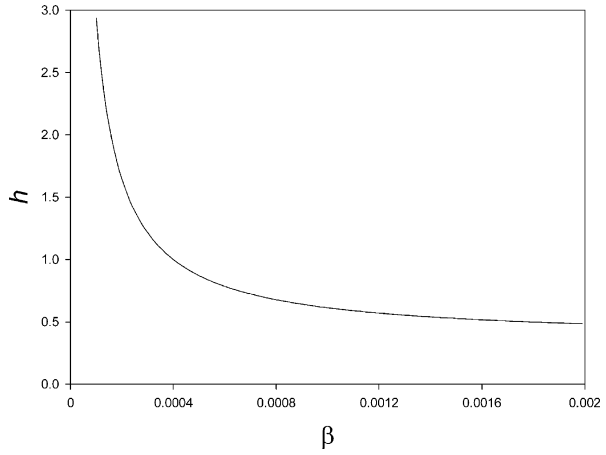

Fig. 2. Values of h as a function of the parameter β (see Eq. (A2) in Appendix) needed to fit a mean parasite burden of 10 worms/mouse.

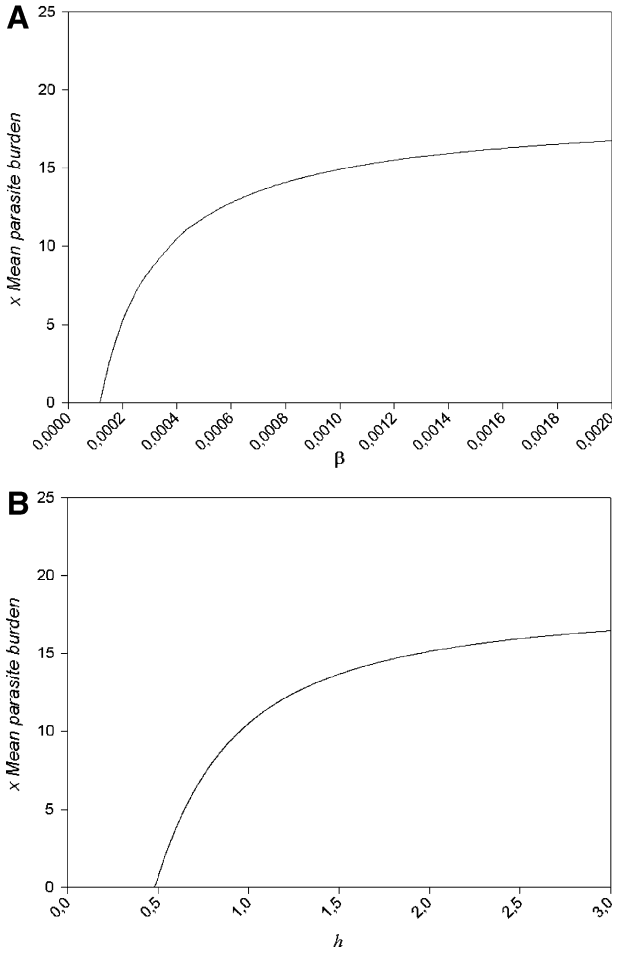

Fig. 3. Sensitivity analysis on β and h over mean parasite burden. When β varies and $h = 1$ (A), when h varies and $\beta = 0.004$ (B). The parameter values were determined as shown in Table 1.

equation for the equilibrium of the mean parasite burden ($\overline{X}$) (see Appendix A) where we know all the parameter values except β and h. The solutions of Eq. A2 (see Appendix A), using the observed value of 10 worms per mouse (Rosso et al., 2002), are shown in Fig. 2.

Based on other studies on *H. polygyrus* infection (Tanguay and Scott, 1992), we selected for our simulations the value of 0.0004 for β and 1 for h. To check the robustness of this choice we evaluated the sensitivity of parasite intensity ($\overline{X}$) to the selected parameter values. All the other parameters are held at the fixed values shown in Table 1 while β and h were alternately allowed to vary. Fig. 3 shows the changes in mean parasite intensity at equilibrium by varying β (Fig. 3A) and h (Fig. 3B).

The full list of parameter values is given in Table 1 where we measured time in days and densities in hectares^{-1} (ha^{-1}).

Simulation of host–parasite interaction, using Model 1 and the parameter values in Table 1, exhibited damped oscillations for host and parasite populations before reaching a stable co-existence at equilibrium.

3. Results

To explore the two hypotheses: (i) male immunity is compromised, resulting in the infection having a higher egg hatching rate, coupled with increased free-living larval survival, and (ii) male behaviour influences the dissemination of infective stages, leading to increased rates of ingestion, we assumed that the production rate of infective larvae (h) or the ingestion rate of infective larvae (β) varied between sexes while all the remaining parameters were constant.

3.1. Differences in immunity between sexes

Initially we simulated the condition where changes in immunity with host sex affect the fertility of eggs (hatching rate of parasite eggs and the survival of the free-living larval stage). In the model, eggs expelled by males have a higher hatching rate and larval survival than eggs expelled by females (i.e., $h_M > h_F$). The values of h_M and h_F were chosen to provide equilibrium values under natural conditions, similar to those from Model 1. Simulations based on Model 2 showed that the *H. polygyrus–A. flavicollis* system reaches, through damped oscillations, a stable equilibrium with no sex-bias in parasite intensity and host abundance between the two host sexes (Fig. 4).

We then simulated the selective reduction of parasite burden in each sex following the experimental protocol of Ferrari et al. (2004) by increasing, in males or females, respectively, the instantaneous death rate of adult parasites (i.e., σ) by 50-fold, a reduction in survival sufficient to decrease the parasite intensity. We then monitored changes in parasite intensity in the non-treated sex. In this case we ran the simulations for a short period (1 year) to provide the same time-scale of the field experiment, that was carried out over a 6-month period (Ferrari et al., 2004).

When the anthelmintic treatment was simulated on female mice, parasite intensity decreased slightly in males and decreased almost to zero in treated females (Fig. 5 A). A strong increase in female mouse abundance

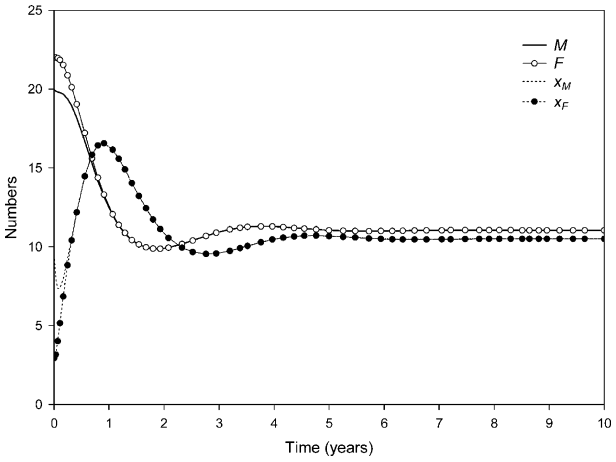

Fig. 4. Temporal dynamics of the mouse population and mean parasite intensity under natural conditions (i.e., no treatment is applied) according to Model 2 when male (M: —) and female (F: -○-) mice share a common free-living larval pool and parasites harboured by males (X_M: - - -) have higher egg hatching rates and free-living larval survival than those in females (X_F: -●-) (i.e., $h_M = 1.67$, $h_F = 0.33$). Parameter values are those of Table 1.

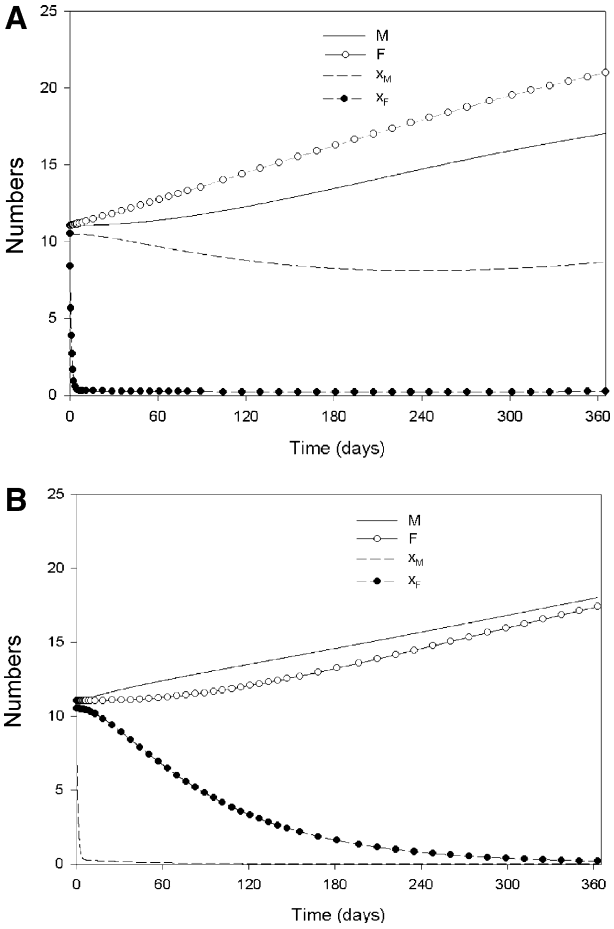

Fig. 5. Model 2: simulations of the effect of selective anthelmintic treatment by host sex. Mouse abundance and mean parasite intensity are shown. Males are assumed to have higher egg hatching rates and free living larval survival, and sexes are assumed to share a common free-living larval pool ($h_m = 1.67$, $h_f = 0.33$). Anthelmintic treatment is applied to females (A) and males (B). Male mouse numbers: M: —; females: F: -○-; mean parasite intensities of males: X_M: - - -; females: X_F: -●-.

was observed as a result of the sharp decrease in parasite intensity and, consequently a reduction in parasite-induced host mortality (Fig. 5A). Whereas, when we simulated the anthelmintic treatment for male mice, parasite intensity decreased progressively in the untreated females and dropped to almost zero in the treated males (Fig. 5B). Moreover, host abundance increased but the effect was less apparent than when females were treated; this is because of our assumption that birth rate depends only on female density.

3.2. Differences in host behaviour between sexes

Using Model 2 we investigated sex-biased differences in host behaviour, where we set a different rate of ingestion of free-living larval stages for each sex (i.e., different β). In this case, the model predicted a sex-bias in parasite intensity and host abundance (Fig. 6), which was not observed in the experimental results of Ferrari et al. (2004).

To mimic the condition where males mainly contribute to the transmission of parasites in the host population but with no sex-bias in parasite intensity, in Model 3 we set the larval ingestion rates higher in the larval compartment of males hosts than in the larval compartment of females hosts (i.e., $\beta_{MM} > \beta_{MF}$ and $\beta_{FM} > \beta_{FF}$) while keeping the overall larval intake equal for the two sexes (i.e., $\beta_{MM} + \beta_{MF} = \beta_{FM} + \beta_{FF}$).

Holding this inequality, we may have a symmetrical contribution of the two larval compartments (i.e., $\beta_{MM} = \beta_{FM}$ and $\beta_{FF} = \beta_{MF}$) for each sex. However, under natural conditions it is likely that females are exposed more to their own infective pool ($\beta_{FF} > \beta_{MF}$) and males to their infective pool ($\beta_{MM} > \beta_{FM}$) despite the overall contribution of the male larval compartment being the main pool (i.e., $\beta_{MM} > \beta_{MF}$ and $\beta_{FM} > \beta_{FF}$). In the absence of estimates of free-living larval ingestion rates, we set arbitrary values: $\beta_{MM} = 0.0007$ host^{-1} day^{-1}, $\beta_{MF} = 0.0001$ host^{-1} day^{-1}, $\beta_{FF} = 0.0002$ host^{-1} day^{-1}, $\beta_{FM} = 0.0006$ host^{-1} day^{-1}. These βs were selected to obtain similar equilibrium values to the natural values in Model 1. Hence, when no treatment was performed, the system reached a stable equilibrium with no significant sex-biased parasitism or differences in host abundance (Fig. 7).

The simulations of the anthelmintic treatment showed that when *H. polygyrus* is removed from female mice, the parasite intensity decreased moderately in the non-treated males and decreased almost to zero in females (Fig. 8A); in contrast, when *H. polygyrus* was removed from males, parasite intensity decreased considerably in females (Fig. 8B). Interestingly, host abundance increased in anthelmintic-treated males and females.

Finally, assuming both sex differences co-occur (i.e., difference in immunity plus difference in behaviour) similar qualitative results (not shown) were observed; the role of

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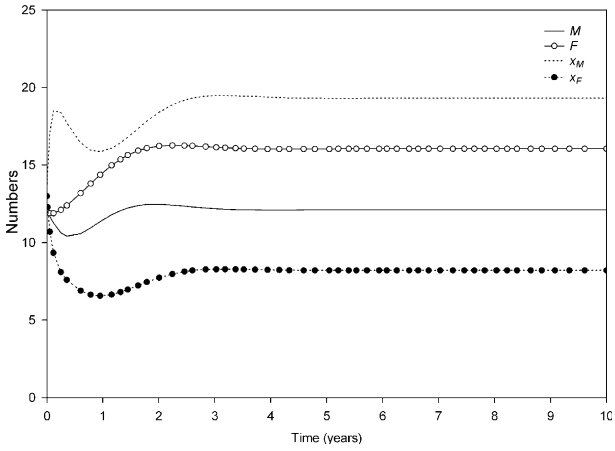

Fig. 6. Temporal dynamics of mouse population and mean parasite intensity (i.e., no treatment applied) according to Model 2 where host sexes share a common free-living larval pool and the rate of encounter between hosts and free-living stages for males is higher than for females ($\beta_M = 0.0006 > \beta_F = 0.0002$). The other parameter values are those of Table 1. Male numbers: M: —; females: F: -○-; mean parasites intensities of males: X_M: - - -; females: X_F: -●-.

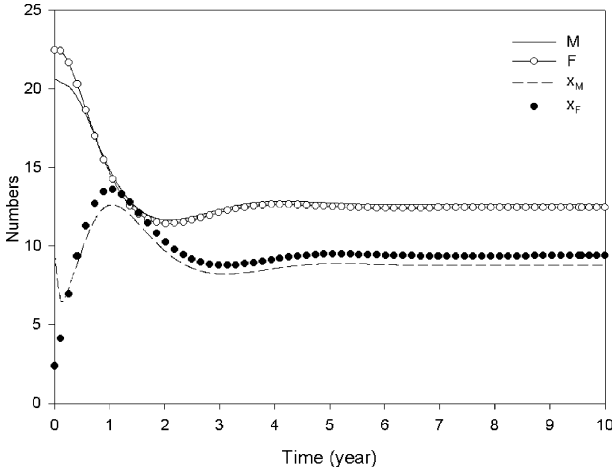

Fig. 7. Temporal changes for mouse population and mean parasite intensity (i.e., no treatment is applied) according to Model 3 when the free-living infective larvae are split into two sub-populations and mice are more exposed to larvae coming from male mice ($\beta_{MM} = 0.0007$, $\beta_{MF} = 0.0001$, $\beta_{FF} = 0.0002$, $\beta_{FM} = 0.0006$). Male mouse numbers: M: —; female: F: -○-; mean parasites intensities of males: X_M: - - -); females: X_F: -●-.

males in driving infections increased slightly, while females confirm their secondary role, as observed when a single mechanism is active.

4. Discussion

In our experimental field study on the effects of host sex on parasite transmission, we found empirically that male *A. flavicollis* drive *H. polygyrus* infection, while females have little role in persistence of the parasite (Ferrari et al., 2004). Here, we extended this study and investigated the possible biological mechanisms that could cause sex-bi-

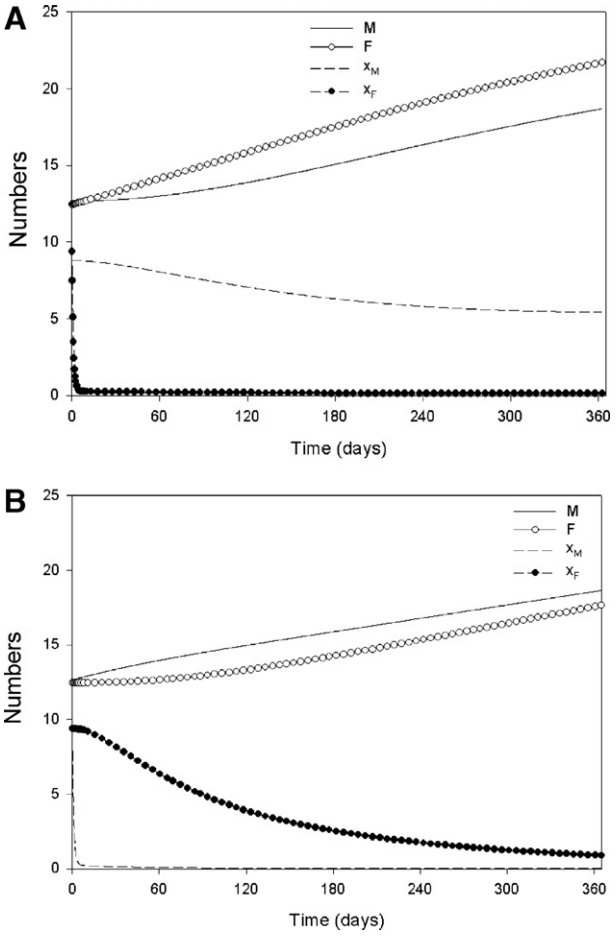

Fig. 8. Model 3 simulations of the effects of anthelmintic treatment on mouse numbers and mean parasite intensity when the free-living infective larvae are divided into two groups and mice are exposed predominantly to those coming from males ($\beta_{MM} = 0.0007$, $\beta_{FM} = 0.0001$, $\beta_{FF} = 0.0002$, $\beta_{MF} = 0.0006$). Anthelmintic treatment is applied to females (A) and males (B). Male mouse numbers: M: —; female: F: -○-; mean parasites intensities of males: X_M: - - -; females: X_F: -●-.

as transmission, using a modelling approach and compared two, non-mutually exclusive hypotheses: sex-biased parasite transmission is caused by differences of immunity on transmission parameters between sexes, or is due to behavioural differences between males and females in the dissemination of infectious stages. Model simulations predicted sufficiently well the experimental field results for both hypotheses, highlighting that different dispersion of free-living larvae is needed for each hypothesis.

Observed differences in parasite load between sexes have drawn the attention of various researchers (Wilson et al., 2002). While many investigations have identified the role of host susceptibility, little evidence exists on sex influence over other traits of host–parasite interactions (Wilson et al., 2002). Recently, field studies on different host–parasite systems have provided evidence that host sex influences parasite transmission, with males being responsible for driving the infections (Skorping and Jensen, 2004; Ferrari et al., 2004). While it seems likely that the hosts that harbour more parasites are also the individuals with higher

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parasite transmission rates, field manipulation experiments of *H. polygyrus* in *A. flavicollis* did not corroborate this, suggesting that the mechanism that affects parasite transmission must reside in sex difference in host–parasite interaction rather than quantitative parasite load differences (Skorping and Jensen, 2004). The two mechanisms explored here involve alternative sex influences on host–parasite interactions implicating sex differences on the spreading of free-living stages either quantitatively or through their spatial distribution.

Sex differences in immune response of the host can affect the parasite's egg hatching rate or the survival of infective stages (Finkelman et al., 1997). Under such conditions, even if males and females harbour the same number of parasites and expel the same number of eggs per nematode, the qualitative/quantitative contribution to successful infective stages will be greater if they arise from hosts with a weak immune response. For example, males with reduced immunity, induced by testosterone, can distribute more successful free-living infective stages (Folstad and Karter, 1992). Our simulations suggest that the contribution of males to the pool of free-living infective stages is quantitatively more significant than the contribution from females.

Behavioural differences between the sexes may affect parasite transmission and determine a differential contribution to parasite persistence. When sex differences in behaviour influence the overall contact rate, a sex bias in parasite load would follow (Model 2, Fig. 8). Therefore, for transmission to be male-biased without strong male bias in parasite intensity, we need to assume that the free-living stages are split into two distinct sub-populations with respect to host sex. Among the different biological mechanisms that may occur in nature, one may be induced by territorial behaviour. For example, males of *Apodemus sylvaticus* tend to have more overlapping territories with their neighbours than females (Randolph, 1977). Thus, males would be more effective at transmitting parasites if the infective stages they produce are exposed to a greater number of hosts. A second possible mechanism considers that females may have more hygienic habits and tend to defecate away from nesting areas or interact only with a small number of males (de Mendonça, 2003. Aspects of the social ecology of the yellow-necked mouse *A. flavicollis*. Ph.D. Thesis. University of Cambridge, Cambridge). The results of these behavioural differences can be represented as two distinct free-living infective pools, which differ in their host sex origin, and the probability of encounter, where faeces from males are more often encountered than those from females. Our simulations suggest that once parasites are removed from males, there is a reduction in the infective larval pool and, consequently, the probability for a female to encounter the males' faeces decreases. Vice-versa, this should not occur when parasites are removed from females if their faeces are spread in areas that are not used or rarely used by the host population.

Our two proposed mechanisms are not mutually exclusive and under natural conditions it is likely they may occur simultaneously. Moreover, it is possible that other mechanisms may have been involved besides those analysed here. For example, our models assume that host sexes do not differ in their biological traits except for transmission rates (β) and parasite fertility (h). However, under wild conditions sexes may differ in their demographic traits, such as different lifespan, or mechanism of host–parasite interaction, such as parasite-induced host mortality, or differences in the proportion of larvae that develop to adult parasites or even differences in adult parasite lifespan. While these aspects have been deliberately omitted in our modelling, in order to focus on host–parasite interactions, preliminary simulations manipulating one parameter at a time would produce sex-bias in parasite intensity which has not been observed in the field (Ferrari et al., 2004). However, effects of sex differences on biological traits should be investigated in greater detail as multiple sex-related differences may counter-balance one another, producing an unbiased parasite load. In addition, our models do not include other important biological aspects such as seasonality or host reproduction that are known to have important effects on the dynamics of *A. flavicollis* and *H. polygyrus* (Gregory, 1992). We used flexible models and they can easily be modified to add these further levels of complexity in the future.

In conclusion, while we cannot quantitatively compare the model simulations with field results without more accurate parameter estimations, our simulations allowed us to investigate qualitative trends of the potential mechanisms responsible for sex bias in parasite transmission, allowing us to exclude the hypothesis that a sex-bias in parasite transmission is not simply related to an overall difference in host susceptibility/exposure. At the same time, the model simulations suggest that sexes can differ in their ability to spread the free-living parasite stages either through changes in host immunity or behaviour, emphasising that besides the effects on susceptibility, host gender may profoundly influence the dynamics of host–parasite interactions. This study is a step towards our understanding of the mechanisms causing sex-biased parasite transmission, and provides the basis for future experiments.

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Appendix A

We studied the values of N, X and L at an equilibrium point of Model 1. Setting the right hand sides of (1)–(3) to 0, we obtain:

$$N = K[1 - \alpha X/(b-d)]$$
$$\beta\psi L = X[\sigma + b + \alpha(X/k + 1)]$$
$$L = hNX/(\delta + \beta N)$$

The first equation yields N, once X is known. Substituting the third into the second, and using N as given by the first, one obtains the following equation:

$$\beta\psi hK[1 - \alpha X/(b-d)] = [\sigma + b + \alpha(X/k + 1)] \times [\delta + \beta K(1 - \alpha X/(b-d))] \quad \text{(A1)}$$

from which the equilibrium value of X can be found, hence those of N and L.

Going in the other direction, if we know the equilibrium values of (1)–(3), the parameter values have to be such that Eq. (A1) is satisfied.

In particular, if we wish to estimate β and h, we find:

$$h = \frac{[\sigma + b + \alpha(X/k + 1)][\delta + \beta K(1 - \alpha X/(b-d))]}{\beta\psi K[1 - \alpha X/(b-d)]} \quad \text{(A2)}$$

References

Anderson, R.M., May, R.M., 1978. Regulation and stability of host–parasite population interactions. I Regulatory processes. Journal of Animal Ecology 47, 219–247.

Begon, M., Bowers, R.G., 1995. Beyond host-pathogen dynamics. In: Grenfell, B.T., Dobson, A.P. (Eds.), Ecology of Infectious Diseases in Natural Populations. Cambridge University Press, Cambridge, pp. 478–509.

Dobson, A.P., Hudson, P.J., 1992. Regulation and stability of a free-living host parasite system – *Trichostrongylus tenuis* in Red Grouse. II Population models. Journal of Animal Ecology 61, 487–498.

Enriquez, F.J., Scarpino, V., Cypress, R.H., Wassom, D.L., 1988. *In vivo* and *in vitro* egg production by *Nematospiroides dubius* during primary and challenge infections in resistant and susceptible strains of mice. Journal of Parasitology 74, 262–266.

Fernàndez, S., Šarkunas, M., Roepstorff, A., 2001. Survival of infective *Ostertagia ostertagi* larvae on pasture plots under different simulated grazing conditions. Veterinary Parasitology 96, 291–299.

Ferrari, N., Cattadori, I.M., Nespereira, J., Rizzoli, A., Hudson, P.J., 2004. The role of host sex in parasite dynamics: field experiments on the yellow-necked mouse *Apodemus flavicollis*. Ecology Letters 7, 88–94.

Finkelman, F.D., Shea-Donohue, T., Goldhill, J., Sullivan, C.A., Morris, S.C., Madden, K.B., Gause, W.C., Urban Jr., J.F., 1997. Cytokine regulation of the host defence against parasitic gastrointestinal nematodes: lessons from studies with rodents models. Annual Review of Immunology 15, 505–533.

Folstad, I., Karter, A.J., 1992. Parasites, bright males and the immunocompetence handicap. American Naturalist 139, 603–622.

Greenman, J.V., Hudson, P.J., 2000. Parasite-mediated and direct competition in a two-host shared macroparasite system. Theoretical Population Biology 57, 13–34.

Gregory, R.D., 1992. On the interpretation of host–parasite ecology: *Heligmosomoides polygyrus* (Nematoda) in wild wood mouse (*Apodemus sylvaticus*) populations. Journal of Zoology (London) 226, 109–121.

Gregory, R.D., Keymer, A.E., Clarke, J.R., 1990. Genetics, sex, and exposure: the ecology of *Heligmosomoides polygyrus* (Nematoda) in the wood mouse. Journal of Animal Ecology 59, 363–378.

Gromov, V., 2006. Territory marking in gerbils: verification of Gosling's hypothesis. Hystrix, The Italian Journal of Mammalogy (Suppl. 2006), 57–59.

Iannelli, M., Martcheva, M., Milner, F.A., 2005. Gender-structured population modelling: mathematical methods, numerics and simulationsFrontiers in Applied Mathematics. SIAM, Philadelphia, USA.

Ims, R.A., 1987. Response in spatial organisation and behaviour to manipulations of the food resource in the vole *Clethrionomys* rufocanus. Journal of Animal Ecology 56, 585–596.

Keymer, A.E., Hiorns, R.W., 1986. *Heligmosomoides polygyrus* (Nematoda): the dynamics of primary and repeated infection in outbred mice. Proceedings of the Royal Society, London B 229, 47–67.

Poulin, R., 1996. Sexual inequalities in helminth infections: a cost of being males? American Naturalist 147, 287–295.

Randolph, S.E., 1977. Changing spatial relationships in a population of *Apodemus sylvaticus* with the onset of breeding. Journal of Animal Ecology 46, 653–676.

Rosso, F., Manfredi, M.T., Ferrari, N., Scalet, G., Rizzoli, A., 2002. Nematode infections in *Apodemus* spp. and *Clethrionomys glareolus* (Shreber, 1780) from Trentino (Italian Alps). Parassitologia 44 (Suppl. 1), 163.

Scott, M.E., 1990. An experimental and theoretical study of the dynamics of mouse-nematode (*Heligmosomoides polygyrus*) interaction. Parasitology 101, 75–92.

Shaw, D.J., Dobson, A.P., 1995. Patterns of macroparasite abundance and aggregation in wildlife populations: a quantitative review. Parasitology 111 (Suppl.), S111–S133.

Shaw, D.J., Grenfell, B.T., Dobson, A.P., 1998. Patterns of macroparasite aggregation in wildlife host populations. Parasitology 117, 597–610.

Skorping, A., Jensen, K.H., 2004. Disease dynamics: all caused by males? TRENDS in Ecology and Evolution 19, 219–220.

Slater, A.F.G., Keymer, A.E., 1988. The influence of protein deficiency on immunity to *Heligmosomoides polygyrus* (Nematoda) in mice. Parasite Immunology 10, 507–522.

Tanguay, G.V., Scott, M.E., 1992. Factors generating aggregation of *Heligmosomoides polygyrus* (Nematoda) in laboratory mice. Parasitology 104, 519–529.

Tompkins, D.M., Greenman, J.V., Robertson, P.A., Hudson, P.J., 2000. The role of shared parasites in the exclusion of wildlife hosts: *Heterakis gallinarum* in the ring-necked pheasant and grey partridge. Journal of Animal Ecology 69, 829–840.

Wilson, K., Bjørnstad, O.N., Dobson, A.P., Merler, S., Poglayen, G., Randolph, S.E., Read, A.F., Skorping, A., 2002. Heterogeneities in macroparasite infections: patterns and processes. In: Hudson, P.J., Rizzoli, A., Grenfell, B.T., Heesterbeek, H., Dobson, A.P. (Eds.), The Ecology of Wildlife Disease. Oxford University Press, Oxford, pp. 6–44.

Woolhouse, M.E.J., Dye, C., Etard, J.F., Smith, T., Charlwood, J.D., Garnett, G.P., Hagan, P., Hii, J.L.K., Ndhlovu, P.D., Quinnell, R.J., Watts, C.H., Chandiwana, S.K., Anderson, R.M., 1997. Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. Proceedings of the National Academy of Sciences USA 94, 338–342.

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