A model to explain the replacement of *Schistosoma intercalatum* by *Schistosoma haematobium* and the hybrid *S. intercalatum* × *S. haematobium* in areas of sympatry

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SUMMARY

Numerous hypotheses have been postulated to explain the rapidly changing parasitological situation in Loum, Cameroon as a result of the interaction between *Schistosoma haematobium* and *S. intercalatum*. The aim of this study is to test the various hypotheses using a simple mathematical model, incorporating equal and unequal sex ratios of adult schistosomes, recombinations, and levels of compatibility with the intermediate molluscan hosts, *B. forskalii* and *B. truncatus*. The model assuming an equal sex ratio does not fit with the existing field data in that it predicts a continued presence of *S. intercalatum*, *S. haematobium* and the hybrids. The model assuming a sex bias in favour of males, which reflects the situation usually observed in schistosome populations, predicts the loss *S. intercalatum* which indeed concurs with the most recent data.

Key words: geographical distribution, mathematical model, *Schistosoma haematobium*, *Schistosoma intercalatum*, hybrids, *Bulinus forskalii*, *Bulinus truncatus*, unequal sex ratio.

INTRODUCTION

In Loum, Cameroon, field observations clearly show that *Schistosoma haematobium* and the hybrid of *S. haematobium* and *Schistosoma intercalatum* have completely replaced *S. intercalatum* in a period of less than 30 years (Southgate & Rollinson, 1980; Tchuem Tchuenté *et al*. 1997).

S. haematobium utilizes at least 11 species of *Bulinus* spp. over its geographical range (Brown, 1994), but in Loum only *B. truncatus* transmits *S. haematobium* and only *Bulinus forskalii* transmits *S. intercalatum*. Unlike the parental species the hybrid parasite is able to develop in both *B. truncatus* and *B. forskalii* (Southgate, van Wijk & Wright, 1976).

Several hypotheses may explain why *S. haematobium* has replaced *S. intercalatum*. *S. haematobium* males are more successful than *S. intercalatum* males at pairing (Southgate *et al*. 1982) and this was thought to be one possible explanation of the replacement of *S. intercalatum* by *S. haematobium*. The superior advantage of male *S. haematobium* to mate with females of *S. intercalatum* is enhanced by the disequilibrium in sex-ratio, in favour of males.

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Sex-ratio desequilibrium in *Schistosoma* species has been reported in many species (Liberatos, 1987; Mitchell *et al*. 1990; Basch, 1991; Théron *et al*. 1992; Morand *et al*. 1993; Barral *et al*. 1996; Boissier, Morand & Moné, 1999; Morand & Müller-Graf, 2000). The causes of this unequal sex-ratio are not fully understood (Boissier *et al*. 1999), but the consequences in terms of population dynamics (May & Woolhouse, 1993; Morand *et al*. 1993) or sexual competition (Morand & Müller-Graf, 2000) are of importance.

The crossing of *S. haematobium* males and *S. intercalatum* females produces viable hybrids, the reverse cross (*S. haematobium* females and *S. intercalatum* males) is less fertile (Southgate *et al*. 1976). No significant differences in the percentage of infected surviving snails between hybrid and parental species were detected (Wright & Southgate, 1976). Hence, hybrids are compatible with both intermediate host snails. The hybrids are more infective to hamsters compared with the parental species and the uterine egg counts are greater than those of the parental species therefore suggesting increased fecundity (Wright & Southgate, 1976). The aim of this paper is to test the various hypotheses (see above) using a simple mathematical model explaining why *S. haematobium* replaces *S. intercalatum* in areas of sympatry incorporating unequal sex-ratio, recombination, and compatibility towards the intermediate hosts.

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MATERIALS AND METHODS

The model

A discrete time model was developed. The building of the model was based on previously published studies (Tchuem Tchuenté *et al*. 1996; Morand, Manning & Woolhouse, 1996; Morand, Pointier & Théron, 1999).

Three genetic entities were considered with compatibility determined by a simple genetic determinism (1 locus, 2 alleles): (i) pure *S. haematobium*, which infects only *B. truncatus* as intermediate host; (ii) pure *S. intercalatum*, which infects only *B. forskalii* as intermediate host; (iii) hybrid, which infects both *B. truncatus* and *B. forskalii* as intermediate hosts (Fig. 1). All parasite entities infect human as definitive hosts.

The dynamics of snail infection are as follows

$$\Delta y_i = \beta \Phi(q_i, m_i, k) \lambda_i m_i H - \mu_j y_i, \quad (1)$$

where i is the parasite genetic entity, y is the prevalence of snail infection, β is the rate of miracidium infection, λ_i is the fecundity of adult worms of genetic entity i, μ_j is the mortality rate of snails of species j and H is the number of humans.

According to May & Woolhouse (1993) the expression of the mating probability taking into account sex ratios is $\Phi(q_i, m_i, k)$

$$\Phi(q_i, m_i, k) = \mathcal{J}(q_i) - 2(1-q_i) I(k, \alpha_i, \gamma_i),$$

where $\mathcal{J}(q_i) = 1$ for $q_i < 1/2$

$$\mathcal{J}(q_i) = (1-q_i)/q_i \text{ for } q_i > 1/2$$

$$I(k, \alpha_i, \gamma_i) = \frac{(1-\alpha_i)^{1+k}}{\pi} \int_0^{\pi} \frac{(\sin^2\theta)\, d\theta}{(1+\alpha_i\gamma_i \cos\theta)^{1+k}(1+\gamma \cos\theta)},$$

where $\gamma_i = 2(p_i q_i)^{1/2}$ and $\alpha_i = m_i/(m_i+k)$; and q_i is the proportion of females of genetic entity i, and $p_i = (1-q_i)$ is the proportion of males of genetic entity i, m_i is the mean number of parasites of genetic entity i per host, and k is the binomial negative parameter (it is assumed that k is the same whatever the genetic entity of the parasites).

The dynamics of adult worms in humans, following Morand *et al*. (1999), are

$$\Delta m_i = \gamma S_i y_i - m_i(\mu_i + \mu_h + \delta_i) - \frac{(\mu_i + \delta_i)(k+1) m_i^2}{k}, \quad (2)$$

where γ_i is the rate of infection of cercariae, μ_h is the human mortality rate, μ_i is the adult mortality rate of worm of genetic entity i, δ_i is the interspecific competition, and S_i is the density of snails of species i.

Within humans, it is assumed that pairing among worms follows a series of events (Fig. 1): (i) *S. haematobium* males first mate with *S. haematobium* females, (ii) the unmated *S. haematobium* males mate with *S. intercalatum* females and secondly with hybrid females, and (iii) the *S. intercalatum* males mate with unmated *S. intercalatum* females and the hybrid males mate with unmated hybrid females. These correspond to the following steps of computation. Step 1: compute the mean number of *S. haematobium* females mated (m_{haef}) with *S. haematobium* males

$$m_{haef} = q_{hae} * m_{hae} * \Phi(m_{hae}, q_{hae}, k),$$

where q_{hae} is the proportion of *S. haematobium* females and m_{hae} the abundance of *S. haematobium* males and females. Step 2: compute the mean number of *S. intercalatum* females mated with unmated *S. haematobium* males. The mean number of unmated *S. haematobium* males is

$$m_{haem1} = (1-q_{hae}) * m_{hae} * (1 - \Phi(m_{hae}, q_{hae}, k))$$

and the mean number of *S. intercalatum* females mated with *S. haematobium* males is

$$m_{intf\times haem} = q_a * m_a * \Phi(q_a, m_a, k),$$

where q_a is the proportion of *S. intercalatum* females to the unmated *S. haematobium* males, m_a is the mean number of *S. intercalatum* females and unmated *S. haematobium* males. Step 3: compute the mean number of hybrid females mated with remaining unmated *S. haematobium* males. The mean number of remaining unmated *S. haematobium* males is

$$m_{haem2} = m_{haem1} - m_{intf\times haem1}$$

then, the mean number of hybrid females mated with remaining unmated *S. haematobium* males is

$$m_{hyb\times haem2} = q_b * m_b * \Phi(q_b, m_b, k),$$

where q_b is the proportion of hybrid females to the unmated *S. haematobium* males and m_b the mean number of hybrid females and unmated *S. haematobium* males. Step 4: compute the mean number of mated hybrid females with hybrid males. The mean number of unmated hybrid females is:

$$m_{hybf1} = (mh_{yb} * q_{hyb} - m_{hyb\times haem2})$$

then, the mean number of mated hybrid females with hybrid males is

$$m_{hybf2} = q_c * m_c * \Phi(q_c, m_c, k),$$

where q_c is the proportion of unmated hybrid females to the hybrid males and m_c the mean number of hybrid males and unmated hybrid females. Step 5: compute the mean number of *S. intercalatum* females mated with *S. intercalatum* males. The mean number of remaining unmated *S. intercalatum* females is

$$m_{intf1} = m_{intf\times haem1} - q_{int} * m_{int}.$$

Then, the mean number of mated *S. intercalatum* females with *S. intercalatum* males is:

$$m_{intf2} = q_d * md * \Phi(q_d, m_d, k),$$

where q_d is the proportion of unmated *S. intercalatum* females to *S. intercalatum* males, and m_d is the mean

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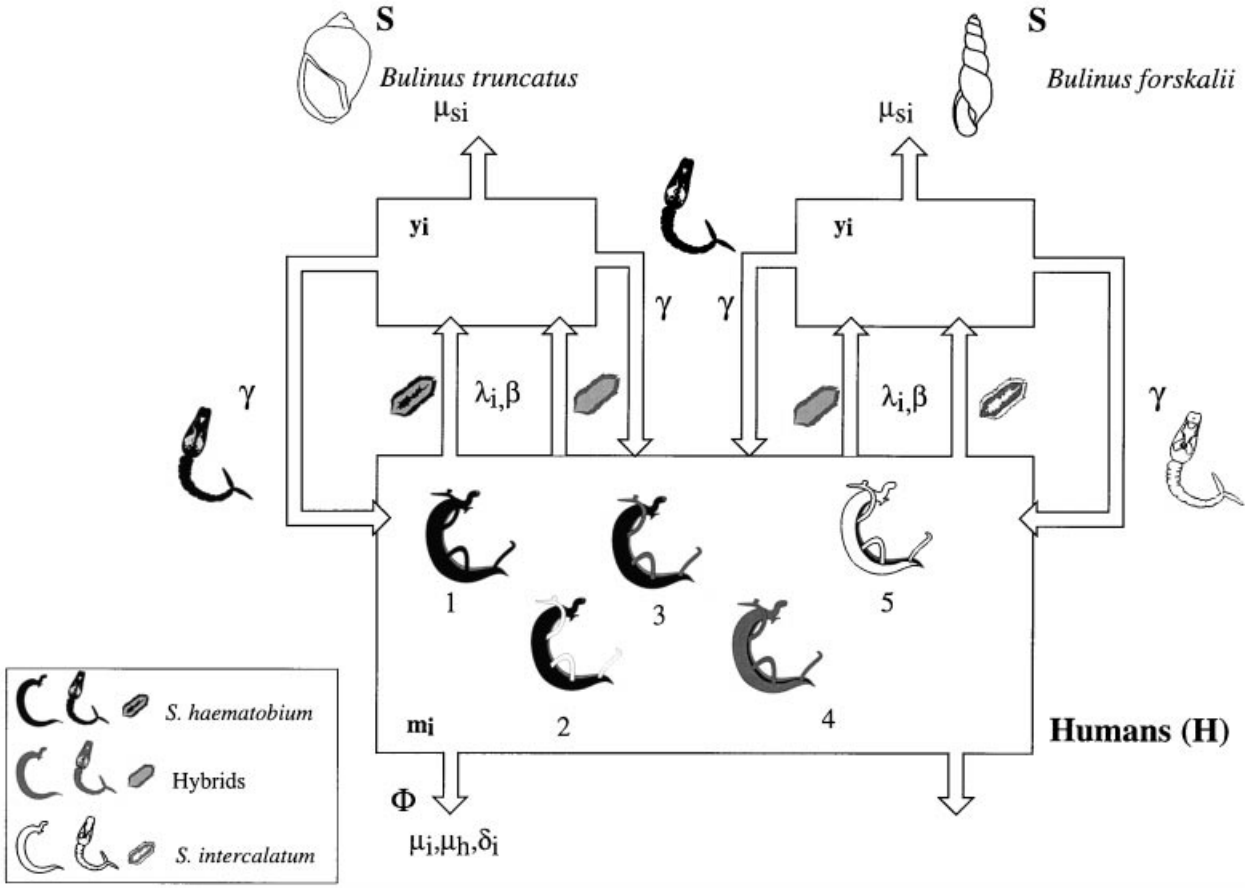

Fig. 1. Flowchart of the model (see Materials and Methods section).

Table 1. Values of the parameters used in the model

(Data from Trouvé *et al.* 1998; Loker, 1983; Morand *et al.* 1999.)

Parameters	*S. intercalatum*	*S. haematobium*	Hybrid *S. intercalatum* × *S. haematobium*
Fecundity (day) (λ)	207	166	> 207
Adult longevity (days) (μ)	2555	3832·5	Assumed to be within the parental species
Sex ratio (males to females)	40 % Females[1]	26 % Females[2]	Assumed to be within the parental species
Cercariae production (total)	2729	5091	Assumed to be within the parental species (?)
Rate of miracidium infection (β)	5×10^{-7}	5×10^{-7}	5×10^{-7}
Rate of cercaria infection (γ)	0·4	0·4	0·4
Interspecific competition between adult stages (γ)	0·001	0·001	0·001
Snail species	*B. forskalii*	*B. truncatus*	*B. forskalii* *B. truncatus*
Snail longevity (μ_3)	1 month	1 month	–
Snail density[3]	1614	572	–

[1] Wright *et al.* (1972).
[2] Wright & Bennett (1967) (Hamsters).
[3] Southgate *et al.* (1976).

number of unmated *S. intercalatum* females and *S. intercalatum* males. We consider that the probabilities of *S. intercalatum* males mating with hybrid females or *S. haematobium* females are negligible.

At the end, using equation (1), we computed (i) the changes in prevalence of *S. haematobium* in *B. truncatus*, which are infected by miracidia produced by *S. haematobium* females mated with *S. haematobium* males (m_{haef}) and 1/4 miracidia produced by hybrid females mated with hybrid males (m_{hybf2}) and 1/2 miracidia produced by hybrid females mated with *S. haematobium* males ($m_{hyb \times haem2}$); (ii) the changes in

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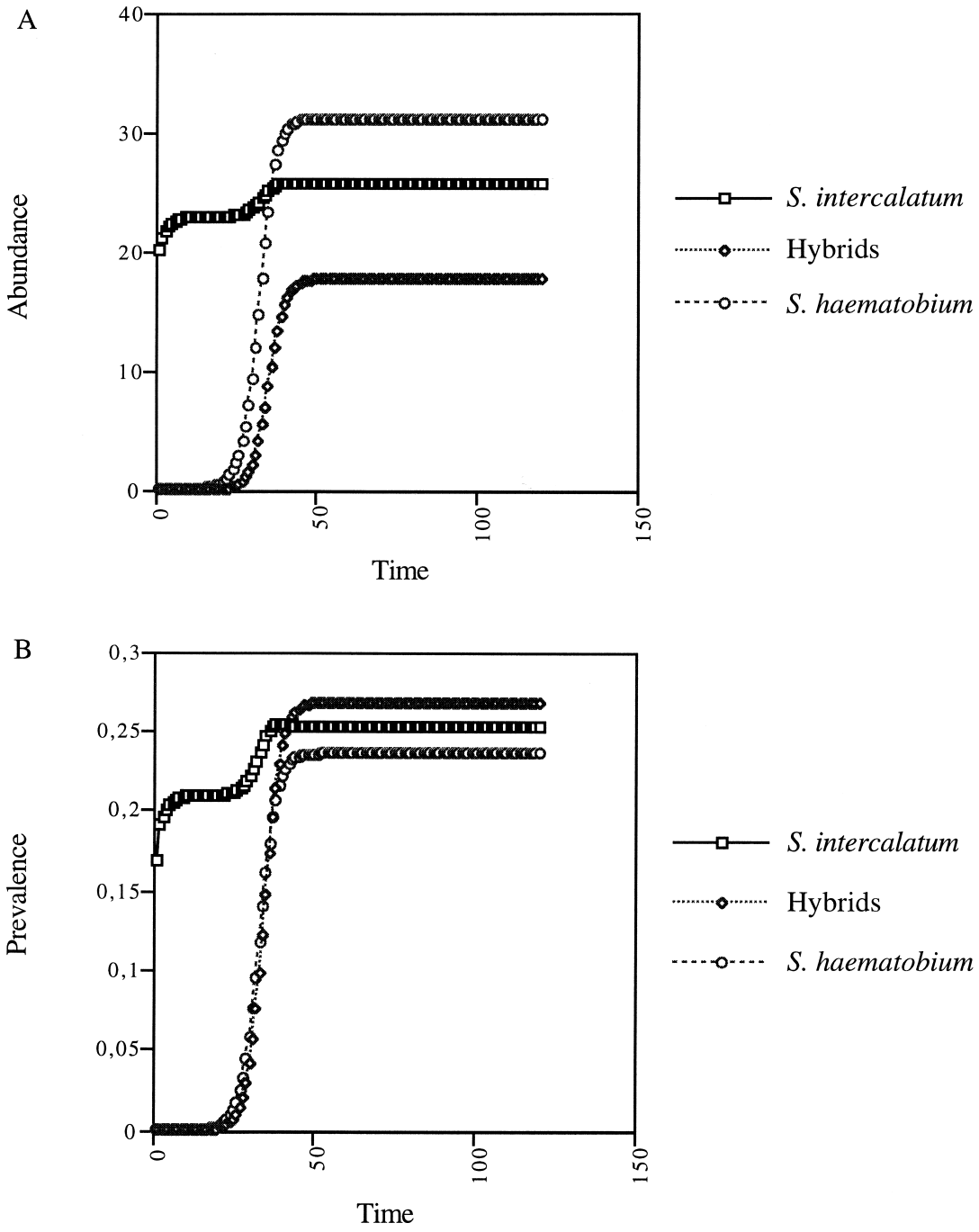

Fig. 2. Simulation results with equal sex-ratio (values of parameters in Table 1). Changes in abundance (A) and in snail prevalence (B) of each genetic entity (*Schistosoma intercalatum*, *S. haematobium*, and their hybrids) following the introduction of *S. haematobium*.

prevalence of *S. intercalatum* in *B. forskalii*, which are infected by miracidia produced by *S. intercalatum* females mated with *S. intercalatum* males (m_{intf2}) and 1/4 miracidia produced by hybrid females mated with hybrid males (m_{hybf2}), and (iii) the changes in prevalence of hybrids in both *B. truncatus* and *B. forskalii*, which are infected by miracidia produced by *S. intercalatum* females mated with *S. haematobium* males ($m_{intf\times heam1}$), 1/2 miracidia produced by hybrid females mated with hybrid males (m_{hybf2}), and 1/2 miracidia produced by hybrid females mated *S. haematobium* males ($m_{mhyb\times haem2}$).

The changes in abundance of worms of different genetic entities are now given by equation (2).

RESULTS

Two models were simulated. The first one assumes an equal sex-ratio of worms (all $q_i = 0{\cdot}5$) and the second assumes an unequal sex-ratio. The values of most parameters used in the model are taken from the literature (Table 1). However, 3 parameters are unknown, δ, the intraspecific competition between adult worms and we used an estimation ($\delta = 0{\cdot}001$)

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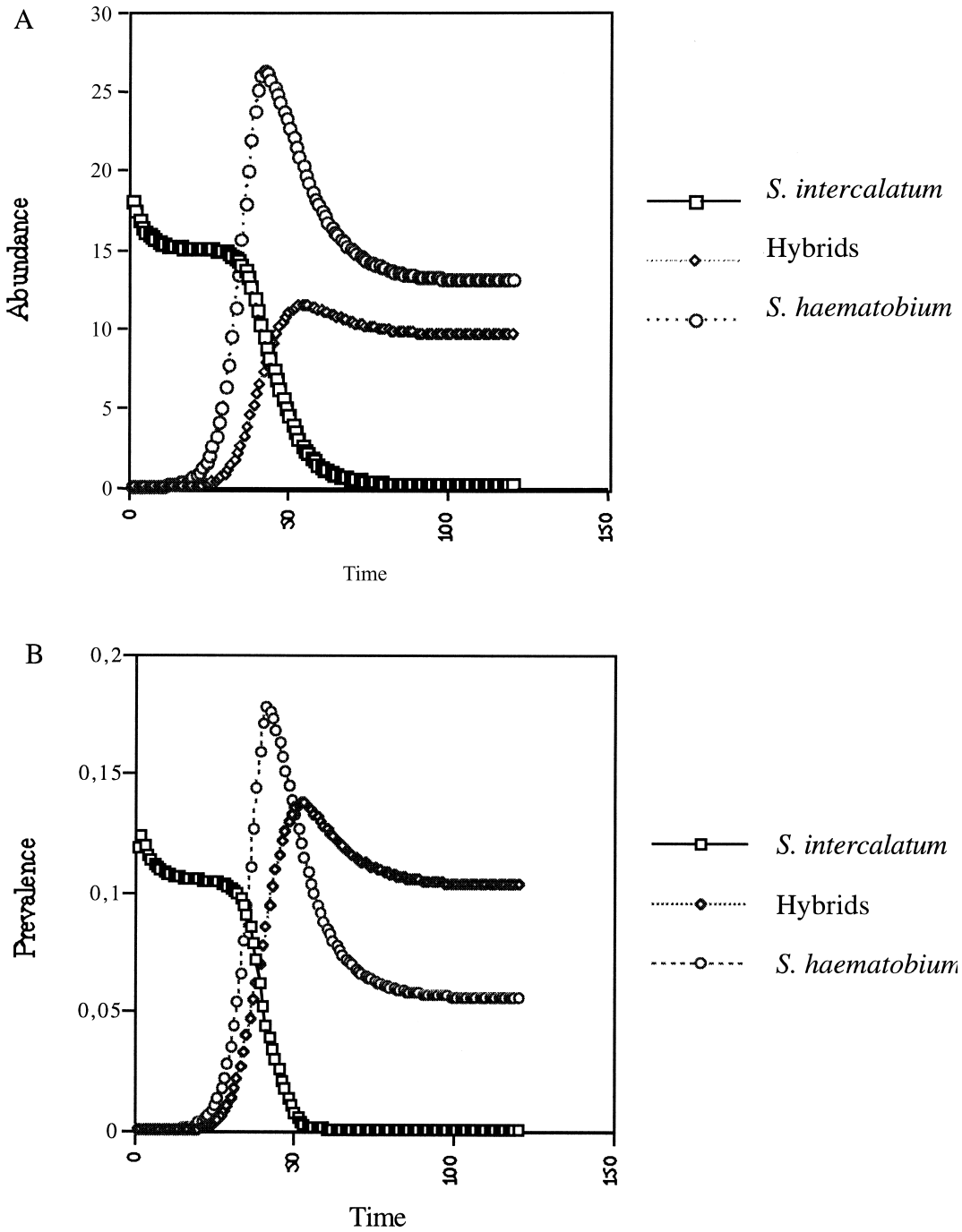

Fig. 3. Simulation results with unequal sex-ratio (values of parameters in Table 1). Changes in abundance (A) and in snail prevalence (B) of each genetic entity (*Schistosoma intercalatum*, *S. haematobium*, and their hybrids) following the introduction of *S. haematobium*. Unequal sex ratio leads to the replacement of *S. intercalatum* by *S. haematobium*, and the hybrids.

given by Morand *et al.* (1999). The second, β, the rate of infection is very low (Morand *et al.* 1999) and is assumed to equal 0·0000005. The third is the rate of cercariae infection, γ, which is assumed to be equal to 0·4 for all genetic entities.

Equal sex-ratio

The result of the simulation is given on Fig. 2. Following the introduction of *S. haematobium*, a rapid increase in both mean abundance in the definitive hosts and prevalence in the intermediate hosts of all entities is observed.

Unequal sex ratio

The introduction *S. haematobium* is followed by a dramatic decrease and extinction of *S. intercalatum* in less than 30 years of simulation (Fig. 3). However, the hybrid entity remains stable over time. The

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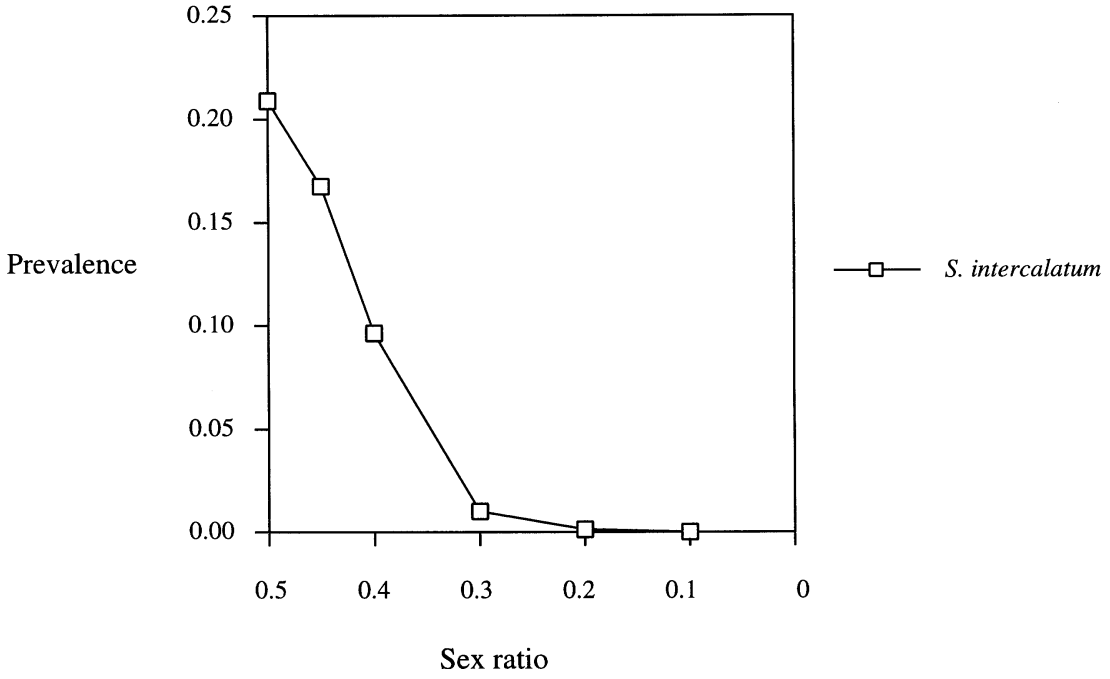

Fig. 4. Sensitivity analysis of the effect of unequal sex ratio on the prevalence of *Schistosoma intercalatum* following the introduction of *S. haematobium*.

values of parameters do not dramatically effect the output simulations in both cases (equal or unequal sex ratio), but have only an effect on the times needed to reach the equilibrium. The relative values of abundances and prevalences of each genetic entity are not affected. Nevertheless, better estimates of some parameters, such as δ, β, γ, are necessary in order to describe accurately the dynamics through time.

However, changes in sex ratio have a dramatic effect on the persistence of *S. intercalatum* (Fig. 4). The decrease in equilibrium values of prevalence of *S. intercalatum* in snails is directly linked with an increase of sex ratio bias toward adult males.

DISCUSSION

There is evidence of numerous occurrences of natural hybridization between *S. intercalatum* and *S. haematobium* in Cameroon and Gabon, respectively (Southgate *et al.* 1976; Ratard & Greer, 1991; Burchard & Kern, 1985; Zwingenberger *et al.* 1990). The situation in Loum, Cameroon has been monitored at irregular intervals over a period of approximately 30 years (van Wijk, 1969*a*; Southgate *et al.* 1976; Rollinson & Southgate, 1985; Tchuem Tchuenté *et al.* 1997). In the late 1960s *S. intercalatum* was the only species of schistosome found in the human population, with a prevalence rate of 54·2 % in children aged between 4 and 15 years (van Wijk, 1969 *b*). *S. haematobium* became established in Loum, possibly as a result of environmental changes i.e. deforestation facilitating the establishment of *Bulinus truncatus*, an intermediate host of *S. haematobium*, in the streams of Loum, a prerequisite for the creation of a focus of *S. haematobium*. After *S. haematobium* became established occurrences of hybridization between the two species of schistosome soon occurred, and in a comparatively short period, less than 30 years, *S. haematobium* completely replaced *S. intercalatum* through introgression (Southgate *et al.* 1976; Tchuem Tchuenté *et al.* 1997). Therefore the pathological symptoms suffered by the those infected changed gradually from the mesenteric vessels and the alimentary canal (*S. intercalatum*) to the urinary tract and bladder (*S. haematobium* and the hybrid of *S. haematobium* male × *S. intercalatum* female).

Experimental studies are in progress using molecular techniques, examination of ribosomal and mitochondrial genes, to characterize recent isolates from Loum collected in 1998, 2000 and to search for genes that are common to *S. intercalatum* and/or *S. haematobium*.

As stated in the introduction numerous hypotheses have been postulated to explain the rapidly changing situation in Loum, Cameroon as a result of the interaction between *S. haematobium* and *S. intercalatum*. The aim of this study is to test the various hypotheses using a simple mathematical model, incorporating equal and unequal sex ratios of adult schistosomes, recombinations, and levels of compatibility with the intermediate molluscan hosts, *B. forskalii* and *B. truncatus*.

The 2 models proposed assume either an equal or an unequal sex ratio of adult schistosomes. Interestingly, the model that is produced assuming an equal sex ratio does not fit with the existing field data

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in that it predicts a continued presence of *S. intercalatum*, *S. haematobium* and the hybrids. The field data suggest the loss of *S. intercalatum*, and possibly the hybrids from the Loum focus (Tchuem Tchuenté *et al*. 1997). However, the model assuming a sex bias in favour of males, which reflects the situation usually observed in schistosome populations, predicts the loss of *S. intercalatum* which indeed concurs with the most recent data (Tchuem Tchuenté *et al*. 1997). The model predicts the persistence of the hybrid population in addition to that of *S. haematobium*, but the most recent interpretation is that only *S. haematobium* now exists in Loum, Cameroon (Tchuem Tchuenté *et al*. 1997). These data are based primarily on morphological and biological criteria. However, Webster (personal communication) using single-stranded conformational polymorphism (SSCP) analysis of the nuclear, ribosomal second internal transcribed spacer (ITS2) has demonstrated that hybrids were still present in Loum in the year 2000. Using this approach Webster (personal communication) compared samples of natural populations of schistosomes isolated in 1990, 1999 and 2000 with laboratory-produced hybrids. She was able to show that in 1990 100% of individuals with characteristic hybrid eggs gave a hybrid profile, whereas the overall figure for hybrids dropped to the 5% level in the 1999 and 2000 samples. Perhaps surprisingly, no individual worm analysed gave a *S. intercalatum* profile. Clearly, when assessing the situation in Loum the presence/absence of hybrids cannot be based solely on morphological and biological data, it is essential to use more sophisticated molecular methods. Nevertheless, it should be recognized that the current model assumes a simple determination of compatibility with the intermediate hosts (1 locus, 2 alleles) but the actual situation may be much more complex. For example, a model incorporating several loci (i.e. neutral genetic markers) will lead to a complete disappearance of the hybrids. Nevertheless, it appears that the unequal sex ratios in schistosome populations in favour of the male sex, and the greater ability of male *S. haematobium* worms to pair with female worms than male *S. intercalatum*, are critical factors in driving the outcome of this interaction, that is, the replacement of *S. intercalatum* by *S. haematobium* through introgression. The model has clear implications for the distribution of *S. intercalatum* explaining why there is little correlation between the distribution of the parasite and that of its intermediate and definitive hosts. It seems highly probable that *S. intercalatum* is at risk of elimination when the parasite becomes sympatric with the much more widely distributed *S. haematobium*, and provides an explanation of why *S. intercalatum* is firmly established, for example on Sao Tomé where there is no known interaction with *S. haematobium* or *S. mansoni* or in the Edea focus, Cameroon where the intermediate hosts for *S. haematobium* and *S. mansoni* are not present (Jourdane *et al*. 2002). Tchuem Tchuenté *et al*. (1996) demonstrated in a series of laboratory experiments that *S. intercalatum* is at a disadvantage when it is sympatric with *S. mansoni*. However, in the natural situation it seems that sympatry between *S. intercalatum* and *S. haematobium* is more common than between *S. intercalatum* and *S. mansoni*.

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