Coevolutionary interactions between host life histories and parasite life cycles

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SUMMARY

Several recent studies have discussed the interaction of host life-history traits and parasite life cycles. It has been observed that the life-history of a host often changes after infection by a parasite. In some cases, changes of host life-history traits reduce the costs of parasitism and can be interpreted as a form of resistance against the parasite. In other cases, changes of host life-history traits increase the parasite's transmission and can be interpreted as manipulation by the parasite. Alternatively, changes of host's life-history traits can also induce responses in the parasite's life cycle traits. After a brief review of recent studies, we treat in more detail the interaction between the microsporidian parasite *Edhazardia aedis* and its host, the mosquito *Aedes aegypti*. We consider the interactions between the host's life-history and parasite's life cycle that help shape the evolutionary ecology of their relationship. In particular, these interactions determine whether the parasite is benign and transmits vertically or is virulent and transmits horizontally.

Key words: host–parasite interaction, life-history, life cycle, coevolution.

INTRODUCTION

Host–parasite relationships coevolve. This rather obvious statement forms the basis for many current ideas about sexual selection (Hamilton & Zuk, 1982) and the maintenance of sexual reproduction (Hamilton, Axelrod & Tanese, 1990; Ladle, 1992). However, in most other areas of research on host–parasite relationships the possibility of coevolution is generally neglected. Most studies, for example, on the evolution of parasite virulence consider evolutionary pressure on the parasite while holding the host constant (Frank, 1996). A reasonable justification for this approach is that parasites often have shorter generation times, higher population densities and higher mutation rates than their hosts; thus the parasite is expected to evolve much more rapidly (Hafner *et al.* 1994).

However, many parasites have generation times that are similar to, or even longer than, their host's. To illustrate this, two examples should suffice. First, various nematodes have identical generation times as their insect hosts, e.g. mermithid parasites of mosquitoes (Blackmore, 1994). Second, the microsporidian *Edhazardia aedis* often requires two generations of its mosquito host to complete its life cycle. In such cases coevolutionary interactions – where host and parasite evolve in response to each other's pressure – can be important.

In this paper, we discuss one aspect of this coevolution: the interactions between host life-history and parasite life cycle. We review some recent studies that have investigated the evolutionary pressure of the parasite on the host's life-history and vice versa (see Michalakis & Hochberg [1994] for a similar review). Then we consider in more detail the relationship between the microsporidian parasite *Edhazardia aedis* and its host, the yellow fever mosquito *Aedes aegypti*.

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A BRIEF REVIEW

Parasites often manipulate their host's life-history to enhance their transmission. Parasites that castrate their hosts are extreme examples of this (Kuris, 1974). The decreased reproductive effort by the host following castration presumably gives rise to higher host survivorship and more rapid growth, which in turn gives rise to higher parasite transmission (Baudoin, 1975) (although this view has been disputed [Ballabeni, 1995; Minchella, 1985]). Though there has been a tendency to focus on castration of animal hosts, it also occurs, with some interesting variations, in plants infected by systemic fungi. The vertical transmission of many fungi is more efficient through vegetative buds than through sexually produced seeds; accordingly some fungi prevent their host plants from reproducing sexually, but increase asexual reproduction and thereby increase their transmission (reviewed in Clay [1991]). The fungus *Atkinsonella hypoxylon* destroys only the outcrossed seeds of grasses in the genus *Danthonia*, but uses their self-fertilised seeds as a means of vertical transmission (Clay & Kover, 1996). The anther-smut fungus *Microbotryum violaceum*, which infects the dioecious plant *Silene latifolia* , not only castrates its host by causing females to produce a

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sterile, rudimentary ovary, but also induces the female flowers to produce anthers (Alexander, 1989). In neither males nor females do the anthers contain any pollen; instead they contain the fungal spores that are transmitted by the plant's insect pollinators. Furthermore, infected plants are more likely to initiate flowering during their first growing season and produce more flowers; both factors are suggested to increase the plant's attractiveness to pollinators and thus the transmission of the fungus (Shykoff & Kaltz, 1997).

Other changes of the host's life-history can be seen as an adaptation by the host to reduce the parasite's effect. Such changes can, of course, come in two varieties: phenotypic and genetic evolutionary changes. Phenotypic changes were first shown in the snail *Biomphalaria glabrata* in response to the trematode parasite *Schistosoma mansoni*: exposed snails mature earlier and initially produce more eggs than uninfected snails (Minchella & Loverde, 1981). The increased early reproductive effort is thought to partly compensate for later losses due to the parasite. Thus the response of the snail can be thought of as an expression of trade-offs among life-history traits, trade-offs that are influenced by parasite infection (Minchella & Loverde, 1983). Great tits provide a further example of life-history responses to parasitism. If males are forced to work harder in order to keep their chicks fed (Tripet & Richner, 1997), they are more likely to become infected with malaria (Norris, Anwar & Read, 1994; Richner, Christe & Oppliger, 1995). Furthermore, malaria prevalence is higher among females that have compensated for the removal of two eggs by laying an additional one (Oppliger, Christe & Richner, 1996). Finally, if nests are experimentally infested with hen fleas, the males increase their reproductive effort (at the possible cost of their future reproductive success) to compensate for the damage induced by the fleas (Christe, Richner & Oppliger, 1996). A similar example comes from the lizard *Lacerta vivipara*, that increases its clutch size, and thus its reproductive effort, when it is heavily infected with endocellular haemogregarines (Sorci, Clobert & Michalakis, 1996). Though parasite load itself is not associated with survival, the lizards that increase reproductive effort suffer higher mortality, in agreement with classical life-history theory (Sorci *et al.* 1996).

If the trade-offs between life-history theory traits and parasite resistance have a genetic basis, parasite pressure can lead to an evolutionary change in a host's life-history. The theoretical background for this can be illustrated by considering the evolution of age at first reproduction: if hosts are subjected to severe parasite pressure and if they are unable to resist the parasite by other means, they will evolve to mature earlier (Hochberg, Michalakis & de Meeus, 1992). Examples documenting either a genetic correlation of resistance with a host's life-history or an evolutionary response of the life-history are rare. Recently, a genetic correlation was found in the mosquito *Aedes aegypti*. Selection of mosquitoes for resistance to malaria infection brought with it a correlated response in two life-history traits: developmental time and adult size of the mosquitoes (Yan, Severson & Christensen, 1997). The silene *S. latifolia* and its fungal parasite *M. violaceum*, mentioned above, may offer an example of an evolutionary response of the host's life-history. Since long-lived flowers are at a higher risk of contracting the fungus than short-lived flowers (Shykoff, Bucheli & Kaltz, 1996), the fungus should select for shorter-lived flowers. This selection pressure would be counteracted by the necessity for the female flowers to be open long enough for pollination to occur. Therefore, the parasite has been suggested to be one of the selection pressures that led to the difference in longevity of male and female flowers (Shykoff *et al.* 1996).

Little is known about the evolutionary influence of the host's life-history characteristics on the parasite; most of our knowledge is based on nematode worms. Comparative studies have shown that large, long-lived hosts are associated with large nematode worms (Morand & Sorci, 1997; Poulin, 1996; Sorci, Morand & Hugot, 1997). The longest known nematode, *Placentonema gigantissima*, is 7500 mm long, and was discovered in the placenta of a sperm whale (Skrjabin, 1949; Skorping & Read, personal communication). In a second example, the virulence of nematodes infecting fig wasps is influenced by details of the wasps' life cycles (Herre, 1993). Female wasps enter a fig to lay their eggs (and pollinate the fig); the development of the offspring takes place within the fig. Each species of wasp is infected by an associated species of nematode; worms hatch from the foundress wasp within the fig and infect the next generation of wasps. In some wasp species, several wasps usually colonize an individual fig. The nematodes of these wasps have higher virulence (measured as the reduction of the infected wasp's fecundity) than those specific to wasps that colonize figs individually. There are several possible explanations for this pattern (Herre, 1993; Lipsitch, Herre & Nowak, 1995). First, in figs colonized by individual wasps, parasites must transmit vertically from infected females to their offspring. This links the transmission success of the parasite to the reproductive success of the host and selects for low virulence. Second, in individually colonized figs it is also likely that nematodes compete with their close relatives for infection of the next host generation, which relaxes the selection pressure for increased virulence (Frank, 1992). Third, the highly structured population of hosts and parasites weakens the relationship between higher virulence and increased transmission, thus weakening selection for increased virulence (Lipsitch *et al.*, 1995).

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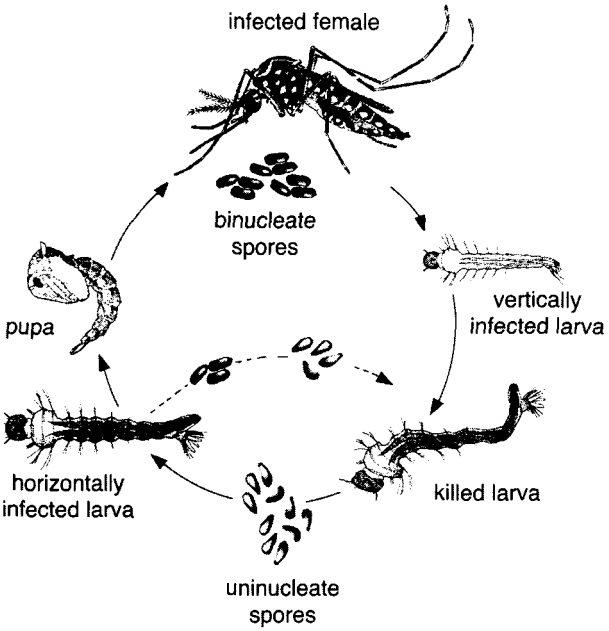


Fig. 1. Life cycle of the microsporidian parasite *Edhazardia aedis* infecting the yellow fever mosquito *Aedes aegypti*. The life cycle normally involves transovarial infection of eggs, the formation of uninucleate spores, oral infection of larvae, and the formation of binucleate spores in the pupae and adults (solid line). In some mosquitoes the entire developmental cycle of the parasite – from binucleate to uninucleate spores – is completed in the larval host, leading to repeated horizontal transmission (dashed line).

Although detailed studies on other systems are lacking, it is clear that the host's life-history will often constrain the evolutionary possibilities of the parasite. As an example, consider a malaria parasite developing within a mosquito. As the adult mosquito's life-expectancy is similar to the parasite's developmental time (Macdonald, 1957), the mosquito is quite likely to die before the parasite has completed its development and is ready to transmit to the next host. Therefore, any increase of the host's mortality, whether due to genetic or environmental factors, will decrease the parasite's transmission success; the parasite will have to modify its development to compensate for changes of its host's life history.

A recent theoretical study has emphasized the interactions between host and parasite life cycles by predicting the best feeding strategy for a given combination of victim and exploiter life histories (Lafferty, 1997). In this model, body sizes of general exploiters and victims are combined with allometric relationships of their life spans, metabolic rates and other traits to determine if the exploiter should evolve to be a predator, a parasitoid, a castrator or a parasite. In particular, parasitism is a better strategy than predation, if the victims are long lived and large enough to resist parasite-induced pathology. Parasitoids and parasitic castrators are favoured when victims are only slightly larger than exploiters. Parasitic castration is more profitable when victims are long lived and invest a lot of energy into reproduction.

Edhazardia aedis vs. *Aedes aegypti*

The above examples show some of the interactions between host life histories and parasite life cycles that can influence the direction of evolution. However, they consider the evolution as a one-sided process by investigating the influence of the parasite on the evolution of the host's life-history or vice versa. What they do not consider are the reciprocal interactions that determine the coevolutionary process. These have been investigated in very few relationships. Here we review one example: the microsporidian parasite *Edhazardia aedis* and its host, the yellow fever mosquito *Aedes aegypti*.

E. aedis has a complex life-cycle involving horizontal and vertical transmission with two different spore types (Fig. 1). Horizontal transmission occurs when larvae ingest uninucleate spores from the environment. After going through several developmental stages, the parasite produces binucleate spores. In adult females, these infect the developing eggs to transmit vertically. The infected offspring rarely survive to adulthood. Rather, their death is induced by the continued development of the parasite and the production of a second generation of uninucleate spores. When the larva dies, these spores are released into the environment to initiate the cycle once again. Under certain circumstances, in particular when infected larvae develop slowly, an alternative pattern of transmission is observed. Binucleate spores germinate before the host emerges as an adult and go on to produce the second generation of uninucleate spores, kill the host and initiate another round of horizontal transmission, thus bypassing vertical transmission (for further details see Becnel *et al.* [1989] and Johnson, Becnel & Undeen [1997]).

Thus, after horizontal infection of the larvae two pathways are possible: (1) the infection can be benign, the larvae survive to adulthood and the parasite transmits vertically, or (2) the infection can be virulent, the mosquito dies before it emerges as an adult and the parasite transmits horizontally. As we discuss below, which pathway is followed depends on details of the interactions between the host's life-history, in particular its developmental time, and the parasite's life cycle. We investigated these interactions in a laboratory setting by manipulating two parameters this host–parasite relationship experiences: the intensity of larval exposure to horizontally transmitting uninucleate spores (from 10 to 10000 spores/ml) and the mosquito's developmental time (by varying larval food availability from 25 to 100% of a standard diet). The results of these experiments

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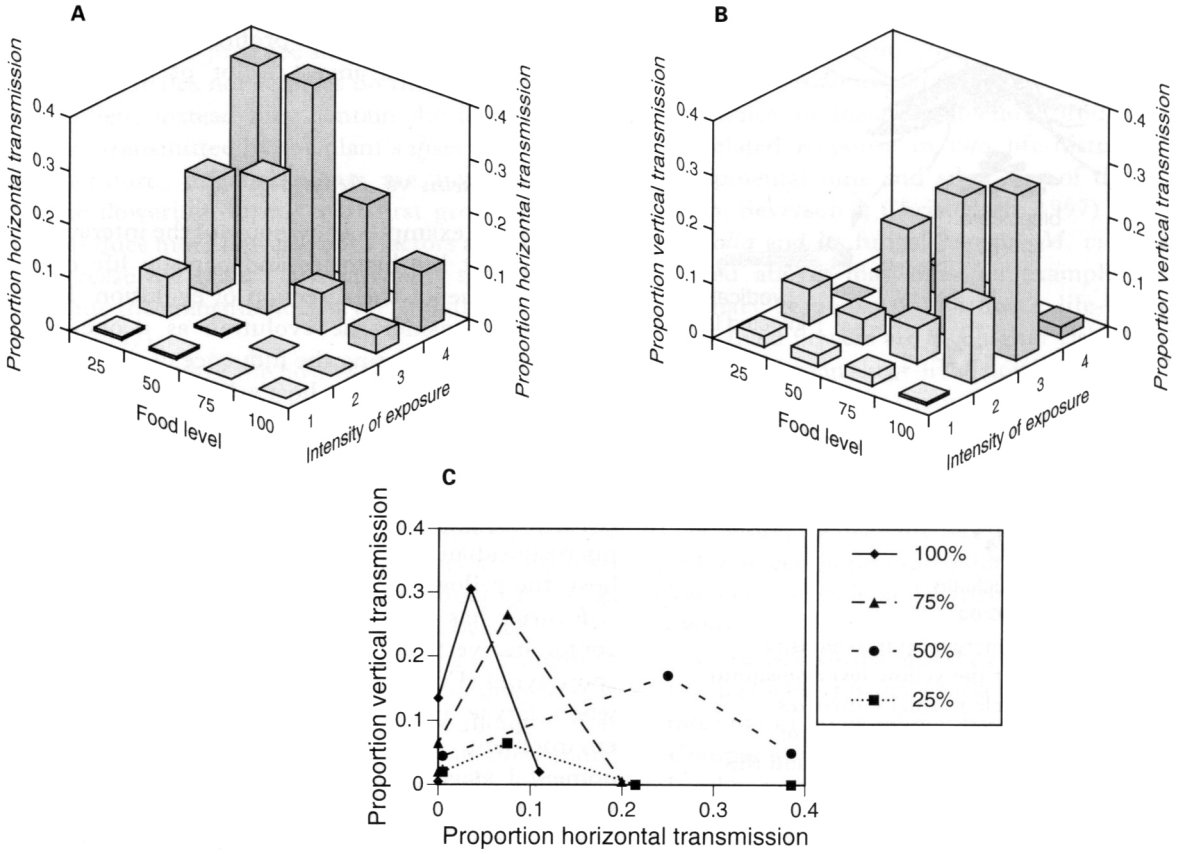


Fig. 2. Potential for vertical and horizontal transmission of *E. aedis* at intensities of exposure ranging from 10 to 10000 spores/ml and larval food levels ranging from 25 to 100% of a standard diet. (A) The potential for horizontal transmission is defined as the proportion of the cohort that dies before emergence and harbours uninucleate spores. (B) The potential for vertical transmission is defined as the proportion of the cohort that develops into an adult females harbouring binucleate spores. (C) Potential for vertical transmission as a function of horizontal transmission. The lines connect treatments with the same food levels; intensity of infection increases along each line from 10 spores/ml on the left to 10000 spores/ml on the right.

are described in more detail elsewhere (Agnew & Koella, 1997; 1998; Koella & Agnew, 1997; 1998); here we restrict ourselves to a short overview.

Effect of the host's life-history on the parasite's transmission and virulence

Both of the parameters that were varied in these experiments had a major effect on the parasite's transmission and virulence (Agnew & Koella, 1998). As might be expected, virulence (the mortality induced by the parasite) increased when hosts were exposed to higher densities of spores and when they were fed less food. Perhaps more surprising is that the two parameters also influenced the parasite's mode of transmission (Fig. 2). Increasing the intensity of exposure and decreasing the food availability led to an increase in the proportion of the mosquitoes that died before emergence harbouring uninucleate spores, i.e. to an increase in the potential for horizontal transmission (Fig. 2A). On the other hand, intermediate exposure at high food availability was most likely to result in surviving adult females harbouring binucleate spores, i.e. to an increase in the potential for vertical transmission (Fig. 2B). Increasing intensity of exposure or decreasing food led to higher mortality and therefore reduced the potential for vertical transmission. Showing these results from a slightly different viewpoint emphasizes that transmission is shifted from mostly vertical transmission in high food conditions to mostly horizontal transmission in low food conditions, while substantial amounts of both vertical and horizontal transmission are observed only at an intermediate intensity of exposure and intermediate food availability (Fig. 2C).

An explanation for this pattern could be based on a constraint in the parasite's life cycle: after horizontal infection the parasite must produce the vertically transmitting binucleate spores before it can produce its horizontally transmitting uninucleate spores. One would therefore expect that the timing of the host's life-history and the parasite's life cycle are important determinants of transmission; in rapidly developing mosquitoes, the parasite does not have enough time to produce uninucleate spores.

Our data confirm this expectation. The reduction of food availability led to later pupation. Accord-

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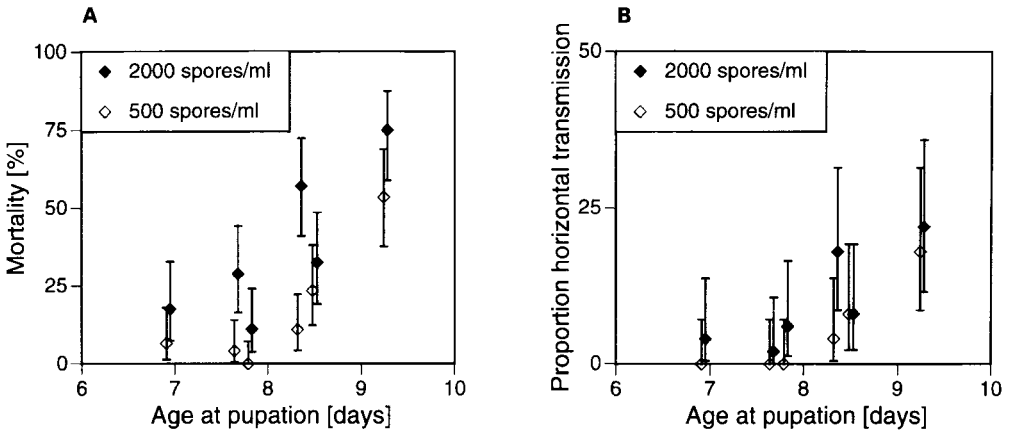


Fig. 3. Effect of selecting the mosquito for early or late pupation on the parasite's virulence and potential of horizontal transmission. In both panels, the x-axis shows the age at pupation of the corresponding lines raised under identical food conditions but without having been exposed to the parasite. The symbols show the proportion within each line; the vertical lines show the 95% confidence interval based on a binomial distribution. (A) The proportion of mosquitoes that died before emergence was used as a measure of virulence, as less than 5% of uninfected mosquitoes died before emergence. (B) The potential for horizontal transmission is defined as the proportion of the cohort that dies before emergence and harbours uninucleate spores.

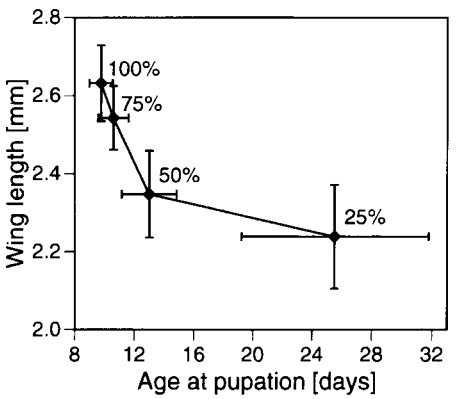


Fig. 4. The effect of larval food levels on age at pupation and wing length of adult female mosquitoes that had not been exposed to infection. Diamonds represent the means within treatments and the lines show the standard deviations of cohorts receiving 100, 75, 50 or 25% of the standard diet.

ingly, the mosquitoes that received the least food were the most likely to transmit the parasite horizontally, while the well-fed, rapidly developing mosquitoes were more likely to transmit the parasite vertically. An alternative explanation for this pattern could be that the parasite's own development depends on the food obtained by its host. This, however, can be discarded with two observations: (1) the timing of production of the two spore types was independent of food availability; in all food conditions binucleate spore production began about 4 days post-infection followed by uninucleate spore production about 8 days post-infection, and (2) we selected mosquitoes over 4 generations for early or for late pupation, which resulted in a divergence of about 1.5 days in mean age at pupation. After exposure to infection, virulence and the potential for horizontal transmission were highest among the mosquitoes selected for slow development, although all of the mosquitoes were fed 100% of the standard diet (Fig. 3) (Koella & Agnew, 1998).

However, this constraint in the parasite's life cycle – that after horizontal infection binucleate spores are produced before uninucleate spores – can only help to explain why the parasite transmits vertically from rapidly developing mosquitoes. But why should the parasite not also transmit vertically from slowly developing mosquitoes?

We propose that the parasite's developmental pattern reflects its evolutionary response to two aspects of its host's life-history. First, the distribution of *Ae. aegypti* larvae is patchy; females oviposit in a range of containers such as bamboo shoots, water storage jars or discarded rubber tyres. Most females distribute their eggs across several sites, so that breeding sites contain a mixture of unrelated larvae (Apostol *et al.* 1994). Therefore, the parasite's transmission success depends on a combination of vertical transmission to spread its infection among breeding sites and horizontal transmission to infect unrelated individuals within a breeding site. Second, the development of *Ae. aegypti* is variable within and among breeding sites. Generally, mosquitoes that develop slowly under poor food conditions not only pupate later than well-fed individuals, but also develop into small adults (Fig. 4). As body size is closely related to the mosquito's fecundity and survival (Briegel, 1990; Lyimo, 1993), poor food conditions also result in low reproductive success of the mosquito, and thus low potential for vertical transmission of the parasite. Therefore, by killing the larva and transmitting horizontally, the parasite can maintain a higher potential for its transmission success (Agnew & Koella, 1998).

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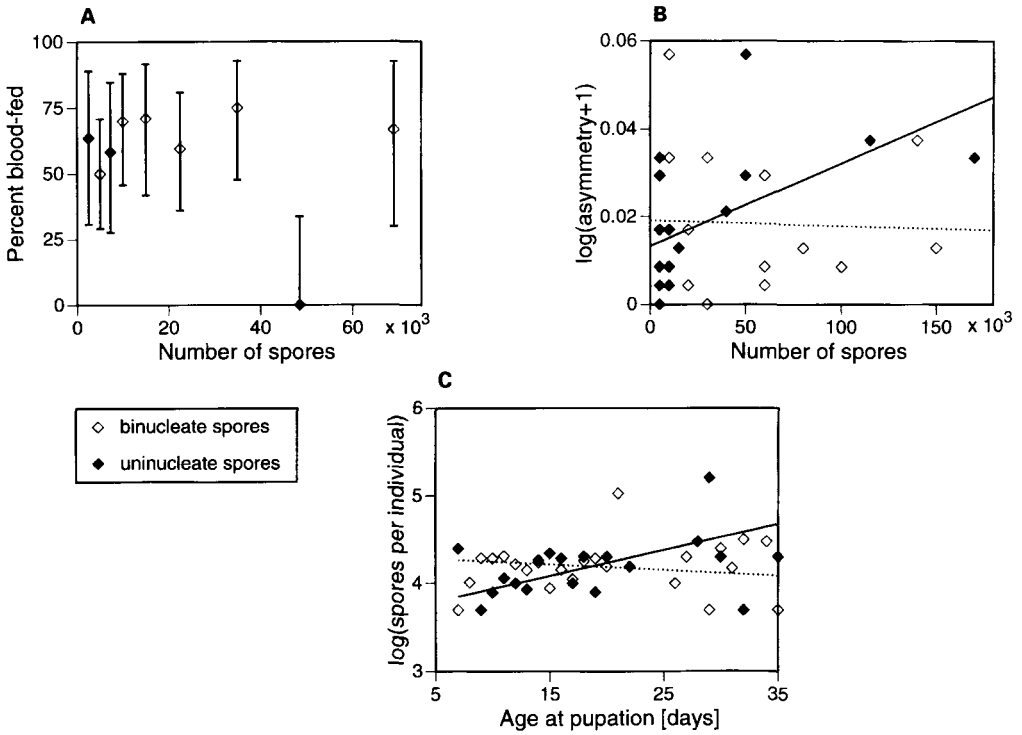


Fig. 5. The effect of parasite infection on (A) blood-feeding success and (B) wing asymmetry. (C) The number of spores harboured in an adult mosquito as a function of the mosquito's age at pupation. In all panels, open symbols represent binucleate spores and closed symbols represent uninucleate spores. In (A) the symbols represent the percentage of blood-feeding success within groups mosquitoes harbouring similar numbers of spores. The groups are chosen so that more than 10 individuals are in each group. The vertical bars show the 95% confidence interval of the percentage, based on a binomial distribution. In (B) each symbol represents an individual mosquito. The solid line shows the regression for uninucleate spores, the dotted line the regression for binucleate spores. In (C) the symbols represent the mean of the mosquitoes pupating on a given day. The solid line shows the regression weighted for the number of individuals in each group for uninucleate spores, the dotted line the weighted regression for binucleate spores. Note that the 3 panels represent different experiments; therefore the number of spores varies among the panels.

In summary, the parasite's life cycle appears to be well-suited for a host living in patchy and ephemeral habitats, combining vertical transmission to spread its infection among sub-populations and with horizontal infection to infect individuals within sub-populations. The life cycle appears to be tuned to use the mode of transmission with the higher potential of transmission success. The parasite transmits vertically in good growth conditions, where the mosquito develops rapidly and its reproductive success can be expected to be high; it transmits horizontally in environmental conditions that would lead to low reproductive success of the host and thus would allow only low vertical transmission success of parasite.

Selection pressure of parasite on host's life-history

Though we have been considering the effect of the host's life history on the parasite's transmission success, it is clear that the host's life-history will also respond to infection by the parasite. In particular, the parasite will select for mosquitoes to pupate earlier, since slowly developing mosquitoes will be killed by the infection. Even if they survive, the parasite can continue to select for earlier pupation because of its effect on adult female mosquitoes. The parasite reduces fecundity (Becnel, Garcia & Johnson, 1995) and blood-feeding success (Koella & Agnew, 1997) and increases the asymmetry of host wings (Agnew & Koella, 1997) and mortality (Becnel *et al.* 1995). Moreover, the effect of the parasite on the mosquito depends on the type of spores produced (Agnew & Koella, 1997; Koella & Agnew, 1997). The mosquitoes harbouring binucleate spores suffer less than those harbouring uninucleate spores, and the parasite's effect increases with the number of uninucleate spores (Fig. 5A,B). As the number of uninucleate spores harboured in an adult mosquito increases with its age at pupation (Fig. 5C), rapidly developing mosquitoes suffer less than the slowly developing ones from infection by the parasite.

Thus, slowly developing mosquitoes suffer from the parasite in two ways. Very slow mosquitoes are killed by the parasite; mosquitoes with intermediate developmental rate survive the infection, but have less reproductive success than the most rapidly developing mosquitoes.

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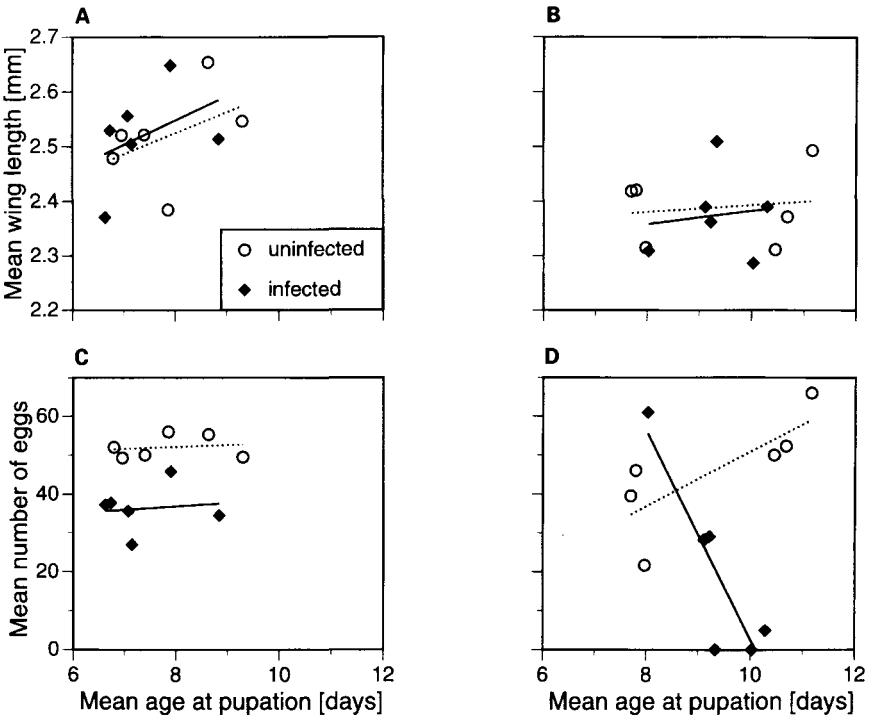


Fig. 6. Correlated responses of wing length and fecundity to selection for early or late pupation. In each panel, the symbols show the means of a cohort and the lines show the regression for the mean values as an approximation of the correlated response. Open symbols and dotted lines represent uninfected mosquitoes, solid symbols and lines represent infected mosquitoes. In (A) and (B) mosquitoes had been reared at 100% of a standard diet, in (C) and (D), mosquitoes had been reared at 50% of the standard diet. The true correlated response was found with a nested analysis of covariance. In this method, the covariance among all individuals is split into a component due to the variability within selection lines and a component due to variability among lines.

The extent to which the mosquitoes respond to this selection for earlier pupation partly depends on the genetic correlations between age at pupation and other life-history traits of the mosquito. If the genetic correlation between age at pupation and the mosquito's reproductive success were positive, the response to the selection invoked by the parasite for earlier pupation would be constrained by selection for higher reproductive success and therefore later pupation.

In the Rockefeller strain of *Ae. aegypti* used in these experiments, selection for early or late pupation led to a correlated response in the body size of the adults and in the number of eggs laid in the first clutch (Fig. 6A,B). Note that a mosquito's body size, often measured as its wing length (Siegel *et al.* 1992), is a central trait of its life-history, since large mosquitoes generally have high survival (Landry, De Foliart & Hogg, 1988), high blood-feeding success (Nasci, 1986), and high fecundity (Briegel, 1990). These positive correlations, however, were measured on unparasitized mosquitoes that have been reared as larvae at 100% of the standard diet.

The correlated responses changed as the environment deteriorated. When the mosquitoes were fed only 50% of the standard diet, pupation was delayed slightly, adults were smaller and laid fewer eggs. Furthermore, the correlation between age at pupation and adult size decreased to a non-significant value (Fig. 6C). When, additionally, the larvae were exposed to parasites at an intensity low enough to allow the mosquitoes to survive, the fecundity in the lines with slow development decreased strongly. Thus the correlation between age at pupation and fecundity switched from a positive to a negative value (Fig. 6D).

In summary, the parasite can not only exert considerable selection pressure on the mosquito's life-history, but it will also affect the genetic correlations among life-history traits, which in turn determine the host's response to selection. These complex interactions may lead to two different pathways of evolution, depending on the parasite's prevalence. In populations where only few breeding sites are infested, only a small proportion of the population will be selected for earlier pupation. The evolutionary trend, however, will be governed by the selection in the uninfested breeding sites. In these, the positive genetic correlations maintain a balance between selection for early pupation and selection for higher fecundity and survival. The response of the host's life-history to the parasite will therefore be negligible, which will maintain virulent parasites with low potential of vertical transmission. Thus, if the parasite's prevalence is low, selection is likely to lead to virulent parasites with horizontal trans-

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mission. On the other hand, if prevalence becomes sufficiently high, most mosquitoes will experience selection for earlier pupation. Furthermore, the decrease of the genetic correlations to low or negative values will enhance, rather than counteract the selection imposed by the parasite for earlier pupation; earlier pupation will then lead to avirulent parasites with high potential of vertical transmission. Thus, high prevalence is likely to select for predominantly vertical transmission of avirulent parasites.

CONCLUSIONS

Of course, many factors will determine the evolution of a host's life-history or a parasite's life cycle. However, we argue that the interactions between the life-history and the life cycle form an important part of the host–parasite relationship. Subtle details of the interactions can determine the outcome of selection; thus, without explicitly considering these interactions, it is difficult, if not impossible, to predict the direction of evolution.

Such considerations can be important for practical decisions in, say, biological control or public health. *Edhazardia aedis*, for example, is being tested as a biological control agent of *Ae. aegypti*. Our studies suggest that the increase of prevalence associated with a control programme will eventually lead to a change in the mosquito's life-history to earlier pupation. This may lead to avirulent, vertically transmitted parasites, rendering the attempts at mosquito control counter-productive.

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