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Discussion

Behind the scene, something else is pulling the strings: Emphasizing parasitic manipulation in vector-borne diseases

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Abstract

Merging the field of epidemiology with those of evolutionary and behavioural ecology can generate considerable fundamental knowledge, as well as help to guide public health policies. An attempt is made here to integrate these disciplines by focusing on parasitic manipulation in vector-borne diseases. Parasitic manipulation is a fascinating strategy of transmission which occurs when a parasite alters phenotypic trait(s) of its host in a way that enhances its probability of transmission. Vector-borne parasites are responsible for many of the most harmful diseases affecting humans, and thus represent public health priority. It has been shown for several decades that viruses, bacteria and protozoa can alter important features of their arthropod vector and vertebrate host in a way that increases their probability of transmission. Here, we review these changes, including, the feeding behaviour, survival and immune system of the vector, as well as attraction, defensive behaviour, blood characterictics and immune system of the vertebrate host. Based on the classic measure of vector-borne disease transmission R_0, additional changes, such as, vertebrate host choice by infected vectors or parasite development duration in the vector are expected. Reported or expected phenotypic changes are discussed in terms of costs and benefits to the parasite, its vector, and the vertebrate host. Introducing the parasitic manipulation concept into vector-borne diseases clearly highlights fruitful avenues not only for fundamental research, but also for developing strategies for disease control.

Keywords: Parasitic manipulation; Vector-borne diseases

1. Introduction

Sit down on the bank of a river in the south of France during the summer and you may witness a spectacular scene: a cricket going straight towards the river and jumping in the water, even tough all his conspecifics remain in the shady wood. Wait 10 s and you may well observe a Gordian worm bursting out of the body of the ''diver cricket'' and swimming into the water, where it will continue its life cycle. The suicidal behaviour of the insect illustrates a case of behavioural manipulation: water seeking is not part of the normal behavioural repertoire of crickets; it is induced by the parasite. The ability of parasites to cause such changes has usually been considered to be adaptive as it enhances host-to-host transmission, or ensures the parasite (or its propagules) gets released in an appropriate location. The scientific literature is now rife with examples of behavioural, morphological and physiological alterations and such parasitic manipulations have been well documented in a variety of host–parasite systems (Fig. 1, Moore, 2002).

To date, many vector-borne parasites have been shown to alter phenotypic traits of their insect vectors and vertebrate hosts in a way that increases contact between them and hence increases the probability of parasite transmission. Emerging and re-emerging infectious vector-borne diseases present one of the most pressing issues facing public health systems. In response, there has been progress in understanding disease transmission, but many challenges remain to be overcome. In this context, studying this intriguing strategy of transmission may help to understand pathogen dynamics and hence bring crucial information on disease control measures.

The first part of this review deals with the concept of parasitic manipulation and discusses the adaptiveness of host behavioural alteration. The subsequent section adresses parasitic manipulation in vector-borne diseases and reviews reported cases of host behavioural and physiological alterations that result, or appear to result, in increased transmission of the parasite. Finally, we end by proposing future avenues of

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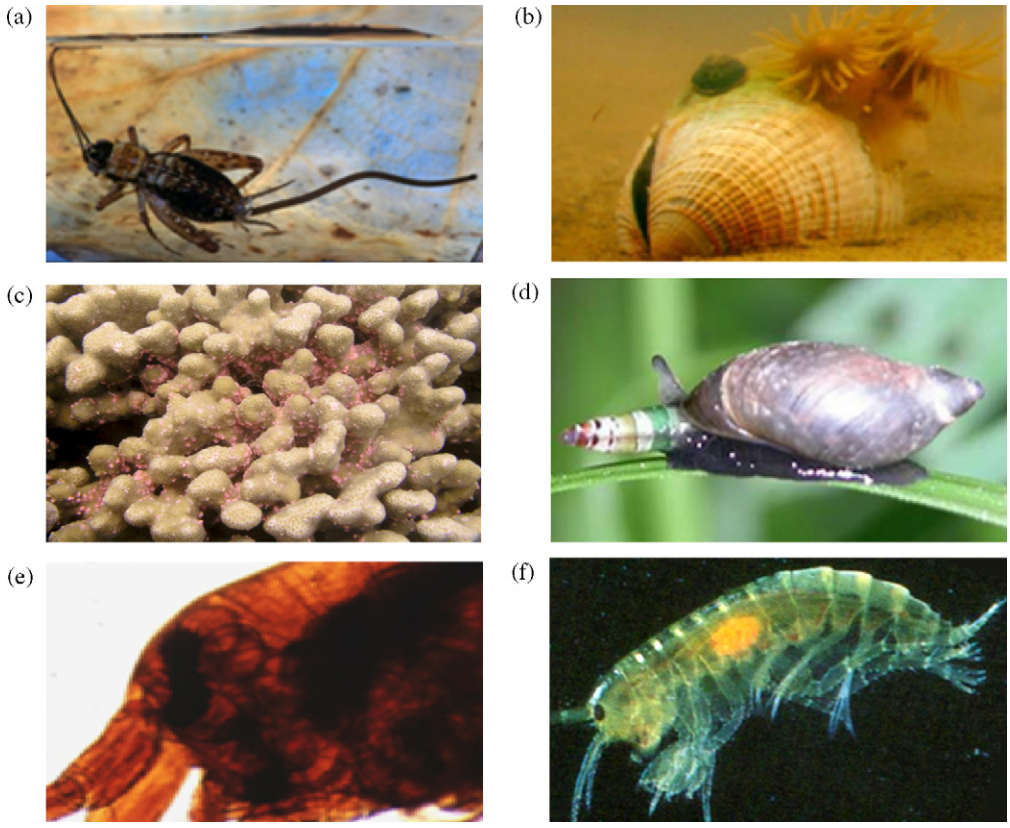

Fig. 1. Examples of parasitic manipulation. (a) The Gordian worm (*Paragordius tricuspidatus*) exiting the body of a cricket (*Nemobius sylvestris*) (Photo P. Goetgheluck). (b) A cockle (*Austrovenus stutchburyi*) parasitized by a trematode (*Curtuteria australis*). The parasites impair the natural burrowing behaviour of their cockle intermediate hosts, making them more likely to be eaten by aquatic bird (final host) (Photo F. Thomas). (c) Coral polyps infected with a trematode (*Podocotyloides stenometra*). The parasite induces pink, swollen nodules on the coral colony and impairs their retraction ability. Infected polyps are, therefore, both conspicuous and vulnerable to predation by the coral-feeding butterflyfish, *Chaetodon multicinctus* (parasite's definitive host) (Photo G. Aeby). (d) The sporocysts of *Leucochloridium paradoxum* develops in the snail's tentacles, where they can be seen conspicuously pulsating. This make the tentacles look to a bird, definitive host, like caterpillars (Photo P. Vogel). (e) Metacercariae of *Microphallus papillorobustus* encyst in the brain of the intermediate host, *Gammarus insensibilis* (Photo F. Thomas). (f) Cystacanth of *Polymorphus minutus* encysts in the body cavity of *Gammarus pulex* (Photo F. Cézilly). Infected *G. pulex* and infected *G. insensibilis* show similar behavioural changes (i.e. negative geotaxis, aberrant evasive behaviour and in infected *G. insensibilis* a positive phototaxis). Since both parasites are phylogenetically distant, these changes can be considered as a case of convergence.

research in order for this topic to prosper in the emerging field of evolutionary epidemiology.

2. The 'spread' of parasitic manipulation

The field of host manipulation by parasites acquired a conceptual framework with the Richard Dawkins' book entitled 'The Extended Phenotype' published in 1982. In this book, Dawkins proposes a vision of life where the unit of natural selection is the gene and where its influence can extend outside its 'vehicle', i.e. the body in which the gene resides. For instance, a bird's nest is a phenotype like any other, under the control of the bird's genes in the same way as the shape of its beak is under the control of its genes. This vision has helped scientists to establish a framework for research on parasitic manipulation of infected hosts. Henceforth, host alteration may be regarded as the expression of the genes of the parasite in the host phenotype. In this view, genes of the parasite are selected for their effect on host phenotype. For example, in behavioural manipulation, one could expect that the parasite secretes chemicals (or induces their production in the host) acting on the central nervous system of the host to induce altered behaviour. Recently, it has been shown that the Gordian worm mentioned earlier alters the normal functions of the grasshopper's central nervous system by producing certain ''effective'' molecules. In particular, a protein from the Wnt family was found that act directly on the development of the central nervous system. These proteins show important similarities with those known in insects, suggesting a case of molecular mimicry (Biron et al., 2005).

Dawkins' theoretical explanation, namely, that host behavioural changes can be parasite adaptations, has led researchers to consider all behavioural changes observed in an infected organism as beneficial for the parasite. However, other explanations are possible. First it has been proposed that the host may benefit from these changes. For instance, suicidal behaviour may reduce the risk of infection for the host's kin. Similarly, behavioural fever and elevated body temperature may help the host to eliminate its parasite (Hart, 1988) in raising its body temperature. Alternatively, changes might be pathological consequences of infection, adaptive to neither host nor parasite, and that not all behavioural modifications

following infection are mediated by parasites. Indeed, not all behavioural modifications have evolved to increase the reproductive success of the parasite.

Since it is difficult to distinguish between these different possibilities, four criteria have been proposed by Poulin (1995) to consider changes as adaptive in the context of transmission: complexity; purposiveness of design (i.e. conformity between a priori design and the alterations); convergence (similar changes in several independent lineages) and fitness consequences. This important paper has helped to highlight the need for a novel and more rigorous approach to studying and interpreting potential cases of parasitic manipulation. The first criterion, i.e. complexity, is perhaps the least useful since it is difficult to judge if a trait is complex or not. Simple host behavioural changes may indeed rely on complex physiological modifications induced by the parasite. Natural selection does not always favour complex solutions over simple ones; it favours the solutions that work. Concerning the second criterion (i.e. purposiveness of design), the host behavioural changes are indeed often exactly those we could expect to enhance parasite transmission. This aspect is well illustrated when looking at different types of parasite life cycles. First, in direct life cycles, host phenotypic alterations leading to increased contacts among conspecifics are likely to be selected. For instance, the rabies virus, Hantavirus, and borna disease virus induce increased aggression and physical contacts in the host population. Second, in complex life cycles involving trophic transmission, many parasites alter the behaviour of their intermediate host in a way that increases the risk of them being preyed upon by final hosts, by, for example, changing intermediate host microhabitat or inhibiting anti-predatory behaviour. The third criterion proposed to assess the adaptiveness of behavioural alteration is convergence. When a similar phenotypic trait in several organisms has not been inherited from their most recent common ancestor but conversely has independently evolved, the trait is said to be a homoplasy or a convergence. A convergent trait is likely to be an adaptation since it results from the same selective pressures acting on phylogenetically distant organisms. For instance, three species of parasites (i.e. two acanthocephalans, *Polymorphus minutus* and *P. paradoxus* and a trematode, *Microphalus papillorobustus*) are known to induce in their crustacean gammarids (intermediate hosts) similar aberrant evasive behaviour making them more prone to be eaten by aquatic birds (definitive hosts) (Bethel and Holmes, 1973; Helluy, 1984; Cézilly et al., 2000). As parasitism has independently evolved in *Trematoda* and *Acanthocephala*, the induced aberrant evasive behaviour can be seen as convergent (Fig. 1). Conversely, between the two acanthocephalan species it is likely that the ability to induce this aberrant evasive behaviour was inherited from the common ancestor; it is thus less likely to be convergence than in the latter case. The last criterion proposed, undoubtedly the most convincing evidence in favour of adaptation, is the demonstration of fitness benefits. For several decades researchers have attempted to show that behavioural modifications result in more successful transmission. Linking behavioural modification with increased probability of transmission is difficult, that is why the case of trophic transmission by intermediate hosts is surely the easiest to investigate. The first study considering this conjecture was that carried out by Holmes and Bethel (1972). In this study, a predator (definitive host) was experimentally offered known numbers of infected and uninfected gammarids. At the end of the experiment, numbers of infected and uninfected individuals that survived were counted. Holmes and Bethel showed that the behavioural alterations induced by the parasite lead to a significantly increased predation rate of infected gammarids. Since results obtained in the laboratory may not reflect precisely that which occurs naturally, a second method has been devised by researchers in attempt to show that behavioural alteration actually increases transmission rates. In this approach, the prevalence of infected individuals in the intermediate host population is compared to the prevalence of infected individuals in the final host's diet. An over-representation of infected preys in the gut contents of an appropriate definitive host is considered as evidence for an increased rate of transmission. For instance, Moore (1983) showed that terrestrial isopods parasitized by an acanthocephalan were more active compared to uninfected ones, and were consequently more likely to be found in the diet of the definitive host, the starling.

The publication of Poulin's critical review (1995) has marked the start of a new period during which many studies taking into account the previous recommendations appeared in the scientific literature. This paper has nonetheless contains one obscure point: should we consider the changes due to pathological consequences of infection and that are coincidentally beneficial for the parasite as adaptations? Poulin answers no: ''Experiments can also serve to distinguish between behavioural modifications that are truly adaptive and those that are coincidentally beneficial. For instance, parasitized hosts can make themselves more visible to predators because they have increased energy requirements and must forage more, not because they are manipulated by the parasite''. In this case, even if the link between behavioural alterations and increased rate of transmission is demonstrated, we cannot consider the changes as adaptive. Another situation illustrating this restriction corresponds to what is called ''fortuitous payoff of other adaptations''. For example, the eye fluke trematode inducing blindness in his intermediate host fish could have been selected to encyst in the eye of the fish to avoid the host immune system, affording later the ability to alter the host evasive behaviour. In this case, the manipulation can be regarded as the consequence of traits that have evolved for other purposes. This definition clearly looks like the definition of exaptation sensu Gould and Vrba (1982): an exaptation is a trait that evolved for other functions, or no function at all, but which has been co-opted for a new use. Concerning this point, it is also possible that more than one advantage to the eye fluke trematode could immediately occur from encysting in the eyes and that selection pressures for this phenotype will be much stronger if several benefits ensue (i.e. increased transmission and immune system avoidance). Unfortunately, we often take a simplistic approach by only looking at a single consequence of an action at a time.

As for the confusion between these ''by-products'' (i.e. changes coincidentally beneficial and fortuitous payoff) and adaptation, a review written by Reeve and Sherman (1993)

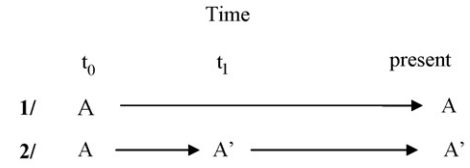

Fig. 2. Two evolutionary sequences of a trait illustrating the confusion concerning the label "exaptation". (modified after Reeve and Sherman, 1993).

helps to clarify the issue. This paper deals with the slippery concept of adaptation. Reeve and Sherman stressed the fact that it is dangerous to confuse the product of the selective process and the process itself. For instance, exaptation and adaptation are actually similar, because both refer to traits that exist because they have been, and continue to be favoured over alternative traits. Do host behavioural modifications result from energy depletion, from the consequences of another adaptation, or from a true manipulation by parasites? Let us imagine two evolutionary sequences for a trait (Fig. 2). In the first sequence, the present trait with function A would be interpreted as an adaptation, i.e. as a trait selected for the purpose it has served in the past and continues to serve. In the second sequence, a trait having a new function *A*' would be an adaptation if we examine the trait between t_1 and the present time, but it would be considered as an exaptation if we examine the trait between t_0 and t_1. Thus, since the label "exaptation" depends on the point in evolutionary history at which we investigate the trait's function, this concept generates ambiguity, rather than clarification. Moreover, concerning our trait of interest, that is, host behavioural modification, it is virtually impossible to identify its original role (no fossil records). To circumvent these problems, Reeve and Sherman (1993) proposed an operational, non-historical definition of adaptation, particularly "adapted" to behavioural ecologists interested in questions of phenotype existence in the field of parasitic manipulation: "an adaptation is a phenotypic variant that results in the highest fitness among specified set of variants in a given environment". Considering this definition, all hosts' behavioural modifications that lead to an enhancement of parasite transmission are maintained by natural selection and thus are a parasite adaptation. To return to the "by product" hypothesis, being more visible to predators because of an increased energy requirement would be an adaptation under this definition if it increases transmission towards a definitive host and the parasite's reproductive success, when compared to an infected host no more visible to predators. For the moment no studies provide information concerning the link between variability in manipulative effort and an increased rate of transmission (and subsequently the parasite's reproductive success), but one could expect that, all else being equal, a parasite that manipulates more than other parasites increases the probability of being transmitted. It could be possible to experimentally select over several generations the phenotypes of parasites with high, medium and low manipulative effort and to examine the rates of transmission between the selected phenotypes.

But why does the host not resist and why does it act in a way that favours the parasite? Behavioural modification must be seen as a co-evolved trait, i.e., a phenotype shared by the host and his parasite. The host is under strong selective pressures to resist manipulation and the parasite is under strong selective pressure to manipulate. The changes might thus be interpreted as an equilibrium state, nonetheless often biased toward the parasite (e.g. in the case of trophic transmission). Understanding why the benefits are often balanced in favour of parasites is easy when highlighted by the life—dinner principle proposed by Dawkins and Krebs (1979). This principle states that the rabbit runs faster than the fox because the rabbit is running for his life, while the fox is only running for his dinner. Thus, the consequences of failure are asymmetric for those involved: one has more to lose than the other. We can apply this principle to the case of parasitic manipulation (Barnard, 1990; Poulin et al., 1994). Transmission is always a matter of life and death for the parasite, while parasitic manipulation does not necessarily have such drastic consequences for the host. The host is descended from a long line of ancestors, only a proportion of which ever met a manipulator parasite. Moreover, some of the individuals subjected to parasitic manipulation may have already reproduced and others may survive to reproduce (depending on the type of host–parasite interaction). Host genes coding for a lack of resistance can thus be transmitted to the next generation. In contrast, every single parasite alive today is descended from a long line of ancestors who have all negotiated successfully the passage between two suitable successive hosts. Therefore parasite genes coding for an effective transmission, e.g. manipulation, have a greater chance to be passed on to the next generations. This reasoning helps us to understand why the host is more likely to capitulate. The stable compromise resulting from this arms race is dynamic and depends on many parameters, such as the prevalence of the parasite, the cost of host resistance, the cost of being manipulated, the cost of parasite manipulation and the cost of the parasite's failure.

3. Parasitic manipulation and vector-borne diseases

Haematophageous insects, when feeding on their host can transmit numerous blood pathogens. An increasing number of studies demonstrate, or suggest, that vector-borne parasites are able to manipulate several phenotypic traits of their vertebrate hosts and vectors in ways that render parasite transmission more probable (Molyneux and Jefferies, 1986; Moore, 1993, 2002; Hurd, 2003; Lacroix et al., 2005). The basic case reproduction number, R_0, the fundamental and classic measure of infectious disease transmission (Macdonald, 1957) can help establish the framework for research on parasitic manipulation in vector-borne diseases. R_0 describes the average number of new infections arising from a single current infection, for vector-borne disease: $R_0 = ma^2p^n/-r \ln p$ (Dye, 1992; Garrett-Jones and Shidrawi, 1969).

Thus, the parasite transmission depends on the number of insect vectors per individual vertebrate host (m), the daily biting rate of an individual vector on vertebrate hosts (a) (once to become infected, and once to transmit, hence a^2), the daily survival rate (p), the number of days required for the parasite to develop (n, i.e. the extrinsic latent period), and r the daily

recovery rate of infected hosts (note: the value $ma^2p^n/-\ln p$ is the vectorial capacity (C), thus $R_0 = C/r$ and the value $p^n/-\ln p$ describes the expectation of infective life of the vector population; Garrett-Jones and Shidrawi, 1969). Generally, methods of estimating these parameters assume that uninfected and infected vectors are similar. However, evidence suggests that this assumption may not be valid and the influence of parasitism on host phenotype is well documented (Combes, 2001; Moore, 2002). Since the R_0 equation gives us a checklist of the key transmission components, it can serve as a basis to determine which traits are likely to be parasitically modified in vertebrate and insect hosts. In this section, we briefly review reported cases of physiological and behavioural modifications that indeed increase, or appear to increase, parasite transmission. Examples are drawn from field and laboratory studies and include a wide range of parasites (viruses, protozoa, bacteria), arthropod vectors (mosquitoes, sandflies, tsetse flies, fleas, bugs, ticks) and vertebrate host species (humans, mice, oxen, lizards, birds).

3.1. The biting rate: 'be aggressive'

According to this equation, parasite transmission is particularly sensitive to biting rate (a^2). It is then not so surprising that in many systems where pathogens are transmitted by bloodfeeding insects, an increased biting rate has been often reported (Table 1). Such a behavioural alteration

Table 1
Reported cases of behavioural and physiological alterations in the arthropod vector

Physiological and behavioural alterations	Host–parasite systems	References
Feeding behaviour: increased biting rate (BR) and increased biting duration (BD)	Virus–Mosquito	
	LaCrosse virus–Aedes triseriatus (BR)	Grimstad et al. (1980)
	Dengue 3–Aedes aegypti (BD)	Platt et al. (1997)
	Malaria–Mosquito	
	P. gallinaceum–A. aegypti (BR) (BD)	Rossignol et al. (1984, 1986), Koella et al. (2002)
	P. yoelii nigeriensis–Anopheles stephensi (BR)	Anderson et al. (1999)
	P. falciparum–An. gambiae (BR) (BD)	Wekesa et al. (1992)
	P. falciparum–An. gambiae (BR)	Koella et al. (1998)
	Plasmodium spp.–*An. punctulatus* (BR) (BD)	Koella and Packer (1996)
	Trypanosomes–Bugs	
	T. rangeli–Rhodnius prolixus (BR) (BD)	D'Alessandro and Mandel (1969), Anez and East (1984), Garcia et al. (1994)
	T. cruzi–Mepraia spinolai (BR)	Botto-Mahan et al. (2006)
	Bacteria–Flea	
	Yersina pestis–Xenopsylla cheopis (BR)	Bacot and Martin (1914)
	Leishmania–Sand fly	
	Leishmania mexicana–Lutzomyia longipalpis (BR)	Killick-Kendrick et al. (1977)
	Leishmania major–Phlebotomus duboscqi (BR) (BD)	Beach and Leeuwenberg (1985)
	African Trypanosomes–Glossina	
	Trypanosoma brucei–G. morsitans morsitans (BR) (BD)	Jenni et al. (1980)
	T. congolense–G. morsitans morsitans (BR) (BD)	Roberts (1981)
	Mite–Nematode	
	Litomosoides carinii–Ornithonyssus bacoti (BD)	Jefferies (1984)
Lifespan: increased (IL) and same (SL)	Malaria–Mosquitoes	
	Plasmodium falciparum–Anopheles. gambiae (SL)	Chege and Beier (1990), Robert et al. (1990), Hogg and Hurd, 1997
	P. falciparum–An. funestus (SL)	Chege and Beier (1990)
	P. falciparum, *P. vivax–An. tessellatus* (SL)	Gamage-Mendis et al. (1993)
	P. vivax–An. maculipennis (SL)	Sinton and Shute (1938)
	P. gallinaceum–A. aegypti (SL)	Freier and Friedman (1987), Rossignol et al. (1986)
	African Trypanosomes–Glossina	
	Trypanosoma gambiense–Glossina palpalis (IL)	Duke (1928)
	T. Rhodesiense, *T.brucei–G. morsitans* (IL) (SL)	Baker and Robertson (1957) Maudlin et al. (1998)
	T. vivax, *T. congolense*, *T. brucei–G. morsitans morsitans* (SL)	Moloo and Kutuza (1985)
	Protozoa–Ticks	
	Babesia microti–Ixodes trianguliceps (IL)	Randolph (1991)
Temperature preference	Malaria–Sand fly: *Plasmodium mexicanum–Lutzomyia vexator*	Fiahlo and Schall (1995)
Immune response	Malaria–Mosquito	
	P. gallinaceum–Aedes. aegypti	Boëte et al. (2004)
	P. falciparum–An. gambiae	Lambrechts et al. (2007)

has indeed been shown for tsetse flies infected with African trypanosomes, in bugs infected with *Trypanosoma* spp., in sandflies infected with *Leishmania* spp., in fleas infected with the plague bacterium, in mosquitoes infected with *Plasmodium* spp. and viruses (Molyneux and Jefferies, 1986; Moore, 2002; Hurd, 2003). Interestingly, in almost all cases, the infective stages of the parasites appear to interfere with the ingestion process of the insects by, for example, obscuring phagoreceptors (e.g. trypanosome-infected tsetse flies), blocking the foregut (e.g. leishmania-infected sandflies) and reducing apyrase activity in salivary glands (e.g. malaria-infected mosquitoes). These different mechanisms seem to impair the vector's ability to fully engorge and therefore induce them to bite vertebrate hosts several times.

An increased biting rate was first observed by Bacot and Martin (1914) in fleas parasitized with the plague bacillus, *Yersina pestis*. In this system, infected fleas probe more often and sometimes without ingesting blood (Bibikova, 1977). The bacteria multiply in the midgut and proventriculus causing occlusion of the proventriculus and blockage of the gut. The block prevents the flow of host blood from the foregut into the midgut. As a consequence, to obtain a blood meal, a blocked flea regurgitates the plug and injects it into the host (Hinnebusch et al., 1998).

Infected sandflies have also difficulty in feeding and hence will often bite a host several times before a blood meal is taken (Table 1, Killick-Kendrick et al., 1977; Beach and Leeuwenberg, 1985). In this system, the parasite produces a gel-like plug, the promastigote secretory gel (PSG) that blocks the foregut (Rogers et al., 2002; see also Volf et al., 2004). Rogers et al. (2004) demonstrated that the parasite, *Leishmania mexicana* accumulates behind the plug and are actively regurgitated during biting. An average of 1086 parasites was egested per bite, and 86–98% of them were infective metacyclic promastigotes (Rogers et al., 2004). In addition, this study sheds light on an important structural component of the PSG, the filamentous proteophosphoglycan (fPPG), which beyond its role in blocking the foregut, actively participates in the success of vertebrate host infection. First, by comparing infections caused by a single fly bite with those caused by a syringe inoculation, Rogers et al. (2004) found that an exacerbation factor, facilitating mice infections, was egested along with the plug containing metacyclic promastigotes. Then, they demonstrated that this factor was of parasite origin, and finally that egested fPPG was responsible for this infection exacerbation.

In tsetse flies parasitized with trypanosomes, Jenni et al. (1980) showed that *Glossina morsitans morsitans* and *G. austeni* infected with *Trypanosoma brucei* probed three times more often and fed more voraciously than uninfected flies. Working on *G. m. morsitans* infected with *T. congolense*, Roberts (1981) reported that infected flies probed significantly more frequently and took longer to engorge than uninfected flies. The increased probing may be caused by physical interference of the parasite with phagoreceptors in the tsetse fly labrum (Thevenaz and Hecker, 1980; Livesey et al., 1980; Molyneux and Jenni, 1981). However, such findings have not been confirmed by studies carried out by Moloo's group (Moloo, 1983; Moloo and Dar, 1985; Makumi and Moloo, 1991). Combinations of vectors and parasites from different locations and/or parasite intensities may help explain these contradictory results.

Malaria-infected mosquitoes bite their vertebrate hosts longer (Rossignol et al., 1984, 1986; Wekesa et al., 1992), more often (Rossignol et al., 1986; Wekesa et al., 1992; Koella et al., 1998, 2002, but see Li et al., 1992) and are more persistent in seeking out blood meals (Koella and Packer, 1996; Anderson et al., 1999) (Table 1). These three aspects of feeding appear to be crucial for parasite transmission since it arouses vertebrate host defensive behaviour, leading to interrupted feeding, which in turn, could multiply host contacts per gonotrophic cycle (Rossignol et al., 1986; Wekesa et al., 1992). Disruption of feeding activity, and hence multiple biting, occur in this system probably as a result of altered apyrase activity. Apyrase is a salivary enzyme that inhibits platelet aggregation, facilitates blood vessel location and thus promotes blood-feeding by the insect (Ribeiro et al., 1984). For instance, in malaria-infected *Aedes aegypti*, apyrase activity is reduced to a third following maturation of sporozoites (i.e. the mature transmissible stage of *Plasmodium* spp.) and results in a longer biting period (Rossignol et al., 1984, see also Ribeiro et al., 1985).

Triatomines infected with *Trypanosoma* spp. also experience difficulties in engorging (Tobie, 1965; D'Alessandro and Mandel, 1969; Schaub, 1989; Garcia et al., 1994). It has been shown that the biting rate of *Rhodnius prolixus* and *R. robustus* was increased by infection with *Trypanosoma rangeli* (D'Alessandro and Mandel, 1969; Anez and East, 1984; Garcia et al., 1994) and that it probably results from reduced apyrase activity (Garcia et al., 1994; Azambuja and Garcia, 2005). In this system, it has been also proposed that the sluggish movements observed in infected bugs might be parasitic manipulation of locomotory activity aiming at facilitate the parasite transmission by predation and/or cannibalism (Schaub, 2006). Recently, Botto-Mahan et al. (2006) demonstrated that *Trypanosoma cruzi*, transmitted through defecation and responsible for Chagas disease, manipulates the behaviour of the kissing bug vector, *Mepraia spinolai*, in two ways. First, it induces an increased biting rate and second it reduces the defecation time after feeding. As a consequence, parasite transmission may be enhanced because more bites induce more wounds for parasite contamination from faeces deposited shortly afterwards (Botto-Mahan et al., 2006).

Reduced feeding success, increased biting rates and their duration have also been reported in *Aedes triseriatus* infected with La Crosse virus (Grimstad et al., 1980) and in *A. aegypti* infected with dengue virus (Platt et al., 1997, but see Putnam and Scott, 1995). Although no mechanism has been demonstrated, Grimstad et al. (1980) and Platt et al. (1997) suggested that infection of the salivary gland coupled with heavy infection of the nervous system, eyes and abdominal ganglion (all involved in host seeking and blood feeding processes) may provide proximal explanations of altered feeding behaviour in virus-infected mosquitoes.

Following the examples of feeding alterations described above, two striking features must be emphasized. First, behavioural changes often occur with precise timing. Altered

feeding behaviour indeed often takes place only when parasites are fully developed, i.e. once the parasites reach the infective stage for the next host. For instance, Koella et al. (2002) (see also Anderson et al., 1999; but see Ferguson and Read, 2004) showed that *P. gallinaceum* manipulates the mosquito vector, *A. aegypti,* in two different ways and in a stage-specific manner: when ready to be transmitted to the vertebrate hosts (sporozoite stage), the parasite increases the biting rate of his vector. In contrast, at an earlier developmental stage (oocyst) which is not transmissible to the vertebrate hosts, the parasite decreases the contact between vector and vertebrate hosts, by decreasing the natural host seeking behaviour of the insect. Since biting is risky and could lead to the death of the insect, this change seems to be beneficial for the parasite. Beach and Leeuwenberg (1985) also observed that uninfected sandflies and sandflies with immature infections probe only once or twice and are fully engorged within 10 min, whereas mature-infected flies probe more often and never result in complete engorgement.

Second, it appears that vector-borne parasites have evolved slightly different mechanisms (i.e. blocking the foregut, reducing apyrase, obscuring phagoreceptors) aimed at inducing similar feeding alterations (i.e. interference in ingestion process leading to new feeding attempts). Poulin (1995) (see also Thomas and Poulin, 1998) pointed out that convergence in manipulative processes is a likely scenario when host alterations bare on the same function, but are derived from different proximal mechanisms. Both the timing of feeding alteration and its independent evolution in phylogenetically distant organisms (i.e. convergence) are strong arguments for parasitic manipulation. Unfortunately empirical evidence in support of increased transmission induced by increased biting rate is still lacking.

3.2. Longevity and survival rate: 'have a long life'

The R_0 equation describes that the longer vectors live, the more the parasite can be transmitted. Life history theory suggests that a reduction or suppression of reproductive effort will result in increased lifespan (Stearns, 1992). Thus, it has been suggested that vector-borne parasites should be able to manipulate resource allocation of their insect vectors in a way that changes the optimum trade-off between reproduction and longevity, which in turn, could favour longer vector survivorship and hence the parasite's overall transmission (Hamilton and Hurd, 2002). Globally, studies on the effects of infection on survival reported no significant lifespan differences between infected and uninfected vectors. However, studies on the effects of infection on fecundity (i.e. number of produced gametes) often report a reduction in fecundity. Since parasites use vector resources to develop and reproduce, it has been suggested that the observed fecundity reduction in infected vectors does not induce a longer lifespan but the same lifespan as uninfected insects (Hamilton and Hurd, 2002).

Parasite-induced fecundity reduction has been reported in many insect vector—parasite associations (Hurd et al., 1995; Hurd, 2003). The association between malaria parasites and mosquitoes provides the most reported case of parasite-induced fecundity reduction. Potential proximate causes for this phenomenon in malaria have been extensively reviewed in Hurd (2001, 2003) and will not be developed here.

Whereas parasite-induced fecundity reduction of insect hosts seems to be a widespread phenomenon, lifespan comparisons of infected and uninfected insect vectors have provided much more conflicting results. Some studies found reduced vector lifespan, while others showed no effect of infection, and even increased lifespan (Table 1). For instance, Ferguson and Read (2002) used a meta-analysis on several published laboratory studies to demonstrate that overall, malaria does reduce mosquito survival suggesting that no such manipulation is occurring in this system. However, they also showed that morbidity effects are more likely to be found in unnatural vector–parasite combinations and in studies of longer duration. As a consequence, when considering studies carried out on natural associations, no effect of infection on longevity is found. Concerning tsetse flies, sandflies and bugs, the picture that emerges is also far from conclusive. For instance, greater longevity of trypanosome-infected tsetse flies has been reported by Duke (1928) and Baker and Robertson (1957). In contrast, Moloo and Kutuza (1985) found no difference in longevity and fecundity between infected and uninfected individuals, while Makumi and Moloo (1991) reported a higher longevity for tsetse males but the reverse for females, and no effect of infection on fecundity. Comparison of the survival distributions of uninfected glossina with those exposed to infection with either *Trypanosoma congolense* or *T. brucei* showed that the first significantly reduced glossina survival, while the second had little or no effect on the survival (Maudlin et al., 1998). In the sandflies, *Phlebotomus papatasi* and *P. langeroni*, infection with *Leishmania major* and *L. infantum* results not only in a significant reduction in fecundity but also in longevity (El Sawaf et al., 1994). Such findings are consistent with those reported for Rocky Mountain wood ticks, *Dermacentor andersoni*, when infected with *Rickettsia rickettsii*, the causative agent of Rocky Mountain spotted fever (Niebylski et al., 1999). Reduced survival has also been found for ticks infected with several protozoa (e.g. Gray, 1982; Watt and Walker, 2000; but see Randolph, 1991), in mosquitoes infected with several viruses (e.g. Faran et al., 1987; McGaw et al., 1998; Scott and Lorenz, 1998), and finally in mosquitoes infected with filariasis (Krishnamoorthy et al., 2004).

As conditions in the laboratory may not reflect precisely those which occur in the field, the influence of parasitism on survival and longevity has not yet been well addressed. Insect vectors are often naturally exposed to adverse conditions which are rarely considered in laboratory studies, and might act synergistically with parasitism. In addition, one might assume that the optimal survival rate of the insect may differ between parasite developmental stages: immature stages are expected to increase the vector's survival to increase their chance of becoming mature, while mature stages are potentially confronted with a trade-off between increasing the vector's lifespan and thus survival rate and increasing biting rate (see Section 3.1) that may decrease the survival rate since biting is risky *in natura* (Koella, 1999; Schwartz and Koella, 2001). For

instance, it has been shown under natural conditions that sporozoite-infected mosquitoes have higher feeding associated mortality than those without sporozoites (Anderson et al., 2000). This finding suggests that malaria parasites might harm their mosquito host more than usually thought.

Unfortunately, many studies exploring the influence of parasitism have concentrated only on either vector reproduction or vector survival/longevity. As a consequence, studies on the links between infection, vector reproduction and vector longevity/survival are still rare (but see Makumi and Moloo, 1991; Hogg and Hurd, 1997) and clearly more investigation is needed to fully explore this interesting hypothesis. In addition, a better understanding of the effects of infection on longevity and fecundity will be achieved after more investigations of naturally infected vectors.

3.3. The parasite development duration: 'become infective early'

In vector-borne parasites, one might expect that natural selection will favour an optimal developmental schedule for each parasite stage that ensures transmission between successive hosts. Once in the insect vector, a major challenge facing the parasite is to reach its infective stage before the insect takes its last blood meal and dies. This idea is particularly valid in systems involving short-lived vectors, such as, mosquitoes and sandflies. In this context, shortening the duration of development should permit the parasite to become infective earlier and hence to increase its probability of transmission. So, why is this period so long? In many vector-borne pathogens, this period is indeed as long as their insect vector's average lifespan. For instance, estimates for the probability that a 'newly' infected mosquito will live long enough to transmit *Plasmodium* spp. range from 80% (Macdonald, 1956) to less than 10% (e.g. Rodriguez et al., 1992). In fact, this duration probably results from constraints and/or trade-offs aimed at increasing the overall parasite transmission.

In malaria–mosquito systems, the vector injects a very small number of sporozoites (i.e. 10–20) into the host compared to the huge quantity available in the salivary gland (Paul et al., 2003). Koella (1999) thus asked: ''if only a few (sporozoites) are necessary, should evolutionary pressures not lead the parasite to produce the sporozoites earlier, if doing so would increase the likelihood that mosquito survives the developmental period?'' At a first glance, we can suggest that it results from a constraint, that is, a large number of sporozoites are needed in salivary glands to enable the injection of only a few. However, it has been demonstrated that this large number is neither correlated to the number of those injected nor to the probability of successfully infecting the host (Ponnudurai et al., 1991; Beier et al., 1991). As a consequence, knowing that the vector's biting rate increases with the sporozoite load (Koella et al., 1998), Koella (1999) proposed a model to investigate whether the developmental pattern could be, in fact, a mechanism that increases the overall parasite's transmission. The model showed that if mortality increases no more than linearly with biting rate, maximal parasite transmission success can occur when all sporozoites are released from the oocyst simultaneously. Consequently, Koella (1999) concluded that the development time of *Plasmodium* within its insect may be a mechanism for manipulating vector-biting behaviour to increase its transmission. Atlhough interesting, further work is necessary to fully clarify this point.

Another argument in favour of an adaptive development period over constrained development period is the case of *Plasmodium mexicanum*. In Central America, this parasite is transmitted to the fence lizard, *Sceloporus occidentalis*, by the sandfly, *Lutzomyia vexator*. Sandfly species have the particularity of having very short lifespans; that is, only about 2% live long enough to take a second blood meal (Fiahlo and Schall, 1995). As a consequence, compared to other *Plasmodium* species, *P. mexicanum* has evolved toward rapid development that ensures the matching with the high vector's mortality. In addition, Fiahlo and Schall (1995) showed that infected sandflies were attracted by higher temperatures compared to uninfected counterparts. It turned out that this higher temperature is optimal for the rapid development of the parasite, but sub-optimal for the development of sandfly eggs, suggesting a parasitic manipulation of host temperature preference (Table 1).

It is well known that the development rate of vector-borne parasites is sensitive to temperature (e.g. Garnham, 1964). However studies like the one performed by Fiahlo and Schall (1995) are scarce. Extending such investigations to other insect vector–parasite systems, particularly those affecting human welfare, is promising and could shed light on new insights into parasitic manipulation of vector-borne diseases.

3.4. The recovery rate: 'evading the immune response'

Escaping the immune system of both the vertebrate and insect host is a *sine qua non* condition to the success of parasite transmission. As a consequence, vector-borne parasites evolved the ability to manipulate the immune response of their hosts (Tables 1 and 2).

In human for instance, malaria parasites, *Giardia* and African trypanosomes evolved an evasion mechanism known as antigenic variation. These parasites have a large multigene family of proteic variants and the evasion involves a sequential dominance of antigenic variants. Any one-parasite individual expresses only a single variant and only a few individuals exhibit a new variant per generation. As a consequence, parasites that exhibit the rare variant avoid the immune system and those that exhibit the frequent variant are killed. This enables the parasites to persist in the host. In addition, other strategies have been developed by protozoan parasites (i.e. malaria, African trypanosomes, *T. cruzi* and *Leishmania*) to avoid and/or suppress both adaptive and innate immune responses of their vertebrate host, such as eliminating their protein coat, induction of blocking antibodies, molecular mimicry, modulation of dendritic cells maturation and alterations of memory T-cell, macrophages, and cytokines functions (Zambrano-Villa et al., 2002; Sacks and Sher, 2002).

Table 2
Reported cases of behavioural and physiological alterations in the vertebrate host

Physiological and behavioural alterations	Host–parasite systems	References
Attraction (A), defensive behaviour (D), blood characteristics (B)	Malaria–Mosquito–Vertebrate	
	P. chabaudi, P. berghei, P. yoelii–A. aegypti–mouse (D) (B)	Day and Edman (1983), Day et al. (1983), Rossignol et al. (1985)
	P. chabaudi, *P. berghei, P. yoelii–Culex quinquefasciatus–mouse* (D)	Day and Edman (1983)
	P. chabaudi, *P. berghei*, *P. yoelii–An. stephensi–mouse* (D)	Day and Edman (1983), Taylor (2001), Ferguson et al. (2003), Ferguson and Read (2004).
	P. falciparum–An. gambiae–human (A)	Lacroix et al. (2005)
	Virus–Mosquito–Vertebrate	
	Rift Valley fever virus–A. aegypti–mouse (B)	Rossignol et al. (1985)
	Rift Valley fever virus–Culex pipiens–hens (A)	Mahon and Gibbs (1982)
	Rift Valley fever virus–Culex pipiens–lamb (A)	Turell et al. (1984)
	African trypanosomes–Glossina–Vertebrate	
	T. congolense–Glossina pallidipes–boran steer (A) (B)	Baylis and Nambiro (1993), Baylis and Mbwabi (1995), Moloo et al. (2000)
	Leishmania–Sandfly–Vertebrate	
	Leishmania infantum–Lutzomyia longipalpis–hamster (A)	Rebollar-Téllez (1999), O'Shea et al. (2002)
	Protozoa–Ticks–Rodents	
	Babesia microti–Ixodes trianguliceps–rodents (B)	Randolph (1991)
Immune response	Malaria–Vertebrate	
	P. falciparum–human	Holder et al. (1999), Riley et al. (1989), Urban et al. (1999)
	P. berghei–mouse	Xu et al. (2001)
	Trypanosomes–Vertebrate	
	T. cruzi–human	Norris (1998), Hall et al. (1992), Brodskyn et al. (2002)
	Leishmania–Vertebrate	
	Leishmania–human	Belkaid et al. (2001), Brittingham et al. (1995), Desjardins and Descoteaux (1997), Piedrafita et al. (1999).
	African Trypanosomes–human	
	T. brucei–human	Raper et al. (2001)

In the insect vector, it has been shown that although *Anopheles gambiae* was able to encapsulate and melanize foreign bodies, it failed to encapsulate *P. falciparum* (Schwartz and Koella, 2002). This failure probably results from the suppresssion of the insect immune encapsulation response both directly by the parasite and indirectly via the effects of the blood stage infection on the host vertebrate immune response (Boëte et al., 2004). It has been indeed demonstrated that in *P. gallinaceum*-infected *A. aegypti*, ookinete stages first actively suppress the insect immune melanization response and second the parasite appears to suppress the immune response indirectly by changing blood quality in the vertebrate host. It has been suggested that this indirect suppression results from complex interactions between the vertebrate and the mosquito immune responses (Boëte et al., 2004). However this hypothesis has been recently questioned. *Plasmodium falciparum* may rely in fact on a different strategy to avoid the immune response of *An. gambiae*. By comparing the ability to melanize a Sephadex bead of infected mosquitoes, of mosquitoes that had fed on infectious blood without becoming infected, and of control mosquitoes fed on uninfected blood, Lambrechts et al. (2007) found that infected mosquitoes had a stronger melanisation response than uninfected counterparts and mosquitoes in which infection failed. This result contrasts with the previous example and seems to indicate that *P. falciparum* relies on immune evasion rather than immuno-suppression to escape the immune response of *An. gambiae* (Lambrechts et al., 2007). A note of caution is however warranted, immune evasion of insect vectors by malaria parasites does not systematically occur. It has been indeed evidenced that *P. falciparum* can be melanized by *An. gambiae* after selection tratments in the laboratory (e.g. Collins et al., 1986) but also in nature (e.g. Riehle et al., 2006). However, the extend to which such resistance occurs in natural populations remains somehow obscure (Schwartz and Koella, 2002; Riehle et al., 2006).

Although parasite's strategies to overcome the vertebrate host's immune response have been widely explored and demonstrated (Zambrano-Villa et al., 2002; Sacks and Sher, 2002), little is known concerning such phenomena in the infected insect vector. It is also important to recognize that immune evasion could, in some cases, simply result from the absence of selective pressures on the vector to develop costly immune responses against malaria parasites. In other case, inability of insect to resist infection is unlikely to result from a lack of selective pressures, since evidence of fecundity and sometimes longevity reduction continue to accumulate (see Section 3.2). As a consequence, one might imagine that insect immune avoidance and suppression is also a common strategy used by parasite and more investigations are needed.

3.5. The vertebrate host attraction: 'be quiet and rapturous'

Once the parasite has reached maturity in the vertebrate host, any traits that could render its transmission from the vertebrate to the insect more probable should have a selective advantage. In this context, several malaria parasites, filarial worms and trypanosomes have evolved synchronicity between the peak number of infective stages and the peak biting time of their vector species (Lehane, 2005). Another way to optimize transmission would be for the parasite to respond positively to the presence of vectors. Recently, it has been shown that malaria parasites accelerate the growth of asexual stages and the development of infective gametocytes (i.e. gametocytogenesis) when exposed to a high number of mosquitoes (Billingsley et al., 2005). A last way to optimize transmission from vertebrate to insect would be to induce a bias for vectors toward hosts with mature infections. This can be achieved by alterations of vertebrate host (i) attraction, (ii) behavioural defences and (iii) blood characteristics (Moore, 2002).

Increased attractiveness of infected vertebrate host has been reported in many (e.g. Mahon and Gibbs, 1982; Baylis and Mbwabi, 1995; O'Shea et al., 2002; Ferguson et al., 2003; Lacroix et al., 2005; Table 2) but not all studies (Freier and Friedman, 1976; Burkot et al., 1989; Kruppa and Burchard, 1999). It has been suggested that fever and its symptoms (i.e. increase in body temperature, in lactate production and in hyperventilation) that accompany infections (e.g. arboviruses, malaria) might increase attractiveness of infected individuals (Turell et al., 1984; Nacher, 2005). However, in many cases, no consistent differences in body temperature are found between infected and uninfected individuals (e.g. Mahon and Gibbs, 1982; Day and Edman, 1984). Recently, through an elegant semi-natural study, Lacroix et al. (2005) demonstrated that people infected with transmissible stages of malaria appear to produce something attractive to mosquitoes. First, they found that mosquitoes are more attracted to humans harbouring the transmissible gametocyte stages of the parasite than to uninfected individuals and individuals harbouring non-transmissible asexual stages of the parasite. As the infection was asymptomatic, a raise in body temperature could not explain this differential attractiveness. Second, they showed that after the clearance of the parasite, previously infected individuals were no more attractive than other individuals. Therefore, the observed increased attractiveness was not the consequence of intrinsic attractiveness (and thus making these individuals infected frequently) but rather the consequence of infection with transmissible stages of the parasite.

At shorter distances, reducing host defensive behaviour is a good way to facilitate the vector blood meal and hence the transmission. In this context, Day et al. (1983) and Day and Edman (1983) found that infection with *Plasmodium chabaudi*, *P. yoelli* and *P. berghei* make mice less defensive and consequently preferentially bitten and fed upon by mosquito vectors. In addition, they showed that reduced defensive behaviours coincided with peaks in gametocyte numbers and consequently would result in increased transmission (see also Turell et al., 1984). In this case, the general lethargy associated with infection may be the cause of reduced vector-repellent behaviour (Rossignol et al., 1985).

Hosts infected with malaria but also with other vector-borne diseases (e.g. dengue, African trypanosomiasis, babesiosis, etc.) often exhibit altered blood characteristics, including anaemia (i.e. loss of erythrocytes), and thrombocytopenia (i.e. loss of platelets). These modifications seem to reduce blood viscosity that may facilitate blood ingestion, and also decrease the vector's mortality during the blood meal (Ribeiro et al., 1985; Taylor and Hurd, 2001). For instance, Rossignol et al. (1985) found that the time taken by mosquitoes to feed on mice and hamsters experimentally infected with *P. chabaudi* or Rift Valley fever was reduced by at least one minute. In the field, tsetse flies feed more successfully on cattle infected with *T. congolense* than on uninfected cattle (Baylis and Nambiro, 1993; Baylis and Mbwabi, 1995; Moloo et al., 2000). The increased feeding success of tsetse flies may not be related to changes in the level of anaemia, but rather because of vasodilatation in infected cattles (Moloo et al., 2000).

3.6. The vertebrate host selection: 'make the good choice'

Vector host choice is a very important key predictor for the transmission intensity of vector-borne diseases. This choice may be influenced by genetic and environmental factors such as the innate host preference of the bloodsucking insect and the host availability. Beside this aspect, vector-borne parasites show some degree of vertebrate host specificity and one might imagine that parasites acquired, during the course of evolution, the ability to target appropriate host and/or avoid unsuitable ones. In the context of parasitic manipulation, studying specificity is one way to estimate the costs associated with the changes and thus is one way to address the adaptiveness of this strategy. The costs for a manipulative parasite can include energetic expenses that are necessary to induce the changes and also mortality associated with these changes. For example in the case of trophically transmitted parasites, increased susceptibility to predation by unsuitable hosts should be very costly (e.g. Mouritsen and Poulin, 2003). In vector-borne diseases, the ''qualitative manipulation'' hypothesis has been recently proposed, according to which generalist blood-feeding insects, once infected, would develop a feeding preference for hosts targeted by the parasite (Lefèvre et al., 2006). Alteration of host choice could theoretically occur at inter- and/or intra-specific level with infected vectors preferentialy feeding on host species or on host individuals that are suitable for the parasite.

First, maximising transmission towards a suitable host could be achieved by parasites by inducing in the vector a sensory bias for host traits that are correlated with optimal suitability for the parasite. Second, the parasite may induce changes in the generalist vector such as an alteration of microhabitat choice, in order to spatially match the microhabitat of the suitable host. Finally, the parasite may induce changes in the vector such as an alteration of time activity in order to temporally match the time rest or activity of the suitable host. These scenarios can be

easily tested, by for example, sampling at distinct period and comparing the proportion of infected vectors between samples. However, if we observe a difference in habits such as microhabitat choice, temporal activity and host choice between infected and uninfected vectors, one might argue that infection can be more a consequence than a cause of these habits. In other words, an infected vector may prefer a host species that is suitable for parasite not because of being infected but just because of an innate or acquired preference for this host, and thus making these vectors infected. To test between these two alternatives, comparison of habits (e.g. host choice) between uninfected vectors, vectors with mature infection and vectors with immature infection could be performed in the field. For instance, if vectors with mature infection do not exhibit the same habits than uninfected vectors and those with immature infection, then the observed habits are more likely to result from a manipulative process rather than from innate or acquired processes. In addition, comparisons between uninfected vectors and experimentally infected ones could be also performed at laboratory.

Qualitative manipulation deserves consideration and its investigation would permit to adress the complexity and multidimensionality in host manipulation by parasites. Indeed, many studies concentrated on only one character whereas manipulative parasites are known to modify more than a single dimension in their host phenotype (Thomas et al., 2005; Cezilly and Perrot-Minnot, 2005). Studies exploring the qualitative manipulation hypothesis may yield considerable information about the diversity of transmission strategies used by vector-borne parasites and find, for instance, that insect vectors infected with transmissible stages of the parasite bite more but also bite better.

4. Conclusion and future directions

Taken together the examples presented above suggest that many vector-borne parasites manipulate their hosts to increase their probability of transmission. Unfortunately, we have little evidence that such changes indeed affect transmission, although it is reasonable to expect that it would (Moore, 2002). For example, evidence have been accumulating showing that vector-borne parasites alter their vertebrate hosts to improve the attraction and feeding success of their vectors (see Section 3.5) and important epidemiological consequences of such parasitic influences have been demonstrated by models of vector-borne disease transmission (Dye and Hasibeder, 1986; Kingsolver, 1987; Rossignol and Rossignol, 1988; Burkot, 1988; Randolph and Nuttall, 1994).

Whereas some authors consider these changes as examples of parasitic manipulation (e.g. Lehane, 2005), others interpreted these as non-adaptive side effects of infection or modifications that are coincidentally beneficial for the parasite (e.g. Clements, 1999). As discussed in the first section of this review, such notion emanates from Poulin (1995) and can sometimes bring confusions that may lead to sentence such as: ‘‘All these potential benefits are a direct result of infection pathology rather than any direct manipulation of the host. Although it is feasible that increasingly virulent pathology is selected for increased transmission to the insect vector, it is more likely that these are simply side-effect, rather than selected trait’’ (Paul et al., 2003). We fully agree that many of these changes may result from indirect processes (see Thomas et al., 2005 for discussion on indirect/direct mechanisms in manipulative process), however if the trait that affects parasite transmission has a genetic basis, and presents some variation, one could expect that natural selection has not been blind, and that consequently this trait has been selected over the course of evolution. Could a side-effect not be a selected trait?

It has been also suggested that such changes might be considered as examples of mutualism (Rossignol et al., 1985; Clements, 1999): the vector benefits from the pathological conditions induced by the parasites in the vertebrate host (e.g. reduction of blood viscosity facilitating blood ingestion) while the parasite gains from the choice of the vector. However, one might argue that it is not clear whether this short-term benefit for the vector would outweigh the long-term costs of becoming parasitized. Indeed, it appears that parasites harm their vectors in many ways (Lehane, 2005).

In the future, it will be useful to perfect the empirical and theoretical study of parasitic manipulation in vector-borne diseases to move from documenting the existence of parasitic manipulation to asking how and why parasitic manipulation is expressed in some instances and not others. For this we will need a sharper quantification of the benefits and costs of manipulating and being manipulated. Beyond potential energetic expenses to induce phenotypic changes, costs for a manipulative parasite can also include mortality associated to these changes. For example, the balance between the transmission benefit of an increased biting rate and the costs of mortality associated with this behavioural change may partly explain why this change is expressed in many but not all cases. From the insect vector’s perspective, increased biting rate is also very risky. It has been indeed shown that sporozoite-infected mosquitoes have higher feeding associated mortality than those without sporozoites (Anderson et al., 2000). However theoretical analysis showed that the optimal biting rate is higher for infective stages of malaria parasites than for their mosquito vectors (Koella, 1999; Schwartz and Koella, 2001). Usually, selection to reduce the effects of manipulation is expected, when the extent with which the parasite reduces its own fitness by manipulating its host reaches a certain threshold. Additional research is requiered to fill gaps in our knowledge of the balance between costs and benefits of parasitic manipulation.

As pointed out by Paul et al. (2003), the strategies used by vector-borne parasites to optimize interaction with one host may also be subject to selection for optimization in the other. For instance, the ‘‘transmission enhancer’’ fPPG produced by leishmania parasite (see Section 3.1) appears to participate in both increased feeding rate of infected sandflies and the success of infection within the host (Rogers et al., 2004). Recasting the parasite in its two host-life cycle may clearly offer new research avenues in manipulative process. For instance in malaria, conflict of interest between immature stages (i.e. oocyst) and

mature ones (i.e. sporozoite) in the mosquito have been suggested concerning the optimal biting rate of the vector (Koella, 1999; Koella et al., 2002). Such conflicts may also occur between different stages in the mosquito and in the vertebrate host: when a mosquito infected with malaria feeds on an infected vertebrate host, sporozoite stages within the mosquito would prefer a higher blood viscosity than what is optimal for gametocyte stages within the host. Indeed, infection in the host may cause anemia to facilitate the insect bloodmeal, whereas infection in the insect may cause apyrase reduction to impair the insect bloodmeal (see Sections 3.1 and 3.5).

Recently, emphasis has been placed on the role of co-occuring parasite species within manipulated hosts. What should we expect if the same insect-vector harbours different parasite species that may or may not have the same vertebrate host? This within-host interaction creates opportunities for either synergistic or conflicting interests between different parasite species and has thus the potential to affect the result of manipulation. In trophically transmitted parasites, several scenarii have been proposed to illustrate this phenomenon and empirical evidence begins to accumulate (Lafferty, 1999; Thomas et al., 2005). For example, when different parasite species share both vectors and vertebrate hosts, all parasites may benefit from a higher transmission success if one of them is a manipulative parasite. Non-manipulative parasites can be simply 'lucky passenger' (in the vector and/or in the host) when randomly associated with a manipulator. In trophic transmission it has been shown that selection may even favour non-manipulative parasites able to preferentially infect intermediate hosts already manipulated, a strategy named 'hitchhicking'. Mixed trypanosome infections in tsetse flies seem to be common and hitchhicking has been hypothesized to explain the non-random associations between the savannah and riverine forest taxonomic groups of *T. congolense* (Solano et al., 2001). The riverine-forest type of *T. congolense* appears to benefit from the presence of the savannah type within the glossina both for its development and transmission. Parasite species may also have conflicting interests in the use of the insect vector shared with manipulative species when it requires different definitive hosts. Such a situation may theoretically occur in *Glossina* (e.g. *palpalis* or *morsitans* group) that are important vectors for both human and non-human trypanosomes. For example, conflicts may be solved by the sabotage of the manipulation. However, the prevalence of the parasites should be high in order to exert a selection pressure strong enough for such a strategy to evolve. Co-occuring parasites within manipulated host is a fruitful area for further research and we therefore encourage to examine the entire community of parasites in manipulated insect vectors and vertebrate hosts.

Another interesting avenue is the investigation of the variation in the intensity of alterations. Several studies on host manipulation by parasites indeed indicated that the level of manipulative abilities in parasites and/or the level of resistance in hosts show some degree of variability (Thomas et al., 2005). Another similar situation occurs in a much more investigated topic, that is, the variation in virulence and resistance in malaria parasite—rodent systems (e.g. Grech et al., 2006). Exploring variability in manipulative processes in vector-borne diseases and integrating the approach developed to understand the evolution of virulence would certainly provide novel information to understand the evolution of parasitic manipulation and may offer new insights into control measures. Intra-specific (host and/or parasite) variation may be responsible for the variation in manipulative processes; in an ecological context, another cause that warrants investigations is the variation due to seasonality. As for some trophically transmitted parasites (Helluy and Holmes, 2005), seasonal patterns can also occur in manipulative vector-borne parasites. For instance, the optimal manipulative effort (sensu Poulin, 1994) to make the vertebrate host attractive (see Section 3.5) may decrease when the vector abundance increases.

Future research emphasizing the molecular and physiological mechanisms of altered behaviour in vector-borne diseases will probably provide a considerable gain to knowledge. Fundamentally, exploring the proximate mechanisms underlying behavioural manipulation could partly address the existence and magnitude of the costs of manipulation. Do manipulative parasites produce themself the molecules (e.g. neuromodulators) leading to the altered behaviours or do they use instead the products of the immunity responses they induce in the hosts? (Adamo, 2002; Thomas et al., 2005). Such investigations require significant input from field biologists, evolutionary ecologists, neurobiologists, biochemists and epidemiologists. Combining the different approaches, techniques, and backgrounds of such disciplines is likely to produce information of wide interest.

Vector-borne parasites induce many changes in their insect and vertebrate hosts in a way that renders their transmission more probable. Studying these strategies and the interplay with the hosts has the potential to bring important amount of fundamental knowledge as well as define potential ''Achille-s'heels'' for control measures.

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