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# Malaria parasites prepare for flight

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**Life in seasonal environments often means facing extreme environmental fluctuations. Many multicellular organisms have evolved strategies to cope with this lifestyle. Single-celled malaria parasites are no different. An elegant experiment reveals that they respond to the availability of mosquitoes to make the most of seasonal transmission opportunities.**

Many species and populations of malaria parasite live in seasonal environments in which mosquito vectors are only available for part of the year. Given how quickly new malaria cases arise at the start of the transmission season, it has long been suspected that parasites modulate transmission effort to coincide with the re-appearance of mosquitoes [1]. Previous studies have not supported this hypothesis [2], but the puzzle is now one step closer to being solved. Cornet *et al.* [3] reveal that parasites of the avian malaria *Plasmodium relictum* detect when mosquitoes blood feed on their host and respond by enhancing transmission.

These findings support the predictions of mathematical models also presented by Cornet *et al.* [3]: seasonality can select for the evolution of a ‘plastic strategy’ (Box 1), in which parasites invest in transmission by upregulating within-host growth only when vectors (and susceptible hosts) are available (Figure I in Box 1). This avoids wasting resources, or causing too much harm to the host, during periods when investing in transmission would not be rewarded. While it seems intuitive that parasites should not invest in transmission when vectors are unavailable, there are substantial evolutionary hurdles (costs) involved in plastic strategies [4]. Plasticity in a trait requires expending valuable resources on mechanisms to detect environmental change. If organisms monitor important aspects of their environment directly, then there may be a costly time lag between detecting and responding to change. Alternatively, organisms can respond to factors (cues) that correlate with relevant changes in the environment, which allows change to be anticipated and prepared for in advance, at the potential cost of responding to inaccurate information and making bad decisions. Due to these costs and risks, plasticity pays in regions where the start/end times of the transmission season are hard to predict. At the opposite extreme, when year-round trans-

mission is possible, parasites are better off with a fixed strategy in which transmission investment is hardwired into the genome at a constant level (Box 1).

Why have previous studies failed to show that parasites monitor mosquito availability to schedule their transmission investment? The approach used by Cornet *et al.* [3] is superior in several respects. First, they used the natural host (canaries) and vector species (*Culex pipiens*) for *P. relictum*, which matters because parasites may not respond to non-vector mosquito species. Second, the parasites have a long evolutionary history of seasonal transmission because they were isolated from a temperate region. Third, instead of assessing only the impact of mosquito biting on blood stage infections, Cornet *et al.* [3] measured the intensity and prevalence of mosquito infections too. Fourth, Cornet *et al.* [3] investigated both the acute and chronic phases of infections because parasites appear insensitive to mosquitoes during the acute infection. Parasitaemia is highest in the acute phase, so there may be constraints limiting further growth (and thus investment in transmission) that do not apply in the chronic phase. Additionally, as investment is already high in the acute phase [3], if transmission success is a saturating function of parasite number [5] then the benefits of responding to mosquitoes may be marginal.

Exactly how transmission is enhanced following mosquito biting is unclear. The blood of a malaria-infected host contains asexual and sexual (gametocytes) stages. During every asexual replication cycle a small proportion of parasites differentiate into gametocytes, which are able to infect mosquitoes. Cornet *et al.* [3] propose that upon detecting mosquitoes, parasites increase their replication rate and the larger pool of asexual stages results in more gametocytes. There are several other possibilities. A larger pool of asexuals could potentially shield gametocytes from transmission blocking immune factors that are produced by the host but act in the blood meal when gametocytes differentiate into gametes [6]. Alternatively, the proportion of parasites differentiating into gametocytes is itself a plastic trait [7], so allocation towards gametocytes – as well as replication rate – could be increased in response to mosquitoes. Countering this hypothesis, there was no consistent significant difference in the number of circulating gametocytes in mosquito-exposed versus unexposed hosts, although Cornet *et al.* [3] point out that using microscopy to detect gametocytes may not be sufficiently sensitive to see this effect.

Teasing apart the roles of increased replication and increased gametocyte allocation is important: increasing allocation to gametocytes could mitigate the cost of increasing replication (because gametocytes contribute little to

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### Box 1. Plasticity and transmission strategies of malaria parasites

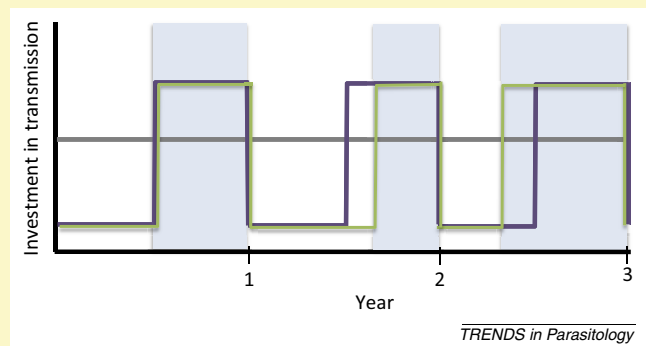
**Adaptive phenotypic plasticity:** The ability of an organism to change its phenotype or behaviour to fit the environment. Adaptive plasticity is a ubiquitous solution to the challenges of life in a changing environment. Plasticity enables organisms to maintain fitness by altering their phenotype, through mechanisms such as differential gene expression and epigenetic regulation, to best suit their circumstances [4]. As well as enabling organisms to respond quickly when environmental change is detected, organisms may also respond to predictors of future conditions which enables appropriate phenotypes to be adopted without a time-lag. It has traditionally been assumed that parasite responses to environmental perturbation are directed at maintaining homeostasis rather than using plasticity to produce adaptive changes to phenotypes during infections. Thus, variation in parasite behaviours is often – and potentially incorrectly – attributed to the footprint of host regulation rather than parasites making ‘strategic’ decisions [7,8].

**Fixed and plastic transmission strategies:** In general, plastic strategies evolve when different behaviours or phenotypes are required to maximise fitness in different environments and organisms experience these different environments during their lifetime. A fixed strategy generally refers to when organisms adopt the same behaviour or phenotype regardless of the environment. In the context of matching transmission investment with transmission opportunities (i.e., the appearance of mosquitoes and availability of new hosts; Figure 1), parasite strategies could take the following forms:

- (i) Invest the same in transmission (e.g., replication and/or allocation to gametocytes) throughout infections, regardless of temporal variation in mosquitoes. This is a fixed strategy and is predicted to return the highest fitness when year-round transmission is possible.
- (ii) Increase investment into transmission at regular intervals. This strategy could evolve when the transmission season predictably starts and ends around the same time each year. In this case, parasites could use a rule of thumb such as ‘after  $x$  asexual replication cycles for  $y$  cycles’ and more often than not, they would match investment with transmission opportunities. This strategy avoids the costs of detecting mosquitoes, but mistakes will be made in years when the timing of the transmission season departs from the norm. This is technically a plastic strategy (because transmission investment varies during infections), but it is a genetically hardwired (constitutive) rather than inducible phenotype. Cornet *et al.* [3] refer to this sort of strategy as ‘fixed’ to differentiate it from strategy (iii).

- (iii) Increase investment into transmission when mosquitoes appear. This is the plastic strategy referred to by Cornet *et al.* [3] and its flexibility enables parasites to precisely match the appearance of mosquitoes when the start and duration of transmission seasons varies across years.

Cornet *et al.* [3] demonstrate that the avian malaria *P. relictum* adopts strategy (iii) but which strategy applies to human parasites remains to be determined. Periodic waves of parasitaemia in the blood due to recrudescence and relapses from dormant liver stages are notorious features of malaria. Whether this is simply a consequence of temporal variation in the host’s ability to control parasite replication or a parasite strategy has remained mysterious. Could recrudescence/relapse enable parasites to time the production of gametocytes with the start of the transmission season, i.e., either strategy (ii) or (iii)? While both recrudescence and relapse can occur independently of mosquito biting, an intriguing observation of *P. vivax* populations suggests that the duration between relapses correlates with seasonality in transmission [3,10]. Whether the timing of relapses matches the appearance of mosquitoes, whether such relapses can be induced – or even anticipated – and whether there are transmission benefits, remain to be determined.



**Figure 1.** Fixed and plastic parasite transmission strategies. Seasonal patterns of mosquito abundance (shaded areas). The grey line shows a fixed strategy of investing into transmission [form (i)]. The purple line indicates a strategy that is plastic [form (ii)] that varies over the course of each year, but is ‘fixed’ (sensu [3]). Year 1 represents the historical seasonal pattern that these parasites have evolved to follow and so exhibit this timing every year. They cannot respond to the unusually late or early onset of mosquito abundance in years 2 and 3. The green line shows an inducible plastic strategy [form (iii)] that responds to an environmental cue, increasing investment in transmission only when mosquitoes are abundant. This strategy ensures investment coincides with mosquitoes even when seasonal timing is unpredictable.

virulence). Developing theory to explore the joint evolution of plastic virulence (replication) and plastic gametocyte allocation is now required. Rather than altering gametocyte density or allocation in response to mosquito biting, parasites may have altered the ratio of male to female gametocytes produced. Sex ratio is another highly plastic trait that can influence infectivity to mosquitoes independently of gametocyte number [8]. Finally, a parasite strategy may not be involved: blood parameters could be altered by the host reaction to mosquito biting, though whether a host immune response to biting could coincidentally make gametocytes more infectious and/or increase replication rate is unknown. It is also unlikely that such a ‘host footprint’ only affects parasites in chronic infections unless hosts do not respond to the first period of mosquito biting (in the acute phase) but become primed to respond in subsequent exposure sessions.

Precisely how parasites detect the presence of mosquitoes remains an open question. Parasites could indirectly assess mosquito availability by monitoring host responses

to biting or – given how quickly transmission enhancement occurred (within 3 days) – they may directly detect mosquito salivary proteins. Detecting mosquito products would also enable parasites to determine when the transmission season ends and downregulate investment at the right time. Elucidating how environmental sensing interacts with the epigenetic control of sexual differentiation (e.g., [9]) is the next step to link mechanism to evolution and reveal the sophistication of parasite strategies.

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