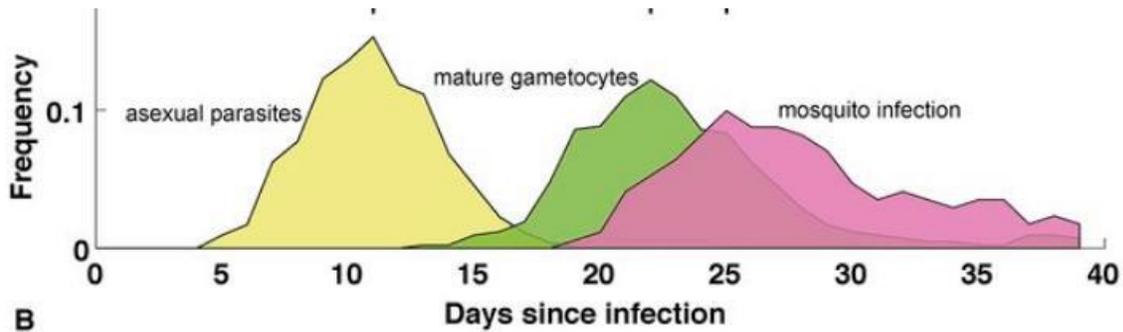


Darwin and gametocytes

Malaria transmission is an interplay between host and parasite. And *in vitro* trials can hardly elucidate this Darwinian fight for fitness.

The lack of data on genetic variation, virulence, transmission rate and clearance rate of *Plasmodium* parasites and gametocytes is surprising, given that these traits determine the population-level burden of disease. In fact, the aim of control programs (e.g. drugs and vaccines) should be to reduce the burden by acting directly on these traits. The success of such programs will depend on what parasite and host factors influence these traits and how they are biologically related to each other. Importantly, if these traits really are the prime determinants of parasite fitness, then drugs and vaccines which do no more than just reduce disease will bring about evolutionary change in the parasite population with dramatic long-term consequences. Parasite populations are expected to generate genetic variation and evolve new levels of virulence (damage to host).

A benefit of Darwinian fitness possibly is slower parasite clearance rate and hence a longer infection from which to transmit.



Mature gametocytes of *Plasmodium falciparum* first appear in the bloodstream about 10 days after the asexual parasites. Current malaria drugs want to eliminate asexual parasites. ACTs for example are taken during the first 3 days when fever and virulence caused by the asexual parasites show up. The drugs have been completely metabolized after a few hours or days, long before mature gametocytes show up in the peripheral blood. Published evidence indicates that a reduction in parasitemia may cause an increase in infectivity of gametocytes to the mosquito vector. Therefore, the impact of strategies aiming to control asexual parasites needs to be re-examined. Inefficient strategies might be predicted to increase and not suppress malaria transmission.

R. E. Sinden. Asexual blood stages of malaria modulate gametocyte infectivity to the mosquito vector – possible implications for control strategies. Parasitology. Volume 103, Issue 2 October 1991, pp. 191-196

Factors which could influence the success of experimental infections of *Anopheles gambiae* with *Plasmodium falciparum* were investigated in Cameroon. 139 experimental infections with different gametocyte carriers were performed. Only gametocyte density was identified as a factor which determined the success and the level of mosquito infection. No significant influence was found for sex and age of the gametocyte carrier, body-temperature, presence of asexual erythrocyte stages, rhesus factor, blood group and use of antimalarial drugs (chloroquine and amodiaquine). Artemisinin and chloroquine even increase transmission.

Tchuinkam T, Mulder B, Dechering. Experimental infections of Anopheles gambiae with Plasmodium falciparum of naturally infected gametocyte carriers in Cameroon: factors influencing the infectivity to mosquitoes. Tropical Medicine and Parasitology 1993, 44(4):271-276

Sulfadoxine-pyrimethamine (SP) is currently the drug of choice for intermittent preventive treatment of *Plasmodium falciparum* both in pregnancy and infancy. A prolonged parasite clearance time is believed to be responsible for increased gametocyte prevalence and mosquito infection.

Aminatou Kone, Marga van de Vegte-Bolmer. Sulfadoxine-pyrimethamine impairs Plasmodium falciparum gametocyte infectivity and Anopheles mosquito survival. Int J Parasitol. 2010 Aug 15; 40(10): 1221–1228.

In a trial, mosquitoes were fed at all stages of infection on 88 cases of *Plasmodium falciparum*. Observations were made on the relations of gametocyte densities and length of patency to infectivity. Mosquitoes were infected as late as day 321 of parasite patency in a South Carolina strain and 410 in the Panama strain. It is concluded that the long enduring parasitemias of these strains of *P. falciparum* are of considerable epidemiological importance and may be responsible for a large part of the transmission of this species in certain endemic areas.

Geoffrey M. Jeffery, Don E. Eyles. Infectivity to Mosquitoes of Plasmodium falciparum as Related to Gametocyte Density and Duration. The American Journal of Tropical Medicine and Hygiene, 1955, 4, 781 - 789

A study from Scotland showed that vaccines designed to reduce pathogen growth rate and/or toxicity diminish selection against virulent pathogens. The subsequent evolution leads to higher levels of intrinsic virulence and hence to more severe disease in unvaccinated individuals. This evolution can erode any population-wide benefits such that overall mortality rates are unaffected, or even increase, with the level of vaccination coverage. By suppressing asexual parasites and thus lowering levels of crisis serom factors gametocyte carriage will become higher. All this will evidently occur on timescales longer than those of clinical trials

Sylvain Gandon, Margaret J. Mackinnon. Imperfect vaccines and the evolution of pathogen virulence, Nature, 2001, 414, 751-755.

If pharmaceutical drugs fail to inhibit transmission, Artemisia plants may do it. Drugs are monotherapies, herbal medicine is a true polytherapy. A large randomized, double-blind clinical trial in Maniema RDC showed that *Artemisia afra* completely eliminates gametocytes in peripheral blood up to day 28.

Jerome Munyangi, Lucile Cornet-Vernet, Michel Idumbo, Chen Lu, Pierre Lutgen, et al., Artemisia annua and Artemisia afra tea infusions vs. artesunate-amodiaquine (ASAQ) in treating Plasmodium

falciparum malaria in a large scale, double blind, randomized clinical trial. *Phytomedicine* 57 (2019) 49–56

This is a tremendous hope for Africa. Already in 1980, a study showed that only patients with at least 300 gametocytes/mm³ are likely to produce a high infection in mosquitoes. 45 feeds were carried out on blood donated by *P. falciparum* gametocyte carriers. The immune system of Anopheles may be able to cope with a few intruding gametocytes, but not with thousands.

Graves PM. Studies on the use of a membrane feeding technique for infecting *Anopheles gambiae* with *Plasmodium falciparum*. *Trans R Soc Trop Med Hyg.* 1980;74(6):738-42

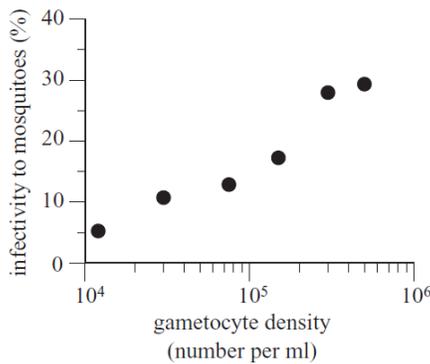


Fig 2: from Tchuinkam, op.cit.

This is confirmed by a Belgian study from 1989 in Burkina-Faso. Below a carriage of 100 gametocytes/mm³ the infection of mosquitoes is very low.

Relations entre le pourcentage d'infection chez le moustique (*A. gambiae*) et la densité gamétocytaire de *P. falciparum*

Densités gamétocytaires	0-50	50-100	100-200	200-450	+ de 450	Total
Nombre de sujets	9	17	13	22	11	72
Moyenne des densités gamétocytaires	10 +/- 10	68 +/- 10	147 +/- 31	318 +/- 83	1197 +/- 910	
Nombre de moustiques survivants	609	2047	1989	2584	947	8176
Nombre de moustiques infectés	52	553	746	1272	418	3041
Pourcentages d'infection	8,5	27	37,5	49	44	37,2
Khy carré		91,13 DS	50,89 DS	62,59 DS	7,17 DS	244,7 DS

Légendes: Densité gamétocytaire exprimée en nombre de gamétocytes/mm³.
Pourcentage d'infection calculé après dissection des glandes salivaires des femelles survivantes.

Boudin Christian, Lyannaz J., Bosseno M-F. Production de sporozoïtes de *Plasmodium* humains à Bobo-Dioulasso (Burkina Faso. *Annales de la Société Belge de Médecine Tropicale*, 1989, 69 (1), p. 3-23. ISSN 0365-6527

It is a shame that these findings, mostly 20 years old have been ignored, that research has neglected prevention and transmission of malaria, and was uniquely focused on therapy, mostly by ACTs. That's where the money came from to finance the laboratories.