Prophylaxis with *Artemisia annua* is Very Efficient: The Role of Chelators

Opinion

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4 years ago, a heated debate concerning malaria prophylaxis had been triggered on. It concerned the very promising results obtained by Patrick Ogwang, with an herbal product called Artavol; he had developed with the Ministry of Health in Uganda. Peer reviewed papers and press releases concerning these findings are easily found on internet. Merlin Willcox, UK, Honorary Secretary of RITAM, questioned the validity of the therapeutic and prophylactic results obtained by the research team from Uganda; that like many other studies they were poorly designed with fundamental flaws. And that it would be unethical to promote Artemisia teas at the expense of ACTs in young children. ACT is the acronym for Artemisinin Combined Therapy, the first line drug recommended by WHO. It combines artemisinin derivatives with lumefantrine or amodiaquine. So far, no prophylactic effect could be evidenced for these drugs. Willcox is right in stating that no large scale, randomized, double blind clinical trials confirming the efficiency of Artemisia plants against malaria are available. Indeed, they are forbidden by WHO. Only clinical trials with ACTs have been run in high numbers. OXFAM and others even claim that Africans are guinea pigs for pills or vaccines from Bigpharma WHO. Fortunately, some African medical doctors have decided not to obey the ludicrous veto of WHO Geneva and obtained the authorization of their health authorities to run clinical trials, small or large scale, with *Artemisia annua* or *Artemisia afra*: in Cameroon, in Mali, in Kenya, in RDCongo, in Senegal, in The Gambia, in Benin, in Ethiopia, in Tanzania, in Uganda, in Mozambique. They all assess a cure rate of >95 % for uncomplicated malaria, much higher than for ACTs. This all was confirmed by a large-scale trial in the province of Maniema, RDCongo of *Artemisia annua* and *Artemisia afra* vs ASAQ: 1000 patients, randomized, double blind. The herbal treatment was in all aspects superior: for fever clearance, parasitemia clearance, gametocytemia clearance, with no adverse effects and a virtual absence of recurrence on day 28. The trial included 465 children from 2-5 years of age. But these were all symptomatic patients and the question of the efficacy of Artemisia tea infusions on asymptomatic carriers remained open. Dr. Jerome Munyangi has now completed a first randomized trial with 2x100 primary school children in the province of Maniema. The objective was to study the impact of a prophylactic treatment of 3 cups/week *Artemisia annua* infusion. The results are overwhelming. In the second and third month of the treatment parasitemia and gametocytemia have completely disappeared in the Artemisia arm, but in the control arm the parasite carriage remains constant over the 3 months The seminal discovery in this small trial, which will be repeated in more schools, is of course that the prophylactic effect is evident, but more important: that the treated children will not transmit gametocytes to mosquitoes biting them. Based on these results it may be concluded that only Artemia tea infusion or powdered leaves have a lasting gametocytocidal effect. ACT's do not, and dihydroartemisinin-piperaquine may even prolong the gametocyte carriage [1].

The question needs to be asked. Are afebrile malaria infections truly asymptomatic, benign, or even beneficial to the individual? The evidence suggests the contrary. A recent review paper financed by the Bill&Melinda Gates Foundation and by the European Community's 7th Framework Program addresses this critical issue [2]. So-called asymptomatic malaria infections are associated with recurrent episodes of symptomatic parasitemia, chronic anemia, maternal and neonatal mortality, co-infection with invasive bacterial disease, cognitive impairment, and ongoing transmission of the parasite. They have significant health and societal consequences. A prophylactic effect as *Artemisia annua* infusions had been noticed in 2012 in a study of the Ministry of Health in Uganda [3]. Patrick Ogwang (personal communication) found that when asymptomatic carriers started taking Artemisia infusion, the parasites are kind of forced to progress quickly, to cause fever and disease, and once persons are treated and continue taking Artemisia they don't catch malaria easily. A similar positive effect of *Artemisia annua* powdered leaves in the form of capsules had been noticed by a study in Bangui. During surgical interventions, asymptomatic children often suffer a severe malaria crisis and don't survive. For the 11 patients treated during 36 hours, the parasitemia decreased from 395 to 142, i.e. a 64% (23%-100%) improvement. For the 14 patients treated during 60 hours, parasitemia decreased from 461 to 183, i.e. a 60% (<14%-85%) improvement. The prevention of malaria during the surgical intervention was effective in all cases and an antinociceptive effect was even noticed [4]. Adults contribute significantly to the infectious reservoir, particularly in areas of intense seasonal transmission [5,6]. The concept to reduce the parasite load in asymptomatic carriers is not new. Intermittent preventive treatment (IPT) with antimalarials has repeatedly been tried. But it has often been hampered by serious side effects. Let's just mention the increased gametocyte load after sulfadoxine-

pyrrimethamine treatment [7] and the severe haemolysis in G6PD patients after primaquine or artesunate treatment [8,9]. A paper reviewing IPT studies involving 5 antimalarial finds that the highest protective effect against symptomatic parasitaemia was obtained with dihydroartemisinin-piperaquine (95%). Sulfadoxine-pyrimethamine did not provide any protection [10].

The average protective effect was 55% which is much lower than in the trial run by Jerome Munyangi [11] with *Artemisia annua* infusion in Maniema. The gametocyte carriage is of much longer duration than generally believed. Several cases of infection of naïve patients after blood transfusion indicate that the parasite carriage lasts up to 3 years [12]. In fact, not many studies have addressed the longevity of gametocytes. A very recent *in vitro* study shows alarming data. The longevity was assessed on three different strains by microscopy, flow cytometry and RT-qPCR and find similar results: 50 days with peak concentrations at 22 days [13]. Previous studies have shown that if gametocytes remain viable, a small number of gametocytes (sub-microscopic level) is sufficient for transmission [14]. Artemisinin and its derivatives do not explain the prophylactic efficiency of *Artemisia annua*. A traveler returning from Nigeria to Canada suffered severe malaria after taking artesunate prophylactically [15]. Endothelial dysfunction in malaria is nearly universal in malaria disease, symptomatic and/or asymptomatic. It is reversible with arginine. Furthermore, arginine produces NO which inhibits the development of gametocytes [16,17]. A working hypothesis which has been advanced is that the high content of saponins in Artemisia infusion releases parasites in dormancy in the late trophozoite stage from erythrocytes by saponin lysis. Inulin is a dietetic fiber, a polysaccharide and some Artemisia species may contain up to 9% polysaccharides of their dry weight. Capsules of Chinese origin containing *Artemisia annua* leaf powder also contain inulin. The main reason may be reduction of iron absorption in the intestine [18,19]. Pentacyclic triterpenes (amyrin, asiatic acid, maslinic acid, betulinic acid) also have a long lasting effect on the reduction of symptomatic and asymptomatic malaria [20]. Immunity to malaria is hard won, and yet it is imperfect. $CD4^+$ helper T cells are critical orchestrators of immune responses [21]. In Nigeria a significantly lower $CD4^+$ count was observed among *Plasmodium falciparum*-infected truck drivers compared to those uninfected. Malaria seems to have a negative impact on the $CD4^+$ lymphocyte count.

This is in line with our findings in Katanga where we confirmed that administration of capsules containing Artemisia leaf powder raised the $CD4^+$ [22]. 44 volunteers carrying trophozoites were treated with capsules containing *Artemisia afra*. The total dose of Artemisia powder administered over 10 days was 20 gr. It was found that on day 10 the $CD4^+$ count had on the average increased by 20% and the trophozoite count was reduced to zero except in a few cases. A low $CD4^+$ T cell count is indicative of a weak immune system. In Guinea-Bissau it was found that the $CD4^+$ cell percentage was inversely correlated with the density of malaria parasites [23,24]. Another study group finds that with age there is a significant decline in the percentage of naïve T cells and $CD8^+$ T cells, and an increase in the percentage of $CD4^+$ and NK cells [25]. In Nigeria a significantly lower $CD4^+$ count was observed among *Plasmodium falciparum* infected truck drivers compared to those uninfected. Malaria seems to have a negative impact on the $CD4^+$ lymphocyte count [26]. The role T lymphocytes are complex. Loss and dysfunction of proinflammatory Vδ2+ γδ T cells was associated with a reduced likelihood of symptoms upon subsequent *P. falciparum* infection. Together, these results suggest that repeated malaria infection during childhood results in progressive loss and dysfunction of Vδ2 (+) γδ T cells that may facilitate immunological tolerance of the parasite [27]. The humoral response is also important for malaria protection because passive transfer of IgG from immune African adults to children and nonimmune adults with acute malaria rapidly reduces parasitaemia and abrogates fever [28]. Typhoid fever and salmonellosis kill more than 100000 people per year in Sub-Saharan Africa. These diseases are directly linked to a weakened immune system, by symptomatic and asymptomatic malaria [29-31]. A recent paper from Saudi-Arabia opens new doors. Trophozoites where gametocytes are born and developed accumulate hemozoin and trophozoites where the asexual cycle continues are void of hemozoin, like it is absent in merozoites and ring forms [32].

If the trophozoite containing the gametocyte carries its load of hemozoin it is because heme is essential in the mosquito and liver stages. The sporozoite even generates its own heme in the liver stage, but parasites in erythrocytes do not [33,34]. ACTs are not able to eliminate gametocytes, nor do antibiotics, nor does chloroquine, nor do quinolines. They may even enhance transmission of more resistant parasites. Quinine had a strong reputation to be a prophylactic against malaria. But it is imposible to find a single scientific paper confirming this statement. The only clinical trial retrievable is from 1918 and finds the same number of infections in two arms; in the control arm (n=252) and in the treatment arm where 140 patients received 10 gr of quinine per day. The reputation of quinine as prophylactic rests probably on the fact that the continuous intake of the drug was suppressive and curative in case of infection [35]. In fact gametocytes in the stages I-IV hide in bonemark as it was found recently. This may explain why gametocytes can survive for a much longer period than the asexual stages. It is only in stage V that they become vulnerable [36]. The hemozoin carried by the gametocytes is not carried inside, but on the outside in Granham bodies [37]. Some proteasome and protein synthesis inhibitors seem to be effective against gametocytes [38]. Iron chelators also have an effect. Results of the double-blind, placebo controlled trial of desferrioxamine in humans with asymptomatic parasitemia provided unequivocal evidence that this iron-chelating agent has antimalarial activity. Depriving the parasite of a metabolically important source of iron may represent a novel approach to antimalarial drug development. Desferrioxamine has no effect on the early intra-erythrcytic stages of the parasite. Iron supplementation annihilates the effect of this chelator on gametocytes in asymptomatic malaria. The efficiency of the treatment with chelators is not immediate. It requires several days of administration. This appears logical and recommendable as the gametocytogenesis and gametocyte circulation spread over several weeks after the asexual stage [39]. In fact the efficiency of these chelators is known since 25 years [40]. It is likely that the Artemisia plants contain some molecules which interfer with the storage of hemozoin in the Granham bodies of the gametocytes. Proanthocyanidins and other tannins for example are well known for their chelating effect. Comparison with the gametocytocidal effect of other plants may be useful. Extracts of *Azadirachta indica* although they have little therapeutic effect during the asexual stage have a strong gametocydocidal effect, at 50 ppm. But here again the molecules responsible for this effect have not been identified [41].

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Conflict of Interest

None.

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