"Using *Artemisia annua* L. tea to fight malaria"

What is *Artemisia annua*

It is a plant (*Artemisia annua* L.[1] fam. Asteracee) which has been known by the Chinese for more than 2,000 years with the name of *qing-hao*, and according to written records was already used as antipyretic as early as a few years after Christ.

It grows spontaneously or is grown to yield several active ingredients used as basis to produce the most effective antimalarial medicines, the ACT-Artemisinin-based Combination Therapy[2]. Its therapeutic effectiveness is mainly due to the active ingredient artemisinin which can reach 1% in the leaves (dried basis) of the selected genotypes. This point is crucial to the efficacy of simple preparations like infusions. No scientific evidence is available on the geographic variability of artemisinin percentage, but it is assumed that it varies according to the latitude since several physiological stages are controlled through day length. Local experiments carried out under scientific monitoring are required to assess the actual effectiveness.

Recognized effectiveness and harmlessness.

Derivatives from artemisinin (artesunate, arthemeter etc.) are very fast acting, and 5 to 10 times more effective than other molecules commonly used to produce conventional antimalarial drugs. Having a short life within the human body, the risk of developing tolerance is minimum. In addition, artemisinin dramatically reduces the number of gametophytes (the sexual form of the parasite), responsible for transmitting the *plasmodium* and the eventual tolerance developed by it.

[1] for further details: http://en.wikipedia.org/wiki/Artemisia_annua
[2] for further details: http://www.mmv.org/article.php3?id_article=27

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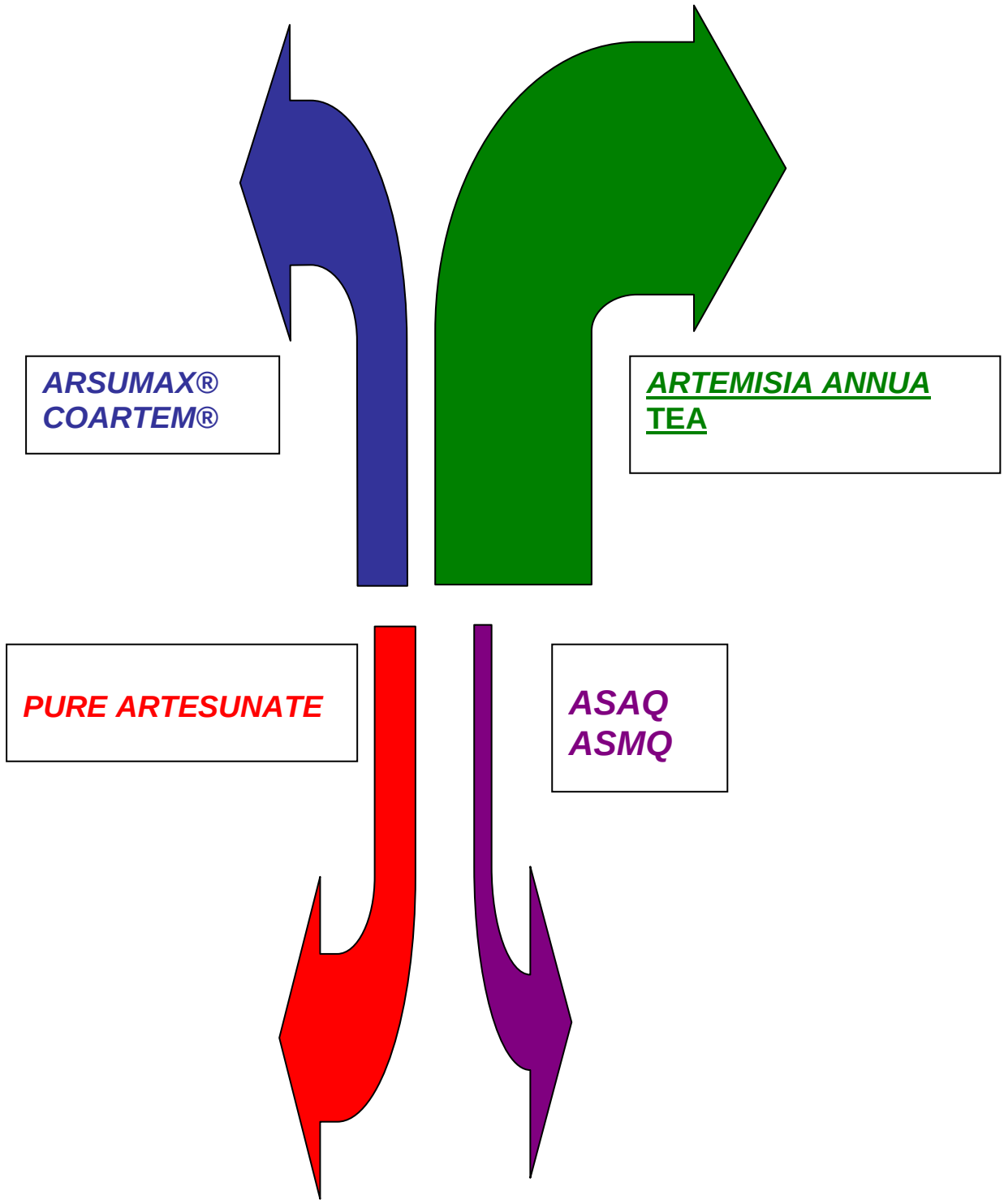
Figure 1. *Indicative flows of access to major antimalarial treatments (Icei processing of WHO data).*



Source: 'Access to malaria treatment among the poor: what can the AMFm contribute?', paper prepared for the RBM AMFm Task Force, april 2008

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A reduction of gametophytes, in endemic areas, especially in peak transmission periods, could help to break out the transmission of the disease as well as to reduce drug tolerance mechanism.

Therapeutic use of *Artemisia annua* tea

The use of tea made with the natural hybrid of *Artemisia annua*, yielding high and steady levels of active ingredient (0.8-1% of the leaves), has already spread in more than 25 African countries following the pioneering work done by several organizations including Anamed, a German NGO, using the tea in combination with conventional antimalarial drugs.

Stages of Artemisia cultivation and harvesting in Africa

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Map 1. Countries including ACT (Artemisinin-based Combination Therapy) in malaria treatment: 2004.

Source: World Health Organization

ICEI introduced in 2004 under one of its development cooperation programmes, financed by the European Union and still ongoing at Silves (Amazonas State, Brazil), experimental cultivation of hybrid *Artemisia annua*, unprecedented in the Amazonas region, using seeds and scientific advice provided by the University of Campinas (more precisely, the CPQBA, Centro Pluridisciplinar de Pesquisas Químicas, Biológicas e Agrícolas, Agrotechnology Division, coordinated by Prof. Pedro Melillo de Magalhães). After 6 months, the first plants generated by the seeds provided by the CPQBA were certified by Unicamp as containing a more than satisfactory level of artemisinin (ranging between 0.8-1 per cent).
The seeds produced by these plants are viable, reproductive and reproducible. The second-generation seeds have already been harvested, and the third generation is about to be ready for harvest. During these generations the better plants are selected in terms of late flowering and high artemisinin content.

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Seeds and cultivation of artemisia at Silves (Manaus, Brazil), 2006

In the area of Silves (State of Amazonas, Brazil) an early distribution of bags containing *Artemisia annua* dried leaves provided by Unicamp-CPQBA has already taken place, in collaboration with basic healthcare services.

Artemisia kits for the controlled distribution at Silves

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The results, as empirically collected by local voluntary personnel, so far appeared very satisfactory; plasmodium levels have shown a vertical decrease since the very first administration.

By putting 5/7 grams of artemisia dried leaves in 1 liter of boiling water and drinking the infusion for 7 days, 4 times a day, the efficacy seems to be comparable to those obtained by taking the conventional antimalarial drugs.

This evidence is partly supported by a study carried out at Bukavu, Republica Democratica del Congo, by Dr. Mueller from the University of Tübingen, Germany (in *Transaction of the Royal of Tropical Medicine and Hygiene,* 2004, 98, pp. 318-32), "Randomized Controlled Trial Of A Traditional Preparation Of *Artemisia Annua* L. (Annual Wormwood) In The Treatment Of Malaria", Markus S. Mueller,*, Nyabuhanga Runyambo, Irmela Wagner, Steffen Borrmann, Klaus Dietz, Lutz Heide".

The encouraging results obtained so far support the effectiveness of the tea in malaria *falciparum* treatment, showing it is a viable alternative to quinine and other conventional drugs against which the plasmodium has already developed resistant strains in different geographical areas.

For the most part of the world population (about 70 per cent), deprived of access to effective commercial drugs, growing this plant and administering the tea would mean appropriating a costless treatment of proven effectiveness, available locally following a short controlled cultivation test.

Artemisia annua tea today

The latest statistics confirm that malaria is the third important world pandemics; 40 per cent of world population (2.4 billion people) is exposed to this disease that affects half billion people/year and kills almost 2 millions.

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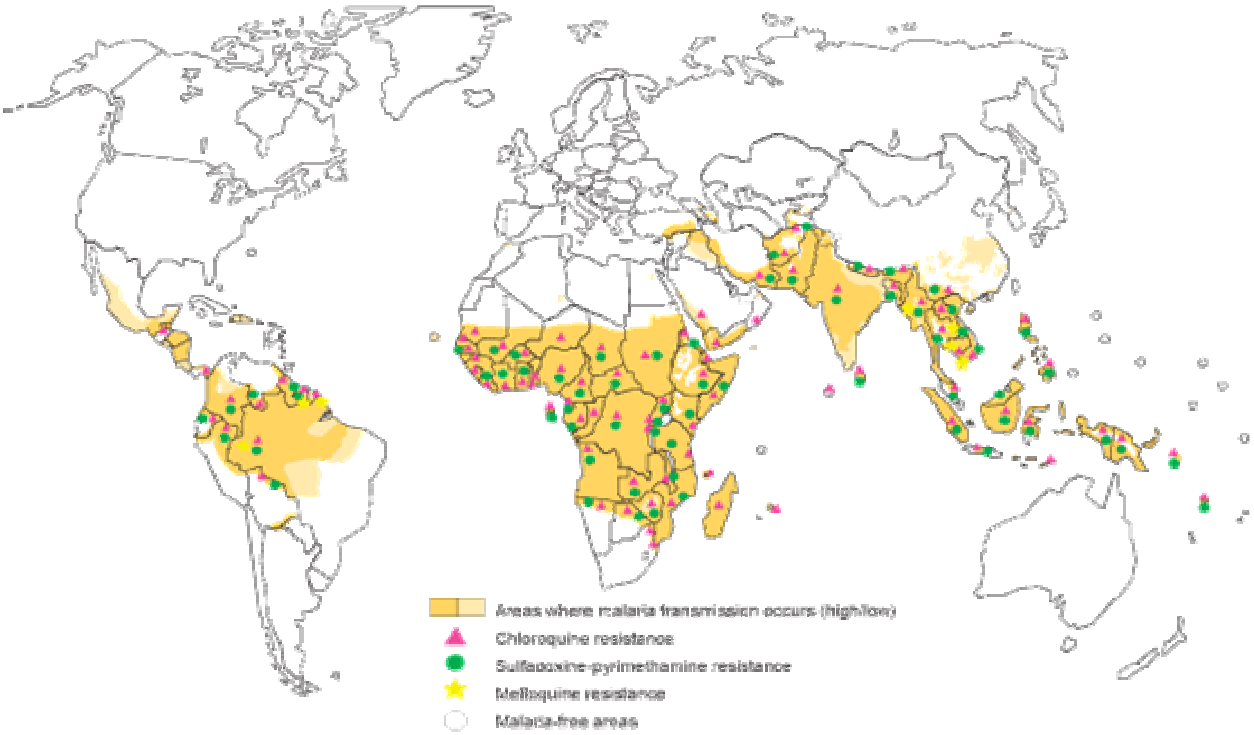
Map 2. Drug resistance developed by *P. falciparum*. WHO Pilot Centres data, 2004



Source: World Health Organization

Several measures have been undertaken to stop this awful situation, ranging from efforts in pharmaceutical R&D (e.g. the cases of Asaq[3], the new nonprofit drug resulting from the collaboration between Sanofi-Aventis and Médecins Sans Frontières, and Asmq[4], the patent-free drug developed by Farmanguinhos/Fiocruz and DNDi-Drugs for Neglected Diseases).

Also, to innovation in entomology, envisaging the creation of a genetically modified *anopheles* (vector of the *plasmodium*).

[3] for further details: http://www.msf.org/msfinternational/invoke.cfm?objectid=117D4F12-5056-AA77-6CA4A3B4A95E178B&component=toolkit.pressrelease&method=full_html

[4] for further details: http://www.dndi.org/cms/public_html/insidearticleListing.asp?CategoryId=166&SubCategoryId=167&ArticleId=477&TemplateId=1

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Among these innovative tools to fight malaria, which is the role for artemisia tea? Can it still be considered a valuable tool to fight malaria?
The answer of scientists and physicians is affirmative: artemisia tea is an effective tool for fighting malaria in endemic, marginal and hardly accessible areas.

ICEI's proposal is not to use artemisia tea in urban areas where medical services are available and the disease can be controlled by low-cost drugs.

Our target are marginal and hardly accessible areas, where people have no access to any kind of drug if not episodically and often randomly.

We have so far identified two lines of action:
A) The first concerns the use of artemisia tea as an emergency tool enabling people affected by the most virulent and aggressive form of malaria to reach health clinics that are often located many travelling days away. Using the tea in these cases could save many lives otherwise threatened by marginality conditions. Today this dramatic situation is somehow addressed by providing artesunate-based suppositories[5] (an UNICEF-UNDP-WORLD BANK-WHO project, that saved many children's lives by enabling them to reach the nearest medical services). Again, it is obvious that the crucial issue, access to drugs, is not removed in this way. In such difficult contexts, artemisia tea can represent today the only hope to survive for thousands of people, notably children and elderly.
B) A second intervention strategy is based on the argument that assuming artemisia tea since the early years of life could help to control the huge infant mortality rates due to malaria. While this might delay the development of immunity that normally occurs in children aged about seven years, it could enable many children, the weakest ones, who would be bound to certain death, to survive for the time needed to develop immunity to the *plasmodium falciparum*, normally occurring only in the most resistant subjects living in endemic areas. Here again, artemisia tea offers the only opportunity for a normal life, or nearly so, in contexts where malaria is a health and economic plague.

[5] for further details: http://www.who.int/tdr/publications/tdrnews/news69/artesunate.htm

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Doubts

While part of the academic/medical world supports the use of artemisia tea, the rest remains sceptical and opposed.

Perplexities concern: 1) the possible insurgence of resistance to artemisinin, the very last bastion against malaria; 2) the use of plain tea instead of the effective conventional drugs available on the market.

1) Insurgence of resistance:

The *Plasmodium falciparum* has already developed strains resistant to most conventional antimalarial drugs, with the relevant exception of artemisinin.

Arguments **against** using *A. annua* tea :

a) using artemisia tea, as a monotherapy, might speed up the development of the much-feared resistance to the last effective tool against malaria; conversely, most commercial antimalarial drugs combine two molecules (e.g., artesunate and amodiaquine, or artesunate and mafloquine), just in order to hamper the process of developing resistance.

b) In addition, concerns have been expressed about an improper use of tea by the populations with access to artemisia cultivation, so adding a further factor of risk of development of resistant strains.

In the face of this criticism, that part of the scientific world **in support of** the use of artemisia tea argues that:

a) Using a natural tea cannot be considered a monotherapy. Besides artemisinin, the plant *Artemisia annua* contains other ingredients effective against malaria *falciparum*: artemetin, casticin, chrysoplenetin, chrysosphenol-D and cirsilineol, and other 50 substances compounding the biochemical structure of the plant, and no case has been recorded in the literature of a parasite developing resistance to the total extracts of any plant. “Monotherapy” means assuming only one molecule, one active ingredient, that can only be obtained by complex laboratory processes. In addition, several monotherapy drugs based on one molecule already exist, e.g. artesunate, that are used in many areas of the world as emergency tools against the most virulent and aggressive forms of malaria, or as surrogates of conventional antimalarial drugs against which the plasmodium has already developed resistance;

b) The issue of improper use of drugs has nothing to do with their form, whether tea or tablet, syrup, suppository…

The incorrect use of drugs involves all countries, including the Western ones, and all treatments, even the most common drugs which have been available on the market for many years, such as the antibiotics.

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Only an adequate and steady flow of information and training on how to use any drug may reduce the problem of improper use or premature abandonment of therapy. Training the local personnel in production, preparation and use of artemisia tea is a fundamental part of the programmes that ICEI intends to implement. Based on our previous experience in the Amazons, we are convinced that the local populations are able, also because of their long-standing familiarity with phytotherapies, to learn very quickly the importance of a correct use and to transmit the acquired knowledge. Indeed, this is precisely what happened in the past with quinine, an antimalarial drug that saved millions of lives and was used, as a plant bark extract, precisely in form of tea.

2) Why a tea instead of conventional drugs:

Another point of criticism by many concerns the use of a natural tea instead of clinically tested drugs, with precise percentages of active ingredients and exact dosage.

The problem here would be related to the assumption of a lower than-needed quantity of active ingredient, that in the long term could create a risk of raising the much-feared resistance.

In response to such fears, experts object that the variety of *Artemisia annua* that should be used for the tea is, as above mentioned, the result of plain hybridization of *Artemisia annua* that has been used for over 2,000 years in China, where no evidence of resistance has been detected. Based on this hybridization, prof. Pedro Melillo de Magalhaes at Unicamp-CPQBA bred a variety of *Artemisia annua* with a high and steady level of artemisinin, ranging between 0.8-1 per cent of the plant biomass. This means that the natural hybrid of *Artemisia annua* produces exactly the required level of the active ingredient, thus preventing risk of assuming insufficient doses and thereby the insurgence of resistant strains.

Healthcare self-reliance

The aim of ICEI (necessarily to be shared with other public and private bodies) is to free marginal communities from relying on intermittent supply of effective, but expensive commercial drugs. Indeed, in these difficult contexts the problems of malaria and impaired access to care are further compounded by the equally serious plight of counterfeit drugs.

Self-reliant, controlled artemisia cultivation practice would meet two crucial need:

1) access to a safe and effective treatment against malaria for everybody:

Growing artemisia in remote, isolated areas could solve the problem of access to drugs, thus offering to local communities an opportunity for healthcare self-

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reliance. Following adequate training on cultivation techniques, the populations of malaria-plagued areas could be able to produce autonomously just the quantities of artemisia they need and, once trained on the simple procedures of tea preparation and assumption, become self-reliant in malaria treatment. Considering the high share of cases occurring each year, mostly in rural, isolated areas, this could mean ensuring better and more decent life conditions to millions of people.

2) a zero-cost therapy

In marginal, rural areas, where malaria is endemic, the problem of access to drugs is further compounded, even when drugs are available, by their unaffordable costs. In rural areas, notably in Africa, families are numerous (on average, 7 to 10 members), with a very low average age and incomes that can hardly cover food subsistence. It is obvious that when the members of the family are affected by malaria four-five times a year, even the least expensive drug (e.g., 1 US $ per dose) becomes unaffordable.

Establishing controlled cultivation and training local volunteers and healthcare operators on artemisia tea use would offer marginal communities a steady access to effective, zero-cost malaria treatment, with an enormous social impact that will hopefully spread in time to the whole African continent. It is noticeable that one hectare cultivated with selected *Artemisia annua* produces sufficient doses to cure about 100,000 people.

Work at the institutional level

In Brazil ICEI, following intense exchanges with several public and private bodies, has finalized an important agreement with ArtePharma contributing to the purchase of one lot of 2 tons of *Artemisia annua*, with standard certified artemisinin content, needed to start the first proper clinical trial of artemisia tea, that will be carried out at the hospital of Tucuruì (State of Parà). The protocol for this clinical trial was approved by the Brazilian Ministry of Health, ANVISA (Agência Nacional de Vigilância Sanitaria), and the packing by a precise dosage was ensured by Farmanguinhos Laboratory (Ministry of Health -FIOCRUZ)

This clinical trial will be aimed to show, on a scientific basis, the efficacy of artemisia tea as a stand-alone treatment for malaria, putting an end to its role of mere supplement to conventional drugs, so far imposed by the lack of systematized and certified data.

Another crucial achievement was the reinforced partnership with Prof. Pedro Melillo and Unicamp-CPQBA, the most important biochemical and agricultural research centre of Latin America; partnerships have also been established with the University of Salento, the University of Bari and other public and private institutes.

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Artemisia with standard level of active ingredient for clinical trial

The first clinical trial

The latest step of this process was the recent decision of the Instituto Evandro Chagas and The Hospital of Tucuruí to carry out a clinical trial of *Artemisia annua* tea according to WHO guidelines. For this, The University of Campinas provided a certified lot and Farmanguinhos laboratory packed it following the GLPs.

The trial, the first ever carried out anywhere in the world in accordance with international scientific standards, should definitely erase any doubts concerning the safety and effectiveness of *Artemisia annua* tea.

As emerged in the meeting held on March 13, 2008 at Campo do Jordão[6], even if artemisia tea could hardly find its application in Brazil, a country with a properly functioning national health system, it will represent a valuable tool to save many lives in those countries, mainly in Africa, where malaria is endemic and weak national health systems are unable to offer proper care.

The number of African countries willing to join the same clinical trial of *Artemisia annua* tea, with the same material, is on steady increase. Gambia, Nigeria, Cameroon, Senegal, and the D.R. of Congo will soon start implementing the study,

[6] During the Tropical Medicine Symposium held at Campos do Jordão (State of S. Paulo, Brazil), a technical meeting was held 'behind closed doors'; it was attended by the most outstanding Brazilian experts of malaria, officers of the Brazilian Ministry of Health, members of OPAS (Pan-American Organization of Health), UNICAP-CPQBA (Research Centre of San Paolo State, Brazil) and ICEI as the organization which started the process of sensibilization and lobbying at the institutional level..

and many others are about to take a decision that, while imposed by the present emergency, is also sending a strong political signal to the international agencies.

Pack of *Artemisia annua* dried leaves to be used for clinical trial, produced by University of Campínas and packed by Farmanguinhos in collaboration with ICEI

An ethical choice

The option to adopt or not the treatment based on artemisia tea in marginal, rural and malaria-endemic areas, cannot be discussed exclusively in scientific terms.

The legitimate concern, by part of the medical/scientific world, about the possible insurgence of resistant strains of *Plasmodium falciparum*, may result in a myopic debate (mostly internal to the Western scientific world), leaving in the background the emergency ongoing in Africa, where malaria is killing one child every 30 seconds.

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Children affected by malaria in Africa

Even the most skeptical scientists, (like most social workers, basic healthcare operators, missionaries, local officers), faced with the question of saving or not a single human life, must admit that, where no access exists to any kind of drug, using artemisia tea would undoubtedly be an ethical choice.

Some data

A mature plant of *Artemisia annua* ensures about 10 complete treatments;

- One hectare cultivated with *Artemisia annua* hosts 8,000 to 10,000 artemisia plants;
- One cultivated hectare can therefore yield **80.000/100.000 doses.**
- One soccer field cultivated with *Artemisia annua* can heal all the spectators!

Based on our previous work in the Brazilian Amazons, meetings with outstanding malaria experts and members of several agencies active in endemic areas, and internal discussion between ICEI members, we are convinced that carrying forward our programme to spread the use of *Artemisia annua* tea is, more than an ethical choice, a moral duty. Tens of thousands are dying today not because a cure does not exist, but because they are not reached in time by it, because they are living too far from urban centres or too poor to afford it; *Artemisia annua* can already now prevent all this by making the lives of many people more human and decent.

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