The world of Artemisia in 44 questions

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THE WORLD OF ARTEMISIA IN 44 QUESTIONS

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EXECUTIVE SUMMARY

Around 1.5 million people die every year of malaria; every 30 seconds a child dies due to this preventable and curable disease. Over 90 % of malaria cases and the great majority of malaria deaths occur in sub-Saharan Africa. Most of the affordable anti-malaria drugs have become ineffective because *Plasmodium falciparum* – the malarial parasite responsible for the most severe malaria cases and deaths - has developed resistance to them.

According to the World Health Organization (WHO) and other agencies, artemisinin-based combination therapy (ACT), derived from the plant *Artemisia annua*, is the most promising anti-malaria drug for tackling this problem. It has been estimated that there are roughly 500 million episodes of clinical malaria per year, the majority of which should ideally be treated with ACT.

Supply does not yet meet demand. The production and supply chain needs to grow and significant public and private interventions are required to make an effective and affordable anti-malaria drug available to African patients.

From a technical point of view, it is possible to cultivate sufficient amounts of *A. annua* to produce enough ACTs to cure all the malaria patients in the world. An ACT could be made available at an affordable price within just 2 to 3 years. However, this would require not only substantial investments, but also a total redesign of the supply and distribution chain.

This paper, commissioned by the Netherlands Directorate-General for International Cooperation (DGIS), aims to inform stakeholders of the most pressing questions surrounding *Artemisia* and ACT production. In addition to outlining their potential in treating malaria, this paper identifies numerous of issues and opportunities that need to be addressed in order for the production and distribution of ACT in sufficient quantity to become a reality in the near future.

One of these obstacles is the slow and cumbersome implementation of the WHO's drug pre-qualification policy, which has resulted in a monopoly-like situation of only one pre-qualified ACT by just one pharmaceutical company. As a result, the retail price is far too high for the drug to be accessible to for the poor. In addition, growing *Artemisia* plants is risky and will not be profitable for long because of the synthetic

production that is expected to begin in the near future. Small-scale farmers in tropical Africa are the ones being exposed to these risks by poorly informed policy makers and organisations that promote the plant's production.

These and other obstacles can be overcome by several means involving public and private stakeholders. The implementation of the WHO's pre-qualification policy should be better resourced for speeding up the process; an *Artemisia* procurement fund could be established in Africa; quality seed could be made available to African farmers; other medicinal crops could be promoted to reduce the economic risk to farmers; and, a task force could be established to enhance transparency, coherent policy making and knowledge sharing.

It is hoped that the increase in stakeholder knowledge about *Artemisia* and ACT will result in more effective interventions. Stakeholders wishing to contribute to the production and promotion of ACTs will be able to make evidence-based decisions and thereby to target their intellectual and physical resources in ways that will make a real difference. The case of Artemisia production and ACT promotion stresses the need for more unbiased knowledge that is shared as a 'global public good' amongst various stakeholders. Only in that way can we make an obscure venture more transparent and thus contribute to public goals, such as better health care in regions that are among the most economically impoverished parts of the world.

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PREFACE

Is artemisia just a myth? Could it really cure 300-500 million malaria patients, the majority of whom live on or below the poverty line in rural Africa? And if - according to WHO and other agencies - artemisinin-based combination therapy (ACT) is the most promising anti-malaria drug, why is it not available on a massive scale? What is the position of the drug on the anti-malaria agenda 30 years after the active component was first isolated in China?

A look into the world of artemisia reveals today's reality regarding a global disease as malaria. Around 1.5 million people die every year of malaria; a child dies of it every 30 seconds. Most of the affordable anti-malaria drugs have become ineffective because the parasite has developed resistance to them. Rural people in remote areas of Africa still rely on these drugs, and still die from them. Yet, a simple plant from China that can grow on the foot slopes of Africa's mountains has turned out to be the most effective drug against the disease. Can a plant solve the problem so easily? Is it possible that African farmers could grow the plant and thus solve one a prominent barrier to Africa's development?

Complex problems seldom have a simple solution – and artemisia is no exception to this rule. From a technical point of view, it is possible to cultivate sufficient artemisia and to extract sufficient artemisinin from it to cure all the malaria patients in the world. An ACT could be made available at an affordable price within just 2-3 years. However, this would require not only substantial investments, but also a total redesign of the supply and distribution chain. During our investigation, which was commissioned by DGIS (Netherlands Directorate-General for International Cooperation), we came across numerous logistical, administrative and economic obstacles to the production and promotion of ACT, notably in Africa. However, both Vietnam and China have been successfully reducing the burden of malaria with artemisinin-based drugs In Africa, national procurement systems and private dispensaries distribute artemisinin-based drugs. Unfortunately, the price of each treatment is as much as USD 3.5, putting it out of reach for all but tourists, military forces and the urban elite. Until very recently, WHO had pre-qualified only one ACT from a single pharmaceutical company. This market – which is subject to international interventions – does not function properly because of the formation of a manufacturing and supply chain with monopolistic features. Therefore, the situation is one of confusion rather than of transparency and collaboration, which are required to solve such an immense problem.

Artemisia is a hot subject. After 30 years of international silence, we are now confronted with loud, and sometimes conflicting, voices. Production initiatives are mushrooming all over Africa, even in areas that are unsuitable from the agronomic point of view. Economic

feasibility seems to have become of secondary importance and in East Africa small farmers are being advised to grow the crop even though the market is still dominated by uncertainty and extreme price fluctuations. Agro-economic analysis indicates that, worldwide, between 17 000 and 27 000 ha of *Artemisia annua* are required to satisfy global demand for ACT. An approximate, depending on numerous factors, 4 000 hectares are required for every 100 million ACT treatments. Present acreage stands at an estimated 5 000 hectares. A sound analysis of the market and the supply chain is required so that the livelihoods of vulnerable households that start producing artemisia are not jeopardized. In the meantime, the question is whether these initiatives will provide a shortcut to the 300 million treatments urgently required to save lives.

Decision-making about public and private interventions in artemisia and ACT production suffers from knowledge barriers, miscommunication and a chain of complexity. In the world of artemisia, there are many who are experts in a single discipline, but few who have an overview of the whole subject. This in itself has stagnated decision-making significantly. Policymakers are often the last to join the debate on what has to be done, and are overruled by the body of knowledge and the entrenched position of the experts. Despite the many individual interventions, the required domino effect has not occurred. The domino tiles fall, but do not trigger an acceleration of the supply chain.

We do not claim that this book is the standard work on artemisia and ACT. We have produced it in order to inform all the relevant stakeholders and other people interested of the 44 most pressing questions and the answers to them. We believe that knowledge of artemisia and ACT, and of their potential, among all stakeholders will result in better collaboration and more effective interventions. We hope that our explorations of and answers to the 44 most pressing questions will allow the stakeholders to take evidence-based decisions that will optimise the intellectual and physical resources of those organizations that want to contribute to making ACT accessible to the poor. Our hope is that, in due course, this seemingly insignificant Chinese plant will make a significant contribution to reducing the impact of malaria on Africa's development.

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This booklet is the result of a collective effort made by many people, institutions and private companies. We would never have been able to present the answers to our 44 questions without their willingness to share information. We realize that the debate on ACT and its production and promotion is highly politicised and often charged with emotion. We wish to stress that all conclusions presented in this document are solely the responsibility of the authors.

We would like to express our gratitude to the Directorate-General for International Cooperation of the Netherlands Ministry of Foreign Affairs for financially supporting the project.

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ABBREVIATIONS

AAL	African Artemisia Ltd.
ABE	Advanced Bio-Extracts (holding company for East-African Botanicals Uganda and Kenya Ltd and African Artemisia Ltd.)
ACT	Artemisinin-based combination therapy
AQ	Amodiaquine
ART	Artemisinin
AT	Artemisinin-based monotherapy
CQ	Chloroquine
DALY	Disability Adjusted Life Years
DFID	Department for International Development
DGIS	Directorate General for International Cooperation
DHA	Dihydroartemisinin
EAB	East-African Botanicals Ltd.
EMEA	European Medicines Agency
EurepGAP	Euro-Retailer Produce Working Group Good Agricultural Practices
F1 hybrid	First-generation plant obtained from crossing two selected pure-breeding parents to produce uniform, vigorous and high-yielding offspring
F2 hybrid	Plant that results from the self- or cross-fertilization of F1 hybrids
Faida Mali	Small-scale enterprise supporting NGO in Arusha
FDA	Food and Drug Administration
GAP	Good Agricultural Practices
GFATM	Global Fund to Fight Aids, TB and Malaria
GMP	Good Manufacturing Practice
IRR	Internal Rate of Return
KIT	Royal Tropical Institute, Amsterdam
MMSS	Malaria Medicines and Supply Service
MMV	Medicines for Malaria Venture
RBM	Roll Back Malaria partnership
SP	Sulphadoxine-Pyrimethamine
WB	World Bank
WHO	World Health Organization

SECTION 1: MALARIA AND ITS CURES

1. What is malaria?

Malaria is caused by single-cell (protozoan) parasites of the genus *Plasmodium*. Four species can cause human disease: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. The parasites are transmitted between humans by the bite of an infected female mosquito (*Anopheles*). The malaria parasites multiply extremely rapidly in the human liver. At a certain point, they leave the liver and infect red blood cells (erythrocytes). A subsequent wave of *Plasmodium* replication takes place in the erythrocytes; the red blood cells burst and new red blood cells are infected by the parasites. Infection with malaria parasites may result in a wide variety of symptoms, ranging from very mild ones to severe disease and even death. *P. falciparum* is the main cause of severe clinical malaria and death. Therefore, the focus of this paper is on malaria caused by *P. falciparum*.

Malaria begins as a flu-like illness 8-30 days after infection. The disease can be categorized as uncomplicated or complicated (severe) malaria. Symptoms include fever (with or without other indications such as headache, muscular aches and weakness, vomiting, diarrhoea, coughing). Typical cycles of fever, shaking chills and drenching sweats may then develop. Destruction of the erythrocytes leads to severe anaemia. Persons infected with *P. falciparum* are at great risk of dying when severe malaria occurs. Severe malaria develops when *P. falciparum* infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. Especially cerebral malaria – which is caused by parasites blocking the blood vessels in the brain and leads to abnormal behaviour, impairment of consciousness, seizures, coma or other neurological abnormalities – often results in the death of the patient.

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- www.cdc.gov
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2. What is the health impact of malaria?

Malaria is the most important tropical disease. It is widespread throughout the tropics and also occurs in many temperate regions. Although malaria is found in more than 100 countries, over 90 % of malaria cases and the great majority of malaria deaths occur in tropical Africa. It exacts a heavy toll of illness and death, especially amongst children and pregnant women. It also poses a risk to travellers and immigrants; imported cases are increasing in non-endemic areas. The global burden of the disease is phenomenal.

According to WHO, at least 1.1 million people die each year from malaria. Most deaths occur in children under the age of five. Every 30 seconds in Africa, a child dies of this disease. There are at least 300 million clinical episodes of malaria, and over 40 % of the world's population is at risk of contracting the disease. Estimates indicate the disease burden is approaching 50 million disability-adjusted life years (DALYs). The figures have recently been adjusted (Snow et al., 2005; WHO, 2005), and alternative estimates suggest that there were 515 million episodes of clinical *P. falciparum* malaria in 2002. In line with this, it can be assumed that the number of deaths is approaching two million a year. A significant number of these deaths are not directly caused by malaria, but a result of low birth weight or severe anaemia that is a result of malaria.

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3. What is the impact of malaria on economic development?

Malaria has a tremendous impact on both economic and social development. There is extensive literature available on the economic and social burden of malaria. In brief, 'where malaria prospers most, human societies have prospered least' (Sachs and Malaney, 2002). Malaria-endemic countries are not only poorer than non-malarial countries, but they also have a lower rate of economic growth. It has been estimated that the annual economic growth of countries with intensive malaria is 1.3 % lower than that of countries without malaria. The direct costs of malaria include community expenditures on both the prevention and the treatment of the disease, personal expenditures and public expenditures. Personal expenditures comprise, for example, individual or family spending on insecticide-treated bed nets, doctors' fees, treatments, transport to health facilities and support for the patient (and sometimes for an accompanying family member) during hospital stays. Public expenditures comprise government spending on maintaining health facilities and healthcare infrastructure, vector control, health education and research. In some countries with a heavy malaria burden, the disease may account for as much as 40 % of public health expenditure, 30-50 % of inpatient admissions and up to 50 % of outpatient visits. The indirect costs of malaria include the loss of productivity / income resulting from illness or death. Furthermore, the development of new sources of income (e.g. tourism) may be hampered by malaria. The disease also has great demographic consequences, as it kills 1-3 million people per year and it severely affects the development of human capital. Malaria hampers children's schooling and social development through both absenteeism and permanent neurological and other damage

associated with severe episodes of the disease. Data suggest that malaria accounts for approximately 5 % of all reasons for school absenteeism. Of all the preventable medical causes of absenteeism, malaria accounts for 13-50 % of school days missed each year. Of course, the tremendous human suffering caused by malaria cannot be expressed in figures.

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4. Which regions suffer the most from malaria?

The global distribution of malaria depends mainly on climatic factors such as temperature, humidity and rainfall. Malaria is transmitted in tropical and subtropical areas, where the *Anopheles* mosquitoes can survive and multiply and where the parasites can complete their lifecycle inside them. Temperature is particularly critical. For example, at temperatures below 20°C, *P. falciparum* cannot complete its lifecycle in *Anopheles* and cannot be transmitted. The different species causing human disease have roughly the following geographic distribution: *P. falciparum:* throughout tropical Africa, Asia and Latin America; *P. vivax:* worldwide in tropical and some temperate zones, common in South-east Asia and parts of Latin America, but less abundant in Africa, with the exception of the Horn of Africa where people live with a special blood group (Duffy blood group positive) that makes them more susceptible for infections with this parasite; *P. ovale:* all over tropical Africa, but less common than *P. falciparum*; *P. malariae:* worldwide but very patchy distribution. Malaria transmission has been eliminated in many countries, including the United States and western European countries. However, cases of malaria still occur in these countries, mostly in returning travellers or immigrants ('imported malaria'). All patients must be diagnosed and treated promptly not only for their own benefit but also to prevent the reintroduction of malaria.

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- http://www.mara.org.za/

5. What can we do about malaria?

In principle, malaria is a curable and preventable disease. Preventive measures focus mainly on the avoidance of mosquito bites and vector control measures to reduce mosquito transmission. These include: insecticide-impregnated bed nets, spraying houses with residual insecticides, environmental management to minimize potential mosquito breeding sites or to make aquatic sites unsuitable for the development of mosquito larvae. However, these measures are fast becoming less effective, on the one hand as a result of the emergence of insecticide-resistant strains of mosquito vectors. On the other hand Africa has witnessed a decline of investment in prevention & control technology.

Malaria is a severe, potentially fatal disease (especially when caused by *P. falciparum*) and treatment should be initiated as soon as possible. Therefore, early and accurate diagnosis is a prerequisite for treatment of malaria. The clinical diagnosis of malaria is not always very easy, as the primary symptoms may resemble those of other diseases (like the flu). Therefore, laboratory diagnosis is also very important. At present, the laboratory diagnosis of malaria largely depends on the screening of blood slides by microscopy, which is still considered to be the "golden standard" (Makler *et al.*, 1998). With an experienced microscopist, microscopy is said to have a detection limit of 20 parasites/µl however it is labour intensive and time consuming (30-60 minutes). In recent years a variety of rapid diagnostic tests (RDTs) have been developed for the diagnosis of malaria (Makler *et al.*, 1998). These tests are fast, easy to perform and do not require electricity or specific equipment. These tests are based on the recognition of parasite-derived molecules (antigens) in the circulation of the patient. The RDTs can detect less than 100 parasites/µl. (WHO, 2003). However, the use of RDTs may be limited due to the fact that *Plasmodium* antigens can persist in the circulation of the patient after parasite clearance and thus false positive test results (Makler *et al.*, 1998). Research towards the development of more specific/sensitive RDTs, is however ongoing and may result in devices that overcome this problem of antigen persistence.

WHO recommends that, in malaria-endemic countries, treatment should start within 24 hours after the symptoms have appeared and immediately in patients originating from non-endemic countries. Several drugs can be used to cure the disease: chloroquine (CQ), sulphadoxine-pyrimethamine (SP; Fansidar®), mefloquine (Lariam®), atovaquone-proguanil (Malarone®) and quinine. However, the malaria situation is worsening because the parasite has become resistant to the action of the affordable anti-malaria drugs like chloroquine or sulphadoxine-pyrimethamine. In many African countries, chloroquine is still the most widely used drug for treatment, because of its availability and low cost. However, if monotherapy is reaching a level of >15% treatment failures, WHO recommends initiation of a change to another first-line treatment. By the time resistance

reaches 25% a change in the national control policy should be in place. Recent WHO recommendations are that a drug being introduced to a national programme should have an efficacy >95%, and that efficacy should not fall below 90%. *(WHO Treatment Guidelines 2006)* Unfortunately, resistance to sulphadoxine-pyrimethamine is on the rise in Africa.

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6. Why do we need alternative drugs?

Alternative drugs, such as mefloquine and atovaquone-proguanil, are too expensive to be used to treat malaria in rural Africa. Furthermore, there are several reports that describe treatment failure of malaria because of the resistance of *P. falciparum* to the action of more expensive / newer drugs, such as the atovaquone-proguanil combination. It will most likely be only a matter of time before these drugs, too, become ineffective against *P. falciparum*. There is therefore an urgent need for affordable, effective treatment alternatives.

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7. What are the international and domestic malaria policies?

All African countries in which malaria is endemic have a national malaria control programme. The ministries of health recommend the use of first- and second-line drugs. Some countries are more proactive than others and change their drug policy in the face of emerging drug resistances. Until 1993, all disease-endemic countries in Africa relied on monotherapy (mostly chloroquine) for malaria treatment. South Africa and Malawi were the first countries to change their policy towards SP or amodiaquine (AQ). By 2003, 14 countries had changed their drug policy. At present, WHO recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulfadoxine-pyrimethamine, should use combination therapies, preferably artemisinin-based combination therapies (ACTs) for *P. falciparum* malaria.

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8. What is the historical background to malaria medicines?

Medicines against malaria have been available for centuries. One of the most potent and effective is quinine, which is derived from the bark of the cinchona tree and used to be the mainstay of malaria treatment. Quinine was discovered the early 17th century, when the Spanish learned from the Indians that a medicinal bark could be used to treat fever. The bark was used to cure the Countess of Chinchón (the wife of the Viceroy of Peru) of her fever. The bark was then called 'Peruvian bark' and the tree was named 'cinchona', after the Countess. Unlike chloroquine, quinine is still effective against *P. falciparum* malaria, but it is difficult to use because treatment takes longer.

Hans Andersag at BAYER I.G. FARBENINDUSTRIE A.G. laboratories in Eberfeld, Germany discovered chloroquine in 1934. Andersag named the compound 'resochin'. The disruption caused by World War II, however, meant that its effectiveness was not recognized until 1946. The substance was renamed chloroquine. Within 20 years after its introduction, resistance to chloroquine occurred in Southeast Asia and Latin America. The resistance in Africa appears to have been imported from Southeast Asia and is now largely prevalent throughout the whole of Africa. This has set the scene for the introduction of

antifolate drugs, and the combination sulphadoxine-pyrimethamine has increasingly become the drug of choice for the treatment of uncomplicated *P. falciparum* malaria. Malawi was the first country to implement sulphadoxine-pyrimethamine as first-line treatment (1993); Kenya followed in 1998. However, both in Southeast Asia and Latin America the unexpectedly rapid development of resistance to sulphadoxine-pyrimethamine has limited the useful therapeutic life of the drug to about five years. Indeed, just five years after its introduction in East Africa, (the selection of *Plasmodium* parasites resistant to sulphadoxine-pyrimethamine is evident and the clinical effectiveness of the drug is declining. Unfortunately, the development of new anti-malarials is not a priority for most pharmaceutical companies and the alternative options currently available are not affordable for Africa. However, for over 20 centuries now, the Chinese have been using Qinghao (*Artemisia annua* – sweet wormwood or Chinese wormwood) as an anti-fever medicine. Chinese scientists isolated the active ingredient of Qinghao in 1971. Known as artemisinin, it is a very potent and effective anti-malarial drug, especially in combination with other medicines. Artemisinin (or its derivatives) is now acknowledged as an important ingredient for new drug combinations to treat malaria when drug resistance to monotherapy is experienced.

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SECTION 2: ARTEMISININ-BASED COMBINATION THERAPY (ACT)

9. What is 'artemisinin-based combination therapy'?

Artemisinin-based combination therapy (ACT) uses a combination of anti-malaria drugs, one of which is an artemisinin derivative (e.g. artesunate, artemether or dihydroartemisinin). Artemisinin can be extracted from *A. annua*. Under the name 'Qinghaosu', it has been used in traditional Chinese medicine to treat fever for over 2000 years. The active molecule is a sesquiterpene lactone containing a bridged endoperoxide. The following chemical derivatives[3] are important:

- two lipophilic derivatives: artemether and arteether;
- a hydrophilic derivative: artesunate;
- a metabolite: dihydroartemisinin.

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10. Why ACT?

The use of drugs in combination is broadly accepted in the treatment of several diseases, such as TB, HIV infection and cancer. The idea behind the therapeutic effect of ACT is that the artemisinin rapidly kills most of the *Plasmodium* parasites, and those that survive are subsequently killed by a high concentration of the companion drug. One of the main advantages of combination therapy is the likelihood that this strategy will reduce the chances of an infectious agent becoming resistant to the action of the drugs. In the case of malaria, combination therapy has been applied since around 1990. This strategy is being hampered because the *Plasmodium* parasite has developed resistance, as a result of monotherapy, to certain components of currently applied combination drugs.

The efficacy and very short half-life (<6 hours) of the artemisinin derivatives make it less likely that resistance develops. Furthermore, the artemisinins have broad stage specificity and can be used to treat both uncomplicated and severe malaria.

[3] i.e. chemically changed structures of the active molecule

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11. Why not artemisinin-based *mono*therapy?

Artemisinin-based monotherapy can cure malaria (Giao et al., 2001). However, monotherapy must be adhered to for at least five days, but often seven days, if it is to result in a radical cure, and in practice adherence to these relatively long treatment regimens is low. A three-day regimen is generally accepted as the maximum, because most people discontinue treatment when they feel better (in most cases a few days after the start of treatment) and to save the costs for the expensive drugs.This behaviour may, however, result in late recrudescence; i.e. a repeated attack of malaria, due to the survival of malaria parasites in red blood cells. Recrudescence of *P. falciparum (*and *P. malariae*) results from exacerbations of persistent undetectable parasites that reappear in the blood stream after the treatment has been terminated resulting in another malaria episode. An additional, but very important, other result of this patient behaviour is that the surviving parasites can develop resistance against the action of the drug.

Artemisinins are readily available as monotherapy, and this is a major threat to the ACT strategy, because monotherapy may as outlined above lead to the development of drug resistance. Recently, WHO has called for an immediate halt to provision of single-drug artemisinin malaria pills (see press release of 19 January 2006 at www.who.int/mediacentre/news/releases/2006/pr02)

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- World Health Organization (2006) Facts on ACTS (see: www.who.int/malaria)
- http://www.cdc.gov/malaria/glossary
- http://mosquito.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm

12. How did Artemisia contribute to malaria treatment in Southeast Asia?

In the late 1950's chloroquine resistance to *Plasmodium falciparum* occurred on the Indochina Subcontinent. Since then it has conquered most of the areas where the parasite species is endemic. This has necessitated the use of alternative drugs such as sulphonamide-pyrimethamine combinations and mefloquine, but In wide areas of South-east Asia these drugs have also lost adequate efficacy soon after their introduction (Wensdorfer, 1994). At the end of the 1980s / early 1990s, the treatment of *P. falciparum* infections in Southeast Asia was seriously threatened by multi-drug resistant parasites (Singhasivanon, 1999). However, the introduction of effective artemisinin drugs in combination with other measures revolutionized the treatment of malaria in these regions. For example, the present National Malaria Control Program (NMCP) in Vietnam is based on application of insecticide-treated bed nets, spraying of insecticides and early microscopic diagnosis of malaria and treatment with artemisinin drugs (Van Nam et al., 2005). The Vietnamese NMCP has successfully reduced the burden of malaria in the country. In Vietnam, the malaria situation was at it worse in 1991 with a recorded incidence of > 1 million clinical cases, >30.000 severe cases and 4646 deaths. The implementation of the NMCP resulted in a dramatic decline of the disease with a total recorded incidence of <300.000 clinical cases, 1.161 severe cases and only 148 deaths in 2000 (data obtained from: Giao, 2004) and the situation seems to be further improving (Van Nam et al., 2005).

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13. What about *A. annua* tea?

The use of *A. annua* extracts as medicinal tea is not acceptable in the treatment of malaria (Mueller et al., 2000, 2004; Jansen, 2006). For example, the artemisinin content of a tea extract is unknown (it might even not be present, as artemisinin does not readily dissolve in water) and therefore it is not possible to establish the right dosage of the drug. Quality control and quality assurance of the product is almost impossible, and the WHO GMP guidelines are not applicable to this kind of product. In general, these products will never meet the prerequisites for drug registration. A very practical limitation of the use of artemisinin tea is the fact that the product has a very bitter taste, which makes it unsuitable for paediatric use. There are some initiatives, like Anamed (2004), that actively recommend the home production of *A. annua* for the local consumption of its dried leaves to control malaria and fevers in general.

Tea and herbal extracts will continue to have a place in traditional and alternative medicine, but are very unlikely to be adopted by malaria programmes for use in regular health services.

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- www.anamed.net

14. Which ‘C’ in ACT?

In principle, artemisinin derivatives can be combined with any other anti-malaria drug as long as the latter is safe and efficacious. Many potential combinations are currently studied for the efficacy in treating malaria. It is out of the scope of this report to extensively discuss all possible combinations. Only a few are mentioned below.

The currently most extensively used ACT is Coartem, which is a combination of Arthemether (a artemisinin derivative) and Lumefantrine. This product, which is being manufactured and distributed by Novartis Pharma (Basel, Switzerland), has been adopted

by several African countries in their National Control Programmes as first or second line drug for the treatment of malaria. WHO and Novartis have a special pricing agreement. Novartis produces the drug at cost price (US$ 0.90 for infant treatment or US$ 2,40 for adult treatment) for use in the public sector in malaria endemic countries. WHO reviews requests for supply of Arthemether-Lumefantrine and, together with UNICEF, procure Coartem from Novartis for governments of malaria endemic countries. The drug has also been placed on the pre-qualification list of WHO.

Besides Coartem, there are several other potential ACTs. The Drugs for Neglected Diseases Initiative is currently developing two ACTs (DNDi, see www.dndi.org). DNDi has announced that it will be delivering two fixed dose ACTs[4] in 2006:

- Artesunate – amodiaquine (AS/AQ); this combination will be very useful in African countries where resistance to amodiaquine has not yet been significantly developed. AS/AQ will be manufactured and distributed by Sanofi-Aventis and the company will also ensure registration of the product. The target price is US$1 per adult and US$ 0.50 per infant treatment.
- Artesunate – mefloquine (AS/MQ); this drug combination is mainly intended for the treatment of malaria in South-east Asia and Latin America at an estimated price of around US$ 2.

The choice of the combination drug is crucial and may increase the price of the ACT combination (>USD 1.0 per treatment), hampering the wide use in resource poor countries. There is, however, hope that within the next three to five years it will be possible to produce ACTs at lower cost price.

One such ACT is the combination of chloroproguanil-dapsone (Lapdap) with artesunate (CDA), which is currently being developed by GlaxoSmithKline in collaboration with several academic institutes, under the sponsorship of the Medicine for Malaria Venture. Extensive phase III clinical trials are planned for 2006.

Another potentially promising anti-malaria drug that can be combined with artemisinin derivatives is piperaquine (for an extensive review, see Davis et al., 2005). Piperaquine is a bisquinoline, first synthesized in 1960s in China and France, which is as effective as chloroquine. The tolerability, efficacy, pharmacokinetic profile and low cost of piperaquine make it a promising combination drug for an ACT. Currently, a fixed-ratio drug combination of piperaquine-dihydroartemisinin is being developed to treat uncomplicated malaria.

[4] These are the two ACTs currently being developed in co-formulation. However, these combinations are already in use in many countries eg AS + AQ is the national 1st line drug in Burundi and in Sierra Leone and AS + MQ in many parts of SE Asia.

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- www.dndi.org
- www.gsk.com
- www.mmv.org
- http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm

15. Is ACT an alternative for the poor in Africa?

It is difficult to predict the exact need for ACTs in the coming decade. Based on the forecast that approximately 500 million clinical cases will occur on a yearly basis, an equivalent number of treatments will be needed, assuming that ACT is the ideal treatment. Several countries are recommending the use of ACTs as a first-line drug for the treatment of malaria, and this number is increasing (see the Roll Back Malaria partnership (RBM) website5. However, the need for ACTs is currently not met by the production capacity. In November 2004, WHO announced a shortage of artemether-lumefantrine combination and this shortage is expected to continue in 2005.

Poverty can be defined best in terms of economic and social exclusion. A frequent economic indicator of poverty is people who have less than USD 1.0 a day. 'The poor' comprise both urban and rural households composed of people in all age categories, of all literacy levels and in all health situations. Whether they will use ACT depends on numerous factors including the retail price (affordability), geographical accessibility, availability in local drug stores, public information, and government drug and distribution policies.

Currently, the retail price of ACTs and ATs fluctuates between USD 1.0 and beyond USD 3.5 per course. This implies that a poor family living on less than USD 1.0 a day cannot afford the drug. The effectiveness of national distribution systems also affects poor

[5] www.rbm.who.int

people's access to ACTs. This applies particularly to the rural poor who often live in remote areas. It is therefore not sufficient to intervene in the retail price of ACT, although important additional efforts are required to make the drug available to the masses of people, notably in sub-Saharan Africa.

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16. What are the potential alternatives for ACTs?

New anti-malaria drugs must meet all international standards that are required for a new medicine to come on the market. It must pass all phases of (pre-) clinical testing and must be produced according to international accepted Good Manufacturing Practice standards. A system that ensures good quality drugs to be available for the African market should be in place. Such a system should prevent counterfeit drugs or anti-malarials of poor quality entering the market. The perfect anti-malarial should be effective against all life stages of the malaria parasite and it should kill *Plasmodium* extremely rapidly. Furthermore, the drug should have little to preferably no side effects, so that it is safe for use in children and pregnant women. Importantly, the drug should be affordable for the poorest of the poorest as this population is most severely affected by malaria.

There is a significant lack of research on alternative drugs for the treatment of malaria. The largest research portfolio is managed by the Medicines for Malaria Venture (MMV). This public-private partnership is dedicated to reducing the burden of malaria in disease-endemic countries by discovering, developing and delivering new anti-malaria drugs. The MMV research portfolio covers 21 projects ranging from molecules in early discovery phase to products in clinical phase 3. Some of the projects are jointly managed with a large pharmaceutical company. The most promising molecule in the MMV research portfolio is synthetic peroxide, known under the name of 'OZ 277' (or recently re-named: OZ277/Rbx11160). A patent on this molecule was assigned to MMV in November 2002. The molecule is currently passing through phase 2 of clinical trials and, if it fulfils its early promise, it could be registered as a new anti-malaria drug as early as 2008/9. However, it should be noted that many candidate drugs, even those with great potential, fail clinical testing

On average it takes about 10 years for a potential new drug to move through the drug development pipeline from exploratory phase via discovery, pre-clinical and clinical development. Besides new mono and combination therapies based on artemisinin derivatives, academia and industry have several other compounds under development that

may ultimately lead to new anti-malaria medicines. It is outside the scope of this document to provide a complete review of all compounds that are being explored as new anti-malarials. This is in part also impossible as this type of research is often heavily protected for competition reasons. However, some initiatives, like the MMV's and GlaxoSmithKline's research portfolios allow us to provide an insight in some of the new developments in this field. For example, a very interesting group of molecules are the 4(1H)-pyridones. This group of compounds has a very negative effect on the metabolism of *Plasmodium* parasites. In interesting property of the 4(1H)-pyridones is that they are very effective against malaria parasites that are already resistant against some of the modern anti-malarials. Further research revealed that 4(1H)-pyridones derivatives, in particular a compound called GW844520, have excellent *in vitro* activity against *P. falciparum*. Further safety studies demonstrated that GW844520 has excellent safety properties. Although these developments are very promising it should be noted that it will take approximately 3 – 5 years before GW844520 may be sufficiently developed to be allowed to enter the market.

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17. What about children and ACT?

Most deaths due to malaria occur in children under the age of 6. Therefore it is very important to have drugs available that are safe for use in small children. ACTs such as Coartem are safe to use in children with a weight >10kg A paediatric formulation of artemether-lumefantrine for children as small as 5 kg has been registered since 2004. The other ACT's have no lower weight restriction except that SP should not be used under 2 months. This project was fostered by MMV in collaboration with Novartis and WHO/RBM. Approval in endemic countries is anticipated approximately this year later (see MMV site).

References:

- www.mmv.org
- www.novartis.com

18. What about pregnant women and ACT?

The treatment of malaria is difficult during pregnancy and there is a strong correlation with reduction in birth weight of infants born from mothers having malaria. In particular, the adverse effects are the greatest in women that are pregnant for the first time ('primigravidae'). Developing anti-malarial drugs for pregnant women is extremely difficult, because the drugs must be effective for the mother and the developing foetus. The application of ACTs in pregnancy requires extensive safety studies, which – in the pre-clinical stage – are conducted in laboratory animals.

There is currently controversy over the safety of the use of artemisinins in pregnancy. Studies in animal models showed that artemisinin-based drugs used in early pregnancy may cause severe effects (teratogenicity) on the developing foetus (Clark et al. 2004). In contrast, human data obtained from >1000 women who have been followed to delivery after treatment with artemisinin containing drugs, indicate that the safety profile of artemisinins is good enough to recommend the use of ACTs in the second and third trimester of pregnancy. ACTs are not recommended in the first trimester of pregnancy. However, they should not be withheld if treatment with ACTs is considered to be lifesaving for the mother and other antimalarials are considered to be unsuitable (WHO, 2003).

An excellent review on malaria in pregnancy can be found in Whitty et al., 2005.

References:

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19. Is ACT effective against *P. vivax*, *P. malariae* and *P. ovale*?

The impact of drug-resistant *P. falciparum* malaria is significant and has driven the need for the development of alternative strategies, like ACTs. The other malaria causing species (i.e. *P. vivax, P. ovale* and *P. malariae*) cause less severe disease problems. Furthermore, with the exception of *P. vivax*, infections caused by these parasites can be treated with currently available, cheap anti-malaria drugs. The emergence of drug-resistant *P. vivax* might create the need for the development of alternative treatment in the near future. For the moment, priority should be given to the development of an alternative treatment of *P. falciparum* malaria, because the disease is severe and drug resistance is increasingly becoming a problem. It is generally acknowledged that ACT is effective against other malaria causing species, with the exception that AS + SP is less effective against *P. vivax*

References:

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20. What are the sources of artemisinin?

Artemisinin can be obtained only from the *A. annua* plant, although efforts are being made to mimic the artemisinin biosynthetic process in a micro organism. Artemisinin-like products are also being produced and tested. The following is an overview of the sources.

Wild plants

A. annua is endemic to China and is commonly found in the wild as a weed and as a roadside plant. The first collection of the plant for medicinal purposes was recorded in 150 AD. After the discovery of artemisinin in 1972, demand for the dry leaves increased rapidly. Wild Qinghao, which has low artemisinin content, is still being collected in China (Wright, 2002). A. annua can also be used as a source of essential oils, which are used in the perfume industry. These plants are collected in the wild in South-Eastern Europe (Bulgaria, Yugoslavia and Romania). However, the world demand for artemisinin cannot be satisfied by the collection of wild plants, and cultivation is increasing in importance. In some areas, intensive collection has led to the near extinction of the plant. The traditional belief that plants gathered from the wild are more effective than cultivated plants has persisted, notably in China. Therefore, the collection of plants for traditional medical use continues.

Cultivated plants

A. annua has been cultivated in China and Vietnam since the late 1970s. The acreage devoted to the plant rapidly expanded after the identification of more productive

composite varieties with higher artemisinin content. Since the early 1990s, the crop has also been planted in Africa and many other parts of the world. Section 3 elaborates on the production of *A. annua*.

Production in micro organisms

Several universities (e.g. Wageningen University Research Centre and UC Berkeley) are carrying out research on the process of biosynthesis of artemisinin in plants. The common aim is to discover the biosynthetic process and the various enzymatic steps and the corresponding *A. annua* genes. The elucidation of the biosynthesis of artemisinin can contribute to enabling artemisinin production in micro organisms as well as the breeding of new varieties of *A. annua*, which are more efficient producers of artemisinin. Presently the plants are relatively inefficient producers of artemisinin, but the content can potentially be doubled (see Box).

The UC Berkeley research has advanced and aims at transferring a number of microbial and plant genes required for biosynthetic artemisinin production from *A. annua* to *E. coli* bacteria. This 12-step process has advanced to step 9. The Bill and Melinda Gates Foundation (BMGF) is financing (USD 43 million) a consortium of UC Berkeley (for the technology), Amyris

Biotechnologies of the Albany Company (for the manufacturing) and One World Health Institute (for the clinical trials). Production is expected to start in a few years, after which clinical trials could be initiated.

Prospects of artemisinin biosynthesis

Bertea et al. (2005) showed that the early steps in artemisinin biosynthesis involve amorpha-4, 11-diene hydroxylation to artemisinic alcohol, followed by oxidation to artemisinic aldehyde, reduction to dihydroartemisinic aldehyde and oxidation to dihydroartemisinic acid. Amorpha-4,11-diene as an early precursor is derived from farnesyl diphosphate, but the latter is also transformed into other sesquiterpenes. If the first process can be enhanced and/or the latter suppressed the artemisinin production in the plant can potentially be doubled (H.J. Bouwmeester, pers. com.). The genes encoding the enzymes responsible for the artemisinin pathway can also be isolated from *A. annua* and then it is potentially possible to mimic the biosynthesis in a micro-organism or to modify artemisia plants accordingly through genetic engineering and traditional breeding.

Synthetic production

The University of Nebraska Medical Centre (Vennerstrom et al., 2004) has come up with a five-step chemical process to make compounds that can mimic the action of artemisinin derivatives. One of them, OZ-277, a synthetic ozonide derivative of artemisinin, has proved more effective than artemisinin itself in both the test tube and in animal models of malaria. It was also shown to be safe in recent trials in human volunteers, and a full clinical trial in Thailand is planned soon. If this trial is successful, further testing will be carried out to see how well the new molecule performs in combination therapy. If OZ-277 lives up to expectations, such a therapy might be ready for market by 2008 at less than USD 1 a course. OZ-277 has just completed the phase I clinical trials, which means that it will take at least another five years to have the new product released in combination with other drugs (WHO, Schapira, pers. com.). The target is to produce OZ-277 as cheaply as possible (at less than one-tenth of the cost of present ACTs).

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21. Will malaria parasites develop resistance to ACT?

The occurrence of drug resistance has rapidly decreased the efficacy of several affordable anti-malarials, like chloroquine and pyrimethamine-sulphadoxine. If the artemisinins would be lost due to resistance, there will be a serious gap in the options to treat malaria. It is therefore absolutely necessary that every possible precaution is made to prevent this from happening.

Stable, therapeutically significant resistance to the artemisinin derivatives has not yet been identified in *Plasmodium* species isolated in the field. However, in light of previous experience with other antimalarial drugs and because increasing numbers of parasites are currently being exposed to artimisinin compounds, several researchers have their concerns about the possibility that *Plasmodium* will become resistant (Meshnick, 2002). Very recent laboratory experiments indicate that malaria parasites can develop stable genetic resistance to artemisinin artesunate (Afonso et al., 2006), but putative mutations in the *Plasmodium* genome conferring resistance have so far not been identified. Furthermore, the use of artemisinins in combination therapy will also reduce the chances of occurrence of drug resistance.

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SECTION 3: PRODUCING *A. ANNUA*

22. Where is *A. annua* produced?

A. annua is an annual herb endemic to Asia, most probably China. It occurs naturally as part of steppe vegetation in the northern parts of Chahar and Suiyuan provinces at 1 000 to 1 500 m above sea level. *A. annua* is cultivated as an annual crop in China and Vietnam as a source of artemisinin, and in Romania and Bulgaria for its essential oils. It is also cultivated on a small scale in the United States as a source of material for aromatic wreaths (Janick, 1995).

The best plants are found in the wild only in certain parts of China, such as Guangxi and Hunan, which (along with Vietnam) produce most of the world's supply. In China, firms such as Guilin Pharmaceuticals are stimulating the cultivation of the plant, both on their own plantations in Chongqing and through contracts with local farmers, rather than relying on the collection of leaves from wild sources. Chinese scientists started to domesticate the wild species of A. annua after the curative effect of artemisinin was discovered in 1972. Vietnam and Thailand followed in the 1980s. In 2004, China claimed that it was growing a total acreage of 2 000 ha of A. annua. Recently, Novartis stated that China is taking the lion share in a total cultivated area in Asia of 9 000 hectares, but this statement has not been verified. It is generally thought that China still collects some of its A. annua from the wild. Vietnam is growing A. annua on some 1 500 ha through three main producers, while some production is also reported from India. Production has also started in West Africa, notably Ghana and Gambia, and an extraction plant is planned for Senegal. In Brazil, the production of A. annua is being promoted, while the crop has been grown in the United States and Australia on an experimental scale. A. annua is also collected in Eastern Europe for the extraction of essential oils for the perfume industry. The plant is increasingly grown for this purpose in such countries as Romania and Bulgaria.

Estimated production of A. annua

Country	**Acreage in 2004 (ha)**	**Total acreage in near future (ha)**
China	2 000	5 000
Vietnam	1 500	2 000
India	100	200
Kenya	400	2 000
Tanzania	200	1 000
Uganda	0	500
Eastern Europe	500	500
Total	**4 700**	**11 200**

(Various sources and pers. com.)

A. annua was introduced in Tanzania in 1994. Since then, large-scale farmers have been experimenting with its production elsewhere in East Africa, notably Kenya, Tanzania and Madagascar. In recent years, experiments have taken place in another 20 or so countries, mainly in sub-Saharan Africa; however, most of the efforts have remained rather small scale, sometimes for the local consumption of A. annua tea.

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23. What is the world acreage required to satisfy global demand?

Yields of *A. annua* vary according to the variety planted and various growing factors, such as altitude, precipitation, soil moisture, soil type and farmer management. One of the major determinants of the yield is the quality of seed: 'pure' F1 seed of a superior hybrid produces significantly higher yields in terms of leaf foliage, which also has higher concentrations of artemisinin than does second-generation F2 hybrid seed. If all these factors are averaged and applied by quality of seed, then a world peak demand of 400 million adult treatments will require between 17 000 and 27 000 ha.

Based on his experiences with artemisinin production in Vietnam, Dr Charles Lugt (pers. com.) has made another calculation: the curative dosage of arteether (a lipophylic derivate of artemisinin) is 11.2 mg per kg (intramuscularly). For an adult of 50 kg, this is equivalent to 560 mg. Orally applied dihydroartemisinin averages around 600 mg per treatment. If we fix the average adult dosage at 750 mg artemisinin (as there are important losses in the derivation process from artemisinin to dihydroartemisinin and other derivates, see appendix 5), 75,000 kg of artemisinin are required per 100 million adult patients. In Vietnam, farmers obtain yields of 27-43 kg of artemisinin per ha. If we include harvest losses, we may assume that the net yield is approximately 20 kg/ha6. Thus, we can estimate that 3 750 ha are required to produce 100 million adult treatments or 15 000 ha for 400 million adult treatments.

These estimates do not take into account genetic and crop management improvements that will enhance both the yield of A. annua and the concentration of artemisinin. Nor do they

[6] It is worthwhile noting that references to high yields obtained in Vietnam are strongly contested by other experts who dispose of data that indicate that yields are obtained of 10 kg of artemisinin per ha or less. Moreover, there are indications that the bulk of Artemisia annua from China is not produced, but collected from wild sources

take into account improvements in extraction technology and the fact that many patients are children requiring a lower dosage. This implies that the estimated required acreages are maximum values, and that in time the total world acreage required will be significantly smaller.

References:

- www.anamed.net
- http://siteresources.worldbank.org/INTMALARIA/Resources/377501-1114188195065/WB-Malaria-Strategy&BoosterProgram-Lite.pdf
- Wright Colin W (ed.), 2002. *Artemisia.* Taylor & Francis, London, 2002. First edition, 344 pp.

Cultivation requirements of *A. annua*

A. annua is a labour-intensive crop whose cultivation requires close attention to detail, especially at planting and harvesting time:

- it has a tiny seed (12-14 thousand seeds per gram) which must be germinated in a well-managed nursery;
- the seedlings are delicate and must be planted out with great care into a well-prepared seedbed, at a density of 3-4 plants per square metre (30-40 thousands plants per ha);
- control of weeds around the young seedlings is critical: weeding may need to be done 3-4 times by hand before the canopy is formed;
- irrigation may be needed if there is any risk of water stress, especially in the four weeks after transplanting;
- harvesting, which is normally done by hand, must be precisely timed for just before the plants begin to flower; if left too late, the artemisinin content in the leaves falls off rapidly; and,
- the crop must be dried in the field or store: the leaves are then stripped off by hand or stick or by driving a tractor over the plants. The process must be rapid to avoid the deterioration and loss of the artemisinin content.

Source: TechnoServe, 2004

24. What are the cultivation requirements of *A. annua*?

The wild *A. annua* is a short-day photosensitive plant of temperate zones or highlands (i.e. land at more than 1 000-1 500 metres above sea level). Breeding programmes have developed varieties that can adapt to the tropics and have lost their short-day characteristics.

Little is known about the crop requirements in Asia, apart from the fact that in Vietnam the recommendation is to grow it as a winter crop (December-June)

The plant is reported to do well in the 18-25 C temperature range, hence the need to grow the crop at 1 000-1 500 metres above sea level in the tropics; where temperatures are higher, shade is required. A minimum rainfall of 600 mm is required during the growth period (5-6 months). Irrigation is required to avoid the negative effects of dry spells.

Little is known about the crop requirements in Asia, apart from the fact that in Vietnam the recommendation is to grow it as a winter crop (December-June) in the highlands on relatively deep, preferably clay soils and after a crop of potatoes.

References:

- www.anamed.net
- TechnoServe, 2004. *Report into the feasibility of: Production of Artemisia annua in Tanzania and Kenya and Extraction of Artemisinin in Tanzania and Kenya*. TechnoServe, Tanzania, October 2004.
- De Vries et al., 1998
- Bremner, Nigel. 2004. *Artemisia annua* in Kenya. Prepared for the Royal Netherlands Embassy in Kenya.

25. Is there a comparative advantage of cultivation in East Africa?

A. annua is not endemic to Africa and is not collected from the wild in Africa. The cultivation of *A. annua* is slowly increasing in East Africa due to the introduction of the newly developed hybrid, which is insensitive to day length and shows superior performance in content and total yields, also compared to Asian genotypes. The East African highlands from Ethiopia to southern Tanzania, northern Mozambique and Madagascar provide suitable production ecologies for this hybrid, though irrigation facilities are required to reduce the impact of erratic rainfall regimes.

The combination of high altitude, high light intensity (due to its proximity to the equator) and the cool night temperatures means that the artemisinin content and the biomass production in East Africa are high. Similar findings have been reported from Vietnam,

where the artemisinin content was higher in the high-altitude north than in the low-altitude south.

However, the comparative advantage depends more on other properties of the supply chain, such as the logistics, level of technology, farmer know-how and market integration. Rural Africa does not generally score well on these properties. Remote areas often suffer from poor logistics, low levels of technology, sound but traditional know-how and low levels of market integration. However, there are geographical pockets in Africa where the situation is more suitable. Such pockets can be found in East Africa, where large-scale farmers have settled in the areas relatively close to an airport, such on the foot slopes of Mount Kenya and around Arusha on the foot slopes of Mount Mere and Mount Kilimanjaro. Here, all the logistics are in place, the levels of technology and know-how are high, and farmers produce for export markets. The large-scale farmers have developed working relationships and contract modalities with small-scale producers, and thus have increased their production volumes. These benefit from price security, farm inputs, know-how and access to export markets.

Although artemisinin production per ha might be higher in East Africa, the costs of production are likely to be lower in China and Vietnam because of lower labour costs and higher labour productivity. As economic and technical data on production in China and Vietnam are not available, a sound comparison of comparative advantages cannot be made at this stage.

References:

- www.anamed.net
- WHO, 2003. *WHO guidelines on good agricultural and collection practices [GASP] for medicinal plants*. World Health Organization, I-vi + 72 pp.
- Wright Colin W (ed.), 2002. *Artemisia.* Taylor & Francis, London, 2002.
- TechnoServe. 2004. *Report into the feasibility of: Production of Artemisia annua in Tanzania and Kenya and Extraction of Artemisinin in Tanzania and Kenya.* TechnoServe, Tanzania, October 2004.

26. What is the advantage for East African farmers?

There are three categories of *A. annua* producers in sub-Saharan Africa:

- Small, unregistered growers who grow only a few plants or rows in between other crops in their vegetable gardens. *A. annua* is used for local consumption and/or marketing associations are being formed.
- Registered smallholders who cultivate at least an acre and have contracts for the supply of inputs and the marketing of the dry artemisia leaves with one of the three daughters of ABE (Advanced Bio-Extracts): East-African Botanicals Ltd-Kenya, East-African Botanicals Ltd-Uganda or African Artemisia Ltd (AAL).
- Larger-scale farmers who run their central nurseries from where they can supply outgrowers with seedlings.

Both large- and small-scale farmers will engage in the cultivation of *A. annua* only if they have market security and obtain a higher return on investment as compared to other crops. Large-scale farmers may be more sensitive to returns to capital investment, while for small-scale farmers the return on labour and land may be more dominant in decision-making. The latter compare these returns to other ventures, such as coffee, maize, beans and banana production for local and commodity markets. The study by TechnoServe, which is confirmed by data from Faida MaLi (Arusha) and AAL (Arusha), shows that the gross margin of *Artemisia* production is more or less equivalent to that of maize and beans, and higher than that of coffee.

However, price security may be even more important than the absolute rate of return. All international and regional commodity markets suffer from erratic price fluctuations that make commercial farming a risky enterprise. East African farmers will therefore engage in the production of *A. annua* only if they gain access to a stable export market.

Various reports indicate that in 1999, the world market price for artemisinin was approximately USD 400-500/kg, while in 2002 it was USD 200-300/kg. In 2004, the price increased to USD 600-800/kg and is reported to have been as high as USD 1 100-1 300/kg. It is generally assumed that the world market price for artemisinin will stabilize at around USD 250/kg. So far, however, there is no stable and predictable market in sight.

References:

- TechnoServe, 2004
- Interview with CEO of ABE (the holding company for East-African Botanicals Uganda and Kenya Ltd and African Artemisia Ltd.)
- Wright, 2002
- Prof. Michaela von Freyhold, University of Bremen

27. What has happened so far in East Africa?

Successful production in East Africa depends on reliable markets and the availability of technology, extraction capacity and adequate capital investments.

Reliable markets

The main obstacle to the rapid expansion of production in East Africa was the absence of a reliable market. Since 1994, East-African Botanicals Ltd (Uganda, Kenya) and its sister company in Tanzania, African Artemisia Ltd, have been the major buyers of dry leaves in East Africa. They operate a system of two subsequent down payments and an additional payment based on the artemisinin content of the leaves (i.e. USD 350/ton dry leaves in instalments and an additional USD 40 for each 0.1 % artemisinin above 0.5 %). However, the quantities produced and marketed have been small. One has to be careful with extrapolating from these results because of price fluctuations and market insecurity on the world market.

Availability of technology

A major leap forward for the production *A. annua* came through the introduction of a hybrid variety developed by Mediplant, which is suitable for production in East Africa. This variety ('Artemis') and subsequent varieties (e.g. 'Madiplant') are based on the crossbreeding between varieties from China and South-Eastern Europe. Hybrids have the disadvantage that their genetic properties do not remain constant over future generations. Generally, the F1 'pure' hybrid degenerates into less performing F2 generations. A major challenge, which has been taken up by few stakeholders (e.g. ABE and CIMAP, an institute in India), is to develop a composite variety that can be multiplied from seed and will be particularly suitable for small-scale farmers.

The technology for *A. annua* in East Africa is constantly being updated. The ABE manuals for commercial and smallholder production are being rewritten based on the experiences already gained. Anamed and Laughlin et al. (2002) have presented other descriptions of crop practices.

Major questions for technology improvement are related to more efficient production and extraction methods (CEO of ABE, pers. comm.). Some of these issues (apart from using varieties with a stable high artemisinin content) are time of harvesting, and optimal planting and fertilizer application rates (Director of AAL, pers. com.).

Local extraction capacity

Local extraction is essential to successful market development for artemisinin production in East Africa. It would not be economically feasible to produce the raw material in Africa

and process it in Switzerland (China and Vietnam have extensive extraction capacities and only export artemisinin or end products).

Initiatives to establish extraction facilities in East Africa have been started only very recently. In Uganda, Kenya and Tanzania, Novartis and partners are constructing or rehabilitating extraction plants that will be soon operational.

Investments

The subsidiaries of ABE-Nairobi have struggled for years to get finance for their operations (input supply, production, marketing and extraction). Novartis has finally come up with the finance for these operations, in which Novartis claims 60 % exclusiveness in sourcing the artemisinin for the first generation of extraction plants. Through its subsidiaries, ABE provides seasonal credit to smallholders for the supply of inputs such as seeds / seedlings, fertilizers and, recently, small-scale irrigation equipment. AAL-Tanzania asserts that funds are required for the establishment of another extraction plant in the Southern Highlands of Tanzania, where production has started.

Feedback from East Africa Botanicals Ltd. and African Artemisia Ltd. has shown that the private sector has clearly taken the initiative. The consortium with Novartis has made considerable investments without public financial support. This is illustrative for some other initiatives that so far have functioned without support from the public sector. However, opportunities have been proposed for public-private partnerships at different levels in the chain, such as public sector service delivery for smallholders (research, extension, seeds and seedlings, irrigation technology for smallholders) and investment in GMP-certified extraction plants.

References:

- Wright, 2002.
- Personal communications at the KIT-Artemisia expert meeting
- Interviews with CEO of ABE
- Prof. Michaela von Freyhold, University of Bremen
- TechnoServe, 2004

28. Are there other uses for *A. annua*?

In India and South-Eastern Europe (Bulgaria and Yugoslavia), *A. annua* is collected from the wild and cultivated for the extraction of essential oil. The essential oil is used in perfumery, cosmetics, antibacterials and aromatherapy. Yields of 20-40 (and even as high as 111) kg oil/ha have been reported. The oils are mainly extracted through steam distillation (Laughlin, 2002). It was reported that one lot of just 600 kg was sold in Bulgaria for USD 16 000. Various reports suggest that oil yield in *A. annua* ranges between 0.02-0.49 % on fresh weight basis and 0.04-1.9 % on dry weight basis. The maximum concentration of oil was found in the middle portion of foliage. The oil was reported to contain artemisia ketone, 1,8-cineole and camphor as major components.

References:

- www.anamed.net
- http://www.hort.purdue.edu/newcrop/proceedings1993/v2-620.html
- Laughlin et al., 2002.

29. What are the sources of plant materials in East Africa?

The *A. annua* crop can be established from F1 seeds, F2 seeds or vegetatively propagated material (cuttings). At present, all planting material used in Africa is directly or indirectly sourced from Mediplant in Switzerland. Although the recommendation in East Africa is to plant 10 000 seedlings per ha, two grams of seed (24 000 seeds) are required. Seeds are planted in nurseries and the seedlings are transferred to the field 6-8 weeks after sowing. In some cases, producing cuttings from seedlings compensates for a shortage of seedlings.

Although there are other potential sources of seed, hybrid seed development costs are high. Particularly smallholders urgently require a composite variety; here, the role of local research and seed production firms is essential. The East-West Seed Company, which has an office in Arusha, considered starting seed production but decided that the investment would be too large for this relatively small market. The total development costs of a new variety were estimated by Prof. Von Freyhold at USD 100 000, which at 50 % recovery at USD 70/g would require seed sales for 15 000 ha – which is clearly excessive for the East African acreage.

References:

- Annex with sources of seed and seed supply
- Prof. Michaela von Freyhold, University of Bremen

30. What is the optimum moment for harvesting?

Several studies have shown that the artemisinin content of plants starts to decrease when plants flower. However, biomass increases when the plant is very close to flowering, and this leads to a higher artemisinin yield per ha. In the case of artemisinic acid (a precursor of artemisinin), this is similar but the artemisinic acid content declines faster. The essential oil content is highest during flowering. All these developments have a strong genotype x environment interaction and the optimum harvesting time will have to be established locally. In general, the recommendation is to harvest just before flowering; this is also important because of the allergic reaction the pollen can cause.

References:

- Laughlin et al., 2002.
- TechnoServe, 2004

31. What are 'Good Agricultural Practices'?

WHO requires the application of Good Manufacturing Practice (GMP) as conditions for the use of artemisinin in WHO-approved ACTs. Good Agricultural Practices are equally required and promoted by the WHO, but are not conditional to WHO sanctioning. GAP includes the application of integrated crop management practices, such as the minimum use of pesticides and the control of the environmental impact during all production stages. Traceability of the production of *A. annua* and the subsequent artemisinin is an overriding principle.

East African large-scale farmers and their outgrowers can easily comply with the GAP standards. But little is known about integrated crop management or sustainable collection from the wild in the area of origin in China. Most of the Chinese and Vietnamese artemisia production is GAP certified, while the extraction and derivation is becoming increasingly GMP certified. Novartis and Sanofi produce most of their ACT in China, and claim that their products are GMP certified. Novartis and other ACT producers are interested in a sustainable supply of artemisinin, which is not from a single source and liable to climatic fluctuations. It is for these reasons that Novartis has entered into partnership with Advanced Bio Extracts in East-Africa for the production of GAP and GMP certified artemisinin.

References:

- WHO, 1997. A WHO guide to good manufacturing practice (GMP) requirements Part 1: Standard operating procedures and master formulae. Global programme for vaccines and immunization. Vaccine supply and quality global training network. World Health Organization, Geneva, 1997
- http://cws.huginonline.com/N/134323/PR/200506/997306_5.html

SECTION 4. EXTRACTION OF ARTEMISININ AND MANUFACTURING OF ACT

32. What are the comparative advantages of local extraction compared to the export of dried leaves?

Because the transportation costs of dry *A. annua* leaves are high, there is enormous pressure to develop local extraction capacity (see Appendix 5). Some local entrepreneurs have exported dry leaves to Europe for extraction, for example from Tanzania and Kenya to the UK and Switzerland. However, in 2005 extraction will take place locally, and the only transport will be regional, for instance from the Tanzanian Southern Highlands to Arusha, and from within Kenya to Athi River. It was assumed that the existing pyrethrine extraction capacity in Kenya could be a starting point, but this has not proved to be a viable option. Apart from slightly different processes used, one enormous hurdle is complying with the GMP guidelines, which has proved impossible.

Three main artemisinin extraction methods are being used or considered:

- *Mixed liquid extraction*: ethylacetate/n-hexane extraction, with ethyl acetate as a modifier. This process has the advantage that it can be GMP certified. The usual problems are: small residual amounts of the solvents in the final product, explosion and poisoning risk, and the relatively low extraction efficiency (70-75 %). In addition, the first extract is not pure (90 %) and requires a second extraction.
- *Hypercritical carbon dioxide extraction*: this has the advantage that the extraction efficiency is nearly 100 %, although higher capital investments are required.
- *Ethanol extraction*: this has the disadvantage that many substances other than artemisinin are extracted, which leads to higher purification costs.

References:

TechnoServe, 2004: comparison of the three methods
Prof. Michaela von Freyhold, University of Bremen
http://cws.huginonline.com/N/134323/PR/200506/997306_5.html

33. What are the extraction techniques and technological requirements?

The different extraction methods differ in terms of the processes followed and especially in the types of solvents used in pure form or in combinations. The characteristics of the main solvents are given in the following table.

Properties of different solvents for artemisinin extraction

Solvent	Solubility	Selectivity	Preservative	Polarity	Boiling point
Water	No	None	No	High	100^0 C
Hexane	Poor	High	Not known	Non-polar	60-80^0 C
Ethanol	Slight	Poor	Good	Polar	78^0 C
Ethyl acetate	High	Medium	Not known	Mild	67^0 C
Carbon dioxide	Poor	High	Good	Non-polar	15^0 C (at 50 bar)

Source: Hill and Associates (www.hill-assoc.com)

Different combinations of solvents can be used in the three main extraction options that have been identified and tested. The three methods have the following characteristics.

Extraction methods and their characteristics

Extraction method	Process efficiency (inc. solubility and selectivity)	Total capital and running costs	Environmental impact assessment
Mixed liquid extraction ethyl acetate / n-hexane	Ethyl acetate has the best *solubility* properties, while carbon dioxide and n-hexane have the best *selectivity* characteristics. Only carbon dioxide can	Significantly higher for carbon dioxide than for either ethanol or mixed solvents. Carbon dioxide plant of approximately the	Impact greater with mixed solvent than with a carbon dioxide extraction plant. However, newer equipment can minimize
Hypercritical carbon dioxide extraction			

Ethanol extraction	significantly alter its properties through changes in temperature and pressure and may have wider alternative uses than ethanol or mixed solvent. Ethanol was determined not to be a recommended option because mixed solvents are more selective solvents than ethanol, and the latter is more expensive (due to special tax).	same capacity as a mixed solvent plant requires almost 100 % greater capital cost (estimated). In addition, carbon dioxide plant requires additional maintenance and repair of high-pressure equipment (up to 50 bar).	solvent losses in conventional mixed solvent extraction plant. Major competitors in developing countries are utilizing mixed solvent extraction plants.

Source: TechnoServe, 2004: extraction study

34. Will local extraction lead to local ACT production?

Local ACT production requires GMP standards in order to qualify for distribution through WHO as well as for subsidies through the Global Fund to Fight Aids, TB and Malaria (GFATM); it also a prerequisite for standard registration of the drug. The present ACT production in China does not fully meet these standards.

Artemisinin extraction in Kenya will be GMP certified (CEO ABE, Pers. Com.) and is potentially a source for local GMP-certified ACT production. Other bottlenecks to overcome are the relatively easier process of producing ATs (for which there is still a demand, despite WHO's warning about triggering resistance) and the costs of getting ACTs registered.

Dafra Pharma is supporting the start of local branches for AT production in various countries in Africa).

References:

- Personal communication by F. Herwig Jansen of Dafra Pharma
- Personal communication by CEO of ABE

35. What are the Good Manufacturing Practices for ACT?

WHO requires that drugs be produced under a strict set of guidelines, namely the widely accepted Good Manufacturing Practice guidelines (WHO-GMP). GMP ensures that products are consistently produced and controlled according to quality standards. The guidelines are designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. The major risks are:

- Contamination of products, causing damage to health or even death;
- Incorrect labels on containers, which could mean that patients receive the wrong medicine;
- Insufficient or excessive amount of active ingredient, resulting in ineffective treatment or adverse effects.

The GMP guidelines address all aspects of production, from the raw materials, the premises and the equipment used, to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that the correct procedures are consistently followed at each step in the manufacturing process, every time a product is made.

For more information see:

- http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html

SECTION 5. THE ECONOMICS OF ACT

36. How many farmers might be involved in East Africa?

In 2005, 400 ha and 200 ha of *A. annua* will be planted in Kenya and Tanzania, respectively, during the agricultural season, which runs from March/April to September/October. This total acreage will be roughly equally divided between small (< 0.5 ha) and large-scale farmers. This means that approximately 1 000 small-scale farmers (average 0.3 ha) and 100 larger scale farmers (average 3 ha) will be involved. If markets remain stable, this figure could in the near future grow to 3 000 ha (5 000 smallholders and 500 larger scale farmers). In addition, the number of persons growing *A. annua* for local consumption in the form of tea is likely to increase. Some farmers (both small and large) are specializing in seed production and the raising of seedlings.

References:

- Personal communications by CEO of ABE, Nairobi
- Personal communications by representatives of EAB and AAL
- TechnoServe, 2004
- http://cws.huginonline.com/N/134323/PR/200506/997306_5.html

37. What are the crop budgets and risks?

TechnoServe (2004) calculated crop budgets based on data provided by AAL. The budgets were verified by Faida MaLi, Arusha. Crop budgets are elaborated for both small-scale and large-scale farmers. Break-even financial yields amount to USD 340-570 per ha, which amounts to USD 170-258 per ton of dry leaves at the farm gate. The return to labour of *A. annua* production, which is important for smallholders, at USD 3.48/day is lower than that of maize (USD 4.69/day) and beans (USD 7.16/day), but considerably higher than that for coffee (USD -0.16/day).

The production of *A. annua* is attended by a variety of risks, both biological, physical and climatic, such as drought during the early stages of growth. The major risks, however, are the unpredictable markets and, related to that, the financial risks of using credit to buy such inputs as seeds / seedlings and fertilizers.

If the market for *A. annua* collapses and prices drop, small-scale farmers can still produce at a minimum price of USD 340/ha or USD 170/ton of dry leaves, which is the sum of the costs of the input and of (family) labour, which is valued at USD 1/day/person. This minimum price amounts to an intrinsic value of USD 21 per kg of artemisinin at the farm gate before extraction (at 0.8 % content and 2 tons of dry leaves per ha).

References:

- TechnoServe, 2004.

38. Can we quantify all the steps in the East African ACT chain?

Worldwide, the annual economic losses due to malaria have been estimated at USD 2000 million, which includes a global annual mortality of 1 million people (WB, 2005) or a growth penalty in some African countries of 1.3% (WHO/RBM, 2005). The bottom line is that as part of a wider campaign to roll back the malaria epidemic, an estimated 500 million treatment courses will be required per annum. The effective demand for these treatments will depend on the price of the treatment, and is therefore probably much lower.

The demand for artemisinin-based therapies is high since the parasite is rapidly developing resistance to all other drugs. The cost of the artemisinin-based therapies should not exceed USD 0.10-0.20 per treatment course in order to have an effective demand of 500 million/annum. At present, only tea made of dried *A. annua* leaves can meet this criterion (prices are even lower), but it has other shortcomings and cannot be mainstreamed into conventional health systems, as mentioned earlier. The herbal pastilles produced by Malarlife (Doctors for Life and NUS AG) cost USD 0.60 and the retail price can still go down (Von Freyhold, pers. com.)

Artemisinin-based monotherapies – which are available in sub-Saharan Africa - cost the consumer USD 1.00-3.50, or sometimes more. Novartis provides Coartem (presently the only WHO pre-qualified ACT) at a cost price of USD 2.40. ACTs are presently the only strategy recommended by WHO.

The Global Fund to Fight Aids, TB and Malaria provides subsidies for the free donation of ACTs to countries, which subsequently have to charge for the costs of domestic distribution. In fact the GF will pay for more than just the cost of the drug. It all depends on the proposal put to the GF from the country in question. This leads to a drastic reduction of ACT course prices through the GFATM. However, there is a strong need to make the chain more efficient, from production through extraction to the actual manufacturing. A more efficient chain based on naturally produced artemisinin will benefit both consumers and producers and will compete with synthetic alternatives more easily.

Each step in the chain is quantified as accurately as possible in the table in the appendix. Full quantification of fixed and variable costs is not possible because of the lack of experience in Africa and a lack of data from China and Vietnam. The table also indicates

the value added in each step of the chain, starting from USD 20 for a kg of artemisinin in the field (i.e. the intrinsic value of artemisinin in the dry leaves), to USD 20 000 per kg after it has been combined with lumefantrine, as an ACT, and is available in the pharmacy in Africa.

References:

- WHO, 2003
- TechnoServe, 2004
- http://www.rbm.who.int/cmc_upload/0/000/015/363/RBMInfosheet_10.htm

39. What are the cost/benefit ratios by chain component?

Cost-benefit analysis can be made for each of the three major steps in the chain, namely production, extraction and manufacture of the drug. The extraction is to take place in the country of production, mainly because the export of the bulky leaves would be too costly, although some suggest that this could be offset by enhanced quality when extracted in Europe (e.g. UK experience with the extraction of leaves from Tanzania). Data on the manufacturing process (apart from derivation) are not available, but interviews with Novartis and GlaxoSmithKline indicate that companies are keen to recover their costs only and are not expecting major returns except in terms of goodwill. The company's definition of recovering costs could however not be pursued, notably whether these costs include all investments in Research & Development, as well as activities to compile a file for compliance with the pre-qualification criteria. Other (smaller) companies have however to compete in this market in which profits are necessary to survive.

Production

Crop budgets have been prepared for production in Africa for both smallholder and large-scale production. The breakeven price of artemisia production would be USD 340-570 per ha or USD 170-228 per ton of dry leaves. For smallholders, this would mean a minimum return to family labour of USD 1/day, which is low compared to other crops. The breakeven price could decrease further if the biomass yield and artemisinin content were to increase, for example with new varieties it could be more than doubled to 4 tons of dry leaves at 1.5 % artemisinin. Other options lie in the production of additional essential oils, but the extraction of both artemisinin (by solvents) and oil (by steam) needs further research.

Extraction

TechnoServe has compared different extraction methods relevant for the establishment of plants in Uganda, Kenya and Tanzania. Each extraction plant will be able to process 2 500

tons of dry leaves, with a potential extraction capacity of 25 000 kg of artemisinin each. The plants are being established by Advanced Bio-Extracts and financed and technically supported by Novartis, also to make the process GMP certified. According to TechnoServe the investment costs are USD 6 million for each plant; the annual operating costs will amount to approximately USD 3 million. Mixed solvent extraction and carbon dioxide extraction have shown the best internal rates of return (IRR), namely of 41 % and 26 %, respectively, which were subjected to sensitivity analysis for raw artemisia leaves. If prices double, the investment loses some attractiveness but still shows an IRR of 34 % for the mixed solvent plant.

Doubling the capacity of the plant from 2 400 tons to 4 800 tons will increase the IRR to 59 %. TechnoServe (2004) concluded that a larger plant would be more attractive but it would not eliminate the attractiveness of two plants of smaller capacity size in two different countries. The economic and financial returns of a mixed solvent plant with a capacity of 2 600 tons is still quite attractive.

Manufacturing

The cost of the final product – that is, an ACT – is determined by many variables, some of which can be indicated. As mentioned, a full cost-benefit analysis of this step in the production process is not possible due to a lack of data. The cost of an ACT is determined by:

1. The cost of the traditional drug in the combination therapy. There is a trade-off between the costs of the drug and the level of resistance it has provoked in the parasite. Lumefantrine (in Coartem, from Novartis) has led to little resistance but is expensive, while chloroquine is cheap but is not effective in many parts of the world. Piperaquine is a relatively cheap alternative with good performance (in Artekin , which is being developed by a consortium comprising Chongqing Holley Holding, a Chinese pharmaceutical company, Sigma-Tau, an Italian pharmaceutical company, Medicines for Malaria Venture, a non-profit organization and the University of Oxford
2. The cost of the artemisinin derivate. Artemether, which is used in Coartem, is more expensive than dihydroartemisinin or artesunate. The trade-offs here are cost and quality, and effectiveness and shelf life in warm humid conditions.
3. The cost of pre-qualification and the related need for clinical trials. To qualify for WHO pre-qualification, the drug will have to pass both registration in Europe and clinical tests I, II and III, which normally takes several years. At the same time, the whole manufacturing process requires GMP certification. In addition, a drug can only be distributed if it is also recommended and, often, formally registered in the country where it will be used. These requirements greatly increase the costs of an ACT. In addition, the costs prohibit any small company from entering this process.

References:

- Minutes of the KIT-Artemisia expert meeting
- Interviews with Novartis and GlaxoSmithKline
- TechnoServe, 2004

40. What is the market prognosis for ACT?

As indicated, it is assumed that there will be a demand for 500 million ACT courses if the price is acceptable and can be afforded by consumers, the public sector and all kinds of civil society organizations. The price should be comparable to the price of a conventional treatment, that is, USD 0.10-0.20 per treatment course. However, the GFATM could make available annual subsidies amounting to USD 300-500 million.

This would imply that the ACT price ex-pharmaceutical company should not be more than USD 1 per course. Competition in the ACT market is required in order to bring the price down from USD 2.40-3.50 to USD 1. If the prices do not come down, the demand for ACTs will be limited and alternatives (ATs, herbal tablets, teas) will conquer the market with possible negative consequences.

The present high prices for artemisinin (up to USD 1 000/kg) are generally considered to be temporary, as production is likely to expand rapidly in China, Vietnam and East Africa. An overreaction is even likely, hence the concern of ABE–Nairobi and the request for a stabilization fund. Planned extraction capacity in East Africa alone amounts to 75 000 kg of artemisinin, which is considerably higher than the current estimated world production of 47 000 kg.

Based on the quantification data of the chain (see appendix 5), a sensitivity analysis can be performed for the effects of the price of dry artemisia leaves at the factory gate. A doubling of this price (to USD 300-600/ton) would lead to, at the most, an estimated 33 % increase in the price of the ATs or ACTs, mainly due to the fact that there are many fixed costs in the chain, such as extraction, registration and development costs.

If the effective demand for ACTs does not increase as a result of the lowering of the price, the world market for artemisinin is in serious risk of collapsing in a few years' time. Another threat is the longer-term appearance of alternatives to the naturally produced artemisinins.

SECTION 6. NATIONAL AND INTERNATIONAL POLICIES TOWARDS ACT

41. What is the relation between WHO and national health policies?

In response to the increasing problem of anti-malarial resistance, WHO (2001) has recommended that all countries experiencing treatment failures with conventional monotherapies should use ACT as first line treatment.

Fifty-six countries have now adopted ACTs in their policy, and 24 are currently implementing it (DFID Health System Resource Centre, 2005b). In Africa, 34 countries have formally adopted the use of ACT, although it should be noted that adoption into national policy and treatment guidelines does not necessarily imply implementation, since only ten actually use them (WHO/RBM, November 2005)

WHO is supporting ACT adoption policies by providing technical support to ministries of health and by monitoring the therapeutic efficacy of ACTs.

> The rapid increase in forecast demand for ACTs, and the need to match this with increase supplies have led to a number of problems. Although the GFATM financing is there to support ACT scale-up and roll-out, there have been problems in getting final approval of GFATM grants, in getting the supply side to respond quickly to the increase in finance (due to the 18 month cycle between artemisinin planting and finished product availability) and various other country level bottlenecks. Consequently, while a number of countries have expressed their intention to order ACTs, only a small fraction of the GFATM funds approved for ACT purchase has already mobilized into actual orders. The potential for a vicious cycle was consequently recognized, as the potential consequence of this lack of orders may be a reluctance of manufacturers to make commitments necessary to increase production.
>
> DFID Health Systems Resource Centre, 2005a

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42. What is the role of WHO in developing an ACT chain?

WHO has established, in collaboration with other United Nations agencies like UNICEF, an instrument to pre-qualify manufactures of artemisinin products on the basis of compliance with internationally accepted standards of manufacturing (GMP) and quality. To date, one ACT (artemether-lumefantrine or Coartem of Novartis in Basel Switzerland) and a number of products for mono-therapy (e.g. Artesunate of Sanofi-Synthelabo in France or Guilin Pharmaceutical Co Ltd, PR China and Artecef®50 en 150 of ARTECEF/ACE Pharmaceuticals BV in Zeewolde, The Netherlands) have been pre-qualified. An ACT can be procured via WHO if the quality of the product conforms with WHO quality requirements. The pre-qualification for new ACTs is a challenge, as the qualification process is rigorous. It looks at the quality of the product and the manufacturer. The WHO prequalification scheme examines clinical studies for New Chemical Entities but also looks at evidence of bioequivalence for generic products and GMP quality of the manufacturer. But as the WHO prequalification scheme is a voluntary process, it can happen that a drug is purchased by WHO even if not prequalified. Currently WHO's procurement department is purchasing co-blisters of Artesunate/Amodiaquine that are not yet prequalified.

Furthermore, several pharmaceutical companies, like for example Dafra-Pharma that produces, amongst others, Arinate artesunate) are attempting to conquer the market with their relatively cheap artemisinin-based drugs although they have not been pre-qualified by the WHO.

This study finds that a subsidy to ACTs is likely to slow the rate of emergence of resistance to artemisinin and partner drugs, even if such a subsidy were to increase the use of ACTs significantly. This conclusion is robust to alternative assumptions regarding the responsiveness of demand to the lower price fro ACTs and a wide range of epidemiological and economic parameters. However, the simulation results show that a subsidy of two or more ACT combinations is likely to be much more cost-effective than a subsidy of a single ACT. The only consideration is that the drugs used as partners to artemisinin be unrelated to each other and to artemisinin in mechanism of action and in genetic bases of resistance, so that a single mutation cannot encode resistance to both components. Such a subsidy program for ACTs, administered globally, that reduces reliance on any single combination, and discourages monotherapy, not only of artemisinin but of any effective antimalarial that could potentially be used as a partner drug with artemisinin, is likely to be effective (and cost-effective) both in buying time for ACTs and in saving lives.

Will a global subsidy of artemisinin-based combination therapy for malaria delay the emergence of resistance and safe lives? World Bank Policy Research Working Paper 3670, July 2005

The statements by WHO and the World Bank that 300-500 million ACT courses will be required annually and must be distributed at affordable prices, is no incentive for Novartis as such to invest in the production of these ACTs at cost price. At the same time, the suppliers of artemisinin are not sure of a sustainable demand, which is required for longer-term investments, such as investments in extraction capacity. WHO (Schapira, pers. com.) has suggested that the following steps be taken:

- The GFATM should develop mechanisms to ensure long-term demand and establish some sort of procurement facility.
- The establishment of a publicly funded foundation to operate as an artemisinin bank to secure and stabilize the market in terms of both supply and demand. The sourcing of artemisinin could thus be facilitated by such a foundation, and could include a guaranteed minimum price.
- Support of the production in order to meet the demands through special measures in services provision, for example seasonal credit, seed / seedling supply and agricultural extension.

One major dilemma is the paradox between the need to rapidly establish an effective chain for the almost immediate production of ACTs, and the need to produce ACTs efficiently and cheaply through pre-qualification and enhanced competition in the chain.

43. Is there interaction between policymaking and private-sector lobbying?

WHO and Novartis (the manufacturer of Coartem) have signed a special pricing agreement: Novartis provides the drug at cost price (USD 0.9 and 2.4 per child and per adult treatment course, respectively) for use in the public sector in malaria-endemic countries. WHO, through a panel of experts, reviews requests for supplies of Coartem and procures the drug for the governments of malaria-endemic countries, UN agencies, bilateral agencies and NGOs.

Whilst it may have been true six months ago that countries could not order largely because they were caught up in the GFATM processes, we found that the majority of countries currently have GFATM finances approved and available for ACT purchase. For artemether/lumefantrine purchase, USD 177 million of GFATM funds has been approved for Coartem purchase. This is money that has been through all GFATM disbursement phases (including approval of the Procurement and Supply Management – PSM- plan) and can be used immediately to place an order.

On the supply side, Novartis has announced that it will be producing 210 million treatments over this time period. At average prices of $1.5 per treatment, this equates to $ 315 million of needed budget to buy Novartis's entire production over the two-year

period. This means that Novartis will be producing in excess of the GFATM financed demand, and there will be a short fall of $80 million to buy the entire production over the two-year period. However, this shortfall may be met by i) Novartis sales to the private sector, ii) the ACT portion (not yet decided) of the $500 million from the World Bank (Booster program) devoted to Africa to fight Malaria over the next 5 years, iii) by new countries winning GFATM grants for ACT procurement in GFATM Round 5, or iv) other donor, (e.g. EC, Bush initiative July 1 2005 declaration) and v) GFATM Phase II of grants currently in operation. It should also be noted that the shelf life of the artemisinin is approximately 5 years, and time to bring artemisinin to finished product only several months, thereby allowing some flexibility to hold stock for subsequent years if a firm happens to over-contract for supply. As for artesunate/amodiaquine, Sanofi production in 2006 might reach 15 million treatments, and IPCA will soon be producing 2 million treatments (co-blister) per month (which is a fraction of what they are capable of producing).

DFID Health Systems Resource Center, 2005a

Sanofi-Aventis and its non-profit partner Drugs for Neglected Diseases Initiative (DNDI) announced recently that they are working on the release of an inexpensive ACT. Sanofi-Aventis intends to sell the treatment at a target price of less than $1 for adults and 50 cents for the version made for children.

References:

- DFID Health Systems Resource Centre, 2005a, 2005b
- World Bank, 2005

44. What about the certification and registration of new medicines?

This is a complex process that involves national or regional pharmaceutical authorities. In principal, a new chemical entity always requires approval by a national agency before it is put on a market, in particular with regard to quality, safety and efficacy. In Europe, the European Medicines Agency (EMEA), a decentralized body of the European Union with headquarters in London, is actively involved in this process. This is the same with the US Food and Drug Administration.

The Global fund's procurement policy on Quality Assurance related to the purchase of single and limited source pharmaceutical products was recently updated. There are now three acceptable quality assurance standards:

- approval by WHO pre-qualification scheme;
- approval by a drug regulatory authority that participates in the International Conference on Harmonisation (essentially a "stringent" authority from a developed country); or,
- if there are less than two suppliers that meet the criteria of 1 and 2 then the product can be procured from any supplier that is compliant with Good Manufacturing Practice (GMP) and is in the process of applying for prequalification of regulatory approval from a stringent authority. If the above is not possible it can be procured from any supplier that manufactures from a GMP-compliant site.

GFATM, 2005

The WHO prequalification project is not an international pharmaceutical authority but it works as an international body using expertise from various highly regulated countries to assess mainly the quality and the proof of equivalence of generic products. They also list innovator products that have been registered in highly regulated countries like by US FDA, EMEA, and by individual European authorities. The aim of the project is to give support to developing countries that have little or no capacity to do this assessment, however each national authority needs to register the product or not for its market.

For Coartem follow-on drugs, gaining pre-qualification is relatively easier. This is because Novartis went through the lengthy process of conducting clinical trials to establish safety and efficacy, therefore follow-on products can refer to the originator's clinical trial data to establish safety and efficacy, and simply have to prove level two (or in-vivo) bioequivalence, though this process may be difficult for all but the most advanced Asian firms.

The situation with the ART+AQ suppliers is different, and more challenging, since there is no originator's clinical trial data to refer to in order to establish safety and efficacy data. In theory, safety and efficacy can be established via good clinical trials using the loose combination. The first amodiaquine combination producer to gain pre-qualification status will either have to conduct clinical trials or may gain pre-qualification status via reliance on existing literature/data plus a good quality bioequivalence study. For firms who are primarily generic producers, this is outside their normal capabilities and resources, and requires fulfilling a role they are not really equipped to fill. This is a challenge for other ACT combinations as well. Sanofi is expecting to be the first with a pre-qualified product, anticipating approval of their ART+AQ co-blistered product by July 2005

DFID, Health Systems Resource Center, 2005a, 2005b

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- www.emea.eu.int
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- GFATM, 2005

CONCLUSIONS

1. Currently, artemisinin-based combination therapy (ACT) is the optimal treatment option for non-complicated *P. falciparum* malaria in areas where there is resistance against accepted monotherapies. ACTs are at present highly effective against the malaria parasite. WHO has considered combined therapy as safe and effective in a wide range of situations. This implies that conventional health systems should adopt ACT as the anti-malaria drug to be administered. Importantly, at present there are no indications that resistance will rapidly develop against artemisinin derivatives.

2. Several ACTs are required for effective first and second line treatment of malaria. Currently, the WHO has pre-qualified Coartem (Novartis), no Asian or other ACT has been pre-qualified by the WHO although at the time of writing there are some artemisinin-based products and manufacturers undergoing the the prequalification review[7]. This monopoly-like situation has created an imperfect market defined by scarcity of raw materials, speculation and extremely high retail prices. The current dysfunctional supply chain is the main cause that ACT is not available to the vast majority of poor malaria patients

3. Health systems in China and Vietnam promote the treatment of malaria with artemisinin-based monotherapy (AT). However, AT is not advised as the treatment of choice by the WHO for such reasons as patient compliance and the risk of developing resistance. However, ATs have also penetrated the African markets through both formal and informal procurement systems. These ATs can only be effectively removed from these markets by ensuring the cheap supply and wide distribution of ACTs. Under the prevailing price regimes of ACT, we expect ATs to expand their market share in Africa.

4. Artemisinin derivatives can be combined with any other anti-malaria drug as long as the latter is safe and efficacious. The price and stability of the combination drug is of great importance. Alternative combination drugs, such as piperaquine or chloroproguanil-dapsone, deserve attention.

5. Artemisinin-based tea as a malaria treatment is not an option for mainstreaming into conventional health systems. Extracts or tea cannot be registered and prescribed because of their non-standardized and variable composition. However,

[7] In addition to this prequalification, the WHO has pre-qualified an artesunate product, produced by Sanofi and 2 artmisinin-based products of Ace Pharmaceuticals.

traditional and non-conventional practitioners are promoting the use of extracts and tea, and this will have an impact on public health, notably where *A. annua* is introduced and promoted for cultivation. In addition, the cost of a treatment based on herbal extracts or tea is currently less than USD 0.30. The low retail or user price may catalyse the diffusion of these treatments in Africa, especially in situations where no affordable alternative is available.

6. Considerable efforts are being made and both human and financial resources are being allocated to the synthetic production of artemisinin. It is generally anticipated that a synthetic ACT will be available within 10 years, although some experts believe that the synthetic production will start to be of importance as soon as 2006/2007. At the moment, no forecast can be made about its retail price. The advantage of synthetic artemisinin is the combination of its predictability and, eventually, cheap production. Pharmaceutical companies will be able to enhance their control over the production process and will not have to depend on numerous supply chain actors, such as thousands of individual producers and local extractors. Long transportation distances across multiple borders will be replaced by on-the-spot production and manufacturing. However, there are also disadvantages: pharmaceutical companies will accumulate control and power over the production process; artemisia producers will lose a source of income; and local production, extraction and (possibly) manufacturing of ACT in regions where malaria is prevalent will shift to the main production sites of Western pharmaceutical companies. At the moment, it is not known how Chinese and Vietnamese companies will respond to synthetically produced ACT.

7. During the coming years, the demand for ACT will reach a peak of 500 million treatments per year. The demand for naturally produced ACT will stabilize at approximately 100 million treatments per year after alternative treatments have become available at similar procurement prices. It is estimated that 20,000 ha of *A. annua* will be required to satisfy the global peak demand. A stable demand of 100 million treatments will require approximately 4,000 ha of *A. annua*. These figures do not take into account the higher artemisinin concentration found in plants grown in East Africa as compared to China and Vietnam. Nor have current efforts to develop new hybrids with even higher artemisinin concentrations been taken into account. Thus, the production of *A. annua* is subject to various interventions that will gradually reduce the acreage required to satisfy the global demand.

8. The need and the demand for ACT are insufficiently related in the chain. The market comprises a subsidized and a commercial component. There are ATs and ACTs on the commercial market that have been registered, procured and

distributed by national systems. The retail price of these drugs varies between USD 1.0 and USD 3.5 per treatment. These drugs are not accessible to the vast majority of malaria victims in sub-Saharan Africa because these people lack the required purchasing power. WHO is the dominant actor in the subsidized market and until very recently had pre-qualified only one ACT – Coartem, for which Novartis has a patent. Novartis, as the present main WHO provider of ACT, in a subsidized market, which lacks competition.

9. In 2004, Novartis procured most of the artemisinin available on the world market in order to meet its contractual obligations to the WHO. This resulted in a great increase in the procurement price of raw materials. Artemisinin has become scarce on the commercial AT and ACT markets, which has resulted in higher prices. Novartis has signed contracts with East African Botanicals and African Artemisia Ltd in order to assure itself of an artemisinin supply in the short-term future..

10. There are numerous initiatives in sub-Saharan Africa to produce *A. annua*. Novartis and other pharmaceutical companies, as well as international NGOs, are endeavouring to increase the production capacity, notably in East Africa. In this, the principle motive of the pharmaceutical companies is the erratic and untraceable supply of artemisinin from China and Vietnam. East Africa has some competitive advantages and transparency of the chain is higher. Good production and manufacturing practices can be more easily endorsed in East Africa, and the artemisinin concentration in plants is higher. However, the enhanced control of the pharmaceutical companies over the supply chain is perhaps the principal reason to increase the production capacity in East Africa. The main reason the NGOs are promoting the crop is to offer small-scale farmers a new source of income. From a public point of view this might justify considerable investments even though small-scale production is not strictly economically feasible. The question is whether *A. annua* is an adequate crop for small-scale farmers in view of production requirements, long-term market developments and the concentration of chain ownership in the hands of the pharmaceutical companies.

11. The greatest technical bottleneck to artemisia production is the shortage of good quality F1 hybrid seed. To date, Mediplant is the single source of the hybrid seed that is suitable for the ecological conditions in sub-Saharan Africa. Large-scale farmers in East Africa are competing for F1 seeds and are developing methods for vegetative propagation. Small-scale outgrowers may become increasingly involved once *A. annua* is under large-scale production. It is very unlikely that small-scale farmers will benefit unless they have a secure, contractual supply from large farmers. The cost-benefit ratio of *A. annua* is competitive with common

commodities, such as bananas, but the technological requirements and medium-term risks are higher for the producers. Such risks can be reduced by a steady supply of the agricultural inputs as well as technical support and a good knowledge of the market.

12. Significant public and private action is required to achieve the objective of making available an effective and affordable anti-malaria drug to African patients in the short run. Interventions can be proposed at various levels:
    - At the level of production the availability of quality F1 seed is a considerable bottleneck to expansion of the acreage under artemisia. Moreover, public and private research and extension are required to involve small-scale outgrowers in the supply chain. Genetic improvement of the plant will result in higher concentrations of artemisinin and hence improve cost-benefit ratios at farm level. Public research could focus on the development of an 'African variety' for use by smallholders.

    - It is difficult to predict for how long smallholders in Africa can be gainfully engaged in artemisia production. Public and private efforts to identify and promote other medicinal plants for cultivation by these farmers would mitigate the possible adverse effects of reduced market demand for artemisia. Opportunities exist in the field of other anti-malarials as well as herbal-based drugs for other diseases.

    - An African procurement fund could be created to stabilize the nervous and fluctuating market. The procurement price could be fixed for a certain period, thus enhancing certainty in the supply chain. This would replicate itself through the chain and enhance the contracting of producers. Cartel formation would thus be discouraged. At a certain moment (i.e. when there is sufficient artemisinin to satisfy the global demand for ACT), this might result in overproduction, which would require a readjustment of policy.

    - Another public intervention involves the WHO prequalification of ACTs. The subsidized global market would benefit from an increase in the number of ACT suppliers. This would result in a drastic fall in the retail price and in the enhanced availability of a variety of ACTs for first- and second-line treatment. Support to WHO prequalification process is needed in the form of financial and human resources to shorten the process for evaluation and inspection. But there is also a need for manufacturers to invest and work to match WHO standards. Support is already given by the MMSS to help manufacturers match those standards. Pharmaceutical companies are still

responsible for these investments, which are often considered to be too expensive or are included in the retail prices.

- Knowledge and information about artemisia and ACT markets is still very scattered: market players do not communicate and policymakers remain generally uninformed. This lack of transparency and the failure to share information is a serious obstacle to the development of a more effective supply chain and, hence, an obstacle to the availability of affordable drugs to the detriment of poor households. Public and private key players could establish a task force in order to share information and discuss collaboration and fine-tune interventions. Policymakers would thus remain informed and be able to act and react to new trends. Private-sector players would benefit from more effective public interventions. An international task force would considerably enhance the sustainability and transparency of an artemisia / ACT supply chain.

The decision to invest public funds in the promotion of ACT production in Africa is and remains a political one and cannot be fully justified on economic grounds. At the same time, the private sector is investing in East African production and extraction capacities in the context of cartel formation and lack of information about Southeast Asian production. Would African patients not benefit more from a rapid production effort in China and Vietnam? Should public money be directed towards enhancing the good production and manufacturing practices of Chinese and Vietnamese companies? Should we not develop public-private partnerships with these companies and facilitate the pre-qualification of their ACTs?

We hope that we have provided sufficient facts and evidence for those who consider contributing to the production and promotion of ACTs. We realize that there is no single solution to this complex problem. We have to collaborate, make choices, explore new roads and diversify our efforts. Above all, we must ACT.

APPENDIX 1 ADDITIONAL REFERENCES

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APPENDIX 2 IDENTIFICATION OF SUITABLE LOCATIONS FOR PLANTING *ARTEMISIA ANNUA*.

Source: TechnoServe, 2004

CRITERION	REQUIREMENT
Physical Characteristics	
Altitude	1000-1500 m above sea level is ideal: can be a little higher or lower if maximum/minimum temperature is within desired norms
Soil type	Reasonable fertility, good water-holding capacity, not liable to water-logging pH not above 5.5
Climate	Temperate climate preferred, but *A. annua* tolerates daytime temperatures up to 28ºC and down to 15ºC. Frost is undesirable, especially at young stages
Rainfall/water availability	Distribution more important than absolute amount. Reliable rainfall or irrigation potential essential at planting and for 2-3 months after transplanting
Topography	Slopes steeper than 15% are unsuitable, though once established *A. annua* gives reasonable protection against soil erosion
Vegetation	Open area needed – not too many trees or other obstructions – but if planted by smallholders, plots can be small scale and still profitable
Access	Easy road access is required for seedling and input delivery, leaf collection and extension/supervision. Distance from farmer's home should not be too great
Land Availability and Use	
Land availability	There should be enough unused or under-utilised land in the area that can be planted (or switched) to *A. annua* cultivation, to ensure that: (a) large areas of land are not taken away from food production, putting food security at risk (b) farmers are not tempted to plant the bulk of their holding to *A. annua*, possibly putting their livelihoods at risk in case of crop failure (it should be recognised that *A. annua* is still in many respects an experimental crop in East Africa)
Land tenure	(a) Smallholder planters should have secure tenurial rights, sufficient at least for investment in annual crops and as security for loans (b) If estate cultivation is envisaged there should be no dispute over land rights
Current land use	(a) The ideal location is one where farmers have few profitable and reliable cash crops, meaning that they would jump at the

	opportunity to earn good money from *A. annua* (b) If tree crops (tea, coffee, etc.) are the current cash crops, there should be additional land available to avoid the need for immediate and costly uprooting (c) In areas where individual farm sizes are very small, land currently used for food production should be avoided where possible, to avoid exposing farmers to undue economic risk (d) Land reserved for forestry or water source protection should be avoided, to reduce the risk of causing environmental damage
Labour Availability	
Household labour	If *A. annua* is proposed as a smallholder crop, the farming calendar should be checked to make sure that competition for labour, especially at transplanting, weeding and harvesting time, will not cause problems by clashing with other essential demands on family labour
Plantation labour	If *A. annua* is proposed as a plantation crop, availability of hired labour especially at transplanting, weeding and harvesting stages must be sufficient
Grower Interest	
Farmer willingness to try	Assessment should be made of small farmers' willingness to plant perhaps a small area of *A. annua* in Year 1, to see how it grows and how they like growing it
Plantation owner interest	Interest of larger farmers in growing *A. annua* should be assessed, and estimates made of the area they might be ready to plant

APPENDIX 3 ARTEMISIA RELATED STAKEHOLDERS AND THEIR BACKGROUNDS

Address	Contact person	Type of stakeholder	Aims and objectives	Activities	Scale and resources
ACE Pharmaceuticals ARTECEF BV Zeewolde	www.ace-pharm.nl ace@ace-pharm.nl	Manufacturing	Production of anti-malarial drugs	Registered AT after seven years. Involved in Vietnam study as well as project in the 1990s	Public sector
Advanced Bio-Extracts (ABE) Holding Company Nairobi, Kenya	Patrick Henfrey CEO + 254 735 710345. +44 7968063288	Marketing	Promotion of production, extraction and marketing in East Africa	Holding company of AAL, EABL Kenya and EABL Uganda Involved in F1 seed supply and production through contracts	Financial investment by Novartis in extraction facilities (60 %)
African Artemisia Limited PO BOX 425 Arusha Tanzania	Mr Geoff Burrell 0748651762	Marketing and input supply	Promotion of artemisia production, extraction and marketing in Tanzania	Develops growers' production manual and supports production on 200 ha	Long-term contract with Novartis Part of ABE Holding

ANAMED Germany, c/o Dr Hans Martin Hirt, Schafweide 77, 71364 Winnenden, Germany. Fax: +49 7195 65367	Keith Lindsey anamed@t-online.de Tel: +49 (0)7195 74572	Seed supply (A-3), extension	To promote natural medicine, traditional medicine and modern medicine. To promote the use of tea from locally grown artemisia	Operates in 29 SSA countries Anamed groups in Eritrea, Ethiopia, Kenya, Mozambique, Nigeria, DR Congo, RSA, Sudan, Tanzania, Uganda	Sells A-3 seeds Training workshops in Tanzania (Musoma), Ethiopia and Mozambique
Anthony Ellman Dr Ellis Njoka (Kenya) Tabu Likoko (Tanzania NH) Esther Meela (Tanzania SH)	Ellmans@aol.com +44 7905 723348 +44 208 878 5882 (mobile)	Planning, resource persons	Consultant	Executed feasibility study for TechnoServe	Study funded by USAID Also DFID studies
Botanical Developments Ltd Rowley House Tokenspire Business park http://www.botanicaldevelopments.com/	Ian Hatton Director of Regulatory Affairs and Licensing Ian.Hatton@botanicaldevelopements.com +44 1482886421	Development	Promotion of production and use of medicinal plants	Contacts with producers in Kenya	

Centro Pluridisciplinar de Pesquisas Químicas, Biológicas e Agrícolas (CPQBA) Universidade de Campinas Brazil	http://www.cpqba.unicamp.br/plmed/ Dr Pedro Melillo de Magalhães (pedro@cpqba.unicamp.br) Dr Mary Ann Foglio	Seed supply and phytotherapy research	A. annua seed production for the tropics/subtropics	Produced variety adapted to Brazil's latitude and day length. Focus on the Brazilian market	Brazilian public support Collaboration with Mediplant Sales of seeds
CORDAID	Jacob Winter 070 3136300 jwi@cordaid.nl	NGO	Support of small-scale artemisia production	Received request from EABL to support production in Kenya	NGO
Dafra Pharma Turnhout	Dafra.pharma@skynet.be www.dafrapharma.be Herwig Jansen and Platteeuw	Manufacturing	Production of anti-malarial drugs	Arinate production (AT)	Private sector
Deventer Hospital, the Netherlands +31 570 542830 (home) +31 570 623050 (office)	Paul Lamberts, hospital pharmacist lambertsnl@wxs.nl	Drug distribution	Interest in AT/ACT drug promotion	Part of an NGO promoting artemisinin-based drugs	Public sector
DFID	Nick Banatvala, n-banatvala@dfid.gov.uk Team Leader Global	Financier	Support of Roll Back Malaria programme and agro-chain promotion	Financed feasibility of proposals	Public sector

DGIS	Harry van Schooten Harry.schooten@minbuza.nl	Financier	Promotion of the artemisia chain for health reasons	Support of the stocktaking study	
Dr Charles Lugt	Tel +31 (70) 3504465 cha.ma@inter.nl.net	Resource person	Promotion of artemisinin production and use for 20 years	Worked for Artecef Produced A. annua in the Netherlands (Almelo)	Retired
East African Botanicals Kenya Ltd Naivasha	artemisia@africaonline.co.ke	Marketing and input supply	Promotion of artemisia production, extraction and marketing in Kenya	Support to 400 ha of production	Part of ABE Holding
East African Botanicals Uganda Ltd		Marketing and input supply	Promotion of artemisia production, extraction and marketing in Uganda	Extraction plant in operation, extracting production from Kenya No production yet	Part of ABE Holding

East-West Seed Company Arusha Office	Rene Geelhoed rene@tvsp-tz.org mobile +255-748-957833, office -27-2501990; -27-2501791, TVSP PO Box 14387 Arusha Gerard Grubben (Advisor) +31.35.6950903	Seed supply	To supply quality seeds in the East and West	Considers the artemisia seed market too small to invest in	Private sector
FAIDA MaLi	Steven Kijazi Agribusiness officer stevenkijazi@yahoo.com	Extension	Promotion of SME and agro-chains in Tanzania	Contract person on artemisia Working with TechnoServe	
Farmco Dronrijp, Holland	Nammen H. Schaap farmco@schaapagroholland.com +31 517 239922	Agricultural consultancy	Consultancy company	Support the development of commercial artemisia production	Private sector

GlaxoSmithKline (GSK) 980 Great West Road Ware Hertfordshire SG12 0DP UK	Ian Boulton ian.c.boulton@gsk.com Director, Commercial Strategy Disease of the developing World	Manufacturer	Production of ACTs at low prices	Final clinical tests for a new ACT to be approved by WHO	Private sector
HanzeHogeschool Groningen	Henk Goris h.goris@pl.hanze.nl	Production	Promotion of local production and use of artemisia-based quality herbal extracts	Artemisinin projects in Madagascar (de Waal et al.), Artemisinin in Tanzania (Saeijs et al.)	Miscellaneous
Holleykin Pharmaceutical Co.	www.holleykin.com	Pharmaceutical company	Promotion of artemisia production, extraction and processing in China	Produce Artekin (DHA and piperaquine)	Private sector
IDA Foundation International Dispensary Association	Henk den Besten Telephone: + 31 20 4033051 Fax: + 31 20 4031854 info@ida.nl	Drug distribution	Distribution of artemisinin blisters through pharmacies	Involved in earlier studies on artemisia	

Institute Plant Biotechnology for Developing Countries (IPBO) Gent http://www.ipbo.rug.ac.be/	Nancy Terryn Nancy.terryn@ugent.be	Research	Increasing artemisinin content of Artemisia plant	Research in biosynthesis of artemisinin Genome research	Public sector VIT Finland is a partner
Manyara Estate Arusha	Martien manyara@habari.co.tz 0744/40 19 61	Production	Large-scale commercial artemisia production	Pilot in Arusha of one acre Scaling up to 40 ha	Private sector
Mediplant, Centre des Fougeres CH-1964 Conthey, Suisse Tel.: +41 27 3453511 mediplant@rac.admin.ch www.mediplant.ch	Simonnet Xavier, Project Chief, agronomic engineer,	Seed supply	MEDIPLANT is a research centre devoted to medicinal and aromatic plants and their cultivation. MEDIPLANT is an association, executes work on the domestication and genetic improvement of new medicinal and aromatic plants.	MEDIPLANT specialises in plants adapted to mountain regions and farming techniques which are environment-friendly Produces two *A. annua* hybrids: Artemis and Madiplant	Three senior staff Artemisia hybrid seed production and supply DEZA assistance

MSF	Margriet den Boer: margriet.den.boer@amsterdam.msf.org Nathan Ford: nathan.ford@london.msf.org Christa Hook: christa.hook@london.msf.org	NGO	Promotion of low-cost and sustainable anti-malaria drugs	Close cooperation with WHO and field	
MSF/AEDES:	Jean-Marie Kindermans International Office MSF Brussels 6 rue de la Fontaine 92120 Monrouge Belgie	NGO	Promotion of low-cost and sustainable anti-malaria drugs	Close cooperation with WHO and field	

NOVARTIS Novartis Pharma 103.2431.P.05 CH-4002 Basel Switzerland	Hans Rietveld hans.rietveld@pharma.novartis.com 00-41-61-3244020 Global Marketing Manager Tropical Medicine	Manufacturing	Supply of ACTs at cost price to WHO	COARTEM and RIAMET (ACTs) production Support to EA production and extraction	Private sector Invest in ACTs not for direct commercial reasons
Rijks Universiteit Groningen (RUG) Groningen Research Institute of Pharmacy (GRIP) T: 050-3633351 T: 050-3634615 (secr.)	Dr Herman J. Woerdenbag h.j.woerdenbag@rug.nl	Research	Pharmaceutical research	Pharmaceutical research into artemisinin production in the 1990s	Likes to be kept informed
Rijks Universiteit Groningen (RUG) Pharmaceutical Biology	Prof. Wim Quax w.j.quax@rug.nl http://www.rug.nl/farmacie/onderzoek/basiseenheden/farmaceutischebiologie/onderzoek/index?lang=en	Research	Research in *A. annua* and. in the broader sense. in terpenoids	T.E. Wallaart, 2005 *Investigations on the biosynthesis of the novel antimalarial drug artemisinin in the plant Artemisia annua*	PhD studies

Saokim Pharma	www.saokim.com.vn	Pharmaceutical company	Promotion of artemisia production, extraction and processing in Vietnam	2000 ha of artemisia	Collaboration with WHO Private sector
Selian Agricultural Research Institute		Research	Improved artemisia production technology	Little progress so far	Contract research with DGIS
SPDC Nigeria PO Box 263 Port Harcourt -Nigeria Tel: +234 84 4 24532	Rowland, Ayo Economic Empowerment Coordinator, SPDC-East ayo.rowland@shell.com	Extension	Interested in growing the crop in Niger Delta	Searching for production options in the Niger delta	Private sector
TechnoServe Tanzania Thom Dizon, Country Director PO Box 2117 Arusha Tel: +255 27 2509657 Dixon@tnstanzania.org	Mick Baddeley, Artemisia Project Advisor mick@tnstanzania.org 0744-081327	Marketing, extension. extraction	To support small-scale *A. annua* production in East Africa Chain development	Implemented feasibility study for production and extraction of artemisinin	Investing USD 700 000 (USAID and IFAD) in Tanzanian artemisia chain. Has some extension staff

Tongu Fruits Ghana Ltd Sogakope in the Volta Region. Ghana	Daan Luteijn Mobile 024- 325 551; Sat 00871- 762 749 732	Production	Production of *A. annua* in higher parts (>1000m) of Ghana	Joint venture between TFG and Ghanaian pharmacist	Private sector
University of Bremen	Prof. Michaela von Freyhold enro@uni-bremen.de	Research	Social research development of artemisia production in Africa	Testing different varieties of artemisia through AAL Extraction options Herbal extracts promotion	Public sector
USAID Tanzania Arusha Project	S. Fondriest Sfondriest@usaid.gov	Financier	Financing promising international agro-chains	Supporting TechnoServe for artemisia promotion	
WUR (Wageningen University and Research Centre)	Dr Harro Bouwmeester Plant Research International Tel: +.31.317.475582 Harro.Bouwmeester@wur.nl http://www.plant.wur.nl/projects/terpnet/	Research	Research into the biosynthesis of artemisinin		

WUR (Wageningen University and Research Centre) Chair group Crop and Weed Ecology	Dr Willemien J.M. Lommen +31 317 48 4697 (office) +31 317 48 5315 (secretariat) Willemien.Lommen@wur.nl		Research into the biosynthesis of artemisinin	Research in physiology of artemisinin production in the plant. Terpenoid profiling	Public sector

APPENDIX 4 *A. ANNUA* SEED AND SEEDLING SUPPLY

Source: TechnoServe, 2004, Others

Source	Description of the varieties
China	Plants collected naturally from the wild in China have an artemisinin content of 0.6-07 % and produce around 1.5 MT/ha.
China Yonyang County	Selective breeding is being done by the Chongqing Holley Group. High yielding varieties are reported from Szechuan Province. Seed from China for Africa is not available ('national strategic asset').
Vietnam Institute of Materia Medica, Hanoi	Varieties in the Red River Delta with 1.0 % artemisinin in dry leaves, capable of producing 27-43 kg artemisinin/ha (C. Lugt, pers. com.). Hybrid varieties have been developed based on crossing of selections from China and Vietnam with high artemisinin content (1-1.5 %) (Laughlin, 2002). Composite varieties with 0.5-0.8 % artemisinin can already be obtained from Vietnam and are cheap, but have not yet been tested in Africa (Von Freyhold).
Switzerland, Mediplant www.mediplant.ch	Selected clones from Europe (high vigour but low artemisinin content) and Chinese clones (low vigour but high artemisinin content) led to some high yielding hybrids. 'Artemis' hybrid (F1) with 1-1.3% and 'Madiplant' with 1.5 % artemisinin, capable of producing up to 40 kg artemisinin/ha. Prices of seed: USD 70/g (USD 140/ha) (Von Freyhold). Limited quantities are available (500 g)
CBQBA Universidade de Campinas, Brazil	Based on experience from Mediplant, CBQBA developed hybrids for use in Brazil. These varieties for the tropics which yield up to 25 kg artemisinin/ha (Magalhaes et al., 1997). Very limited quantities (150 g) are available at USD 55/g.
ANAMED, Germany	In collaboration with Namedo (Uganda) seeds are being produced, probably F2 seeds, which are sold at EUR 70/g. The leaves have 0.5-0.75 % artemisinin concentrations. Developing a new hybrid in 4-5 years will cost some USD 100 000 in development costs (Von Freyhold).

Advanced Bio-Extracts, Nairobi (EABL, AAL)	Has started its own seed production in East Africa. Presently through the production of F2 seeds. No details were disclosed.
India CIMAP, Lucknow	The Central Institute of Medicinal and Aromatic Plants in Lucknow, India, has started producing and supplying artemisia composite varieties, which yield up to 60 kg artemisinin per ha at 0.8 % artemisinin. Varieties have not yet been tested in Africa.

APPENDIX 5 COSTING OF THE *ARTEMISIA ANNUA* PRODUCTION CHAIN

Sources: Wright, TechnoServe, various publications

Economic chain	**Prices and outputs**	**Fixed costs**	**Variable costs**	**Value of 1 kg artemisinin** (based on 25 kg/ha)	**Trends and developments**
Initial investments	Seeds: USD 140-280/ha (F1 seeds) Fertilizer: USD 20-35/ha Labour: minimum USD 1/day	Total cash inputs: USD 98-570/ha	Total labour costs: USD 175 (hired) - 242 (family)/ha	Breakeven: USD 14-23	Costs of seeds can be reduced through composites
Production in East-Africa	Commercial growers in EA: 2500 kg dry leaves at 1 % artemisinin Smallholders: 2000 dry leaves at 0.8%. USD 470-550/tonne (250 + 100 + 40x (X* 0.1%-0.5) USD)/tonne dry leaves in Tanzania	Break-even: USD 340-570/ha or USD 170-258/tonne dry leaves (USD 200/tonne in general)	Present factory gate: USD 940-1375 (i.e. USD 55-60/kg artemisinin)	Factory gate: USD 55-65	Production is increasing
Production in China and Vietnam	Commercial growers in China and Vietnam produce up to 40 kg artemisinin per ha, in India even up to 60 kg/ha USD 500-600/tonne leaves in China in 2004, at 2.5 tonne production	Factory gate USD 1250-1500/ha		Factory gate: USD 50-60	

Marketing leaves	Difference between farm gate and the gate of the extraction plant extremely variable	In-country transport up to USD 60/tonne excluding taxes.	Roughly 10 %		Bulky dry leaves Transport expensive
Local processing (extraction)	Extraction plant price of artemisinin: USD 230-280 (TechnoServe in 02/03) and USD 330 (Saokim, 2004). Mixed-solvent extraction at 75 % efficiency artemisinin	Artemisinin factory price is USD 55-60/kg	Cost price of extraction/kg artemisinin is USD 204/kg (Tanzania-TechnoServe)	Ex-factory: USD 230-330/kg	Extraction efficiency and GMP certification to be improved
Export Artemisinin	Price might level at USD 250 /kg artemisinin (Abbot laboratories) or as high as USD 1000 China: USD 420/kg (2002) Tanzania: USD 600/kg GSK (up-to 1100 USD/kg) and up to 1300 from China and Vietnam (artemisinin)	Export prices up to USD 1000/kg in 2004 Average: USD 600/kg (TechnoServe)	Transport Trading costs Export levies etc.	Export price: USD 250-1000/kg; average USD 600	In TechnoServe study use USD 600/kg
Processing: derivates	Conversion rates (TechnoServe, p. 22) Artesunate = 75 % artemisinin Dihidroartemisin (DHA): USD 550/kg Artesunate: USD 400-500/kg Artemether: USD 630/kg Artemether/Arteether: USD 900-1100/kg(2002)		Derivation costs from artemisinin to DHA (USD 220), from DHA to artesunate or artemether USD 200-300/kg	Artesunate: USD 400-500/kg Artemether: USD 630-1100/kg	

AT manufacturing pharmaceutical companies	1 kg artemisinin can lead to 1250 full treatment courses (adult course=800 mg artemisinin) Adult course=600 mg artesunate Sanofi (12*50 mg artesunate blister or 600 mg)		1250 courses at USD 0.6	Ex-factory: USD 750/kg	
ACT manufacturing pharmaceutical companies	Novartis: Coartem course: USD 2.4/course GSK: USD 1/course	Development costs Registration costs	Lumefantrine costs Manufacturing costs	Ex-factory: USD 1667/kg	
Retail suppliers of ATs	Single artesunate drugs (AT): USD 0.6-1.25/dose 1 artemisinin-based course= USD 4-6	Not subsidized: private retailers	USD 1.0-3.5/course	Consumer price: USD 5000-7500	
Retail suppliers of ACTs	Coartem: Up to USD 10-15 per ACT course. Raimet: 24x20mg pill blister at USD 40.5 (480 mg artemether)	Subsidized, Public system	USD 3.0-5.0/course	Consumer price: USD 12,500-18,750	Ambition is to produce ACT course at USD 1
ACT subsidies	USD 1-2/course	USD 200-800 million/year: WHO + Global Fund			
Total requirement	200 m ACT courses at 1250 courses per kg of artemisinin at 25 kg/ha 500 m ACT courses	4800-9600 ha required			

APPENDIX 6 CROP BUDGETS

Source: Adapted from TechnoServe, 2004 and verified by FAIDA MaLi

6A Large-scale and small-scale *A. annua* production (in USD)

Description	**Small-scale production**		**Large-scale production**	
Yield in kg/ha	2 000	0.8%	2 500	1.0%
Producer price per kg at farm gate	0.47		0.55	
Gross revenue per ha	**940**		**1 375**	
Production costs	**Cash inputs**	**Family labour**	**Cash inputs**	**Hired labour**
Nursery costs		30		
Seed/seedlings	10		180	
Land preparation	35	40	75	
Transplanting		30		30
Infilling		5		5
Irrigation		20	40	40
Fertilizer application		20		25
100 kg DAP and urea	20		35	
Weeding		40		40
Plant protection	8	2	10	
Plant cutting		35	10	30
Drying				
Threshing	0	15	20	
Cleaning				
Storage/bagging	5	5	5	5
Transport	13		20	
Bags	7			
Total labour days		**242**	**395**	**175**
Total cash inputs	**98**		**570**	
Gross margin	**842**		**805**	
Return to labour		**3.48**		**4.60**

6B Small-scale *Artemisia annua* production versus small-scale maize production (in USD)

Description	**Small-scale production**		**Maize production**	
Yield in kg/ha	2 000	0.8%	3 750	
Producer price per kg at farm gate	0.47		0.20	
Gross revenue per ha	**940**		**767**	
Production costs	**Cash inputs**	**Family labour**	**Cash inputs**	**Family labour**
Nursery costs		30		
Seed/seedlings	10		34	
Land preparation	35	40	27	
Transplanting/seeding		30		17.5
Infilling		5		
Irrigation		20		
Fertilizer application		20		5
Fertilizer	20		111	
Weeding		40		22
Plant protection	8	2	15	2.5
Plant cutting		35		17.5
Drying				
Threshing	0	15		37.5
Cleaning				
Storage/bagging	5	5	44	
Transport	13		57	
Bags	7		13	
Total labour days		**242**		**102**
Total cash inputs	**98**		**289**	
Gross margin	**842**		**479**	
Return to labour		**3.48**		**4.69**

6C Small-scale *Artemisia annua* production versus small-scale bean production (in USD)

Description	**Small-scale production**		**Bean production**	
Yield in kg/ha	2 000	0.8%	937.5	
Producer price per kg at farm gate	0.47		0.48	
Gross revenue per ha	**940**		**455**	
Production costs	**Cash inputs**	**Family labour**	**Cash inputs**	**Family labour**
Nursery costs		30		
Seed/seedlings	10		55	
Land preparation	35	40	24	
Transplanting/seeding		30		14
Infilling		5		
Irrigation		20		
Fertilizer application		20		5
Fertilizer	20		34	
Weeding		40		14
Plant protection	8	2	7	2
Plant cutting		35		6
Drying				
Threshing	0	15		4
Cleaning				
Storage/bagging	5	5		
Transport	13		14	
Bags	7		13	
Total labour days		**242**		**45**
Total cash inputs	**98**		**132**	
Gross margin	**842**		**322**	
Return to labour		**3.48**		**7.16**

6D Small-scale *Artemisia annua* production versus small-scale coffee production (in USD)

Description	**Small-scale production**		**Coffee production**	
Yield in kg/ha	2 000	0.8%	385	
Producer price per kg at farm gate	0.47		0.36	
Gross revenue per ha	**940**		**140**	
Production costs	**Cash inputs**	**Family labour**	**Cash inputs**	**Family labour**
Nursery costs		30		
Seed/seedlings	10		23	
Land preparation	35	40	27	42
Transplanting/seeding		30		8
Infilling		5		1
Irrigation		20		
Fertilizer application		20		2
Fertilizer	20		40	
Weeding		40		21
Plant protection	8	2	68	9
Plant cutting		35	10	128
Drying				
Threshing	0	15		
Cleaning				
Storage/bagging	5	5	6	
Transport	13			
Bags	7			
Total labour days		**242**		**211**
Total cash inputs	**98**		**175**	
Gross margin	**842**		**-35**	
Return to labour		**3.48**		**-0.16**