

## **Artemisia, Agriculture and Malaria in Africa: The Interplay of Tradition, Science and Public Policy**

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*As to diseases, make a habit of two things –  
to help, or at least to do no harm.*

- Hippocrates, 460-377 BC

### **Abstract**

The key ingredient in the leading treatment for malaria in Africa - artemisinin - comes not from high-tech research, but from an ancient medicinal plant, *Artemisia annua*. Drugs developed to replace quinine have lost effectiveness with the development of resistance. This has led to attempts to increase cultivated production of *Artemisia* in the short run and to develop, through biological and chemical research, synthetic substitutes in the longer run. The resulting juxtaposition of activities and players provides both opportunities and challenges for society. While individual components have been examined, there is little in the way of comprehensive analysis. This paper attempts to weave the many complex and dynamic components - historical, scientific, technical, economic - together in order to aid understanding of the issues and facilitate development of informed public/private policies and actions. Although focused on Africa, the main components and issues are global in nature and resolution and relate to more general issues in infectious disease control and economic development.

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## Preface

This paper is an outgrowth of a project supported by the U. S. Agency for International Development, within the context of the Roll Back Malaria Initiative, to provide technical support to farmers, particularly small farmers, in East Africa in the production of *Artemisia annua* for use in the manufacture of artemisinin-based combination drug therapies (ACTs). In the course of participation on the evaluation of the proposal in 2004, as the agricultural member of the Artemisia Team, I developed a broader interest in the topic.

This led to extensive correspondence with specialists in the field and an extended review of literature, a process which continues. Along the way, I found many highly knowledgeable specialists in various aspects of the subject, but comparatively few individuals with a broader interdisciplinary knowledge of the topic. Moreover, there appears to be considerable asymmetry of knowledge: much more on (i) malaria than artemisinin, (ii) artemisinin than *Artemisia*, and (iii) biological science than social science. Comprehensive policy analyses are rare (the most notable being NA 2004).

The paper represents an attempt to bridge and help balance these varied dimensions. It builds on my early training in plant science and agricultural economics, a taste for history, some experience with agricultural processing and marketing, long experience in international agricultural research and development, and more recent involvement with some aspects of science policy. Hence my approach and emphases may differ from those taken by malaria specialists, though I have drawn liberally from their work and advice throughout the paper.

While my focus is on issues that are ultimately of a broad policy nature, the path taken may illuminate other topics and be of some value to those with more specialized and local interests. In order to make the paper as broadly useful as possible, I have tried to focus the main text - which is fairly compressed - on more general topics and issues and have provided additional details and linkages in numerous footnotes (78). There is also an extended list of references (291). Readers can readily pick and choose.

The paper is, as ultimately any study of such a complex and dynamic subject must be, a work in progress. It is subject to further additions, modifications and corrections. Revised versions will be posted from time to time. Given the evolving state of the paper, it should not be quoted without consultation. A somewhat similar study has recently been issued by the Royal Tropical Institute in the Netherlands (Heemskerk, et al. 2006) and may also be of interest.

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## I. Introduction: the Burden of Malaria in Africa

Malaria is thought by some to be the oldest of human diseases (Bray 1996, p. xiii). It has long had serious effects on morbidity and mortality. It is of particular importance in the developing nations, especially in Africa where perhaps 80% of the one million global deaths reported annually occur.<sup>2</sup> Africans are particularly likely to be bitten by infectious mosquitoes, largely because one species (*Anopheles gambiae*) feeds preferentially on humans (NA 2004, p. 198; Greenwood and Mutabingwa 2002, p. 670). Children under the age of five and pregnant women are especially at risk. It is primarily a disease of the poor (Barat, et al. 2004; Worrall, et al. 2005) and increases susceptibility to infection by other diseases such as HIV/AIDS (WHO 2004a; ter Kuile 2004).

In economic terms, the total household cost burden of malaria is high in Africa, especially for the very poor.<sup>3</sup> This constrains economic growth: one study found that African nations with high levels of infestation had economic growth rates that were 1.3% lower than other countries from 1965-1990 (Gallup and Sachs, 2001, pp. 85, 91; Sachs and Malaney, 2002, p. 681). Estimates of the annual cost to Africa vary, but range in the billions of dollars.<sup>4</sup> Lifting the burden imposed by malaria would have significant effects on African economic growth. This task, however, is challenging and previous efforts to eradicate malaria met with mixed outcomes at best.<sup>5</sup>

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<sup>2</sup> The proportion has been widely reported to be 90%, but a recent global study suggests that the African proportion in 2002 was about 70% (Snow, et al. 2005). The 80% figure was recently cited by a WHO official (Brown 2006). A special section on malaria in Africa appeared in *Nature*, August 19, 2004, pp. 921-945

<sup>3</sup> Total costs (direct and indirect) of malaria have been estimated to range between 5 and 18% of household income in four African nations (Russell 2003, p. 23) and as high as 32% for the very poor in Malawi (Ettling, et al. 1994; also see Chima, et al. 2003, pp. 18-23). Problems and issues in measuring the economic burden in Africa are reviewed by Ettling and Shepard (1991), Lennox (1991), Shepard, et al. (1991), Aseso-Okyere and Dzator (1997), Onwujekwe, et al. (2000), Goodman, et al. (2000) and Worrall, et al. (2005). The nature of the public health burden is analyzed by Snow, et al. (2003), Malaney, et al. (2004), and Breman, et al. 2006).

<sup>4</sup> It is commonly reported (e.g. Anonymous 2005c, Specter 2005, pp. 59-60) that malaria costs sub-Saharan Africa \$12 billion per year. While the derivation of this figure is obscure (it is only known that it circulated around WHO headquarters some years ago and was perhaps first cited by Samba in 2001), a comparable figure of about \$4.9 billion per year, 41% of the above figure, can readily be derived from aggregate estimates over the 1980-1995 period for 31 African nations reported by Sachs and Malaney (2002, p. 683, Table 1). Mills and Shillcutt, drawing on other data, calculated that the annual net benefit of eliminating half of the malaria in Africa between 2002 and 2015 would be between \$10-37 billion. By comparison, Sinton (1935) estimated that the direct costs of malaria in India totaled about £80 million annually (cited in Bray 1996, p. 101).

<sup>5</sup> A League of Nations report (Malaria Commission 1927, p. 9) observed that “The history of special ‘antimalarial campaigns’ is chiefly a record of exaggerated expectations followed sooner or later by disappointment and abandonment of the work.” Subsequent DDT-based eradication efforts, which excluded Africa “because of the perceived magnitude of the region’s malaria problem and the lack of technological capability” (NA 1991, p. 43; also Litsios 1996, pp. 106-108), were generally unsuccessful (Barlow 1967 & 1968; Cohen 1973; Brown, et al. 1976; Harrison 1978; Desowitz 1991; NA 1991, pp. 198-203; Packard 1997 & 1998; and Spielman and D’Antonio 2001). Subsequent experience with DDT in southern Africa is assessed by Mabaso, et al. (2004) and health risks and benefits were reviewed by Rogan and Chen (2005).

Malaria is caused by a unicellular parasitic microbe known as a protozoan, which is neither a virus nor bacteria. The main current control measures are (1) prevention of spread through mosquito control,<sup>6</sup> (2) the use of bednets, and (3) drug treatment. Vaccines offer promise for the future (Arnot 2005). Traditional single drug treatments (monotherapies), such as chloroquine, have lost appreciable effectiveness due to the development of drug resistance (e.g., White 2004, and Talisuna, et al. 2004) and a search has been on for replacements. The heir designate, by a wide margin, is a combination therapy involving two drugs, one of which is artemisinin, an extract from one species of the *Artemisia* plant (*Artemisia annua*) and is effective against the most virulent form of malaria, *falciparum*. It is termed an artemisinin-based combination therapy (ACT). Combinations based on other drugs are also possible (Meshnick and Alker, 2005; Zongo, et al., 2005).

While there is a great deal of information available on malaria, its treatment, and lately on ACTs,<sup>7</sup> considerably less has been written about the supply of *Artemisia* and artemisinin. This paper provides an overview of these issues and the principal historical, scientific, technical, economic, and policy dimensions. It also reveals something of the interactions between traditional medicine, modern medicine, and science – a prospective “golden triangle” (Mashelkar 2003, 2005, p. 1417).

## II. The Approach: Artemisinin-Based Combination Therapies

Effective malaria control involves efforts on a variety of fronts. Drugs, especially plant-based quinine, have played a key role for centuries. Here we focus on *Artemisia*, which is at once both ancient in its use and modern in its derivation and formulation.

### 1. *Artemisia*, Artemisinin, and ACTs

*Artemisia* is a well-known medicinal plant that has been utilized for a number of purposes, including malaria, for centuries.<sup>8</sup> A component and extract, artemisinin - which is the source of further derivatives which are more suitable for pharmaceutical use - has a very rapid onset

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<sup>6</sup> As long known, agricultural practices - particularly water management - can play a role on mosquito control (Litsios 1996, pp. 133-142; Keiser, et al. 2005). This led the Consultative Group on International Agricultural Research to establish a Systemwide Initiative on Malaria and Agriculture in 2001 (van der Hoeck 2004) [[www.cgiar.org/sima/index.asp](http://www.cgiar.org/sima/index.asp)]. A study in Ethiopia has shown a correlation between the expansion of maize production and malaria in one area (McCann, 2005, pp. 174-196; Kebede, et al. 2005).

<sup>7</sup> Particularly comprehensive reviews were provided in two special supplements to *The American Journal of Tropical Medicine and Hygiene*: “The Intolerable Burden of Malaria: A New Look at the Numbers,” January/February 2001 (vol. 64, nos. 1, 2) 106 pp. and “The Intolerable Burden of Malaria II: What’s New, What’s Needed,” August 2004 (vol. 71, no. 2), 282 pp.

<sup>8</sup> Further details are provided in Section II/2 and in Willcox, et al. 2004. Artemisinin is, of course, not the only plant extract to be used to treat malaria. Quinine, derived from the bark of the cinchona tree, has long played a major role (see Duran-Reynals 1946, Dobson 1998, Honigsbaum 2001, Rocco 2004, and Hobhouse 2005 for details). Quinine bark is also a source of quinic acid, an alternative to shikimic acid (derived from the fruit of the star anise tree which grows in southern China), which is the usual starting point in the manufacture of Tamiflu, used for avian flu (Goodman 2005, Pollack 2005a, Wright 2005).

of action against the malaria parasite.<sup>9</sup> Other drugs have a more persistent effect in preventing the recurrence (recrudescence) of malaria. Thus, the inclusion of a second drug in ACTs “confers even greater protection against the development of drug-resistant mutants” (NA 2004, pp. x, 4-5; also see Martin, et al. 2003). The combination, in mathematical terms, can be quite potent,<sup>10</sup> though it can be constrained by biological factors. Artemisinin also has another important characteristic: it can reduce retransmission of the disease from humans to mosquitoes in areas of low transmission (which, unfortunately are not frequent in Africa).<sup>11</sup>

The potential of ACTs was perhaps first explored by Chawira, et al. in 1987 (also see White 1999, p. 746). ACTs have subsequently been widely tested in the developing world and have proven their worth (IASG 2004).<sup>12</sup> According to an Institutes of Medicine (U.S.) study, “The artemisinins are the *only* first-line anti-malarial drugs appropriate for widespread use that still work against all chloroquine-resistant malaria parasites” (NA 2004, p. 2).<sup>13</sup> A technical consultation in April 2001 called by The World Health Organization “strongly endors[ed] the potential of combination therapy for use in Africa” (WHO 2001, p. 23) and WHO recommended the use of ACTs in April 2002 (WHO 2002).

The demand for ACTs has increased sharply since 2002 and is expected to continue to grow. In 2005, WHO (2005a, 2005b) indicated that demand increased from 2 million treatment courses in 2003 to 30 million in 2004, an estimated 70 million in 2005, and a projected 130 million in 2006.<sup>14</sup> This expansion has in turn led to a corresponding increase in demand for

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<sup>9</sup> The primary derivative, which is not chemically the same, is dihydroartemisinin. Three others are drawn from it: artesunate, artemether, and arteether (the latter two are very similar) (NA 2004, pp. 253, 261-267; also see Jansen 2002, pp. 4-10, 15). Artemisone is the most recent derivative (Haynes, et al. 2006).

<sup>10</sup> As Yeung, et al. (2004, p. 181) postulate: “if the probability of a parasite being resistant to drug A is one in  $10^9$  and to drug B is one in  $10^9$  then the probability that a parasite will be simultaneously resistant to both is one in  $10^{18}$ , representing a billion-fold reduction in probability.” Also see: Hastings, et al. (2002, pp. 517-518); White and Pongtavornpinyo (2003, p. 552); Bell and Winstanley (2004, p. 33); and Hastings and Watkins (2005).

<sup>11</sup> It does this by acting “against the gametocyte (sexual) stage of the malarial parasite as well as the asexual forms responsible for malaria symptoms” (NA 2004, p. 23). Also see: Dunaven (2005, p. 82); Duffey and Sibley (2005, p. 1909); and Mutabingwa (2005, p. 306).

<sup>12</sup> There are several types of combination therapies, most of which are artemisinin-based. These may be used in combination with other drugs such as chloroquine, amodiaquine, mefloquine and lumefantrine (WHO 2001, pp. 9-18). Examples of trials of initial combinations with other drugs are provided in: NA (2004, pp. 264-265); IASG (2004); and Kremsner and Krishna (2004). More recent trials in Africa are cited in Section II/3.

<sup>13</sup> There are four malaria species that cause human disease; the most lethal and prevalent form in the tropics and subtropics is *Plasmodium falciparum* (NA 2004, pp. 136-137). In certain cases of severe malaria, intramuscular injections of artesunate or artemether may be the appropriate course of action (SEAQUAMAT 2005; Jansen 2002, pp. 8, 11). The question of naturally acquired immunity is taken up by Hviid (2005).

<sup>14</sup> The Institute of Medicine study (NA 2004, p. 6), in making cost estimates, assumed “that ACTs will be used to treat up to half a billion episodes per year, which roughly equals the number currently treated by chloroquine or SP.” “Demand” in the WHO context refers that expressed by the public sector; in this case it exceeds effective (funded) demand. The difference is met by subsidies (to be discussed in Sections II/3 and IV/2).

artemisinin (the price in China nearly quadrupled in the fall of 2004; McNeil 2005) and the need to substantially and quickly increase the supply of Artemisia.<sup>15</sup>

Most of the production of Artemisia, and in turn artemisinin, has come from Southeast Asia, principally China (which is viewed by some as having monopoly status) and to some extent in Vietnam. In China, Artemisia has long been grown in the wild but an increasing proportion is cultivated (French 2005). Production of artemisinin is heavily concentrated in a few firms. Drugs derived from artemisinin, principally monotherapies, have been widely used in Southeast Asia and were introduced in Africa in the mid 1990s.

While these Asian nations are the principal sources of the artemisinin used in the manufacture of the ACTs presently used in Africa, changes are underway. The high prevalence of malaria in Africa has led, not for the first time,<sup>16</sup> to interest in increasing the very limited level of production of Artemisia and artemisinin. Significant progress has been made, and unlike Asia, for which virtually no data are available, some important statistics are available.

## 2. Artemisia: The Plant and Production in Africa

Artemisinin is derived from the leaves and flowers of *Artemisia annua* L., also termed *A. annua* or, as here, Artemisia (see [Figure 1](#)).<sup>17</sup> Artemisia has long been used for medicinal purposes in China and was recommended for chills and fevers (symptoms of malaria) in 340 AD. The active ingredient, artemisinin, was first isolated by Chinese scientists in 1972 and named qinghaosu, as part of an antimalarial drug discovery program established in response to a request from North Vietnam during the Vietnam War (Klayman 1985, p. 1049; Anonymous 1992; Hein and White 1993; Jansen and Yin 2002, pp. 25-28; NA 2004, p. 133; further details are provided in QUACRC 1979, Jiang, et al. 1982, and Li, et al. 1982).

Botanically, the plant is a vigorous weedy annual which is single-stemmed and ranges in height from one to two meters. It grows easily in temperate areas and tropical areas at higher altitudes. It is well suited to both small-scale and plantation culture. The seed is extremely

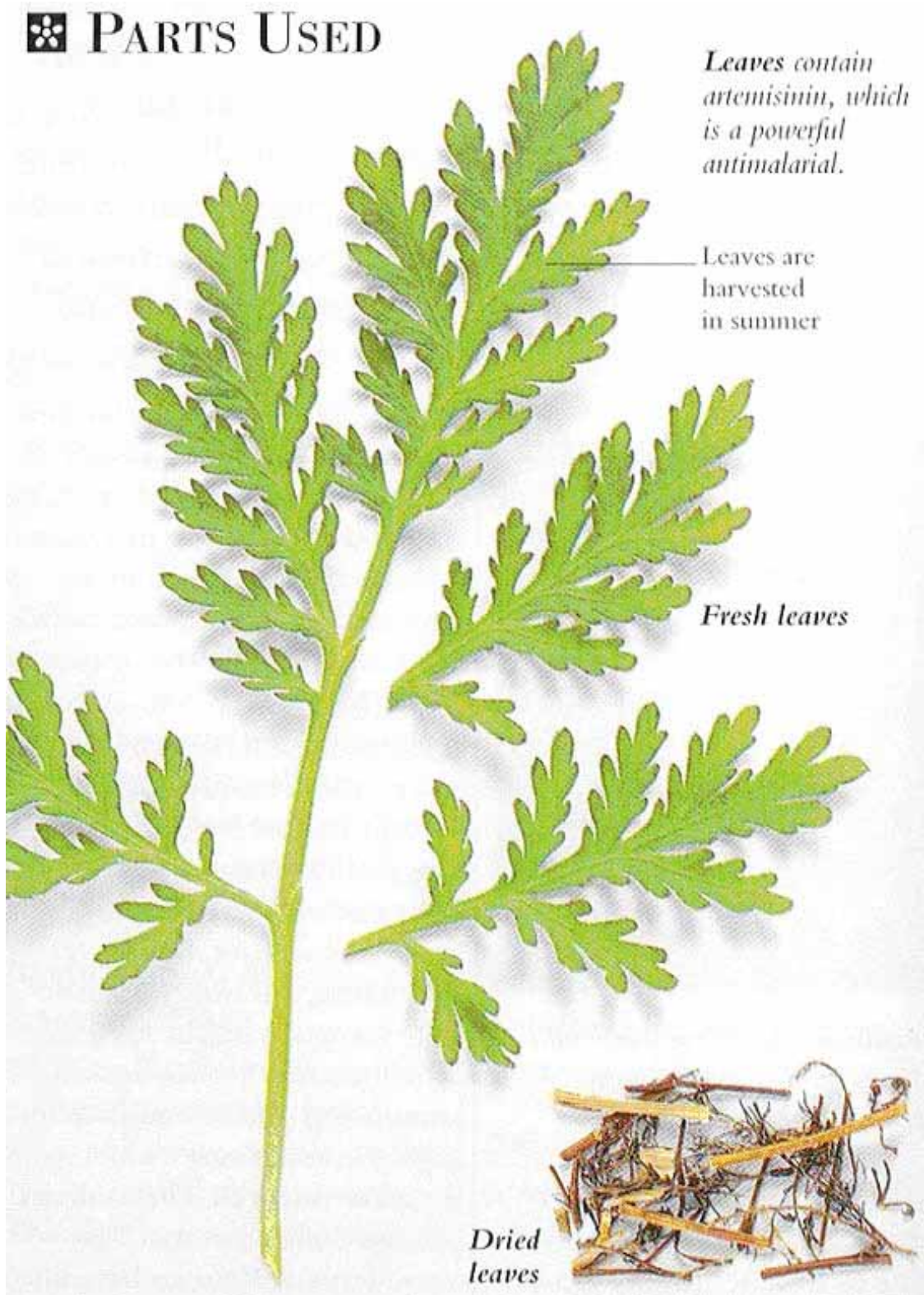
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<sup>15</sup> This problem was quite thoroughly covered in the press (e.g., Anonymous 2004b, Bond 2004, England 2004, McNeil 2004a, 2004c, 2005a, Jack 2005a) and in scientific journals (e.g., Anonymous 2004a, Buck 2004, Cyranoske 2004, Senior 2005). A particularly good analysis was provided by Erserink (2005). The shortage was anticipated in 2001, when a WHO Technical Consultation noted that “Because artemisinin compounds are derived from plant extracts and at least a two-year lead time is needed to cultivate the plants, the supply of raw materials may become a substantial problem and may slow the deployment of ACT” (WHO 2001, p. 13).

<sup>16</sup> In 1998, discussions were initiated between African Artemisia Ltd. (AAL) and the U.K. Department of International Development (DFID) which led to a review of the “current situation regarding the use of Artemisia based antimalarial treatment and to investigate the viability of local production of these drugs in East Africa at a price which is affordable by the local community” (USAID file copy of report, title page missing, 1999, p. 2). A proposal for support of an initial investment in the cultivation and extraction of artemisinin in East Africa was made to a leading foundation but was not funded (pers. comm. from Brian Greenwood, LSHTM, May 2005). AAL continued to seek investment for a processing facility (TechnoServe 2004, pp. 22-23).

<sup>17</sup> Numerous other species of Artemisia exist, but they do not have the anti-malarial qualities of *Artemisia annua*.

Figure 1



Source: Chevallier (1996)

small and is usually grown to the seedling stage and transplanted. The best quality seed, in terms of production of leaves and yield of artemisinin, is provided by certain forms of purchased seed, which are generally limited in supply (see Annex 1). Relatively few inputs are needed, aside from some fertilization, because the plants at present do not seem to have any particular insect or disease problems (this could change). Normally, some water is required at the start of the season and dry weather is needed at the harvest and for drying. Artemisinin levels of the plants tend to vary by variety, but the influences of area and growing conditions are not yet clear (see Ferreira, et al. 2005 for a full account).

Commercial production of *Artemisia* in Africa has largely been limited to Kenya, Tanzania, and Uganda and has essentially been tied to the activities of one holding company, Advanced Bio-Extracts Ltd (ABE), and two principal subsidiaries: East African Botanicals (EAB), Ltd. in Kenya and African Artemisia Ltd. (AA) in Tanzania. *Artemisia* is principally planted early in the calendar year and needs five to six months (estimates vary) to mature. Contract production is utilized and the firm supplies seed that has proven well adapted to the region; this process also provides a relatively uniform level of artemisinin. Following harvest, leaves are dried at the farm level. Extraction of artemisinin, however, is a more complex matter and requires a fairly sophisticated facility, as discussed below.

The increased demand for artemisinin stimulated efforts to increase the production of *Artemisia* in East Africa. ABE, already active in this area, having access to sufficient quantities of improved seed (Annex 1), and in concert with some other steps (Sections II/3 and III/2), was in a position to do so. The area under various production arrangements (leased or joint venture efforts) in Kenya, Uganda, and Tanzania (north) expanded to approximately 1,650 ha. (4,100 acres) in 2005.<sup>18</sup> Most of the planting for the calendar year (58.4%) was carried out in the second quarter, followed by lesser amounts in the third (23.8%) and fourth quarters (17.7%). The planted area was principally in Kenya (nearly 65%), followed by Uganda (19%) and Tanzania (north, over 19%) (TechnoServe 2005). Both small and large farms were involved.<sup>19</sup> Concurrently, production was also being expanded to a much more limited, and in some cases more preliminary extent, in new areas such as the Chinyanja Triangle (Mozambique, Malawi, and Zambia), Senegal, Ghana, Rwanda, South Africa, and Madagascar.<sup>20</sup>

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<sup>18</sup> Derived from table in TechnoServe (2005b). The data cover the last three quarters of 2005. In addition, approximately 300 ha. (740 acres) were planted in southern Tanzania in the first quarter of 2006 (pers. comm. from Mick Baddeley, TechnoServe, March 2006).

<sup>19</sup> Slightly more than half of the overall area was on 1,526 small farms and slightly less on 69 large farms (52.2% vs. 48.8%). The average area planted on small farms was 0.54 ha. (1.34 acres) and 11.48 ha. (28.37 acres) on large farms, with some variation by country (farm size was smaller in both categories in northern Tanzania). "Potential" yield levels were 1.5 tons/ha on small farms, 2 tons/ha on large farms, and over 3 tons/ha on large farms (ABE 2006). In general, due to cost considerations, small farms used F<sub>2</sub> seed and larger farms F<sub>1</sub>; F<sub>1</sub> seeds would normally be expected to produce higher yields (see Annex 1b) but this could be partially offset by denser planting of less expensive F<sub>2</sub> seed (pers. comm. from Barney Gasston, ABE, April 2006).

<sup>20</sup> Pers. comm. from: Patrick Matakala of ICRAF, Maputo, and Jerry Brown of USAID, Gabarone, December, 2004; and James Simon, Rutgers University, October 2005, February 2006. Simon and his team (Annex 1b) are actively involved with several of these countries. Also see Das (2005) and Mueller, et al. (2000).

Naturally, there are many problems - as there would be with most crops - in trying to introduce cultivation of a plant to areas where it is not widely grown or known. These are compounded in the case of *Artemisia*, which until recently, had not been cultivated but was essentially a wild crop. Appropriate varieties have to be identified, farmers attracted to production and there must be a steady market for the product. The marketing of *Artemisia* leaves is further complicated by the need to link it with the extraction process. In the case of East Africa, the principal challenges have been weed control, harvesting and drying at a time when drenching rains are possible, transportation of a bulky crop, and determining an appropriate pricing system (straight weight or as modified by artemisinin level ) (pers. comm. from Barney Gasston, ABE, April 2006).

### 3. Artemisinin: Extraction and Use in ACTs

While the major world activity in these areas has been in Asia, particularly China, and with a few international pharmaceutical firms, Africa is becoming a significant producer of *Artemisia* and as we will see, now has a significant extraction facility (though production of pharmaceuticals will largely be carried out elsewhere).<sup>21</sup>

**a. Extraction of Artemisinin.** The construction of adequate extraction facilities is an expensive and challenging task, and may be particularly challenging in Africa. Aside from their technical complexity and cost,<sup>22</sup> they need to be constructed in sequence with the expansion of production of *Artemisia*. And arrangements must be complete for the sale of the raw artemisinin to pharmaceutical firms for manufacture of the actual ACTs.

ABE, along with its expansion of *Artemisia* production, has been in the midst of this. The process has involved two phases: (i) processing of crude extract, and (ii) final purification. Initially, the firm converted a former pyrethrum factory in Kabale, Uganda for the production of crude extract (200 tones of leaf) and also arranged for a similar step to be carried out in India (300 tons of leaf); in both cases, final purification was carried out in the U. K.

Secondly, ABE started construction of a new facility in the export processing zone in Athi River, Kenya - to be registered as Botanical Extracts Ltd. - which will be able to carry out both crude extraction and purification. It will have the capacity to process 4,000 tons of leaf and further refine the crude extract from Uganda. It is expected to be in operation by mid-

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<sup>21</sup> As of mid-2006, WHO had identified 40 manufacturers, of widely varying size, of artemisinin monotherapies: 11 in India, 10 in Europe, 6 in Vietnam, 6 in Africa, 5 in China, and 1 each in Malaysia and Cyprus (data provided by Edward Vela, Global Malaria Programs, WHO, June 2006). Much of the Indian production is thought to be based on *Artemisia* from China, but no data exist.

<sup>22</sup> A 1999 study (DFID) concluded that: "The technology for the extraction and processing of artemisinin derivatives is known but complex" (p. 2). "Although the process is complicated, it is similar to other processing techniques used for the extraction of quinine, de-cafeinated tea and pyrethrum. This would not be a problem for a large pharmaceutical company but for a small company the investment needed in equipment is high..." (p. 5). The potential for extraction is examined in TechnoServe 2004, pp. 92-132), with particular attention to three solvent extraction technologies; the initial capital cost was placed at \$6-12 million (pp. 4, 101).

2006 and produce 15 tons of pure artemisinin in 2006 (with an annual capacity of 20 tons).<sup>23</sup> In June 2005, Novartis announced its intention to provide financial support (Anonymous 2005b and Thayer 2005); a bridging loan of \$14 million was made, largely for expanding processing capacity. Novartis will purchase a significant portion of production (pers. comm. from Lisa Amenya and Barney Gasston of ABE, February to April 2006, and ABE 2006.)

**b. ACT Drugs.** Only three artemisinin-based combination drugs have been qualified by WHO and UNICEF as meeting international standards.<sup>24</sup> Coartem®, produced by Novartis, is the best known.<sup>25</sup> It represents a fixed dose combination of artemether (see fn. 8) and lumefantrine (NA 2004, pp. 264-267). Within Africa, it was first adopted in KwaZulu-Natal province in South Africa in 2000 (Barnes, et al. 2005), the Zanzibar region in Tanzania in 2002 (Sisowath, et al. 2004, p. 1014), and in Zambia in late 2002 (Zurovac, et al. 2005, p. 734).<sup>26</sup>

Initially, in November 2004, WHO announced a shortfall in supply of Coartem due to “a continued lack of raw materials,” first artemisinin and then arteether, from its Chinese suppliers (WHO 2004b, Cyranoski 2004, McNeil 2004b). This problem appears to have subsequently eased (Anonymous 2005c), in part because of increases in production in China (Section 5) and Africa.

ACTs are, however, expensive by most developing country standards. WHO reached an agreement with Novartis to make Coartem available at cost to ministries of health in developing nations. The negotiated price is \$2.40 per adult course of treatment (four tablets twice a day for three days), which makes it roughly comparable with oral quinine and nearly 20 times as expensive as chloroquine.<sup>27</sup> New ACT combinations are under development (Section III/1); two are expected to be released in late 2006 and be lower in cost (Das 2005,

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<sup>23</sup> The latter figure would represent about 17.5% of the artemisinin estimated to be needed (114 tons) for 120 million adult courses of treatment needed globally (Haynes, et al., 2006, pp. 2086-2087).

<sup>24</sup> This process is known as prequalification and is described in WHO 2005f. The other two drugs are Artekin (dihydroartemisinin-piperaquine) and Duo-cotexin (dihydroartemisinin-piperaquine phosphate), produced by Chongqing Holley Holdings in China (Ferreira, et al. 2005, p. 224).

<sup>25</sup> Coartem is presently only available in an adult formulation. It can be used in reduced dosage for children under appropriate supervision. A pediatric Coartem, which would be safer for general use, is in advanced clinical development (phases II-III) as part of the Medicines for Malaria Venture (Lucas, et al. 2005, p. 17). Pediatric formulations generally may take the form of pills, powders, or syrups.

<sup>26</sup> For recent studies demonstrating the effectiveness of this combination in Africa, see T.K. Mutibingwa, et al. (2005); Piola, et al. (2005); Ramharter, et al. (2005); Barnes, et al. (2005, also Naik 2005). In the case of South Africa, it was combined with a vector control program involving DDT sprays in traditional structures.

<sup>27</sup> The actual price for Coartem to patients may be higher, depending on whether it is distributed through public or private channels, e.g. drug stores. In what is presumably the latter case, a price of \$8 has recently been cited in Kenya (Kimani 2006).

DNDi 2005a & b, McNeil 2005b, Davidson 2006).<sup>28</sup> Others are under study (Mutabingwa 2005, pp. 312-313).

An international group of scientists, primarily at the Hong Kong University of Science and Technology and supported by Bayer and the Medicines for Malaria Venture, has recently developed a more active derivative of artemisinin: artemisone. It has greatly enhanced bioavailability which means that lower dosages will be necessary, thus reducing cost, and has other desirable properties (Haynes, et al. 2006; Mutabingwa 2005, p. 313). But considerable further testing and development are needed.

The cost of ACTs is obviously a major concern in Africa - though may be less so elsewhere (see Ruebush, et al., pp. 337, 340) - and was discussed in some detail in the Institutes of Medicine study (NA 2004, pp. 61-78). It stated that “The real price breakthrough will likely occur only when a fully synthetic artemisinin is developed, eliminating the growing and extraction process” (p. 64). The study went on to explore a global subsidy system (pp. 79-111). At present, the ability of developing countries to purchase ACTs is underwritten by the Global Fund to Fight AIDS, TB and Malaria.<sup>29</sup> They are then normally distributed through public channels. Costs, however, are only one side of the story and need to be balanced with benefits: this is a more complex analytical process.<sup>30</sup>

#### 4. Development of Resistance.

While ACTs are much less likely to develop resistance than monotherapies, they are not immune to this threat.<sup>31</sup> Resistance to one ACT was noted in an area of Thailand in 2003,

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<sup>28</sup> The drugs were developed under the aegis of the Drugs for Neglected Diseases initiative (DNDi) and represent combinations of artesunate with (i) amodiaquine, produced by Sanofi-Adventis of France and (ii) mefloquine, produced by Far-Manguinhos of Brazil. Both will be provided in three-day packs. The goal is to get the cost down to less than \$1 a dose, but this is at least partly dependent on the cost of Artemisia. A field trial of (i) is reported in Sowunmi, et al. 2005. Both have encountered drug resistance and one malaria specialist suggests that they may not have a long life (Mutabingwa 2005, p. 312; also see Mutabingwa, et al. 2005).

<sup>29</sup> The Global Fund has, through its first four rounds of funding, approved grants totaling \$3.7 billion, of which 31% or nearly \$1.5 billion is for malaria. The specific allocation for ACTs is not readily evident, but one recent news account placed it at \$230 million from 2002 to 2004 (Brown 2006) and is increasing. One expected outcome of the approved grants after five years is the delivery of 145 million ACT treatments. Leading contributors, as of August 2005, were Europe (58%) and the United States (25%) (Global Fund 2005a & b; also see Mueller, et al. 2005, pp. 10-11, 17). When Global Fund data are combined with other donor contributions for 1999-2004, it appears that less than 2% of all contributions for malaria have been earmarked for research and development (Waddington, et al. 2005, pp. 4, 9, 13).

<sup>30</sup> The general issues in an African context are reviewed by Goodman, Coleman and Mills (1999) and Mills and Shillcutt (2004, pp. 72-87). An *ex ante* cost-benefit analysis of ACTs for Africa is provided by Coleman, et al. (2004). Country-level studies of ACTs have been conducted in South Africa (Mukehi, et al. 2004) and Senegal (Agnamey, et al. 2005).

<sup>31</sup> One possible explanation is that its half life is short (less than one hour for artesunate) “which protects them from resistance” (NA 2004, p. 263). Quinine also has a short half life, although not as short as for artemisinin, and “this may be the main reason why this drug has ‘lasted’ so long, despite misuse” (pers. comm. from William Watkins, March 2005). Hastings and Watkins have examined the matter of malarial drug elimination half life (2002, 2006). Resistance can develop in other less easily controlled ways (e.g., Shetty 2005).

though it was not determined whether it was due to the artemisinin derivative, the partner drug, or the combination (Vijaykadga, et al. 2006). Resistance is most likely to occur in highly endemic areas where monotherapies, including teas made by boiling *Artemisia* leaves (Annex 2), have been used for some time and have not been replaced by ACTs (Yeka, et al 2005; NA 2004, pp. 5, 71-72, 80-81). Reports of incipient resistance to artemisinin derivatives have recently been reported in French Guiana and Senegal (Duffy and Sibley 2005, Jambou, et al. 2005).

The nature of the ACT combination is an important factor. As Panosian (2005, p. 716) puts it: “one ACT does not fit all...partner drugs effective at one site [geographical area] may be ineffective at another.” Bloland, et al. (2000, p. 1380) were perhaps the first to observe that “It is not obvious which drug combination is best for use in Africa.” Similar observations were subsequently made by others.<sup>32</sup> Hence, it is not surprising that reports of parasite resistance to, or tolerance of, *partner* drugs have appeared: to amodiaquine in Uganda (Yeka, et al. 2005) and to lumefantrine, the companion drug of Coartem, in Zanzibar (Tanzania) (Sisowath, et al. 2005, p. 1014).<sup>33</sup> Clearly, identifying and maintaining the appropriate ACT combination, in the face of the development of resistance, will be a continuing challenge.<sup>34</sup>

Concern about resistance arising from the use of monotherapies has recently led WHO to publicly request firms producing monotherapies to cease and desist (Bohannon 2006, Brown 2006, McNeil 2006a, 2006b). Some 28 countries do not authorize the marketing of oral monotherapies or are moving toward withdrawing authorization of these products.<sup>35</sup>

<sup>32</sup> See: Bell and Winstanley (2004), Kremsner and Krishna (2004), Mutabingwa, et al. (2005); Ramharter, et al. (2005), van den Broek, et al. (2005), and Yeka, et al. (2005).

<sup>33</sup> Sisowath, et al. (2005, p. 1014) note that “the weak link in the combination is the period during which the unprotected partner remains alone during its elimination period, particularly at subtherapeutic concentrations,” possibly accelerating “the development of resistance to Artemisinin derivatives.” Similarly, Meshnick and Alker (2005, p. 821) note that this could be a particular problem in sub-Saharan Africa where reinfection rates are high and the subtherapeutic concentrations provide “an ideal scenario for the development of resistance.” Ian Hastings, however, maintains that this is a misconception (pers. comm. December 2005) and he and Watkins (2006, box 1) argue that “drug tolerance is unaffected by intensity of transmission.”

<sup>34</sup> One key element is that partner drugs vary in their elimination half life: lumefantrine (the partner in Coartem) has a comparatively long half life while Lapdap (in Lapdap-artesunate or CDA) has a relatively short half life. Each characteristic has advantages and limitations with respect to the development of resistance: in the latter case, long half-lives accelerate the development of *tolerance* in the parasite, while short half lives may not *eliminate* all the parasites if the drugs are not present for a sufficient period (personal correspondence with William Watkins, October 2005). Tolerance is further discussed in Hastings and Watkins (2006); the problems associated with *mismatches* - when one drug has a considerably longer half life and persists as a monotherapy - are also discussed but the question of what might constitute more optimal matches is not taken up.

<sup>35</sup> As of June 2006, 40 manufacturers had been identified: 17, including the largest, indicated their intention to comply (Europe 5, Asia 12) and 23 had not responded (Europe 5, Asia 11, Africa 6, other 1) (based on data provided by Edward Vela, Global Malaria Program, WHO, June 2006). WHO has no power to directly enforce this request but did persuade the Global Fund to require that countries or groups buying ACTs not procure them from companies also producing monotherapies (McNeil 2006a, 2006b). The private market for malaria treatment in Africa is estimated to be about 15-20 million treatments a year (Jansen as cited by Brown 2006).

Other problems, of less certain proportion, include the marketing of fake or highly diluted artemisinin drugs (e.g. Newton, et al. 2003, 2006; Lon, et al. 2005) and the possible reproductive toxicity of artemisinin derivatives (Meshnick and Alker 2005)

### **III. The International Context: Supply, Demand, and Assistance**

Malaria, while principally an African problem, is a significant global health issue. As such, it should be viewed in a broader context. Developments in one region - be they scientific or economic - influence another. And foreign assistance agencies operate throughout the developing world. The former issue will be reviewed in terms of supply and demand factors relating to Artemisia and artemisinin, and the latter illustrated by the historical sequence of activities undertaken by the U.S. Agency for International Development.

#### **1. Supply and Demand: Artemisia and Artemisinin**

The demand for Artemisia is largely a function of the demand for artemisinin: it is a derived demand. While the current demand for both is very strong, the situation is likely to change in the medium to longer run in response to shifts in the supply of Artemisia and in the demand for artemisinin.

**a. Supply of Artemisia.** The present demand for Artemisia will undoubtedly stimulate increased production a number of countries. China, as noted earlier, is a leader. One recent and partial set of figures, presumably for cultivated area, suggest that 2,000 ha. of Artemisia were grown in 2004, 6,000 ha. were projected in 2005, and 9,000 ha. in 2006.<sup>36</sup> Vietnam is also a substantial producer and is reportedly expanding output (Enserink 2005).<sup>37</sup> India has the potential to do so (Sharma 2006). One estimate suggests that area in East Africa might increase to 4,000 ha. in 2006 (pers. comm. from Barney Gasston and Lisa Ameyna, ABE, February and March 2006). New areas could appear elsewhere.

Two plant-related factors play a role: the quantity of leaves produced per unit of land and the yield of artemisinin extract from those leaves. Variety influences both; climate and soil (nutrition and pH) are also important, though this seems less clear in the case of extract levels. Improved hybrid lines (see Annex 1b) appear to rate well on both counts, but it cannot be said in advance that they provide a particular advantage to one area over another (except perhaps as one area has the seed to take up production or more quickly and widely than another and

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<sup>36</sup> Corresponding biomass volumes were placed at 3,000, 10,000, and 14,000 tons. These figures were reported by a representative of the Chongqing Holley Holdings, the largest producer of Artemisinin in China, in June 2005 and are for Chongqing, Hunan and Sichuan. Production is carried out under contract and Holley supplies the seed. A news report from one contract area indicated that Artemisia had replaced "plots of corn, tobacco and potato" (French 2005). Further expansion of area has been encouraged (Jiajiao 2005). Little is known about overall Chinese statistics (it would be particularly difficult to account for uncultivated or wild production).

<sup>37</sup> This process will be further stimulated by an agreement, formed with support by the Danish International Development Agency (DANIDA), between two Danish firms and a Vietnam-based pharmaceutical company in 2006, to upgrade the latter's facilities, help register the products with WHO, and market the resulting ACTs worldwide with a focus on donor agencies (GHR 2006a, Holm 2006).

has extraction facilities available). Current research efforts to improve varieties with higher yields have just been boosted by a \$13.6 million grant by the Bill & Melinda Gates Foundation (University of York, 2006; see Annex 1b for further detail).

Overall, the potential for expanding the cultivated area of *Artemisia* in Africa and elsewhere is substantial – probably far in excess of needs. Estimates of the area likely to be required at the global level may vary considerably given the many biological and economic variables involved, but are relatively modest compared to other agricultural crops (though not medicinal plants).<sup>38</sup> Moreover, the area needed will be reduced in time as a result of crop improvement efforts.

**b. Demand for Artemisinin.** Several factors, varying in nature, influence the potential level of demand for artemisinin by pharmaceutical producers of ACTs. The primary economic factor for them is the level of effective (funded) demand for ACTs. In the case of Africa we have seen that this is largely conditioned by the level of international assistance available to nations to subsidize their purchase of ACTs in both the short and longer run.

But *Artemisia* is not the only possible source of artemisinin and ACTs are not the only drug-related treatment for malaria. *Artemisia* can also be obtained through chemical and biological synthesis, an approach that could provide cost and other advantages to manufacturers. And the development of vaccines, long sought, could provide an alternative to ACTs. Both are being actively pursued and could, over the medium to longer term, lead to a diminishing demand for plant-derived artemisinin.<sup>39</sup>

Chemical and biological *synthesis* of artemisinin is being pursued on several fronts:<sup>40</sup>

- The Medicines for Malaria Venture [www.mmv.org], established in 1999 as a public-private enterprise, has a number of drug development projects underway, several of which involve artemisinin derivatives (NA 2004, pp. 303-305; Widdus and White 2004, pp. 7-8).<sup>41</sup> The most advanced product, OZ 277/RBX11160 (a synthetic peroxide), is

<sup>38</sup> For example, one recent set of estimates of area needed for a peak level of demand averages about 20,000 ha (nearly 50,000 acres) for a peak level of demand of 500 million treatments per year and about 4,000 ha (10,000 acres) for a “stable” level of 100 million treatments (Heemskerk, et al. 2006, pp. 26-27, 51).

<sup>39</sup> Of \$323.4 million spent of malaria R&D in 2004, \$120.2 million or 35.9% went for drug development and \$78.7 million or 23.5% for vaccines (Malaria R&D Alliance 2005, pp. 16, 29). In October 2005, the Bill & Melinda Gates Foundation allocated an additional \$100 million to accelerate work on promising drugs and \$107.6 million to complete testing for the most advanced malaria vaccine candidate (Gates Foundation 2005). Further details on specific R&D activities are provided by Moran and Guzman (2005) and Thayer (2005).

<sup>40</sup> The chemical synthesis of plant medicinals has a long history, starting with aspirin (Jeffreys 2005). In the case of malaria, the best known were/are, in sequence: abatrane, resochin/chloroquine, sulfadoxine-pyrimethamine, and mefloquine (NA 2004, pp. 130-133). Synthesis has also been undertaken for shikimic acid, the basic ingredient for the manufacture of Tamiflu (Guo and Frost 2004, Pollack 2005, Laurance 2005, Wright 2005, Enserink 2006).

<sup>41</sup> In 2004, MMV received donations of \$26.3 million, of which \$20 million was from the Bill & Melinda Gates Foundation, \$1.8 million from DFID (UK), and \$1.5 million from USAID (MMV 2005, p. 42).

entering phase IIb clinical development in cooperation with Ranbaxy Laboratories in New Delhi. It will be combined with piperazine phosphate (PQP). Targets include a launch in 2009 with a price of less than \$1.00 per treatment (O'Neill 2004, Vennerstrom, et. al 2004; Daviss 2005; Lucas, et al. 2005; MMV 2006).

- The Bill & Melinda Gates Foundation contributed \$42.6 million to a nonprofit drug company, the Institute of OneWorld Health, in late 2004 to develop a new process that uses bacteria to synthesize an equivalent of artemisinin. It is expected to significantly reduce cost but is not expected to “make it to market” for some time (Anonymous 2004d, Daviss 2005). Research results are promising (Ro, et al. 2006)<sup>42</sup>
- Scientists at Johns Hopkins, supported by the National Institutes of Health, have been developing a set of trioxane compounds (dimeric endoperoxides) that mimic the effect of artemisinin and proved to be considerably more effective in laboratory tests (Johns Hopkins 2004; Posner, et al. 2004; Paik, et al. 2006).<sup>43</sup>
- Dafra Pharma (Belgium) and Plant Research International (Netherlands) are attempting the biosynthetic production of artemisinin by combining microbial fermentation and chemistry (PRI 2005).

These approaches may have both therapeutic advantages in terms of effectiveness and/or may be significantly cheaper. But the degree to which this may take place remains to be seen and could be narrowed by (i) increased yields of *Artemisia* and/or percentage of artemisinin, (ii) bio-availability of artemisinin derivatives (Section II/3), or (iii) other approaches.<sup>44</sup>

Research on *vaccines*, long underway, has proven very difficult (NA 2004, pp. 223-229; Arnot 2005). Efforts have been reinforced by the establishment of the Malaria Vaccine Initiative (MVI) [www.malariavaccine.org] by the Bill and Melinda Gates Foundation (Diggs, et al. 2004). Four levels of trials are required (Greenwood 2005b); the first stage results of one in Mozambique proved promising (McNeil 2004b, Vogel 2004). Subsequently, they were termed “a revolution in our time” (Enserink 2004). This led to a critical response by scientists in Kenya and Thailand who were concerned with its likely cost (\$10-20 a shot), partial effectiveness, and a need for further study; they also said that insecticide-treated bed nets and “a new group of drugs based on artemisinin can save lives right away at lower cost.” A representative of the MVI responded that “Its not either this or that – its both” (Enserink 2004; Snow and White 2004). Once developed, licensing of vaccines for use by children can take more than a decade (Moorthy, et al. 2004, p. 154).

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<sup>42</sup> The Institute has in turn partnered with (i) the University of California, Berkeley which - under the leadership of Prof. Jay Keasling - is conducting research to perfect the microbial process and (ii) Amyris, a new biotech company founded on the research in synthetic biology pioneered at UC Berkeley (news release, OneWorld Health [www.oneworldhealth.org], 12/13/04; also see McNeil 2005 and Bower 2005).

<sup>43</sup> These compounds have, in addition, prove promising in the treatment of prostate cancer (Posner, et al. 2004). Also see Chen, Zhou and Fang (2003) and Ferreira, et al. (2005, pp. 208, 225).

<sup>44</sup> One admittedly distant possibility could involve gene synteny. A comparison of the genomes of related parasites may reveal similarities that could provide the basis for development of drugs that could be used for both. A recent comparison of *P. falciparum* and *Theileria parva*, which causes East Coast Fever in livestock in Africa, could be a first step in this direction (Gardner, et al. 2005, TIGR&ILRI 2005); Gardner was the lead investigator in the genetic sequencing of *P. falciparum* (Gardner, et al. 2002).

Time is an important factor. Even when synthetic forms of artemisinin are developed, other key steps remain such as the need to develop the appropriate combination with another drug to provide an ACT, carry out clinical trials, and get the appropriate approvals of national authorities. Even so, it has been speculated that some new ACTs, and perhaps even vaccines, could reach the market in six to eight years.<sup>45</sup> While predictions of this type may well prove to be optimistic, with the range and intensity of current research, the prospects for developing at least partial substitutes for artemisinin are increased and the time horizon shortened.

**c. Implications.** These international and global developments mean that efforts to increase the *supply* of Artemisia at the farm level and of the artemisinin extract at the processing level may reflect only a limited window of *demand* (and profitability) before the pharmaceutical industry turns to other sources of supply and forms of ACT treatment. The latter promise many advantages from their perspective, and may better serve society. Industry's *demand* for artemisinin, however, may be further influenced by a diverse array of other factors such as the build-up of parasite resistance on one hand and the continued availability of funding to subsidize public purchases in developing countries on the other. Given these and other variables, both biological and economic and in and outside of the normal market process, the equating of supply and demand is, and will continue to be, a challenging process.<sup>46</sup>

## 2. Foreign Assistance Efforts: USAID

Malaria has long attracted international attention, and since WW II the involvement of national foreign assistance programs. Initial efforts involved support of international malaria eradication efforts (noted in Section I) and were followed by a variety of multilateral and bilateral activities. These have not been well recorded or reported, but are relevant to the issues at hand. Some such information is available for the U.S. and may be illustrative.<sup>47</sup> The Agency was familiar with the Chinese work with qinghaosu (artemisinin) but did not pursue it at the time (Shuler 1985, pp. 21, 48). A vaccine development program was, however, initiated in 1965 (Ibid, pp. vii, 51-60, 67) and continues to present, with two vaccine candidates currently undergoing safety or efficacy trials in Kenya and Mali.<sup>48</sup>

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<sup>45</sup> Estimates of as little as three years (synthetic artemisinin) and five years (vaccine) have recently been reported (Jack 2005), but it is not clear whether they include the whole clinical trial and approval process.

<sup>46</sup> Public/private interactions and issues will be discussed more fully in a subsequent section (IV/2); difficulties in aligning supply and demand for Coartem will also be noted (fn. 64 therein).

<sup>47</sup> The initial malaria programs were undertaken after WW II by the International Cooperation Administration (ICA) and then, starting in 1962, by the Agency for International Development (AID). They emphasized large scale assistance to individual nations and support for the eradication efforts built around DDT (Shuler 1985, pp. 5-12; Cowper 1987; NA 1991, pp. 47-50). The latter led, unfortunately, to a decision to de-emphasize research: of the \$1 billion AID and ICA spent over the initial 30-year period, only \$2 million went for this purpose (Shuler, p. 14; Spielman and D'Antonio 2001, pp. 157-158; Packard 1998, pp. 219, 228) and then generally not for development of new drugs (Shuler, pp. 47, 49).

<sup>48</sup> A review of the vaccine program though 1991 is provided in Diggs (1991) and recent developments are summarized in USAID (2005b, pp. 8, 17-18). The program has faced tribulations (Marshall 1990; Diggs 1991; Hills 1994) and criticism (Desowitz 1991, pp. 221-276; Spielman and D'Antonio 2001, pp. 168-169).

Following a global consultative meeting on drug resistance and combination therapy in 1998 (WHO 1998), USAID began a systematic program of support to efforts to accelerate an effective response to growing drug resistance, including development of appropriate combination therapies (USAID 2005a). From 1998-2003, it supported several activities relating to ACTs globally and in Africa.<sup>49</sup> One, initiated in 2000, was a study by the Center for Disease Control of the use of ACTs and the development of drug resistance high transmission areas in Tanzania. It is expected to provide population-based data on inhibition of drug resistance and health outcomes; cost and effectiveness; and acceptance and use by health care providers and patients (Kachur, et al. 2004; USAID 2005a & b, pp. 46-47; WHO 2005e). In 2002, in cooperation with the Gates Foundation, USAID sponsored the study by the Institute of Medicine of the National Academies (NA 2004) cited frequently in this paper.

More recently USAID has, in collaboration with Roll Back Malaria (RBM) initiative [www.rbm.who.int], supported efforts to identify and evaluate options for increasing production of Artemisia and artemisinin in Africa. USAID's Global Development Alliance sponsored a preliminary investigation by TechnoServe (previously cited) on prospects and possible programs to expand production of Artemisia and the extraction of artemisinin in Kenya and Tanzania. Subsequently, a decision was made to assist the expansion of production by USAID's Office of Global Health in association with WHO. TechnoServe was engaged to provide technical support, principally for small-holder production in northern Tanzania in cooperation with African Artemisia Ltd. (Figure 2).<sup>50</sup> As an outgrowth, WHO sponsored a globally oriented meeting on "The Production of Artemisia and Artemisinin" in Arusha, Tanzania in June 2005 (Anonymous 2005b, WHO 2005b). Some USAID mission support has also been provided for other national efforts in Africa (Section II/2).

On June 30, 2005, President Bush announced a new five-year, \$1.2 billion program - the President's Malaria Initiative (PMI) - to rapidly scale up malaria control interventions in high burden countries in Africa. The goal is to reduce malaria-related mortality by 50% in selected countries by achieving 85% coverage of vulnerable groups with: ACTs, insecticide-treated bed nets, intermittent preventative treatment, and indoor residual spraying.<sup>51</sup> The PMI and related malaria activities in USAID are to be under the purview of a new Malaria Coordinator.

Thus the USAID effort, which may be somewhat typical of others, consists of a mixture of bilateral and multilateral efforts with participation of the private sector.

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<sup>49</sup> USAID was criticized by some for moving too slowly in stimulating the adoption of ACTs in Africa, but as of 2000 there were some significant questions about relevance and application of the Asian experience (Bloland, et al. 2002). Differing viewpoints as of 2002 are portrayed by McNeil (2002) and an analytical study of the broader issues and tradeoffs is provided by Laxminarayan (2004). The agency supported studies leading up to the adoption of ACTs in Peru in 2000, the first Latin American country to do so (Ruebush, et al. 2004).

<sup>50</sup> Other foreign assistance agencies have provided grant support to ABE, totaling about \$700,000 and generally for activities involving small-scale farmers (pers. comm. from Lisa Ameyna, ABE, April 2006).

<sup>51</sup> A recent commentary on activities is provided in Dugger (2006).

Figure 2



Three month old smallholder field of *Artemisia annua* at Olkakola, Arumeru District, Tanzania, 2005. Source: TechnoServe.

## IV. Policy Issues: Public, Public/Private, and Social

Clearly the spotlight is on Artemisia/artemisinin. How long it will stay there is uncertain, but while it lasts, it/they can make an important contribution to public health in Africa and in other developing regions. And rather unusually, this is a case where a key role is to be played by agriculture in supplying the essential ingredient. The resulting policy issues take a variety of forms: some are economic and commercial, some relate to the public-private interface, and some arise from the need to think about social dimensions both locally and globally.

### 1. Public Needs, Public Goods, and Resource Allocation

Infectious diseases are clearly a public health problem and their resolution represents a public need. Just as they are in themselves public bads, their control requires public action and the utilization of public goods.<sup>52</sup> This takes us further into economic issues and questions.

**a. Public Needs and Public Goods.** In 1927, the Second General Report of the Malaria Commission of the League of Nations made two comments that are remarkably relevant to the current situation. The first was that “We are persuaded that the wide distribution of quinine is a public duty which, whenever and wherever necessary, should be organized and paid for by the State” (p. 21). The second was that “A central malaria-research organization continuously occupied with the subject, and in close touch with similar organizations in other countries, would be in the best position to advise as to the kind of measures upon which funds available for antimalarial work could most profitably be spent” (p. 10).

Seventy four years later, in 2001, another commission (Sachs, p. 17) similarly concluded that “An effective assault on diseases of the poor will...require substantial investments in global public goods [GPGs], including...research and development into diseases that are concentrated in poor countries.” This report, by the Commission on Macroeconomics and Health for WHO, noted that “GPGs are public goods that are underprovided by local and national governments, since the benefits accrue beyond a country’s borders” (p. 76). As a result, “the R&D for diseases specific to poor countries – such as malaria or other tropical parasitic diseases – tends to be grossly underfinanced” (p. 77). Funding for research on malaria, provided by a variety of sources, has markedly increased in recent years and has highlighted the need for a clearer perception of the types of global public goods involved.

There is also a need to consider the nature of the disease. As noted by Onwujekwe, et al. (2004, p. 111), the public good effect is enhanced because “the overall reduction in the number of people suffering from malaria will reduce the overall parasite prevalence in the population and ultimately the level of transmission of malaria” (also see NA 2004, pp. 80-81 and Barrett 2005). The effect can be further broadened to the extent that a reduction in

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<sup>52</sup> Pure public goods are freely available to all and are not diminished by use. Scientific knowledge has long been considered a classic example (see Dalrymple 2003). The general relationship between global public goods and health is discussed in: Arhin-Tenkorang and Conceicao (2003); Chen, et al. (1999); Kaul and Faust (2001); and Smith, et al. (2003).

malaria helps to lessen the prevalence and severity of other diseases and medical problems, especially in children and pregnant women – a positive externality (NA 2004, pp. 148-156; Schulman and Dorman 2003; Snow, Korenromp and Gouws 2004; WHO 2005b). In this way, as Mushkin (1958, p. 790) noted more generally, the social value of medical services can be far larger than the private marginal value.

The traditional treatments for malaria have not been the result of any formal research process and have long been in the public sector; they are clearly public goods.<sup>53</sup> In the case of ACTs, however, we are dealing with impure public goods, ones that incorporate both public and private dimensions.<sup>54</sup> This is not uncommon. Musgrove, in writing about health economics, states that “the boundary between public and private goods is not sharply defined” and refers to “mostly” private goods and to “nearly pure” public goods (2004, pp. 39-42). They are, to varying degrees, joint products.

Such goods are difficult to map in theoretical terms and, as in this case, can be even more complex to design and execute in short order, especially at the international/global level. In some cases, however, private firms or universities holding patents may differentiate their markets and allow their use in the case of developing countries. This has happened in a few cases noted earlier - the two new ACTs developed under the auspices of DNDi (Section 4) and the bacterial synthesis process sponsored by the Gates Foundation in California (Section III/1) - and while not yet common, is receiving more attention.<sup>55</sup>

**b. Allocation of Resources.** There are also complex and long recognized issues associated with the allocation of resources between and within malaria programs (Barlow 1967, 1968; Newman 1967). As one economist stated in this context, “it is easier to analyze and identify the economic effects of public action than it is to specify rules for the allocation of resources in the public sector” (Borts 1967, p. 149). More recently, another commented that “the standard tools of public economics can help make the case for public intervention,

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<sup>53</sup> This was only intermittently the case for quinine: “Throughout the history of quinine, the word ‘monopoly’ keeps recurring at every step” (Duran-Reynals 1946, p. 214). By the mid-1800s, Peru held a monopoly on the cinchona tree. “Hence,” English plant explorer Forbes Royle wrote in 1857, “it becomes a duty to humanity...to increase the supply of the cinchona trees” (Honigsbaum 2001, p. 81). This meant breaking the monopoly by surreptitiously “liberating” some of their best varieties for use elsewhere – which led to a subsequent sharp drop in price (p. 139). Another plant explorer involved, Markham, wished to bring to price down to everyone in India; by 1880 it was reportedly sold at a subsidized price of half a farthing at post offices in Bengal (Hobhouse 2005, pp. 25-28). The steps taken to develop “poor man’s quinine” employing government plantations - “a philanthropic proposition” - are vividly described by Duran-Reynals (1946, pp. 185-188, 200-209).

<sup>54</sup> Impure public goods are reviewed in [i] an *agricultural* context by Dalrymple (2006a); in [ii] a *health* context by Musgrove (2004, pp. 35-76, 170-184), Sandler and Arce (2002, pp. 202-203), Smith, et al. (2003), and Sandler (2004, pp. 107-112); [iii] in terms of *communicable diseases* by Smith, et al. (2004a & b); and [iv] with respect to *malaria* by Hanson (2004) and Laxminarayan, et al. (2005, p. 2, fn. 5). As scientific knowledge gets entangled in property rights and embodied in commercial products, it becomes more impure (Dalrymple 2003).

<sup>55</sup> The University of California at Berkeley, under its “socially responsible licensing program,” designed to cover technologies that promise “exceptional benefit to the developing world,” provides a royalty-free license” (Daviss 2005, p. 43). Several other universities have similar provisions see Chokshi (2005) and Brewster, et al. (2005).

but are less useful in determining the form that intervention should take, and in financing and providing interactions” (Hanson, 2004, p. 17).

Some of the early allocation decisions were made, as noted in Section I, within an economic development context. A “malaria blocks development” model, for instance, influenced Italian policy starting in 1900 (Brown 1997). Similarly, Packard (1997) suggested that “Malaria eradication was a product of a postwar [WW II] vision of economic and social development” (p. 279) “as much as a problem of public health” (p. 283). But evidence that eradication promoted longer-term development was slim and this led host and donor governments to look for other programs with a quicker and more visible impact on development (p. 286).<sup>56</sup>

Subsequent efforts to quantify the effects of malaria and of control programs have involved both macro- and micro-economic measures. Estimates of the macroeconomic burden utilize, as noted in Section I, cross-country comparisons, while microeconomic studies “apply a cost of illness (COI) methodology with a narrowly defined set of costs for inclusion;” both omit analysis of the pathways affecting economic growth (Willis, et al., 2005, p. 282). A recent massive study of disease control priorities in developing countries utilized a cost effectiveness approach and compared several forms of malaria control, including ACTs, with costs for a number of other diseases (Laxminarayan, Chow and Shahid-Salles 2006). Even with this data, it is difficult to determine impact because of the interaction between malaria control and improved growth; one feeds on the other (Sachs and Malaney 2002, p. 681; Sen 1999).

Other issues arose in the early 2000s when there was less agreement on the use of ACTs and the Global Fund was in the process of being created. Given limited national resources, what allocation pattern constituted the best use of funds: the older drugs that were losing their effectiveness vis-à-vis the newer and much more expensive ACTs? This led to one study (Laxminarayan 2003) and a rather vigorous and emotion-tinged debate (see, for example, McNeil 2002, Attaran, et al. 2004). A longstanding issue concerns the appropriate balance between developing new knowledge through research and expanding access to existing treatments (Das 2005b, Packard 1998, p. 219). A larger issue is the question of how much should be spent of infectious vs. chronic diseases (see Senek and Botta 2005).

In the current setting, it must also be recognized that ACTs are basically a replacement for therapies that have fallen prey to disease resistance. They essentially represent a higher cost holding position – a stage in what will probably be a never-ending sequence of efforts to develop and maintain a reasonable level of control. The research component thus serves a vital maintenance function.<sup>57</sup> But to move beyond this and to stimulate economic growth will

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<sup>56</sup> In the case of India after WW II, there was a reduction in mortality but the resulting population growth partly offset the effect on economic growth (Cohn 1973). In Sardinia (1946-1950), the project produced “by-products of great value for development” (Dean Rusk in Logan 1953, p. vi) and “made it possible to live and work safely on the island” (Logan, p. 302). A personal visit in western Sardinia and comments by older residents in June 2005 added anecdotal credence to these views.

<sup>57</sup> There is a parallel here with maintenance research conducted in agriculture to maintain existing yield levels in the face of continuing biological and other changes and challenges (Dalrymple 2004; Ruttan 1982, p. 60). This has recently been noted for health by Ruttan (2006, p. 60).

likely require continuing and additional research efforts on several fronts along with a variety of other control programs.<sup>58</sup>

## 2. Public/Private Interactions

Medicinal plants such as *Artemisia* are not a common component of agricultural production and processing systems. Nor are linkages to pharmaceutical firms.<sup>59</sup> Thus, there are many questions – some traditional, some quite new – to be answered concerning the stepping up of cultivated production of *Artemisia*, the associated extraction of raw artemisinin, the subsequent linkage with pharmaceutical firms, and public policies relating to distribution of ACTs in the developing countries.

The whole process reflects a remarkable, complex, and delicate interaction between the public and private sectors at both the global and local level. It also involves foundations (the Gates Foundation is particularly important in Africa; Spector 2005) and other donors and a series of cooperative efforts. The steps and principal players, from seed to consumer, are depicted in [Figure 3](#).<sup>60</sup> Research on the development of drugs has been greatly stimulated in recent years by funding provided through the Medicines for Malaria Venture (Lucas, et al. 2005).

Since the poor in developing nations cannot afford ACTs, subsidies are necessary.<sup>61</sup> The effective demand (ability to purchase) at the government level is underwritten by the Global Fund to Fight AIDS, TB, and Malaria.<sup>62</sup> The Fund, in turn, interacts with the World Health Organization which has negotiated a purchase price with pharmaceutical firms that is close to cost. The drug firms then provide the market for the artemisinin provided by extracting firms, who then provide the market for the *Artemisia* produced by farmers. From an economic perspective, the whole process hinges on the combined effects of (1) the negotiated price for the ACT and (2) the subsidy provided the developing nations. As of June 2005, 25 African nations had received such funding (WHO 2005a).<sup>63</sup>

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<sup>58</sup> A very successful program in South Africa (Section II/3) combined an ACT with vector control (Barnes, et al. 2005). Some more localized efforts, which could have an impact on growth, have been suggested by Spielman and D'Antonio (2001, pp. 219-222) and Spielman, et al. (2002).

<sup>59</sup> Medicinal plants are to be distinguished from conventional agricultural plants such as corn, soybeans, tobacco and rice which may be genetically modified to produce certain drugs, presumably faster and more cheaply. This is known as the “pharma” sector of agriculture in the U.S. (Weiss 2004, Wisner 2005).

<sup>60</sup> A more general diagram portraying health innovations systems is provided in Morel, et al. (2005, p. 402).

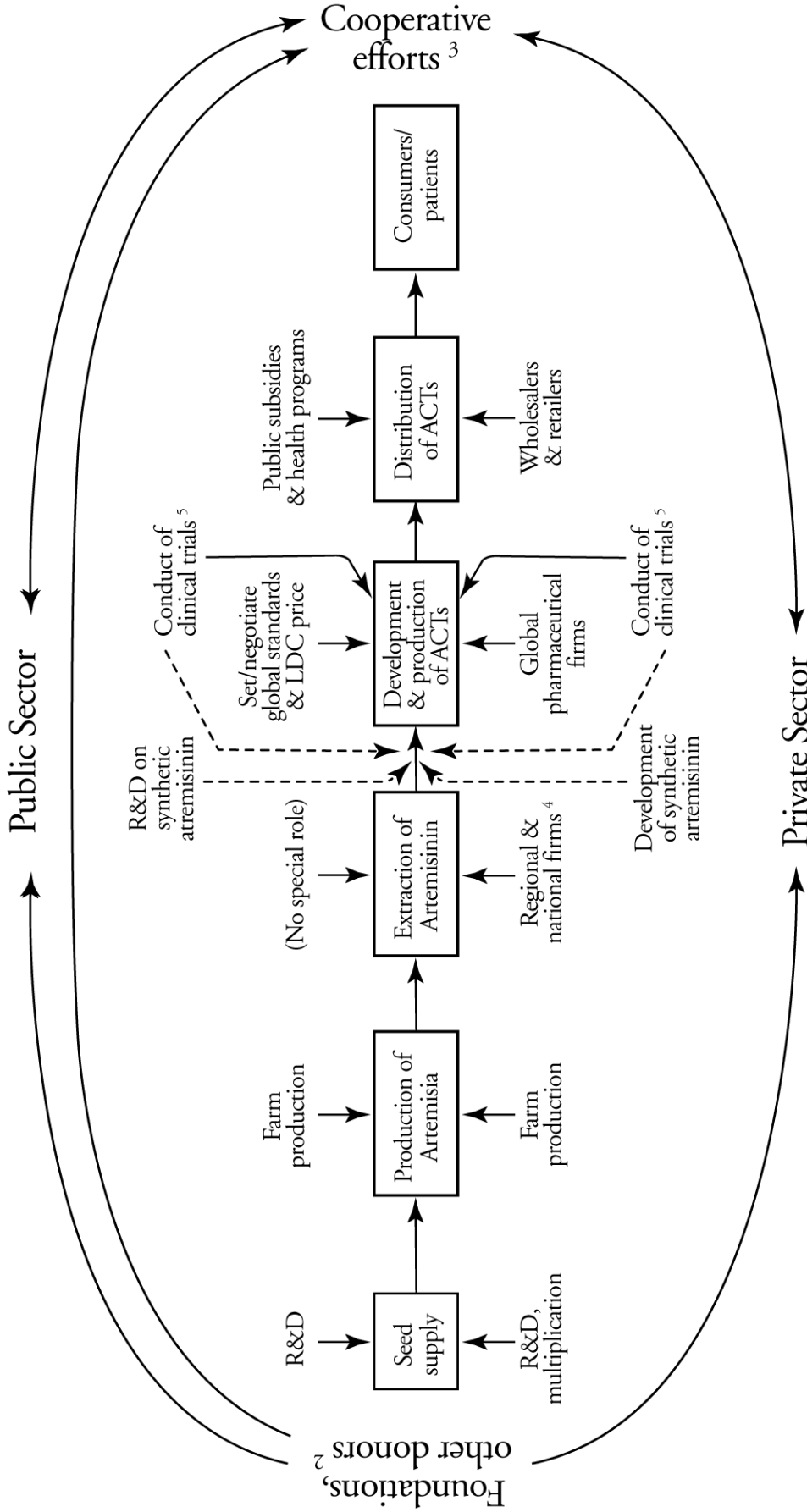
<sup>61</sup> The key issues relating to Africa are reviewed by Whitty, et al. (2004) and for Nigeria by Onwujekwe, et al. (2004) and Tanzania by Wiseman, et al. (2005). The major economic issues associated with global subsidies have been analyzed in NA (2004, pp. 79-111) and by Laxminarayan et al. (2005, 2006).

<sup>62</sup> As noted earlier (Section II/3/b), ACTs purchased using the Fund are usually distributed through government channels. Where this is not the case and the private sector is utilized, prices to users may be much higher – raising the question of whether an additional domestic subsidy program is necessary.

<sup>63</sup> More African nations had changed their national drug policies - 34 - than had applied for, or received, funding (current information at the national level can be gleaned from GHR 2006b).

Figure 3.

# Generalized Roles of the Public and Private Sectors in the Global Artemisia → Artemisinin → ACT Chain for Developing Nations <sup>1</sup>



<sup>1</sup> ACTs: artemisinin-based combination therapies.

<sup>2</sup> These groups could be considered as a third dimension since they interact with both public and private sectors, and help fund some of their research and development.

<sup>3</sup> These represent joint public-private efforts such as the Medicines for Malaria Venture and the Malaria Vaccine Initiative.

<sup>4</sup> Global firms may, in some cases, help fund these firms for this purpose.

<sup>5</sup> Dotted line refers principally to trials of synthetic artemisinin and less to cases where artemisinin is used as a monotherapy.

Should, however, the overall financial resources of the Global Fund malaria prove inadequate over time, whether due to donor fatigue or the need to direct funding to other critical health needs such as avian flu, the whole structure could be threatened (Ahmad 2005; Anonymous 2005c, Global Fund 2005c). Its sustainability cannot be taken for granted. Moreover, there is a need to balance supply (the production of ACTs) with demand (placement of orders by developing nations) and this may be difficult to do in the absence of normal market mechanisms.<sup>64</sup> The World Bank has proposed the establishment, following more detailed study, of a global subsidy of at least \$100 million per year to encourage production by drug companies (Jack 2005b).<sup>65</sup>

There are further challenges for both the public and private sectors. National governments face a host of policy questions relating to the operation of their programs: should expensive ACTs be used just for those with proven cases of *P. falciparum* (most people treated for malaria do not actually have the disease); how can they be most effectively deployed, etc. (Barnes and Abdulla 2005; Malenga, et al. 2005, p. 707; Mutabingwa 2005, pp. 307-311; Panosian 2005, pp. 716-717; Kimani 2006)? The private sector - both producers of Artemisia and extractors of artemisinin - geared up quickly, while the demand was strong, but face an uncertain future due to the emergence of other competitors and in time from other lower cost forms of artemisinin.<sup>66</sup> This is not the sort of investment situation for the faint of heart.<sup>67</sup>

### 3. Social/Individual Interactions

Many examples of these interactions are possible, but two - both with a biological base - might illustrate the range.

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<sup>64</sup> In late October 2005 (Anonymous 2005c) it was reported that Novartis “will produce 30 million treatments this year but has received orders for only 13 million. Nevertheless it plans to produce 100 million treatments next year even without orders” [in May 2006, the company stated that it had delivered 9 million treatment courses in 2005 and has the capacity to deliver 70 million by the end of 2006; Novartis 2006]. “Meanwhile, many African leaders are reluctant to commit to higher cost drugs with no assurance that there will be money to continue to purchasing indefinitely” [concerns of this nature continue: e.g. Kimani 2006]. Another account (Jack 2005b) indicated that “The company has long complained that orders for Coartem - currently placed country-by-country - are well below estimates of demand.” Changes in policy, however, have subsequently been made in some African nations. A related problem, not discussed, is difficulty in preparing successful proposals (USAID is now sponsoring assistance).

<sup>65</sup> A concurrent a simulation study by Laxminarayan, et al. (2005) suggests that “a subsidy for two or more combination therapies is likely to be much more cost effective than a subsidy to a single ACT” if the partner drugs are unrelated “so that a single mutation cannot encode resistance to both components” (p. i).

<sup>66</sup> A somewhat parallel situation was faced by the Pyrethrum Board of Kenya with the entry of new synthetics which, while not a complete technical substitute, could “mimic almost every individual attribute of the natural product” and led to shifts in demand (Winter-Nelson 1996, pp. 470, 473).

<sup>67</sup> Other uses may be needed in time. While Artemisia has long had a variety of uses as a medicinal plant (it was first recommended for hemorrhoids in 168 B.C.; Klayman 1985, p. 1049) and has promise of others (as noted in Section III/1 and by Utzinger, et al. 2001 and Heping 2005), they are unlikely to provide a similar level of demand for plant-derived artemisinin.

**a. Development of Resistance.** This relates to the speed and degree to which resistance builds up to artemisinin and ACTs.<sup>68</sup> There are, as noted earlier, indications that this is happening in several areas (French Guinea and Senegal) where there has been “uncontrolled use” of artemisinins (Jambou, et al. 2005). This is defined as “monotherapy or in conjunction with ineffective partner drugs” (Duffy and Sibley 2005, p. 1909). Jambou, et al. state that while “Reduced...susceptibility is not synonymous with diminished therapeutic effectiveness...it is the probable first step of an alarming cascade and definitely pleads for increased vigilance and a coordinated deployment of drug combinations” (p. 1962). It also raises the question of whether the concept of ACTs might usefully be expanded from double to triple drug combinations.<sup>69</sup>

The key ingredients in the development of resistance might be viewed as (i) the relative degree of use of monotherapies and combination therapies, (ii) the likely pace of development of resistance to each, (iii) time, and (iv) individual and social benefits. The latter are important because what is true at the social level may not be equally true at the individual level, and vice versa (the fallacy of composition).

- From a *social* perspective, the wider the use of combination therapies (assuming they are correctly used) the slower the rate of growth of resistance and the greater the degree of social benefit; conversely, the greater the use of monotherapies and the more rapid the development of resistance, the lower the degree of social benefits.
- The same, however, may not be true in terms of *individual* benefits: while combination therapies are better for the individual, some - especially those who do not have access to, or cannot afford, combination therapies - benefit from monotherapies. But to the degree this practice accelerates the development of resistance, social benefits are lowered over the longer run.

The relative effects of these variables on resistance may be viewed graphically in terms of a quadrant model, as in [Figure 4](#).<sup>70</sup> Policies that result in the least development of resistance are associated with the greatest social benefit; others have more mixed results. In reality, the boundaries between the quadrants are likely to be porous and several of them, or all, could exist to varying degree in various areas of a country or over time. There are significant implications in taking different paths, though this may not be so evident at the margin, and need to be considered in the establishing an appropriate blend of public policies.

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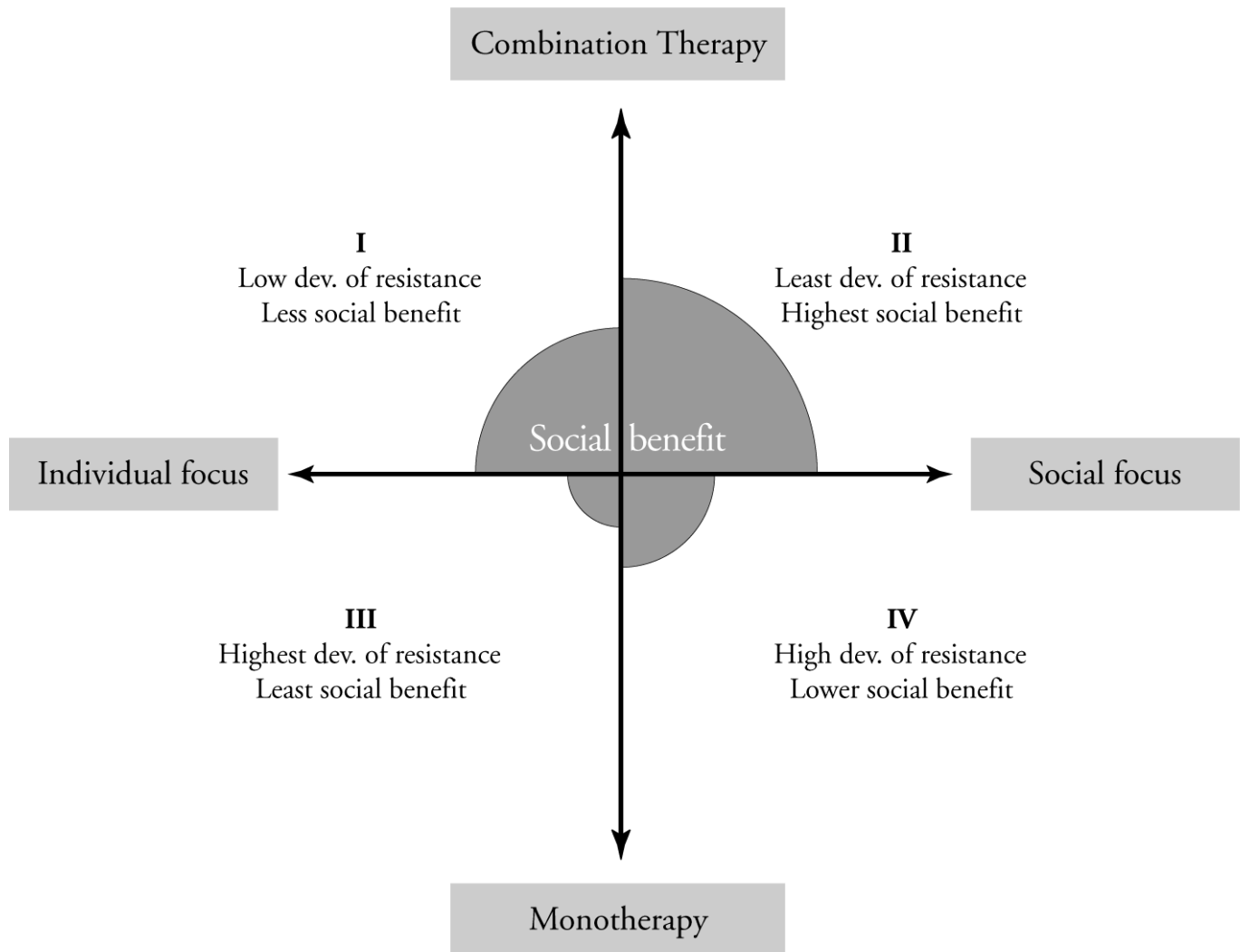
<sup>68</sup> This issue, a negative externality, is discussed in terms of antimicrobial resistance by Coast, Smith, and Millar (1998, pp. 30-31); Smith and Coast (2003), and Smith, et al. (2005).

<sup>69</sup> Triple combinations are used in treating HIV/AIDs and tuberculosis, and a few have been tested for malaria (Mutibingwa, et al. 2005, Souwummi 2005), but not yet in ACTs. The concept has received some thought and at least one public mention (Simon Croft, ASTMH meeting, December 2005, Symp. 22), but evidently no concerted study. It is not clear that they would be “unambiguously advantageous from a resistance standpoint” (pers. comm. from Ramanan Laxminarayan, January 2006) and could entail increased drug-drug interactions and adverse events (pers. comm. from William Watkins, December 2005).

<sup>70</sup> They might also be expressed algebraically. Coast, Smith and Millar (1998, pp. 30-31) outline a series of three simple equations for negative externalities, positive externalities, and net benefits.

Figure 4.

### Conceptual Categorization of Monotherapies and Combination Therapies for Malaria in Terms of Likely Development of Resistance and Social Benefit



Notes: While the horizontal *benefit* line represents a continuum, the vertical *therapy* line usually is one or the other. The *benefits* line is asymmetric in that cases where social benefits may be highest do not necessarily mean that individual benefits are less, while the reverse is much less likely to be true. The development of resistance has a time dimension to it and is implicit in the designation of the quadrants.

Other factors may also be relevant. When, for instance, the point is reached when the demand for Artemisia for pharmaceutical use in ACTs diminishes - for reasons discussed earlier - continuing excess supplies could find their way to a more informal market for use in monotherapies, both herbal and manufactured, and thus accelerate the loss of resistance. Encouraging individual farm production that is not part of a larger program to provide artemisinin for the production of ACTs could lead to a similar outcome.

There clearly a need for much more policy analysis centered about the consequences of present programs on resistance and the ensuing policy issues.

**b. Prevention and/or Cure?** This is one of the oldest issues in malaria policy (e.g. Litsios 2006, pp. 132-138) but is less common now since both are needed. In the context of this paper, it has another dimension: the relative degree of focus on residents who may have built up some immunity, or visitors and those who have not. In Africa, *curative* treatments for malaria are more likely to be undertaken for the native population and *preventive* treatments for visitors, but there may be some overlap. Quinine and Artemisia, blended with some liquid (famously gin and tea respectively), have long played both roles for both groups, but to varying effect. To be an effective *preventive*, they have to be consumed regularly (up to weekly for quinine and for three days for artemisinin) and in sufficient dosage. To be an effective *curative*, a quick treatment with prompt effect and without immediate re-infection is desired. ACTs can accomplish both tasks, but because of their cost and need for regular ingestion, are normally not recommended the preventive role.<sup>71</sup>

## V. Concluding Remarks: the Wisdom of the Red Queen

Artemisia is a seemingly simple, though versatile, medicinal plant suddenly at the heart of international attention. It was long a traditional remedy for a variety of ills. But by virtue of some extraordinary qualities of an extract, artemisinin, is now a key player in global efforts to help control malaria, a particular scourge in Africa. In this, it is following in the footsteps of quinine, another plant derivative. And, in doing so, it has become - at least for the moment - one of the most important medicinal plants in the world.

Some hail the use of natural products (Mashelkar, 2003, 2005; Paterson and Anderson 2005). Others find this disquieting: Bond (2004) has observed that “in the 21<sup>st</sup> century, we need not rely on plants to cure malaria.” Thus, the search is on for chemical substitutes, no mean scientific challenge. But artemisinin of any source faces the inevitable challenge of parasite resistance - a process that is accelerated by the use of monotherapies rather than combination therapies (ACTs). Replacement treatments will eventually be needed.

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<sup>71</sup> This discussion is partly based on material in NA (2004, pp. 212-219), Curtin (1998, pp. 23-27), and Litsios (1996, pp. 70-72). Curtin states that in the 1800s, quinine was “most effective in a sufficient prophylactic dose, taken daily; but its unpleasant taste discouraged people from taking it either regularly enough or in sufficient dosage, so that acceptance was uneven to the end of the century and beyond” (p. 23). It also has other unpleasant side effects. Watkins notes that it would “be extremely difficult (in practical terms) to define a chemoprophylactic regimen for artemisinin monotherapy, using either tea or tablets...” (pers. comm, September 2005). A subsequent study concludes that “there is currently no role for artemisinin derivatives as a chemoprophylactic agent” (Franco-Paredes and Santos-Preciado 2006, p. 146).

These and other issues are linked to an unusually wide range of international scientific, technical, economic, and social considerations. The result is a complex interplay and presents some difficult and challenging policy and operational issues. How well they are resolved will be of considerable importance, not only as they bear directly and indirectly on public health in Africa, but also more globally in other tropical nations.

There is great social promise in all of these activities - and major challenges. One group recently stated that “ACT has the potential to be one of the greatest public health interventions for Africa this decade.” But it also said: “We must get it right” (Malenga, et al. 2005, p. 707). And Moree (Das 2005b) has cautioned: “one thing that malaria has proven is that when we are just about to conquer it, it comes back again.” Infectious diseases such as malaria, HIV/AIDS and avian flu represent never-ending threats to global society.

As Makel (2004) concluded in a review of a book on the influenza pandemic of 1918: “we never really conquer germs: we merely wrestle them to a draw.” This is akin to the famous advice the Red Queen gave Alice: “Now here, you see, it takes all the running you can do to keep in the same place.” Malaria provides, with care and resources, reasonably good prospects for maintaining a draw and possibilities for improvement. But to accomplish the latter will require even more effort. As the Red Queen went on to say, “If you want to get somewhere else, you must run at least twice as fast as that” (Carroll, 1871/1984, p. 204).

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## Annexes

### Annex 1. Artemisia: Genetic Resources

As a medicinal plant, *Artemisia annua* falls outside the mainstream of agricultural research and has been essentially an orphan crop, except in a few cases. This creates some problems as far as traditional agricultural seed supply and varietal improvement is concerned.<sup>72</sup>

**a. Traditional Seed.** Although *Artemisia annua* has been kept at the Chelsea Physic Garden (established in 1673), in London since the mid 1700s and possibly at some other such gardens,<sup>73</sup> it is not a common component of agricultural genebanks. As of early 2005, the National Plant Germplasm System of the U.S. Department of Agriculture, which only recently

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<sup>72</sup> Artemisinin, aside from quinine, is not the only plant-derived treatment for malaria. Comprehensive accounts are provided in Willcox, et al 2004 and Rukunga and Simmons 2006. Additional studies may be found in Asase, et al. (2005), Bertani, et al. (2005), and Wright (2005).

<sup>73</sup> The seed arrived “pre-records” or without an entry number (pers. comm. from Mark Poswillo, head gardener, June 2006). The first mention of its inclusion in the Garden occurred in 1759 (in Miller’s *Garden Dictionary*), though it may have arrived before 1741, and reportedly came from Russia (Siberia via St. Petersburg). It was first mentioned in the botanical literature in 1739. An introduction from China to Portugal was noted in 1790 (pers. comm. from David Frodin, taxonomist, June 2006). Also see Dobson 1998, pp. 78-79.

began to focus on medicinal plants, had only one holding.<sup>74</sup> Seed can be obtained from various nurseries (see Isaacson 1996) but the original source of germplasm and the artemisinin content is usually unknown and may have derived from more than one source and “bulked.” Limited supplies of hybrid seeds may be obtained from other sources, noted below.

**b. Varietal Improvement.** While some selections have undoubtedly been carried out over centuries in China, no information seems to be available about present plant improvement efforts there or elsewhere in SE Asia. Recent activities are as follows

- **Switzerland and Germany.** The principal program has been carried out by the Research Center on Medicinal and Aromatic Plants, Mediplant, a public/private non-profit organization in *Switzerland* (Mediplant 2003) [www.mediplant.ch]. Early work was focused on selection and breeding for high artemisinin (Delabays, et. al. 1993, 2001), resulting in the variety “Artemis,” a cross of Chinese and Vietnamese varieties. Mediplant subsequently has developed a “Var M” variety. Both have been used in the ABE/TechnoServe project noted earlier in East Africa<sup>75</sup> and have been crossed to produce a third variety. Seed of a “hybrid” variety named “*Artemisia annua* anamed (A3),” probably an offspring of Artemis, is available from ANAMED (Action for Natural Medicine), *Germany* [www.anamed.net]. The Mediplant and ANAMED seeds are more expensive than others because the hybrid breeding process is more complicated than selection and is complicated by the extremely small size of the seed (12,000 seeds per gram). As a hybrid, new (F<sub>1</sub>) seed is needed each year if the yield drops normally involved with the second generation (F<sub>2</sub>), roughly 20%, are to be avoided. Other commercial seed probably largely represents selections of traditional varieties.

- **United Kingdom.** In June 2006, the Centre for Novel Agricultural Products, Department of Biology at the University of York, announced the award of a \$13.6 million 4.5 year grant from the Bill & Melinda Gates Foundation to develop “a non-GM variety” of *Artemisia* with greatly increased yields of artemisinin for use in ACTs. The project is led by Dianna Bowles and Ian Graham and uses “Artemis” as starting material (Mediplant is a collaborator). “A chemical treatment widely used for breeding food crops will be applied to increase the genetic diversity of...Artemis. The researchers will... track the metabolic and genetic profile of thousands of plants to find the ones that produce the most artemisinin” which will then be used as breeding stock for new varieties which will be tested in developing nations. Early support for the project was provided by the Garfield Weston Foundation, GlaxoSmithKline and the Medicines for Malaria Venture (University of York 2006).

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<sup>74</sup> Pers. comm. from: Rich Hannon, Western Regional Plant Introduction Center, Agricultural Research Service, U.S. Department of Agriculture (ARS/USD), Pullman, Washington, February, 2005; Ned Garvey, Plant Exchange Officer, ARS/USDA, Beltsville, Maryland, February 2005.

<sup>75</sup> “Var M” has proved bushier than “Artemis,” adapted to mechanical harvesting, and has a high artemisinin level (an average of 1% in the field and up to 1.4% in trial plots); it will be more widely planted in 2005 and 2006 (pers. comm. from Barney Gasston, ABE, April 2006). A 1.4% level was reported by Mediplant (2004) for a selection from Artemis. These levels are near the upper bounds found elsewhere and for other varieties (pers. comm. from Jorge Ferreira, USDA, April 2006).

- **United States.** Several plant scientists in the public sector in the United States - notably Jorge Ferreira of the *U.S. Department of Agriculture* (Agricultural Research Service, Appalachia Farming Systems Research Center) and James Simon at *Rutgers University* - have carried out extensive physiological research with the *Artemisia* plant (see, for example, Ferreira and Janick 1996; Ferreira, Simon and Janick 1997; and Wang, et al. 2005). Simon has accumulated selections, improved lines and hybrids from a number of sources and is growing them out under controlled conditions; attention is being given to both high yield and high artemisinin levels (pers. comm. October 2005).

- **Brazil.** A line of plants with high artemisinin, known as “3M,” has been developed by Nicolas Delabays of Mediplant in cooperation with Pedro Magalthes (pers. comm. from Jorge Ferreira, December 2005).

- **International Agricultural Research Centers.** The *World Agroforestry Center* (formerly the International Center for Research on Agroforestry, ICRAF) and the *International Center for Insect Physiology and Ecology (ICIPE)*, both headquartered in Nairobi, are involved, in somewhat similar ways, with *Artemisia*. ICRAF is focusing on herbal combination therapies (HCTs) involving *Artemisia*. It is seeking to assemble a diverse range of *Artemisia* germplasm, identify other anti-malarial plants, and carry out tests on the safety and efficacy of such plants individually and in combination with *Artemisia* (Simons 2005). It jointly organized an African Herbal Antimalarial Meeting in March 2006. ICIPE has long been engaged in a variety of malaria control programs at the farm level and has more recently focused on *Artemisia*. It has developed and tested an unfractionated whole plant extract made into tablets, with initially promising clinical results (ICIPE 2005, p. 27).<sup>76</sup>

Until the Gates Foundation grant to the University of York noted above, the financial investment in varietal improvement had been miniscule, especially when compared to the investments in synthetic forms of artemisinin and vaccines.

## **Annex 2: Artemisia: Use in Tea**

*Artemisia* teas clearly qualify as a traditional practice. They have long been used for medicinal purposes, including malaria, in China and are still included in its pharmacopoeia. This has, historically, been in the form of herbal teas. Manufactured monotherapies, using artemisinin extracts of varying concentration, are a more recent development. The actual degree of use of each type in China is uncertain.

There has been a particular interest in the possible usefulness of *Artemisia* teas in areas where conventional drug therapies are not readily available or are too expensive. Several recent studies have shown that it is possible to obtain some clinical effects through the use of an

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<sup>76</sup> Preliminary clinical trials at ICIPE’s St Jude’s Clinic Mbeta Point on Lake Victoria showed an “impressive efficacy even at the lowest-dose regime” (Ibid). The unfractionated *Artemisia* preparation “contains both aqueous and organic soluble constituents” and hence may provide more than one antimalarial ingredient (pers. comm. from Hans Herrin and Onesmo ole-MoiYoi, March 2005).

Artemisia tea.<sup>77</sup> However, as reported by others, there were “relatively” or “unacceptably high” “recrudescence rates” (reemergence ) after termination of the treatment (Rath 2004, pp. 128, 131; also see Mueller 2004, pp. 320-321 and Klayman 1985, pp. 1052-1054).<sup>78</sup>

There may be two principal reasons for this. First, the concentrations of artemisinin were found to be below those in conventional drug therapies. One study compared the dosage recommendations found that the current Chinese pharmacopoeia contained 19% of the artemisinin provided in modern tablets or capsules (94.5 mg. in one liter vs. 500 mg in one usual daily dose) (Rath, 2004, pp. 130-131). When insufficient doses are used and no complete cure is achieved, there is a risk of inducing resistance to artemisinin (Mueller 2004, p. 492). Second, even if the dosage level is sufficient, it is necessary to continue it for a week, to “ensure parasite clearance” (pers. comm. from William Watkins, March 2005). This may be, as it would be for other artemisinin monotherapies which have a very quick effect, a long regimen to maintain under African conditions (Hastings, et al., 2002, p. 516).

The Rath and Mueller studies state, in almost identical language, that “monotherapy with tea preparations from *Artemisia annua* can therefore **not** be recommended as a treatment option for malaria” (Mueller 2004, p. 321; Rath 2004, p. 131; bold lettering added). Jansen (2005) subsequently tested the concentrations of artemisinin using their methods and got much lower levels, leading him to conclude that the concentration was “far too low to be responsible for the antimalarial activity” and to suggest that the tea approach is “totally misleading.”

Simmons (2005), as noted in Annex 1, has recently proposed the development of herbal combination therapies (HCTs) for use in remote areas. Similarly, ANAMED has encouraged the combination of Artemisia tea with other malarial medicines or other herbal teas, a package they refer to as A-3CT, and encourage clinical studies [www.anamed.org]. Some suggest that tea is not strictly a monotherapy because the whole leaf is used, not just an extract.

Overall, there is so much that is unknown or highly variable in the case of Artemisia teas that it is difficult to fully judge their value, real or potential, as one form of treatment for malaria. This is a case where tradition and science appear to differ sharply. In such a setting, the last words of Hippocrates cited at the beginning of the paper - “at least do no harm” - provide a challenging and somewhat haunting backdrop.

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<sup>77</sup> While artemisinin is not readily soluble in water, it appears to be sufficiently so at high temperatures to provide antimalarial effects. Ferreira (pers. comm. December 2005) has extracted 75% artemisinin at 85-90°C; he maintains that boiling Artemisia, which may sometimes occur in making teas, destroys most of the artemisinin. Also see Willcox, et al. (2004, pp. 45-46, 54-56).

<sup>78</sup> This is also true of artemisinin monotherapies. In areas where malaria is endemic, true recrudescence is hard to distinguish from re-infection (pers. comm. from Onesmo ole-MoiYoi, ICIPE, April 2005). Another quite different problem is that the Artemisia teas have a bitter taste which may discourage or limit use among some groups, especially children (Simmons 2005).

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