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Artemisia annua, Artemisinin, ACTs and Malaria Control 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[2]

The ends of this branch of knowledge [chemical philosophy] are the applications of natural substances to new uses, for increasing the comforts and enjoyments of man…
- Sir Humphry Davy, 1812

It would be foolhardy of anyone to predict when and how malaria will be conquered.
- Socrates Litsios, 1996

Abstract

The key ingredient in the leading treatment for malaria in Africa - artemisinin - comes not from high-tech research, but is an extract of an ancient medicinal plant, *Artemisia annua*, commonly known as Artemisia. Chloroquine and replacement drugs have lost effectiveness with the development of resistance and have increasingly been replaced by derivatives of artemisinin combined with other drugs. Known as artemisinin–based combination therapies (ACTs), they provide the most effective treatment at present. This has led to efforts 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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[1] The preparation of this paper through September 2008 was carried out while I served as Senior Research Advisor and Agricultural Economist, International Research and Biotechnology Team, Office of Environment and Science Policy, Bureau for Economic Growth, Agriculture and Trade, U.S. Agency for International Development, Washington, D. C. Following retirement, I have continued work on the paper as a personal effort and may be contacted at dana.dalrymple@verizon.net. The views expressed are my own and not necessarily those of USAID. Mention of commercial firms and products does not imply endorsement. This is a revision and update of he December 10, 2009 version of the paper which was posted on the Medicines for Malaria Venture website [www.mmv.org/research-development/optimizing-artemisinin-production/related-publications].

[2] "Hippocrates was the first to clearly describe the different types of malaria depending on the periodicity of the fever – tertian and quarten fever patterns" (Cunha and Cunha 2008, p. 195).

Preface

This account of a plant-based pharmaceutical drug and one of the world's oldest and most important diseases had a somewhat unusual provenance. It grew out of a project supported by the U. S. Agency for International Development to provide technical support to farmers in East Africa in the production of Artemisia (*Artemisia annua*) for use in the manufacture of artemisinin-based combination drug therapies (ACTs). I participated in the evaluation of the proposal in mid to late 2004, as the agricultural member of an informal agency Artemisia Team. While we had good documentation at hand (TechnoServe 2004), it appeared to me that much more needed to be known before an adequate overall assessment could be made.

Initially this led to extensive correspondence with specialists in the field and an extended review of literature, a process which continues. Along the way, I have encountered many highly knowledgeable specialists in various aspects of the subject, but few individuals with a broader interdisciplinary knowledge of the topic (principally historians). And while the volume of literature on malaria is massive, the distribution is definitely asymmetric. There is much more on (i) artemisinin and ACTs than *Artemisia annua*, and (ii) biological science than social science. Comprehensive policy analysis, with one notable exception (NA 2004), is scarcely in evidence and remains more of a goal than an achievement.

The manuscript began as a modest briefing paper on Artemisia for the USAID Administrator in late 2004. It represents an ongoing attempt to bridge and balance several varied dimensions. As an agricultural economist with early training in plant science, my approach and emphases obviously may differ from those of formally trained malaria specialists, though I have drawn liberally from their work and advice over a number of years. The focus, as suggested in the title, is ultimately on public policy aspects and hence reflects and incorporates a number of additional dimensions of a historical, economic, and social nature. It also reflects a longstanding interest in science and technology policy and more recent attention to international health policy research and issues.

The result is a broad, and hopefully fairly analytical, review that may be of background interest and value to both specialists and generalists. To facilitate this, the main text - which is fairly compressed and somewhat complex at points – is focused on broader topics and issues. Additional details, dimensions, and linkages are provided in 13 Annexes and 205 footnotes. There is also an extended and varied list of references (over 1,100). Thus readers can pick and choose; the paper may be read and used at several levels and in different ways.

Useful collateral reading is provided in (1) three recent and excellent histories of malaria and malarial control efforts (Packard 2007, Webb 2009, Shah 2010), (2) the annual *World Malaria Report* (WHO 2008, 2009), and (3) annual reports of a U.K. Parliamentary Committee (APPMG 2010). An overview of technical and scientific aspects of malarial drugs is provided by Eastman and Fidock (2010), while a technical book on artemisinins by Lin and Weina is scheduled to be published in early 2011.

Much has happened since the first version of this Working Paper was posted on the WHO/RBM website in July 2006. I have tried to incorporate the highlights, though some areas have been less well covered or remain elusive. This has involved, as before, a process of reading and consultation leading to corrections, clarifications, revision, and updating. It remains, as ultimately any study of such a complex and dynamic subject must be, incomplete, subject to error, and a continuing work in progress. Comments and corrections are welcome.

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Chapter I. Introduction

Malaria is thought to be among the oldest of human diseases (Russell 1955; Bray 1996; Carter and Mendis 2002; Sallares 2002; Nerlich et al. 2008; **Annex 1**). It has long had serious effects on morbidity and mortality, and in turn on the economic and social fabric of nations and society. Various methods have long been utilized to mitigate its frequency and effects in both temperate and tropical climates. This has proven to be a never-ending battle requiring constant attention. As stated by Hackett in 1937: "Everything about malaria is so molded by local conditions that it becomes a thousand different diseases and epidemiological puzzles" (p. 235). This paper recounts the events relating to the most recent chemotherapy (drug) approach to its control in, or pertaining to, Sub-Saharan Africa.

1. The Importance of Malaria in Africa

Malaria is of particular importance in developing nations, especially in Africa where it first appeared in severe form (*P. falciparum*) some 8,000 to 10,000 years ago (Wade 2001; Tishkoff et al. 2001). While estimates of the number of **cases** of malaria caused by *P. falciparum* have varied, a recent study places the global total at about 451 million yearly of which 271 million were in Africa (Hay et al. 2010). The corresponding global number of **deaths** has long been placed at about one million (NA 2004, p. 169; Shah 2010, pp. 133-134), though some lower figures have been reported.[3] Children under the age of five and pregnant women are especially at risk; 89% of the deaths in children in 2008 were in Africa (UNICEF 2010, p. 8). Malaria is primarily a disease of the poor and malnourished (Barat et al. 2004; Worrall et al. 2005; Krefis et al. 2010) and increases susceptibility to infection by other diseases such as HIV/AIDS (WHO 2004a; ter Kuile 2004). Traditionally considered a rural disease, it is becoming of increased concern in urban Africa (Touré 1999; Klinkenberg et al. 2006).

In economic terms, the total household cost burden of malaria is high in Africa, especially for the very poor.[4] 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.[5] Lifting the

[3] An earlier WHO estimate was 881,000 globally and 802,000 in Africa (WHO 2008, p. viii; also see Snow, et al. 2005, Brown 2006). It was lower because of a change in methodology which reduced the estimates for Asian countries (McNeil 2008e). Within Africa, the toll is highest by far in Nigeria and the Congo (D. R.), though the precise figures are very uncertain (WHO 2008, pp. 12, 14; Hay et al. 2010).

[4] 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). Further estimates of economic costs and burdens, and discussions of issues in measurement, in Africa are provided in: Ettling and Shepard (1991), Lennox (1991), Shepard, et al. (1991), Aseso-Okyere and Dzator (1997), Onwujekwe et al. (2000), Goodman et al. (2000), Worrall et al. (2005), Deressa et al. (2007), Somi et al. (2007), and Onwujekwe et al. (2010). The nature of the public health burden is analyzed by Snow, et al. (2003), Malaney et al. (2004), and Breman, et al. (2006).

[5] 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

burden imposed by malaria would have significant effects on African economic growth. This task, however, is challenging and in Africa, the cost of malaria control programs can represent a high proportion of the national health budget (e.g. Ghana; Anonymous 2007f)

2. Evolution of Control Programs and Emphasis

a. Global Programs. Malaria is a global problem and beginning in the early 1900s has been the subject of many control efforts and programs. They initially were conducted at the national level; perhaps the most comprehensive and notable was conducted in Italy beginning in 1900 (Snowden 2006). This and others were followed by a coordinated set of mid-centurty eradication programs on a global level sponsored by the World Health Organization (WHO). .

An early League of Nations report observed, however, that "The history of special anti-malarial campaigns is chiefly a record of exaggerated expectations followed sooner or later by disappointment and abandonment of the work" (Malaria Commission 1927, p. 9). This was no less true of the "global" program initiated by WHO in 1955 to eradicate malaria based on the use of what was then seemed to be a wonder drug, DDT. While unsuccessful in terms of eradication, it did reduce the prevalence of malaria in some areas for a while. [6] But there were also high opportunity costs: research was neglected and funding for a concurrent smallpox eradication program constrained (Henderson 2009).

One irony of the so-called "global" program was that it did not include Africa. This occurred despite the fact that a "Conference on Malaria in Equatorial Africa," partly sponsored by WHO, in Kampala in 1950 recommended that "malaria should be controlled by modern methods as soon as feasible" (Dobson et al. 2000, pp. 155-160[7]). This was "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). Lack of data may also have played a role Dobson et al., p. 158). As a consequence, "There was never a 'failure' of malaria eradication in Africa – it simply never got off the ground" (Malowany 2000, p. 343).

The subsequent path of global efforts in support of malaria control in Africa has also had its ups and downs, as noted by Webb (2009a, pp. 160-187) and in the pages that follow.

b. Donor Emphasis. Control programs and measures clearly reflect the tenor of their times, particularly among their providers. Keusch et al. (2010) provide an insightful historical

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1980-1995 period for 31 African nations reported by Sachs and Malaney (2002, p. 683, Table 1). Mills and Shillcutt (2004), 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 (also cited in Bray 1996, p. 101).

[6] The program has drawn extensive critical comment. See, for example, Barlow 1967 & 1968; Cohen 1973; Brown et al. 1976; Harrison 1978; Desowitz 1991; NA 1991, pp. 198-203; Garrett 1994; Packard 1997 & 1998; Spielman and D'Antonio 2001; Carter and Mendis 2002; and Staples 2006. Subsequent experience with DDT in southern Africa is assessed by Mabaso, et al. (2004) and its health risks and benefits by Rogan and Chen (2005).

[7] This paper was an outgowth of a project titled "The history of malaria and its control in twentieth century East Africa" funded by the Wellcome Trust and directed by the Wellcome Unit for the History of Medicine, Oxford and the Wellcome Trust Laboratory/KEMRI, Nairobi. Regrettably, the work of the project was never fully written up, in part because of illness. Files of the research materials that were gathered, however, remain and have been used by visiting scholars (pers. com. from Mark Harrison, Wellcome Unit, July 2008).

review and perspective. They divide their historical analysis into three principal phases (italics added): **I,** the late 19th century through the 1950's, characterized by a focus on "*national* public goods;" **II,** the 1960s to 1980's, by an "*international* health perspective;" and **III,** the 1990's to the present, by "*global* health and malaria research and control." In looking to the future, phase **IV**, they focus on lessons learned and *global* public goods for global health. One relative constant has been military interests.

The three phases may be briefly characterized as follows. Phase **I** was initially motivated by *colonial interests* and focused on individual nations. In Phase **II**, malaria was initially an example of a neglected disease and was mostly financed as *bilateral* assistance, but increasingly reflected *internationalization* in public health. Phase **III** was marked by "increasing attention to the concept of *global* public goods" and recognition that "malaria R&D merited increased funding because of its "global impact and the potential for scientific progress" (also see Varmus 2009, pp. 227-230). There was also increased emphasis on public-private product development partnerships and the creation of many new efforts of a multilateral nature. The future, **IV**, involves *new actors* and *modes of operation*. Many of these dimensions are touched on in the body of this paper (public goods in Chapter IV/1/a).

3. Malaria and Its Treatment

Malaria is caused by a unicellular parasitic microbe known as a protozoan, which is neither a virus nor a bacterium. There are two principal forms of malaria: (1) uncomplicated, which is not life threatening and where the purpose is to cure the infection; and (2) severe, which includes cerebral forms, where the purpose is to prevent death (WHO 2006b). The main symptoms of uncomplicated *P. falciparum* malaria - the main focus of this paper - are very similar to those of other diseases, which can lead to problems in diagnosis and treatment.[8]

Both preventative and curative measures are employed. The principal current *preventative* measures in Africa involve vector control (e.g. Michalakis and Renaud 2009), barriers to transmission (e.g. WHO 2010d), and increasing human resistance to the parasite . The principal *curative* measures seek to control the parasite within the body and utilize drugs. Both employ a variety of chemical, physical and pharmacological techniques, as shown in Figure 1. Various combinations are possible and under study/use.

Quinine, a plant-based extract, has been used to treat malaria for centuries. It is still in use in Africa and is approved as a second-line drug for uncomplicated *Falciparum* malaria and as an injection for severe forms (WHO 2010b, pp. ix-x). It has not yet shown serious resistance problems (Parquet, et al., 2010), but it has a bitter taste, side effects are common (NA 2004, p. 291), and requires a 7-day course of treatment. Its continued use in Africa as a monotherapy has recently been debated (Yeka et al. 2009; Barennes et al. 2010; Chico et al. 2010). (Also see: Chapter IV/3/c; footnotes 43, 60, 67, 90, 91, 113, 114, 140, 145, 146 & **Annexes 9c/d**.)

[8] As described by Talisuma and Meya (2007, p. 375): "People living in areas where malaria is endemic are often familiar with these symptoms and frequently diagnose themselves" ("presumptive treatment; without laboratory confirmation)"; this contributes to widespread over-diagnosis and unnecessary treatments. But even where tests are available and show negative results, health workers may continue treatment (Ibid.; Reyburn et al. 2007).

Traditional single synthetic drug treatments (monotherapies), such as chloroquine, have lost appreciable effectiveness due to the development of drug resistance (e.g., Peters 1987, White 2004, Talisuna et al. 2004, Jenson and Mehlhorn 2009). This is not a new or uncommon development. As Slater (2009, p. 181) has indicated: "knowledge of the ability of microorganisms to evolve resistance is as old as chemotherapy itself" and that "Paul Ehrlich suggested in 1907…that the use of single agents at subcritical doses would lead to drug-resistant organisms." In response, Ehrlich, the father of chemotherapy or artificial antibodies (Porter 1997, p. 448), pointed to the use of "a suitable combination of substances" in the "attack on the malaria parasites by employing quinine and methylene blue" (1907, p. 134).[9]

Presently the most effective combinations are based on derivatives of artemisinin, an extract from the plant *Artemisia annua*. These combinations, referred to as ACTs, are effective against the most virulent form of malaria in Africa, *P. falciparum*, though the method of their action is still uncertain. They are generally dispensed in pill form for uncomplicated malaria, but also may be used for more serious (cerebral) forms (Kyu and Fernandez 2010; also see Chp II/3/a). By June 2008, all but four nations and territories worldwide had adopted ACTs as the first-line treatment (WHO 2008, pp. ix, 16-17). Levels of use in children in 2008, however, were generally low (UNICEF 2010, p. 28). ACTs also may be, and are, used for *P. vivax* malaria in other regions, particularly southern Asia and western Pacific (Douglas et al. 2010).

While there has been a great deal of information available on malaria and its treatment in tropical regions, [10] and lately on ACTs, considerably less has been written about the supply of Artemisia and artemisinin. This paper provides an overview of these issues, their interactions, and their principal historical, scientific, technical, economic, and policy dimensions.[11] It also reveals something of the interactions between traditional medicine, modern medicine, and science - a prospective "golden triangle" (Mashelkar 2003, 2005, p. 1417; Anonymous 2007c:

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[9] "In 1891, with quinine's action in mind, he treated malaria with methylene blue, one of the analine dyes…: the results, he thought, were promising" (Porter 1997, p. 451; Guttman and Ehrlich 1891). And over a century later a report of the Institute of Medicine of the National Academies (NA 2004, p. 309) noted that it "very rapidly kills malaria in animal studies, and appears to be nontoxic at effective doses. It may be a good partner for a combination antimalarial regimen. Its potential utilility in malaria prophylaxis [is] still being explored." Such a study, conducted in late 2006 in Burkina Faso, demonstrated its effectiveness in combinations with artemisinin derivatives (Zoungrana et al. 2008; also see Coulibaly et al. 2009 and Bountogo et al. 2010).

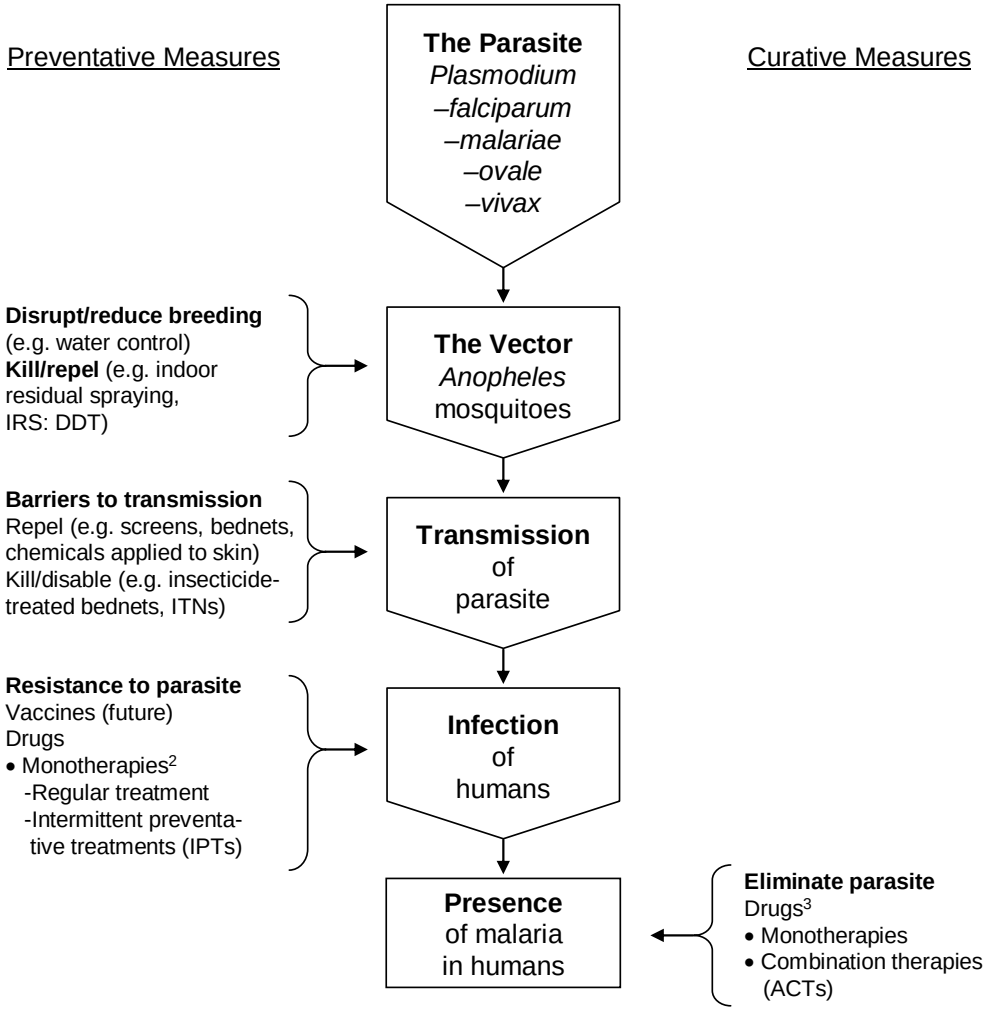
[10] Comprehensive reviews were initially provided in three special supplements to *The American Journal of Tropical Medicine and Hygiene*: "The Intolerable Burden of Malaria: A New Look at the Numbers," January/February 2001 (vol. 64, nos. 1, 2) 106 pp.; "The Intolerable Burden of Malaria II: What's New, What's Needed," August 2004 (vol. 71, no. 2), 282 pp.; and "Defining and Defeating the Intolerable Burden of Malaria III, Progress and Perspectives," December 2007 (vol. 77, no. 6, Suppl.), 327 pp. Subsequently, special sections on malaria control appeared in: *Nature*, August 19, 2004, pp. 921-945 and recently in the *Financial Times*, April 23, 2010 ("Combatting Malaria," pp. 1-6), and *Science*, May 14, 2010, pp. 842-851, 862-871.

[11] It does not attempt to examine the important interactions between agricultural practices and the incidence of malaria and vice versa. Some coverage of these issues is provided in (i) historical terms for Italy in Sallares 2002 and Snowden 2006, (ii) a special issue of *Acta Tropica* (vol. 89, no. 2, 2004), and (iii) Asenso-Okyere et al. (2009). Their role in vector control is also noted in Litsios 1996, pp. 133-142; Keiser et al. 2005; McCann, 2005; Kebede et al. 2005; Diuk-Wasser et al. 2007; and Oladepo et al. 2010. The parasites that cause potato late blight and malaria may use similar cellular mechanisms (Talbot 2007 and Whisson et al. 2007). The Consultative Group on International Agricultural Research (CGIAR) sponsored a Systemwide Initiative on Malaria and Agriculture from 2003-2006 (van der Hoeck 2004, Mutero 2006, SC/CGIAR 2008). It also does not consider the effect of malaria on corporate operations such as mining (see, for example, Batchelor 2010).

Zhiyong 2007). In terms of history, "As a practice, medicine is nearly as old as mankind. But as a science, it is one of the latest to mature" (Bruno 1987, p. 169).

Figure 1

Malaria Control: Principal Preventative and Curative Measures[1]



Notes:

[1] General and individual categories are not mutually exclusive: combinations are possible and under study or use. Does not include new and early-stage proposals such as breeding malaria-resistant mosquitoes.

[2] Due to the relatively high cost of ACTs, their short half-life, and other factors, they are not normally used for prevention.

[3] Recurrent malaria may occur following drug treatment without reinfection due to (i) dormant parasites with latent stages in the liver (relapse: *P. vivax* and *P. ovate*), or (ii) to surviving parasites (recrudescence: *P. falciparum* and *P. malariae*) (source: NA 2004, p. 140).

DGD 6/6/08

Chapter 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. All have lost effectiveness over time due to the development of resistance. Currently, derivatives of artemisinin, an extract from the Artemisia plant (*Artemisia annua L.* or *A. annua*), when combined with other drugs, provide the most effective treatment. They are known as artemisinin-based combination therapies, or ACTs.[12] The result is a drug which is both ancient in its use and modern in its formulation.

1. Artemisia, Artemisinin, and ACTs

The genus Artemisia comprises a group of plants known as wormwoods that have been utilized for a number of medicinal purposes, including malaria, for centuries.[13] A component and extract, artemisinin, has a very rapid onset of action against the malaria parasite (and is then very rapidly expelled from the body).[14] Certain other drugs have demonstrated a more persistent effect in preventing the recurrence (recrudescence) of malaria.

Thus, the inclusion of a second drug with these qualities in an artemisinin-based combination therapy (ACTs) "confers even greater protection against the selection 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[15] but can be constrained by biological factors such as significant numbers of drug-resistant parasites. Artemisinin can also markedly reduce the mosquito infection rate in areas of low transmission (which are decreasing in Africa).[16]

a. Early Development of Artemisinin and Derivatives. The traditional herbal remedy Qinghao (*A. annua*) has long been used in China. It was first noted in a document found in a

[12] The origin and first use of this very logical term are not entirely clear. One suggestion is that it was the Shoklo Malaria Research Unit, Faculty of Tropical Medicine, University of Thailand (e-mail from Nick White, April 2007), but dates and documentation are needed. In terms of more general adoption, the WHO Informal Consultation on the Use of Antimalarial Drugs in Geneva in November 2000 has been proposed (e-mail from Allan Schapira, April 2008; WHO 2001a). It was used in a similar consultation in April 2001 (WHO 2001b).

[13] Further details are provided in Wright, ed., 2002 and Willcox, et al. 2004. Other uses are listed in fn. 123, Chp. IV. 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, Headrick 1981, Philip 1995, Dobson 1998, Honigsbaum 2001, Rocco 2004, Hobhouse 2005, and Webb 2009 for details). Three other cinchona alkaloids – cinchonine, quinidine and cinchonidine – were isolated by 1847; they proved moderately effective and were less expensive; cinchodine became the "poor man's remedy" (Webb 2009, pp. 94, 102-116).

[14] According to Warhurst the "regularly quoted blood plasma half life for artesunate, for example, is 45 minutes. Even quinine, which is well known for its rapid excretion, has a longer half-life than this. For chloroquine…it is several weeks" (pers. com., April 2008)

[15] 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).

[16] It does this by (1) acting "against the gametocyte (sexual) stage of the malarial parasite [in the blood] as well as (2) the asexual forms responsible for malaria symptoms" (NA 2004, p. 23). The gametocyte role has recently been examined in two ways (a pooled analysis and mathematically) by Okell et al., 2008a, 2008b. Also see: Dunaven (2005, p. 82); Duffey and Sibley (2005, p. 1909); Mutabingwa (2005, p. 306); Bhattarai et al. (2007).

tomb dating from 168 B.C., while the first record of its use for malaria was made by Ge Hong in 341 AD.[17] In 1596, Li Shizen wrote in his pharmacopeia *Ben Cao Knog [Gange] Mu*, that qinghao "cures hot and cold fevers." (These and related matters are noted in **Annex 1** and more fully in QUACRC 1979, p. 811; Klayman et al. 1984, p. 715; Klayman 1985, p. 1049; Huang 1999, pp. 12, 452; Hsu, 2001, p. 8, 2006a, pp. 505-506; Zamiska and McKay 2007, p. A14.) It may also have played a role in the herbal "Englishman's cure" for malaria - largely attributed to quinine - developed by Robert Talbor in 1672 (Dobson 1998, pp. 76-79).

The emergence of chloroquine-resistant *P. falciparum* in southeast Asia in the 1960s (see Peters 1987, pp. 670-682) "brought the attention of the Chinese government to the seriousness of the malaria problem" (Jiaxing 1991, p. ii). A National Steering Committee on Antimalaria Research was set up in 1967 and an antimalarial drug discovery program – encouraged by a war-time request from North Vietnam – was established in 1969. As part of the latter, Chinese scientists, led by Zhenxing Wei and You-Tou Li (see **Annex 2**), examined hundreds of ancient folk remedies and were drawn to qinghao by Ge Hong's comments (Tu 1999). They noted the antimalarial qualities of Artemisia in 1971, developed an effective extraction process, and identified artemisinin as the active ingredient in 1972 (Klayman 1985, p. 1049; Anonymous 1992; Hien and White 1993; NA 2004, p. 133; Zamiska and McKay 2007; White 2008, p. 330; Ye 2008. Also see Li and Wu 1998, Jansen and Yin 2002, Hsu 2006b, Zhang 2006).

Further research was carried out by scientists at the Centre for Traditional Medicine and at the Second Military College in Beijing. The first report on this work in English appeared in 1979 (QUACRC 1979) and others appeared in 1982 (Jiang et al.) and 1984 (Li et al.). Two western visitors in 1979 learned more: Dr. Keith Arnold of Roche was shown data on comparative trials (Arnold 1993) and Dr. Adetokunbo Lucas of the World Health Organization discussed artemisinin, among other matters (WHO/TDR 2007a, p. 15). In 1980 the Overseas Development Administration sponsored a visit by Professor Wallace Peters of the London School of Hygiene and Tropical Medicine (LSHTM) and Chairman of the Scientific Working Group on the Chemotherapy of Malaria (CHEMAL) of TDR in February (pers. com. from W. Peters, April 2008).

The Chinese were interested in internationalization of artemisinin and subsequently contacted WHO for assistance (TDR 2007, p. 14). As the first step, Prof. Peters led a CHEMAL team, which included two malaria specialists from the United States and one from India, to Beijing in October 1981.[18] Their purpose was "to identify lacunae in present knowledge and to develop a research programme with Chinese scientists to determine the future application of these drugs to malaria control programs." In the period since 1972 the drug and several derivatives (dihydroartemisinin, artemether and artesunate) had been studied "with regard to efficacy in laboratory malarial models, pharmacology and pharmacokinetics (PHC) and toxicology (TOX) and clinical trials had been conducted" (CHEMAL 1981, p. 2; also see Jiang et al. 1982; Li et al. 1982). The major research lacunae were thought to be in PHC and TOX and

[17] The former was titled "The recipes for 52 Kinds of Diseases'" (or "52 Prescriptions") and was found in the Mawangdui Han Dynasty tomb. The latter was recorded by Ge Hong in "Zhouhou Bei Ji Fang," "The handbook of prescriptions for emergencies."

[18] U. S. members of the team were: Dr. A. Brossi, National Institutes of Health, Bethesda, Md. and Colonel C. J. Canfield, Walter Reed Army Institute of Research (WRAIR), Washington, D.C. (CHEMAL 1981, p. 17). For background on Chinese medicine and malaria drug development prior to this period, see Lei (1999).

he team prepared a research program which gave highest priority to them (pp. 2, 11-15). A program of future collaboration between the Chinese institutions and CHEMAL as well as the U.S. Food and Drug Administration, was also proposed (pp. 15-17; TDR 2007, p. 15).

The 1981 CHEMAL team also sought to "obtain a kilogram of purified artemisinin to be tested through its network of partner laboratories." When this proved to be difficult to get from Chinese sources, TDR commissioned researchers at the University of Mississippi in 1985 to grow the plant and provide one kilogram (see CHEMAL 1986, pp. 7-8 and **Annex 2**).[19] Shortly thereafter the original request to China was fulfilled. Both were distributed to participating institutions (including WRAIR) for additional study and development.

Concurrently, at the end of 1981, Dr. Nick White (a Wellcome Trust researcher stationed at Mahidol University, Bangkok) and three others met with two of the authors of the landmark QUARC report of 1979, Prof. Li Guo-Qiao and Jing-Bo Jiang (see Jiang et al. 1982) in Gunangzhou at the end of 1981. About a year later White was given artesunate for parenteral (intravenous or intramuscular) use to evaluate. He wanted to begin testing, but was dissuaded from doing so in view of other efforts and still has the sample (pers. com. July 2008).

Multilateral research activities during the 1980s centered about CHEMAL and TDR/WHO. Since some of the early research had shown artemisinin to have certain limitations such as water insolubility and bioavailability, various derivatives (discussed more fully in Chp. II/3/b) were studied. Initial attention was given to **artesunate**, but it too had limitations, relating to instability and possible fetal toxicity. By 1985 attention had turned to **arteether**, prepared by a laboratory process developed by a CHEMAL member, Dr. Brossi of NIH, which was similar to **artemether**. Though some CHEMAL members questioned whether it was the optimum compound, it became a major focus of the group, particularly for severe and complicated cases. This focus continued for the rest of the decade. Ultimately, however, it did not prove to be superior to semisynthetic artemether originally developed by the Chinese and faded from attention. The 1995 TDR report stated that "With hindsight some think that the decision to develop arteether was a mistake." Fortunately, the Chinese continued their development work. (CHEMAL: 1981, pp. 9-11; 1985, pp. 10-11; 1986, pp. 12-15; 1989 [Jiaxiang 1991]; TDR: 1987, p. 28; 1995, p. 71; Brewer et al. 1993; Canfield 1989; pers. coms., W. Peters and D. Warhurst, July 2008.)

Kunming Pharmaceutical Corp. in Yunnan Province was involved with the research and development process for artemisinin from 1971 and the firm began producing *artemether* in 1978 (Jansen and Zhimin 2002, p. 26; QACRG 1979). Chinese artemisinin was reportedly first marketed as a monotherapy in the late 1980s by Kumming (Zamiska and McKay 2007).

b. Artemisinin-Based Combination Therapies

The next step in the development process was the combining of qinghaosu with other drugs that had been experimentally tried with success during initial studies in China. Drug

[19] Subsequently, Klayman of the Walter Reed Army Institute of Research (WRAIR) sought a domestic source of *A. annua*. He found one along the Potomac River in Harpers Ferry west of Washington, D.C. in 1983. Plants were harvested that summer and used for research, which was hampered by short budgets and a neurotoxicity problem (Klayman et al. 1984, 1985; Li, Wilhouse and Weina 2007, p. 6; Milhouse and Weina 2010, p. 280).

combinations were not uncommon in China and had more generally been suggested for mefloquine in 1981 (WHO 1983, p. 176). The first written suggestion of the potential and limitations of combinations involving qinghaosu in an international publication appears to have been provided by a largely Chinese team in mid 1982 (Jiang, et al. 1982, p. 288): "An antimalarial with the combined advantages of mefloquine and qinghaosu would be very valuable in the treatment of acute falciparum malaria, but the combination of a short-acting and a long-acting drug, although very effective therapeutically, does not avoid the potential problem of resistance developing against the long-acting component."

From 1981 onwards, Chinese scientists brought samples of artemisinin to the London School of Tropical Hygiene and Medicine where considerable research was done on it, on interactions with other drugs, and drug resistance (CHEMAL 1986, p. 15; Chawira, et al. 1984, 1986a/b/c, 1987; Gu, et al. 1986; Peters, et al. 1986, Peters 1990; Wilkinson and Hardy 2001). In the early 1990s, the Chinese developed benflumental, later called lumefantrin, and used it in a combination with artemether.[20] The rights to sell it outside of China were purchased by Ciba-Geigy, later to become Novartis (Zamiska and McKay 2007), which named it *Coartem*®.[21]

Just when and where the term "Artemisinin [-based] Combination Therapy", ACT, was first coined is uncertain. It most likely occurred during the early developmental work by François Nosten and Nicholas White in Thailand in the late 1980s and early 1990s (Enserink 2010d). The subject was first discussed at the international level in an "Informal Consultation" on "The Use of Antimalarial Drugs" at the World Health Organization in Geneva in November 2000 (*WHO 2000a*). The list of abbreviations included "ACT: artemisinin-based combination therapy" (p. 4) and the section on "Combination Therapy" defined ACT as "antimalarial combination therapy with an artemisinin derivative as one component of the combination" (p. 17). This was followed by a more complete discussion and a subsequent review of derivatives (pp. 69-80). At that point, however, there were doubts "about the quantitative impact it will have in real-life situations" (p. 19).[22] The meeting led to a similar consultation on April 4-5, 2001 in Geneva (WHO 2001b); "Artemether-lumefantrine was noted for the first time and rated as "the most valuable artemisinin combination treatment available…" (p. 15).

[20] Lumefantrine is an aryl amino-alcohol compound, a category that includes quinine, mefloquine and halofantrine (NA 2004, pp. 253, 294). One account indicates that the "inventor" of this combination was Zhu Dayuan, now a Shanghai-based scientist (Wu 2007).

[21] They reportedly paid "a few" million dollars and agreed to pay a royalty on annual sales. The intellectual property rights are said to held by the Academy of Military Medical Science and co-owned by, or leased to, Novartis until 2011 (Dugue 2006). Novartis contracted with a Chinese group for further development work in 1994; studies for international registration began in 1995 and it was registered in Switzerland in 1999 (Olliaro and Taylor 2003, p. 3755). Further preclinical and clinical work was done to comply with western drug regulations (pers. coms. from Allan Schapira, March 2007 and David Warhurst, April 2008). It was to be sold in the developed world as *Riamet*® (Olliaro and Taylor 2004, p. 42). Subsequently it was submitted to the Food and Drug Administration in the U. S. for approval and was approved in April 2009 (see **Annex 8**).

[22] The meeting differed from the highly technical CHEMAL meetings of the 1980's in that it was much more policy-oriented. It was held at a time when there was increasing concern about drug resistance and a paucity of low-cost options. The meeting itself was quite structured and drew a wide group of participants (not, oddly, including China). A substantial report was issued (it even contained a bibliography with 338 entries). In retrospect it appears to have been a transformational event for ACTs and placed them squarely on the international stage. Background on WHO's involvement with medicines is provided in Greene 2010.

c. Subsequent Trials and Adoption of ACTs. Pioneering trials of various ACT combinations were conducted in southeast Asia in the mid to late 1990s under the direction of WHO/TDR and with USAID and Wellcome Trust funding (NA 2004, pp. 264-265; Olliaro and Taylor 2004, p. 41). ACTs were widely tested in the developing world and proved their worth (IASG 2004).[23]

A technical consultation in April 2001 called by WHO "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). By 2004, the artemisinins were considered "the *only* first-line anti-malarial drugs appropriate for widespread use that still work against all chloroquine-resistant malaria parasites" (NA 2004, p. 2). As of November 2008, 46 African nations had *adopted* ACTs as their first line therapy; 41 had *deployed* them (Bosman 2008, p. 2).

The demand for ACTs increased sharply after 2002 and was 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.[24] This expansion has in turn led to a corresponding increase in demand for 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.[25]

Most of the production of Artemisia, and in turn artemisinin, has come from Southeast Asia, principally China (which virtually has a monopoly), followed at some distance by Vietnam. India has only limited production. In China, Artemisia has long grown wild but an increasing proportion is cultivated (French 2005; CHAI 2008). 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 have been the principal sources of the artemisinin used in the manufacture of monotherapies and ACTs, changes are underway. The high prevalence of malaria in Africa led, not for the first time,[26] to interest in increasing the very limited level of

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[23] There are several types of artemisinin-based combination therapies involving combinations with other antimalarial drugs such as chloroquine, amodiaquine, mefloquine and piperaquine (see Chapter II/3/b). 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 Chapter II/3/b.

[24] 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 [sulfadoxine-pyrimethamine]." "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 (Chapters II/3 and IV/2).

[25] 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).

[26] In 1999, discussions were initiated between African Artemisia Ltd. (AAL) and the U.K. Department of International Development (DFID) which funded a study by FSC/RIO Ltd. into 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

production of Artemisia and artemisinin in that region. Significant progress has been made and unlike Asia, for which virtually no data are available, some statistics are at hand.

2. Artemisia: The Plant and Production

Artemisinin is, as noted earlier, derived principally from the leaves of Artemisia (*A. annua*).[27]

a. The Plant. Botanically, *Artemisia annua* (see Figure 2) 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 and is raised in an increasing number of countries. It is well suited to both small-scale and plantation culture. The seed is extremely 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 2b**).

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 to establish the crop 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. It is principally planted early in the calendar year and needs five to six months to mature (Ferreira et al. 2005, WHO 2006, Ellman 2009, 2010).

b. Production in Africa. Production was initially largely limited to East Africa - Kenya, Tanzania, and Uganda - and was essentially tied to the activities of one holding company, Advanced Bio-Extracts Ltd (ABE) (www.abextracts.com), and two subsidiaries: East African Botanicals (EAB), Ltd. in Kenya and African Artemisia Ltd. (AA) in Tanzania. In 2007, the name of the firm, reflecting a new investor, was changed to Botanical Extracts Ltd. (BEEPZ). Contract production was utilized and the firm supplied seed that has proven well adapted to the region; this process also provided a relatively uniform level of artemisinin.

The increased demand for artemisinin, starting in **2004**, stimulated efforts to increase the production of Artemisia in East Africa. ABE clearly was in a position to do so. The area subsequently placed 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**.[28] 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

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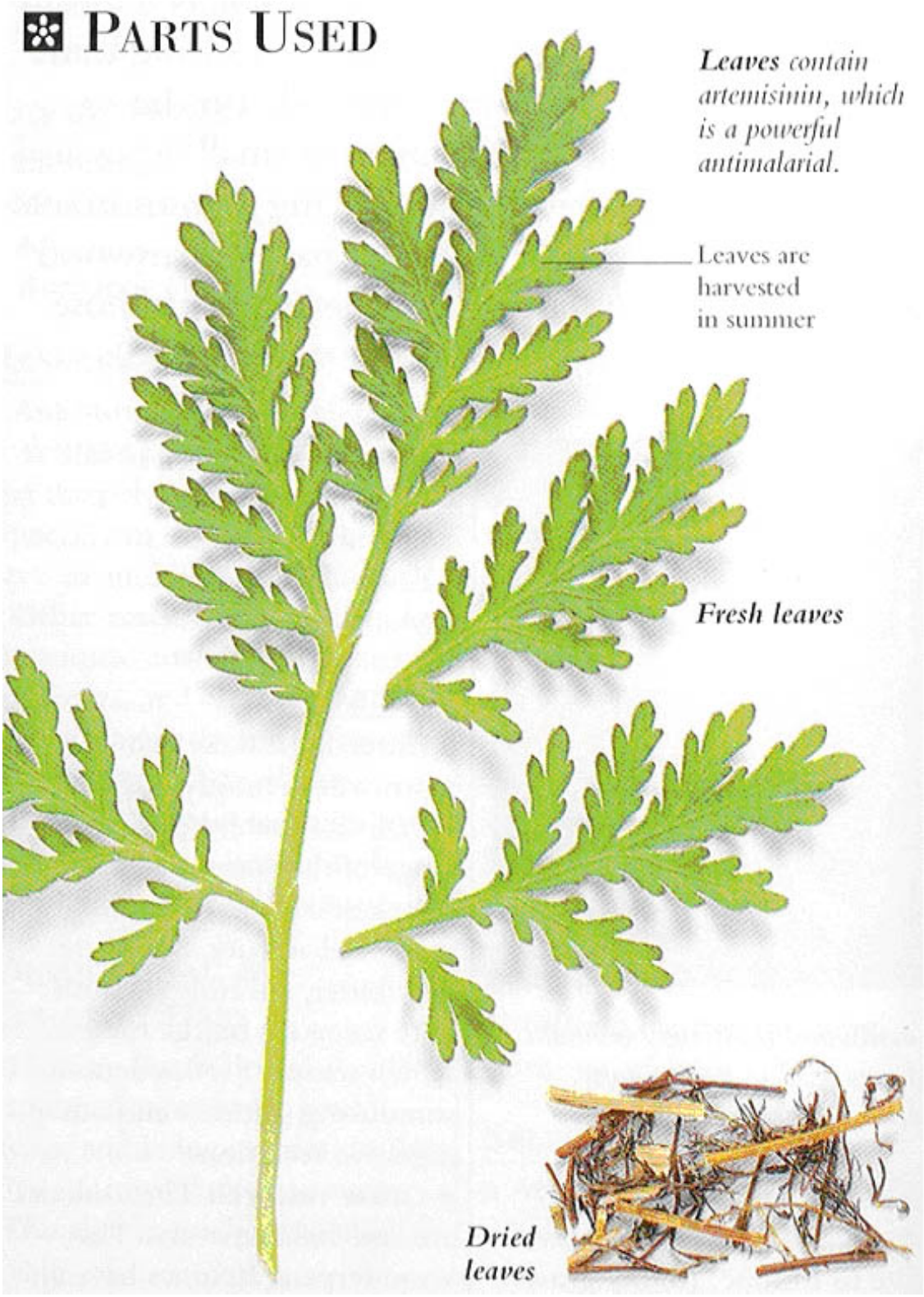
page missing, 1999, p. 2). A proposal for support of an initial investment in the cultivation and extraction of artemisinin in East Africa was made to a leading foundation but was not funded (pers. comm. from Brian Greenwood, LSHTM, May 2005). AAL continued to seek investment for a processing facility (TechnoServe 2004, pp. 22-23).

[27] Numerous other species of Artemisia exist, but they do not have the anti-malarial qualities of *Artemisia annua*. A Brazilian study indicated that the yield of artemisinin by plant part was, as a percent of the total yield, from the plant): upper leaves 41.7%, middle leaves 25.0%, lower leaves 22.2%, and side shoots 11.1% (Magalhaes 2007).

[28] 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. com. from Mick Baddeley, TechnoServe, March 2006).

Figure 2



Source: Chevallier (1996)

planted area was principally in Kenya (nearly 65%) followed by Uganda (19%) and Tanzania (north, over 16%) (TechnoServe 2005). Both small and large farms were involved.[29] In **2006**, 7,500 farmers were reportedly involved, but area was not revealed. Area estimates for **2007** ranged from 3,500 to 4,000 ha. (8,650 to 9,900 acres) (ABE 2007), but in **2008** dropped to about 2,000 ha. (5,000 acres) (pers. com. from Cutler 2008), and in **2009** to about 1,500 ha. (3,700 acres), including Madagascar (Pilloy 2009).

In northern *Tanzania* in 2006, the number of small farms involved reportedly increased from 227 at the start of the year to 3,957 by the end (TechnoServe 2007). They produced 515 tons of leaf. ABE provided F_1 seeds and paid farmers in two steps: first by weight and secondly by artemisinin content (generally in the 0.7 to 1.0% range). The overall price was cut about 25% in 2006 and in 2007 a modified payment plan was introduced, giving more weight to artemisinin content, lowering prices further for lots with artemisinin levels below 0.9%, and raising them proportionately for higher levels.[30] Another account states that production was discontinued in 2008 because payments were irregular and too low, in part due to high costs of transport to Kenya (von Freyhold 2009, p. 6).

Production activity has been reported in *Uganda* by Afro Alpine Pharma, beginning with pilot activities in the Kabale District in 2005. Subsequently it was stated that production agreements had been made with 5,000 farmers and were acquiring and storing dried Artemisia in Kabale (Afro Alpine 2006; Kajoba 2007).

In *Nigeria*, which has the largest number of malaria cases and deaths in the world (WHO 2008, pp. 10, 12, 14) – about 25% of the global malaria burden (NA 2007, p. 51) - preliminary trials of Artemisia were initiated in 2003 and study of the extraction of artemisinin in 2005. As of August 2007, over 1,500 ha (3,700 acres) was reportedly ready for production and of that 500 ha. (1,240 acres) had been planted with seeds from Brazil, China and some that had been bred locally for harvest by the end of the year. A number of public agencies and private firms are involved (pers. coms. from E. A. Brisibe, 2006-2007; Jegede, Brisibe, et al. 2007; Anonymous 2007d; NA 2007, pp. 50-54). No further information or confirmation, however, has since been received or found.

Plantings were also being initiated, to variable degrees, elsewhere in Africa. As of early 2006, areas included the Chinyanja Triangle (Mozambique, Malawi, and Zambia), Senegal, Ghana, Rwanda, South Africa, and Madagascar – which is presently the leader by far.[31] Production in other areas of the world is reviewed in Chapter IV/2/b and **Annex 3b**.

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[29] A large grower's perspective is provided in **Annex 3**. 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, small farms used F_2 seed and larger farms F_1 (which would normally be expected to produce higher yields; see Annex 2b) but this could be partially offset by denser planting of F_2 seed (pers. com. from Barney Gasston, ABE, April 2006).

[30] A survey of 100 farmers in 2006 revealed that they earned about 40% of their income from Artemisia and that in particularly promising areas, farmers were abandoning other cash crops. The increased incomes from Artemisia were largely spent on renovating houses, investing in education, and family health needs.

[31] Pers. com. from James Simon, Rutgers University, October 2005, February 2006. Simon and his team (**Annex 2b**) are actively involved with several of these countries. Also see Das (2005) and Mueller et al. (2000). In

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.

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). Problems identified by farmers in northern Tanzania at the end of 2005 included payment delays, insufficient training, shortage of seedlings, and lack of communication and transparency.[32] More generally, it can be difficult to consistently meet quality standards set by extractors and processors.

3. Artemisinin: Extraction and Use in ACTs

While the production of Artemisia is becoming more dispersed, the extraction of artemisinin and the production of artemisinin-based drugs are more industrial in nature and more concentrated. China has long been the leader, and there it has largely been in the hands of two firms which are jointly owned - a virtual monopoly.[33] Although a number of firms are known to produce monotherapies,[34] the ranks of those producing co-formulations of ACTs in one pill have been more limited.[35] Novartis has been the major source at the international level, but at least two Chinese ACTs have been reported sold or tested in Africa.[36] More recently, African firms have entered the scene with generic forms or different formulations.[37] Since Africa is becoming a significant producer of Artemisia, there has been a concurrent need for the expansion of extraction capacity.

Madegascar, a group known as Bionexx has been undertaking extensive trials of Artemisia and has recently acquired a existing local natural products extraction unit (see Giblain 2008 for further details).

[32] Key steps in the production and harvesting process are illustrated in: http://picasaweb.google.co.uk/abextracts

[33] Chongqing Holly is a major extractor and Kunming Pharmaceutical is the largest producer of derivatives and artemisinin-based drugs. Both are largely owned by the Holley Group of Hangzhou (Zamiska and McKay 2007; pers. com. from Malcolm Cutler, August 2008).

[34] 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. Also see Section 4d which follows.

[35] Blister packs containing separate pills (NA 2004, p. 61, fn. 1), most commonly amodiaquine and artesunate, are more widely produced.

[36] One is known as *Arco* and is manufactured by Kunming; it represents a combination of artemisinin with napthoquine (from the 4-aminoquinoline group that includes chloroquine) (Ouma 2007, Toure et al. 2009). The other involves co-formulations of dihydroartemisinin-piperaquine, and is noted in Section 3b which follows.

[37] A recent example is *Maladar*, introduced by Shelly Pharmaceutical in Tanzania in August 2007. Other local ACTs (non GMF) are produced by Cosmos in Kenya and Tanzania Pharmaceutical Industries (TPI) (pers. com. from Malcolm Cutler, August 2008).

a. Extraction of Artemisinin. Extraction can sometimes be carried out in existing facilities used for other products, but for the greatest efficiency, a new and largely dedicated unit may be called for. The construction of such facilities is an expensive and challenging task, and may be particularly so in Africa. Aside from their technical complexity and cost,[38] extraction plants need to be constructed in sequence with the expansion of production of Artemisia, and arrangements must be completed for the sale of the raw artemisinin to pharmaceutical firms for manufacture of the actual ACTs. Quality has been uneven.[39]

ABE, now known as BEEPZ, has also been in the forefront of artemisinin extraction. Initially, the firm (then established as EAB Ltd.) converted a former pyrethrum factory in Kabale **Uganda** for the production of crude extract (200 tons 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. Subsequently it constructed a new extraction facility in the export processing zone in Athi River, **Kenya** - registered as Botanical Extracts Ltd. - to carry out both crude extraction and purification. It was designed to process up to 4,000 tons of leaf, purify up to 60 tons per year of crude artemisinin (including the extract from Uganda), and produce 20 tons of pure artemisinin per year.[40] Operations began in January 2007. The firm is planning to become a multi-extraction company for pyrethrum (an insecticide extracted from the flowers of certain chrysanthemums which can be used to treat bed nets) and other locally produced natural products (ABE 2007; Cutler 2008; Duchon et al. 2009).[41]

In **Uganda**, Afro Alpine Pharma (AAP) of Kampala stated in October 2007 that it was about to begin its first export of artemisinin to CIPLA Pharmaceuticals in India (Mugisha 2007). A 15-acre pharmaceutical plant in Kampala, representing a joint venture between Quality Chemical Industries (QCI) and CIPLA, reportedly started production of an ACT named *Lumartem*, an artemisinin and lumefantrine combination similar to *Coartem*, in the summer of 2008 (Wendo 2007; GHR 2007, 2008), though this is now less certain. It reportedly took two years of trials before CIPLA certified the AAP powder as meeting required standards and WHO only recently certified the Kampala plant as prequalified. Moreover, AAP's

[38] 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-caffeinated 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 was 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).

[39] Standardization has been a problem: "Quantification of artemisinin purity and amount in plant material and extract to date has been characterized by a considerable inconsistency in values" (Lapkin et al. 2009, p. 908).

[40] 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).

[41] Initial financial support to ABE was provided by Novartis (Anonymous 2005b, Novartis 2005, Thayer 2005). A bridging loan of $14 million was made, largely for expanding processing capacity; Novartis was to purchase a significant portion of production. Additional support was subsequently provided by the Acumen Fund (Novogratz 2006, Friedman 2007). In 2007, Industrial Promotion Services (IPS) of the Aga Khan Fund for African Development (AKFED) became a major investor. IPS was reported planning to build an ACT facility in Arusha, Tanzania in cooperation with Kampala Pharma (also part of the IPS group) (Cutler 2008).

artemisinin will be shipped to CIPLA's facitities in in India for extraction and combined with lumefantrine and shipped back to the Kampala plant for final packaging (Wakabi 2010).

Nigeria, as part of its program to initiate production of Artemisia, arranged to import equipment from three firms in China for an extraction facility that would produce 20 tons of artemisinin. It was to be ready for a test run by January 2008. Artemisinin was to be sold to pharmaceutical firms in Nigeria, some of whom are already producing ACTs using imported artemisinin derivatives (pers. com. from E. A. Brisibe, August 2007; Anonymous 2007d; NA 2007, pp. 50-54).[42] Again, current information and documentation is lacking.

b. Artemisinin Derivatives and ACTs. Artemisinin, chemically a sesquiterpene lactone peroxide, is the source of four other derivatives which have a higher level of antimalarial activity (NA 2004, pp. 204-205; Novartis 2008b, pp. 18-19). The first is **dihydroartemisinin** (a.k.a. artenimol), which is intrisically unstable (Jansen 2010) . Three others are derived chemically from it - **artesunate**, **artemether**, and **arteether** (a.k.a. artemotil**) -** and are converted back to it in the body (NA 2004, pp. 253, 261-267; Jansen 2002, pp. 4-10, 15).

Each derivative has it own qualities and has been favored by one group or another over time. As noted in Chapter II/1/a, initial emphasis was in WRAIR was given to **arteether,** now viewed as a mistake, and then to **artemether**. Recently, **artesunate** has come into increased favor: it is preferred in areas of low to moderate transmission and can be given intravenously or as a suppository in severe or complicated cases (SEAQUAMAT 2005, Gomes et al. 2008, WHO 2008, p. 3).[43]

The artemisinin derivatives in turn are combined with another anti-malaria drug with a different chemical structure and mode of action against the parasite. These have been grouped in one study as: (1) aryl aminoalcohol compounds, and (2) antifolate compounds. The first, termed the **quines** here, includes quinine, chloroquine, amodiaquine, mefloquine, lumefantrine, and piperaquine; aside from quinine, they are the product of chemical synthesis. The **antifols**, include pyrimethamine, proguanil, and chloroproguanil (NA 2004, pp. 130-133, 252-253, 291-294). The **antifols** are often used in combination with sulfa drugs, which act on the same pathway, or with the quite different **quines**.

Four combinations were recommended by WHO as of 2006: (1) artemether+lumefantrine, **AL**; (2) artesunate+amodiaquine, **AS+AQ**; (3) artesunate+sulphadoxine-pyrimethamine, **AS+SP**; and (4) artesunate+mefloquine, **AS+MQ** (WHO 2006b, pp. 21-26).[44] A fifth,

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[42] One news report stated that eight companies were producing ACTs in Nigeria (Lyn 2007). In October 2006, Emzor Pharmaceuticals announced the manufacture of *Diasunate*, a combination of artemisinin and amodiaquine (Galadima 2006) and in November 2006 Greenlife Pharmaceuticals announced the launch of *Lonart*, "essentially a combination of artemether and lumefantrine" (Haruna 2006). A government agency, NIPRD, has reportedly "produced a new phytomedicine from local natural products...now at phase III clinical trial" (Rabiu 2008).

[43] A much earlier parallel is provided by the four alkaloids derived from cinchona bark: quinine, cinchonine, quinidine and cinchondine, all isolated by 1847. Quinine was the most effective, but also the most expensive. Cinchonine was termed the "poor man's remedy" in the U.S. and Europe but was still too expensive for most of the population in India and China (Webb 2009, pp. 102-103, 110-117, 122-123; also see Porter 1997, p. 334).

[44] A comprehensive review and assessment of ACT formulations is provided by Nosten and White (2007). Also see Jansen et al. 2007, Falade et al. 2008, Owusu-Agyei et al. 2008, and Kayentao et al. 2009. The public-private development of **AS+AQ** is reviewed by Pecoul et al. 2008, and field trials reported by Sirima et al 2009

dihydroartemesinin+piperaquine (**DHA+PPQ**), was added in early 2010 (WHO 2010b, p. 16).[45] Each differs in some quality and provides useful diversity over the African continent.[46]

AL was the only fixed-dose combination (FDC) up to about 2006; the other three were sold as co-blistered products (separate pills packaged together) but since then greater emphasis has been placed on FDCs (Dugue 2007b). Lumefantrine, while resembling mefloquine and other aminoalcohols, has the unique quality in terms of resistance of not having been available as a monotherapy. However, its bioavailability is quite variable and is enhanced by co-administration with fat (Laufer et al. 2007, p.163; WHO 2006b, p. 24).[47]

Other artemisinin derivatives used for special purposes include rectal suppositories (WHO 2007B, Gomes et al. 2008, 2009) and injections for severe/complicated malaria (NA 2004, pp. 256-257; WHO 2010, p. xi). An artemether-based oral spray for young children, ArTiMist™, has completed phase IIa trials in Rwanda (Berlin Pharma 2010, EMS 2010).

Only two of the ACTs have so far been prequalified by WHO as meeting international standards.[48] The first was *Coartem*® (**AL**), a combination of 20 mg of arthemether and 120 mg of lumefantrine, produced by Novartis in an adult formulation; a pediatric formulation, *Coartem*® *Dispersible*, was released in early 2009.[49] Other prequalified firms include Ajanta, Cipla and Ipca of India. *Coartem* was first adopted in South Africa in 2000 (Barnes et al. 2005), Tanzania in 2002 (Sisowath et al. 2004, p. 1014), and in Zambia in late 2002 (Zurovac et

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and Thwing et al. 2009. Field trials of **AS+SP** are provided by Nahum et al. 2009, Sagara et al., 2009, Allen et al. and **AS+MQ** by Agomo et al. 2008 and Faye et al. 2010. (Also see Chapter III/1/b and **Annex 12**.)

[45] It was first developed in China by Guangshou University of Chinese Medicine in 2003 and Marketed by Hollykin Pharmaceuticals under the brand name Artekin (NA 2004, p. 294; www.hollykin.com/). Trials in Rwanda and Uganda were promising (Karema et al. 2007) and several European groups and MMV supported its Phase III development and registration as *Eruartesim* (Nyanzi 2007, Möhrle 2008). It is to be marketed by Pfizer and Sigma Tau (Anonymous 2008h). A recent review of studies (Sinclair et al. 2009) and two sets of studies in Africa (Arinaitwe et al. 2009, Bassat et al. 2009) indicated that it had performed well.

[46] This is reflected in the patterns of deployment. As of 2008, **AL** was the principal first and second line ACT (23 of 44), followed by **AS+AQ** (18 of 44). **AL** was used over a wide area while **AS+AQ** was mainly used in West Africa (Bosman 2008, p. 2).

[47] One Chinese study found that the antimalarial potency of a gelatin capsule manufactured with oil soluble extract was more than 3.5 times that artemisinin "suggesting that artemisinin in oil might be easier to be absorbed by organism" (Yao-de et al. 1993). Similarly, a recent study showed that "concomitant food intake increased lumefantrine absorption in children with malaria" (Borrmann et al. 2010).

[48] This program was set up in 2001 to facilitate access to medicines that meet unified standards of quality, safety and efficacy and is described in http://mednet3.who.int/prequal, WHO 2005f and Kiivet 2008. For current information see: "Prequalification Programme" [http://apps.who.int/prequal/].

[49] About 75% of those using *Coartem*, usually in crushed form, were children and adolescents (Novartis (2006, 2008c, p. 25). A pediatric formulation underwent advanced clinical development and trials in cooperation with the Medicines for Malaria Venture (Chanda et al. 2006, Abdulla et al. 2008, Teklehaimanot et al. 2008). It was placed on the market in January 2009 and 16 million treatments were distributed to 13 countries during the year (MMV 2010, pp. 4, 6). It contains the same dosage level, has a cherry flavor (favored in trials), and dissolves easily (Novartis 2009; Guth 2009; MMV & Novartis 2009; Abdulla et al. 2010). A recent review/ meta-analysis confirmed its value in improving tolerability and treatment of children (Kurth et al. 2010).

al. 2005, p. 734).[50] The second is **AS+AQ** manufactured Sanofi-Aventus in Morocco, IPCA in India, and by Guilin in China.

Two fixed dose combinations, involving **AS+AQ** and **AS+MQ**, were expected to be lower in cost (Das 2005, DNDi 2005a & b, McNeil 2005b, Davidson 2006).[51] One, which has four formulations (adult, child, toddler, and infant), was released in March 2007 under two names: *Artesunate-Amodiaquine Winthrop*® (*ASAQ)* for public entities, and *Coarsucam*® for private markets (Cheng 2007, Diap 2007, McNeil 2007a, Sanofi-Aventus 2007). WHO prequalification approval was achieved in October 2008 (Sanofi-Aventus 2008).

c. Additional ACT Combinations. Other ACTs have been developed and are under trial in Africa. They may also be effective, sometimes with particular advantages or limitations (Kremsner and Krishna 2004; Mutabingwa et al. 2005).

Artemisinin-piperaquine**,** a promising new ACT, developed by Professor Li Guoqiao of Guangzho University (one of the first scientists to study artemisinin and ACTs), is known as *Artequick*®. A two-day dosage has proven promising in trials in South East Asia, Sudan and the Comoros Islands off the east coast of Africa. It has been used in mass treatment programs, first in Cambodia and then in Comoros with dramatically reduced carriage rates and no adverse events. (Pers. coms. from: Keith Arnold, Xin-zhuan Su, and Jianping Song, April 2009. On Artequick also see www.artepharm. On piperaquine see NA 2004, p. 294 and Somé et al. 2010.)

Other combinations include: (1) artesunate/sulfamethoxypyrazine/pyrimethamine (**AS/SMP**), developed by Dafra Pharma as *Co-arinate*, a 24 hour therapy (Sagara et al. 2006; Penali and Jansen 2008); (2) artemisinin/naphtoquine (**AN**), Arco®, a one-day ACT introduced in Nigeria (Isah 2007), Côte d' Ivoire (Toure et al. 2009), and Liberia (Anonymous 2008e); and (3) artesunate+azithromycin (**AA**), an antibiotic with mild antimalarial activity (Sykes et al. 2009; also see Padma 2009). As noted in Chapter I, combinations of methylene blue and **AS** and **AQ** have proved effective in trials in Bourkina Faso (Zoungrana et al. 2008, Coulibaly et al. 2009). Non-ACT combinations are also being sold.[52]

d. Multiple Combinations and Terminology. There have been an increased number of ACT combinations of two or more drugs with different forms of action.[53] This has raised

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[50] For early studies demonstrating the effectiveness of this combination in Africa, see T. K. Mutabingwa et al. (2005); Piola et al. (2005); Ramharter et al. (2005); Barnes et al. (2005, also Naik 2005). Seven recent African studies of *Coartem* are grouped in a supplement to the *Malaria Journal* (see Hommel 2009).

[51] The drugs were developed under the aegis of the Drugs for Neglected Diseases initiative (DNDi). **AS+AQ** is produced by Sanofi-Adventis of France and **AS+MQ** by Far-Manguinhos of Brazil. Both were provided in three-day packs and the goal was to reduce the cost to less than $1 a dose. Field trials of **AS+AQ** are reported in Sowunmi et al. 2005 and Sagara et al. 2008 (under the brand name *Artequin*); a pediatric version (*Artequin Pediatric*) has performed well in trials (Tietche et al. 2010). Both combinations experienced drug resistance earlier and may not have a long life (Mutibingwa 2005, p. 312; also see Jack 2007a).

[52] In a survey in four African nations (noted above) they were more commonly found in private markets (formal/licensed and informal/unlicensed) than *Coartem,* which predominated in public sector outlets such as hospitals and some clinics (Seiter and Andreasen 2007, p. 21). Numerous non-artemisinin combinations are available and some have been used in comparative studies (Zongo et al. 2005, 2007; Meshnick and Alke, 2005).

[53] Some of the first experiments with **pre-ACT** multiple combinations were reported by Peters (1970) and Peters et al. (1973, 1974), the latter involving combinations of chloroquine with pyrimethamine-sulfadoxine. Further

some questions of terminology, particularly on the non-ACT side where some of the partner drugs often represent combinations in their own right. When can it be said that one has meaningfully moved from double to triple combinations?[54] How different do the component drugs need to be to qualify as a triple combination? This general question will likely increasingly be with us, and could be of some importance as it involves drug-drug interactions and possible difficulties in gaining regulatory approval (see Pollack 2007). Peters provided and discussed a classification of combinations in 1987 (vol. 2, pp. 1003-1034),[55] but the matter does not seem to have been directly taken up in the more recent literature reviewed.

4. ACTs: Introduction and Implementation

As a relatively new and expensive pharmaceutical, ACTs were and are bound to face a number of challenges. They occur agaist a backdrop of what Shah has termed the "Karma of Malaria" (2010, pp. 121-140) and reflects experience that malaria is a normal problem of life and no cause for heroic measures. And if there is a problem, many will turn first to traditional medicines. But while this may be true of adults who have acquired a degree of immunity, babies and young children are far more susceptible and call for different measures.

a. Initial Availability of ACTs. At the outset, in November 2004, WHO announced a shortfall in supply of *Coartem* due to "a continued lack of raw materials," first artemisinin and then artemether, from its Chinese suppliers (WHO 2004b, Cyranoski 2004, McNeil 2004b). This problem subsequently eased (Anonymous 2005c), in part because of increases in production in China and Africa (Chapter III/2), and appears to have reversed itself by 2006 or 2007, with supply exceeding demand.

WHO reached an agreement with Novartis to make *Coartem* available at cost to ministries of health in developing nations. The negotiated price was $2.40 per adult course of treatment (four tablets twice a day for three days), which made it roughly comparable with oral quinine

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studies (Merkle et al., 1980, Peters et al. 1984) with a combination of mefloquine and pyrimethamine-sulfadoxine, indicated that "resistance developed to all the components far more slowly than when only two compounds were used." A larger study of this combination - later known as *Fansimef*® - was launched in cooperation with a manufacturer (Hoffman La roche) under the auspices of TDR and "proved its value" in extensive clinical trials, but they also provided reports of sulfadoxine toxicity, mainly in non-immune travelers and its future was in question (Peters 1990, pp. 505-506). The preexistence of sulfadoxine and pyrimethamine resistance in parts of Thailand together with developing mefloquine-resistance may have been an additional concern (pers. com. from David Warhurst, April 2009).

[54] Perhaps the first **ACT** combination that might be termed a triple, dihydroartemisinin-piperaquine-trimethoprim (also termed *ArtecomTM*) combined with primaquine (known as CV8 or CV8TM), was successfully used on a limited scale in Vietnam in the 1990s (Bosman and Mendis 2007, pp 193-194; White 2008b; pers com. from David Warhurst April 2009). An artesunate-atovaquone-proguanil combination proved effective in Thailand (van Vught et al. 2002). Other multiple combinations have been compared with ACTs (Mutabingwa et al. 2005, Sowunmi 2005; Zongo et al. 2005, 2007).

[55] The three principal categories, following more general practice in chemotherapy, were: (1) drugs with complementary actions including those on different stages of the life cycle and those acting sequentially on the same stage; (2) compounds with additive effects; and (3) potentiating drug combinations including action on pathways related to folate metabolism and in other ways, including triple combinations [pp. 1024-1028]. Two others of possible value were: (4) antagonistic combinations [e.g. as possibly between mefloquine and Fansidar], and (5) combinations with antimutagenic agents.

and nearly 20 times as expensive as chloroquine. The actual price for Coartem to patients may be higher, depending on whether it is distributed through public or private channels.[56] The overall cost differentials may be widened even further when there is over-diagnosis of malaria and consequent over-dosing of ACTs.[57]

b. Transition to ACTs in Africa. The shift from traditional drugs to ACTs has not been without its difficulties or difficulties, be they price or pace (Ogbonna and Uneke 2008).

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).[58] 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, and a further program for ACTs is being implemented (Chps. III/2/b/i and ii). Costs, however, are only one side of the story and need to be balanced with benefits and effectiveness: this is a more complex analytical process, but to date ACTs have fared well in several country studies.[59]

There were also substantial differences, at least initially, about the pace of research and development of ACTs and their adoption, both at the global and at the national level. Two key components involved "Viewpoint" letters to *The Lancet*. The first, by a group of leading scientists (White, et al. 1999), advocated combination therapy involving artemisinin. The second, five years later and by a more mixed group (Attaran et al. 2004), was directed to WHO and the Global Fund. It castigated both for continuing to endorse the conventional therapies and urged that they adopt ACTs as the first-line treatment for malaria. A debate followed, but four months later "the Global Fund held a closed door meeting in Geneva African countries

[56] A survey in four African nations - Burundi, Rwanda and, Uganda and Ghana - in December-January, 2006/07 revealed the following ranges for Coartem: public (public hospitals and certain health clinics) $4.80, private (licensed pharmacies, health clinics) $7.60; for other ACTs they were $1.50 (public), $5.00 (formal private) and $7.20 (informal private) (Seiter and Andreasen 2007, p. 21).

[57] Studies in Tanzania revealed, for example, that more than half the prescriptions for antimalarial drugs in three public hospitals went to those who had negative test results (Talisuma and Meya 2007, Reyburn et al. 2007). This in effect continues a practice that originated "during an era of cheap and virtually limitless antimalaria drugs" when it was assumed that it was better to treat febrile (feverish) cases than to miss one true malarial case (Reyburn p. 405). Self diagnosis at home may also lead to over-dosage (Hume et al. 2008).

[58] While plausible, no data were available in 2004 on the relative cost of synthetics yet to be developed. Moreover, the proportion of the cost of ACTs represented by plant-derived artemisinin is still unclear.

[59] As noted, overdosage will reduce *cost* effectiveness (Reyburn, et al 2007, p. 405). General measurement issues in an African context are reviewed by Goodman, Coleman and Mills (1999) and Mills and Shillcutt (2004, pp. 72-87). Economic studies can take two forms: traditional cost-benefit analysis and a health-oriented assessment of cost-effectiveness: CBA focuses on the degree to which a treatment is profitable; CE compares the relative profitability of several treatments (some correlation may be expected between the two, but this is not always the case). A contingent variation approach has two subsets: willingness to pay and willingness to accept. 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), Senegal (Agnamey et al. 2005), Tanzania (Wiseman et al. 2006), Nigeria (Mokuolu et al. 2007, Jimoh et al. 2007), and Zambia (Chanda, et al. 2007).

should retrospectively adjust all malaria grants awarded to specify ACTs" (Anonymous 2006). Others, such as national and international development agencies, were more cautious: while traditional drug formulations were still effective and in stock, they were inclined to a more gradual phasing-in (USAID's role is discussed in Chapter III/3). However, complex issues of supply and implementation existed at the country level and are still being worked out.

One unexpected twist was that over the period from 2000/01 to 2006, the use of any antimalarial drug fell in 10 out of 13 countries in Africa. Household surveys suggested that the supply of alternative drugs (including ACTS) were "still inadequate to compensate for progressive chloroquine disuse" (WHO 2008, pp. 22-25). Yet overall progress as of 2010, appears to have been promising except in central Africa (O'Meara et al. 2010).

c. Development of Resistance to ACTs. As Peters noted in 1985, "we must face the fact that drug resistance in the malaria parasites, notably in *P. falciparum*, has emerged as one of the outstanding public health problems that today endanger the endemic countries of the Third World" (p. 90). ACTs are much less likely to develop resistance than monotherapies because the half life of artemisinin and its derivatives is short, from less than one to only a few hours. This means that "after a course of treatment the next infective mosquito bite will give rise to a blood infection which is not likely to meet the drug immediately" and that "this avoids having selection pressure on the new infection until it gives rise to symptoms." [60]

Still, ACTs are not immune to this threat. Resistance to one ACT was noted in an area of *Thailand* in 2003 (Vijaykadga, et al. 2006). It is most likely to occur in highly endemic areas where monotherapies have been used for some time and not been replaced by ACTs (Yeka et al. 2005; NA 2004, pp. 5, 71-72, 80-81). Reports of incipient resistance to artemisinin derivatives appeared in 2005 in *French Guiana* and *Senegal* (Duffy and Sibley 2005, Jambou et al. 2005). Susequently, tolerance to ACTs, in the form of delayed clearance of parasites in the blood of some patients, was noted in *western Cambodia* along the border with *Thailand* – a "cradle of anti-malarial drug resistance" where artemisinin monotherapies have been available for 30 years (Enserink 2008b; Dondorp et al. 2009; Egan 2009; Enserink 2010c).[61] Resistance to AS+AQ also appeared to be increasing in *southern Cambodia* (Rogers et al. 2009), but recent efforts to improve control with nets and training seem to be having some impact (Anonymous 2010c). *Burma* is considered "a 'black hole,' a source of disease untouched by international funding" and "a disaster waiting to happen" (Johnson 2010). These events may well become of global concern because resistance can be spread by infected humans traveling, especially flying, from one malarious area to another and, in effect, infecting local mosquitoes;

[60] Pers. com. from David Warhurst, May 2008; also see NA 2004, p. 263. 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). Quinine, also a plant derivative, has a short half life, although not as short as artemisinin. Hobhouse (1985/2005, p. 36) suggests that "unlike the synthetics, quinine is not known to have produced or encouraged the development of resistant strains of the malaria parasite…." However, there are natural variations in the response and quinine resistance became relatively common after the Vietnam war (pers. coms. from Wallace Peters and David Warhurst, August 2008; also see Peters 1987, pp. 543-559).

[61] According to Warhurst (pers. com. April 2009), "The Thai/Cambodia border is an area where non-immune smugglers and illegal gem miners cross, mining excavations exacerbate mosquito problems, etc. Non-immune workers are most likely to want treatment, hence high selective pressure which renders drug resistant Plasmodium mutants fitter than the wild type." Also see IRIN 2009 and Samarasekera 2009.

chloroquine–resistant *P. falciparum* has been shown to have spread, perhaps in this way, from S.E. Asia (probably Thailand) to East Africa about 1978 (NIH News 2002; Wootton et al. 2002).

The nature of the ACT combination is an important factor in determining resistance. 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." As Panosian (2005, p. 716) put it: "one ACT does not fit all…partner drugs effective at one site [geographical area] may be ineffective at another." Similar observations were subsequently made by others (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).

Hence, it is not surprising that reports of parasite resistance to, or tolerance of, *partner* drugs have appeared to: (1) amodiaquine (**AQ**) in Sierra Leone (Grandesso, et al. 2006), Tanzania (Mutabingwa et al. 2005) and Uganda (Yeka et al. 2005); (2) **AQ** and sulfadoxine/pyrimethamine (**SP**) in Mali (Djimde et al 2008) and Gabon (Nsimba et al. 2008); and (3) lumefantrine, the companion drug in *Coartem*, in Zanzibar (Tanzania) (Sisowath et al. 2005, p. 1014).[62] Lumefantrine has the advantage that it has not been used as a monotherapy (Dorsey et al. 2007, p. 2218). Clearly, identifying and maintaining the appropriate ACT combination and dosage, in the face of the development of resistance, will be a continuing challenge.[63] Yet, once developed, they might be used in different combinations for different groups.[64]

While developing an appropriate combination is critical, resistance can be influenced by a number of other factors. Some start with individual decisions relating to the degree of adoption of ACTs because of issues of access, cost and the quick effect of artemisinin. Others relate to matters beyond individual control, such as (1) the instable nature of artemisinin and the possible perishability of ACTs at higher temperatures (Jansen and Shahid 2007, pp. 3254-3256), and (2) poor quality of some ACT drugs, either unintentional or intentional. And both may be influenced by international health policies and subsidies and the effectiveness of

[62] Sisowath et al. (2005, p. 1014) state 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 subtheraputic concentrations provide "an ideal scenario for the development of resistance." Ian Hastings, however, maintains that this is a misconception (pers. com. December 2005) and he and Watkins (2006, box 1) argue that "drug tolerance is unaffected by intensity of transmission."

[63] 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; NA 2004, p. 22) 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 (pers. comm. 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. The implictations of post-treatment prophylaxis also need to be considered (Price and Douglas 2009). Dosage levels may be important in patients with heavy parasite burden (White et al. 2009).

[64] Smith et al. (2010), following a modeling exercise, propose the possibility of using different ACTs within a specified region as part of a program to reduce resistance. This could consist of "distributing different ACTs at the clinic and for home-based care or formulating different ACTs for children and adults." The challenge would be to get two ACTs with sufficiently different modes of action and yet equally effective and acceptable.

national health policies and systems. A graphic portrayal of the interaction of these forces, some of which will be discussed more fully, is provided in Figure 3.[65]

d. Implications for Artemisinin Monotherapies. Although the focus of this paper is on ACTs, artemisinin monotherapies have been produced for decades. The nature and extent of this industry is not well recorded, but as noted earlier (Chp. II/3, fn. 34) much of it appears to have been linked to existing pharmaceutical production in China, S. E. Asia, and Europe.

The attitude toward them has changed sharply over time. Initially they were welcome in Africa. Dafra Pharma of Belgium, for example, introduced artemether tablets and injections in 1993 in Uganda, Kenya, and Burundi, and in the Congo (DR) and Zambia in 1995 where they proved effective. At that time very few fixed-dose (co-blister) ACTs existed and the firm introduced a combination of artesunate and SP tablets in 2002. The was followed by a combination of artesunate and amodiaquine and later by *Co-Arinate*, a artesunate/SP tablet, and *Artisiane*, used as an injection, and a paediatric fomulation of artesunate-lumfantrin in powder form. The production of Arinate was discontinued in 2007 (pers. com. from H. Jansen, July 2010). As of 2006 about 75-80% of the firm's annual sales reportedly came from monotherapies (Jack 2006a; also cited in Shah 2010, pp. 116-117).

The same year, however, concern about resistance arising from the use of monotherapies led WHO to publicly request *drug manufacturers* to cease and desist (Bohannon 2006, Brown 2006, McNeil 2006a, 2006b). By 2007, 40 out of 74 companies had indicated that they would stop producing them (WHO 2008, p. 17).[66] But as of mid-2009 the situation appeared no better: of 69 identified manufacturers, only 21 had withdrawn them, 14 said they intended to reply, and the remaining 34 had not disclosed their plans (Butler 2009; also see Bosman 2009). Similarly, as of April 2010, of 73 manufacturers identified since 2005, 36 had ceased production of of monotherapies, 6 declared their intention to comply, and 30 had not disclosed their position (Schwarte et al. 2010, pp. 100-101). Nearly all those complying were larger firms who had declared their intentions earlier, but "smaller companies [21 of which are in India and 5 in Nigeria] mainly targeting the private sector… are more prone to ignore the WHO appeal." They fill the void left when larger manufacturers withdraw monotherapies.

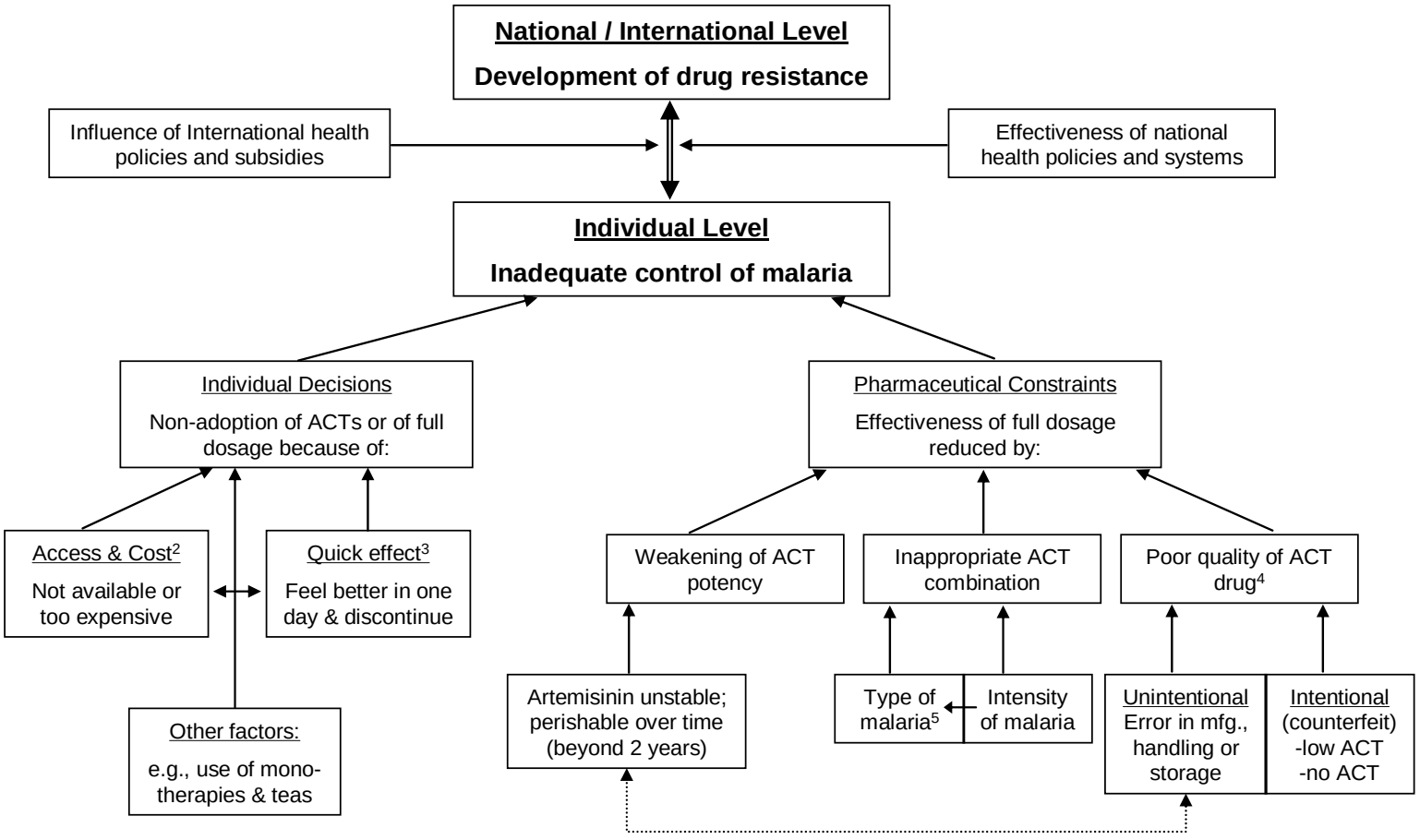
In terms of *national drug regulatory authorities*, in April 2008 36 of 78 or 47% were in line with the WHO recommendations compared to about 35% in January 2006 (Bosman 2008, p. 13). At the end of 2008, 41 countries still allowed marketing of monotherapies; the largest number was in Africa (WHO 2009b, pp. 12, 13); this was still true in February 2010 (Schwarte et al. 2010, p. 101). The Indian government mandated the cessation of sales of monotherapies by July 31, 2009 (CDSCO 2008, Singh 2009) and ten S.E. Asian nations agreed to ban the use of monotherapies by 2015 (Lyn 2009). One suggestion at the international level is an

[65] The figure is, of course, a simplification of more complex relationships and issues. It does not reflect the pernicious effects of artemisinin monotherapies. And counterfeits with no ACTs, while dangerous for the patient, will not cause resistance. A more fundamental issue is the relationship between underdosing and the development of parasite resistance (see Barnes, Watkins and White 2008). Other factors influence pharmacokinetics – the interaction of drugs and users (Laufer et al. 2007; NA 2004, pp. 254-259).

[66] For examples of press accounts of these events see Zamiska and McKay 2007 and Wu 2007. WHO has no power to directly enforce its 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).

Figure 3

Generalized Relationship of Varying Levels of Effectiveness of ACTs at Individual Level to Broader Development of Drug Resistance[1]



1. Individual entries are suggestive only; others may be possible or more appropriate in individual settings.
2. The two may be closely related, especially in the polar cases of subsidized public sectors and unsubsidized private sectors.
3. Individuals may save remaining pills for next attack or for other family members.
4. Except for subsidized purchases involving the Global Fund, which must meet WHO prequalification standards, drug regulation is a national responsibility and highly variable.
5. P. falciparum tends to predominate in areas of intense transmission.

DGD: 5/12/07

amendment to the International Health Regulations, which are binding on all member states of WHO, to obligate collective action to promote ACTs and to "discourage, or even prohibit, monotherapies" (Walker et al. 2009, p. 1346).

e. WHO Guidelines for Use of ACTs. As noted earlier in this chapter (II/3/b), WHO (2010b) recommends the use of five ACTs for the treatment of uncomplicated malaria: (1) artemether + lumfantrine, **AL**; (2) artesunate + amodiaquine, **AS+AQ**; (3) artesunate + sulfadoxine-pyrimethaine, **AL+SP**; (4) artesunate + mefloquine, **AS+MQ,** and (5) dihydrartemisinin + piperaquine, **DHR+PPQ**. In the latter case, WHO stated that "there is now sufficient evidence and efficacy…for its addition to the list." (p. 16). This point, however, is questioned by Jansen (2010) who states that "due to its intrinsic chemical instability, dihydroartemisinin is not suitable to be used in pharmaceutical formulations" (also see Haynes et al. 2007). As of the time of issuance of the Guidelines, "no DHA+PPQ product [had] been prequalified by WHO or registered by any stringent medicine regulatory" (*Ibid*). There is also the question of their use during pregnancy. Severe malaria (*P. falciparum*) is a leading cause of maternal mortality in areas where the disease is endemic. ACTs were endorsed by WHO in 2006 for use in uncomplicated cases in the second and third trimesters of pregnancy, but the need for more information on safety and dosing was noted.

While a number of such studies had been conducted on artemisinin monotherapies (NAS 2004, pp. 268-270), none had been done on fixed-dose ACTs. The first was carried out in northeast Thailand from 2004-2006 in an area "with unstable but highly-drug resistant malaria transmission" (McReady et al. 2008, Morris 2009). It compared standard doses of artemether-lumefantrine (**AL**) and **artesunate** and revealed that **AL** was very well tolerated, safe, and had no adverse effects. But its efficacy was less than **artesunate**, and both were below the 90% threshold recommended by by WHO. The pharmacokinetic properties of both were reduced in the latter stages of pregnancy and a dosage increase may be needed. Further tests under other conditions are needed, particularly it would seem, in Africa.[67]

5. Artemisinin Drugs: A Question of Efficacy

A more ubiquitious set of problems, dating back as far as quinine and endemic and to virtually all medications, involves marketing of counterfeit and/or sub-standard artemisinin drugs (see Figure 3, lower right). **Counterfeit** drugs have been "*deliberately* manipulated or made to resemble a specific (normally branded) product on the market." They may contain (1) a sub-therapeutic amount of active pharmaceutical ingredient, (2) no active ingredient, or (3) an inappropriate active ingredient. **Substandard** drugs "do not meet internationally accepted standards of identity, strength, purity and quality" (CGD 2010, p. 37; italics added).

Both have become pervasive in developing nations. Drawing the line between them ex post and at the margin may be difficult because of problems in determining degree of intent. The

[67] Comprehensive reviews of the use of artemisinins during pregnancy are provided in WHO/TDR (2006), WHO (2007d), and for artemisinins and other drugs in Ward et al. (2007). A recent study in Zambia is reported in Manyando et al. (2010). It has also been suggested that quinine might play a role in combination therapies with azithomycin for uncomplicated malaria throughout pregnancy (see Chico and Chandramohan 2010; on this combination more generally, see Noedl et al. 2006, Noedl 2009, Barennes et al. 2010, and **Annex 9b**.)

problem has been accentuated in the case of artemisinin-based drugs, in part due to their cost, shelf life, and the extent to which they essentially take the form of a monotherapy and thereby - paradoxically - threaten the efficacy of ACTs. Artemisinin is necessary, but is not sufficient by itself; the correct combination is essential.

a. Counterfeit Artemisinins. These initially were most evident in Asia (e.g. Newton et al. 2003, 2006, 2008; Lon et al. 2005; MacKinnon 2007). [68] One sampling in Southeast Asia showed that 53% were fakes; China is considered the chief source. The problems reported range from a total lack of artemisinin to very low levels (McNeil 2007a). The latter is more pernicious than it might seem because it "greatly increases the risk of the emergence and spread of drug-resistant parasites" (Newton et al. 2008).

In the case of Africa, counterfeit medicines are viewed as a major reason why malaria had become the "biggest child killer" and that they have been faked on an "industrial scale" (Nick White as cited by Shah 2007). In one case, Holley-Cotec announced plans to recall 20,000 doses of duo-cotecxin, an ACT, in Kenya because of the spread of a counterfeit version which did not contain active ingredients; the firm also said that it would introduce different packaging (Mwaniki 2007). And China initiated a new regulation that would limit exports to Africa to a group of government-appointed pharmaceutical firms and impose examination of the products before export (Anonymous 2007g). Still, counterfeits persist in Africa (Milton 2010); a new project would allow buyers to check authenticity by cell phone (Cheng 2010a).

b. Substandard Artemisins. These are not uncommon and can arise for a variety of reasons, intentional or unintentional, which are not always examined.

An early study of artemisinin derivatives purchased in Kenya and DR Congo in 2004 (Atkemnkeng et al. 2007a, pp. 70, 72) indicated that of 24 registered drugs analyzed, (1) all contained artemisinin, though in varying amounts ranging from 77.0% to 107.8%; (2) only 15 (62.5%) met the requirement of 95- 105% of active drug substance (in the case of Kenya, half were substandard); and (3) that 8 of the 11 (72.7%) substandard drugs (3 by 1% or less) were manufactured in China and India. (On transnational trafficking see UNODC, 2009.)

Furthermore, a study in six African nations in 2007 revealed that 35% of seven malaria drugs sold by private pharmacies were substandard, failing one or both of two tests (TLC and dissolution). The rate varied by formulation and region of manufacture: (a) it was highest for dihydro-artemisinin (55%) and lowest for artemether-lumefantrine (19%; 0 for *Coartem*); and (b) highest for drugs manufactured in Africa (48%) and lowest (0) for the drug manufactured in the U.S., again *Coartem*). Artemisinin monotherapies were common, representing 33% of all treatment packs tested (Bate, et al. 2008; McNeil 2008c). The researchers, however, did not test whether the drugs collected were poorly made, substandard, or fakes (Odora 2008).

A further study in Kenya in November 2007, found that 16% of the 113 brands from 20 countries were substandard and that popular older drugs such as amodiaquine and

[68] The International Medical Products Anti-Counterfeiting Taskforce, established by WHO and partners, reported in 2007 that they represented more than 10% of drug sales in developing nations and that "in parts of Africa, Asia and Latin America, more than 30% of the medicines on sale can be counterfeit" (WHO) 2007). Another estimate indicated that "the global fake drug racket is worth $40 bn. a year, and between 50 and 90% of medicine in some African and Asian countries is counterfeit" (Shah 2006).

sulfadoxine-pyrimethamine (SP) had high failure rates (45% & 30% respectively) (Gathura 2009a). A subsequent spot check conducted by the *Daily Nation* in Nairobi on June 2, 2009 revealed that the artemisinin monotherapies were still readily available "in almost all drug stores" (Gathura 2009b).

The most recent and comprehensive survey was conducted by U. S. Pharmacoeia for the U.S. Agency for International Development in Madagascar, Senegal and Uganda as part of a 10-country study (USP 2009). It included ACTs, SP (sulfadoxone-pyrimethamine) and other anti-malarials acquired from the public sector, regulated private sector and informal market. ACTs containing lumefantrine and artemether (coartem and duo-cotecxin) represented 21% of the total, were found in all three countries, and all samples passed the testing requirements. Other ACT combinations, generally manufactured locally, did not fare so well, but did better than the other anti-malaria drugs such as SP. There was no evidence of counterfeits.

Some unintended problems may arise from variability in production processes, poor quality control, poor storage conditions, and other technical problems such as a low dissolution profile (Atemnkeng et al. 2007a, 2007b; Gaudiano et al. 2007). It has long been thought that artemisinin derivatives have only a two-year life in hot climates, though the evidential basis for this is unclear. A recent study in Africa suggests that fixed-dose combinations of **AL** were "chemically and physically stable well beyond its stated shelf-life in uncontrolled tropical conditions" and "strongly suggested that a re-evaluation of the two-year shelf-life by regulatory is warranted" (Bate et al. 2009a).

In any case, "substandard [artemisinin] compounds have the potential to do as much harm as counterfeit drugs or even more" (Atemnkeng et al. 2007a, p. 72; also see Caudron et al. 2008) and underline the need for regulations and enforcement – the latter being particularly difficult in developing nations. Moreover, the wide availability and use of artemisinin monotherapies is becoming an increased source of concern, especially as their use threatens to undermine the unique efficacy of ACTs. Thus while the availability of artemisinin is a necessary condition, it is not a sufficient one: well chosen partner drugs are essential.

Since, as noted, the line between counterfeit and substandard drugs may be difficult to draw in some circumstances, it is unlikely that quick and easy overall solutions will be found.[69] While biology plays a role, the outcome depends largely on appropriate human action in the public and the private sectors.

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Altogether, ACTS are the product of a complex four-stage technical process involving (1) production of the Artemisia plant, (2) extraction of artemisinin, (3) the preparation of more effective derivatives, and (4) their blend with an appropriate companion drug. A host of implementation and operational issues complicate the process. The global context, the subject of the next section, adds daunting technical, policy, economic and development assistance issues. While the Artemisia plant is relatively simply grown in Africa, preparation of the final ACT and getting it into the hands of those who need it most is anything but simple.

[69] One possible exception has been suggested in the case of fake drugs: the use of cell phones, which are becoming ubiiutiousin Africa, to check on the authenticity of code numbers on the packages (Bennett 2010).

Chapter III. The Global Context: Supply, Demand, Subsidies, and Aid

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 activities of a multilateral and bilateral nature are carried on 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 two multilateral subsidy programs and a sequence of activities undertaken by the U.S. Agency for International Development.

1. Technical Dimensions of Supply and Demand

The demand for Artemisia is largely a function of the demand for artemisinin: it is a derived demand. While the initial demand for both was very strong, the situation has fluctuated in recent years, and 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. The technical dimensions of the shifts will be reviewed here and broader economic, policy and other issues in Chapter IV/2/b.

a. Supply of Artemisia and Artemisinin.

i. Artemisia: Area and Yield. The initial growth in demand for Artemisia led to increased area planted in a number of countries, but this has recently reversed due to a drop in prices, to be discussed in Sect. IV/2/b. One set of *global* estimates made in 2007 and subject to an uncertain degree of error, is: **2003**, 2,000 ha.; **2004**, 4,100 ha.; **2005**, 8,500 ha.; **2006**, 24,000 ha.; and **2007**, 14,500 ha. (Pilloy 2007; also see Cutler 2007 and Dugue 2007). Some of these estimates were further revised in late 2008 as follows: **2003**, 2,000 ha.; **2004**, 3,000 ha.; **2005**, 9,500 ha.; **2006**, 26,000 ha.; **2007**, 14,500 ha.; **2008**, 4,500–5,000 ha.; and **2009**, about 6,000 ha. (Pilloy 2008, RBM 2009). Clearly there was a sharp rise and fall in area.

The trends are particularly vivid for S. E. Asia. One partial set of indicative figures for a major *Chinese* firm indicate that 2,000 ha. of Artemisia were grown in **2004**, 6,000 ha. were projected in **2005**, and 9,000 ha. were expected in **2006** (Tan 2006).[70] The overall area in China, however is estimated to have fallen from 20,000 ha. in **2006** to 2,000 ha. in **2008** (Cutler 2008). *Vietnam* is also a substantial producer but the area is reported to have dropped from 10,000 ha. in **2006** to 3,000 ha. in **2007,** 1,000 ha. in **2008,** and 700 in **2009** (Cutler 2008, Artepal 2008). *India* has the potential for Artemisia production but no estimates of commercial production has been identified (Sharma 2006, Cutler 2008). The area in *East Africa* was placed at about 4,000 ha. in **2006** and **2007** (various sources) and perhaps half that in **2008** (Cutler 2008). Estimates are not available for other countries and areas.

Overall, the biological potential for expanding the cultivated area of Artemisia globally and in Africa and elsewhere is substantial – probably far in excess of needs. Estimates of the area

[70] The data were for Chongqing Holley sites in Chongqing, Hunan and Sichuan. Related biomass volumes were placed at 3,000, 10,000, and 14,000 tons. Production is carried out under contract and Holley supplies the seed. In one contract area, Artemisia had replaced "plots of corn, tobacco and potato" (French 2005). Further expansion of area has been encouraged (Jiajiao 2005). Nothing is known about overall Chinese statistics; it would be particularly difficult to account for wild production (see CHAI 2008).

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).[71] Moreover, the area needed for a given level of production will be reduced in time as a result of crop improvement efforts.

Two plant-related factors play critical roles in terms of yield: the *quantity* of leaves produced per unit of land and the *yield* of artemisinin extract from those leaves. Variety influences both; climate and soil pH and nutrition are also important, though this seems less clear in the case of extract levels. Improved hybrid lines 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 has extraction facilities available). Current research efforts to improve varieties with higher yields have been greatly boosted by two substantial breeding programs in England, one sponsored by the Gates Foundation at the University of York and the other with government support at the National Institute of Agricultural Botany, Cambridge (**Annex3b**).

ii. Artemisinin: Extractors and Extraction. Expansion in the production of Artemisia needs, of course, to be accompanied by a comparable increase the capacity to extract artemisinin; decreases in production produce a comparable change. One estimate suggested that the number of extractors/producers of artemisinin in *China* expanded from less than 10 to more than 80 in **2006**, and in *Vietnam* from three in **2004** to more than 20 in **2006** (Pilloy 2007). Another estimate placed the number of extractors in *China* at 100 in **2006** (Cutler 2007). Since then the number of extractors in China is estimated to have dropped to ten, of which five or six are significant (Cutler 2007, Artepal 2008).

These annual fluctuations have been reflected in dramatic form in the production of artemisinin. Precise data are not available but one set of estimates places the figures, in metric tons, as about: **2003**, 8-10; **2004**, 30-40; **2005**, 60-80; **2006**, 180-200; **2007**, 100-111; and **2008**, 30-40.[72] Some extractors have had significant carry-over stocks that they have used to meet orders. Even so, if production of artemisia declines as much as expected in **2009**, the overall supply of artemisinin could become serious (see Chapter IV/2/b).

The supply of artemisinin is also influenced by the efficiency of the extraction processes used. These are varied both within and between countries (Vietnam's are viewed as the least efficient[73]). There are, however, opportunities for improvements in existing processes and for new technologies (Lapkin, et al. 2006; Cutler et al. 2006; Cutler 2007). Where realized, the

[71] For example, one early estimate of area needed for a peak level of demand of 500,000 treatments per year was about 20,000 ha (nearly 50,000 acres) and about 4,000 ha (10,000 acres) for a "stable" level of 100 million treatments (Heemskerk et al. 2006, pp. 26-27, 51). A recent estimate placed the range from 23,000 to 28,000 ha. (57,000 to 69,000 acres) for a currently funded demand for 260 million treatments (Ellman 2010, p. 87, fn. 15).

[72] The estimates were prepared by the Procurement and Supply Management Working Group (PSMG) of the Roll Back Malaria Initiative of WHO. While it is composed of some of the most knowledgeable individuals in the public and private sectors, this does not necessarily mean that all proprietary information becomes public.

[73] In 2006 it was reported that Danish International Development Agency supported a project to help a Vietnam-based pharmaceutical company to upgrade its facilities, help register the products with WHO, and market the resulting ACTs worldwide (GHR 2006a, Holm 2006). No further mention of the project has been found.

comparative advantage of firms or regions could be altered and the cultivated area of Artemisia needed could be reduced and/or the effective supply of artemisinin increased.

b. Demand for Artemisinin: New ACTS. This aspect of demand in part depends on the degree of success that is achieved in developing effective new drug combinations to meet general market demands and special needs. The Medicines for Malaria Venture (MMV) has included a number of ACT combinations in its drug development portfolio (NA 2004, pp. 303-305, 307-310; Widdus and White 2004, pp. 7-8),[74] which involves many collaborators and alliances in the private and public sectors.[75]

The ACT portion of this process, as is typical of drug development, carries risks: some formulations which initially look promising may later show weaknesses requiring correction or, if serious, fall by the wayside (*Dacart* is a recent example).[76] As of mid-2009, two other products were in phase III trials (see **Annex 12**) and expected to move to the regulatory phase: (1) *Eurartesim*, dihydroartemisinin-piperaquine (DHA+PQP); and (2) *Pyramax*, pyronaridine-artesunate (Ramharter et al. 2008; Vivas et al. 2008; Bathurst 2008; MMV 2009a, p. 30; Tshefu et al. 2010). Other products under development were: phase II, IV artesunate; phase I, GSK Pyridone 121, Tafloquine, and OZ 439 (MMV 2009a, pp. 25-34; 2009b, p. 3).

MMV has also sponsored work on synthetic artemisinins which might be combined with other drugs (see below) and due to some limitations of ACTS - one being, as noted in Chapter II/4/d, that they should not be used during the first trimester of pregnancy - longer-term plans include the development of non-artemisinin combination therapies (MMV 2006c).

c. Related Considerations. Several factors, varying in nature, should also be taken into account in assessing the supply and demand for ACTs: here we consider other sources of supply, the ultimate need for a different type of drug, and further forms of treatment.[77]

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[74] Counting pledges, MMV expects that from 2000 to 2010 it will have received $323 million from 14 donors, including: Bill & Melinda Gates Foundation, 62.9%, United Kingdom (DFID) 9.0%, Wellcome Trust 6.5%, Netherlands (NDC) 5.3%, Irish Aid 3.4%, USAID 2.5%, Switzerland (SDC) 2.0%, Rockefeller Foundation 1.8%, NIH (US) 1.6%, World Bank 1.5%, Spain 1.5%. WHO/RBM 1.1%,, and others 1.1% (MMV 2008).

[75] One leading collaborator, perhaps not well known outside of the malaria community, is the Walter Reed Army Institute of Research (WRAIR) near Washington, D.C. It has long been involved on malaria research and has been one of the leading developers of new malaria drugs – including doxycycline, mefloquine and primaquine (NA 2004, pp. 305-307; Li, Milhous and Weina 2007, pp. 1-10). Other collaborators include university teams.

[76] In trials, *Dacart* - a combination of *Lapdap* (chlorproguanil and dapsone) and artensuate - which appeared as effective as Coartem, demonstrated a serious side effect (reduced hemoglobin levels in patients with a hereditary enzyme disorder that affects 10-25% of Africans) and development was discontinued by GlaxoSmithKline in February 2008 (Whalen 2008, Hirschler 2008). This effect is attributed to *Lapdap*, which had not been submitted for final trials (Craft, pers. com., March 2008) and was also withdrawn from sale in Kenya, its only and at that limited market (Kimani 2008, Luzzatto 2010). *Lapdap* was examined as a potential partner drug in ACTs in Africa (WHO 2002b), and labeled a "Highlight" for 2000-2005 by the Wellcome Trust (2005).

[77] 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).

i. Other Sources of Artemisinin. Artemisia is not the only possible source of artemisinin and ACTs are not the only drug-related treatment for malaria. Artemisinin can also be obtained, it now appears, from (i) a genetically modified form of the chicory plant, (ii) a new derivative of Artemisinin, and (iii) through chemical and biological *synthesis* - an approache that could provide cost savings and other advantages.

(a) ***New Plant Source***. Two European groups, Dafra Pharma (Belgium) and Plant Research International (Netherlands), who initially intended to biosynthetically produce artemisinin by combining microbial fermentation and chemistry (PRI 2005), subsequently reported the development of genetically modified chicory plants that produce artemisinin.[78] Following further research to determine how it can best be extracted from the root, Dafra hoped to be able to achieve inexpensive, large-scale production of artemisinin in three to five years (Dafra Pharma 2007a/b; no further information has been noted).

(b) ***New Derivative.*** An international group of scientists, largely at the Hong Kong University of Science and Technology and supported by Bayer and the Medicines for Malaria Venture [www.mmv.org], has developed a more active derivative of artemisinin: artemisone (also termed a semi-synthetic endoperoxide). It has greatly enhanced bioavailability, which means that lower dosages will be necessary, reducing the quantity of artemisinin and hence Artemisia, needed. It also has demonstrated other desirable qualities such as greater thermal stability, no detectable neurotoxity, and effectiveness at shorter dose regimes (NA 2004, p. 308; Haynes et al. 2006, 2007). A further study confirmed its effectiveness (Vivas et al. 2007). As noted, it was in phase II trials as of mid-2009 (MMV 2009b, p. 3).

(c) ***Chemical and Biological Synthesis***. The chemical synthesis of medicinals has a long history, starting in the 1800s and including aspirin and attempts to find a less expensive substitute for quinine – something "that every chemist in Europe had been trying to replicate for years" (Jeffrys 2005, p. 62). August Hofmann commented in 1849 that "Everybody must admit that the discovery of a simple process for preparing artificially the febrifuge principle of the Cinchona-bark, would confer a real blessing for humanity" (cited by Slater, 2009, pp. 25, 185).[79] Similarly, 155 years later, an article in *The Economist* stated "the great hope is to find a way of synthesing artemisinin in the laboratory, thereby freeing drugmakers from the vagaries of nature" (Anonymous 2004b). Current attempts at synthesis have taken three paths. (also see Wells and Poll 2010).

Semi-Synthetics. The Bill & Melinda Gates Foundation contributed $42.6 million to a nonprofit drug company, the Institute of One World Health (IOWH), in late 2004 to develop a new process ("metabolic engineering") that uses bacteria to synthesize a precursor of artemisinin at what was projected to be significantly reduced cost (Anonymous 2004d, Daviss 2005; Hale et al. 2007). Research results were promising and further steps included scaling up the process and the selection of a commercial manufacturing partner (Ro et al. 2006, Pontin

[78] This has been done through a "diversion" of a biochemical "pathway" that is already present in chicory plants, but in the genetically modified plants produces a precursor to artemisinin (dihydroartemisininic acid) that can easily be modified to artemisinin. Chicory is a well-established industrial crop in Belgium and the Netherlands.

[79] Work on synthetics originated in Germany during the 1920s and 30s and was taken up in the U.S. for military purposes in WWII (these events have recently been fully explored and well related by Slater, 2009, pp. 59-83). Intitially, emphasis was placed on screening and clinical trials involving atabrine (quinacrine) and mefloquine (resochin); chloroquine was a later product (Slater 2009, pp. 156-176; NA 2004, pp. 131-133, 305-307).

2007; IOWH 2007).[80] In early 2008, Sanofi-Aventis was named as the partner and planned to build a bioreactor in Europe by 2010 (One World Health et al. 2008; Connor 2008; Highfield 2008). By October 2008, an official of IOWH stated that, contrary to earlier expectations, the cost was expected to be "comparable to high quality field production" (Nguyen 2008). In September 2009 the project was considered to be in the pilot scale-up stage and was expected to reach production scale in 2010 and be launched as as an ACT in 2112 (Nguyen 2009; also see Specter 2009, pp. 56-59). By August 2010 it was confirmed that the drug "will be no cheaper than the plant-derived version" and instead of replacing it "will be used to smooth out the cycle of boom and bust in crop-based artemisinin supply" (Van Noorden 2010).

Full Synthetics. Two key efforts have been involved. (1) The Medicines for MalariaVenture (MMV), along with several research teams initially sponsored the development of two related synthetics which could be alternatives to artemisinin. The first was known as **OZ277** and initially appeared very promising, but stage IIA trials demonstrated some pharmaceutical problems and it was discontinued by MMV.[81] A second generation variant, **OZ439**, which is more stable, active and long-lived, is in Phase I trials (MMV 2007b, 2009a, Bathurst 2008, Möhrle 2009). (2) A second full synthetic, **NITD609**, involving many groups and identified through an extraordinarily wide search process, has recently shown strong initial promise. Preliminary tests with rodents have shown it to be as effective as artesunate, though slower acting. However, like OZ439, it is potent in single dose form – which leaves less opportunity for parasites to develop drug resistance – and shows properties compatible with conventional tablet formulation. Further preclinical evaluation is underway and if favorable it could soon move to phase I human trials (Rottmann et al. 2010, Wells 2010, NIH 2010b, Novartis 2010).

Mimic Synthetics. Scientists at Johns Hopkins, supported by the National Institutes of Health, have been developing a set of trioxane compounds that mimic the effect of artemisinin and promise to be considerably more effective at lower doses (Johns Hopkins 2004; Posner et al. 2004; Paik et al. 2006). Tests of a longer-acting version on mice demonstrated their ability to provide a cure after a single low dose (Johns Hopkins 2007; Posner et al. 2007; Rosenthal et al. 2009; also see www.jhu.edu/~chem/posner).[82]

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[80] The Institute 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.oneworldhealthorg], 12/13/04; also see McNeil 2005, and Bower 2005).

[81] OZ277/RBX11160, a synthetic peroxide, was combined with piperaquine (PQF) and entered phase IIb, clinical development, in cooperation with Ranbaxy Laboratories in New Delhi, as RBx11160. Widely reported targets included a 2009 launch at less than $1 per treatment (O'Neill 2004, Vennerstrom et. al 2004; Daviss 2005; Lucas, et al. 2005; MMV 2006). While a study in Colombia and Tanzania reported favorable results (Osorio et al. 2007), it revealed significant reductions in blood plasma concentrations in patients, & was unlikely to meet a three-day ACT treatment regimen (WHO recommends that each ACT component possess 90% efficacy within this period) (Bathurst 2008), and was not stable in the presence of free iron (pers. comm. from J. Carl Craft, MMV, March 2007; MMV 2007b). Ranbaxy, however, reported successful completion of phase II trials, including Africa, in July 2008 (documented in Valecha et al. 2010) and received approval from India's Central Drugs Standard Control Organization in October 2008 (Anonymous 2008f). The firm planned to go to phase III trials and in May 2009 announced that they had been initiated in Asia and Africa (Anonymous 2008a&b, 2009b). OZ277 is referred to as Arterolane maleate or *Arterolane* (Pednekar 2009, Möhrle 2009).

[82] These compounds have, in addition, proven promising in the treatment of cancer. The use of artemisinin and its derivatives in cancer control is discussed more fully in **Annex 9a**.

These approaches could lead to alternatives to both Artemisia and artemisinin. Some may provide therapeutic and other advantages, and may ultimately be cheaper. But the process of moving from the laboratory to the commercial level can be difficult, time consuming, and expensive. Moreover, any cost differential could be narrowed by (i) increased yields of Artemisia and/or percentage of artemisinin, and (ii) improved extraction processes (II/3).

ii. Need for a Different Type of Drug. As resistance to ACTs of whatever origin builds up, there will be an increasing need for a drug with a different mechanism of action against the parasite. Since the precise method of action is not certain,[83] it is not possible to tell in advance whether a potential drug has the same or different mechanism (pers. com. from Ian Bathurst, MMV, October 2008). MMV, in cooperation with other groups, is constantly testing other new drugs (see Möhrle 2009 for a recent graphic summary). One of the most promising characteristics of NIDT609 is that it is derived from a new class of compounds, spiroindolones, that quickly inhibit protein synthesis in both *P. falciparum* and *vivax*. It is thought to have "a mechanism of action different from those of artemisinin and mefloquine" (Rottmann et al. 2010, p. 1176). Even so, as Andrea Bosman of WHO's malaria program stated, "there is no possible replacement of artemisinin until 2016" (Samarasekera 2008, p. 1406). And even then the search for new drugs will likely need to be continued over time along with steps to limit the development of resistance.

iii. **Other Methods of Control: Vaccines.** ACTs are, as noted in Figure 1, only one form of drug treatment and drugs are only one form of malaria control. Development of improved *preventative* treatments such as vector (mosquito) control, barriers (bed nets), and vaccines could reduce the need for *curative* treatments such as drugs, and particularly the more expensive forms. Insecticide-treated bed nets, which are readily available, have proven effective in Africa (e.g. Fegan et al. 2007; Kamya et al 2007; Kulkarni et al 2007; Baume and Marin 2007); they might prove quite competitive in cost-benefit terms, but have been shown to be highly complementary when teamed with ACTs in Zanzibar (Bhattarai et al. 2007).

Development of *vaccines*, long underway, has proven very difficult (NA 2004, pp. 223-229; Sherman 2009), but 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). The promise of victory has been proclaimed several times (McNeil 2004b, Vogel 2004) and the results of one trial were hailed as "a revolution in our time" (Enserink 2004),[84] but then have faded from view. Once developed, licensing of vaccines can typically take

[83] As of 1991, "Most research" suggested that artemisinin acted by an oxidative mechanism and "effected changes in both red cells and in the limiting and other membranes of the malaria parasite" (Butler and Wu 1992, p. 89). Subsequently (1) Hartwig et al. (2008) proposed that artemisinin and its derivatives "are activated by heme-iron within the neutral lipid environment where they initiate oxidation reactions that damage parasite membranes;" and (2) Uhlemann et al. (2005) suggested that artemisinins "interact with the thapsigargin-binding cleft of susceptible SERCAs" (pers. com. from Warhurst 2009). Recent research by Wang et al (2010) indicated that artemisinin and OZ209 kill by "…direct disruption of mitochondrial functions" (p. 6; also O'Neill et al.).

[84] This led to a critical response by scientists in Africa 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 ACTs "can save lives right away at lower cost." MVI responded that "Its not either this or that – its both" (Enserink 2004; Snow and White 2004). For more general background see: Stern and Markel 2005, and Phelps 2003, 2010.

many years (Moorthy et al. 2004, p. 154). Cost-effectiveness tends to be highest in areas of low transmission and with coverage rates of less than 50% (Tediosi et al. 2009).

One of the most promising of at least nine vaccine current candidates, **RTS,S**, was first developed 20 years ago by GlaxoSmithKline (GSK) (McNeil 2007d, Mahler 2008a). In 2007 it passed a small but key safety trial on infants in Mozambique (Aponte et al. 2007).[85] Two further trials with children with relatively low transmission were promising in terms of safety and efficacy (about 50% protection); performance in areas of medium to high transmission was less certain, as was length of protection. In May 2009 a large-scale phase III trial, the first for any malaria vaccine, was initiated in Tanzania and will eventurally involve 16,000 children in diverse transmission settings in 11 sites in seven African nations; each site will involve a research partner from Europe or the U.S. It is hoped that RTS,S (known as Mosquirix) will protect at least half the infants for several years. If successful, the vaccine could be submitted for approval by health authorities in 2012 for children 5 to 17 months old with full availability in 2014 for infants 6 to 12 weeks (McNeil 2007d, Anonymous 2008i, Collins & Barnwell 2008, Abdulla et al. 2008, Bejon et al. 2008, Enserink 2008a, Mahler 2008a/b, Nayar 2009, MVI 2009, MVI & GSKB 2009, Whalen 2009, Anonymous 2009c, Cookson 2010). [86]

Other types of vaccines are under development. One, developed by Seattle Biomed, weakens the parasites and is about to undergo safety and then clinical trials (Heim 2010, Timmerman 2010). Another blocks transmission (Butler 2009b, PATH 2010, Cookson 2010, Szalavitz 2010, Vogel 2010). Further approaches, including vector control, are also under study.[87]

d. Balancing Supply and Demand: Phase I. Even when suitable alternate sources of artemisinin or vaccines are developed, other key steps remain such as the need to: develop the appropriate ACT combinations, conduct clinical trials, and secure appropriate approvals of national authorities. 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.

These and other developments mean that efforts to increase the *supply* of Artemisia at the farm level and of the artemisinin extract at the industrial 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,

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[85] All the infants were in homes that had received indoor residual spraying and insecticide-treated bednets. The investigators stated that "The future use and deployment of a malaria vaccine should be seen in the context of comprehensive malaria control programs. The test of concept trial suggests that vaccine-induced protection adds to the protection attributable to other control methods, particularly vector control methods."

[86] Another vaccine, which uses an adjuvant (an immune system booster from GSK) at a later point, the blood stage, has shown promise for protecting young children (ages 1-6) for at least a year in a Phase I trail conducted in Mali. Three doses were administered. The vaccine had a good safety profile and was well tolerated. The study was led by University of Maryland researchers and funded by several U.S. government agencies, including USAID. A larger Phase II trial has been initiated in Mali (Thera, et. al. 2010, Steenhuysen 2010).

[87] These proposals represent a variety of techniques, including genetically modified mosquitoes resistant to the malaria parasite (Marrelli et al. 2007). More distant possibilities could involve basic knowledge of gene synteny (Gardner et al. 2005, TIGR & ILRI 2005), and parasite delivery systems (Talbot 2007; Whisson et al. 2007).

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. This phase of equating of supply and demand is, and will continue to be, a challenging process.[88]

2. National Policy and Multilateral Programs

Just as malaria is a cross-border affliction of global magnitude, so must be the efforts to control it. Key components are national policies toward adoption and subsidy programs.

a. National Adoption of ACTs. National governments normally have a malaria control program in place. It typically has many components, one referring to the use of and choice of drugs to be used. If a new drug such as an ACT becomes available, national governments have to decide whether it will be part of the package and its place in that ranking. The selections in the past have varied according to their suitability to local conditions and needs. ACTs have to earn their inclusion and placement in this grouping if they are to be part of government-sanctioned or sponsored programs (as compared with the private retail sector).

The number of developing countries globally adopting ACTs as the first-line treatment for uncomplicated *p. falciparum* malaria has grown significantly, reaching a total of 77 by June 2008 (WHO 2008, pp. 16-17). Within Africa, out of 45 nations, 42 have adopted ACTs as first-line treatment and in seven of those cases as the second line treatment as well (quinine is the principal second-line treatment as well as the primary treatment for severe malaria and during the third first trimester of pregnancy) (Yeka et al. 2009; WHO 2009, p. 10).[89] There is usually a delay between adoption and implementation of 12 to 24 months.

As noted earlier (Chapter II/4/e), WHO presently recommends five types of ACTs: (1) **AL**; (2) **AS+AQ**; (3) **AL+SP**; (4) **AS+MQ**; (5) and **DHR+PPQ** (just added). The level of procurement, however, reveals significant differences in their earlier popularity: in 2006, **AL** represented 74.2% of the doses procured, followed at some distance by **AS+AQ**, 17.4%; **AS+SP**, 8.1%; and **AS+MQ**, 0.3% (Dugue 2007b).[90] It would be useful to know what a more recent breakdown might be.

Much of the procurement is subsidized and the ACTs almost entirely distributed through the public sector. But various studies have shown wide variances in availability at the local level (e.g., **Annex 7**, Kangwana et al. 2009) and household surveys in 18 African nations in 2006-2007 revealed that only 3% of children were given ACTs at any time (WHO 2008, p. 21). In 2007-08, in 11 of the 13 countires surveyed, the figure was less than 15% (WHO 2009, p. x).

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[88] For one early example, see Kindermans et al. 2007. As noted earlier, economic and policy issues, as well as steps to better align supply and demand other issues, will be discussed more fully in Chapter IV/2/b/iii & iv.

[89] The continued widespread use of quinine (29 countries) as the second-line treatment for uncomplicated *falciparum* malaria has recently been questioned on the basis of its actual efficacy (its unappealing taste, wide range of adverse side effects, and the need for a 7-day/3x-day regimin of treament discourage its use in the home). It is also a monotherapy. Instead, increased use of another ACT is proposed (Yeka et al. 2009).

[90] A recent meta-analysis involving 92 studies and these five combinations plus one other (AS+SMP) showed no significant difference in performance (Jansen and Lesaffre 2010).

b. Multilateral Subsidy Programs. The relatively high cost of ACTs compared with previous treatments for malaria has meant that they are normally beyond the reach of the poorest members of society, particularly in Africa, and this leads to the purchase of cheaper artemisinin monotherapies and ineffective drugs in the private sector (Coll-Seck 2008). The need for subsidy programs was realized early on and first made feasible with the establishment of the Global Fund to Fight AIDS, TB and Malaria. This effort has been reinforced by a USAID program (Section 3) and will be strengthened even more with the implementation of a special subsidy program for ACTs (also see APPMG 2007).[91] Both have some similar programmatic constraints.

i. The Global Fund to Fight AIDS, Tuberculosis and Malaria. The Global Fund (GF) was created in January 2002 to "attract, manage and disburse large amounts of additional financing to support locally-driven strategies to combat the three pandemics." It was set up as a financial instrument to "support programs that reflect national ownership, to pursue an integrated and balanced approach to prevention and treatment." Funding is provided through periodic multi-year contributions by individual nations and the Gates Foundation.[92] While the totals are very substantial, goals and needs are inevitably even larger (McNeil 2007c). Proposals are evaluated through independent review processes (Global Fund 2007).[93] As of 2006, nearly 30% of total funding went for malaria and composed 64% of overall funding for malaria (Komatsu 2007, p. 205); by 2009 the former figure was about the same (29%) and the latter had risen to about 75% (LaFranchi 2009; Kaiser Foundation 2010).

The available data on commitments and expenditures for ACTs are limited and vary somewhat. Bate (2007, p. 3) reported that "After a somewhat slow start, the Global Fund has

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[91] These are not the first subsidy programs for malaria drugs. In the late 1800s, Clements Markham, a British explorer, focused on introducing chinchona in India with a goal of providing a prophylactic dose of quinine for less than a farthing a day for anyone exposed to malaria. By 1880 quinine was sold at a subsidized price of half a farthing at post offices in Bengal, the most affected province (Hobhouse 2005, pp. 24-28). The program was extended to other provinces between 1890 and 1894 (Webb 2009a, p. 138, fn. 27). Corresponding 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). James wrote in 1920 (p. 198) that "India has led the way to the world" in this respect" (also see citation in Webb, ibid.). In the early 1900s, the Italian government undertook the free provision of quinine, financed by a tax on employers (Snowden 2006, pp. 51-65).

[92] U.S. contributions grew from $458.9 million in FY 2004 to $840.3 million in FY 2008. USAID was initially the main source but funding was fully shifted to the State Department by FY 2008 (Moss 2009, p. 15).

[93] The Global Fund's mode of operation was not without some initial difficulties for African nations. The *first* was the process of application. In 2006, "just over one quarter of all malaria control proposals…from sub-Saharan African countries were considered worthy of financing by the Technical Review Panel…." As a result the Roll Back Malaria Partnership initiated a campaign (a Harmonization Working Group) in early 2007 to help improve the quality of malaria proposals (RBM 2007b) and by rounds 7 and 8 the proportion of approvals had increased to 41% and 51% resoectively (Logez 2009). *Second*, while the Fund recommended that 5 to 10% of grant funding be used to strengthen the capacity for monitoring and evaluation systems, by mid-2006 only 3.9% was so used (Low-Beer and Nahlen, 2007, p. 325). A report issued in October 2006 indicated that the Fund "needs much better oversight of programs on the ground and must find ways to help countries make the initiatives work." USAID "designated $12.5 million in technical assistance" (Donnelly 2006, citing the Center for Global Development in Washington). *Third*, while the recipient countries are supposed to buy from WHO-qualified manufacturers, this is not always done and the fund is considering adopting central purchasing (McNeil 2007a, p. 4). Other criticisms of the process are provided by Bate: 2007a, pp. 3-4, and 2008b.

become the largest financier of ACTs…accounting for over 70% of the total purchased in 2006". Total Fund ACT expenditures in 2005/06 and 2006/07 were placed at $230 million, followed by UNICEF at $22.5 million and USAID (including other malaria drugs) at $21.4 million (Ibid, Table 1; USAID 2007; Brown 2006). By December 2006 the Fund stated that it had "committed finance to purchase more than 250 million treatments" (Global Fund 2007a, b, undated; also see Mueller, et al. 2005, pp. 10-11, 17). According to another source, in 2006 about 85% of the ACTs were procured with GF funding (Dugue 2007, p. 2).

Comparable data are evidently not available for subsequent years. A recent report on the first decade of Roll Back Malaria indicates that of its expenditures in Africa in 2008 on malaria, about 36% was for drugs and that while the Fund "does not disaggregate their "pharmaceutical category by drug type," the vast majority is for ACTs (WHO 2010c, pp. 42, 58). Similarly, a recent Fund report referred to the number of treatments for malaria as "increasingly using …(ACTs)" and that they totaled 29.5 million for Sub-Saharan Africa in 2009 and 90 million for the 2002-2009 period (Global Fund 2010a, pp. 16, 18-19, 21). The Fund clearly continues to play the major role in funding purchases of ACTs by developing nations,[94] but the implementation of these treatments, at least in terms of reaching goals, has evidently been more difficult than for the other Fund activites.[95] A recent effort to encourage use of international competitive bidding encountered difficulties (Tren et al. 2009).

ii. The Affordable Medicines Facility for Malaria. The Institutes of Medicine report noted earlier (NA 2004), headed by noted economist Kenneth Arrow, gave a lot of attention to the need for a subsidy program and it has subsequently received further study by Laxminarayan (2003) and Laxminarayan et al. (2005, 2006a, 2006b). In 2005 the World Bank 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).

A turning point took place in January **2007** when a group of health experts proposed the establishment of a fund to subsidize the purchase of ACTs for Africa (Max 2007). A key characteristic is that it would go beyond public clinics and involve the private retail sector, a major source of drugs for many Africans. Buyers would place orders directly with pharmaceutical companies and would be billed for only a fraction of the cost; the

[94] The Global Fund data on ACTs, where found, refer to approved funding and not the actual amount disbursed. Moreover, there is a lag between approval and expenditure, and countries do not usually log the actual numbers of ACTs provided (pers. comm. from Justin Cohen, Clinton Foundation, October 2008). In a recent study, predicted disbursements were placed as follows (in millions): 2003, $0.17; 2004, $7.48; 2005, $25.54; 2006, $90.00; 2007, $166.31; and 2008, $252.21 (Cohen et al. 2008, Table 2). Detailed survey data have been reported on (i) proportion of children treated and average expenditure per capita for Ghana, Tanzania and Zambia from 2005-2008, and (ii) annual ACT procurement expenditures per person by the GF, US/PMI and World Bank for 12 African nations from 2005-2008 ("often too low and too variable from year to year") (WHO 2010, p. 68-70).

[95] An assessment of the Fund's grant programs as of December 2008 showed that the antimalarial treatments (ACTs) had the lowest score of the ten programmatic indicators: 62% vs. 80% for the distribution of bednets (the third lowest). Also the malaria programs had the fewest A-rated grants (Global Fund 2009a, pp. 21-21, 54). Another Fund-sponsored study indicated that ACT purchases, based on country reports, were substantial in 2005 and 2006 (19.3 and 24.4 million courses). National health surveys (DHS, MICs) through 2007, however, revealed no or limited use of ACTS, with the exception of Zambia. But scattered DCA reports of availability in clinics in four nations in 2008 ranged from 36 to 94%, suggesting a substantial lag between orders and actual distribution (Global Fund 2009b, Chp. 7, pp. 9-10, 22-24, 39-40; also see Global Fund 2010, pp. 45-47).

manufacturers would invoice the global fund for the remaining amount.[96] Initial estimates of funding needs were about $80-100 million the first year, building up to about $250 million per year in subsequent years. The proposal was endorsed by the Roll Back Malaria (RBM) Partnership (Anonymous 2007, Associated Press 2007).

In February, RBM approved the creation of a Global Subsidy Task Force, which submitted a set of objectives, design principles and next steps to the RBM Board in May. The overall objective was to increase "the use of ACTs and drive mono-therapies and ineffective drugs from the market by [1] reducing end-user prices to an affordable level through a properly supported global subsidy of ex-manufacturer prices (CIF basis)… and [2] Introducing supporting interventions including proper use of ACTs." Six Principles were adopted, including the need for products to meet "internationally recognized quality standards" and the need for in-country "Regulatory preparedness" and the means to control local markups.

In October, the program was named the "Affordable Medicines Facility for malaria" **(AMFm)**. A comprehensive and balanced analysis of the proposal prepared for a committee of the House of Commons in the U.K. reviewed the rational and dimensions of AMFm as well as the risks of investing and not investing in it and concluded that "the concept…is sound, and it is right to proceed" (APPMG 2007b, p. iv). Reportedly, several agencies were interested in hosting the group (Enserink 2007). A detailed technical plan for launching the subsidy was considered and endorsed by the RBM Board in November; it placed the cost at $1.4 to $1.9 billion over the first five years (for details, see AMFm 2007).

The U.K. study indicated that the most significant risk is that such a fund "will in effect reduce the competition in the market" (p. 10). Others note that some dealers may be tempted to charge high prices for ACTs and middlemen may profit from the subsidy. Setting and maintaining appropriate quality standards for ACTs to be covered by the program in the face of an increasingly diverse array of branded and generic producers and formulations which are distributed in a variety of ways in both the public and private sectors could also be a formidable task.[97] It may require Africa governments to exercise a higher degree of monitoring and control than they can readily handle (Enserink 2007, also see Bate 2007b).[98]

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[96] As outlined by Seiter and Andreasen (2007, p. 11), the process "provides a simple, demand-driven payment." Orders for the ACTs, accompanied by a small payment, would be passed from retailers to distributors and then to manufacturers. They would provide the ACTs along with invoices to both the distributors and the ACT facility. The ACT facility would then provide the bulk of the payment to the manufacturer. The retail drug sector in Africa includes both (i) pharmacies with a qualified pharmacist, and (ii) other "commercial medicine sellers" who are a more heterogeneous group (Goodman et al. 2004, 2007). The AMFm materials reviewed to date refer only to "retailers" and do not seem to distinguish between the two categories; one writer suggests the former (Bate 2008b). This is an important point that needs to be clarified, particularly since ACTs are a prescription-only medicine in many African nations (Abuya et al. 2009, p. 911).

[97] The Global Fund, as noted, only supports drugs that have met WHO prequalification standards. For years, only ACTs produced by Novartis, Sanofi Aventis and Ajanta (India) qualified. Some other ACT formulations may meet less demanding international and/or regional standards. Where to draw the line and/or how to move from one set of criteria to the other over time? And who is to regularly monitor and enforce quality standards?

[98] The Clinton Foundation tested "the practicality of subsidizing ACT drugs" in two areas in central Tanzania (Kwitama 2007; Kerr 2007). As of April 2008, progress appeared promising (Samarasekera 2008).

Events accelerated in **2008**. In May, it was reported that the Global Fund had "agreed in principle to take responsibility for managing the subsidy" but that because of criticism, the final decision had been postponed until November (Jack 2008). The proposal drew differing reactions, principally as to its feasibility. One writer has identified the proponents "economists" - which they partly are - who are following through on proposals provided in the 2004 Institute of Medicine report (*Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance*, NA 2004), and the questioners as skeptics or "realists." The "economists want to get off to a fast and widespread start and make modifications through a learning by doing process. The "realists", who include USAID, want more evidence that the proposal will work and propose a "small, scientifically rigorous pilot program" before expanding (Rauch 2008). At an AMFm forum in September in Washington, the United Kingdom (DFID) announced a pledge of £40 million for the first stage (Enserink 2008; also see Laxminarayan and Gelband 2009). It was thought that if the Global Fund Board approved sponsorship in early November, and additional funding found - an initial effort could be undertaken in 10-11 countries (Witherspoon 2008, author's notes). Further funding would be needed to operate at levels initially contemplated (Samarasekera 2008).

In early November 2008, the Board approved the Policy Framework and Inplementation Plan and reaffirmed "its decision to host and manage the AMFm for an initial phase ('Phase 1') in a limited number of countries." The Secretariat was to "commission an independent technical evaluation of the rollout" which will be the basis for a recommendation to the Board on its completion (about the second half of 2010), "at which time the Board will determine whether to expand, accelerate, terminate or suspend the AMFm business line" (Global Fund 2008).

The program was formally unveiled on April 17, **2009**. Initial funding of $225 million was to be provided by Norway, the United Kingdon, the Netherlands, and UNITAID, a group of countries raising funds by a tax on airline fares (Witherspoon 2009). There were 12 eligible countries - 10 African nations, Madagascar, and Cambodia. Applications were reviewed by a Technical Panel and decisions made by the Fund Board in November 2009. The Pilot phase, involving funding of $216 million from the UK, UNITAID and the Gates Foundation, includes nine African nations and Cambodia (Global Fund 2009c).

Eligible products include **AL**, **AS+AQ**, **ASAQ**, and **DHP-PQP**, and must comply with the Fund's quality assurance policy, and manufacturers must commit not to sell oral artemisinin-based monotherapies or above "maximum prices". Co-blistered ACTs, a source of some controversy, are initially acceptable but the Fund may discontinue payments during Phase 1. Fund co-payments will be specific to each formulation and pack size and uniform across all suppliers. The Fund has the right to perfom random quality control testing before shipment and monitor manufacturing performance. The program is designed to provide supporting interventions and a "robust" monitoring and evaluation package (Jouberton 2009).

A major step toward implementation was announced in July 2010 when the Fund (aided by the Clinton Foundation) and six manufacturers of ACTs completed negotiations that would bring their price down "to the same level as for public sector buyers." The firms are Ajanta Pharma, Cipla and Ipca (India), Guilin (China), Novartis and Sanofi-aventus. All meet the Fund's quality criteria and have agreed not to market any monotherapies. Other firms may participate on the same terms (Global Fund 2010b), but these may be too strict for local firms

which could end up as, in the words of a Nigerian writer, "mere sales agents of foreign companies" (Anonymous 2010d).

As anticipated, USAID is not participating initially, pending further evidence of the effectiveness of the program – a position mandated by Congress (until there is "compelling evidence of success") (McNeil 2009a&b; Gumbel 2009). Similar concerns have been expressed, along with others such as misprescribing, stockouts and high opportunity costs.[99]

Some evidence on performance recently appeared for in rural Tanzania based on a study begun in October 2007 and involving a 90% subsidy through the normal supply chain to district drug shops in rural areas. The proportion of customers purchasing ACTs rose from 1% to 44.2% in one year and was significantly higher among those purchasing for children under 5 than for adults. Customers paid a mean price of $0.58 for ACTs, which did not differ significantly from the price paid for commonly-used alternatives (such as **SP**). There was very little price gouging, but drug shops in populaton centers were significantly more likely to stock ACTs than those in remote areas and hence "additional interventions may be needed…in these regions and for poorer individuals" (Sabot et al. 2009). A follow-up study revealed that "although totat ACT purchases rose from nearly negligible levels to nearly half the total antimalarial sales…considerable geographic variation in stocking and sales persisted and was relatedll to a variety off socio-spatial matters (Cohen et al. 2010). Similar results were obtained in Uganda (Talisuna et al. 2009; MMV 2010, p. 15; also see Patouillard et al. 2010).

iii. Similar Programmatic Constraints. Both the Global Fund and AMFm share the common limitations of virtually any subsidy program: they are tricky to design and operate, carry substantial reoccurring annual costs (bringing up issues of opportunity costs for public funds), and likely will prove controversial in some way.[100] Drugs intended for free distribution trough public clinics may be stolen and sold through the private sector (Bate 2010, Cheng 2010b). Moreover, initial enthsiasm for their funding may fade over time or be pushed aside by other emerging priorities.[101]

Subsidy issues can be mitigated if: (1) they are time-limited, which could prove to be the case if the development of synthetic forms of artemisinin actually result in sharply lower costs of ACTs, (2) the need for curative drug measures is reduced through less expensive preventative measures such as bednets, and (3) the over-diagnosis of malaria - which can lead to a wasteful

[99] Moon et al. 2009, Kamil-Yanni 2010, and Bate 2009. Doctors Without Borders notes that the program does not differentiate between combination (fixed dosage) pills and two-drug blister packs of ACTs. Some buyers remove the artemisinin tablets to sell as a monotherapy or take only the artemisinin because most companion pills taste bitter (Anonymous 2009a, McNeil 2009a).

[100] For example, Brown (2008) has noted that the Global Fund differs from traditional support for health care, which "was limited to one-time interventions such as vaccinations," in that it is used for treating chronic diseases in what may be viewed as an open-ended commitment. "The Global Fund already recognizes that treatment, once started, is essentially an irrevocable entitlement" (also see Jack 2007b and Navario 2009). Food subsidies in developing countries are "often viewed as stop-gap measures…(Fan 2008, p. 1).

[101] AIDs is a current example. Donors, reportedly fatigued by the high and continuing cost of treatments, have decided that "…more lives can be saved by concentrating on child killers like malaria." Under its new Global Health Initiative,"the Obama administration has announced plans to shift its focus to mother and child health." The same is true for the British government and the Gates Foundation (McNeil 2010, pp. A1, A10).

use of expensive ACTs - could be reduced.[102] But whether such steps would be sufficient to eliminate the need for subsidies is most uncertain. The funding problem will be particularly serious for Africa where it will be difficult to increase domestic financing appreciably: a recent study indicates that "there is still a possible 80% - 90% deficit in per capita funding for effective malaria control" for that region (Snow et al. 2008, p. 1075).

ACT stockouts reflect a more general distribution problem with essential medicines in Africa (PLoS Medicine Editors, 2009). In response several groups, including Oxfam and Health Action International, initiated a "Stop Stockouts" campaign in Africa in early 2009 that provides information and reports "incidents" for a number of drugs, including "First-line anti-malarials, AMs" (see: http://www.stopstockouts.org). A pilot project in Zambia sponsored by the World Bank showed that improvements in supply chain management led to significant increases in the availability of pediatric malaria drugs (World Bank 2010). And a recent study "at the outer edges" of the Tanzanian public health system using innovative everyday communication technologies in a public-private partnership showed that it is possible to provide more efficient stock management and significantly reduce stockouts of ACTs (Barrington et al. 2010). There are, however, other aspects of access and "pharma-covigilance" that also need to be considered (Chuma et al. 2010; Stergachis et al. 2010).

Marketing margins in the private sector may present another difficult issue. The complexity concerns their nature and size. They may be fixed, variable, or of quite different nature. Subsidies are linked to the price and income elasticity of demand for the product. Since malaria is largely a disease of the poor, those in need of ACTs in Africa have little or no discretionary income and thus negligible effective demand. Purchases of drugs or other methods of control come at the expense of other basic essentials such as food which may also have an influence on health. Hence what may seem like slight changes in the cost of ACTs could be of major importance in influencing purchases and the level and degree of their use by the poor.[103] The determination of subsidy levels under these conditions could become useful and may merit additional study.[104]

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[102] While there is general agreement on the extent of this problem (e.g. Drakeley and Reyburn 2009, Nankabirwa et al. 2009, Olliaro 2009, Sanson et al. 2009), there may be a question about how readily it can be mitigated. Recent experience has been variable. One study in Nigeria found that "Testing for malaria made almost no impact on ACT prescription or on all other antimalarials and antibiotics" (Nomhwange and Whitty 2009, p. 91; also see fn. 57). But another study in Kenya indicated that the use of **AL** only after laboratory confirmation reduced treatments by 63%; health workers "generally adhered to test results" (Skarbinski et al. 2009). The subject is discussed in greater detail in Chapter IV/2/c ("The Key Role of Diagnosis").

[103] Although "Sub-Saharan Africa is home to three quarters of all ultra poor" (Ahmed et al. 2007), a study at one hospital in central Nigeria indicated that many patients were willing to pay more for ACTs, even at current prices (Mokuolu et al. 2007). Further studies on willingness to pay are provided in Onwujekee et al. 2004, Wiseman, et al. 2005, and Staub, et al. 2008. Since the AMF will operate at the retail level, the nature of marketing margins and price and income elasticities of demand become relevant (some data on the size of margins in Uganda is provided in **Annex 7**). Preliminary data have been gathered by Bitrán (2008), but much more information of this nature is needed. There are also related concerns that (1) the system might leak at either end and benefit producers of monotherapies while distributors keep subsidy profits for themselves (Hartford 2009), and (2) as a variant of the latter, that "local market power may prevent may prevent such subsidies from being passed on on to rural consumers" (Goodman et al. 2009).

[104] A recent analysis by Laxminarayan et al. (2010) indicated that large subsidies "are warrented on externality ground across many scenarios…due to large efficiency gains…" "However, at extremely high infection

3. Bilateral Assistance & Multilateral Participation: 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 Chapter I) and were followed by a variety of multilateral and bilateral activities. These have not been well recorded or reported.

Some such information is available for the U.S. and may be illustrative.[105] 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.[106]

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). In 2000 a cooperative Drug Quality and Information Program was initiated with U.S. Pharmacopea to ensure drug quality, provide continuing education, develop and distribute drug and therapeutic information, and provide technical support for regional and international cooperation; although seldom noted in malaria literature it continues to the present [www.usp.org/worldwide/index.html?USP_Print]. From 1998 to 2003, the agency supported several studies relating to ACTs globally and in Africa (Kachur et al. 2004; USAID 2005a & b, pp. 46-47; WHO 2005e). [107] 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. Since 2004, USAID has provided $1.5 million per year to the Medicines for Malaria Venture and also support for the Special Programme for Research and Training in Tropical Diseases (USAID 2006).

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transmission rates [>70 infectious bites per year] subsidies may not be efficient because recovering individuals quickly become re-infected and there is little impact on reducing the size of the infected population."

[105] The initial malaria programs were undertaken after WWII by the International Cooperation Administration (ICA) and then, starting in 1962, by the Agency for International Development (AID). They emphasized (1) large scale assistance to individual nations and (2) in line with Congressional action (led by Sens. Humphrey and Kennedy) massive funding - $23 million a year for five years - for the global eradication efforts built around DDT (Shuler 1985, pp. 5-12; Cowper 1987; NA 1991, pp. 47-50; Shah 2006). 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). Some years later, in July 1997, "U.S. proposals to establish a common, centrally managed fund for malaria research were firmly rejected at an international meeting in Scheveningen…" (Butler 1997, p. 219; Varmus 2009, pp. 227-230).

[106] A review of the vaccine program though 1991 is provided in Diggs (1991) and further developments are summarized in USAID (2005b, pp. 8, 17-18). The early program faced tribulations (Marshall 1990; Diggs 1991; Hills 1994) and criticism (Desowitz 1991, pp. 221-276; Spielman and D'Antonio 2001, pp. 168-169). A detailed and well-informed overview has recently been provided by Sherman, 2009, pp. 124-157, 308-311.

[107] USAID was criticized by some for moving too slowly in stimulation the adoption of ACTs in Africa, but as of 2000 there were some significant questions about the 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 in 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).

Figure 4

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

USAID in collaboration with Roll Back Malaria (RBM) initiative [www.rbm.who.int], also 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 (2004) 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 4). 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 been provided for other national efforts in Africa (Chapter II/C).

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 was to reduce malaria-related mortality by 50/ in selected countries by achieving 85% coverage of vulnerable groups with ACTs, insecticide-treated bednets, intermittent preventative treatment, and indoor residual spraying (see Dugger 2006). Considerable emphasis has been given to commodity delivery.[108]

Numerical results in terms of ACTs have been as follows. In **FY 2006**, PMI allocated almost $2.4 million for ACTs (not all necessarily *Coartem*) and to other malaria drugs out of a total budget of $30 million in three countries: Uganda, Tanzania, and Angola. In **FY 2007** the allocation increased to nearly $19 million, four countries were added (Malawi, Mozambique, Rwanda and Senegal (USAID 2007), 11.54 million ACT treatments procured, 6.66 million distributed, and over 29,000 health workers trained in their use (USAID 2008, pp. 5, 67). In **FY 2008**, eight countries were added (Benin, Ethiopia, Ghana, Kenya, Liberia, Madagascar, Mali and Zambia), 15.35 million treatments procured, and more than 35,000 health workers trained (USAID 2009, pp. 2, 7, 96). In **FY 2009** the number of ACT treatments increased to 29.6 million, plus 8.9 million procured by other partners and distributed by PMI to the 15 focus countries. More than 41,000 health workers were trained in the use of ACTs (USAID 2010, p. 2). In addition, support was provided for control efforts in the DR of Congo, Nigeria and Sudan: more than 6.2 million ACTs were procured of which 5.4 million were distributed (USAID 2010, pp. 2, 30).[109] The report also goes on to review PMI operations research

[108] An editorial in *The Lancet* (Anonymous 2008g) stated that "Too frequently, donors tend to be commodity-driven…" In USAID's case this partly reflected the wishes of Congress and other groups and has represented about 50% of the program, recently lessening as other groups have, for instance, become involved in the provision of bednets. The overall proportion was placed at 47% in focus countries in FY 2008, varying from 33 to 66% (Kaiser Foundation 2009a). There are, however, no formal earmarks (personal conversation with Trent Ruebush, USAID, August 2008). The latter could have been the case if Senate bill S. 950, introduced in April 2005 (109th Congress, 1st Session), had been adopted as submitted. One provision (Sec. 3/7/D stated: "Not more than 5 percent may be used to carry out research, including basic research or operational research or vaccine snf therapeutic research and development" (also noted by Brainard 2007, p. 50). Other lesser restrictions would have required insecticide-treated bednets (now standard practice) and limitations of the purchase of drugs that contained chloroquine or sulfadoxine pyrimethamine if resistance rates reached certain levels.

[109] While these numbers clearly reflect an increase in *quantitative* terms, they do not reflect an interesting and important ongoing change in *qualitative* terms that will influence statistical inference. Increasing emphasis, as mentioned in Chapter IV/2/c, has recently been placed by WHO on diagnosis of malaria before treatment with ACTs. This means, as the AID report puts it: "With increasing use of diagnostic testing for patients with

activities designed to improve program implementation as well as contribute to the global malaria control effort more generally, vaccine development and drug development, and relations with U.S. government research organizations (pp. 54-58).

Plans for the 2009-2014 period include, resources permitting, (1) expanding "malaria control measures to reach large areas of the DR/Congo and Nigeria ($100 million) and up to seven additional high burden countries, and (2) technical assistance on forecasting, procurement, testing and monitoring of the quality of anti-malarial drugs, regulatory response to sub-standarrd druges, distribution, storage and inventory management, and post-marketing surveillance" (USAID 2010b, pp. 5, 8). It is difficult to predict overall PMI funding of ACTs as it is very dependent on country experiences and needs, but preliminary indications are that it "will continue to increase in 2010 and 2011" (Murphy and Kordi 2009).

In terms of legislative background and Congressional action, the key initial step occurred in July 2008 when President Bush signed an *authorization* bill (which also included AIDS and tuberculosis) to make up to $5 billion available for malaria programs over a five-year period running from October 2008 to September 2013 (Barber 2008, Kaiser Foundation 2009a). The actual amount *appropriated* depends on annual Congressional action. Recent budget data for overall malaria programs as a whole have shown significant increases: 2009 enacted, $550 million; 2010 enacted, $730 million; and 2011 budget request, $830 million (Kaiser Foundation 2010b, pp. 4, 6). In recent years, the PMI has focused on individual African nations, while multilateral funding for the Global Fund has been shifted to the State Department (fn. 92).

Since FY 2007, USAID has represented the largest proportion of U.S. government expenditures for malaria. By 2009, the breakdown by agency was: USAID 68.6%; Health and Human Services (Centers for Disease Control and the National Institutes of Health) 25.9%; and Department of Defense (WRAIR) 5.5% (Kaiser Foundation 2009c). The latter two agencies are particularly involved in research. In July 2010, the National Institute of Allergy and Infectious Diseases announced first year funding of $14 million to establish 10 International Centers of Excellence for Malaria Research (ICEMRs) around the world, each with a link to an American university/institution and a principal investigator (NIH 2010).

Thus the US effort in malaria over time has been a mixture of bilateral and multilateral efforts with some participation of the private sector. But overall, "the U.S. response to global health, as measured by funding and programs, has largely been bilateral. Over the past decade approximatly 86% has been channeled bilaterally. "As a result, some have called for increased multilateral engagement given the global nature of the health challenges…" (Kaiser Foundation 2010b, p. 10).

It would be useful to have a clearer picture of overall malaria activities by other countries and *national* assistance agencies.[110]

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suspected malaria, the ACT coverage indicator (proportion of of children under five with a fever in the last two weeks who were treated with an ACT) no longer accurately reflects progress with ACT scale-up" (p. 4). ACT treatments are and will be increasingly selective. Thus from a social accounting point of view, today's or tomorrow's measure of number of treatments will be more meaningful than those used in the past, and hence that simple comparisons of time series data may increasingly understate what has been accomplished.

[110] Summary data on malaria activities by the Department of International Development in the *United Kingdom* may be found at: [http://www.dfid.gov.uk/pubs/files/mdg-factsheets/malariafactsheet.pdf]. *China* also provides

At the *multilateral* level, the World Bank initiated a Booster Program for African nations in 2005, including provision of ACTs (World Bank 2007, 2009). More general multilateral programs have been reviewed by Nantulya et al. (2007), Rugemalila et al. (2007), and Bates and Harrington (2007).

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Drug control programs for malaria in Africa, while national or provincial in execution, ultimately operate in an international context. Artemisia, its extract artemisinin, subsequent derivatives, and ACTs are all part of a vast and interdependent regional and global chain of participants, processes, and programs. In the case of Africa it could be said to start with local producers of Artemisia, move to regional extractors of artemisinin and its derivatives, and then to national/international pharmaceutical firms. Thus, as shown in this chapter, the ultimate context is global in nature. Some of the policy dimensions of these varying levels and dimensions, which are of increasing complexity, are taken up in the next section.

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assistance, but this is a mixed package in Africa. On one hand, it has formal trade agreements with one (Nigeria) or more nations involving provision of technical assistance and equipment for Artemisia production and extraction. Loans are repayed in oil or other resources (Brautigam 2009, p. 306; French 2010). It has also invested in pharmaceutical firms in Nigeria and Tanzania that produce artemisinin (Ibid. pp. 223-243). On the other hand, its private sector exports artemisinin and ACTs to several African nations. In 2006 China promised to provide 30 malaria prevention and treatment centers in Africa; a recent account indicates that they have been completed and that artemisinin-based drugs are dispensed (Anonymous 2009d; Cyranoski 2010).

Chapter IV. Policy Issues: Public, Public/Private, Social, and Program

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. Moreover, 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.[111] In the recent words of the UK's chief medical officer: "Public-health interventions, such as effective therapy for a disease, epidemic control, or dissemination of research, are global public goods that address problems irrespective of national borders" (Donaldson and Banatvala 2007, p. 859).

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, undoubtedly building on the experience of Italy,[112] 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, another commission (Sachs, 2001, 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,

[111] 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).

[112] Italy passed a series of laws between 1900 and 1907 that attempted to control malaria through the use of quinine and sanitary legislation. As described by Snowden (2006, pp. 52-55), "The central government purchased quinine wholesale on the international market, packaged it in tablets at its factory in Turin, and distributed it to municipalities in all the malaria zones in Italy." The intention was that "every poor Italian at risk would receive regular medication for both prevention and cure at no cost and with the certainty that the chemical was unadulterated." The program was paid for by a quinine tax that local governments were required to levy on landlords and other employers of outdoor labor in malarial zones. Similarly, in an effort to prevent profiteering and assist citizens, a law was passed in Greece in 1932 giving the state the sole right to buy quinine and distribute it to retailers for sale at a price fixed by Royal decree (Bowden et al., 2008, p. 1102). "Quninization" in India in the early 1900s is discussed by Bhattacharya, forthcoming.

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.

The *interaction effect* is one. 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 when a reduction in 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, et al. 2004; WHO 2005b; also see **Annex 11**).[113] 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.[114] In the case of ACTs, however, we are dealing with *impure public goods*, ones that incorporate both public and private dimensions.[115] This is not uncommon. Musgrove (2004, pp. 39-42), 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. 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

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[113] Pigou, in his *Economics of Welfare* (1920), noted the situation where one person "in the course of rendering some service for which payment is made…incidentally also renders services or disservices to other persons" for which "payment cannot be extracted" (Coase 1960, p. 12). Externalities in medicine and health are important but relatively neglected in the literature reviewed to date. Coast et al. (1998, pp. 30-31) propose a series of three equations for negative and positive externalities and net benefits (see **Annex 11**, fn. 201). Smith (2004/2005) has provided a useful introduction in a power point lecture available on Google. Stewart and Ghani (1991) provide a more advanced general treatment cast in terms of dynamic externalities in developing nations - "the nonmarket transmission of technological innovation and the cumulative interaction of learning economies, scale economies, innovation and market growth" (p. 569).

[114] 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. Forbes Royle, a Reporter to the East India Company, recognized the value of cinchona in 1852 and expressed concern that supplies could run out (Honigsbaum 2001, pp. 11, 96). In 1857 he wrote that it was the "governent's 'duty to humanity' to gather cinchona seeds before the forests were stripped bare and raise the plant in India," thus "recasting the theft as philanthropy" (p. 98). This was subsequently done (pp. 99-168; also see Jarco 1993, Philip 1995, and Jardine 1999). A similar pattern was followed for Chinese tea (Rose 2010).

[115] 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).

cases noted earlier - the two new ACTs developed under the auspices of DNDi (Chapter II/3) and the bacterial synthesis process sponsored by the Gates Foundation in California (Chp. III/1) - and while not yet common, is receiving more attention.[116] The key issue here is the provision of incentive structures for the production and distribution of malaria drugs and vaccines in situations where (1) knowledge exists or does not and (2) usage is either limited to poor countries or both poor and other countries (see matrices in WHO 2010, pp. 15-17).

b. Allocation of Public 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, but are less useful in determining the form that intervention should take, and in financing and providing interactions" (Hanson, 2004, p. 17). Still, economic analysis can be of some use in defining (i) policies and (ii) relationships among policy instruments (Hammer 1993, pp. 3-12).

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).[117]

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 et al, 2006). Even with this data, it is difficult to determine impact because of the interaction between malaria control and improved economic growth; one feeds on the other (Sen 1999; Sachs and Malaney 2002, p. 681; Jimoh et al. 2007; Teklehaimanot and Mejia 2008; Bowden et al. 2008; Bleakley 2009).[118]

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[116] 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). Other universities have similar provisions see Chokshi (2005) and Brewster et al. (2005).

[117] 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). Similarly, Baker (2008) has recently noted, drawing on Indian experience, that "even if complete eradication cannot be secured, economic gains and reduced suffering may be worth the effort."

[118] The presence of a reciprocal effect provides substantial problems in interpreting the results of correlation analyses, such as those cited in Section I, involving the two. Generally such calculations focus on the presumed contributions of control to economic growth. It would be just as logical, and possibly quite useful, to think in

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).[119] A larger issue is the question of how much should be spent on 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 in a probably never-ending sequence of efforts to develop and maintain a reasonable level of control.[120] The research component thus serves a vital maintenance function.[121] But to move beyond this and to stimulate economic growth will likely require continuing and additional research efforts on several fronts along with a variety of other control programs.[122]

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.[123] 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.

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terms of the effect of economic development on the ability of individuals and governments to carry out control programs. See Chapter IV/4/c and Packard (2007, pp. 225-226, 245-246) for a fuller discussion of the issues.

[119] For example, when Global Fund data are combined with other donor contributions for 1999-2004, it appears that less than 2% of all contributions for malaria were earmarked for research and development (Waddington et al. 2005, pp. 4, 9, 13). Also see the issues raised in fn. 100.

[120] The costs of doing so can be very substantial for national health programs. A study in Tanzania assessed costs in one district for the period from August to September 2005 and extrapolated them to the national level. Drug and related costs would have represented 9.5% of the health sector budget and 28.7% of annual expenditures on medical supplies – a sixfold increase in the national budget for malaria control. A Global Fund subsidy was not available until December 2006 (Njau, et al. 2007; pers. com. from Njau, February 2007).

[121] 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 been noted for health by Ruttan (2006, p. 60).

[122] A very successful program in South Africa 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).

[123] Medicinal plants are to be distinguished from conventional agricultural plants such as corn, soybeans, tobacco and rice which may been 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, Kaiser 2008).

a. The Overall Framework. 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), other donors, and a series of cooperative efforts. The steps and principal players, from seed to consumer, are depicted in Figure 5.[124]

i. Research. The development of drugs has been greatly stimulated in recent years by funding provided through the Medicines for Malaria Venture (Lucas et al. 2005) and by the Gates Foundation. In the latter case, three programs are particularly relevant: (1) fast-track breeding of more productive varieties of the Artemisia plant (see **Annex 3a**), (2) development of a semi-synthetic artemisinin, and (3) development of a new and quite different set of synthetic drugs (noted in Chapter III/c/i). They form a logical sequence with different time spans and likelihood of success: (1) is very likely to provide improved plant varieties within two years; (2) is a medium-term effort which is now viewed as providing a supplement to Artemisia and that is in a transition stage from laboratory to commercial production; and (3) is a longer-term project to develop a drug with an entirely different form of action which could replace artemisinin when resistance develops but which still faces many hurdles and at best might not be launched until 2013. But beyond this, overall research efforts to date have been relatively uncoordinated and fragmented. Change, however, is under study in Europe[125]

ii. Subsidies. Since the poor in developing nations cannot afford ACTS, subsidies are, as we have seen, necessary.[126] The effective demand (ability to purchase) at the government level has been underwritten by the Global Fund.[127] 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 supplied by extracting firms, who then provide the market for the Artemisin produced by farmers. Thus the whole process hinges on the combined effects of (1) the negotiated price for the ACT and (2) the subsidy provided the developing nations. The picture will likely get more complex with the enactment of the subsidy program for ACTs (Chapter II/b/i) that will have a different way of handling payments. It is not yet certain how the two programs will interact.

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[124] The figure is incomplete in one respect: it does not specifically reflect the preparation of artemisinin derivatives (Chapter II/3/b). This may be done by independent companies or the pharmaceutical forms themselves. For another graphic treatment, see "Projected Stakeholder Map of the ACT Supply Chain" (CGD 2007, p. 21). A more general depiction of health innovation systems is provided in Morel et al. (2005, p. 402).

[125] The newly established CRIMALDDI Consortium, funded by the European Union, is a "co-ordinated, rational, and integrated effort to set logical priorities in anti-malarial drug discovery initiatives" over a two-year period (see Boulton, et al. 2010 and www.crimalddi.eu).

[126] 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 by in NA (2004, pp. 79-111) and by Laxminarayan et al. (2005, 2006).

[126] As noted earlier (Chapter 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 have generally been higher.

Figure 5

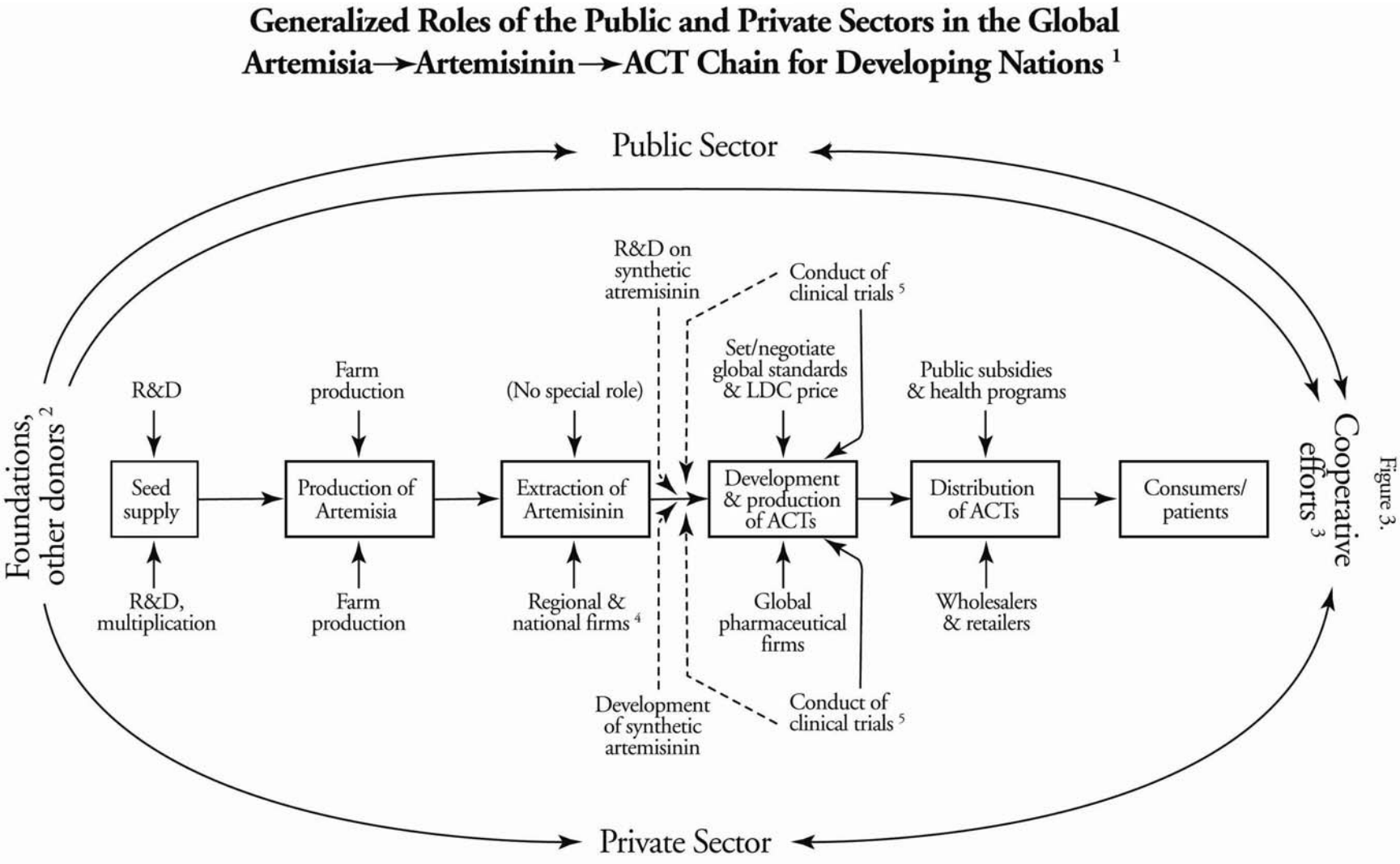

Figure 3.

[1] ACTs: artemisinin-based combination therapies.

[2] 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.

[3] These represent joint public-private efforts such as the Medicines for Malaria Venture and the Malaria Vaccine Initiative.

[4] Global firms may, in some cases, help fund these firms for this purpose.

[5] Dotted line refers principally to trials of synthetic artemisinin and less to cases were artemisinin is used as a monotherapy.

DGD: 5/2/05

Should, however, the overall financial resources available 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). The sustainability of subsidies cannot be taken for granted.

b. Balancing Supply and Demand: Phase II. Here we turn to economic and policy-related issues. Balancing market supply (the production of ACTs) with effective market demand (placement of orders backed by adequate funding) is difficult to do in the absence of normal direct market mechanisms. It is also complicated by the relative lack of statistical data, particularly on production, in the public domain.

The need for improved balance was foreseen in some quarters and an early attempt made to cope with it (see Grace and Grupper 2005). In April 2007, the Roll Back Malaria Board approved the establishment of a Working Group on Supply Chain Management which includes a theme on forecasting and quantification of malaria commodities [http://www.rbm.who.int/psmwg.html]. ACTs are included and several surveys have been cited here (Cutler 2008, Kindermans 2007, Pilloy 2007).

Elsewhere, "The ACT Supply Chain" has been further analyzed in some detail as part of a larger study on the need for better demand forecasting for drugs at the global level and options for doing so (CGD 2007; also see figure for Novartis in CNAP 2008, p. 26). It states that most of the risks fall to suppliers and that there is significant scope for better risk sharing.

i. Artemisia and Artemisinin. The market situation for these commodities, as suggested earlier (Chapter III/1/a), seems to have become considerably more unbalanced in 2007 and 2008, with the supply of artemisinin well in excess of market demand.

The result, as reported in mid **2007,** was a serious overstock situation (an estimated 120 mt of artemisinin in China and Vietnam) and resultant depression of prices - reportedly from an average of $1,200/kg in 2005 to $200-400/kg in 2006 (data from cutler as reported in Dugue 2007a, p. 9). This in turn affects the production-marketing chain. *Farm producers* of Artemisia, receiving lower prices suffered reduced incomes and switched to crops which have a more dependable – if not very profitable – level of demand.[128] Once burned, they may be less likely to resume production of Artemisia. *Extractors* of artemisinin and manufacturers of ACTs faced reduced incomes or losses.[129] Since the cost of artemisinin extract reportedly represents 50-70% of the cost of the finished product (Dugue 2007, p. 8; Cutler 2008), this was reflected in lower prices to extractors of artemisinin. *Both groups,* as seen at the time, could (1) scale back operations or go out of business, or (2) reduce or stop investing in better and

[128] In Uganda in early 2008, farmers were "already feeling the pinch" and "growers are complaining that their produce is rotting away in their stores." One said that "I would like to keep growing artemisia, I cannot because of lack of market" and another that "I have stopped planting because I cannot sell" (Muhwezi-Bonge 2008).

[129] Holley Pharmaceuticals announced in August 2007 that they "will record a net loss for the first nine months of this year due to the low price of anti-malaria drugs" ("China Business News," Interfax Group, Shanghai, August 29; cited in "Malaria in the News," WHO/RBM, August 31, 2007, p. 2).

more efficient equipment. Manufacturers, whose functions represent about 35% of the cost of the product (Cutler 2008), might turn to the "informal" private market for monotherapies or diversify into other products.[130] Consequently, there was "a very real fear of shortages, and thus ACT supply, in 2008/9" (Cutler 2007; also Kindermans et al. 2007).

These fears appear to have been borne out by mid-**2008**, in part for ways not foreseen in 2007. *Prices* of artemisinin fell below $150/kg in 2007 but as of July 2008 ranged from $240/kg to $330/$350/kg and, reflecting limited supplies, were expected to increase to, for example, $400/kg. (Cutler 2008). As of July **2010** they are in the $3S0-$420 range and rising. In part, this represents diminished supplies of Artemisia, particularly in China and Vietnam where the rise in price for food crops, including rice, made them more profitable than Artemisia (Cutler 2008, pers com. July 2010).[131] Asian extractors also face rising production costs.

These variations have been reflected in dramatic form in the global *production* of artemisinin. One set of estimates places the annual output, in metric tons, as: **2003**, 8-10; **2004**, 30-40; **2005**, 60-80; **2006**, 180-200; **2007**, 100-111; **2008**, 30-40, **2009**, up to 60 tons (Pilloy 2007-2009, RBM 2009); and **2010**, perhaps 100-110, a shortfall of up to 20 tons (Cutler July 2010).

The dramatic drops in 2007 and 2008 were muted, to some extent, by *carry-over stocks* (Pilloy 2008b). Initial estimates placed the **2009** stocks as about 66 mt (plus unverified stocks), and the most likely **2010** level between 90-100 mt (CHAI 2009, p. 4).[132] But recent estimates suggest their exhaustion by the end of 2009 (RBM 2009).[133]

ii. Manufacture of ACTs. The nature of the ongoing changes in the supply and demand situation for pharmaceutical firms has been amply illustrated by the experience of Novartis when their initial production of *Coartem* exceeded demand.[134] Part of the problem

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[130] One Ugandan firm stated that "We are now a botanical extraction plant. We soon will soon [also] begin extracting oil food flavours, and hand lotions" (Muhwezi-Bonge 2008).

[131] One uncertainty in the case of China is the degree to which wild production, which has been substantial in the past, is utilized in the derivation of artemisinin for commercial use. This was the case in earlier years, but their low levels of artemisinin makes them unprofitable to extract (pers. com. from Malcolm Butler based on discussions at the Guilin Artemisinin Forum, November 2008; also see CHAI 2008 and next note).

[132] In the latter case, supply was defined as having four components: (1) cultivated leaves, (2) wild leaves, (3) verified extractor stock, and (4) unverified extractor/formulator stock. Category 2 included extensive "production in 2005 that has since been abandoned." Moreover, the category "should not be relied upon as quantities are not dependable, their yields and quality are generally poorer," and they are not tracable in the case of quality issues. Category 4 was also problematic because of lack of data. Hence both 2 and 4 were given a lower level of confidence than 1 and 3 (CHAI 2009, p. 5).

[133] As of November 2009, the situation in China was one of tight supply and increasing prices (pers. comm. from Malcolm Cutler, December 2009). Production of artemisia was far below normal levels, in part due to drought (Wang 2010), and artemisinin extraction levels were also low (about 0.5%). Wild varieties could represent about 70% of the supply, with even lower extraction levels. Overall production of artemisinin was placed in the 40-50 ton range, which was viewed as inadequate. As a result, prices for Artemisia and artemisinin were increasing rapidly. The need for long-term (12 month) contracts with manufacturers was viewed as very important (these will be facilitated by the new A2S2 program; see Section v which follows).

initially was that many African leaders were initially reluctant to commit to more expensive drugs with no assurance that there would be money to continue purchasing (Jack 2005b; also see Kimani 2006). This attitude changed over time as governments became more familiar with the Global Fund and how to prepare successful proposals.

It is difficult to pin down actual *production* figures for Coartem, but in the middle of the decade they may well have exceeded deliveries (Jack 2005b). Recently, Novartis reported that *deliveries*, in terms of millions of treatments, were as follows: **2001**, 0.2; **2002**, 0.1; **2003**, 1.3; **2004**. 4.0; **2005**, 9.0; **2006**. 62.0; **2007**, 66.0; and **2008**, 62 (est.) (Teptow 2008; CNAP 2008, p. 29), for a cumulative **total** of 204.6 million.[135] Subsequently, **2005** was raised to 11.2, **2007** to 66.3 and **2008** to 78.0, for a **total** of 223.1 million (WHO 2009b, p. 10). The overall **total** was placed at 250 million by early July 2009 (Novartis 2009b).

The *price* for an adult treatment course was $2.40 from **2003-2005** and then dropped 25% to $1.80 for **2006** and **2007**, followed by another drop of 22% to $1.40 in **2008** (Bosman 2008, p. 7).[136] The latter reductions were attributed to increases in production efficiency in its plants in China and the U. S. (Novartis 2008, Wagwau 2008). The market was viewed as relatively "normalized" in 2006 and WHO forecasts of likely purchases were very close to actual purchases - 60.6 vs. 61.4 million treatments respectively (Dugue 2007a, p. 7).

iii. Procurement and Use of ACTs. The number of doses of ACTs procured globally s estimated to have increased sharply since 2004, as follows (millions of doses): **2001**, 0.5; **2002**, 0.6; 2003, 2.1; **2004**, 5.0; **2005**, 31.3; **2006**, 82.7; **2007**, 97.0; **2008**, 130.0; and **2009**, 160.0 (UNICEF 2010, p. 26).[137] There is an extremely wide variation in use of anti-malarial treatments between countries in Africa (from 50% to 0), and in many cases only a relatively small portion of the children treated actually received an ACT (Ibid., pp. 27, 28).

iv. Projections of Supply and Demand. Three groups have taken on the difficult task of analyzing the prospective supply and demand situation as far as 2015.

The first to do so, or at least report their findings, was the Clinton Foundation (CHAI). They focused on prospective increases in *public sector* demand, stemming from funding provided by the Global Fund and other groups such as PMI, the World Bank, and UNITAID. These grew from 94 million treatments in **2008** to 97 in **2009**, 133 in **2010**, and 148 in **2011**. The

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[134] In late October 2005 it was reported that Novartis would produce 30 million treatments during the year but had received orders for only 13 million. In December, Jack (2005b) indicated that "The company has long complained that orders for Coartem - currently placed country-by-country - are well below estimates of demand." Further details on this period are provided in Bosman and Mendis (2007).

[135] Earlier figures are reported in Anonymous 2005c, Novartis 2006, Novartis 2007, and Novartis 2008a.

[136] The evolution of ACT prices from 2001 to 2008 for several formulations/products is nicely depicted in the context of various forces and actions in Moon et al. (2009, Figure 1) and in WHO 2009.

[137] Other earlier reports placed procurements of all ACTs (presumably *Coartem* and others) in 2006 at 100 million doses (Enserink 2007, p. 561; UNICEF/RBM 2007, pp. 3, 27). This suggests that the "other" category was nearly 40 million doses, a relatively high figure.

proportion represented by **AL** is estimated to range from 60 to 65%, followed by a decline in **AS+AQ** from about 35% to 25% in 2011; the remainder would largely be composed of new formulations (Singh 2008, pp. 6-7). When the demand from other quarters (the private sector, the AMFm subsidized private sector, non-ACT demand involving leakage to low quality ACTs and monotherapies) is considered, the total demand could increase to 116-127 million in 2009 and 175-201 in 2010 (CHAI 2009, p. 3).

Pilloy of ARTPAL first considered the *production* of Artemisia which was below expectations in in 2009 in both area and extraction rates (the latter was partly due to the utilization of wild production in China). Even so, prices were still low in June, ranging from $280 to $315/kg for good quality and did not encourage farmers and extractors (some of the latter also raise Artemisinin) to plant more. Pilloy indicated that a proposed fair price of about $350/kg would be an acceptable level for Asian extractors, but "to reach the quantities needed in 2011 and thereafter, prices will have to increase to a range of $350-400/kg." Pilloy also considered the important role of *inventories* of artemisinin, for which public data are scarce. According to his information they averaged a little below 140 tons from 2006 to 2008 and then dropped to a little less than 120 tons in 2009. They are expected to decline further 2010 when demand may reach nearly 120 tons and production may only be in the range of 50 to 100 tons. Thus there needs to be a sharp increase in plantings of Artemisia in 2010 to cover the needs for artemisinin in 2011.

The Boston Consulting Group, in a study done for the Gates Foundation, also considered both both short-term needs and longer-term prospects. They indicated that without some market internvention there would likely be a shorage of artemisinin by 2011/12 and that with increasing demand associated with implementation of the AMFm program, the number of treatments needed might increase to 275 million in 2015 and then ease off as malaria control programs reduced the number of malaria cases. This level would require, at current levels of technology, about 23,000 ha. of Artemisia, approximately the level reached in 2006 – "but only after prices spiked to $1,000/kg and opportunistic players entered the market." Reaching this level again could be more difficult because of poor past experince, higher prices for alternative crops, credit challenges, and other problems (BCG 2009).

The current supply and demand estimates for artemisinin and ACTs suggest that there is much uncertainty whether the supply of artemisinin may be adequate to meet the demand for ACTs in late 2010 and beyond (CHAI, 2009, p. 2; FSC/I+L/Artepal 2009). The PSM Working Group stated in late November 2009 that they were "…again urgently drawing attention to the risk of shortages of artemisinin…and hence ACTs, for late 2010 and 2011" (RBM 2009). By 2015 the gap could begin to narrow as demand declines due to the effect of other prevention and control efforts now underway. There are, however, many variables on the supply and demandside, and much depends on the level and pace of AMFm funding (see Grewal 2009).

v. Achieving a Better Balance. Several steps have been taken toward this end, one of general nature and the others more specific. The first category was a series of four **industry-wide global artemisinin conferences** beginning in 2005 which have been held key production areas; a fifth is scheduled for October 2010 in Madagascar. They have focused on key issues from the supply of Artemisia to the market for ACTs and have led to further

interaction between various components, some reflected below. They have been held in Mumbai, India (2009), Guilin, China (2008), Bankgok, Thailand (2007), and Arusha, Tanzania (2005). The sponsors have been WHO, Roll Back Malaria and the Medicines for Malaria Venture. Details and reports from the meetings are available and may be obtained from [www.mmv.org/newsroom/events/past-events/past-artemisinin-events].

The **RBM Procurement and Supply Management Working Group** (PSMWG) has been studying supply and demand issues. They were given considerable attention at the Artemisinin Conference in Guilin, China in November 2008 (RBM 2008). Several options were considered and further reviewed in a meeting in Geneva in December involving 21 donors, manufacturers and extractors. While it appeared that the supply situation may be satisfactory for 2009, there were differing views between small and larger ACT manufacturers as to whether 2009 plantings will be adequate for 2010 ACT production. Consideration was given to establishing a short-term revolving fund and a proposal was subsequently developed for an "Assured Artemisinin Supply System" **(A2S2)** (FSC/I+L/Artepal 2009).[138]

Events moved quickly and the **A2S2** initiative was launched on July 20, 2009 for a duration of two years, with funding provided by UNITAID, technical support by three European groups (i+solutions, FSC Development Services, Artepal), and loans by the Triodos Sustainable Trade Fund. It basically provides a global finance facility for artemisinin extractors who supply ACT manufacturers whose products and found eligible by WHO/UNICEF and GFTAM. Up to a maximum of 60% of the sales contract between the extractor and the eligible ACT manufacturer can be financed. The loan was to consist of (1) an advance payment to farmers in order to initiate plantings, and (2) a further payment following harvest and delivery. In addition, A2S2 will provide improved market intelligence (den Besten 2009, i+ solutions and Triodos, July 20, 2009).

On another front, In July 2008, the **Clinton Foundation** announced that it had worked out an agreement with several Chinese and Indian firms that would help stabilize ACT prices. It involves three levels of the supply chain: Chinese suppliers of artemisinin (Holleypharm and PIDI Standard), Indian extractors (Calyx and Mangalam Drugs), and drug manufacturers Cipla Ltd. and IPACA Laboratories). Two ACTs would be made available "at or below average ceiling prices" of 48 cents for artesunate+amodiaquine (**AS+AQ**) and 91 cents for artemether+lumefantrine (**AL**) (Nichols 2008, Schoofs 2008). The Chinese companies agreed to supply artemisinin for no more than $136 per pound, and the drug makers are free to buy elsewhere if they can do so for less than $126 per pound. The Foundation hoped to sign up more suppliers. As McNeil (2008d) noted "It is unclear how much control over the market the arrangement will create," in part because it is grown elsewhere. Just where the farmers and extractors are left in all of this is uncertain at present.

[138] The fund is designed to enable extractors to "finance, with minimal risk, additional plantings that will help meet the forecasted needs of the Global Fund and AMFm programs for 2010/11." "Equally important this project will help to balance future supply demand gaps, based on increasingly efficient ACT forecasting mechanisms." "All extractors and manufacturers contacted have supported the introduction of a revolving fund facility…" "This mechanism will be required for as long as the ACT production will be mainly dependent on the agricultural sourcing of artemisinin…" (FSC/I+L/Atrepal 2009, p. 4).

As a further step, a new group named **ACTwatch** emerged from a competitive tender issued by the Gates Foundation in 2007. Its focus is on "Evidence for Malaria Medicines Policy." It primarily focuses on gathering data and information on: (1) levels and trends in the availability, price, quality, volume, retailer perceptions and knowledge of antimalarial drugs at different service delivery points; (2) wholesaler and retail volumes and the consumer price of antimalarials, current policy influences on the market, and markups from import to outlet; and (3) consumer behavior and volumes of specific antimalarials consumed. It is focusing on five African nations (Benin, D.R. Congo, Nigeria, Uganda, Zambia), Madagascar and Cambodia. Consortia partners include United States Pharmacopeia (USP), the London School of Hygiene & Tropical Medicine (Health Economics and Financing Programme), and Population Services International. Further information and data are provided on the group's web page [www.actwatch.info/home/home.asp]. It is planned to run for five years.

Over the longer run there is the strong prospect, alluded to earlier (Chapter III/1/c), of other lower cost forms of artemisinin that may not be dependent on the vagaries of agricultural production.[139] To the extent that these are not based on Artemisia, growers and extractors will face a decline in demand for use in malaria control. The plant itself, however, is remarkably versatile and shows scientific promise for use in treating a number of other diseases and afflictions.[140] But much of this lies in the future. In any case, at present the balancing of supply and demand for Artemisia and artemisinin is a challenging prospect and may not be considered an attractive one by investors who are faint of heart.

c. The Key Role of Diagnosis. Many ongoing issues remain on the public sector side. National governments continue to face policy questions relating to the implementation and operation of their programs (Barnes and Abdulla 2005; Malenga et al. 2005, p. 707; Mutabingwa 2005, pp. 307-311; Panosian 2005, pp. 716-717; Kimani 2006; Amin et al. 2007; Kouyate et al. 2007).

An underlying issue, noted earlier (Chapter III/2/b/iii), is overdiagnosis of malaria: most individuals treated for it do not actually have the disease. This is largely because malaria-like symptoms - principally fever and chills - can be caused by a number of illnesses. Early practice was to presume that malaria was the cause and treat with inexpensive drugs such as chloroquine. This policy continues for children under five in Africa, but has been questioned and become a source of debate (see English et al. 2009).[141]

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[139] 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). Some of the same factors stimulated the development of synthethic rubber in the United States during WWII (Finlay 2009, pp. 6-11).

[140] Artemisia, as noted earlier, was first recommended for *hemorrhoids* in 168 B.C. (Klayman 1985, p. 1049). It has recently shown promise for *cancer* (see **Annex 9a**), *bilharzia* (Heping 2005), *leishmaniasi*s (Das 2007), and *schistosomiasis* (Utzinger et al. 2001, 2010, Keiser et al. 2010 and Obonyo et al. 2010). Its possible *anti-viral* activities have recently been reviewed by Efferth et al. (2008). **AL** has recently shown promise for the treatment of severe *sepsis* in in one trial in Kenya (Moore et al 2009). By comparison, about 60% of the commercial production of quinine is used in the food industry as the bitter ingredient in soft drinks (Dagani 2005).

[141] A recent study has shown a substantial "reduction of the proportion of malaria among fever over time in Africa" (D'Acremont et al. 2010). But it is still difficult to distinguish between malaria and bacterial disease in areas with limited diagnostic facilities. Azithromycin plus artesunate (AT+AS) has proven to be an effective

With increasing drug resistance and the shift to much more expensive ACTs, the situation has changed, leading to errors of both commission and omission. The use of subsidized ACTs in cases where they are not needed means that (1) they are not available for others who do have malaria and (2) that those suffering malaria-like symptoms are not receiving the appropriate medicine. One study suggests that of the 182 million children (0-4y) in Africa with fevers that were taken to a clinic in 2007, 57% did not have *P. falciparum* malaria (Gething et al. 2010). But as of 2008, only 22% of suspected cases were tested in 18 of 35 African nations reporting (Anonymous 2010a). This situation calls for improved microscopes and rapid and effective diagnostic tests (RDTs, and individuals trained in their use (Perkins et al. 2008, Whitty et al. 2008, Msellem et al. 2009, Scavetta 2010).

Such a test has now been developed – using a dip stick and a drop of blood – and can be used at all levels of the health system. While easy to produce, they need to remain stable under high temperature and humidity as well as sensitive (Murray 2010). WHO has recomended "diagnostic testing in all cases of suspected malaria" (WHO 2010b, pp. xi, 9-12, 117-119). And their use has been shown to reduce the number of prescriptions (e.g. Kyabayinze et al. 2009). Since the tests are cheaper than the cost of ACTs, "the cost…is likely to be lower than the cost of treating all suspected cases. Still, scale-up of diagnostic testing might need financing mechanisms similar to those being used to subsidize the costs of ACTs" and the economics more complicated than they may first appear (Anonymous 2010a; Yukich et al. 2010).

3. Social/Individual Interactions

Many examples are possible, but three - each with a biological base - may illustrate the range.

a. Development of Resistance. This relates to the speed and degree to which resistance builds up to artemisinin and ACTs.[142] There are, as noted earlier (Chapter II/4), 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 in vitro susceptibility is not synonymous with diminished therapeutic effectiveness, but 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).

Even the prospect of triple combinations, discussed earlier (Chapter II/3/d), is of uncertain promise. As Peters put it in 1990: "In the presence of selection pressure by a [triple] mixture of drugs it still remains an open question whether a multiple [triple] drug combination will prove valuable in the long run in slowing down or, much less likely, preventing the

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combination in Asia, but a recently reported trial in Tanzania did not support its use in children in areas with high levels of existing drug resistance (Sykes et al, 2009). See **Annex 9b** for further background and analysis.

[142] This issue, which does not occur with barriers to transmission, 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).

appearance of resistance to the individual components" (p. 506). Such prognoses have implications for subsidy programs.[143]

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 faster the evelopment 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.

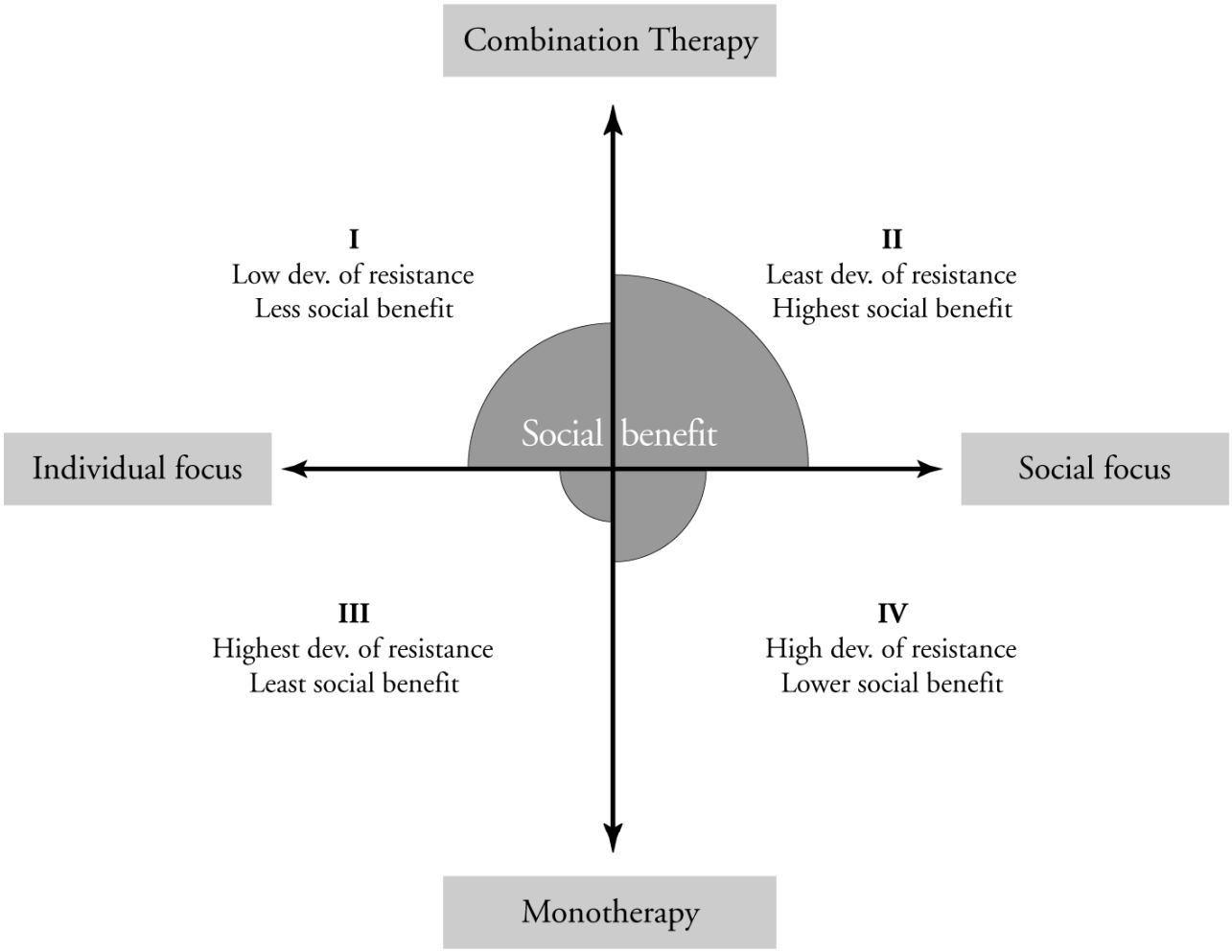
The relative effects of these variables on resistance may be viewed graphically in terms of a quadrant model as in Figure 6, or algebraically as done by Coast et, al. (1998, pp. 30-31). Policies that emphasize a combination therapy and a social focus result in the least development of resistance, as shown by quadrant II. The reverse is true when policies emphasize monotherapy and an individual focus, as in quadrant III. Quadrants I and IV represent intermediate situations. 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. Even so, 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.

b. Ethical Issues. Resistance leads into several important ethical issues which will only be briefly noted here. When, for instance, the point is reached when the demand for Artemisia for pharmaceutical use in ACTs diminishes (Chapter III/b&c), continuing excess supplies could find their way to a more informal market for use in monotherapies, both herbal and manufactured, and thus accelerate the development 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. Similarly, promoting the use of dosage Artemisinin teas, which are essentially monotherapies in nature or below recommended levels (see **Annex 4**) when ACTs are available, can also diminish resistance. Some of these challenges are the same as faced in the case of HIV/AIDS, TB and some other infectious diseases where cheaper

[143] A simulation study by Laxminarayan et al. (2005) suggested 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). This theme was recently elaborated, utilizing a sophisticated computer model, in terms of a multiple first-line therapy (MFT) approach which could result in a 2.5 to three-fold increase in the amount of time a single drug could be used, reducing costly surveillance methods for drug resistance (Boni, Smith and Laxminarayan, 2008).

Figure 6

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.

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but less effective treatments are available along with combination therapies (pers. com. from Jack Killen, Office of International Health Research, National Institutes of Health, September 2008). There is clearly a need for much more policy analysis centered about the consequences of present programs on resistance and ensuing ethical issues.

c. Prevention or/and Cure? This is one of the oldest issues in malaria policy (e.g. Litsios 2006, pp. 132-138). Quinine and Artemisia, blended with some liquid – famously, gin in the former case and more widely with water in teas in the latter - have long played both roles, though separately and with varying effect. In the case of quinine, use was largely related to colonial and military activities in Africa and Asia in the 1700 and 1800s.[144] Amazingly, it continues in use.[145]

In Africa, *curative* treatments for malaria are more likely to be undertaken for the native population, which may have built up some degree of immunity.[146] *Preventive* treatments are generally used for visitors, who have not built up immunity. But there may be some overlap between the two. 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, need for regular ingestion, potential toxicity, and development of resistance with persistent use, are normally

[144] Carlson (1977, p. 388) indicates that Thomas Sydenham had used it or preventative and curative purposes in the 1600s and that James Lind had prescribed it for sailors in the 1700s. Thompson (1846) reported using it on himself for prevention in 1842. By 1854 "quinine prophylaxis had obtained excellent results" for crews of ships in West Africa (p. 395). Curtin (1998), who focused on military situations, 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). An Indian example is cited by Fraser (1935), a tea planter in Assam from 1894-1907. Initially he was prescribed "a course of 60 grains a day of sulfate of quinine taken in four doses of 15 grains each, washed down, according to the taste of the patient, by whisky and water or hot tea. A week of this treatment usually put men back on the teelah [hill] again, a little deaf, perhaps, but able to stand up" (pp. 21-22). In 1903, on home leave, he visited Ronald Ross in Liverpool and was advised to "take ten grains of hydrochlorate of quinine twice a week, so long as I was in region of intense malaria, and…I never suffered from malaria again" (pp. 210-211). Also see Headrick (1981) and Webb (2009, pp. 92-126, "Bitter Medicines").

[145] It is utilized both as an oral drug and as an injection for severe (cerebral) forms of malaria (NA 2004, p. 291; Kyu and Fernandez, 2009). More than half of the national programs in Africa still recommend the oral form, a monotherapy, as the second-line treatment (Reyburn et al. 2009, p. 248). It must, however, be taken three times daily for seven days and has other disadvantages such as a bitter taste and side effects; it is also less effective than ACTs (Lubell et al 2009, Achan et al. 2009). Still, if severe resistance should develop to ACTs in Africa, "there may be few alternatives" (Reyburn, Ibid., p. 249).

[146] Human immunity is yet another incompletely understood area. It develops relatively slowly and is "often said to wane quickly when immune adults leave malaria-endemic regions, which suggests that continued exposure to antigens is [generally] required not only for the generation of memory cells and effector cells but also for persistence." This appears to be particularly true for young children (Langhorne et al. 2008, pp. 725, 729, 730; also see Hviid 2005; NA 2004, pp. 146; 272; Humphreys 2001, pp. 17-19; and Barennes et al. 2010).

not recommended for the preventive role.[147] However, as indicated earlier (Chp. II/1/fn. 16), ACTs also reduce transmission through their effect on the gametocyte phase: a recent study states that "ACTs have the potential for transmission reductions approaching those achieved by insecticide-treated bednets in lower transmission setting" (Orkell et al. 2008b, p. 1617).

Other approaches to *prevention*, outlined earlier (Figure 1), can reduce the need for ACTs and lessen the development of resistance. The importance of *improved diagnosis* has been noted (III/2/b/iii). A second approach is to employ a lower cost drug therapy (such as sulfadoxine-pyrimethamine, SP) as an *intermittent preventative treatment* (IPTp) in high risk groups such as pregnant women and infants, regardless of infection, in areas of high malaria transmission (Kalanda et al. 2006; Ntab et al. 2007; UNICEF/RBM 2007, pp. 24-33; Gosling et al. 2009, Aponte et al. 2009; Vinetz 2010: Schellenberg et al. 2010).[148] A third is the use of *insecticide treated bednets* (ITNs and long-lasting forms, LLINs) during pregnancy and for children (Menendez et al. 2007, WHO 2007c; UNICEF/RBM 2007; Brentlinger et al. 2007; Noor et al. 2009).[149] These and other preventative measures, such as *indoor residual spraying* (IRS) and environmental control (WHO 2007e, van den Berg 2007), may also be combined – though each alone may be insufficient in areas where transmission rates are high (Butler 2007). An assessment of their combined effect on mortality in Africa is provided in a recent Roll Back Malaria study (WHO 2010d). However, as Hay et al. (2008, p. 373) state, the question of how to optimize their combination is "largely unknown."[150]

Adoption of both *preventative* and *curative* treatments, such as ITNs and ACTs, has proven to be very effective in Zanzibar and Kenya (Bhattari et al. 2007; Fegan et al. 2007) and in econometric studies (Morel et al. 2005; Laxminarayan, et al. 2008). The need for them will likely

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[147] This discussion is partly based on material in: NA 2004, pp. 212-219; Litsios 1996, pp. 70-72; WHO/MU/TDR 2004 , p. 12; WHO/MU 1998, p. 22; and pers. coms. from William Watkins, September 2005 and David Warhurst, April 2008. A fairly recent study concluded that "there is currently no role for artemisinin derivatives as a chemoprophylactic agent" (Franco-Paredes and Santos-Preciado 2006, p. 146). On the other hand, ACTs, in playing a curative role, may also have preventative effects in some situations (pers. com. from Allan Schapira, September 2006). The addition of primaquine might also reduce transmission (White 2000b). A case of possible toxicity involving a herbal supplement containing artemisinin has recently been reported by the Centers for Disease Control (CDC 2009).

[148] While SP has been used, in this case as a preventative with promising results, it has been facing increased pathogen resistance in a curative role in Africa and it is not certain that it is the best treatment (pers. comm. from William Watkins, September 2007). IPT may also lead to other beneficial effects (ter Kuile et al. 2007).

[149] LLINs are an attractive preventative: they are effective (WHO 2007c, p. 2), relatively low cost, easily disseminated in a variety of ways (Webster et al. 2007), and generally last at least three years (WHO 2007c, p. 1). They do, however, have limitations. They can be uncomfortable and current designs not well suited for young children (Odora 2007, Kaplan 2008), used for other purposes (Minakawa et al. 2008), and mosquitoes may develop resistance to the insecticide used, generally pyrethroids (Kulkarni et al. 2007). Getting them distributed to the right people can be a substantial challenge (Jack 2010b). Views/studies differ on whether they should be sold at a nominal price (social marketing) or be treated as a public good and fully subsidized for free distribution (Kyama and McNeil 2007, Roberts 2007, Hoffman 2009, Dupas 2009, Cohen and Dupas 2010).

[150] A useful graphic summary of these events, combining (1) one of three measures of the incidence of malaria, and (2) the date of introduction of the several forms of treatment noted here for seven African nations from 1998 to 2008, is provided by O'Meara et al. 2010, p. 552, Figure 3.

be greatest in areas of high transmission, "and require aggressive control with suites of additional and complementary interventions" (Hay et al. 2009, p. 11).

There are also two intermediate cases where *curative* actions may have *preventative* effects. (1) The first arises from "the effects of malaria during pregnancy on…on nutrition and hematological influence" (Snow and Omumbo, 2006, p. 206). A recent study reported that exposure to malaria in the womb leaves some babies more susceptible to both malaria and anemia in childhood (Hviid 2009, Malhotra et al., 2009). Hence, the use of anti-malarial drugs during pregnancy for a curative purpose, may in some cases help prevent malaria in the next generation. (2) The second, suggested by Oguto et el. (2010), relates to *asymptomatic* carriers – individuals who have been infected but who do not display symptoms of malaria, though they may suffer side effects such as anaemia. They do not seek treatment and therefore constitute a reservoir of parasites, providing a public health risk. The identification and treatment of carriers could "reduce the pool of parasites available for the infection of mosquitoes." Artemisin derivatives have been shown "to result in lower gametocyte carriage rates…and reduced infectivity of treated individuals." Rapid diagnostic tests (RDTs) would be used to identify the carriers and the treatment confined to them. The primary focus would be on children less than five years. Pilot studies would clearly be needed to determine the feasibility and cost-effectiveness of this approach, which might well find a place in comprehensive eradication programs.

4. Program Implementation

While *Artemisia annua* is relatively easily produced, we have seen that virtually every other dimension is more complicated and intertwined than it may seem at first. This is particularly evident when it comes to program implementation. Sarewitz (2010) recently wrote in *Nature* that policy makers seeking to address urgent problems with new technologies should "look for what already works, and make it work better." That may be a good starting point, but more is needed in the case of malaria, one of the oldest of recorded human diseases and which holds sway in the poorest regions of the world. As Jack (2010a) has stated: "the big challenges ahead are threefold: deepening, broadening, and sustaining the response."

a. Need for Parallel Actions. While the focus of this paper has been on one curative drug treatment for malaria, a much broader view clearly needs to be taken in analyzing its place and prospects in the panoply of preventative and curative programs at the national and international levels. It has long been acknowledged that no one form of malaria prevention or control will provide a panacea. A comprehensive package of steps was, for instance, involved from the outset of "the control of malaria in Italy" from 1900-1962 (Snowden 2006).

Subsequently, Peters (1982), who was concerned that resistance would develop when mefloquine became available, wrote that "It should only be deployed as one tool in an integrated program of malaria control using all available methods including vector control, health education and, if and when it becomes available, vaccination." He later stated (1990, p. 506): "There is no doubt that the future of malaria control lies in the planning of integrated measures that adapt whatever means are best suited to local epidemiological and economic

situations of the areas concerned…. This is the only reliable way to prevent totally the continuing development of resistance to antimalarial drugs."

Others have since picked up the refrain. One noted: "Because there are good reasons to expect diminishing returns to most single activities for controlling malaria, effective policies are likely to entail a package of instruments" (Hammer 1993, p. 506). In reviewing the experience of Zambia from 2001 to 2006, another study stated "the choice of drug is only one components of a successful program strategy" (Steketee, et al., 2008, pp. 48-49). And a recent article on malaria control research concluded that "fighting a disease is no longer a matter of a single vaccine or drug; it must include an ever-changing arsenal of weapons…" (Humphries, 2010, p. 75; also see Enserink 2010a/b). This situation leads to, among other things, the need to design and estimate costs of the most appropriate overall control package.[151]

Furthermore, there is a continuing need to develop *new and improved control measures*, in part to replace those that fall prey to resistance. It is a question of both maintaining a roster of effective control measures and finding more effective ones that may change the face of control – as would an effective vaccine. While the Gates Foundation has greatly improved the level of support for research, it does not appear to be a prominent part of many other bilateral or multilateral assistance programs (which tend to emphasize control). As Greenwood, et al. have stated (2008, p. 1273): "the international community continues to face difficult decisions on how to balance efforts in discovery, development and implementation of new tools."

Moreover, *improved surveillance systems* for the early identification of the development of resistance to ACTs are needed (Chretien et al. 2007; Butler 2007; Vestegard and Ringwald 2007; Grabowsky 2008, p. 1052). A rationale and plan for one system - a WorldWide Antimalarial Resistance Drug Network (WWARN) containing four types of data - has been developed over a four-year period (Sibley et al. 2007). One form could be used to facilitate the definition of therapeutic drug concentrations, enabling "more prompt correction of suboptimal dosage regimens for each important target population as resistance emerges and spreads" (Barnes,

[151] One approach was demonstrated in a detailed estimate of budgetary needs for *global* malaria programs over the 2006-2015 period, but might be scaled down in scope (Kiszewski, et al., 2007). It started with the estimation of *at risk* populations and their *incidence* of malaria-like episodes by country. The former were used to estimate commodity needs and the cost for *prevention*; the latter to calculate the needs for curative care by age groups. Then it was estimated how much the gradual increase in prevention would reduce the need for *curative* treatment (based on pers. comm. from Allan Schapira, September 2007). Overall annual costs for African nations were projected to be $2.16 billion and to break down as follows: (1) vector control 41.1%, (2) program costs 19.0% [infrastructure and strengthening 11.7%; operational research, monitoring and evaluation 2.6%; training and communication 2.5%, and community health workers 2.2%], (3) ACTs 11.6%, (4) prevention and control of epidemics 11.2%, (5) rapid diagnostic tests 10.1%, (6) management of severe cases 6.8%1, and (7) intermittent preventative therapy (IPT) 0.2%. The ACT portion of the average total costs ranged from $202 million in the optimistic scenario to $251 million in the pessimistic case. IPT was included in the preventative category and was calculated to represent 0.2% of total program costs in the optimistic scenario. A remarkably similar study done about the same time for the same period, but one using a geographic information system (GIS) and different costing assumptions, placed the average annual cost at $3 billion, of which $212 million or 7.1% was for ACTs, within the range derived in the above study (the overall annual cost per person at risk was calculated to be $4.02) (Teklehaimnot, McCord, and Sachs, 2007). A prototype decision analysis approach to aid decision-making has been developed by an American team and tested in Tanzania (Kramer, et al. 2009).

Watkins and White, 2008, p. 130). WWARN was launched in December 2008 (Enserink 2008b) and received a £12.5 million grant from the Gates Foundation in June 2009 (Hindi 2009). Dr. Philippe Guerin of Oxford University is Director of WARN and will head the international collaborative network (Hindi 2009). A regional hub is in the process of being established in Nairobi. (For details, see [http://www.wwarn.org/home].)

There is also great need to *strengthen health systems*, particularly in rural areas. As one malaria specialist has recently put it, "the most important lesson from efforts to control malaria over the past 100 years" is the "need to give priority to the re-organization and general strengthening of health systems, not neglecting the under-serviced rural areas that bear the heaviest malaria burden" (Rieckmann 2006, p. 659; also see Hammer 1993, p. 16).[152]

Beyond these steps, there is a need to think even more broadly. Focusing on individual diseases to the possible relative neglect of interactions between them - such as between malaria and HIV/AIDS in particular or a variety of neglected tropical diseases such as anemia (Hotez and Molyneux 2008) - may overlook the possibility of further synergies (see **Annex 11**). Hence a more holistic disease approach may be called for at the regional and national policy level.

But even that could reflect, as Packard has put it, a focus on malaria as simply "a disease of malaria and mosquitoes," a vector borne disease (2007, 110). What is often missing is recognition of the importance of the larger social, economic, and political context and its implications for the design of appropriate programs. While "many of the most prominent malariologists in the twentieth century "acknowledged that these forces shaped the epidemiology of malaria and that effective control required "simultaneous advances in social and economic development."[153] Yet efforts to control malaria "seldom mirrored these broader views" but rather "relied increasingly on narrow biomedical solutions" (Packard, p. 113).

b. Proposals for Elimination and Eradication. The prospect of control of malaria, at least in certain areas for a while, has led to greater attention to elimination and eradication. *Elimination* means that "a pathogen is no longer transmitted in a defined geographical area, although 'imported' cases may still occur;" this is the case, for instance, in Europe. *Eradication* is a much stronger term, meaning that "a pathogen no longer exists on earth – save for perhaps a few lab freezers – and that control measures can stop." Eradication, in short, is virtually permanent; elimination may be transient (Roberts and Enserink 2007).[154]

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[152] The need to strengthen health services has been mentioned by many (e.g., Marchal et al. 2009); one study went on to focus on system changes associated with the introduction of artemether-lumefantrine in Zambia (Zurovac et al. 2007).

[153] Curiously, less attention may be given to these matters now than in the past. In 2003, for instance, TDR issued a USAID-funded review of *The behavioural and social aspects of malaria and its control; An introduction and annotated bibliography* (see Heggenhougen et al. 2003). Yet I have not seen any references to it and only learned of it accidently in going thru their web site for another purpose. It is almost as if this type of perspective and approach has greatly diminished or disappeared from the standard malarial literature.

[154] Previous experience with the troubled attempts to eradicate malaria were noted in Chapters I/2 and V/1/b (including fns. 6 and 117). That effort did, however, provide some lessons that proved helpful for the smallpox eradication program which closely followed: (1) it set precedents in WHO in establishing a global program that

The proposals have led to considerable debate, with some arguing that just the specter of eradication is counterproductive and that eliminating the last 10% would be a "tremendous task and very expensive;" another states that "unless Africa can end both its poverty and its civic strife, 'eradication is just a pipe dream.'" (McNeil 2008b; for other views, see Tanner and de Savigny 2008 and Okie 2008.) An initial strategy was suggested by Feachem and Sabot (2008). The WHO Global Malaria Program includes limiting its geographical extent in the world, which requires "the complete interruption of mosquito-borne malaria transmission in a defined geographical area." This involves four phases: control, pre-elimination, elimination and the prevention of re-introduction (WHO 2008, pp. 31-32). The implications for research have been reviewed by Greenwood (2008).

Subsequently, a Global Malaria Action Plan (GMAP) was announced in late September 2008 with the goal to reduce malaria deaths to near zero by 2015, and then progressively eliminate it from countries and regions until it is eradicated (Roberts 2008). A Malaria Elimination Working Group (MEG) composed of donors and scientists was to be established to develop a research and development plan for eradication (Roberts 2008, p. 27; Anonymous 2008d). The report of the group was issued in April 2009 under the title *Shrinking the Malaria Map: A Prospectus for on Malaria Elimination* (Feachem, Phillips and Tagart, eds.) and contains a number of references to artemisinin and ACTs (pp. 53-54, 85, 89-90, 96, 134). A companion report is subtitled *A Guide on Malaria Elimination for Policy Makers* (Feachem et al., 2009b).[155] They have, predictably, led to further discussion, both with respect to policy (Enserink 2010b; Roberts 2010) and research implications (Kappe et al. 2010; Mackinnon and Marsh 2010; Snow and Marsh, 2010).

As for the Gates Foundation, one current account (Duncan 2010) indicates that their future emphasis will be on prevention rather than treatment. In the case of drugs, they are, through MMV, "stepping up the search for drugs that kill the stage of the parasite that passes from humans to mosquitoes at the same time as easing the patient's symptoms."

c. Impact, Sustainability and Prospects. To date, the most significant effects of malaria control programs in Africa have been found in "countries, or parts of countries, with relatively small populations, and high intervention coverage" (Eritrea, Rwanda, Sao Tome & Principe,

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could short-circuit some of the troublesome bureauracy of the regional offices; (2) it established the principle of international certification teams to verify elimination; (3) it demonstrated the mistaken nature of the notion that with a striking new technology one could close off the on-going research programs; and (4) it showed that the malaria program structure, which created its own hierarchy and was responsible, if sustained to the head of state, was far too rigid and demonstrated the need to adapt to local social and political factors and to and work within the existing health structures (pers. coms. from Dr. D. A. Henderson, University of Pittsburgh Medical Center, March 2010). For an assessment of the earlier malaria eradication program in Sardinia see Tognotti 2009.

[155] Among the many possible complications in reaching eradication, a new one has recently emerged. Black populations in Africa have traditionally been largely resistant to the second major form of malaria, *P. vivax* (this relates to their lack of the Duffy receptor), as noted in Feachem et al. 2009b, p. 84 and Webb 2009, pp. 20-27. But it appears that *P. vivax* is evolving new strains that enable it to infect previously immune groups. A recent study in Madagascar found that 10% of the malaria cases were occurring in these groups (Ménard et al. 2010, Anonymous 2010b, Cookson 2010b; for a graphic display of the global incidence of *P. vivax* see Vogel 2010b).

and Zanzibar). "These countries have used prevention and cure in rapid sequence or in combination…" (WHO 2008, p. 32). The situation is much less clear in large countries, such as Nigeria and the Congo (D.R.), which have both the largest number of cases of malaria and deaths from it (Ibid, pp. 12-14).[156]

While there has recently been reason to think that "large areas of Africa are more amenable to [malaria] control than appreciated previously" (Guera, et al. 2008), others are concerned that recent progress may be more tenuous than some realize" (see Brown 2008 and McNeil 2008 for examples), in part because of the likely development of resistance and the weak public health structure across Africa.

Further insights have recently been provided in an innovative quantitative modeling assessment of the prosects for controlling *P. falciparum* in Africa (Griffin et al. 2010). While couched in terms of cutting parasite prevalence to 1%, a pre-eradication level, it casts useful light on the nature of the task in six nations with varying transmission levels. The four stages of treament were: (1) ACTs and long-lasting insecticide treated bednets (LLINs), (2) indoor residual spraying (IRS), (3) mass screening and treatment (MSAT) involving rapid diagnostic tests (RDT) and a single dose of an ACT, and (4) a vaccine. These were assessed in three transmission settings. In areas of *low* and in some cases *moderate* transmission, LLINS, ACTs and MSAT "could reduce transmission to very low levels if high levels of coverage and adherence are achieved" and "additional use of IRS and/or MSAT… could speed further this reduction." But in *high* transmission intensity settings and/or where mosquitoes rest and bite outside houses, "current tools…are insufficient to drive prevalence below the pre-elimination threshold." In these cases, "new approaches" including vaccines will be needed. The model is optimistic in that it does not consider the development of resistance to ACTs.

In any case, "keeping up the commitment will be difficult" (Roberts and Enserink 2007). The question of sustainability of externally funded control programs at a high level, especially at times of economic stress, is a definite cause for concern at many levels.[157] Donor fatigue, changing priorities - some for good reason, some for political reasons, and some of a more quixotic nature - are an ever-present characteristic of foreign assistance programs.

5. Role of Economic Development

How is a more sustainable situation to be achieved? Part of the solution may lie outside of the field of biological science. Malaria is, as noted previously (Chapter 1) commonly characterized as largely a disease of poverty and rural areas (e.g. Carter and Mendis 2002, pp. 569-570, 589; Hopkin 2008, p. 1048; Grabowsky 2008, p. 1052). This would suggest, among other things, that efforts to help reduce poverty, particularly in rural Africa, might well play a role.

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[156] Data are available on funding for malaria control at the national level (WHO 2008, Annex 7); it would be useful to see them expressed on a per capita basis.

[157] The uncertainty in a recent study in Kenya extended to the health worker level: one of several reasons that ACTS were not prescribed by some was "concern whether the government would sustain the supply of artemether-lumefantrine" [*Coartem*] (Wasunna et al. 2008, p. 11).

There is some precedent for this thought. In its second general report in 1927, the Malaria Commission of the League of Nations stated that "*Of all indirect methods of reducing malaria, the commission attaches most importance to general schemes of bonification which aim at improving the economic and social condition of the people and their general well-being and standard of life*" (Malaria Commission, 1927, p. 28; also see Russell, 1955, pp. 198-204). In 1929, Dr. Clifford Gill, formerly a malaria medical officer in the Punjab from 1913 to 1923, wrote that "One result of this investigation has been to emphasize the profound influence exercised by economic stress upon the human factor" (p. 209).

Similarily, Dr. Sydney James, a noted British malaria expert and scientific advisor to the Commission, who was sent to Kenya and Uganda in 1929 by the British government to study the malarial situation, subsequently reported that "economic improvement [of the peasantry] is the matter to which attention should first be given" (James 1929a, pp. 30-32). More specifically, he proposed that the appropriate procedure was "…to introduce agricultural, and in some cases industrial, welfare schemes which aim at improving the economic and social conditions of the people and their general well-being and standard of life" (James 1929b, p. 96). In short, as viewed by Malowany (2000, p. 342), "improvements in health conditions would indirectly reduce malaria incidence."

More recently, Packard, noting the case of Zambia, suggested that long-term sustainability requires higher levels of economic development and improvement in the economic status of the population (2007, pp. 244-245). "This does not mean that economic growth will eliminate malaria, especially in Africa. But it will make it possible for governments and individuals to take and sustain actions that will reduce the burden of the disease." The question then is "will the international donor community be willing to sustain the support, not only for malaria control, but also for economic policies that will ensure real long-term economic growth and development?" [158]

[158] The importance of considering the tangible effects of malaria control on older children and adults has recently been emphasized by Muturi et al. 2007. Malaria was also a human and economic problem for these groups in the United States, principally in the south, through the early 1900s (Anonymous 1908; Humphries 2001; Packard 2007, pp. 53-65, 68-78). Among other things, it led to malnutrition, immune disorders, and economic costs. L. O. Howard, a USDA entomologist and mosquito expert (Sutter 2007, pp. 724-725, 735-738; Patterson 2009, pp. 8-16), stated in that "with malaria perhaps as with no other disease does the death rate fail to indicate the real loss from the economic point of view. A man may suffer from malaria throughout the greater part of his life, and his productive capacity may be reduced from 50 to 75 percent, and yet ultimately he may die from some entirely different immediate cause" (Howard 1909, p. 11). He cited a 1903 study that concluded that "malaria is responsible for more sickness among the white population of the South than to any disease to which it is now subject" (p. 13). Overall, he wrote that "it is safe to place the annual loss to the United States from malarial disease…at not less than one hundred millions of dollars" (p. 12). This may seem an extremely high estimate, but Hong (2007), utilizing a vast array of primary data for Union Army recruits during the Civil War, concluded that those who spent their early years in malaria-epidemic counties were shorter due to malnutrition and more susceptible to infections as a result of immune disorders than those from malaria-free regions." "In other words, malaria infection would become one of the major causes impeding public health improvement and economic growth in mid-nineteenth-century America…." (pp. 1001, 1018-1019). And over the past century the U.S. Army and Navy "have suffered more casualties to malaria than to enemy fire" (Li, Milhouse and Weina 2007, p. 3; also see Bell 2010). The effects cited here on adults, however, could well have been greater than in Africa or among African slaves where a degree of immunity (1) existed in those with sickle-cell anemia (Coulter and Burreson 2003, pp. 349-350; NA 2004, pp. 127, 147; Webb 2009, pp. 28, 36-37, 90) or (2) was built up due to previous exposure to malaria. Also, it could be difficult to distinguish between yellow fever and malaria.

The relationship between economic growth and malaria control is, as noted earlier (Chapter IV/1/b), two-way in nature. It is easy to generalize why: malaria control reduces mortality and morbidity, and thus contributes to human productivity; economic growth provides governments and individuals the financial resources to afford better nutrition and medical care. As Sen (1999) has said: "good health and economic prosperity tend to support each other." Yet precise measurement of these effects is difficult: one recent study which focused on malaria at the household level found dual causation but was unable to identify which was stronger (Somi et al. 2007b). There is also the issue of the effect of nutrition on malaria and vice versa: a recent study in Africa reviewed the evidence involving Vitamin A and found that supplementation reduced the incidence of uncomplicated malaria by about one third (but not the rates of death) but that the evidence for a reverse relationship was weak - "although "on theoretical grounds and from indirect evidence this is a distinct possibility" (SanJoaquin and Molyneux 2009). But most treat the overall role of health in economic growth. [159]

Given this situation and the issues raised by Packard, further studies of resource allocation and the associated trade-offs are needed, and at an even broader level. These should include the potential contribution of other development efforts – efforts which may get neglected or squeezed out given limited financial resources (opportunity costs). As in many things, balance is needed in malaria control, but balance is also needed between investments in malaria and other diseases, and between investments in health and other areas such as agriculture that contribute to economic development.

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Clearly there are many complex policy issues to be considered and dealt with in dealing with Artemisia/artemisinin/ACTs themselves and in the context of larger national and international programs. While the biological dimensions have received considerable attention of a high, broad and sustained caliber, it is questionable whether the same can be said of social science. Further, many biologists have spent much or virtually all their career on malaria, but the involvement of social scientists has generally been much more limited and spasmodic, but not unimportant. With a few notable exceptions, this seems to be particularly true of institutions and individual economists. The humanities have been well represented by a number of historians who have made very useful contributions (e.g. Snowden 2006, Packard 2007, Webb 2009). From a policy perspective, what may be needed is a more systematic and sustained global approach, one that would encourage fuller involvement of social scientists and facilitate interaction with biological scientists.[160]

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[159] See Wheeler 1980, Pritchett and Summers 1996, Strauss and Thomas 1998, Meer et al. 2003; Sala-i-Martin et al. 2004; Lopez-Casasnovas et al. 2005; Acemoglu and Johnson 2006/2007. Several studies have indicated that farmers in irrigated areas have higher economic status than those in non-irrigated status and that this may be related to lower malarial presence (Klinkenberg et al. 2003, p. 28; Ijumba and Lindsay, 2001). Katz (2007) has argued strongly for simple steps that would stimulate the economic growth side. The interaction of health and income is most clearly set for the in graphic form by Weil 2005.

[160] This could well be a component of a broader health policy research program and/or center – a subject that is well beyond the scope of this paper, but is outlined in a separate paper by the author (Dalrymple 2008a).

Chapter V. Concluding Remarks: The Wisdom of the Red Queen

Artemisia (*Artemisia annua*) is a seemingly simple, though uncommonly versatile, medicinal plant that has drawn international attention for its role in malaria control. It was long a traditional remedy for a variety of ills in China, including malaria. But it was not until the development of resistance to existing drugs and the Viet Nam War that concerted efforts were made by Chinese scientists to identify the exceptional qualities of a purified extract, artemisinin.

Even more remarkably, considering the times, China freely shared its knowledge of artemisinin with the world – a global public good of the first order. The identification and development of extracts with improved qualities was conducted in open cooperation with a unit of the World Health Organization[161] and western scientists, again during a period when this might not have been expected. The final step, the development of an artemisinin-based combination therapy, an ACT, was more of a public-private commercial venture.

While first used in Southeast Asia, artemisinin soon drew global attention and became a key tool in efforts to help control malaria in Africa where malaria where it has long been a major scourge. In this, artemisinin follows the legendary footsteps of quinine, also a plant derivative (from Cinchona), and hence Artemisia has become - at least for the present - one of the most important medicinal plants in the world.

Some hail the use of such natural products (Mashelkar, 2003, 2005; Paterson and Anderson 2005). And historically, "…the majority of new drugs have been generated from natural products…and from compounds derived from natural products" (Li and Vederas 2009, p. 161).[162] But others find this disquieting: Bond (2004) observed that "in the 21st century, we need not rely on plants to cure malaria." And indeed, there are many limitations in doing so, particularly where subsidies are needed and normal market mechanisms are sidelined, making it difficult to coordinate supply and demand.

For these and other reasons, the search is on for other sources of artemisinin. A principal approach involves the development of synthetic chemical substitutes that are equally effective, safe, and significantly lower in cost.[163] This is no mean challenge for a number of scientific and production (particularly scale-up) reasons.

Efforts of a more technological nature are also underway to improve the yield of (1) Artemisia plants, as measured by total yield and the percentage of artemisinin, and (2) the artemisinin extraction process. Progress on either or both fronts could reduce the cost of artemisinin and

[161] TDR, The Special Programme for Research and Training for Tropical Diseases.

[162] They go on to point out that "the first pharmacologically active compound from a plant was morphine." "By 1990, about 80% of drugs were either natural products or analogs inspired by them." "However, many pharmaceutical forms have eliminated their natural products research in the past decade."

[163] The need for cost reduction is, as we have seen, heightened because continuation of high subsidies for ACTs may well not be sustainable over the longer run. Moreovever, they entail substantial opportunity costs, both within the malaria sector and more broadly.

alter the balance between agricultural and industrial approaches (which so far have not provided a lower cost product) to the provision of artemisinin.

But artemisinin, or comparable drugs of any source, face - as does any malaria drug - the inevitable challenge of a buildup of parasite resistance over time. The process is accelerated by the use of monotherapies rather than combination therapies. Success in this area, which involves both substantial scientific and social challenges, is measured by progress in slowing the rate of development of resistance. Inevitably, replacement drugs or approaches will be needed, and hence the need for continuing longer term research on drug treatments as well as other approaches. At present, no replacement for artemisinin is in sight.

Malaria control, as we have seen, involves a variety of interacting preventative and curative measures. Other preventative measures, including drugs used for their prophylactic properties (generally by visitors to malarial areas), can and do reduce the incidence of malaria. But they cannot substitute for drugs such as ACTs in the curative role. The need for all of these approaches will be lessened if success is ever reached in the development of the quintessential preventative: one or more suitable vaccines. A substantial search has been underway for a long time; promising candidates appear and then disappear. The most promising at present would provide partial protection for a limited period of time.

Malaria and malaria control, perhaps to an uncommon degree, tend to be viewed through many prisims by a wide array of specialists. The issues faced reflect a kaleidoscope of international scientific, technical, economic, and social factors. The result is a complex interaction and presents difficult and challenging policy and operational issues. Balance is critical. How well this is achieved and these matters are resolved will be of considerable importance, both directly and indirectly to public health in Africa, as well as more globally.

While ACTs have played a key role in this process when and where they have reached the needy and been used properly, much remains to be done to maintain and extend their promise and social value. This has been recognized for some time. In the words of one group: “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).

More generally, Moree observed that: “one thing that malaria has proven is that when we are just about to conquer it, it comes back again” (Das 2005b). Similarly, Peters recognized decades ago that “The best we can hope to do probably is to keep ahead of Nature” (1970/1987, pp. 687/1100). Thus, as Makel (2004) observed in the context of the influenza pandemic of 1918: “we never really conquer germs: we merely wrestle them to a draw.”

These views are 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, following the second dictum of the Red Queen that “If you want to get somewhere else, you must run at least twice as fast as that” (Carroll, 1871/1984, p. 204), require even more effort.

Annexes

Note: This section, reflecting the many and often complex dimensions of the overall topic, contains a fairly large number of wide-ranging annexes. The main reason for their grouping here is that they may be of more specialized interest that the preceeding text, though this may seem a close call in some instances. And some of the shorter annexes could conceivably be placed in the main text as boxes or incorporated in the text in future versions. While all are informational in nature, reporting what was or is, two - 11 and 13 - have an additional conceptual dimension to them.

Annex 1. Artemisia: Role in Early Chinese History[164]

As noted in Section II/1/a, *Artemisia annua* is both one of the oldest of medicinal plants to have been prescribed for malaria in ancient pharmacopeia in China, and in recent years the most effective and widely used for malaria therapy and control.[165] Ge Hong (284-363) was the first to recommend *qinghao* for the treatment of "intermittent fevers," which "in all likelihood" were "due to malaria" (Hsu 2006a, p. 506; 2006b, p. 667; 2009, p. 204). Li Shizen made a similar recommendation in 1596 (in addition to the references cited earlier, see Harper 1998, pp. 101-106 and Unschuld 1986, pp. 11-16).

Some of the key issues in its identification and depiction in the early Chinese literature will be noted here. Given the long reach back in time, the limited records and ideograms noted to date are subject to differing interpretations and uncertainties. These include (1) the designation of malaria, (2) the identity of the species of *A. annua* involved or described, and (3) the extent to which Artemisia was used for malaria control.

The designation of malaria is, of course, a matter of key importance. According to one ancient Chinese source, "In the south…the disease is generally called *chang*…whereas in the north…it is known as *yao* (Saburo 1979, p. 91). It is also commonly referred to as *nöe* (intermittent heat and coldness); *hanre* is often synonymous with *nöe*, but may refer to many other conditions (Hsu 2001, p. 60).

While the modern focus of malaria therapy and control is on *A. annua*, it may have shared an early stage in China with *A. apiacea*. Both were common in Chinese antiquity and according to Hsu (2006a, p. 505) "were easily confused with each other." And both provided plant material for the herbal drug *qing hao* (blue-green *hao)* for treating, among other symptoms, "exhaustion due to heat/fevers"). In the view of *Li Shizhen* (1596), according to Hsu, blue green *hao* was to be differentiated from *huang hua hao* (yellow blossom *hao*). But modern

[164] This section draws from a stimulating interaction with Donald Harper (Department of East Asian Languages and Civilisations, University of Chicago), Elisabeth Hsu (Institute of Social and Cultural Anthropology, University of Oxford), John Moffett (Needham Research Institute, Cambridge), Wallace Peters, and David Warhurst (both formerly LSHTM).

[165] Winchester (2008) in his biography of Joseph Needham lists "Antimalaria drugs, 3rd century BC" among the "Chinese Inventions and Discoveries with Dates of First Mention" (2008, Appendix 1, p. 267).

botanists have generally identified the former as *A. apiacea*, now little known, and the latter as *A. annua* (Yu and Zhong, 2002, p. 129).

Yu and Zong (2002) suggest that while "In the early literature, *Qing Hao* referred to two species…nowadays, *Qing Hao* is usually taken to be *A. annua*" (p. 150). They go on to note that the more recently discovered (1972) active compound, *Qinghaosu*…means 'a principle from *Qing Hao*'…(Ibid.). *Hao*, according to Hsu, is a general character for "plant" (pers. comm., May 2008); however Harper refers to it as "artemisia" (1998, p. 487) and in some cases it is referred to as wormwood.

Therefore, on the basis of these sources, *Qing Hao* (or *qinghao*) might be taken to refer to the *Artemisia* plant – either *A. annua* or *A. apiacea* in historical literature in China, but the former in more recent literature – and *qinghaosu* to the extract now known as artemisinin.

Whatever the designation, Artemisia was - and still is (Yu and Zhang 2002, pp. 154-156) - used for a variety of ailments, and malaria may not have initially been one of the most common. Some reviews of early herbal treatments for malaria make no mention of Artemisia (eg. Saboro 1979). Also, other plants, particularly Changshjan (*Dichroa febrifuga*), have played a role in malaria control in at least the recent past and conceivably could be of some use in the future (Lei 1999, 2004; Butler and Moffett 2005; Wright 2010).

Annex 2. Artemisinin and ACTs: Chinese Accounts of Discovery & Development

A brief overview of this subject has been presented in Chapter II/1/2. Further, though hardly complete, details are provided here. They reflect two recent and somewat different accounts by Chinese scientists: Yiqing (2009) and Liao (2009). While the nature of the story is generally similar, they differ in the role played by two leaders in the process and the aspects covered. The governmental research, however, appears to have fairly consistently carried out by the Institute of Chinese Malarial Medica of the Chinese Academy of Medical Sciences in Beijing. A third individual is also briefly mentioned.

Shou Yiqing

This portion consists of excerpts from a recent question and answer session with Dr. Yiqing (2009) who was portrayed as a key scientist in the development of artemisinin and ACTs in China. It is set in the context of Project 523 and subsequent activities and covers a longer time period (much further information on Project 523 in provided, in Chinese, in a book edited by Zhang (2006). Cui and Su (2009), draw heavily from the book (pp 992-1002).

…what spurred you to do research to find antimalaria drugs? "…my official participation in the research project stemmed from the Viet Nam War." "I was ordered to conduct field research on tropical diseases in Viet Nam. China was supporting North Viet Nam and providing it with medical aid." "There I observed rampant malaria that reduced the combant strength by half, sometimes up to 90% when soldiers became ill." "Later, we submitted a report to China's Central Military Committee, stressing the importance of developing China's own anti-malarials."

"Taking our advice, the central government set up a panel of more than 500 medical military and civilian experts to develop new anti-malarial treatment for stricken soldiers. This was classified as top secret state mission project 523, after the date, 23 May 1967, it was established."

What made you and your team think of using artemisinin to treat malaria? "Project 523 included two groups engaged in antimalaria drug development: one to devise chemical medicines, another to examine traditional Chinese medicines." "From 1970, the focus of the project shifted to [the latter]…because producing antimalarials became less of a priority after China produced chemical combination anti-malarials and provided them to North Viet Nam."

"In the end, the Artemisia annua plant was chosen for further research. In the early 1970s, a Project 523 team first isolated artemisinin from the plant." "Between 1976 and 1978, the molecular structure of artemisinin was identified and more artemisinin derivatives were developed."

Why did you research ACT for malaria at a time when there were no concerns about resistance to artemisinin? "There was a risk of resistance in theory…" "We also found that artemisinin when used alone, cannot clear all the parasites…" "Consequently, I proposed a

project to delay possible drug resistance…." "I started research on ACT in 1981. For four years I worked virtually alone." "From 1985, things improved. Professor Ning Dianxi and others joined me. They helped me improve the fixed combination by replacing artemisin with artemether." My colleagues and I had to try many combinations…." "We found that the long-lasting effet of lumfantrine complemented the quick and potent effect of artemether, greatly improving curative effectiveness. Its like combining the short fist and the long fist in Kung Fu. In 1985, we combined [them] into a single tablet, creating the first ACT, which was registered as a new medicine in China in 1992…" In April 2009, Dr. Yiqing and his colleagues won the 2009 European Inventors of the Year Award (Non-European Countries Category) for developing the first ACT.

What role did the World Health Organization (WHO) play in the early development of ACT "In the early 1980s it seemed that antimalarial research was over for good. Fortunately, essays published by Project 523 scientists caught the eye of WHO." In around 1979, TDR…expressed interest in cooperation on antimalaria research. But after Project 523 was disbanded in 1981, ther was on one to negotiate the issue." "The next year, thanks to WHO/TDR's efforts, the National Chinese Steering Committee for Development of Qinghaosu and its Derivatives was set up under the Ministry of Health to replace Project 523. The project was saved." "My research was informed by WHO guidelines."

Why did you introduce ACT outside China? "…I feared a hiatus in research and discountinued state-level attention would mean that it would be lost forever. No Chinese pharmaceutical company was capable of introducing this medicine to the rest of the world. So I went to the Ministry of Scienc and Technology, which introduced me to China International Trust and Investment Corporation (CITIC), the only Chinese state enterprise at the time that was authorized to deal with foreign investors. With the State's approval and CTITC's help, we were introduced to Novartis. At first we were wary about dealing with a Western team but soon the mistrust melted away because of their professionalism and eagerness to cooperate."

How did you and your team manage to patent Coartem? "In 1990, my team and I applied for the original patent in China." "The patent now belongs to my institute, IME [the Institute of Microbiology of the Chinese Academy of Military Medical Science, AMMS] and the nation. In 1991, to help our team get patents around the world, Novartis established a relationship with the IME/AMMS and KuMming Pharmaceutic Corporation, through CTIC. In 1994, Novartis received worldwide licensing rights for Coartem outside China and in 1998 also gained regulatory approval for the drug, which became China's first internationally patented pharmaceutical product."

You-You Tu

This account, by Liao 2009, focuses more on the early and middle years and on Qinghaosu. He notes that in the early 1970s, Dr. Tu was a phytochemist who headed the government's antimalaria research unit. "During the first stage of this research, her group investigated more than 2,000 Chinese herb preparations and identified 640 recipes that might have some

antimalaria activities." "However, progress was not smooth and no significant results were obtained at first."

"The turning point came when an *Artemisia* extract showed a promising degree of inhibition against parasite growth" which was consistent with the activity which had been reported…by Ge Hong [Annex 1]." "Tu brilliantly modified the extraction technique to perform at low temberatures rather than using heating which was conventional." There was an initial problem with toxicity but "Tu was able to separate the extract" into two portions, one of which was a neutral extract, "which exhibited both reduced toxicity and improved anti-malaria activity." "Tu next investigated the isolation and purification of the active component" and "in 1972 her team identified a colorless crystalline substance…and named it 'Qinghaosu.'"

"The structure was first published in 1977"… but "because of the prevailing climate not many papers concerning Qinghaosu were published and these were mostly in Chinese. In addition, authors were not always identified individually in some of the early papers…, which is perhaps why [her name] is not as well known internationally as that of her discovery, Qinghaosu." [166] It was awarded "the status of "national scientific discovery" by the Chairman of Science and Technology in China in 1979." During a meeting of CHEMAL in 1981 [at which time she was listed as "Associate Professor" and "Vice Chief, Department of Chemistry" (CHEMAL 1981, p. 18)] she was invited to present a lecture on it" (which is presumably reflected in the portion of the report on clinical studies (p. 10-11). She is still the director of the Qinghaosu Research Center and was honored on her 80th birthday in 2009.

Xhenxing Wei

Another account states that artemisinin was first discovered by Zhenxing Wei, professor of Chinese Traditional Medicine at the Research Institute of Shandong who became a member of Office 523 in October 1969 and in October 1970 obtained 30 mg. of a pure crystalline product (Jansen and Yin 2002, pp. 25-26). No publications listing him among the authors have been noted.

[166] Still, the paper lists 30 papers by Tu and various associates. Virtually all from 1981 to 2009 bear her name among others.

Annex 3. Artemisia: Genetic Resources and Varietal Improvement

As a medicinal plant, *Artemisia annua* has fallen outside the mainstream of agricultural research and has been essentially an orphan crop, except in a few cases. This has created some problems as far as seed supply and varietal improvement related to artemisin, but changes are underway, particularly in the United Kingdom.

a. Historical Background

Artemisia annua, derived from the bark of cinchona (Honigsbaum 2001), has been kept at the Chelsea Physic Garden (established in 1673) in London since the mid 1700s and possibly at some other such gardens.[167] 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).[168] It was first mentioned in the botanical literature in 1739. An introduction from China to Portugal was noted in 1790 (pers. com. from David Frodin, taxonomist, June 2006).[169]

Artemisia has not, however, been 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 began to focus on medicinal plants, had only one holding.[170] 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."

Despite its ancient origins and early recognition of its medicinal qualites, the conscious selection and breeding of improved varieties of *Artemisia annua* (in terms of the quantity and quality of artemisinin) is a relatively recent process, probably dating back no more than 40

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[167] The garden was established by the Company of Apothacaries and has served "as a living museum of the exotic and medicinal plants of the world…and a laboratory for the study of material medica: herbal and vegetable remedies" (Rose 2010, p. 36; Dobson 1998, pp. 78-79: for a detailed history of the garden by a former curator, see Minter, 2003). Francis Bacon wrote, in his futuristic novel *New Atlantis* (1627), of improved plants that "become of medicinal use" (p. 74) and "dispensatories, or shops of medicines" (p. 76).

[168] Curiously, Minter's Appendix 3, "Medicinal and Useful Plants Growing at Chelsea in 1772" from Joseph Millers *Index Horti Chelseiani of 1772 – The Officinal Quarter*, lists six other species of *Artemisia*, but not *annua* (pp. 121-126).

[169] The Garden's Curator from 1846-48, Robert Fortune, reorganized it according to Linnaeus's system, and "medicinal plants were displayed relative to one another in their natural orders" (Rose, pp. 39-40). Fortune was then hired by the East India Company as a plant explorer to acquire/steal the best tea varieties in China and ship them to India, which he ultimately did with great success – for the Company, if not China (Ibid). Also see Honigsbaum, pp. 72, 114, 116, 172 and Minter, *Ibid*, pp. 48-54.

[170] Pers coms. from: Rich Hannon, Western Regional Plant Introduction Center, Agricultural Research Service, U.S. Department of Agriculture (ARS/USDA), Pullman Washingron, February 2005; Ned Garvey, Plant Exchange Officer, ARS/USDA, Beltsville, Maryland, February 2005.

years and coinciding with the emergence of cultivated production. While this process doubtless originated in China, no information seems to be available, at least in English, about its subsequent plant improvement efforts, if any, or possibly similar activities elsewhere in SE Asia. Known recent activities are as follows.

b. Regions and Nations

i. Switzerland and Germany. The principal ongoing 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[171] 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_1) seed is needed each year if the yield drops normally involved with the second generation (F_2), roughly 20%, are to be avoided. Other commercial seed probably largely represents selections of traditional varieties.

ii. United Kingdom. Two of the most substantial efforts in plant improvement have recently been undertaken in England by the Centre for Novel Agricultural Products (CNAP) in the Department of Biology at the University of York and the National Institute for Agricultural Botany (NIAB) at Cambridge.

- The Center for Novel Agricultural Products. In June 2006, CNAP announced the award of a $13.6 million 4.5 year grant from the Bill & Melinda Gates Foundation to use fast-track breeding develop robust non-GM varieties of *A. annua* with greatly increased yields of artemisinin – at least a doubling compared to the current leading variety - for use in ACTs. A second grant in early 2010 brought the total up to $26 million and will support late-stage delivery to Artemisia producers in Africa and Asia. The project is led by Dianna Bowles and Ian Graham.[172]

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[171] "Var M" 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 was expected to be more widely planted in 2005 and 2006 (pers. com. 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. com. from Jorge Ferreira, USDA, April 2006).

[172] Further background information is provided in University of York 2006; Bowles 2006; CNAP 2007a, b; Graham 2008. CNAP also hosted "The Artemisinin Enterprise Conference", October 8-10, 2008. The Artemisinin Enterprise composes three complementary scientific projects largely sponsored by the Gates Foundation (the other two, noted earlier, include semi-synthetic artemisinin through fermentation [UCBerkley and others] and a new class of synthetic peroxides [MMV and others]). Copies of the principal reports presented are provided in [http://www.york.ac.uk/org/cnap/artemisiaptoject/pdfs/AEconference-report-web.pdf]. Also see their periodic project updates [http://www.york.ac.uk/org/cnap/artemisiaproject/projectUpdates.htm].

CNAP is using "Artemis" as starting material (Mediplant is a collaborator) and seeking to broaden genetic diversity by inducing mutations. Thousands of plants are then grown and screened to identify the highest-yielding varieties. In addition, the group is accessing promising genetic diversity from many populations with the help of the molecular tools that they have developed. An advanced data management system links plants to link plants to information on their characteristics and genetics. New techniques have been developed for accurate assessment of desirable features. This has involved, notably, the development of a genetic map of Artemisia which identifies loci affecting the yield of artemisinin, thus making reducted timelines feasible (Graham et al. 2010). Sequence data have been placed in public databases such as the NCBI (the National Center for Biotechnology Information, U. S. National Library of Medicine).

Plants selected are being used as breeding stock for testing new varieties in developing nations. As of the summer of 2009, over 23,000 plants had been assessed and over 200 high-yielding varieties identified. They were being evaluated for other characteristics, initial crosses made, and testing in glasshouses was initiated. Field testing began in 2008-2009 in the year in cooperation with national partners in Kenya (Botanical Extracts, EPZ), Uganda (Afro Alpine), Madagascar (Bionexx), China (Guilin Pharma) and India (AVT Natural Products) and will run through mid-2011. This will be linked with elite parent selection for hybrid production, the later to begin in 2011 (CNAP 2009, Clayton 2009).

- The National Institute for Agricultural Botany. In November 2009, NIAB announced that they, in cooperation with several partners, had developed varieties of Artemisia that produced sustantially higher yields of artemisinin - over 2.2% of dry material (NIAB 2009b).[173] These levels were said to be almost three times the industry level of 0.8%. This improvement has "been matched by improvements in health and vigor of the plants." Moreover, developmental material in their nursery reportedly yielded nearly twice the concentrations of artemisinin compared with the controls that were the best varieties or lines available from seed gathered in 2004 from a wide range of sources around the world.

The trials are part of a study that began in 2005 to "investigate the feasibility of growing Artemisia in the UK...for artemisinin-based therapies" (NIAB 2009a&b, Kelland 2009). New lines were were tested in Morocco in 2008, Kenya (by ABE) and in Canada in 2009 (Alberta Research Council). Further testing will be conducted in 2010 in Uganda (Afro-Alpine), Kenya (ABE), Madagascar (Bionexx), China (Holly), and probably in Argentina (Sano Mundo) (pers. comm. from Colin Hill, October 2009). The first set of results was presented at the WHO/MMV artemisinin conference at Mumbai, India in September 2009 (Hill 2009).

The breeding and trials, which are headed by Steven Bentley [steven.bently@niab.com], are part of a larger effort including agronomy, herbicides, mechanical harvesting, and commercial drying, which has been carried out on a full field scale. Financial support is provided by three

[173] The NAIB, established in 1919, is an independent, not-for-profit, plant research group (recently integrated with another organization to form the NIAB Group). Parners include East Malling Research, Botanical Developments Ltd. (lead), Frontier Agriculture Ltd. and De Monfort University.

government agencies (the Department for Environment, Food and Rural Affairs [Defra], the Depatment of Energy and Climate change [DECC] and the Biological Sciences Research Council [BBSRC] through the "Renewable Materials LINK Programme" which is designed to encourage collaborative research for innovative and industrially-relevant purposes. Colin Hill is chairman of the Defra Link Consortium, BDL [colin.hill@botanicaldevelopments.com].

- Comparing the Programs. While the two projects have similarities, they also differ. They are *similar* in that they started about the same time, share essentially the same goal (to develop varieties which will yield higher levels of artemisinin), and are currrently conducting field trials with some of the same groups in developing countries. They *differ* in having quite different sponsors/funders, organizational structures, scopes of work, budget levels for the breeding efforts, and target clients (CNAP has a global focus while the LINK project is concerned with several aspects of commercial production in the U.K).[174] Although the two programs have been carried out not far apart in eastern England, they seem to have been quite independent efforts. It will be interesting to begin to compare the fruits of their plant improvement efforts, which should be possible before long. Other aspects of their programs - such as contributions to scientific knowledge - may take longer to assess.

iii. United States. The first systematic effort to cultivate *A. annua* and isolate artemisinin for research purposes outside of China appears to have been conducted at the *University of Mississippi* in the mid-1980s. Dr. Edward Croom, an ethnobotanist with the School of Pharmacy established a medicinal plant garden that included about a dozen traditional Chinese plant species in the spring of 1983; one was *A. annua*. Additional Artemisia species and 22 accesssions of *A. annua* were obtained from 16 nations and were grown in 1984. A colleague, Farouk El-Feraly, a natural products chemist with expertise in sequiterpenes, isolated artemisinin from dried leaves harvested in 1983.

This work was expanded when an application for funding led led to a WHO/TDR/CHEMAL grant of $153,300 in 1985 (Dr. A. Brossi of NIH was the CHEMAL contact) for Croom and two natural product specialists, Mahmoud and Hala ElSohly, to cultivate Artemisia and provide one kilogram of artemisinin by March 1986. This required the planting of three acres to Artemisia (in order to produce the needed 1,200 kg of dried leaves). It was also necessary to complete the development of an agronomic package, develop an improved analytical method, move from laboratory to commercial scale of extraction, and develop and implement an isolation process. Remarkably, all of this was done on schedule (pers. coms. from Croom, March 2009; CHEMAL 1986, pp. 7-8). Other research on artemisinin followed and/or was reported in later years (Duke et al., 1987; ElSohly et al. 1987, 1990; Lee et al. 1989; Bryson and Croom 1991).

Subsequently, 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* - carried out extensive physiological research with the *A. annua* plant (see, for example, Ferreira and Janick 1996; Ferreira, Simon and Janick 1997; Ferreira 2007; and Wang, et al. 2005). Simon accumulated

[174] It is also quite probable that the genetic base of their leading varieties will differ, but more information will be needed about their pedigrees to judge the extent to which this is the case.

selections, improved lines and hybrids from a number of sources and grew them out under controlled conditions; attention was given to both high yield and high artemisinin levels (pers. comm. October 2005). Ferreira (2007) was exploring the potential of Artemisia for crop cultivation under Appalachian ecosystems and its post-harvest physiology for its potential use in animal health.

iv. Latin America

- Argentina. A three-stage program has recently been initiated under the *Fundacion Mundo Sano* involving (1) agronomic production of Artemisia (in cooperation with Mediplant), (2) artemisinin extraction (with the University of Bath), and (3) synthesis of artesunate (Desmarchelier 2009).

- Brazil. A joint program involving the *University of Campinas* and the private sector is underway. Components are: (1) research and development; (2) cultivation; and (3) extraction/purification/derivatives. Part of the production challenge is to increase productivity and artemisinin levels under tropical conditions (Magalhaes 2007). The University (UNICAP) in cooperation with the Chemical, Biological and Agronomical Research Center (CPBQA) is also a source of improved seed (about 1% artemisinin) for the intratropical region and low latitudes close to the equator (pers. com. from Magalhaes, August 2007).

v. Investment.

Except for the recent research being conducted in the United Kingdom, the financial investment in varietal improvement of Artemisia over time has been miniscule, especially when compared to the investments in synthetic forms of artemisinin and vaccines.

c. Other Plant Sources of Antimalarials.

Artemisia is not the only source of plant-derived treatments for malaria. A number of individuals and groups have been, and are, searching for and screening other plants with anti-malarial qualities. Comprehensive accounts are provided in Willcox et al. 2004a, Rukunga and Simons 2006. Additional studies have been conducted by, among others, Asase, et al. (2005), Bertani et al. (2005), Wright (2005), Chung et al. (2009), and Bero et al. (2009). Wright (2010) has provided the most recent and comprehensive technical review of alkaloids and herbals; the latter section includes an entry that may not be well known (*Argemone mexicana*) and clinical studies on another (*Cryptolepis sanguinolenta*). The TDR group in FAO has been sponsoring an effort to build capacity of African institutions to screen and test indigenous herbal remedies in Kenya, involving a number of institutions (TDR 2007b). (Also see **Annex 5b**.)

Annex 4. Artemisia: A Kenyan Grower's Perspective

[*Note: The following comments were originally prepared by a large grower in the Nyeri District of Kenya in November 2007, for the Kenya Development Network and Consortioum (www.kdnc.org) and are reproduced here in slightly abridged and modified form with his kind permission.*]

I have been growing Artemisia for the last three years. I started growing the crop only because I had heard of it and I am always looking for crops with which I utilise my land better. My neighbours followed my example for the same reason.

I started with a hectare in the first season, went on to two hectares then last season did fifteen hectares. The initial production was very encouraging with a yield average of two tonnes of dry leaf for the hectare. That average was sustained during the second year but last year, I averaged 1.250 tonnes to the hectare. The weather was adverse with a lot of rain and flooding and the crop that was planted was not F_1 but F_2 hybrid. Over the years, we have averaged 1.2% Artemisinin at a price of about 1 US dollars per kg. This means that after all the costs which are just slightly less than 1000 US dollars per hectare, there was a decent profit.

This scenario is changing in the current planting year as the price will now be fixed at about 75 US cents per kg and the Artemisinin content will have to be above 1%. This is a complication because the average Artemisinin could be a lot lower than the 1% and this would mean the selling price of the leaf going down to about 37.5 US cents. The growers have no choice but to sign this new contract as there is currently no other buyer of the leaf. The farmers are already tied to this crop as a cash crop.

The land holdings are not big enough and the farmers do not have sufficient capital to lease land and grow a large commercial crop so as to gain from economies of scale. The processes are 100% manual, that is, labour intensive so going really large scale is a challenge. I am not aware of any mechanisation of say harvesting and drying.

Looking into the future, this crop has the potential of becoming very big in Kenya in terms of commercial viability. It is easy to grow, has no known pests but is affected by weather vagaries and unpredictability. We still do not have an understanding of the huge fluctuations of yield but I suspect it has to do with husbandry which I hope we will be able to sort out sooner than later. We get agricultural extension support from the buyer.

I see the need to have more players in the buying and extraction of Artemisia. Currently growers have to carry leaf for long distances for extraction at a cost. I believe with proper pricing and extraction of the Artemisinin at the growing areas, the farmers would realise more. I think this crop is too important as a medical innovation for it to continue being grown in this simplistic way. We should do better as we continue learning and as we get more buyers and processors.

Like all cash crops, including coffee, there is always the danger of people forgetting to leave aside land for subsistence crops. I have seen this happen with vegetable crops for export which has been grown at the expense of cereal crops which people feed on and when there is crop failure, they go hungry. Artemisia could go the same way.

Annex 5. Artemisia: Traditional Medicine and Science

Traditional medicine is, in the recent words of *SciDevNet* (June 30, 2010), "a vital yet often neglected part of healthcare in the developing world. In Africa and Asia more than two in three people rely on [them] "as their primary healthcare." Furthermore, "Pharmaceutical companies and medical researchers in the developed world "are increasingly turning to traditional medicine to find solutions to the world's most pressing health problems."[175] The use of Artemisinin in teas and herbal remedies is a case where tradition and science rub up against each other, and not altogether comfortably.

a. Artemisia Teas.

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 (see Hsu 2006a, 2006b), but little seems to be known about the degree of their impact on individuals or society.[176] Manufactured therapies, using artemisinin extracts of varying concentration and combination, 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 Artemisia tea.[177] 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 Heide 2006).[178]

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 and found that the current Chinese pharmacopoeia contained 19% of the

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[175] The issue is composed of three sections: (1) an *editorial* on "The imperatives for traditional medicine," (2) five *opinion* pieces ("Ending medical dominance…", "Discovering Africa's drug potential," "Modernising traditional medicine…", "Recognising traditional health systems," "Modernising traditional medicine must work for locals" and (3) a *feature* "Integrating modern and traditional medicine: Facts and figures" (very useful).

[176] By contrast, there is considerable and clear evidence that massive efforts made to control flooding and drain swamps in southern China beginning in 960 reduced malaria and led to settlement in fertile river valleys (Marks 1998/2006, pp. 71-77, 334); "Europeans had to await the elixir of quinine to conquer the tropics" (p. 340).

[177] While artemisinin is not readily soluble in water, it appears to be sufficiently so at high temperatures to provide antimalarial effects. Ferreira (pers. com. December 2005) has extracted 75% artemisinin at 85-90^{o}C; he maintains that boiling Artemisia, which may sometimes occur in making teas, destroys most of the artemisinin. Also see Willcox et al. (2004a, pp. 45-46, 54-56; 2004b) for differing perspectives here and below.

[178] This is also true of artemisinin monotherapies. In areas where malaria is endemic, true recrudescence is hard to distinguish from re-infection (pers. com. 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).

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, and this may be, as it would be for other artemisinin monotherapies, 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."[179]

Some groups, such as ANAMED, have encouraged the combining 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]. Others suggest that tea is not strictly a monotherapy because the whole leaf, containing more than one compound, is used. And in China, a whole plant extraction process was recommended in the fourth century B.C. (Hsu 2006a, p. 506).[180]

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 or harm (in terms of the buildup of resistance), real or potential. While they clearly should not, as a general policy, be recommended in areas where better treatments are available and affordable, it may be quite another thing to discourage their use in remote areas where clinics are far away, no alternative treatments are available, and the degree of effect of teas on the development of resistance in these areas uncertain – though greatly in need of study.[181] In any case, teas are largely consumed by adults, not children.

b. Herbal Therapies.

Where herbal remedies are the only antimalarial therapies available and affordable, the challenge is to improve their therapeutic value (Bourdy et al. 2008). The *World Agroforestry Center* (formerly the International Center for Research on Agroforestry, ICRAF) and the

[179] Questions have, however, been raised about his analysis: Heide 2007, Willcox et al. 2007.

[180] The method consisted of "soaking the fresh plant in water, and then wringing out the whole plant and ingesting its juice in its entirety." This process "must have resulted in an emulsion of water, flavenoids and other etherical oils contained in stem and leaves…which may have facilitated the extraction of the Artemisia sequiterpenes" (Hsu, 2006a, p. 506). Potential advantages of whole plant usage are noted in Willcox and Hsu (2008). Recent research has shown that "the ancient Chinese methods that involved either soaking (followed by wringing) or pounding (followed by squeezing) the fresh herb are more effective in producing artemisinin-rich extracts than the current method of preparing herbal teas from the dried herb" (Wright et al. 2010, p. 804; also see Ferreira, et al. 2010).

[181] Willcox and Hsu (2008) also comment on these issues. Ethical issues involved in the use of herbal medicines are reviewed by Tilburt and Kaptchuk (2008) and mentioned by Wright et al. (2010).

International Center for Insect Physiology and Ecology (ICIPE), both headquartered in Nairobi, are or have been involved, in somewhat similar ways, with Artemisia.

ICRAF has given some attention to herbal combination therapies (HCTs) involving Artemisia for use in remote areas. 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 [www.worldagroforestry centre.org/treesandmarkets/antimalariameeting/proceedings/] and a booklet on *The Potential of Plants as a Source of Antimalarial Agents, A Review* (Rukunga and Simons 2006).

ICIPE has long been engaged in a variety of malaria control programs at the farm level and has more recently focused on Artemisia. In cooperation with the Kenya Medical Research Institute (KEMRI) and the Natural Uwamba System for Health (NUSAG) of Tanzania has developed and tested an unfractionated whole leaf extract made into powdered tablets (WLPT), with promising clinical results (ICIPE 2005; Mungai 2005; ICIPE 2006).[182] KEMRI has a Centre for Traditional Medicine and Drug Research that is engaged with others in an ongoing search for additional plant sources of anti-malarials (Anderson 2007).

Another group, the "Research Initiative on Traditional Antimalarial Methods (RITAM) was extablished in Oxford in 1999 to promote research and development of herbal antimalarials [www.giftsof health.org/ritam/].

Two members of the Mali Malaria Research Center provided some appropriate works of caution during a recent conference on African herbal medicines in Nairobi. One stated that "more research must be directed towards finding out the effectiveness of these traditional plants and their safety and efficacy because…using them could be counter-productive." Another called for caution, noting that "Many traditional healers will…give anything as medicine so long as it is a plant – we must urge caution" (ko/mw 2009). And if they basically rely on artemisinin or an analog, they remain monotherapies, with the dangers that poses in terms of the build-up of resistance.

c. Science and/or Tradition?

Teas and herbal preparations are cases where tradition and science may appear to differ sharply and yet may have useful areas of overlap. Some individuals, including scientists, think that there may be situations at the margin – say in remote areas of the Congo - where their use might be acceptable. Still, there is need to apply more scientific analysis to the areas of particular promise and build on traditional practice to provide a safe and useful public good. In such a setting, the last words of Hippocrates cited at the beginning of this paper - "at least do no harm" - provide a challenging and somewhat haunting backdrop.

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[182] Preliminary clinical trials at ICIPE's St Jude's Clinic Mbeta Point station on Lake Victoria showed an "impressive efficacy even at the lowest-dose regime" (ICIPE 2005). It was thought that 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).

Annex 6. Artemisinin: Phytochemical Extraction.

The normal extraction process described heretofore is focused only on artemisinin. Yet the Artemisia plant itself is a rich source of phytochemical diversity: monoterpenes, sesquiterpenes, flavonoids and polyacetylene epoxides. Some of these, it is thought and initial research suggests (e.g. Billia et al. 2006; Elford et al. 1987; and Liu et al. 1992), might also play a useful role in enhancing the medicinal effect of artemisinin, though the mechanism involved - bioavailability, presence of precursors, or other constituents - is uncertain. Given their nature, it is unlikely that these anti-plasmodium effects would also be readily available from non-plant sources or possibly even from other plants (e.g. chicory).

The extent of this effect may vary with the type of extraction process utilized. Beyond the traditional aqueous process represented by tea, there are three other approaches: (1) concentrated non-aqueous extracts in gelatins/tablets (Wan et al. 1992); (2) whole leaf powdered tablets (WLPT, as noted above); and (3) sequential extraction with solvents of increasing polarity (Lwin et al 1991; ICIPE 2006). While some initial proof of concept studies have been carried out for the first two, this is is only recently true for the third.[183] Pharmacokinetic studies after consumption are evidently not available for any.

Should one or more of these approaches - each of which involves a manufacturing process - ultimately lead to a more effective compound, some might view the product as more than a monotherapy and hence possibly a substitute, if only at the margin and in poor and remote areas, for an ACT. This might be helpful for some individuals but not equally good overall public policy. Artemisinin is marked, as noted in the preceding text, by its quick action on malaria parasites and needs to be blended with another longer-acting drug to reduce reinfection. But fuller use of the potential of the Artemisia plant conceivably might contribute to an improved ACT.

[183] Simon, et al. (undated, pp. 23-24) proposed the development of a standardized extract to serve as the Artemisinin source in an ACT. A grant from Dioraphte funded research on the *ethanol* extract of Artemisin in Europe beginning in 2008. Prof, von Freyhold, Univ. of Bremen (Germany), produced the extract and Prof. Oliver Kayser, Univ. of Groningen (Netherlands), project leader, analyzed the extract, formulated the product, and will do further trials and tests (pers. com. from Dirk Rezelman, April 2008). As of October 2009, research suggested that mixing Artemisia extract with peanut oil resolved problems of low bioavailability and stability. Future research will focus on artemisinin particle size and stability in the extract of various partner drugs and the purification of artemisinin from various ethanolic extracts (pers com. from Rezelman, October 2009). Extraction efficiency with ethanol has be 95% and a group at the University of Ghent managed by Arne Heyerick is studying the optimal extract level for cancer treatment (pers. com. from Rezelman June 2010; **Annex 9a**). Also see [http://artemisia-for-all.org].

Annex 7. ACTs: The Supply Situation in Uganda, 2007

Some aspects of the general supply and demand situation for ACTs in Africa have been mentioned previously it the text, particularly in the context of national policy and multilateral programs (Chp. III/2) and bilateral programs (Chp. III/3). While some studies have been conducted of the marketing of anti-malarial treatments (e.g. Goodman et al., 2004, 2007), they are relatively limited in number.

A particularly comprehensive study of the supply was recently completed in Uganda (another is underway on the demand or household side) and may be illustrative of some conditions elsewhere in Africa (MMV 2008b). It was conducted in nine districts, representing high and medium transmission settings, and included 789 outlets of varying types. Of these, 250 were in the public sector and 539 in the private sector. The former included public facilities, community drug distributors, and private not-for-profit clinics and hospitals. The latter included retail pharmacies, drug shops, private clinics, retail stores, and the informal market (including vendors).

Availability. A wide range of treatments was available in the aggregate, though not necessarily in individual cases. The principal main line therapies included ACTs (**AL**, **AS+AQ**), three forms of quinine for special uses (tablets for the first trimester of pregnancy, injections for severe/complicated cases, syrup for children under 5 kg, and SP for internittent preventative therapy). Stocks of ACTs, however, were very limited.

Prices. The price of ACTs was 30 to 60 times higher than for non-artemisinin therapies. Suprisingly, the prices for artemisinin monotherapies were as high or higher than for ACTs for adults, whereas quinine was less than half their cost for adults and children.

Affordability. Thie was expressed in terms of opportunity costs. By this measure, "All antimalarials, let alone the expensive ACTs, are unaffordable to the average household…" (p. 15). A course of treatment of **AL** procured through the the private sector represented: (1) 14 to 25% of total income for an average household or 91 days; (2) 1.5 to 2 month's basic food needs; and (3) 6 to 7 years or 90 months of primary schooling costs.

The Supply Chain. The existing chain is relatively effective. Markups at the wholesale level were not high, 5% to 9%, and averaged 110% in retail pharmacies. Storage conditions for the drugs, however, were in general poor, which is a matter of some concern for ACTS because of their relative perishability.

Stocking. ACTs were found in only 9% of the private sector outlets and were almost entirely **AL**. "ACTs are unlikely to become more widely available in the types of private sector outlet most frequented (drug shops and retail stores) until they are rescheduled for sale at this level by NDA [the National Drug Authority] and prices drop significantly, probably through a subsidy" (p. 14).[184]

[184] A subsequent effort, encouraged by the Global Fund, to purchase ACTs through international competitive bidding, got off to a slow start and could accentuate the stock-out problem (Tren, Hess and Bate 2009). Jack (2010c) and Moszynski (2010) provide more recent commentaries on the supply situation.

Annex 8. Artesunate, Coartem and FDA Approval

Until fairly recently no artemisinin derivatives or ACTs had been proposed or approved by the Food and Drug Administration (FDA) for use in the United States.[185] This is not surprising because malaria is primarily confined to travelers to endemic areas in other countries, and then ACTs would be primarily useful in a curative role. One non-ACT combination, *Malarone*® (atovaquone-proguanil HCL), was been approved but resistance has been shown in some parts of the world and it is thought that it would be beneficial to have an additional treatment available (Novartis 2008b, p. 13).

An initial step had been taken in 2004 when a regulatory dossier was filed with FDA to make artesunate available to treat severe and complicted malaria. On June 21, 2007, FDA approved investigational new drug (IND) protocol #76,725 titled "Intravenous Artesunate for Treatment of Severe Malaria in the United States." "The drug will be made available to…hospitals, upon request and on an emergency basis, by the CDC Drug Service or by one of the CDC Quarantine Stations located around the country" (CDC 2007; Milhous and Weina 2010, p. 280).

Subsequently, Novartis was reportedly "encouraged" to register *Coartem*® in the U.S. and applied to the Food and Drug Administration for approval in 2008 (McNeil 2008f).[186] The process involved the preparation of a detailed briefing document (Novartis 2008c) that was reviewed by the "Anti-Infective Drugs Advisory Committee," a FDA panel of outside experts, on December 3, 2008. The group concluded that the clinical data showed that Coartem worked (18 to 0) and that it was safe (17 to 1), which amounted to a recommendation for FDA approval. An early decision was expected and was received on April 8, 2009 (FDA 2009). As part of a new mechanism approved by Congress, Novartis also earned a transferable priority review voucher for another experimental drug application (Ibid., Dooren 2008, Heavy 2008a, 2008b, Jack 2008b), a procedure which has been questioned (Anderson 2009).

The briefing document, which is now public information, privides a rich source of information, especially about the clinical review program for *Coartem* (discussed in detail on pp. 26-44). It included a total of 4,911 patients in 20 studies conducted by the company between 1993 and 2007. A total of 3,599 patients were treated with *Coartem*, including 1,572 adults (over 16) and 2,027 pediatric (16 and under) patients. The studies were conducted in a range of geographic areas, mainly Asia and Africa with varying levels of multi-drug resistant *P. falciparum*. The firm initially studied the efficacy and safety of a four-dose regimen (1993-97) and subsequently focused on a six-dose regimen (1997-2007), adjusted for varying body weight ranges (pp. 11, 28). Another 40 or so independent studies were also reviewed, including various ACT combinations (pp. 63-70) and various regions (pp. 70-73).

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[185] Similarly, no artemisinins or ACTs are registered in Japan (Kano 2010).

[186] According to McNeil (2008f), "Novartis had little interest in registering it in the U.S. because the market is so small and the …agency's requirements are expensive – even when the application fee, more than $1 million for a new drug, is waived, as it was for Coartem. Novartis came under [government] pressure to register it here…." Its primary use would be for tourists and other Americans stationed overseas, but it "could also help the military, which normaly cannot prescribe drugs lacking F.D. A. approval…."

Annex 9. Artemisinin and Quinine: Other Medical Uses & Linkages

Medicinal extracts such as artemisinin and quinine may (as cited in fn. 140) be useful for, or used for, several medical afflictions. And their derivatives may be combined in numerous, and sometimes unexpected ways. Here we review four rather differing categories, some fairly old, some quite new, some relating to malaria, and others of a quite different nature.

a. Artemisinins and Cancer; Cancer Drugs and Malaria.

There is a degree of symmetry between malaria and cancer when it comes to chemotherapy, though different modes of action are involved. In the case of artemisinin, its derivatives have shown effectiveness against several forms of cancer at the laboratory level. And conversely, several anticancer drugs have shown effectiveness against *P. falciparum*, again at the laboratory level. If born out in more extensive clinical trials, one or both could in time provide an additional weapon in the fight against each disease, and perhaps influence the demand for artemisinin in quite different ways.

- Artemisinin Derivatives and Cancer. In the mid-1990s, the selective cytotoxicity of dihydroartemisinin and holotransferin towards cancer cells became known (Lai and Singh 1995). Cancer cells require larger amounts of iron (specifically intracellular heme iron, the non-protein, ferrous-iron component of hemoglobin) than normal cells to "assist their rapid proliferation" and thus are "more susceptible to the toxic effect of artemisinin" (Lai et al. 2005, p. 1267; Chaturvedi et al. 2010, p. 453). [187]

This iron activates an "endoperoxide bridge" in artemisinin that forms very active free radicals that kill malaria parasites by inducing apoptosis (a form of death in which the cells disintegrate). Normal cells with lower levels of iron are not affected (Berger et al. 2005, pp. 1599-1600; Nakase et al 2008, p. 28; Singh and Lai, 2004, p. 2279).

The addition of another iron source increases the impact of the artemisinin derivatives (Lai et al 2005; Berger et al. 2005). And since the use of artemisinin for cancer treatment is limited by its fast elimination, the use of transferrin (a natural component in blood) could help the compound last longer (Lai and Singh, 1995; Lai et al. 2005, p. 1277; also see Berger et al. 2005, pp. 1599-1600).

As noted earlier (III/1/c/i), Prof. Gary Posner of Johns Hopkins University has long been aware of the cancer dimension and his group has "discovered that some dimeric peroxides [mimic synthetics] are not only highly antimalarial but also highly antiproliferative." They are "actively designing, preparing, and testing such types of dimers for chemotherapy of both malaria and cancer." They are also planning further animal tests.[188]

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[187] Many of the studies cited here represent research conducted by members of the Depts. of Bioengineering and Pharmacology at the University of Washington and in two cases involved researchers from other institutions. Prof. Singh of the former Dept. has been of assistance in providing information on their work.

[188] These are being done in preparation for filing an investigational new drug (IND) application with the U.S. Food and Drug Administration to perform human clinical trials covering both the malaria and cancer portions of

Studies to date have demonstrated effects on numerous forms of cancer (Chen et al. 2003 [reporting research done in China]; Berger et al. 2005; Singh and Lai 2004; Singh and Panwar 2006; Lai and Singh 2006; Qigui et al. 20007, p. 53). In contrast to the relatively high cost of ACTs in malaria control, artemisinin derivatives are viewed as a relatively low-cost cancer therapy (Singh and Lai 2004, p. 2277; Lai and Singh 2006, p. 46; Singh and Panwar 2006). But these results are only a start and the best need to be subjected to clinical trials.[189]

- Cancer Drugs and Malaria. This topic has recently been raised in the context of using several drugs against *P. falciparum* (Nzila et al. 2010). Their initial focus is on methotrexate (MTX), which is also being evaluated for the treatment of several other diseases, and trimetrexate (TMX). The anti-malaria potential for MTX has "been established for almost 40 years" but "has not come into widespread use due to concerns over toxicity." TMX is also reported having "good activity against *P. falciparum*." The authors suggest that toxicity is a function of dosage level and that "there is always a dose range at which a drug is safe" (Paracelsus' law). But research has not reached this stage.

The basic chemical process involves the inhibition of the dihydrofolate pathway enzymes in normal cells by folate derivatives such as sulfadoxine and pyrimethamine (SP) (also see NA 2004, pp. 259-260, 291-292; Peters 2005; Warhurst 1998, 2002; and Yuthavong et al. 2005). Other sources may be more potent or have other useful qualities; one being tested by MMV "works against all resistant strains so far (pers. com. from Ian Bauthurst, MMV, January 2010). More generally, anti-cancer drugs usually have "too small a selectivity window and kill dogs at the dose required by malaria activity" (*Ibid*). And they, too, are subject to the development of resistance

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b. Artemisinin, Antibiotics and Combinations

The use of a combination of artesunate and an antibiotic - azithromycin - in malaria control in Asia and Africa (Stykes et al. 2009) was briefly noted in the text (Chapter IV/2/c, fn. 141).

As Pradel and Schlitzer (2010) have indicated, antibiotics attack the apicoplast and thus cause a slow killing process of the malaria parasite. But "Because of the delayed onset of … [this] effect, these antibiotics are unsuited for malaria therapy when used alone. However, in combination with a faster-acting antimalarial, they are valuable combination partners,,,." Also, "there are no reports on clinically relevant resistance against antibiotics…" which means that "the antibiotic will hopefully protect the faster acting anti-malaria from causing resistance in the parasite" (p. x).

Several studies have been conducted by Noedl and others using a combination of azithromycin with artesunate, and in one case with quinine. The first study, in Thailand

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their work in the Johns Hopkins School of Medicine (www.jhu.edu/~chem/posner/ [Research; also see Publications]; accessed 1/5/10; pers. com. from Prof. Posner, February 2010).

[189] Also see the recent reviews by Krishna et al. 2008, O'Neill et al. 2010, and Ferreira et. al. 2010.

suggested that that the combinations "are safe and efficacious combination treatments for uncomplicated falciparum and they deserve additional study in special patient populations" (Noedl 2006, p. 1264). A larger study was subsequently carried out in Bangladesh with similar results (Thriemer et al. 2010).

Noedl (2009) has further suggested that antibiotic-based combinations – ABCs – might also be suitable for the treatment of severe malaria in high transmission areas, a process that presently involves intravenous quinine or an artemisinin derivative. Thus "…perhaps antibiotics should not be considered as a separate entity for treating coinfections, but rather as antimalarials… simultaneously covering numerous pathogens commonly encountered in coinfections or that cause syndromes which are clinically indistinguishable from severe malaria" (p. 542). Pradel and Schlitzer view this as a unique opportunity to "kill two birds with one stone." In addition, laboratory research with rodents suggests that "induction of protective immune responses by natural infection under antibiotic coverage [with clindamycin and azithromycin] may offer a powerful shortcut towars a needle-free, whole-organism vaccination strategy" (Friesen et al. 2010). Further clinical study in Africa seems warrranted.[190]

c. Malaria, Quinine and Blackwater Fever

One of the oddities of malaria is an associated syndrome, characterized by bloody urine (or in more technical terms "intravascular hemolysis, hemoglolbinuria and acute renal failure" (Bruneel et al. 2001, p. 1133) and known as Blackwater Fever. Moreover, quinine may play some role in both triggering and alleviating it. It has been known under various names, most commonly "malarial haematuria" and assumed some importance in numerous warmer countries or regions around the world in the mid-1800s through the mid-1900s. It was one of the most common causes of deaths of Europeans in West Africa and in some cases the mortality rate was as high as 25%. This seemed to be particularly true of "individuals who have been living in endemic areas for at least several months [and] had a history of irregular chemoprophylaxis with quinine" (Bruce-Chwatt 1987, pp.185-188; also see Macgraith, 1948, pp. 22-23 and Russell 1952, pp. 49-50, 53).[191]

Yet as Christophers stated in 1937 (p. vii), "Blackwater fever is a difficult disease to write about." "Practically nothing is known of the ultimate causes in the bringing about the destruction of red cells to which the disease owes almost all its features. It is…now generally conceded that [it] is in some way a result of preceding malaria, but how malaria brings about the sudden access of blood destruction is entirely unknown. Seemingly also quinine enters into the picture but to what extent and how far as an essential factor and in what way it it acts is again completely a matter of hypothesis. Unlike most important diseases there is no

[190] Curiously, while WHO's 2006 "Guidelines for the treatment of malaria" (WHO 2006b) "included useful advice on the use of antimicrobials in severe severe malaria", this section has been removed in the 2010 guidelines (WHO 2010b). "…this leaves an important gap in recommendations for the treatment of malaria-bacterial co-infection which is present in 14-25% of inpatient deaths from malaria in children" (Reyburn 2010, p. 162). Further review of this matter would seem appropriate.

[191] The experiences of one such individual, who survived five attacks while a tea planter in India from 1894-1907, have been referred to earlier (fn. 145). Ross had written him that "Blackwater fever is usually precipitated in a case of neglected malaria by a sudden dose of quinine, generally sulphate of quinine" (Fraser, 1935, p. 210).

specific organism to describe, no causitive chemical basis to discuss, scarcely really any really relevant investigations on the nature of the disease to set forth. As a consequence there is no rational basis on which treatment, other than empirical or purely pallitive, can be placed."

Fifty years later, Bruce-Chwatt wrote "our knowledge of the cause or mechanism…is still meager and unsatisfactory" (1987, p. 193). But he also stated that "There is no doubt that the incidence of blackwater fever decreased quite remarkably since the 1950s" (p. 191), "when chlorquine superseded quinine" (Bruneel et al. p. 1133; also see Shah 2010, p. 97). Quinine had been favored during the colonial period as a preventative measure over others programs such as mosquito control in irrigation projects - a "quinine policy"- which was not althgether altruistic (Watts cited by Bhattacharya 2010). It was viewed by others, however, as a "triggering" mechanism along with other other aryl aminoalcohol compounds, and hence "a practice to be avoided" (Ibid., Salako 1987, pp. 175-177; Bruneel et al. 2001, p. 1133; NA 2004, p. 253; Shah 2010, p. 97).

Malaria has also long been associated with other diseases such as splenomegaly (enlargement of the spleen) (NA 2004, p. 344; Eamon 2010, p. 72; also see Google Scholar).

d. Malaria Therapy and Quinine

This dimension is a much older one and ultimately led to a Nobel Prize in physiology and medicine. In the late 1800s it had been noted that feverish ("febrile") infectious diseases had often preceeded the improvement of the mental illness ("dementia paralytica").[192] This prompted Dr. Julius Wagner-Jauregg of Austria to, according to his Nobel lecture in December 1927, "propose as early as 1887 that this natural experiment should be imitated by a deliberate introduction of infectious diseases and I…singled out as a particular advantage of malaria that there is the possibility of interrupting the disease at will by the use of quinine." In 1917 he put this to the test and "the result was gratifying beyond expectation."

The practice was adopted in his clinic using one malaria strain. It was recognized that "Induced malaria…is a dangerous disease" but by "various measures, this danger has been decreased" and "cases are now almost never seen." He concluded that "it is certain that induced malaria therapy will yet pose many worthwhile problems for research to explain." According to one account this therapy "was widely used through the 1920s and 1930s, despite the fact that it was not always effective, and not without dangers." "These studies led to all the methods of stress therapy, electric shock, insulin etc. used in psychiatry, but in the mid 1940s were "superseded with the introduction of antibiotics, particularly penicillin."[193]

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[192] Previously, in 1790, Samuel Hahnemann, while writing a book about herbal drugs, became intrigued by the claims concerning the effects of quinine on malaria and conducted a series of self-experiments. "After two weeks [he] found that cinchona evoked malaria-like symptoms in himself'." When he discontinued the drug, the symptoms abated and he was well again. This led [him] to consider that a substance could inexplicably create symptoms that it can also relieve." After six years and thousands of experiments [he]…formulated the basic principles of homeopathy." The first was "similia similibus curantur" (like cures like) (Rutkow, 2010, p. 90).

[193] Wagner-Jauragg's work was recently briefly noted by Crosby (2010). These statements were drawn from two online sources noted by Google, one listed as "Nobelprize.org" which reprinted his lecture as excerpted from a book of Nobel lectures, and the other simply as "Who Named It?" under his last name. See References.

"Malaria therapy" was also used to alleviate the symptoms of tertiary syphillis which was otherwise untreatable, but declined sharply in use with the wider adoption of penicillin for primary and secondary syphillis. Still, some patients were being treated, usually with injections of *P. vivax*-infected blood, up to the 1950s as penicillin was relatively ineffective in the late stages of the disease. Treatment centers in the U.K. were located in Epsom (Horton Hospital) and Manchester (pers. com. from David Warhurst, April 2010).[194]

[194]The Mott Clinic, a special unit for malaria therapy, was established at Horton Hospital in 1925. "Patients were treated by infection with one or other species of malaria parasite and the centre was responsible for providing infective material for use in hospitals throughout Great Britain and Ireland." It became known as the Ministry of Health Malaria Laboratory until 1952 when it became the Malaria Reference Laboratory. In the 1970s it was transferred to LSHTM. [www.aim25.ac.uk/cgi-bin/vcdf/detail?coll_id=8156&inst_id=37].

Annex 10. Artemisia to ACTs: Some Conversion Factors

One quantitative category of importance that has not been reflected in detail in the text of this paper - in order to not complicate the presentation more than it already is - concerns the relationships between (1) the area and production of Artemisia, (2) the quantity of extracted artemisinin, and (3) the production of ACTs. Relevant conversion factors vary widely: those that apply to one situation may not hold elsewhere. Still, it may be useful to report on two sets of estimates that have recently been utilized in order to estimate the relationship between Artemisia area and production and the resulting or needed supply of ACTs.

Pilloy/OTECI-ARTEPAL Estimates (Pilloy 2008a)

Artemisia and Artemisinin (particularly subject to variation)
- Quantity of dried leaves per hectare: 1.5 mt
- Average artemisin content in the leaves at the extraction stage: 0.6%
- Extraction-purification process efficiency: 50%
- Quantity of artemisinin produced per hectare: 4.5 kg. (9.945 lbs.)

Artemisinin and ACTs
- 1 treatment = 0.5g artemisinin[195]
- 1 ha. Artemisia corresponds to: 9,000 to 19,600 **AL** treatments
  14,700 to 29,400 **AS/AQ** treatments
- 1 million treatments require: 50 to 102 ha. for **AL**
  34 to 68 ha. for **AS/AQ**

Clinton Foundation: HIV/AIDS/(Malaria) Initiative (CHAI 2008)

From artemisinin to derivative:
- 1.660 mg. to produce 1 gm. *artemether*
- O.970 mg. to produce 1 mg. *artesunate*

Wastage
- 5% of artemisinin during conversion to derivative
- 5% of derivative during conversion during conversion to ACT

Derivative requirements per tablet (not including wastage)
- **AL** (ACT): 20 mg of artemether
- *Artesunate* (monotherapy): 50 mg. of artesunate

Treatments per MT of artemisinin (adjusted for importance of relative pack size)
- Overall ACTs: 2.08 million
- **AL**: 1.82 million

[195] Assumes that the split between **AL** and **AS/AQ** is about 70/30% and that **AL** = 0.51 artemisinin and **AS/AQ** = 0.34g artemisinin.

Annex 11. Malaria Mortality, Interaction Effects, and Externalities

In 1997, epidemiologist Louis Molineaux, having participated in a WHO/World Bank study to estimate the global burden of disease where he noted that the "sum of the deaths attributed by disease esperts to their respective diseases was much larger…than the total number of deaths available," published a prophetic article in which he suggested that "this discrepancy points again to the importance of indirect (multiple cause) mortality" (p. 814).[196]

Instead of the usual "one death, one cause" process, he suggested a two part classification: (1) deaths where malaria is a "necessary and sufficient cause (i.e. deaths whose prevention requires the removal of malaria through prevention or cure), and (2) deaths of which malaria is a necessary but not sufficient cause (i.e. deaths caused jointly by malaria and some other cause(s), which are preventable either by removal of malaria or the removal of the other cause (s)." The two could be labeled [1] "direct" (unconditionally lethal) and [2] "indirect" (conditionally lethal) mortality (p. 812).

The interventions include (1) control programs including nets and chemoprophylaxis or both, and (2) eradication including the interruption of transmission through residual spraying plus "in some cases, periodic mass drug administration" (p. 813). "If indirect mortality…is important, the other disease control programs could significantly reduce malaria-specific mortality" (p. 814).[197] This is termed a *positive externality* by economists (see Chp. IV/1/a, p. 52).[198]

A significant example of the indirect mortality category is provided by HIV/AIDS. A WHO/RBM technical consultation in June 2004 (WHO 2004c) observed that "Malaria and HIV/AIDS are both diseases of poverty and causes of poverty and they share determinants of

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[196] Philipson (1999/2000) stated that "most research on the public control of infectious diseases is conducted outside economics in the field of epidemiology. However, the evaluation of public health measures from an economic perspective is particularly important since economic analysis separates the health effects of public policies from those of private decision-making" (p. 2). The former suggests, for example, that "there is little role for public prevention of non-communicable diseases…" (p. 32). Gersovitz and Hammer (2001, 2003, p. 1) suggest, however that "the economic approach to infectious diseases is in its infancy." While "epidemiology provides ready-made dynamic models of disease transmission, economics provides methods of dynamic optimization, and ones that provide guidelines for policy. Policy towards infections is of great importance." They attempt to (1) "dissect the externalities involved in infectious diseases when there are the options of both prevention and cures…" and (2) "examine a typolology of infectious diseases" that "include diseases that are spread from perso to person and those that are are spread by intermediate vectors such as mosquitos."

[197] In the past this process frequently involved uniformity of drug treatment – to the point of focusing on one drug. This was due, in the view of Laxminarayan and Weitzman (2002, pp. 710-711), to institutional factors, uniform treatment guidelines and focus on immediate cost effectiveness. It' placed "'excessively' high selection pressures on organisms that are susceptible to that particular drug and increases the likelihood that a resistant strain will evolve and proliferate." Also see Laxminarayan and Brown 2001.

[198] More generally the existence of a positive externality is considered "a necessary rather than sufficient condition for public intervention [which is] warranted on economic grounds only when it will produce a net increase in social welfare" (Philipson and Posner 1993, p. 126, citing Coase 1960).

vulnerability." "The consequences of such interactions are particularly serious for reproductive health: a considerable portion of children born to women with HIV and malaria infection have low birth rate and are more likely to die during infancy." "Among adult men and non-pregnant women, HIV/AIDS may augment the risk of malarial illness" (WHO 2004d) - a *negative externality*.[199]

The key issue, as expressed in the title of one article, is that "Dual Infection with HIV and Malaria Fuels the Spread of Both Diseases in Sub-Saharan Africa" (Abu-Raddad et al. 2006; also see later comment by Andrews et al. 2007). Specifically, a study in Kenya revealed that out of an adult population of about 200,000, since 1980 "the disease interaction may have been responsible for 8,500 excess HIV infections and 980,000 excess malaria episodes." Moreover, coinfection may have also have "facilitated the geographic expansion of malaria in areas where HIV prevalence is high" (p. 1603).

But there is a positive side. In Uganda, anti-retroviral therapy was associated in one study with a "75% decline in the incidence of malaria over four years in a group of 1,020 adults, from 591 to 153 (Kasirye et al. 2009: also see Reithinger et al. 2009). And with the decline of malaria on the Kenyan coast, there has been a decline in admissions to hospitals for bacterial diseases and a halving of all-cause child mortality (Snow & Marsh 2010, p. 137). This effect has also been noted more generally in a recent study of the impact of preventative measures in Africa (WHO 2010d, p. 30).

Clearly, *positive externalities* stemming from a given form of investment in disease control add to the rate of return from that action, while *negative externalities* would subtract from them. These, however, may be difficult to anticipate, measure, value, and would necessarily be of an ex-post nature. Still, they appear to be worthy of further consideration.[200] [201]

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[199] For a further discussion of these issues in the case of HIV/AIDS in developed nations, see Philipson and Posner (pp. 117-118, 126, 183-184, 221). Malaria control in Africa, however, is quite a different matter in several ways, including its involuntary nature and its direct effect on young children. These differences are reflected in the classification of diseases used by public health officials: (1) *infectious*, transmitted by voluntary routes (HIVAIDS) and (2) *contagious*, spready by involuntary routes (malaria). But since a continuum is involved, they use *communicable* to cover both (p. 13, fn. 12).

[200] Another complex dimension is the extent that other pathogens "modulate the immune responses already at birth and/or throughout early life. This neglected area of research will be a challenge to immunologists, vaccinologists and drug developers, and will will help in developing and controlling diseases associated with poverty in Africa" (Troy-Blomberg and Berzins, 2008, p. 951).

[201] It should be possible to depict these important relationships more formally. The only observed case where this has been done **algebraically** is for antimicrobials by Coast, Smith and Millar (1998, pp. 30-31). Three equations are involved and noted here in simplified form. (1) *Negative externality*. Er = f(A X) where Er is the extent of the negative externality in time, A the quantity of antimicrobials consumed in time, and X a vector of other factors which may determine the level of resistance in a community. (2) *Positive externality*. Ep = f(A E X), where Ep is the extent of the positive externality associated with reduced transmission and treatment of subclinical infections, A the quantity of antimicrobials used in time, Er the extent of resistance over time (which may be reduced), and X a vector of exogenous factors which might influence the positive externality. (3) *Net benefit*. NB = f(B Ep C S D Er A X), where Ep, Er, A and X are defined as above, B is the direct benefit to the patient of taking the antimicrobial, C is the drug plus administrative costs, S the cost associated with side effects, and D problems by difficulties in diagnosis. No **graphical** attempts have been noted, and it would be difficult to

While malaria itself is not a simple disease and still holds many secrets and surprises in terms of treatment, no less can be said of its relationships with other infectious diseases and their combined effects on mortality and control programs.

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incorporate as many variables. One path might be to draw from Figures 1 and 4, and initially pose malaria and other diseases as the two principal components. They could be placed at opposite ends in an oval or ellipse. Positive interactions/externalities could be placed in the upper half and negative interactions in the bottom half. The horizontal dividing line might be porous, allowing for crossovers.

Annex 12. Malaria Drug Development: Key Steps & Current Examples

a. Key Steps

The sequence of steps in drug discovery and development for malaria has been well characterized outlined by Ridley (1997) and Nwaka and Ridley (2003) and provide a helpful backdrop for the ACT drugs covered in this paper. Early portions are closely related to Figure 1 (p. 9) in this report. The development portion includes three relatively commonly mentioned, but seldom defined, clinical phases (I, II, III). Economic aspects of relevance relate to funding for research and the costs of the clinical development process.

The **Discovery** stage (Ridley, pp. 292-301; Nwaka and Ridley, p. 923) includes three steps. The first concerns "Target Selection and Validation" and involves exploratory biology on the malaria parasite plus molecular and parasitological screening, complemented by medicinal chemistry. The second is devoted to chemistry-driven and biology-driven efforts (as seen earlier for artemisinin) to identify promising chemical leads and further develop them into potential drugs. The third is compound selection for full pre-clinical development which includes further antiparasitic, metabolic, pharmacokinetic and toxicology studies.

The **Developmental** portion involves non-clinical, pre-clinical and clinical efforts.

Non-clinical efforts address issues such as ease of synthesis, pharmacokinetics, and safety and toxicological studies in *animals*.

Pre-clinical transition. This includes a defined set of tests required before a drug candidate can be tested on any *human* subject and other activities that continue in parallel after the drug candidate has entered Clinical development

Clinical development has three phases (quotations from Ridley 1997):

Phase I is "essentially an exploratory study in healthy *human* volunteers to carry out single ascending dose and multiple ascending dose studies to monitor safety, tolerance, and pharmacokinetics." *Phase 1A* studies "are usually carried out in developed countries but follow-up *Phase 1B* studies might be carried out in disease endemic countries."

Phase II. "Assuming that no serious problems are observed in Phase 1, the pharmacokinetic toxicological information gained is then applied…to adult patients suffering from uncomplicated malaria." Initial *Phase 2A* studies may also look at some of the above issues in less healthy individuals, "but are primarily designed as a preliminary efficacy study to provide proof of principal that the compound can cure the disease. Later *Phase 2B* studies place more emphasis on efficacy and are extended to include dose range finding studies in preparation for the larger Phase 3 trials." "Many changes to a development program can still be made at this stage."

Phase III is composed of large scale efficacy studies which "are pivotal for approval by registration authorities. The emphasis is on safety, tolerance, and efficacy in comparison to

locally used comparator drugs." "Children would normally be included in these studies for a broad use antimalarial."

Post –registration testing is referred to as Phase IV.

The **probability of success** may vary somewhat by step and phase. Based on Medicines for Malaria (MMV) experience for competitively selected projects, Nwaka and Ridley (p. 924 Figure 1) indicate that they have been lowest for exploratory early discovery (30%) and highest at the registration stage (95%). Intermediate success rates have been: preclinical transition, 55%; phase I, 70%; phase II, 50%; phase III, 65%; and phase IV, 95%.

The cumulative result is that the likelihood of final success for an individual candidate is very low. Even for successful candidates, Ridley (p. 302) notes that "Drug discovery and development is a long, complex process requiring numerous types of expertise at its various stages." "Development from Phase 1 to Registration takes on average at least 5 to 7 years."

The **economic dimensions** of these steps are substantial. Total funding for global malaria research and development from both the public and private sectors has been estimated to have been at least $468.5 million in 2007 (the private sector may be under-reported), less than half that for HIV/AIDS but slightly more than for TB. Of this, about 45.7% or $214 million was spent on drug development (Moran et al. 2009). The costs of the clinical development process noted above have been estimated to be about $25 million for a fixed dose malaria drug involving an ACT and a NCE (new chemical entity) and $30 million for two NCEs (Moran et al. 2007, p. 36; also cited in Moran et al. 2009).[202]

b. Current Examples

These are drawn from the Medicines for Malaria Venture portfolio as reported for the fourth quarter of 2009 (MMV 2010, p. 23). There are slight differences in terminology, some general categories, and a Registration entry - reflecting the actual process, which can take some time and effort – have been introduced. We start with the preclinical developmental stage, which of course contains some little known entries and conclude with the Post-Registration period and some more familiar drugs. Details on all but two preclinical (KAE and DHFR O218) and one Phase II (*Arterolane*, Ranbaxy) drugs are provided in MMV 2010, pp. 19-20, 26-30. Collaborators, who are responsible for "lead optimization/lead generation," are listed in parentheses

Preclinical, Developmental. MK4815 (Merck); KAE (Novartis); DHFR P218 (BIOTECH, Monash University, London School of Hygiene & Tropical Medicine).

[202] While these figures may seem high, they are relatively modest compared to the situation for pharmaceuticals in the U.S. (McArdle 2010, pp. 88, 90). In 2009 only 25 new drugs of all types were introduced and the cost of each ranged "between hundreds of millions and nearly $2 billion per drug." The single biggest expense is the clinical trials which cost more than four times as much as they did in 1980, even after adjusting for inflation. This was due largely to (1) the increase in number of trials required, and (2) the near tripling of patients needed in each. Moreover, the firms are having "many dramatic failures in Phase III."

Phase I, Translational. *Tafenoquine* (GlaxoSmithKline); OZ439 (Monash University, University of Nebraska, Swiss Tropical and Public Health Institute), trials completed; GSK Pyridone 121 (GlaxoSmithKline).

Phase IIa, Translational. *Artemisone* (Hong Kong University of Science and Technology, Mandihol University).

Phase IIb and III. Development. *Arterolane* (Ranbaxy); AZCQ [Azithromycin-chloroquine] (Pfizer).

Phase IV. Registration. *Euratesim*™ (sigma tau); *Pyramax*® (Shin Poong, University of Iowa); Artesunate, intravenious (Guilin).

Phase IV. Post-Registration. *Coartem*® Dispersible (Novartis); *Coarsucam*® (DNDI, sanofi-aventis).[203]

In addition to these drugs, others are in the discovery stage (pp. 30-33), a broad category that also includes natural products (pp. 32-33).

[203] The latter is also known as *ASAQ Winthrup*® (see fn. 51). It is currently undergoing further field assessment for additional "safety data collection and risk assessments" (MMV 2010, p. 25).

Annex 13. Typology of Diseases and Incentives for R&D

In late 2001, the World Health Organization received and issued an important report titled *Macroeconomics and Health: Investing in Health for Economic Development.* It was prepared by the Commission on Macroeconomics and Health (CMH 2001) and headed by Jeffrey Sachs, then a professor at Harvard University. One component was a typology of diseases. "Many analysts have recently made the important distinction between [i] diseases that are common to rich and poor nations, where rich country R&D benefits the poor nations, and [ii] diseases that are basically exclusive to poor countries, such as tropical parasitic diseases, where the level of R&D tends to be minimal."[204] These relationships are tentatively outlined here in matrix form and then described in more detail.

	Incentives For R&D Relative to Disease Category		
Level of Income/ Development	Type I (not neglected)	Type II (neglected disease)	Type III (very neglected disease)
rich/developed	#	**	~
poor/developing	**<AIDS>	*<malaria>	*

Code: # = substantial incentives; ** = inadequate; *= few/none; ~ = not relevant

Type I Diseases. Incentives exist in the *rich/developed* country markets, both through public funding of basic science and patent protection for product development, but the result for *poor/developing* countries is that the treatments tend to be high in price and under patent protection. Many vaccines have been developed but have not been introduced in poor countries for these reasons.

Type II Diseases. These are found/incident in both *rich and poor* countries but a substantial portion are in the poor countries. Incentives for R&D, as noted above, exist but the level of R&D spending on a global basis is not commensurate with the disease burden. HIV/AIDS and tuberculosis are examples; more than 90% of the cases are in *poorer* countries. In the case of vaccines for HIV/AIDS, substantial R&D is underway because of *rich* country market demand, but not in proportion to global need or addressed to the specific conditions of the poor countries. In the case of TB, the situaton is even worse, with very little R&D underway for new and better treatments.

Type III Diseases. These are overwhelmingly or exclusively found/incident in the *poor/developing* nations: African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis). Such diseases receive extremely little R&D and essentially no commercially based R&D in the richer countries. When new technologies are developed,

[204] This statement appeared in a footnote (90) rather than in the main text, which contained the bulk of the material cited in the remainder of this section. The note continued: "See Lanjou (2001) for a useful analysis along these lines" [listed in References].

they are usually serendipitious, as when one veterinary drug developed by Merck (ivermectin) proved effective in the control of onchocerciasis in humans.

Diseases Straddling Two Categories. This particularly occurs if treatment and/or prevention is sensitive to distinct strains in *rich* and *poor* countries. AIDS falls between Type I and Type II diseases. Malaria falls between Type II and Type III.[205] Still, the basic principle that R&D tends to decline relative to disease burden in moving from Type I to Type III diseases is considered a robust empirical finding.

[205] The report added in fn. 99 (p. 123) that "the ambiguity about malaria falling between Type II and Type III arises not from incidence but from the fact that the rich-country market for prophylaxis and treatment for travelers and military personnel establishes a modest rich-country interest in malaria R&D."

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Comments:
• Where references include more than two or three authors - generally the case for technical papers - et al. is normally used in the text and here as well in order to save space.
• Some of the reports of research listed here, despite electronic communications, were not published until several years later after it was conducted. This is not always very evident.
Abbreviations:
• *AJTMH*: *The American Journal of Tropical Medicine and Hygiene*
• *TRSTMH*: *Transactions of the Royal Society of Tropical Medicine and Hygiene*

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