Artemisia annua, Artemisinin, ACTs & Malaria Control in Africa

Tradition, Science and Public Policy

Dana G. Dalrymple

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

Hippocrates, 460-377 BC

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

Drawing of Artemisia Annua L. plant found on the bank of the Rhine River near Arnhem in September 1897
(in Kops, J., 1906)

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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 (A*rtemisia annua*) for use in the manufacture of artemisinin-based combination drug therapies (ACTs). The author, an agricultural economist on detail from the Foreign Agricultural Service of the U.S. Department of Agriculture to the agency, participated in the evaluation of the proposal starting in mid-2004, as a member of an informal inter-bureau artemisia team.

Initially this led to extensive correspondence with specialists in the field and an extended review of literature. Both approaches have continued to the present. In the process, many highly knowledgeable specialists in various aspects of the subject have been encountered, 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 on A*rtemisia annua*, and on (ii) bio-medical science than social science. Comprehensive policy analysis, with one notable exception (NA/IW, 2004), is still scarcely in evidence.

The manuscript began as a modest briefing paper on Artemisia for the USAID Administrator in late 2004 (Dalrymple, 2004b) and grew into a more extended attempt to bridge and balance several varied dimensions. The project continued following retirement in October 2008, and the contents reflect information in hand through February 2012, except for Annexes 6 and 7. The approach and emphasis obviously may differ from those of malaria specialists, though it draws liberally from their written work as well as that of others and extensive e-mail interaction. With over 1420 references it could also serve as a guide to the literature.

Its 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. While its principal orientation was to, and remains, Africa, the story is much broader in geographic scope and I

have attempted to reflect that. The result is a broad, and hopefully objective and analytical, review that may be of background interest and current value to both specialists and generalists globally. This is a challenging task given the complex, varied, dynamic and global nature of the subject. It has not been possible to keep as fully informed as I would have wished and errors of omission and commission doubtless persist.

While the novel system of publication used for this book has a number of advantages, particularly in terms of providing a public good, the absence of a traditional publisher has some limitations, such as the lack of an Index. In part to offset this, the Contents pages are quite detailed, reflecting the various components of the text.

Jared Diamond, in the Prologue to his classic multi-disciplinary book, *Guns, Germs, and Steel* (1999), noted that a work of this nature might "seem at first to demand a multi-author work," but stated "that approach would be doomed from the outset, because the essence of the problem is to develop a unified synthesis." Hence, "the single author will have to…assimilate material from many disciplines, and will require guidance from many colleagues." Both have indeed been the case with this book.

In its course, the book also reveals something of the interactions between traditional medicine, modern medicine, and science - a prospective "golden triangle" (Mashelkar, 2003, 2005; Anonymous 2007c; 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).

Washington, D.C.
February 2013

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I have benefited in many ways from my association and interaction with many individuals, both near and far and over the past eight years, in the preparation of the parade of "Working Draft(s)" that preceded this publication. They fall into five categories.

• **Information and advice.** Among those close at hand in USAID at the outset in 1994 were malaria specialists with the Bureau for Global Health, USAID. Further afield, technical and scientific advice was initially provided by Jorge Ferreira of the Agricultural Research Service of the U. S. Department of Agriculture, Allan Schapira of the Global Malaria Program of the World Health Organization (retired), and William Watkins of the Nuffield Department of Medicine at Oxford University.

Subsequently, their ranks grew. Wallace Peters and David Warhurst of the London School of Hygiene and Tropical Medicine (both retired) became major and ongoing sources of technical information and advice on chemotherapy, a basic component of the topic. Ian Bathurst (deceased) of MMV was of assistance on new drug developments. Robert Ridley was of help on numerous matters relating to WHO/TDR. Nick White, Mahidol University, Bangkok, was of aid on a number of historical points. Keith Arnold, formerly with Roche in Hong Kong, shared his personal experience and knowledge of the development of artemisinin and ACTs in East Asia and the unpublished translation (with his wife Muoi) of a key Chinese book on Project 523. Malcolm Cutler of FSC Development Services Ltd., U. K., who has played a key and continuing role in the annual industry-wide artemisinin conferences, gererously shared his global and on-the-ground knowledge of Artemisia production and extraction. Elisabeth Hsu of Oxford University shared information and insights on Artemisia from ancient days in China to the present. William Burns and Dr. Anton A. Poltera were of assistance on Chinese matters (particularly Project 523). Richard Haynes of the Hong Kong University of Science and Technology and North West University, South Africa provided historical information on several key scientific topics.

Throughout, many others, usually cited in terms of "pers. comm." (e-mails), provided valuable information or comment on scientific, technical or economic matters.

• **Manuscript review.** Early drafts were reviewed by Jorge Ferreira, F. H. Jansen, Richard Smith, Trent Ruebush, and Allan Schapira. Subsequent versions were reviewed by Wallace Peters, David Warhurst, and Malcolm Cutler. To the extent possible, new sections and additions were sent to the individuals cited or involved for review. Interaction with Simon Hay prompted a conversion of the format from social science to biological style, not a trivial endeavor. Allan Schapira also provided two detailed and helpful reviews near and at end of the lengthy process of preparation. The pentultimate version of the paper, particularly the portions relating to drug formulation, were closely reviewed by Timothy Wells of the Medicines for Malaria Venture.

• **Library resources.** This project drew heavily on a wide range of literature. The USAID library was, through my tenure with the Agency, my key source of published information, either through its holdings of journals or through inter-library loan. Some key historical documents were provided by the staff of WHO/TDR and Connie Carter of the Library of Congress. I later benefited from the resources of the National Library of Medicine in Bethesda, the Bloomer Science Library at Georgetown University, and the libraries of the Wellcome Trust in London and the London School for Hygiene & Tropical Medicine.

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I am grateful to all. Needless to say, none are responsible for any errors or oversights that remain – and despite repeated efforts to rout them out, there are doubtless still more than a few.

Disclaimer

The views expressed herein are my own and not necessarily those of my former employers, the U.S. Department of Agriculture and the U.S. Agency for International Development. No external financial support has been received. The resulting publication is intended to be a public good and is not copyrighted.

1.1 Introduction

Malaria is thought to be among the oldest of human diseases (Russell, 1955; Bray, 1996; Carter, 2002; Sallares, 2002; Nerlich et al., 2008; Cunha, 2008). 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." This paper recounts the events relating to the most important chemotherapy (drug) approach to the control of its most severe form, P. *falciparum*, which predominates in Sub-Saharan Africa (Guerra, et al., 2008). In the process it provides an introduction to to the vast array of literature available, much of it now on line.

1.1.1. The importance of malaria in Africa

Malaria is of major importance in developing nations, notably Africa where P. *falciparum* first appeared in humans thousands, perhaps eight to ten thousand, years ago (Wade 2001, Tishkoff et al., 2001; some animals were affected far earlier (Cohen, 2010; Holmes, 2010). The total number of cases of malaria globally has been placed at about 451 million yearly and the African figure at 271 million (Hay et al., 2010a).

The global number of deaths has long been put at about one million (e.g., NA/IM, 2004; Shah, 2010), though some lower figures have been reported. An earlier World Health Organization (WHO) estimate was 881,000 globally, of which 802,000 or 91% were in Africa (WHO, 2008; also see Snow, et al. 2005; Brown 2006). Due to control efforts, in part reviewed herein, deaths due to malaria have since declined; of the estimated global total of 655,000 in 2010, about 596 million or 91% were in Africa (WHO, 2011, ix). Within Africa, the toll is highest by far in Nigeria and the D. R. of Congo, which have the highest

populations, though the data are very uncertain (WHO, 2008; Hay et al., 2010b).

Children under the age of five and pregnant women are especially at risk. Globally, about 86% of malaria deaths were in children under five (WHO, 2011, vii.) and 89% of the deaths in children in 2008 were in Africa (UNICEF, 2010). Recent estimates suggest that malaria causes more deaths in children, up from 16 to to 24% in 2008, than previously estimated Murray, et al., 2012). 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; Section 1.6.1.2). Long thought a rural disease, some indicate that it is becoming of increased concern in urban Africa (Touré, 1999; Klinkenberg et al., 2006), though the evidence varies (Mudhune et al., 2011).

In economic terms, the total household cost burden of malaria is high in Africa, especially for the very poor. Early estimates of total costs (direct and indirect) of malaria have ranged between 5 and 18% of household income in four African nations (Russell, 2003) and as high as 32% for the very poor in Malawi (Ettling et al., 1994; Chima et al., 2003). (Further estimates of economic costs and burdens, and discussions of issues in measurement, in Africa are provided in: Ettling and Shepard, 1991; Lennox, 1991; Samba, 2001; Shepard, et al., 1991; Aseso-Okyere and Dzator, 1997; Onwujekwe et al., 2000; Goodman et al., 2000; Samba, 2001; Breman, et al., 2004; ESPD, 2005; Worrall et al., 2005; Deressa et al., 2007; Somi et al., 2007a; and Onwujekwe et al., 2010. The nature of the public health burden was analyzed by Snow, et al., 2003a; Malaney et al., 2004; Breman et al., 2006).

The combined effects of these forces and costs is a severe constraint on economic growth. One study found that African nations with high levels of infestation had growth rates that were 1.3% lower than other countries from 1965-1990 (Gallup and Sachs, 2001; Sachs and Malaney, 2002). Estimates of the annual cost to Africa vary, but range in the billions of dollars. It is commonly reported (e.g. Anonymous, 2005c; Specter, 2005) that malaria costs sub-Saharan Africa $12 billion per year. While the derivation of this figure is obscure (it is only known that it circulated around WHO headquarters some years ago and was perhaps first cited by Samba in 2001), a comparable figure of about $4.9 billion per year, 41% of the above figure, can readily be derived

from aggregate estimates over the 1980-1995 period for 31 African nations reported by Sachs and Malaney, 2002. 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.

Lifting the burden imposed by malaria would have significant effects on African economic growth. This task, however, is challenging and particularly so because the cost of malaria control programs can represent a high proportion of national health budgets (e.g., in Ghana in 2007 it totaled $772.4 million, virtually all of its health budget and equivalent to 10% of the country's gross domestic product in 2006; Makalos, 2007).

1.1.2. Evolution of malaria control programs and emphases

The widespread and serious nature of malaria has inevitably led to interest in control programs, first at the local and national levels, often as a part of colonial activities, and then at the regional and international level. This paper focuses on the latter, and particularly developing nations in Africa that are heavily dependent on more affluent external donors. The donors in turn have played a role in determining the nature of the programs

1.1.2.1. International efforts

Beginning in the early 1900s, malaria has been the subject of many such control efforts and programs. They initially were conducted at the national level; perhaps the most comprehensive and notable was conducted in Italy in 1900 (Snowden, 2006). This and others were followed by a coordinated set of mid-century 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). 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 a wonder chemical, DDT. While unsuccessful in terms of eradication, it did reduce the prevalence of malaria in some areas for a while.

The program drew extensive critical comment (for example, Barlow, 1967 & 1968; Cohen, 1973; Brown et al., 1976; Harrison, 1978; Desowitz, 1991, 2002; NA/IW, 1991; Garrett, 1994; Packard, 1997 & 1998; Spielman and D'Antonio, 2001; Carter and Mendis, 2002; Staples, 2006; Nájera et al. 2011; Stepan, 2011). 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). 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 - 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). This occurred "because of the perceived magnitude of the region's malaria problem and the lack of technological capability" (NA/IM, 1991; also Litsios, 1996). Lack of data may also have played a role (Dobson et al. 2000). Webb (2011) indicates that "By 1962, following on a series of early pilot projects across tropical Africa, WHO specialists had come to the view that, while technically feasible, the logistical and financial problems of eradicating malaria…were insurmountable at the present time." As a consequence, "There was never a 'failure' of malaria eradication in Africa – it simply never got off the ground" (Malowany, 2000). Still, many malaria control projects of varying nature and with differing degrees of international support were undertaken in Africa, as reflected by Webb (2009a, 2009b, 2010, 2011).

The story began to change by 1997 when a pivotal meeting of malaria researchers was sponsored by the Multilateral Initiative on Malaria in Dakar, Senegal (Greenwood and Mutibabingwa, 2002). By 2005 the situation was much improved (Greenwood, et al., 2005).

1.1.2.2. Shifts in donor emphases

Control programs and measures clearly reflect the tenor of their times, particularly among their providers. As Peters (1970b, 1987) observed: "All throughout history war and pestilence have marched side by side. Yet paradoxically war itself has often provided the drive that has, in turn, led to major advances in medicine. In no major condition is this truer than in malaria." And it certainly applies to the early development of artemisinin, as

we shall see in the next chapter.

Keusch et al. (2010) provide an insightful historical review and perspective of broader nature. They divide their historical analysis into three principal phases (in italics): 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, noted above, has been military interests.

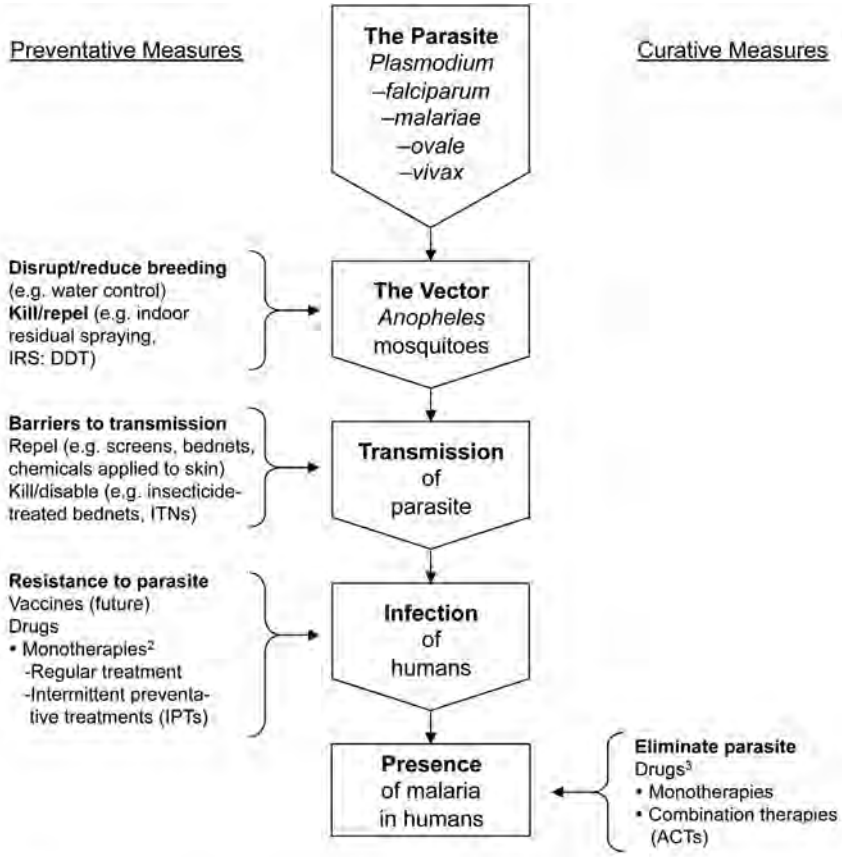
The three phases may be briefly characterized as follows. Phase I was initially motivated by *colonial* interests and focused on individual nations. In Phase II, malaria was initially an example of a neglected disease and was mostly financed as *bilateral* assistance, but increasingly reflected *internationalization* 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). 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.

1.1.3. Malaria and its treatment

Malaria in humans is a disease caused by one of four protozoa, all of which are transmitted by anopheline mosquitoes: P*lasmodium* (L*averania*) *falciparum*, P. *malariae*, P. *ovale* and P. *vivax* (see Figure 1). In addition, P. *knowlesi*, which differs from the others by having a monkey reservoir, has recently been acknowledged as a cause of human malaria (Cox-Singh, et al., 2008). In tropical Africa, P. *falciparum* is by far the most important cause of morbidity and mortality. Disease caused by this parasite can be classified as (1) uncomplicated, which is not life threatening and where the purpose is to avoid progression to the severe form and to cure infection; and (2) severe, which includes cerebral forms, where the purpose is to prevent death (WHO, 2006b). P. *vivax* is also present in Africa but it effects are debilitative, not mortal (Anonymous, 2011b).

The main symptoms of uncomplicated P. *falciparum* malaria - the main

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).

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focus of this paper - are very similar to those of several other diseases, and can lead to problems in diagnosis and treatment. As described by Talisuna and Meya (2007): "People living in areas where malaria is endemic are often familiar with these symptoms and freqently 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).

Both preventative and curative measures are employed. The principal current preventative measures in Africa involve (1) various anti-mosquito measures to achieve vector control at the community, household (e.g. indoor residual spraying; see Musawenkosi, et al., 2004) levels, and/or personal protection (e.g. Michalakis and Renaud, 2009), (2) barriers to transmission (e.g. WHO, 2010b), and (3) preventive use of antimalarial drugs. Malaria vaccines are still at the experimental stage, though one is now undergoing large-scale trials in humans in Africa. The principal *curative* measures seek to control the parasite within the body and utilize drugs. All 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 (e.g., Meshnick 1998, Honingsbaum 2001, Rocco 2004). It is still in use in Africa and is considered a second-line drug for uncomplicated falciparum malaria and as an injection for severe forms (WHO, 2010b). Quinine has not yet shown serious resistance problems (Parquet, et al., 2010), but it has a bitter taste, side effects are common (NA, 2004), requires a 7-day course of treatment, and may be less effective for severe malaria than artesunate (Dondorop, et al., 2010; Jones et al., 2010; Sinclair et al., 2011). The wisdom of its continued use in Africa as a monotherapy has been questioned (Yeka et al., 2009; Barennes et al., 2010; Chico et al., 2010, Anonymous, 2011a), but it may have a place in resource-limited areas (Achan et al, 2009, 2011).

Traditional single synthetic drug treatments (monotherapies), such as chloroquine, have lost appreciable effectiveness due to the development of drug resistance (e.g., Merkli et al., 1980; Peters, 1987; White, 2004; Talisuna et al., 2004; Jenson et al., 2009; Ketema, 2011). This is not a new or uncommon development with malaria drugs (and is depicted graphically in Ekland et al.,

2008). As Slater (2009) has indicated: "knowledge of the ability of microorganisms to evolve resistance is as old as chemotherapy itself".

In 1891, with quinine's action in mind, Paul Ehrlich, the father of chemotherapy (Porter 1997), treated malaria with methylene blue, one of the aniline dyes and thought that the results were promising" (Porter, 1997; Guttman and Ehrlich, 1891). He suggested in 1907…that the use of single agents at subcritical doses would lead to drug-resistant organisms" and pointed to the use of "a suitable *combination* of substances" (italics added) in the "attack on the malaria parasites by employing quinine and methylene blue" (Ehrlich, 1907; also cited by Slater, 2009). Over a century later it was noted that methylene blue "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" (NA/IM, 2004). 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).

Presently the most effective combinations are based on derivatives of artemisinin, an extract from the herbal plant A*rtemisia annua*. These combinations, referred to as ACTs, are very effective against 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 et al., 2010). By June 2008, all but four nations and territories worldwide had adopted ACTs as the first-line treatment for *falciparum* malaria (WHO, 2008). Levels of use in children in 2008, however, were generally low (UNICEF, 2010). ACTs also show varying degrees of promise for control of P. *vivax*, P. *malariae* and P. *ovale* (Douglas et al., 2010; Snow et al., 2010b; Woodring et al., 2010) and may also reduce transmission from malaria patients (Okell et al., 2008a/b).

An immense amount of information is readily available on malaria and its treatment in tropical regions. Comprehensive reviews were initially provided in three special supplements to T*he American Journal of Tropical Medicine and Hygiene*: "The Intolerable Burden of Malaria: A New Look at the Numbers," (2001, 64:1, 2); "The Intolerable Burden of Malaria II: What's New, What's Needed" (2004, 71: 2); and "Defining and Defeating the Intolerable Burden of Malaria III, Progress and Perspectives" (2007, 77: 6, Suppl.). Subsequently,

special sections on malaria control appeared in: N*ature* (August 19, 2004); two annual sections of the F*inancial Times*, both under the title "Combating Malaria" (April 23, 2010 and April 21, 2011); and S*cience* (May 14, 2010).

The important interactions between agricultural practices and the incidence of malaria and vice versa are reviewed in (i) historical terms for Italy in Sallares (2002) and Snowden (2006), (ii) a special issue of A*cta Tropica* (89: 2, 2004), and (iii) Asenso-Okyere et al. (2010, 2011). Their role in vector control is also noted in Litsios (1996); Keiser et al. (2005); McCann, (2005); Kebede et al. (2005); Diuk-Wasser et al. (2007); and Oladepo et al. (2010). Malaria is reviewed in the context of agriculture and malnutrition in Africa by ole-MoiYoi (2010). 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). Among other diseases, anthrax also has an agricultural dimension (Jones, 2010, xvi-xvii).

Useful collateral reading is provided in (1) three fine histories of malaria and control efforts (Packard, 2007; Webb, 2009a; Sherman, 2011), and (2) three current books of more journalistic nature and differing scope (Shah, 2010; Shore, 2010; Perry, 2011). Concise technical introductions are provided in articles by Eastman and Fidock (2009) and Fidock (2010). More detailed information on malaria and medications is provided in White (2009), Li and Weina (2011), and Bucala and Snowden (2012). The annual issues of the W*orld Malaria Report*, issued by the World Health Organization and available online, are a vital source of information, including extensive statistical data, on ACTs (e.g. see Chp. 5 in the 2010 report and Chp. 6 in the 2011 report, both readily accessed online or through Google).

One of the the main purposes of this book is to build on these and many other resources with respect to the role that Artemisia and artemisinin, through their role in ACTs, have played, and have yet to play, in malaria control in Africa and to some extent elsewhere.

1.1.4. Traditional medications and science

These develpments have taken place against a background of traditional medicine. It is "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" (Sci Dev.Net., June 2010). 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." 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.

1.1.4.1. 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.

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. While artemisinin is not readily soluble in water, it appears to be sufficiently so at high temperatures to provide antimalarial effects (see Willcox et al., 2004a; 2004b for differing perspectives).

However, as reported by others, there were "relatively" or "unacceptably high" "recrudescence rates" (reemergence) after termination of the treatment (Räth 2004; also see Mueller, et al., 2004, and Heide 2006). Another quite different problem is that the Artemisia teas have a bitter taste that may discourage or limit use among some groups, especially children (Simons, 2005).

There may be two principal reasons for this. First, the concentrations of artemisinin were found to be below those in conventional drug therapies (Räth, 2004). When insufficient doses are used and no complete cure is achieved, there is a risk of inducing resistance to artemisinin (Mueller et al, 2004). Second, even if the dosage level is sufficient, it is necessary to continue it for a week, and this may be, as for artemisinin monotherapies, a long regimen to maintain under African conditions (Hastings et al., 2002).

The Räth and Mueller studies concluded, in almost identical language, that "monotherapy with tea preparations from Artemisia annua can therefore

not be recommended as a treatment option for malaria" (Mueller et al., 2004; Räth, et al., 2004). Jansen (2006) subsequently tested the concentrations of artemisinin using their methods and got even lower levels.

Some groups, such as ANAMED, have encouraged 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. A whole plant extraction process was recommended in China in the fourth century B.C. (Hsu, 2006a).

The differing views as well as potential advantages of this practice are noted in Willcox (2009) and Willcox et al. (2011). 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; also see Ferreira, et al., 2010).

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 production of Artemisia (where feasible) 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 (Yeung, et al., 2008). In these situations, some refer to "self-reliant" treatments (de Ridder et al., 2008; Meier zu Biesen, 2010). Ethical issues in the use of herbal medicines are reviewed by Tilburt and Kaptchuk (2008) and noted Wright et al. (2010). The degree to which medicinal teas are used for sick young children may also be a consideration (Willcox, et al., 2011).

1.1.4.2. Herbal remedies

These may be the only antimalarial therapies available and affordable, but face the challenge of improving their therapeutic value (Bourdy et al., 2008). Several groups have considered and studied ways of doing so. A North

American team (Weathers et al., 2010) has suggested the use of Artemisia plant materials more directly in compacted form and in combination with an ACT partner; in this way other in *planta* constituents (flavonoids) may enhance the overall activity of the drug. Within Africa, the World Agroforestry Center (WAFC) and the International Center for Insect Physiology and Ecology (ICIPE), both headquartered in Nairobi, have been involved, in somewhat similar ways, with Artemisia.

WAFC 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 and issued a booklet on *The Potential of Plants as a Source of Antimalarial Agents, A Review* (Rukunga & Simons, 2006).

WAFC, 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). 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).

Both groups have cooperated in the study of plants with promise and recently published a book entitled *Common Antimalarial Trees and Shrubs of East Africa* (Dharani et al., 2011) and ICRAF is preserving these and others in its genebank and nurseries (Odogo 2011; joint news release, EurekAlert 2011; Hayward 2011).

Other groups include: (i) the Research Initiative on Traditional Antimalarial Methods (RITAM 2007), established in Oxford in 1999 to promote research and development of herbal antimalarials [www.giftsofhealth.org/ritam/]; (ii) the National Institute for Pharmaceutical Research and Development in Nairobi that develops traditional remedies into drug candidates and has "encouraging results" for a herbal compound to treat malaria (Ndhlovu, 2010); and (iii) the Biotechnology Unit of the University of Buea, S.W. Cameroon that has explored several natural sources of anti-

malarial agents (Zofou, et al., 2011, 2012).

Members of the Mali Malaria Research Center provided some appropriate works of caution during a conference on African herbal medicines. 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" (IRIN, 2009b). 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.

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In recent years natural products have come under increased study for the control of malaria – as reflected above and in the theme of a rather extraordinary recent supplement to the *Malaria Journal* (v. 10, sup. 1, 2011; see particularly Wells). Within this broad category, teas and herbal preparations as noted here are cases where tradition and science may appear to differ sharply and yet may have significant and useful areas of overlap. The complication is that such preparations are "a concoction rather than a single compound and the chemical structures of the active ingredients are unidentified." Yet "the multiple components…offer a unique opportunity to attack multiple disease-causing mechanisms simultaneously" (Xu, 2011, 90). Hence, while often local in their use, some traditional herbal medications – which are under intense study in Asia (see *Nature*, Dec. 22/29, 2011, S81-103) and to a lesser degree in Africa - may potentially be of wider and even more sophisticated value to society. Thus, there is need to apply more scientific analysis to those medications of particular promise. In such a setting, the words of Hippocrates with respect to diseases - "at least do no harm" - provide a challenging and somewhat haunting backdrop for the text that follows.

1.2 The Concept: *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. Most have lost effectiveness to varying degrees over time due to the development of resistance. Currently, derivatives of artemisinin, an extract from the Artemisia plant (A*rtemisia 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. The result is a drug that is both ancient in its heritage and modern in its combinations and formulations. Quinine, derived from the bark of the cinchona tree, has also long played a major role (see Duran-Reynals, 1946; Headrick, 1981; Philip, 1995, Dobson, 1998; Honigsbaum, 2001; Rocco, 2004; Hobhouse, 2005; and Webb, 2009a) and will be noted here as well.

1.2.1. Artemisinin and its mode of action

The genus A*rtemisia* comprises a group of plants known as the wormwoods that have been utilized for a number of medicinal purposes, including malaria, for centuries.

A component and extract, artemisinin, has a very rapid onset of action against the asexual blood stages of the malaria parasite, which cause the disease and is very rapidly eliminated from the body with an elimination half life of approximately one hour (WHO, 2006b). (The active metabolite DHA half life is two hours, depending on how it is measured; Wells, pers. comm., 2012; hereinafter Wells 2012). Even quinine, which is well known for its rapid excretion, has a longer half-life (Warhurst, pers. comm., April 2008). There is also some effect on the sexual blood stages, which do not cause disease in humans, but are infective to the mosquito vectors. However, certain other drugs have demonstrated a more persistent effect in preventing recurrence (recrudescence) of the asexual blood stages.

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/IM, 2004, also see Martin et al., 2003). The combination, in mathematical terms, can be quite potent. As Yeung et al. (2004), postulated: "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; White and Pongtavornpinyo, 2003; Bell and Winstanley, 2004; and Hastings and Watkins, 2005). But it can be constrained by biological factors such as significant numbers of drug-resistant parasites and there has been controversy about the precise mode of action (Cui and Su, 2009).

Artemisinin can also markedly reduce the mosquito infection rate in areas of low transmission (which are less common in Africa than elsewhere). 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/IM, 2004, 23). This is termed the gametocyte role and could become of increasing importance in future control programs (see Okell et al., 2008a, 2008b; Smithuis, et al., 2010; also see Dunavan, 2005; Duffy and Sibley, 2005; Mutabingwa, 2005; Bhattarai et al., 2007).

1.2.2. The key initial role of China

The traditional herbal remedy Qinghao (A. *annua*) has long been used in China. It was first noted in a document found in a tomb dating from 168 B.C., while the first record of its use for malaria was made by Ge Hong in 341 AD. 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." In 1596, Li Shizen wrote in his pharmacopeia *Ben Cao Gange Mu*, that qinghao "cures hot and cold fevers." (These and related matters are noted in Annex 1 and more fully in QACRC, 1979; Klayman et al., 1984; Klayman, 1985; Huang, 1999; Hsu, 2001a, 2006a; Wright. ed. 2002; Willcox et al., 2004a; Zamiska and McKay, 2007; and Hsu, 2010). It may also have played a role in the herbal "Englishman's cure" for malaria - attributed to quinine - developed by Robert Talbor in 1672 (Dobson, 1998).

1.2.2.1. Early development of artemisinin and external advice

The emergence of chloroquine-resistant P. *falciparum* in southeast Asia in the 1960s (see Peters, 1987) "brought the attention of the Chinese government to the seriousness of the malaria problem" (Jiaxing, 1991). 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 and labeled **Project 523**. Chinese scientists (see Section 1.2.4) 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 (Coperative Research, 1977; Klayman, 1985; Anonymous, 1992; Hien & White, 1993; NA/IM, 2004; Zamiska & McKay, 2007; Haynes & Chan, 2007; White, 2008a; Ye, 2008. Also,Li & Wu, 1998; Jansen & Yin, 2002; Hsu, 2006b; and Zhang, 2006).

Further research was conducted by scientists at the Centre for Traditional Medicine and at the Second Military College in Beijing. The first report on

Figure 2: Dr. Wallace Peters, center, during his initial visit to China in February 1980, as welcomed by members of the Beijing Friend Hospital

this work in English appeared in 1979 (QACRC, 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). In February 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 (Figure 2) (pers. comm. from W. Peters, April 2008; also see Peters, 2011 for a retrospective view).

The Chinese were interested in internationalization of artemisinin and

Figure 3: CHEMAL team members and Chinese hosts on the Great Wall of China, October 1981. Team members included, from left to right: (1) Craig Canfield, WRAIR, Washington, D.C., U.S.; (3) Nitya Anand, CDRI, Lucknow, India; (8) Arnold Brossi, NIH, Bethesda, U.S.; (9) Peter Trigg, TDR/WHO, Geneva; (10) Walther Wernsdorfer, WHO, Geneva; and (11) Wallace Peters, LSHTM, London. The names of the Chinese are not readily available.

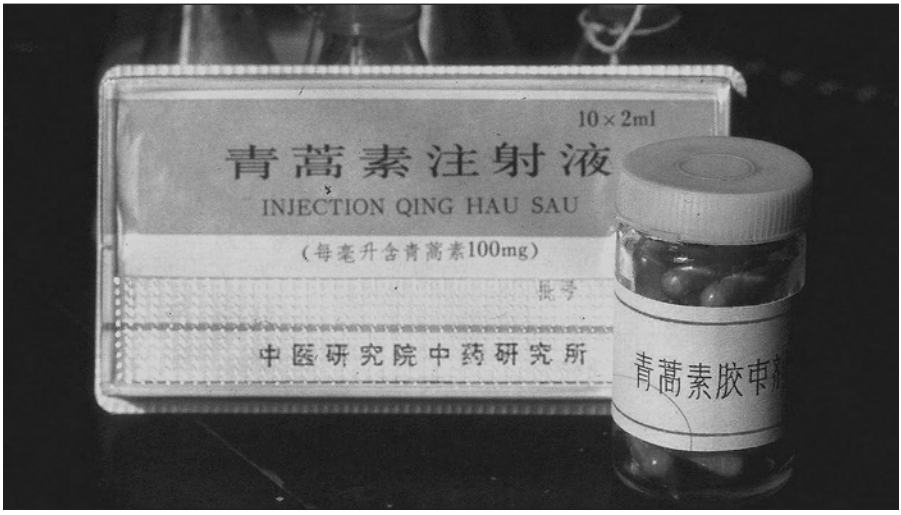

Figure 4: Early preparations of Qing Hao Sau injections and pills. Exact date not known, but was probably obtained by Dr. Peters in October 1981 when attending the CHEMAL meeting in Beijing

subsequently contacted WHO for assistance (TDR, 2007). As the first step, Prof. Peters led a CHEMAL team, which included two malaria specialists from the United States (Dr. A. Brossi, National Institutes of Health, Bethesda, Md. and Colonel C. J. Canfield, Walter Reed Army Institute of Research, WRAIR, Washington, D.C.) and one from India, to Beijing in October 1981 (see Figure 3) (CHEMAL, 1981). 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." Beginning in 1972 the drug (see Figure 4) and three derivatives - dihydroartemisinin, artemether (oil soluble) and artesunate (water soluble) - had been studied "with regard to efficacy in laboratory malaria models, pharmacology,` and pharmacokinetics (PHC) and toxicology (TOX) and clinical trials had been conducted" (CHEMAL, 1981; also see Jiang et al., 1982; Li et al., 1982). The major research lacunae were thought to be in PHC and TOX and the team prepared a research program that gave highest priority to them. A program of future collaboration between the Chinese institutions and CHEMAL as well as the U.S. Food and Drug Administration, was also proposed (TDR, 2007).

1.2.2.2. Western interest in artemisinin and derivatives

The 1981 CHEMAL team also sought to "obtain a kilogram of purified artemisinin to be tested through its network of partner laboratories." This was accomplished, but accounts differ. One has it that Brossi arranged to have 500mg. grown, perhaps as a ploy, in Argentina, but in 1983 a kilogram was reportedly provided by a Chinese assistant director at Rome in 1983 with the comment that "it should not be acknowledged" (Sherman, 2011).

At the end of 1981, Dr. Nick White (a Wellcome Trust researcher at Mahidol University, Bangkok) and three others met with two of the authors of the landmark QACRG report of 1979, Prof. Li Guo-Qiao and Jing-Bo Jiang (see Jiang et al. 1982) in Guangzhou at the end of 1981. About a year later White was given artesunate for parenteral (injection) use to evaluate. He wanted to begin testing, but was dissuaded from doing so in view of other efforts and still has the sample (Anonymous, 2002; pers. comm. from White, July 2008).

Concurrently, Dr. Daniel Klayman of the Walter Reed Army Institute of Research (WRAIR) sought a domestic source of A. annua. Botanists from the Smithsonian Institution found it growing along the Potomac River near Harpers Ferry, west of Washington, D.C. in 1983. Plants were harvested that summer with the help of a Boy Scout group and used for research, which was hampered by short budgets and neurotoxicity associated with high doses of some of the derivatives in experimental animals (Klayman et al., 1984, 1985; Li, Milhouse and Weina, 2007; Weina, 2008; Milhouse and Weina, 2010. For background on WRAIR involvement in malaria research see Weina, 2008 and Sherman, 2011).

Moreover, in 1985 TDR commissioned researchers at the University of Mississippi to grow the plant and provide one kilogram of artemisinin (see Section 1.3.1.1.2.3; CHEMAL,1986; TDR 2007). This was done and the requested quantity was distributed to participating institutions (including WRAIR) for additional study and development. This was a remarkable accomplishment given the state of technical and scientific knowledge.

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 were studied. Initial attention was given to *artesunate*, but it too appeared to have limitations, relating to instability and possible embryo toxicity.

By 1985, attention had turned to a sister drug, *arteether*, prepared by a laboratory process developed by a CHEMAL member, Dr. Brossi of NIH (Brossi, et al., 1988; Canfield, 1989/81). 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" (though a derivative, Artemotil, has recently been used in a preliminary but promising study of cervical cancer treatment; Jansen, et al., 2011).

Fortunately, the Chinese continued their development work with *artesunate* (CHEMAL: 1981, 1985, 1986; 1989 (Jiaxiang, 1991); TDR: 1987, 1995; Brewer et al. 1993; Canfield 1989/91; pers. comms. from 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 Yin, 2002; QACRG, 1979). It was, reportedly, first marketed as a monotherapy in the late 1980s by Kumming (Zamiska and McKay, 2007).

1.2.2.3. Initial development of ACTs

The next step in the development process was the combining of qinghaosu with other drugs that had been tried with success during initial studies in China. Drug combinations were not uncommon in China and had been suggested for mefloquine in 1981 (WHO, 1983).

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): "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; Chawira, et al., 1984, 1986a/b, 1987; Gu, et al., 1986; Peters, et al. 1986; Peters 1990; Wilkinson and Hardy 2001).

In the early 1990s, the Chinese developed *benflumetol*, later called lumefantrin, and used it in a combination with artemether. It is an aryl amino-alcohol compound, a category that includes quinine, mefloquine and halofantrine (NA/IM, 2004). One account indicates that the "inventor" of this combination was Zhu Dayuan, later a Shanghai-based scientist (Wu, 2007).

1.2.3. Moving to a global stage

The rights to sell the combination outside of China were purchased by Ciba-Geigy, later to become Novartis (Zamiska and McKay, 2007), which named it C*oartem*® (see Annex 6 for more detail). 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). Further preclinical and clinical work was done to comply with western drug regulations (pers. comms. from Allan Schapira, March 2007 and David Warhurst, April 2008). It was to be sold in the developed world as R*iamet*® (Olliaro and Taylor, 2004). Subsequently it was submitted to the Food and Drug Administration in the U. S. for approval and received it in April 2009 (see Section 1.3.4.1.3).

Just when and where the term "Artemisinin [-based] Combination Therapy" was first coined is uncertain, but it most likely occurred during the early research by François Nosten and Nicholas White in Thailand in the late 1980s and early 1990s (Enserink, 2010d).

1.2.3.1. WHO endorsement of ACTs

Combination therapies involving artemisinin and its derivatives were *first* discussed and recommended for uncomplicated malaria at the international level in an "Informal Consultation" at the World Health Organization in Geneva in June 1998 (WHO, 1998). This was an important milestone in the steps toward adoption of ACTs as standard WHO policy.

The subject was further discussed in a second "Informal Consultation" in November 2000 (WHO, 2001a). The list of abbreviations at that meeting included "ACT: artemisinin-based combination therapy" and the section on "Combination Therapy" defined ACT as "antimalarial combination therapy with an artemisinin derivative as one component of the combination." This was followed by a more complete discussion and a subsequent review of derivatives. At that point, however, there were doubts "about the quantitative impact it will have in real-life situations." 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 surprisingly long bibliography: 338 entries). In retrospect it appears to have been a transformational event for ACTs and placed them squarely on the international stage.

This led to a third consultation on April 4-5, 2001 in Geneva (WHO, 2001b) at which "Artemether-lumefantrine was noted for the first time and rated as "the most valuable artemisinin combination treatment available…." The consultation "strongly endors[ed] the potential of combination therapy for use in Africa" and WHO recommended the use of ACTs in April 2002 (WHO, 2002a).

1.2.3.2. Subsequent trials of ACTs and agitation for adoption

Pioneering trials of various ACT combinations were conducted in nine nations in Africa, as well as Thailand and Peru in the late 1990s under the direction of WHO/TDR with USAID and Wellcome Trust funding (Olliaro, et al., 2001; Olliaro and Taylor, 2004; Aduijk, et al., 2004; IASG 2004; NA/IM, 2004). Activities began in June 1998 and in-country trials were concucted in 1999 and 2000. Artesunate was added to three existing treatments (chloroquine, amodiaquine, sulfadoxine-pyrimethamine) over a three-day treatment schedule, compared to a 7-day regimen for artemisinin monotherapy. In all, there were 16 trials, 12 in Africa and with 4,616 patients. Only children were included in the African trials. The results showed "a consistent, large effect of adding 3 days of artesunate to any of the existing drug regimens" but varied with the companion drug and location. Also, artesunate "greatly lessened

gametocyte carriage in all drug groups" (IASG, 2004,16).

Thus, 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). As of November 2008, 46 African nations had adopted ACTs as their first line therapy; 41 had *deployed* them (Bosman, 2008). Even so, there was very little apparent progress in the use of ACTs. In January 2004, this situation was forcefully brought to the attention of the global health community in two articles in *The Lancet*, first by Duffy and Mutabingwa (Jan. 3), and then by Attaran and 13 malaria specialists (Jan. 17). Their concern was the continued use by donor agencies and countries of "inferior" and "ineffective" drugs rather than ACTs in the face of increasing deaths from malaria – a situation that had been forecast five years earlier (White et al., 1999a/b). This stimulated an array of responses (Jan. 31, Nafo-Traoré, Nantulya and Lidén; April 3, Duffy and Mutibingwa; April 24, Lidén and Natulya) and a similar article (Bate 2004). While doubtless annoying to some, they are credited by others with getting things moving.

1.2.3.3. Growth in demand for artemisinin

The demand for ACTs increased sharply after 2004 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. The Institute of Medicine study (NA, 2004), 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 to expressed needs by the public sector; in this case it exceeds effective (funded) demand, prompting interest in subsidies (Section 1.4.2.2).

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 and quickly increase the supply of Artemisia. This issue 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; Cyranoski, 2004; Senior, 2005; Erserink, 2005). The subsequent shortage was anticipated 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, 2001b).

Most of the production of Artemisia, and in turn artemisinin, has come from East Asia, largely China followed by Vietnam as of 2006; production in Vietnam subsequently dropped sharply (see Section 1.4.1.2.1). 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 prominent in the export trade. 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, the high prevalence of malaria in Africa led, not for the first time, to interest in increasing the very limited level of production of Artemisia and artemisinin in that region. 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, 1999). 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, May, 2005). AAL continued to seek funds for a processing facility.

1.2.4. Reprise: an internal view of China's efforts

China clearly played a pivotal role in the early discovery of Artemisia and the development of artemisinin and ACTs. How did this come about under the most inauspicious of circumstances? While it has been clear that a government program known as Project 523 was involved, little has been known about its internal operations and its aftermath. An official depiction was published in 2005 in Chinese (Zhang) and has drawn a few references in English language but has not been translated into English. A translation was prepared by Drs. Muoi and Keith Arnold (see Box 1, p. 26) but not immediately published. They

Box 1. A western eye on Project 523 and its aftermath

Dr. Keith Arnold, the co-translator of the book underlying Section 1.2.4 - British by birth and education and American by naturalization - has had a unique window on Project 523 and participation in related activities China and Vietnam. He was first familiar with, and then involved with, both the U.S. and Chinese/Vietnamese sides in the development of artemisinin and its derivatives (see Figure 5).

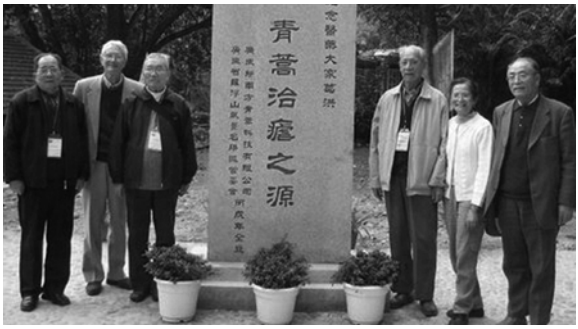

Figure 5: Drs. Keith (center left) and Muoi Arnold (center right) at monument to Artemisinin in Luo Fo Mountain Park, Guangdong, China. They are accompanied by Jianfang Zhang (extreme right) and other editors of the book on Project 523 (Section 1.2.4.1.)

During the late 1960s the U.S. military experienced chloroquine resistance in South Vietnam and was studying the problem at the Walter Reed Army Institute of Research (WRIAR) in Washington and through a medical team in country. Dr. Arnold was research physician with both groups in 1969/70. The American program, after screening over 200,000 chemicals, discovered mefloquine (Lariam); the Chinese program, operating as noted in the midst of the Cultural Revolution, discovered and developed artemisinin, but the derivatives were not sufficiently advanced to put in operational use when the war ended in 1975 and while none were officially provided to Vietnam, other drugs were.

From 1977 to 1991, Dr. Arnold was based in Hong Kong for the Roche Asia Research Foundation and was responsible for clinical trials with mefloquine in Asia. He managed, with some difficulty, to get into China and conduct clinical trials there. Professor Li introduced him to artemisinin and they carried out several trials comparing the two drugs, the results of which were published in The Lancet in 1982 (Jiang et al.) and 1984 (Li et al.). He took “qinghaosu” to Vietnam in 1987, evidently for the first time despite the focus on it in Project 523, and was involved in trials of artemisinin and artesunate as well as suppositories for acute *falciparum* malaria (Arnold et al., 1990; Bailey et al., 2010; Hien et al., 1992; Hien, 1994, 2004).

His experiences were reflected in an unpublished talk at the annual meeting of the American Society for Tropical Medicine and Hygiene in Philadelphia in 2007 (Arnold, 2007).

kindly provided a draft copy in late 2010 and some of the most relevant portions are briefly outlined here along with brief mention of a few key scientists and their roles. It provides a fuller picture of the operations of the group and sometimes a different perspective on some of the events. As of February 2013, the full translation became available in published form; see Jianfang, References/ Addendum, p. 258).

1.2.4.1. Project 523

Thee official history of this enormous effort was prepared over more than two years in the mid-2000s by a group of key personnel officials of the project, both at the Leading Group Office in Beijing and Local Offices. It involved review of official documents and interviews with members of the many research units involved. And in turn, the manuscript underwent an extended review process. While some other accounts have focused on a certain individual or project, the report emphasizes that "Qinghaosu and its derivatives and combinations are the collective achievement of a nationwide collaborative effort." This involved over 500 scientists from 60 research units and extended from 1967 to 1980. The key central government agency was the Institute of Chinese Malarial Medica of the Chinese Academy of Medical Sciences in Beijing. Others, as named in a government award in 1979 for the development of Qinghaosu were: Shandong Institute of Traditional Chinese Medicine (TCM); Yunnan Pharmaceuticals Institute; Institute of Biophysics, Chinese Academy of Sciences (CAS); Shanghai Institute of Organic Chemistry (CAS); and Guangshou College of Traditional Chinese Medicine (copy of certificate provided by Dr. Liao).

The original impetus was an outgrowth of military actions involving the United States and Viet Nam beginning in 1964 and extending through the 1970s. Both sides faced resistance problems with malaria and responded in different ways. The government of North Viet Nam requested Chinese help, and this, along with other considerations including its own military, led to the establishment of Project 523 on May 23, 1967 (5/23). The project was taken up with "Chairman Mao's encouragement and Prime Minister Zhou Enlai's support" – reflecting Mao's willingness "to patronize the developing world" and a "rivalry with Moscow" (Dikötter 2010). The task was particularly challenging because it occurred during the period of the Cultural Revolution "when scientific research was in a state of paralysis" (Chp. 1/3) and which led

to the world's most serious famine from 1958-1962 (Jisheng, 2008; Dikötter, 2010). A "Leading Group of the National Malaria Research Team" was formed comprising seven departments (Chp. I/3; also see Chp. III. Chp. references are to translation).

Two approaches were taken. One, perhaps less well known, involved screening and combining existing antimalarial drugs. Three combinations were identified/developed: (1) pyrimethamine and dapsone; (2) pyrimethamine and and sulfadoxine; and (3) piperaquine and sulfadoxine. They were termed Malaria Prevention (MP) tablets 1, 2, and 3 respectively. Nos. 2 and 3 had successively longer periods of protection (two and four weeks respectively); 2 was later known as Fansidar. Overall, "...several hundred tons" were provided to "allies." Other drugs and combinations were subsequently developed, and in total 14 "passed specialty certification and were widely used" (Chp. III/5; also NA/IM, 2004). One, pyronaridine phosphate, underwent further development under the auspices of MMV in cooperation with Shin Phoong Pharmaceuticals of South Korea and was approved Feb 16, 2012 (Wells 2012).

The other phase, more familiar in the context of this paper, was the search for herbal remedies. This took two forms: one was to search and screen medicinal plants and herbal remedies in use in the country and the other was to "review ancient and modern traditional pharmaceutical written records." Ten possible candidates were identified including Qinghao. In the latter case, several areas of use were identified, which led to the further development of qinghaosu, principally by Youyou Tu of the Beijing Institute of Chinese Materia Medica, from 1972 to 1973. One active unit was named "qinghaosu II' and led to toxicology testing and clinical trials on Hainan. Subsequently, "some research difficulties" were experienced and attention turned to an extract obtained by Wei Zhenxing at the Shandong Institute of Chinese Materia Medica, "Huang 1." The Yunnan Institute of Materia Medica Tropica was then involved in screening local plants and various extraction methods. "The end result...was to encourage and give confidence to Project 523 Head Office that qinghaosu should be the main research target" (Chp. II/3).

In 1974, emphasis was given to identifying the chemical structure of the active component, improve extraction techniques, pharmaceutical testing, clinical trials, and the preparation of qinghaosu. Clinical trials using active

crystals provided by the Shandong and Yunnan institutes and were very favorable. It was noted, however, that the fast action of the extracts led to recurrence, and combinations with other drugs were tried and MP 2 proved effective. But some of the tests were conducted in vivax areas in the north and attention was turned to clinical trials, again involving Li Guoqiao (who was assigned the "clinical trials of the most important drugs" Chp. II/5) against falciparum malaria in Yunnan. The outcome was again very favorable. "From this point on a new page had been turned in the research on huanghaosu!" (Chp. II/4). In 1975 it was decided "to concentrate all efforts from all fronts nationwide in the further development of qinghaosu/huanghaosu" (Chp. II/7). "The drug completed the formal evaluation process in 1978" (Chp. IV).

The chemical structure of qinghaosu was determined by the Shanghai Institute of Organic Chemistry and the Chinese Academy of Science, with contributions by other researchers and institutes. It was determined to be a new chemical compound "structurally different from all the known anti-malaria drugs." In 1976 China learned that a chemist in Yugoslavia was isolating a substance similar to qinghaosu from another species of Artemisia (Jerami & Stefanovic et al., 1972). It was, therefore, decided that Chinese data should be published as soon as possible and it appeared in the *Chinese Science Bulletin* in 1977 under collective authorship - the "Chinese Structure Collaborative Research Group." Another, by the Co-Operative Research Group on Qinghaosu titled "A Novel Sesquiterpene Lactone-Qinghaosu" appeared in Chinese the same year ("Cooperative Research," 1977). A three-dimensional configuration of the qinghaosu crystals appeared in the same journal in May 1978 and a further article on the structure was published in acta *Clinica Sinica* in 1979 (Chp. IV/6).

A second phase in development, as outlined in the book (Chp. VI) concerns derivatives with improved pharmaceutical qualities. In 1976 this task was assigned to the Shanghai Institute of Materia Medica. The first, *dihydro-artemisinin*, had better anti-malarial effects, but its solubility was not improved and it was even less stable. Two derivatives of it - SM224 (methyl ether), SM227 (ether) - were three and six times as effective: SM224 was chosen for testing in humans, again led by Li Guoqiao, which lasted from 1978 to 1980 in five areas and included 829 *falciparum* cases. The short-term

cure rate was 100% with a lower recrudescent rate than for qinghaosu and a number of other "advantageous characteristics." By this stage it - named *artemether* - had successfully completed all the required tests for a new drug and it was ready for industrial production. Other derivatives were also tested, including *artesunate*, and a several institutes were named to undertake its development.

1.2.4.2. Post-project 523 period

When the Cultural Revolution finally came to an end in the mid-late 1970s, scientific and technological research activities in China became more open and progressive. As a result of the changes in the world, a report was issued in August 1980 suggesting discontinuation of the National Malaria Research Leading Group and the elimination of the National and District Project 523 Leading Groups and Offices. A final meeting of the group was held in Beijing in March 1981. An "Artemisinin (Qinghaosu) Directional Committee" (ADC) was established in March 1982 and malaria research continued to be a major project for national scientific research in medicine and health at all levels (Chp. VII/2).

With the increase in publications and the opening of the country more external organizations became interested. Among these was WHO and its Scientific Working Group for Medical Chemotherapy, SWG-CHEMAL, as reported in Section 1.2.2.1 of this report. The meeting revealed that China, due to its previous isolation from the rest of the world, was far behind international standards in terms of drug preparation and pre-clinical pharmacology and toxicology studies. Certain criteria had to be met if China were to register and market their drugs internationally. As a result, SWG-CHEMAL sent three individuals to advise on "good manufacturing practices and problems" (GMP) and a subsequent SWG-CHEMAL meeting in Geneva in March 1982 suggested that U.S. Federal Food and Drug Administration provide a scientific and technical team to visit China and advise. Because of the GMP problem, WHO SWG-CHEMAL was contacted about collaboration outside of China to manufacture *artesunate* and asking them to recommend suitable research units and to suggest an appropriate collaboration agreement. The committee suggested Walter Reed Army Institute of Research (WRAIR) in developing artesunate, but despite extended negotiations they were unable to come to agreement on terms (Chp. VII/3&4).

This was followed by what appears to have been a significant misstep by SWG-CHEMAL, led by one of its members, concerning *artemether* and its sister derivative, *arteether* (presumably SM227). While related, they were quite different in their efficacy, with *artemether* having twice the anti-malaria effects of *arteether*. "But in 1985 the members of CHEMAL" evidently at the behest of Dr. A. Brossi, then head of the Dept. of Drug Chemistry at NIH, "decided on arteether…as the target drug for development by CHEMAL" (he and others reviewed its synthesis and qualities an article in 1988). There were rumors of neurotoxicity but the Chinese suspected other reasons (artemisinin and all its derivatives have this effect when given in high doses in animal experiments, but they have particularly been seen with artemether [*artemoil*], presumably because of sustained concentrations following intramuscular administration: see WHO, 2010b). Two years later they discovered that WHO/TDR had signed an agreement with a company in Holland to develop *arteether*, which was later found to be highly neurotoxic in animals. "In 2000 *arteether* was on the market but not included in WHO's list of essential drugs" (Chp. VII/5). This diversion of resources by CHEMAL away from *artemether* appears to have been highly questionable in retrospect.

1.2.4.3. Development and globalization of ACTs

This section consists of excerpts from a question and answer session with **Dr. Yiqing Zhou** (2009; his work is also noted in Annex 6 and Jiafing/Zhang, Chp. VIII/3&4) and the sections are reproduced referring to subsequent activities, thus covering a more extended time period.

• W*hy 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 the research on ACT in 1981. For four years I worked virtually on my own." "From 1985, things improved. Professor Ning Dianxi and others joined me." "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 on my own." "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 effect of lumfantrine complemented the quick and potent effect of artemether, greatly improving curative effectiveness. It's 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 Category) for developing the first ACT.]

• *Why did you introduce* ACT *outside China*? "…I feared a hiatus in research and discontinued 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 Science 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 partnership with the IME/AMMS and Kunming Pharmaceutical Corporation, through CTIC. Together we co-developed Coartem. 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."

1.2.4.4. Some key participants

While Project 523 was a massive collaborative effort, in addition to Dr. Zhou, two scientists noted earlier appear to have played particularly important roles and a third may stand as an example of others who also merit mention (also see Jansen and Yin, 2002).

• **Youyou Tu.** Liao (2009) 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" (possibly because artemisinin is not soluble in water or ether and it was necessary to develop a method for extraction; Hsu 2006b).

"The turning point came when an A*rtemisia* 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…modified the extraction technique to perform at low temperatures 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 [November] 1972 her team identified a colorless crystalline substance …and named it 'Qinghaosu.'" A sample was provided to the Institute of Biophysics of the Chinese Academy of Sciences which identified the structure in 1975 and the results were published in 1977 (Liao: 2009, pers. comm. Sept. 2010).

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." Still, the paper lists 30 papers by Tu and others; virtually all from 1981 to 2009 include her name. Dr. Tu has recently written an account of her work and edited a book on artemisia and its analogs (2009); while in Chinese, it contains many technical references to western literature (also see Tu, 1999). Her role was reflected in the institutions awarded "the status of "national scientific discovery" by the Chairman of Science and Technology in China in 1979." She was invited to present a lecture on her research during a CHEMAL meeting (CHEMAL, 1981). Decades later she was still the director of the Qinghaosu Research Center and was honored on her 80th birthday in 2009. In September 2011 she was honored with the prestigious Laskar~DeBakey award for clinical research in medicine (Anonymous 2011c; Miller, L.H., 2011; Neill, U.S., 2011; O'Connor, 2011; Tu, Y., 2011), though not without some concern that the roles of other key participants were not given

sufficient recognition (Hao, C., 2011; McNeil, 2012).

• **Guoqiao Li (Li Guo Qiao).** Dr. Li was the clinical malariologist for Project 523 beginning in 1967. He used an extract of Artemisia, which had shown effectiveness in animal studies, to treat patients with *falciparum* and vivax malaria. Initial studies were promising and a decision was made by the Project Committee to fully develop the extract, as noted above. Dr. Li then conducted clinical trials using artemisinin and its derivatives from 1975 to 1990 in China, Cambodia and Vietnam. In 1979 he began collaborating with Dr. Keith Arnold - who came to China to study mefloquine - involving artemisinin and quinine and the results were published in *The Lancet* in 1982 (Jiang et al.) and 1984 (Li et al.). Early studies were also carried out on suppositories (Arnold, et al., 1990). Beginning in 1983, Dr. Li was a staff member at Guangzhou University of Traditional Chinese Medicine, serving as Vice Director of the Tropical Medicine Institute and then as Vice President of the University. In 2003 he introduced the concept of "Fast Elimination by Source Eradication" and demonstrated its effectiveness in Cambodia in 2006 and Comoros in 2009 (on the latter see Section 1.2.3.2)

• **Zhenxing Wei.** A key, but less well known and cited, early role also seems to have been played by Wei, later professor of Chinese Traditional Medicine at the Research Institute of Shandong. He reportedly became interested in Artemisia in the late 1950s and a member of Office 523 in October 1969. A year later he "obtained" 30 mg. of a pure crystalline product, then assisted in a trial with patients, and participated in a research and development team involving scientists from Beijing and a pharmaceutical factory in Kunming. In the process he "collected" 3 kg of pure product. "The Army Pharmaceutical Institute became involved, and industrial production began" (Jansen and Yin, 2002. Wei is also noted in Zhang, 2006, Chp. II/3&4, and Sherman, 2011).

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Clearly both the ancient years of Artemisia and the early 20th century of artemisinin and its derivatives were China-centered. A variety of factors led China to share this vital package with the western world in mid-century. There it underwent further development that came at a time of great need in Africa – the subject of the rest of this book.

1.3 The Components: *Their Nature and Implementation*

Three major steps are involved in moving from plant to product - from artemisia annua to artemisinin to ACT. All present varying characteristics, complexities and challenges. What may appear to be a simple plant is only the start of a challenging process, and one which is far from over with the production of the actual pill, as we shall see in subsequent chapters.

1.3.1 Artemisia: plant and production

Artemisinin is, as noted, extracted from the leaves of A*rtemisia annua*, an ancient herbal plant (Huang, 1999). Numerous other species of Artemisia exist, but they do not have its anti-malarial qualities.

1.3.1.1. The Artemisia plant

Botanically, A*rtemisia annua* is a vigorous weedy annual. It is single-stemmed and ranges in height from one to two meters. Newer varieties are multi-branched from just above the ground level. It grows easily in temperate areas and tropical areas at higher altitudes and is raised in an increasing number of countries. Artemisia 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, that were initially generally limited in supply. 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), but is more equally distributed in later varieties.

Relatively few inputs are needed, aside from some fertilization. The plants at present do not seem to have any particular insect or disease problems, though a form of stem canker has resently been seen in East Africa. Often in plants grown in very humid conditions. Consistent and adequate watering is

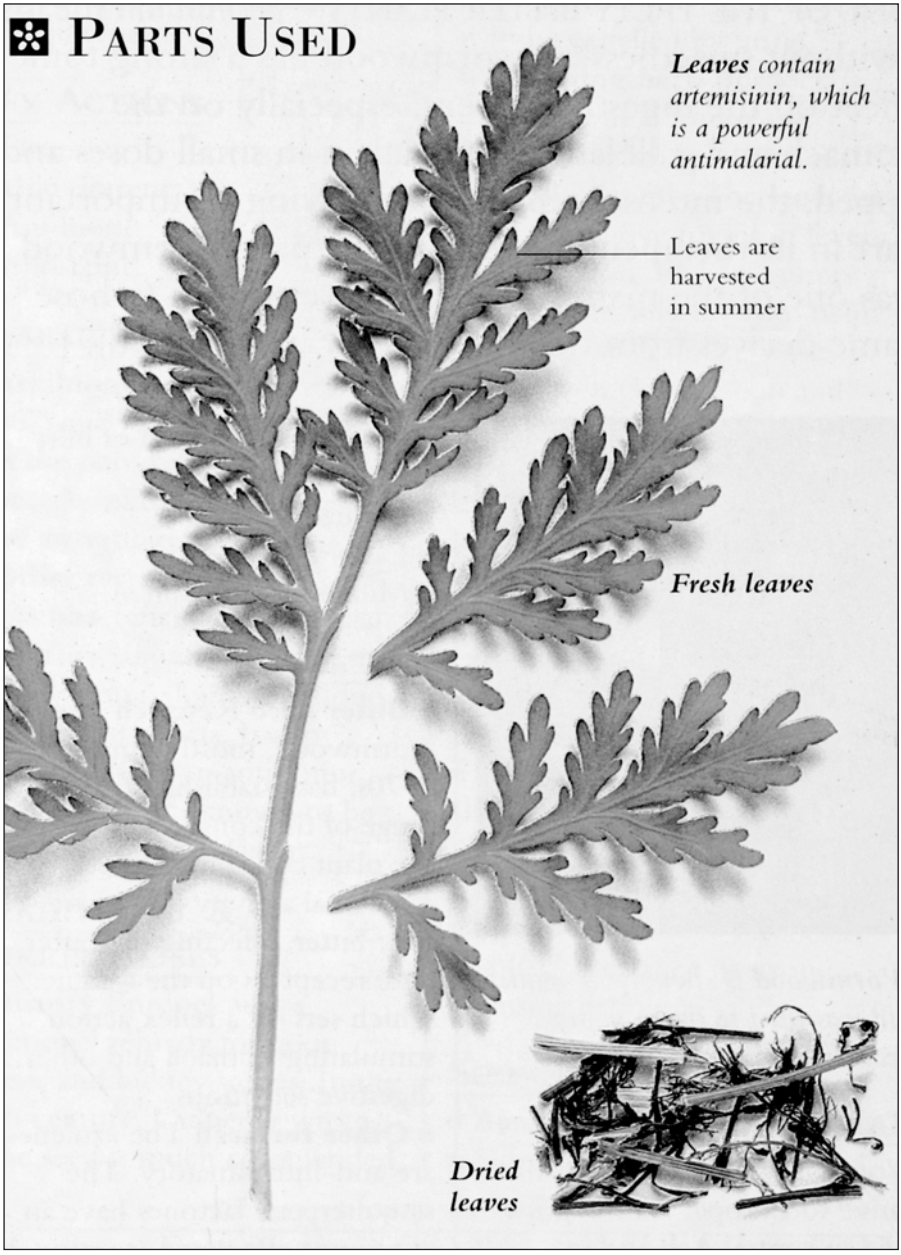


Figure 6: Artemisia annua leaf; Portions used for extraction.

Source: Chevallier (1996)

required to establish the crop and for survival and growth and to get good leaf yields (see Figure 6). Dry weather is needed at the harvest and for drying. Artemisinin levels tend to vary by variety, and commercial experience in many regions over the past four years has shown that region, soil and climate can have a significant effect on yields. Planting is done early in the the calendar year and and the plant requires four to six months to mature (Ferreira, 2004, Ferreira, et al.,1996, 2005; WHO, 2006a; Ellman, 2009, 2010a).

As an ancient medicinal plant, A*rtemisia annua* fell outside the mainstream of agricultural research and plant genebanks and in this context has been largely an orphan crop. It has long been held in one botanical garden but evidently in few if any others until recently. It has, however, been a topic of interest from the medicinal plant perspective (see Willcox et al. 2004 a/b/c; Wright, 2002, 2005, 2010; and Rajalahti et al., 2008) and the subject of a modest but important breeding effort in Switzerland. This relative neglect initially created some problems as far as quantity and variety of seed supply were concerned but more recently has been the subject of two substantial breeding programs in the United Kingdom and some other smaller efforts elsewhere.

1.3.1.1.1. *Botanical garden and genebank holdings.* A*rtemisia annua* has been kept at the Chelsea Physic Garden (established in 1673) in London since the mid 1700s and possibly at some other such gardens, though efforts to document this were unsuccessful. The Chelsea garden was established by the Company of Apothecaries 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; Dobson, 1998: for a detailed history of the garden by a former curator, see Minter, 2003). Francis Bacon wrote, in his futuristic novel N*ew* A*tlantis* (1627), of improved plants that "become of medicinal use" and "dispensatories, or shops of medicines."

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 G*arden* D*ictionary*, though it may have arrived before 1741, and reportedly came from Russia (Siberia via St. Petersburg). Curiously, Minter's Appendix 3, "Medicinal and Useful Plants Growing at Chelsea in 1772" from Joseph Miller's I*ndex* H*orti* C*helseiani of* 1772 – T*he* O*fficinal* Q*uarter*, lists six other species of A*rtemisia*, but not *annua* (pp. 121-126). It was first mentioned in the botanical literature in 1739. An

introduction from China to Portugal was noted in 1790 (pers. comm. from David Frodin, taxonomist, June 2006). The Chelsea 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 2010). (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, 2001 and Minter, 2003.)

Artemisia was not, however, 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 focus of medicinal plants, had only one holding. Artemisia (pers. comms. from: Rich Hannon, ARS, USDA, Pullman, Washington, Feb. 2005: Ned Garvey, Plant Exchange Officer, ARS/USDA, Beltsville, Maryland, Feb. 2005). Seed could and can be obtained from various nurseries (see Isacson, 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 qualities, the conscious selection and breeding of improved varieties of A*rtemisia annua* (in terms of the quantity and quality of artemisinin) is a relatively recent process, probably dating back no more than 40 years and coinciding with the emergence of cultivated production. No information was found, at least in English, about subsequent plant improvement efforts elsewhere in Asia.

1.3.1.1.2. *Varietal improvement programs.* An early and successful effort to produce artemisinin involved the cultivation of Artemisin and the extraction of artemisinin in Mississippi. The most substantial current programs are principally located in Europe, and have links in developing countries. There are also two programs in Latin America.

1.3.1.1.2.1. *United States.* The first, and little known, 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 accessions of A. *annua* were obtained from 16

Figure 7: Three-acre experimental planting of Artemisia annua, the first of its type, at the University of Mississippi before harvest in August 1985

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 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 (see Figure 7) 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 – all with little precedent at the time. Remarkably, all were accomplished, and on schedule (pers. comms. from Croom, March 2009; CHEMAL, 1986). 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, et al., 1996; Ferreira, et al., 1997; Ferreira, 2007; and Wang, et al., 2005). Simon accumulated 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., Oct. 2005). Ferreira (2007) was exploring the potential of Artemisia for crop cultivation under Appalachian ecosystems and for its potential use in animal health.

1.3.1.1.2.2. *Mainland* Europe. The principal ongoing programs have 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 and have been crossed to produce a third variety. "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. comm. from Barney Gasston, ABE, April 2006). A 1.4% level was reported by Mediplant (2004) for a selection from Artemis. These levels were near the upper bounds found elsewhere and for other varieties (pers. comm. from Jorge Ferreira, USDA, April 2006). As of 2011, Mediplant had 20 years of agronomic experience and further agronomic trials were being conducted in Switzerland and Madagascar Simanet, 2011).

Seed of a "hybrid" variety named "Artemisia annua anamed (A3)," probably an offspring of Artemis, is available from ANAMED (Action for Natural Medicine), G*ermany* [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 (F1) seed is needed each year if the yield drops normally involved with the second generation (F2),

roughly 20%, are to be avoided. Other commercial seed probably largely represents selections of traditional varieties.

1.3.1.1.2.3. *United Kingdom* Two very 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 to 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 (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. For reports see http://www.york.ac.uk/org/cnap/artemisiaproject/pdfs/AEconference-report-web.pdf, and http://www.york.ac.uk/org/cnap/artemisiaproject/projectUpdates.htm.)

CNAP used "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 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 reduced 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.

Figure 8: Planting of improved high-yielding varieties of Artemisia annua in Central Kenya, January 2012

National Library of Medicine).

Plants selected are being used as breeding stock for testing potential new varieties in developing nations. As of the summer of 2009, over 23,000 plants (32,000 by March 2011) had been assessed and over 200 high-yielding parental lines identified. They were evaluated for other characteristics, followed by initial crossing to produce experimental hybrid varieties and testing in glasshouses. Field testing began in 2008-2009 in cooperation with national partners in Madagascar (Bionexx) and India (AVT Natural Products) and subsequently with partners in Kenya (Botanical Extracts, EPZ), Uganda (Afro Alpine), India (IPCA Laboratories), China (Guilin Pharma and PIDI Standard Holdings) and will run through 2011/2012.

The trials in Madagascar, Kenya and India are conducted on large flat fields that can accommodate a large number of hybrids per trial while the trials in Uganda and China are being carried out on small plots in mountainous areas where it is difficult to handle large numbers of hybrids per trial. The initial trials in Madagascar showed increases in yields of 25-26% over "Artemis" and 52-63% over local checks in 2009 and 2010 while the trials in India revealed two that resisted early flowering. Further trials were carried

out during 2011 and 2012 at existing and additional sites and were linked with elite parent selection for hybrid production, the later to begin in 2011. It is expected that seed will be available for commercial production in 2012 (CNAP, 2009; Clayton, 2009; Bowles, 2010).

Some clear "front-runners" have been identified at each site and there will be a scale-up of selected ybrids in 2012. Arrangements have been made with a commercial firm (East-West Seed) to produce four of the hybrid varieties: 1077 for Africa, 1209 for Kenya, Uganda and China; 5023 for Madagascar and India; and 1206 for India (van der Feltz, 2011).

• **The National Institute for Agricultural Botany.** The NAIB, established in 1919, is an independent, not-for-profit, plant research group (recently integrated with another organization to form the NIAB Group). Partners include East Malling Research, Botanical Developments Ltd. (lead), Frontier Agriculture Ltd. and De Monfort University.

In November 2009, NIAB announced that they, in cooperation with several partners, had developed parental lines of Artemisia that produced substantially higher yields of artemisinin - over 2.2% of dry material (NIAB, 2009b). 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.

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 tested in Morocco in 2008, Kenya (by ABE) and in Canada in 2009 (Alberta Research Council). Further testing was to 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, Nov., 2009). Initial reports were presented at the WHO/MMV artemisinin conferences at Mumbai, India in September (2009) and in Madagascar in 2010 (Bently, 2010).

The breeding and trials, headed by Steven Bentley, are part of a larger effort including agronomy, herbicides, mechanical harvesting, and commercial drying, which has been carried out on a full field scale (e.g.,

Davies et al., 2009). Financial support was provided by three government agencies (the Department for Environment, Food and Rural Affairs [Defra], the Department of Energy and Climate change [DECC], and the Biological Sciences Research Council [BBSRC]) through the "Renewable Materials LINK Programme" was initially part of a program to to examine thepossibility of commercial production in the U.K., the seed was also made available overseas and is now used in commercial production in Asia and Africa. Regrettably they were not able to obtain get further funding to continue the project but seed from the hybrid developed is available in commercial quantities (pers. comm. from Colin Hill, Jan. 2002). Although the two programs are not far apart, they have been quite independent efforts. Joint discussions began at the 2010 Artemisinin Conference in Madagascar and commercial plantings of their 1062 variety have been widespread in 2011/12 in Vietnam, East Africa and Madagascar.

• **Comparing the programs.** While the two projects have similarities, they also differed. 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 conducted 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 was initially part of a program to look at the possibility of commercial production in the U.K. Seed from the LINK project was also made available overseas and is now used in commercial production in Asia and Africa. It is also quite probable that the genetic base of their leading varieties differed, but more information will be needed about their pedigrees to judge the extent to which this is the case. Although the two programs are independent efforts, joint discussions began at the 2010 Artemisin Conference in Madagascar.

1.3.1.1.2.4. *Latin America.* Two countries have been involved. (1) Argentina. A three-stage program was initiated under the Fundacion Mundo Sano involving (a) agronomic production of Artemisia (in cooperation with Mediplant), (b) artemisinin extraction (with the University of Bath), and (c) synthesis of artesunate (Desmarchelier 2009). (2) Brazil. A joint program involving the University of Campinas and the private sector was underway but

has been suspended. Components were: (1) research and development; (2) cultivation; and (3) extraction and purification of derivatives. Part of the production challenge was to increase productivity and artemisinin levels under tropical conditions (Magalhaes, 2007). The University in cooperation with the Chemical, Biological and Agronomical Research Center (CPBQA) was also a source of improved seed (about 1% artemisinin) for the intratropical region and low latitudes close to the equator (pers. comm. from Magalhaes, Aug. 2007).

1.3.1.1.3. O*ther plant qualities*. In their review of drug resistance, Sá et al. (2011) note the role of two "natural products of the plant kingdom," the qinghao and cinchona bark infusions, among "the "most successful and long-lasting remedies against malaria." They observe that "Little to nothing is known of the natural function of these compounds in the plants, of the protections they provide against pathogens in the bark and leaves from which they are extracted" (151-152). One little-known role, it turns out, is more external in nature: allopathy, "the release of chemicals that affect other plants in the community." A Swiss study has shown that a "water extract from the leaves of artemisinin-rich A*rtemisia annua* proved strongly phytotoxic" and when incorporated it the soil "significantly reduced weed emergence' (between 65 and 80%) and dry weight (>80%), and maintained a presence up to 8 weeks" (Delabays, undated and 2008). Artemisinin, moreover, has considerable promise in malaria control and perhaps other afflictions as we shall see in Section 1.6.2.

1.3.1.1.4. F*urther 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.

Linneaus was one of the first to report on such work in Europe. In his thesis for a medical degree in 1735 he stated that plant extracts were used to cure intermittent fever (malaria) and that if natural or dietetic cures failed, alternates included "The bark of the ash, a much less efficient substitute for the bark of the cinchona tree," and worm-wood (A*rtemisia absinthium*). Aydin-Schmid, et al. (2010) confirmed this finding for ash (F*raxinus excelsior*).

Recent comprehensive accounts are provided in Willcox et al., 2004a, and 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 (A*rgemone mexicana*) and clinical studies on another (C*ryptolepis sanguinolenta*). The TDR group in FAO sponsored an effort to build capacity of African institutions to screen and test indigenous herbal drugs in Kenya, involving a number of institutions (TDR, 2007b), as noted earlier in Section 1.1.4.2.

1.3.1.2. *Artemisia production in Africa.* Perhaps the first trials to be published were conducted in the Democratic Republic of the Congo from December 1997 to July 1998 (Mueller et al., 2000). Initial efforts to establish commercially-oriented production, however, were largely limited to East Africa - Kenya, Tanzania, and Uganda - and Madagascar. It both cases they were largely initiated and conducted by a few firms.

• **East Africa.** These efforts were largely initiated and conducted by a 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 (Mediplant origin) that has been 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 played a key role. 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 (TechnoServe 2005b). The 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. 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 (smaller 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 F2 (second generation) seed and larger farms F1 (which would normally produce higher yields) (pers. comm. from Barney Gasston, ABE, April 2006). By 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),

The situation then changed sharply for reasons to be discussed later. In 2008 the planted area dropped to about 2,000 ha. (5,000 acres) (pers. comm. from Malcolm Cutler, 2008), and in 2009 to about 1,500 ha. (3,700 acres), including Madagascar (Pilloy, 2009). No regional estimates have since been noted. A Kenyan grower's view as of 2007 is provided in Annex 2.

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 F1 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. 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. But as in Kenya, the situation then also deteriorated. 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 for extraction (von Freyhold, 2009).

Production activity was initiated 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), but no further information has been found.

Henfry (2011) indicates that plans for 2012 suggest production of 15-28 tons of artemisinin in East Africa, with the potential to reach 30 tons by 2013.

• **West Africa.** N*igeria* is estimated to have the largest number of malaria cases and deaths in the world (WHO, 2008) – about 25% of the global malaria

burden (NA/IM, 2007) - 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. comms. from E. A. Brisibe, 2006-2007; Jegede and Brisibe, 2007; Anonymous, 2007d; NA/IM, 2007). No further substantive information, however, has since been obtained.

• **Other Africa.** 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, and South Africa, but no further data have been noted.

• **Madagascar.** Artemisinin cultivation was initiated by a new company formed for the purpose, BIONEXX, in 2005. It undertook extensive trials and plantings through contracted "outgrowers" and acquired a local natural products extraction unit which was renamed INNOVEXX to carry out extraction and purification of artemisinin. Production continued to be carried out largely under contracts with small and midsized growers through 2010, when a 650 ha. farm was acquired. The total area involved was about 300 ha, in 2006 and then ranged roughly from 450 ha. to nearly 500 ha from 2007 through 2010, and expanded substantially in 2011. Total production of Artemisia leaf expanded gradually though 2010, when it was over 400 tons, and expanded sharply in 2011 to over 1,000 tons. Further increases were projected. The firm has conducted extensive testing and trials relating both to plants and the extraction and purification process (Giblain, 2008, 2009, 2011).

• **General Production Issues.** 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. Key steps in the production and harvesting process are illustrated in: http://picasaweb.google.co.uk/abextracts. It can be difficult to consistently meet quality standards set by extractors and processors.

1.3.2. 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, initially through two firms, Chongqing Holly, a major extractor and Kunming Pharmaceutical, the largest producer of derivatives and artemisinin-based drugs. Both are largely owned by the Holley Group of Hangzhou (Zamiska and McKay, 2007; pers. comm. from Malcolm Cutler, Aug. 2008). As the market for artemisinin expanded, the number of extractors in China grew rapidly and there are now about 15. The comparable number in Vietnam is about six.

1.3.2.1. 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.

A 1999 study (DFID) concluded that: "The technology for the extraction and processing of artemisinin derivatives is known but complex." "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…." The potential for extraction was examined by TechnoServe (2004), with particular attention to three solvent extraction technologies; the initial capital cost was placed at $6-12 million.

Aside from their technical complexity and cost, 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 (see Annex 3 for

conversion factors and Annex 4 for studies of phytochemical extraction). Quality has been uneven and standardization 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).

ABE, later known as BEEPZ, has also been in the forefront of artemisinin extraction in Africa. 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. The latter figure would represent about 17.5% of the artemisinin estimated needed (114 tons) for 120 million adult courses of treatment needed globally (Haynes et al., 2006). Operations began in January 2007.

The firm also planned 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). Initial financial support 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. Oddly no further public information or news accounts have been noted.

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 L*umartem*, an artemisinin and lumefantrine combination similar to C*oartem*, in the

summer of 2008 (Wendo, 2007; GHR, 2007, 2008).It is now producing the CIPLA generic AL, L*umartem*. 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 artemisinin was to be shipped to CIPLA's facilities 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. comm. from E. A. Brisibe, Aug. 2007; Anonymous, 2007d; NA/IM, 2007). One news report stated that eight companies were producing ACTs in Nigeria (Lyn 2007). In October 2006, Emzor Pharmaceuticals announced the manufacture of D*iasunate*, 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). Again, current information and documentation are lacking.

1.3.2.2. Monotherapies and co-formulations

A number of firms are known to produce monotherapies. 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 (Edward Vela, Global Malaria Programs, WHO, June 2006; Kerr, 2006). Much of the Indian production is thought to be based on Artemisia from China, but no data exist.

The ranks of those producing co-formulations of ACTs in one pill have been more limited. Blister packs containing separate tablets (NA/IM, 2004), most commonly amodiaquine and artesunate, are more widely produced. Novartis has been the major source at the international level, but at least two Chinese ACTs have been reported sold or tested in Africa. One is known as

A*rco* and is manufactured by Kunming; it is a combination of artemisinin with napthoquine (Ouma, 2007; Toure et al., 2009). The other involves co-formulations of dihydroartemisinin-piperaquine. Subsequently, African firms entered the scene with generic forms or different formulations. One example is M*aladar*, introduced by Shelly Pharmaceutical in Tanzania in August 2007. Other local ACTs (non GMF) are produced by Cosmos in Kenya and Zanufa Labs (Dar es Salaam) and Tanzania Pharmaceutical Industries.

1.3.2.3. 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/IM, 2004; Novartis, 2008b). The first is dihydroartemisinin, considered intinsically unstable by some (Haynes, et al., 2007; Jansen, 2010), but manageable with appropriate formulation by another (pers. com. from Wells, March 2012; hereafter Wells, 2012). Three others are derived chemically from it - artesunate, artemether, and arteether (also known as artemotil; Brossi, et al., 1988; NA/IM, 2004, 306) - and are converted back to it in the body (NA/IM, 2004; Jansen, 2002). [Similarly, four alkaloids were derived from cinchona bark by 1847: quinine, cinchonine, quinidine and cinchondine. 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 in India and China (Webb, 2009a; also see Porter, 1997)].

Each derivative has its own qualities and has been favored by one group or another over time. As noted in Section 1.2, initial emphasis 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 as a suppository or intravenously in severe cases (SEAQUAMAT, 2005; Gomes, et al., 2008; WHO, 2008; Lubell et al., 2011). In the latter instance, WHO recently stated that "Intravenous artesunate should be used in preference to quinine for the treatment of severe P. *falciparum* malaria in children;" it has proven both more effective and much easier to administer (AFP, April 2011).

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, sometimes termed the quines, includes quinine, chloroquine, amodiaquine, mefloquine, lumefantrine, and piperaquine; aside from quinine, they are the product of chemical synthesis. The antifols, include pyrimethamine, proguanil, and chlorprguanil and trimethoprim (NA/IM, 2004) and are often used in combination with sulfa drugs, which act on the same pathway, or with the quite different quines. The search for appropriate partner drugs is never-ending and can be very wide ranging (e.g., Cammack, 2011; Yuan et al., 2011).

Four combinations, listed in the 2001 WHO consultation, were recommended by WHO in 2001: (1) artemether+lumefantrine, **AL**; (2) artesunate+amodiaquine, **AS+AQ**; (3) artesunate+sulfadoxine-pyrimethamine, **AS+SP**; and (4) artesunate+mefloquine, **AS+MQ** (WHO 2006b; the bold-faced abbreviations used here could be viewed as technically inadequate and are intended only to simplify the presentation). A comprehensive review of ACT formulations as of the mid-2000s was 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, also known as Arsumax (Moneton and Ducret, 1998), was reviewed by Pécoul et al., 2008, Bompart et al., 2011, Lacaze, et al. 2011; field trials were conducted by Sirima et al., 2009 and Thwing et al., 2009. Similarly, field trials of AS+SP were carried out by Nahum et al., 2009; Sagara et al., 2009; Allen et al., 2009, and for AS+MQ by Agomo et al., 2008, and Faye et al., 2010.

A fifth combination, dihydroartemesinin+piperaquine (**DHA+PPQ**), appears effective and was added in early 2010 (Sinclair et al., 2009; WHO, 2010b,). It was first developed in China by Guangshou University of Traditional Chinese Medicine in the 1990s and later marketed by Hollykin Pharmaceuticals under the brand name A*rtekin* (NA/IM, 2004; Bonn. et al. 2004). 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 E*ruartesim* (Nyanzi 2007, Möhrle 2008). It was to be marketed by Pfizer and Sigma Tau (Anonymous 2008h), but Pfizer pulled out; negotiations are proceding with other possible partners (Wells, 2012). Two reviews of trials (Sinclair et al., 2009; Gargano, et al., 2011) and several studies in Africa (Arinaitwe et al., 2009, Bassat et al., 2009) indicated that it had

performed well, and it has subsequently been approved with some conditions as to range of use (Wells, 2012). Background on piperaquine, not to be confused with primaquine, is provided in NA/IM, 2004.

Each of the five combinations differs in some quality or characteristics and provides useful diversity over the African continent. This is reflected in the patterns of deployment. As of 2008, A-L was the principal first and second line ACT (23 of 44), followed by AS+AQ (18 of 44). A-L was used widely while AS+AQ was mainly used in West Africa (Bosman, 2008).

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. One Chinese study with gelatin capsules "contained oil to enhance the absorption of the artemisinin" (Yao-de et al., 1992). Subsequently others noted that its bioavailability is quite variable and is enhanced by co-administration with fat (Laufer et al., 2007; WHO, 2006b) and a recent study showed that "concomitant food intake increased lumefantrine absorption in children with malaria" (Borrmann et al., 2010).

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

Only two of the ACTs were initially "prequalified" by WHO as meeting international standards, a program that was established in 2001 to facilitate access to medicines that meet unified standards of quality, safety and efficacy (WHO, 2005f and Kiivet, 2008; for details on the program see: "Prequalification Programme" [http://apps.who.int/prequal/]). The first was C*oartem*® (AL), a combination of 20 mg of arthemether and 120 mg of lumefantrine, produced by Novartis in an adult formulation; a pediatric formulation was released in early 2009. Other prequalified firms include Ajanta, Cipla and Ipca of India. C*oartem* was initally approved or adopted in South Africa in 2000 (Barnes et al. 2005), in Tanzania in 2002 (Sisowath et al., 2005), and in Zambia in late 2002 (Zurovac et al., 2005). 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; and Naik, 2005). Seven recent African studies of Coartem are grouped in a supplement to the *Malaria Journal* (see Hommel, 2009). The second prequalified ACT was AS+AQ, manufactured by Sanofi in Morocco, IPCA in India, and by Guilin in China. As of early 2012 it was going to be submitted for review by European agencies (Wells, 2012).

About 75% of those using *Coartem*, usually in crushed form, were children and adolescents (Novartis, 2006, 2008c). A pediatric formulation, Coartem® Dispersible 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 by February 2012, one hudred million treatments had been distributed to 39 countries (MMV, 2012). It contains the same dosage level, has a cherry flavor (favored in trials), and dissolves easily (Novartis, 2009a; 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).

The 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). The drugs were developed under the aegis of the Drugs for Neglected Diseases initiative (DNDi). AS+AQ is produced by Sanofi-Aventis 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. Both combinations have experienced drug resistance and were not expected to have a long life (Mutabingwa, 2005; also see Jack, 2007a). 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). 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). Other prequalified firms include Ajanta, Cipla and Ipaca of India.

1.3.2.4. 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, an ACT developed by Professor Li Guoqiao of Guangzho University, long familiar with artemisinin and ACTs, is known as A*rtequick*®. 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. comms. from: Keith Arnold, Xin-zhuan Su, and Jianping Song, April 2009. Also see: Anonymous 2010f ; on piperaquine see Somé et al., 2010.)

There are currently four further noteworthy combinations: (1) Artesunate/sulfamethoxypyrazine/pyrimethamine (AS/SMP), developed by Dafra Pharma as Co-arinate, a 24 hour therapy (Sagara et al., 2006; Rulisa, et al., 2007; Penali and Jansen, 2008; Rulisa, S., et al., 2011); (2) artemisinin-naphtoquine (AN), A*rco*®, a one-day ACT, considered to be important for this reason as well as being the most potent partner drug available (Wells 2012) and introduced in Nigeria (Isah, 2007), Côte d' Ivoire (Touré et al., 2009), and Liberia (Anonymous, 2008e); (3) pyronardine-artesunate, P*yramix*®, developed by Shin Poong (Korea) and MMV (Peters et al., 1997; Nosten, 2010; Tshefu et al., 2010) and approved by the Korean FDA in October 2011 and the EMA in February 2012 for use in areas of low endemicity (Wells, 2012); (4) artesunate+azithromycin (AA), including an antibiotic with some antimalarial activity (Sykes et al., 2009; also see Padma, 2009). Non-ACT combinations are also available.

1.3.2.5. Multiple combinations and terminology

There have been an increased number of ACT combinations of two or more drugs with different forms of action. White (1999) credits Peters and colleagues as pioneering "the possibility that anti-malaria drug resistance could be prevented by the use of combinations of unrelated antimalarial drugs" (also see Ollario and Taylor, 2004). These studies, with pre-ACT combinations, were first reported in 1970 (Peters, 1970a and 1970b) and subsequently in 1973 (Peters et al.) and 1974. Peters and Robinson reported on the use of a triple combination in 1984.

The 1974 studies involved combinations of chloroquine with pyrimethamine-sulfadoxine. Further studies (Merkli 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 F*ansimef*® - 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; also see Sherman, 2011). The preexistence of sulfadoxine and pyrimethamine resistance in parts of Thailand together with developing mefloquine-resistance may have been an additional concern (pers. comm. from David Warhurst, April 2009). It was abandoned after a few years.

This has raised 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? Perhaps the first triple ACT combination, dihydroartemisinin-piperaquine-trimethoprim (also termed A*rtecom*®) combined with primaquine (which has some toxic effects: see NA/IM, 2004; Baird, 2010), and known as CV8 or CV8TM, was successfully used on an experimental scale in Vietnam in the 1990s (Jianfang/Zhang, 2005; Bosman and Mendis, 2007; White, 2008b; Gargano et al., 2011) and recently in Africa (Menan et al., 2011). TDR/GSK's combination ofchlorproquanil-dapsone-artesunate failed for safety reasons but only reached the 90% efficacy level, demonstrating that three drugs are not always better than two. An artesunate-atovaquone-proguanil combination proved effective in Thailand (van Vught et al., 2002). Other multiple combinations have since been compared with ACTs (Mutabingwa et al., 2005; Sowunmi, 2005; Zongo et al., 2005, 2007).

How different do the component drugs need to be to qualify as a *triple* combination? This general question will likely be increasingly 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 (1987) provided and discussed a possible classification of combinations. 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. Two others of possible value were: (4) *antagonistic* combinations (e.g. as possibly between mefloquine and Fansidar), and (5) combinations with *antimutagenic* agents. AS-AP, for example, is a triple combination but fails the Peters' test since S and P work the same pathway (Wells, 2012). These matters do not seem to have been taken up in the more recent literature reviewed.

1.3.3. ACTs: Introduction and implementation

As a relatively new and expensive pharmaceutical, ACTs were and are bound to face a number of challenges. They occur against a backdrop of what Shah has termed the "Karma of Malaria" (2010) and reflect an attitude that uncomplicated malaria is a normal problem of life and no reason for expensive treatment. If there is a problem, many will turn first to traditional medicines, though these patterns may vary (see Erhun, et al., 2005). 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 - particularly in areas of more intense transmission. In Africa there are many areas where older children and adults are highly vulnerable.

1.3.3.1. Initial availability of ACTs

At the outset, in November 2004, WHO announced a shortfall in supply of C*oartem* 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), and reversed itself by 2006 and 2007, with supply exceeding demand. That was followed by yet another reversal in 2009 and 2010 when supplies again shortened.

WHO reached an agreement with Novartis to make C*oartem* available at cost to ministries of health in developing nations (see Annex 7). 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 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.

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). The supply situation in Uganda in 2007 is illustrated in Annex 6**.**

The overall cost differentials may be widened even further when there is over-diagnosis of malaria and consequent over-treatment with ACTs. 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 (Ibid.). Self-diagnosis at home may also lead to over-dosage (Hume et al., 2008).

1.3.3.2. Transition to ACTs in Africa

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

The cost of ACTs is obviously a major concern - though may be less so elsewhere (see Ruebush, et al., 2004) - and was discussed in some detail in the Institutes of Medicine study (NA/IM, 2004). It stated that "The real price breakthrough will likely occur only when a fully synthetic artemisinin is developed, eliminating the growing and extraction process." 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, which would, of course, be influenced by its price which has varied widely, is uncertain (a very informal estimate by Wells, 2012, placed it at about 1/3 of the total).

The Institutes of Medicine report went on to explore a global subsidy system. 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 (Section 1.4.2.2.1). 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. General economic measurement issues in an African context are reviewed by Goodman, Coleman and Mills (1999) and Mills and Shillcutt (2004).

Economic assessments in this area can take two forms: (1) traditional cost-benefit analysis (CBA) and (2) a health-oriented assessment of cost-effectiveness (CE). CBA focuses on the degree to which a treatment is profitable; CE compares the relative profitability of several treatments (examples of CE include Coleman et al., 2004 and Morel, et al., 2005). 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 were conducted in South Africa (Muheki 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).

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 in The Lancet (WHO/RBM, 2004; Lidén, J., Nantulya, V.N., 2004). Four months later it was discussed at a malaria conference at Columbia University in New York (McNeill, 2004a) and the Global Fund held a closed door meeting on it in Geneva. "Afterwards, the organization's senior officials declared that African countries should retrospectively adjust all malaria grants awarded to specify ACTs" (Anonymous, 2006a). 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 Section 1.4.3.2). However, complex issues of supply and implementation existed at the country level and

were still being worked out (see Section 1.5.2.2.5).

One surprising twist, possibly due to the increased attention given by WHO to the use of diagnosis, 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). Yet overall progress as of 2010 appears to have been promising except in central Africa, where documentation is limited (O'Meara et al., 2010).

1.3.3.3. 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." It is much less likely for ACTs and its derivatives because the half life of artemisinin and its derivatives is short (WHO, 2006b). 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" (pers. comm. from David Warhurst, May 2008; also see NA/IM, 2004). Resistance can also develop in other less easily controlled ways (e.g., Shetty, 2005). Evidence of decreasing parasite susceptibility to artesunate in vitro from 1988 to 1999 was reported from Yunam Province in China (Henglin, et al., 2003). The combination of drugs with independent modes of action confers some mutual protection. However, while the synthetic drugs used in ACTs usually have much longer half lives than the artemisinins, they are still vulnerable. Hastings and Watkins have examined the matter of malarial drug elimination half life (2002, 2006).

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) and 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/IM 2004). Incipient resistance to artemisinin derivatives was reported in 2005 from French Guiana and Senegal (Duffy and Sibley, 2005; Jambou et al., 2005).

Tolerance to ACTs, in the form of delayed clearance of parasites in the blood of some patients, was noted later 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; Fuller, 2009; Enserink, 2010c). Resistance to AS+AQ was also increasing in southern Cambodia (Rogers et al., 2009) and to AS+MQ on the Thai-Myanmar border (Na-Bangchang et al., 2010). The latter is "an area where non-immune smugglers and illegal gem miners cross" (pers comm. from David Warhurst, April 2009; also see IRIN, 2009 and Samarasekera, 2009)

Overall, WHO (2011, xi, 47) concluded that "suspected resistance to artemisinins has now been identified in four coutries in the greater Mekong subregion" (Cambodia, Myanmar, Thailand and Vietnam; also see Hien 2011). It also notes "high treatment failure rates to several ACTs, in particular to dihydroartemisinin-piperaquine [DHR+PPQ] in Palin province in Cambodia. Myanmar (Burma) is considered by others "a 'black hole,' a source of disease untouched by international funding" and "a disaster waiting to happen" (Johnson, 2010).

These regional 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; 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, 2002; Wootton et al., 2002).

1.3.3.4. Nature of the ACT combination

This is a very important factor in determining resistance. Bloland et al. (2000) were perhaps the first to observe that "It is not obvious which drug combination is best for use in Africa." As Panosian (2005) put it: "one ACT does not fit all…partner drugs effective at one site [geographical area] may be ineffective at another." Similar observations have been 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).

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 (Djimdé et al 2008) and Gabon (Nsimba et al., 2008); and (3) lumefantrine, the companion drug in Coartem, in Zanzibar (Tanzania) (Sisowath et al., 2005) even though it has the advantage that it has not been used as a monotherapy (Dorsey et al., 2007). Sisowath et al. (2005) 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) 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." Hastings, however, maintains that this is a misconception (pers. comm. Dec. 2005) and he and Watkins (2006) argue that "drug tolerance is unaffected by intensity of transmission."

Clearly, identifying and maintaining the appropriate ACT combination and dosage, in the face of the development of resistance, will be a continuing challenge. One key element is that partner drugs vary in their elimination half-life: lumefantrine (the partner in C*oartem*) has a comparatively long half life while chlorproquinine-dapsone, no longer used, 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. comms. with William Watkins, Oct. 2005).

T*olerance* 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 implications of post-treatment prophylaxis also need to be considered (Price and Douglas, 2009). Dosage levels may be important in patients with heavy parasite burdens (White et al., 2009).

Yet, once developed, they might be used in different combinations for different groups. 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.

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 and perishable nature of artemisinin and the possible perishability of ACTs at higher temperatures (Jansen and Soomro, 2007), 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 national health policies and systems.

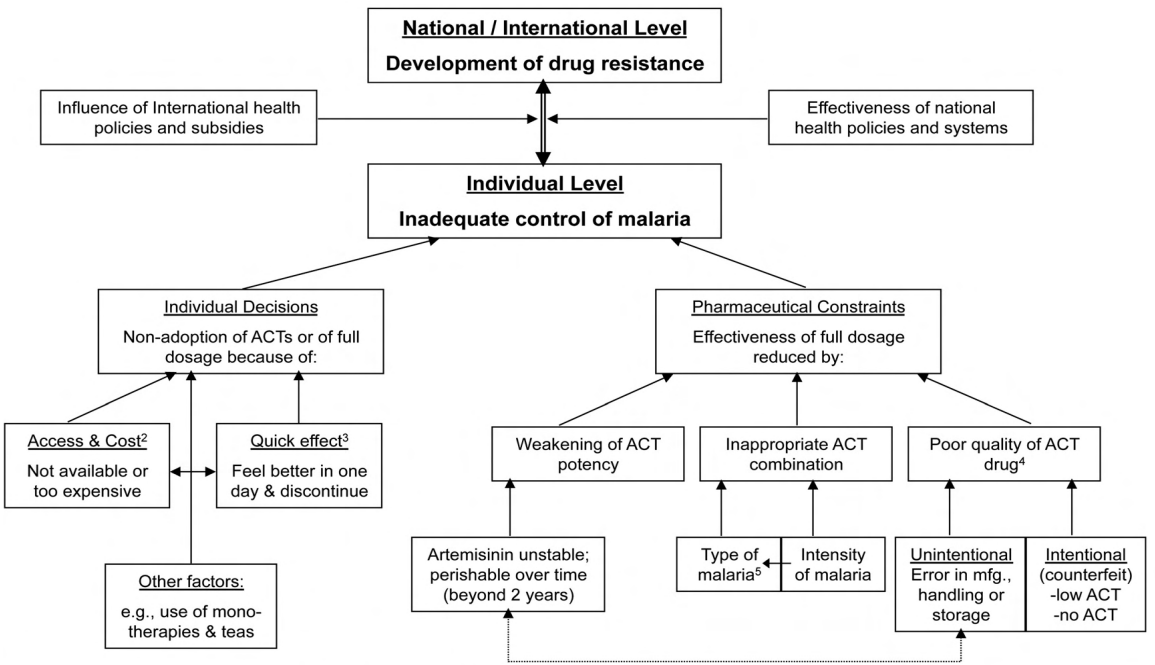
A graphic portrayal of the interaction of these forces, some of which will be discussed more fully, is provided in Figure 9. The figure is, of course, a simplification of more complex relationships and issues. It does not reflect the pernicious effects of artemisinin monotherapies. And counterfeits with 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/IM, 2004). Another problem is adherence to treatment regimens, which is more difficult for medicines that are not coformulated but only copackaged.

O'Brien et al. (2011) note that while "Clinical studies have identified delayed parasite clearance time as the most robust marker of atremisinin resistance…genetic investigations have yet to uncover robust molecular markers." And though "some genes are associated with reduced susceptibility, they have yet to define common genetic determinants that can account for prolonged parasite clearance time in drug-treated patients." This, in Wells' view, is a circular argument for reasons which are too abtruse to get into here.

1.3.3.5. Implications for manufacturers of 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, much of it appears to have been linked to existing pharmaceutical production, first in in China up to about 1990 and then in S. E.

Figure 9: Generalized Relationship of Varying Levels of Effectiveness of ACTs at Individual Level to Broader Development of Drug Resistance



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

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. This was followed by a combination of artesunate and amodiaquine and later by Co-Arinate, an artesunate/SP tablet. Production of Arinate was cut in 2007 (pers. comm. 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).

The same year, however, concern about resistance arising from the use of monotherapies led WHO to publicly request *drug manufacturers* to cease and desist from producing monotherapies except for intravenous or intramuscular injection and suppositories for severe malaria (Bohannon, 2006; Brown, 2006; McNeil, 2006a, 2006b). By 2007, 40 out of 74 companies had indicated that they would stop producing them (WHO, 2008; 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).

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 monotherapies, 6 declared their intention to comply, and 30 had not disclosed their position (Schwarte et al., 2010). Nearly all those complying were larger firms who had declared their intentions (WHO, 2009b); this was still true in February 2010 (Schwarte et al., 2010).

The Indian government mandated the cessation of sales on monotherapies by July 31, 2009 (CDSCO, 2008; Singh, 2009) and as of April 2011 any company "found to be producing or exporting monotherapies will face immediate cancellation of its manufacturing license" (RBM, 2011). Ten S.E. Asian nations agreed to ban the use of monotherapies by 2015 (Lyn, 2009). One suggestion at the international level is an 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).

1.3.3.6. Qualified and "unqualified" ACT producers

As noted previously (Section 1.3.2.3.), WHO has a program of prequalifying manufacturers of ACTs. In early 2012, nine producers in five countries were prequalified: India (4), China, Uganda, Morocco, Switzerland and the Netherlands (1 each). They are: India, Ajanta, Cipla, IPC, Strides Arcolab; China, Guilin Pharma; Uganda, Quality Chemicals (see Section 1.3.4.2); Morocco, Sanofi Maphar; Switzerland, Novartis; and Netherlands, Arcolab (RSMWG, 2012, #6).

There also have been other producers of ACTs of uncertain number who are "not qualified" by this measure. This situation changed in early 2012 when the same source reported, for the first time, a graphic display of their number by country which totaled 264! They were: India, 71; Pakistan, 47; China, 45; Nigeria 36; Ghana, 15; Vietnam, 8; Belgium, 6; Kenya, Italy, U.S., 4; Bangladesh, 3; Dubai and Uganda, 2; and Japan, Korea, Ethiopia, France, Switzerland, Germany, Netherlands, France and Brazil, 1 (Ibid, # 7).

1.3.3.7. WHO guidelines for the use of ACTs

As also noted earlier in this section (1.3.2.3), WHO (2010b) recommends 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." This point, as noted in Section 1.3.2.3, has been a source of debate centering about the question of stability.

There is also the important 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 early studies had been conducted on artemisinin monotherapies (NAS/IM, 2004), none had been done on ACTs.

The first study involving fixed-dose ACTs was carried out in northeast Thailand from 2004-2006 in an area "with unstable but highly-drug resistant malaria transmission" (McGready 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 WHO. The pharmacokinetic properties of both were reduced in the latter stages of pregnancy and a dosage increase may be needed.

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. Also see Noedl et al., 2006; Noedl, 2009; Barennes et al., 2010; and Section 1.6.2.2).

The general safety profile of AL was confirmed in a review of studies in Africa and Asia (Falade and Manyando, 2009). Moreover, both DHP and AL were shown to be effective in chronically malnourished children in a high transmission setting in Uganda (Verret et al., 2011).

1.3.4. Artemisinins: drug discovery, development, and protocols

As the Chinese experience demonstrated, the discovery of artemisinin and initial laboratory development of ACTs is hardly the end of the matter. A continuing research and development program is needed to meet a wide array of needs and the constant threat of drug resistance. Moreover, for the drugs to meet international standards and protocols, much more needs to be done in terms of formulation and testing. While the initial focus in the case of ACTs was on international firms, the question of local manufacture soon follows. And in both cases there is the eternal problem of counterfeit and substandard drugs.

1.3.4.1. Malaria drug discovery and development

As with almost any disease and pharmaceutical product, this is likely to be a never-ending process for a wide variety of reasons, involving users and the drug itself. Hence there is a constant need for research and development and attention to international protocols.

According to a detailed recent study (PATH, 2011) over the period from 2004 to 2005, about 38% of the funding on malaria research was spent on drugs (of the rest, 28% was spent on vaccines, 23% on basic research, 4% on vector control and 1% on diagnostics). But within that period "there has been a steady decline in funding for drug R&D as well as a redistribution of funds away from clinical development and toward discovery and preclinical activities." This was also in part due to the largely successful completion of development of several antimalarials and a general trend away from product development funding and product development partnerships (PDPs) toward discovery and preclinical activities. This "does not align well with the global heath community's agreement on the need for further new antimalarials."

The Medicines for Malaria Venture (MMV), whose early program was reviewed by Fairlamb et al. (2005), is well outlined in the 2011 PATH report (Annexes 1 and 2), estimated that the cost of developing a new malaria medicine is about $100 million, whereas other estimates mentioned in the report range from $150-250 million over 7-10 years. Wells (2012) adds that "it depends on whether you count the cost of failures in the total and also how much of the partners contribution you put in. With the cost of failures it is around $100 million; with the partner contribution (and failures) it is closer to $200 million."

The early development of artemisinin-derived drugs in China did not follow the usual western procedures and protocols in their later stages, but had to do so before attaining international use. This section outlines the nature of the key steps involved in this prolonged and expensive process and provides current examples and an illustration of the process in the case of C*oartem* in the United States.

1.3.4.1.1. *Key stages in discovery and development.* The sequence of steps involved has been well characterized outlined by Ridley (1997) and Nwaka and Ridley (2003). Early portions are closely related to Figure 1 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 was defined as including three steps: (1) "Target Selection and Validation," involving exploratory biology on the malaria

parasite plus molecular and parasitological screening, complemented by medicinal chemistry; (2) chemistry-driven and biology-driven efforts (as seen earlier for artemisinin) to identify promising chemical leads and further develop them into potential drugs; and (3) compound selection for full pre-clinical development which includes further antiparasitic, metabolic, pharmacokinetic and toxicology studies. It was subsequently determined by MMV that the target-based approach had not borne fruit and since 2007 they have been utilizing cell-based screening (Wells, 2010; Rottman, et al, 2010).

The **developmental** stage 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):

P*hase* 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."

P*hase* 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." MMV subsequently learned that if work is being done on combinations, phase 2B has to include the testing of the new compounds in patients. "It is virtually impossible to predict accurately what will happen in human combinations studies from the animal data" (Wells, 2012).

P*hase* 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." MMV has found that there is often an age de-escalation, starting with the big children and working down to tose who weigh only 5k. There also needs to be a balance African and Asian non-immunes (Wells, 2012).

• **Post–registration testing** is referred to as Phase IV.

The probability of success may vary somewhat by step and phase. Based on early Medicines for Malaria (MMV) experience for competitively selected projects, Nwaka and Ridley (2003) indicated that they were, as might be expected, lowest for exploratory early discovery (30%) and highest at the registration stage (95%). Intermediate success rates were: preclinical transition, 55%; phase I, 70%; phase II, 50%; phase III, 65%; and phase IV, 95%. These have subsequently proved to have been the success rates for MMV (Wells, 2012).

As of November 2010, MMV placed the (1) likelihood of launching and (2) earliest possible time to launch, respectively, as follows: Preclinical, 14% />20016; Phase I, 27%/2016; Phase IIa, 38%/2015; Phase IIb/III, 72%/2013; and Registration >90%/2011.

The cumulative result is that the likelihood of final success for an individual candidate is very low at the start. MMV has found it to average about 20% in Phase 1, "a lot better than in other therapeutic areas" (Wells, 2012). Even for successful candidates, Ridley noted 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." MMV experience has shown that it takes "at least 7 years, slowed down by the time to review regulatory dossiers (two years in most cases) and the need to do an extensive phase III" (Wells 2012).

As a former director of the National Cancer Institute observed: "We're not that bad at predicting things that might be part of the future, but we're really bad at predicting the timing and path to them" (cited by Parascandola, 2000, 11).

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; also cited in Moran et al., 2009). The actual costs experienced by MMV have been "closer to $50 million" (Wells, 2012).

While these figures may seem high, they are relatively modest compared to the situation for pharmaceuticals in the U.S. (McArdle, 2010). 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 that 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." The cost of borrowing funds is also a huge expense (Wells 2012).

A "Drug Discovery and Development Center" has recently been established at the University of Cape Town. It is initially funded for four years by the Medicines for Malaria Venture and the national Technology Innovation Agency and will focus on developing and testing preclinical drug candidates for malaria and other diseases affecting the continent and providing training (Makoni, 2011).

1.3.4.1.2. *Drugs under development.* These are drawn from the "Global Malaria Portfolio for the 4th Quarter, 2011" as assembled by the Medicines for Malaria Venture portfolio, which reported all known drugs under development stating with the Research or Lead Optimization stage (another table with similar appearance reports only those under MMV auspices; also see PATH, 2011). This summary starts with drugs in the following stages: Translational (Preclinical, Phase I and Phase IIa) and Development (Phase IIb/III, Registration, and Phase IV) categories. All contain some little known entries and conclude with some more familiar ones. Those in the MMV portfolio are marked with an asterisk (*). Collaborators are listed in parentheses. Antibiotics are marked with a double asterisk (**).

- **Preclinical.** MK4815 (Merck; see Powles, et al., 2012)*; GNF 156

(Novartis)*; DSM265 (USTW/UWI/Monash)*; *Genz-668764* (Broad/Genzyme)*; MK4815 (Merck)*; P218 DHFR (Biotech/Monash/LSHTM)*; NPC-1161-B (Univ. of Miss.); RKA 192 (Univ. of Liverpool); ACT451840 (Actelion); BCX4945 (Biocryst/Einstein Col. Med.); SAR11642 (Palumed).

• **Phase I.** NITD 609 (Novartis)*; CDRI 97/98 (Ipca); DF02 (Dllator); N-tert-butylisoquine (Liverpool/Glaxo Smith Kline); AQ 13 (Immtech).

• **Phase IIa.**. OZ 439* (Monash/UNMC/STI); *Artemisone* (Hong Kong Univ. of S&T); *Artesunate-ferroquine* (sanofi aventis); *Fosmidomycin-clindamycin* (Jomaa Pharma GMbH); *Methylene blue and amodiaquine* (Univ of Heidelberg); SAR97276 (sanofi aventus).

• **Phases IIb and III.** *Azithromycin-chloroquine***(AZCQ/Pfizer); Tafenoquine (GSK)*; PR259CTI, (DRC/Antwerp)*; *Argemone Mexicana* (Mali/Geneva)*; *Pyramax Paediatric*® (Shin Poon, Univ of Iowa)*; *Arterolane*/PQP (Ranbaxy); *Co-trimoxazole Bactrim*** (Inst. Trop. Med.)**; ARCO *Naphthoquine/Artemisinin*; *ArtiMist*™, *Proto Pharma*.

• **Phase IV. Registration.** DHA-*Piperaquine*™* (sigma tau; Europe only; see Jansen, 2010); *Pyramax*®* (Shin Poong; Univ. of Iowa)*; *Mefloquine Artesunate* (Farmaguinhos/DNDI); *Artesunate intarectal* (WHO/TDR.

• **Phase IV. Post-Registration.** *Coartem® Dispersible** (Novartis); ASAQ *Winthrop** (sanofi Aventis/DNDI); IV artesunate* (Guilin); *Eurartesim* (sigma tau). All "*Approved*."

In addition to these drugs, 13 others were in the Research/Lead optimization stage, a broad category that sometimes includes natural products. Of the total of 50 drugs in all categories, 28 were sponsored by MMV. *Coartem*®-D (Novartis) and ASAQ *Winthrup*® (sanofi aventus) were previously noted as "Approved."

The MMV annual report for 2010 provided updated on their most promising products and candidates (most mentioned previously; also see PATH, 2011), some of which will be mentioned later. *Coartem dispersable*: by the end of the year more than 52 million doses had been delivered in 33 African nations since their launch in mid-2009 and they represented 68% of Coartem treatments. IV *Artesunate* (artesunate for injection) had received WHO prequalifcation and proven superior to quinine. DHA-PPQ and *Pyramax*® were proceeding through the European Medicines Agency approval process (since received for *Pyramax*, MMV 2012a); child-friendly versions are under

development. P*yramax*, a combination of artemisinin and pyronardine (not used outside of China for 30 years), is the first ACT that can be used for P. *vivax* malaria (NA/IM, 2004, 294, 307; Ramharter, et al., 2008; Tshefu, et al., 2010; Kurth, et al., 2011). A*zithromycin* could be used by pregnant women. OZ 439 is structurally different from the artemisinins and may not be susceptible to the same resistance mechanisms; with a partner drug they could be a one-dose cure. NITD 609 is a "completely novel antimalarial molecule and will have to be partnered with another antimalarial drug." Overall, a promising package but constantly in flux (for further details on individual drugs see MMV 2011d and Wells and Gutteridge, 2012, 12-13).

1.3.4.1.3. *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 oral use in the United States. Only artesunate was approved for use in intravenous form for severe malaria (CDC, 2010; also see discussion in NEJM, 2008). Similarly, no artemisinins or ACTs have been registered in Japan (Kano, 2010). 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, M*alarone*® (atovaquone-proguanil HCL), has been shown to be highly effective as a protective and cure (Boggild et al., 2007) but it was thought that it would be beneficial to have an additional treatment available (Novartis, 2008b).

An initial step was taken in 2004 when a regulatory dossier was filed with FDA to make artesunate available to treat severe and complicated 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" (CDC, 2007; Milhous and Weina, 2010).

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). According to McNeil, "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 normally cannot prescribe drugs lacking F.D.A. approval."

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, in December 2008. The group concluded that the clinical data showed that Coartem worked and that it was safe, which amounted to a recommendation for FDA approval. An early decision was expected and was received on April 8, 2009 (FDA 2009). Novartis also earned a transferable priority review voucher for another experimental drug application (Ibid., Dooren, 2008; Heavy, 2008a, 2008b; Jack, 2008b; and Anderson, 2009). They have since used it on another drug which was ultimately not accepted by FDA (Wells, 2012).

The briefing document, which is now public information, provides a rich source of information, especially about the clinical review program for C*oartem*. It included a total of 4,911 patients in 20 studies conducted by the company between 1993 and 2007. Of these, 3,599 patients were treated with C*oartem*, 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. Another 40 or so independent studies were also reviewed, including various ACT combinations and various regions.

1.3.4.2. Issues involved with local manufacture

Moving from research and development into actual drug manufacture in Africa involves a number of issues that are common for developing countries (see UNCTAD, 2001) as well as others that arise from the particular nature of ACTs. The manufacturing process is obviously simpler for artemisinin monotherapies, but these are likely to lead to loss of resistance and are not encouraged (for an exception, see Nosten et al., 2006). ACTs are clearly far more socially desirable than monotherapies, but much more difficult to manufacture in a way that conforms to international standards.

That process involves obtaining approval or pre-qualification for each drug before international agencies, such as UNICEF, are allowed to buy them

(Anderson 2010. The Quality Chemicals plant in Kampala, a joint venture with Cipla, an Indian generic drug manufacturer, is the first to receive this approval for the plant. The next step is to get approval for each malaria and HIV drug the firm produces. Even then, the company is "struggling to compete with cheaper imported anti-viral and antimalarial drugs that benefit from state support or export subsidies" (McColl, 2010). As of April 2011 its biggest problem was "access to market" and the plant was operating at only a third of capacity (Manson, 2011). Another issue is the need to amortize the costs of a new facility (Wells, 2012). "Some experts argue that rather than encourage local production, countries would be better focusing on ways of delivering drugs to the people that need them" (McColl, 2010).

1.3.5. Counterfeit and substandard drugs

A more ubiquitous set of problems, dating back as far as quinine in India in the early 1900s (Barton 2007) and endemic and to virtually all medications, involves marketing of low-quality, either counterfeit and/or sub-standard, artemisinin drugs (e.g., Figure 9, McGinnis, 2010). 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).

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 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.

1.3.5.1. Counterfeit artemisinins

These initially were most evident in Asia (e.g. Newton et al., 2003, 2006, 2008; Lon, 2005; MacKinnon, 2007). 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). 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); the most recent survey by Newton, et al. (2011) revealed five types of illicit drug combinations. Cell phones would allow buyers to check authenticity (Cheng, 2010a).

1.3.5.2. Substandard artemisinins

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) 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; also see Odora, 2008).

Another 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 sulfadoxine-pyrimethamine (SP) had high failure rates (45% & 30% respectively) (Gathura, 2008, 2009a). A spot check in Nairobi on June 2, 2009 revealed that the artemisinin monotherapies were still readily available "in almost all drug stores" (Gathura, 2009b). Yet, a study in Nairobi indicated that most of those who complain of failures buy them in open air markets (Odeh and Tatalovic, 2010).

Perhaps the most 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 (sulfadoxine-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 problems may also 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). A recent survey of the use of paediatric ACTs in Africa found that the majority did not meet the "highest international quality standards" (Andandji, et al., 2011).

It has long been thought that artemisinin derivatives have only a two-year life in hot climates. According to Wells (2012), this is based on documentation in the regulatory dossier showing "two years stability at 30°C and 75% relative humidity." 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 agencies is warranted" (Bate et al., 2009a). Wells says that the regulatory authorities would be happy to review the shelf life if there are data.

In any case, "substandard [artemisinin] compounds have the potential to do as much harm as counterfeit drugs or even more" (Atemnkeng et al., 2007a; 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. One possible exception has been suggested in the case of fake drugs: the use of cell phones, which are becoming ubiquitous in Africa, to check on the authenticity of code numbers on the packages (Bennett, 2010). 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.

1.4 The Context: *Global 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, the World Bank program, and a sequence of activities undertaken by agencies of the United States government, principally USAID.

1.4.1. 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 Section 1.5.2.2.

1.4.1.1. Global supply of Artemisia and artemisinin

1.4.1.1.1. *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. 1.5.2.2.1. 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 Bruich, 2004, 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, 2008a; RBM, 2009). Clearly there was a sharp rise and fall in area.

This was vividly demonstrated in East 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). 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 was carried out under contract and Holley supplied the seed. In one contract area, Artemisia had replaced "plots of corn, tobacco and potato" (French, 2005). Further expansion of area was being encouraged (Jiajiao, 2005). The overall area in China, however, was estimated to have fallen from 20,000 ha. in 2006 to 2,000 ha. in 2008 (Cutler, 2008). Nothing, however, is known about overall Chinese statistics, if any; it would be particularly difficult to account for wild production (see CHAI, 2008). *Vietnam* was 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, 700 in 2009, 500-700 in 2010, and then expanded to 1,500 ha. in 2011 (Cutler, 2008; Artepal, 2008; Hiey, 2010; Ut, 2011).

Elsewhere, India has the potential for Artemisia cultivation but no estimates of production have 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). Similar estimates were 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 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). 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). Subsequent estimates ranged from 23,000 to 28,000 ha. (57,000 to 69,000 acres) for 260 million treatments and a maximum of 30,000 to 50,000 ha. (74,000-123,500 acres) for the global market (Ellman, 2010a; Ellman and Cutler, 2010; see Annex 3 for conversion factors). 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. (As previously noted in Section 1.3.1.1.2, research efforts to develop varieties with higher yields have been greatly boosted by two substantial breeding programs in England.)

1.4.1.1.2. *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. Industry estimates prepared by the Procurement and Supply Management Working Group (PSMG) of the Roll Back Malaria Initiative of WHO, composed of knowledgeable individuals in the public and private sectors, place 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 (Pilloy, 2007, 2008a/b). Some extractors had significant carry-over stocks that they used to meet orders. Even so, if production of artemisia declines as much as expected in 2009, the overall supply of artemisinin could reach seriously low levels.

The supply of artemisinin is also influenced by the efficiency of the various extraction processes used, a topic not covered here (see Annex 4; Hill, 2009). Suffice it to say that these are varied both within and between countries (Vietnam's are viewed as the least efficient). Little or no outside assistance

seems to have been provided for the upgrading of facilities. One project would have involved DANIDA (Denmark) and Vietnam but evidently didn't materialize (GHR, 2006a; Holm, 2006).

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 comparative advantage of firms or regions could be altered. Standardization of quality and purity of artemisinin is also important and new techniques for assay have recently been developed (MMV 2011b, c)

1.4.1.2. 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/IM, 2004; Widdus and White, 2004). Counting pledges, MMV indicated 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, 2008a).

The program involves many steps, drugs, and collaborators and alliances in the private and public sectors). 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/IM, 2004; Li, Milhous and Weina, 2007). Other collaborators include university teams and the pharmaceutical and biotech industry which have much of the technical expertise.

The ACT portion of this process, as for other drugs (and noted in Sections 1.3.4.1.1 & 1.3.4.1.2), is perilous: some drug formulations which initially look promising may later show weaknesses requiring correction or, if serious, fall by the wayside; others may take different routes than originally anticipated. D*acart* was a prime example of the former [see Box 2a, p. 84], while OZ277/RBX11160 an example of the latter [see Box 2b, Ibid.]. Two examples of the latter as of mid-2009 were in phase III trials and expected to move to the regulatory phase:

(1) E*urartesim*®, dihydroartemisinin-piperaquine (DHA+PQP); and (2) P*yramax*®, pyronaridine-artesunate. By late 2010 they had proceded to the approved stage, and received European (if not yet more global) approval in 2011 and 2012 respectively (Wellcome, 2011; MMV 2012).

MMV has also sponsored work on synthetic artemisinins which might be

Box 2. The uncertain life and paths of malaria drug candidates

2a. One that didn't make it. In trials, *Dacart* – a combination of *Lapdap* (chloroproquinal and dapsone) and artesunate – that appeared as effective as Coartem, demonstrated a serious side effect (reduced hemoglobin levels in patients with a heriditary enzyme disorder that afftects 10-20% of Africans) and development was discontinued by GlaxoSmithKline in February 2008 (Whalen, 2008; Hirschler, 2008). This effect was attributed to Lapdap, which had not been submitted for final trials (pers. com. from J. Carl Craft, March 2008) and was also withdrawn from sales in Kenya, its only and limited market (Kimani, 2008; Luzzatto, 2010). *Lapdap* had been examined as a potential partner drug in Africa (WHI, 2002b), and named a "Highlight" for 2000-2005 by the Welcome Trust (2005).

2b. One that took a detour. OZ277/RBX11160, a synthetic peroxide initially developed under MMV auspices, was combined with piperaquine (PQ) and entered phase IIb, clinical development, in cooperation with Ranbaxy Laboratories in New Delhi as RBx11160 (O'Neill, 2004; Vennerstrom et al., 2004; Davis, 2005; Fairlamb et al., 2005; MMV, 2006a; Uhlemann et al., 2007). Ranbaxy reported successful completion of Phase II trials, including Africa, in July 2008 (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). MMV listed them in the Phase IIb/III category as of late 2011 but they may have since "made it", though official confirmation has not yet been received by MMV (Wells, 2012). OZ277 is referred to as a "fully synthetic peroxide" and is known as *Arterolane* (Vennerstrom, et al., 2004; Uhlemann et al., 2007; Pednekar, 2009; Möhrle, 2009;). It has been followed by a very promising second generation ozonide, OZ439 (Section 1.3.4.1.2; Charman et al., 2011).

combined with other drugs (see below) and due to some limitations of ACTS - one being 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).

1.4.1.3. Scientific developments and issues

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. Of $323.4 million spent on 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). 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 as of that period are provided by Moran and Guzman (2005) and Thayer (2005). They have since expanded.

1.4.1.3.1. *Other sources of Artemisinin.* Artemisia is not the only possible source of artemisinin and ACTs are not the only drug-related treatment for malaria. Precursors may also be obtained, it now appears, by: (a) using N*icotiana benthamiana* as a "production platform," (b) new derivatives, and (c) through chemical and biological synthesis – all approaches that could conceivably lead to cost savings and a more stable supply. Realizing that potential, however, is not a simple or easy task.

1.4.1.3.1.1. *New plant sources?* 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 "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. Following further research to determine how it can best be extracted from the root, Dafra initially expected to be able to achieve low cost large-scale production in three to five years (Dafra Pharma, 2007a). Nothing, however,

has since been published about the outcome. Rather, they recently reported on a different path: "Biosynthetic genes, leading to artemisinic acid, [that] were combined and expressed in N. *benthamiana* by agrofiltration" (van Herpen et al., 2010). Others have either noted or reported on research in this area (see Covello, 2008; Zhang et al., 2011)

1.4.1.3.1.2. N*ew derivatives*. Two very promising derivatives of dihydroartemisin (DHA), artemisone and artemiside, termed semi-synthetic endoperoxides, have been synthesized by an international group of scientists. A*rtemisone* was the first (Haynes et al., 2006, 2007; Vivas, et al., 2007; Waknine-Grinberg, et al., 2010), has been approved for human use, and and as noted earlier (Section 1.3.4.1.2), completed Phase IIa trials. The project was dropped by Bayer and since has been looking for a new pharmaceutical sponsor (Wells, 2012). A*rtemiside* has proven even more effective – more so than any drug in use - at the laboratory level against P. *falciparum*, but has yet to be submitted for preclinical toxicological evaluation (Guo et al., 2011). Combinations with mefloquine or piperaquine "may confer an optimal half life because of the longer half life of both" (Ibid.). Artemisone in a comparative in vitro screen against a panel of multidrug-resistant parasites provided the most active antimalarial peroxice and was more active than the synthetic trioxolanes OZ 277 and OZ 439 described below (Marfurt, et al., 2012).

1.4.1.3.1.3. *Chemical and biological synthesis*. The chemical synthesis of medicinals has a long history, starting in the early 1800s when Sir Humphrey Davy wrote that "The ends of this branch of knowledge are the applications of natural substances to new uses, for increasing the comforts and enjoyments of man" and included aspirin and attempts to find a less expensive substitute for quinine (Jeffrys, 2005). 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). Similarly, an article in T*he* E*conomist* in 2004 stated "the great hope is to find a way of synthesing artemisinin in the laboratory, thereby freeing drug makers from the vagaries of nature" (Anonymous, 2004a).

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). Initially,

emphasis was placed on screening and clinical trials involving atabrine (quinacrine) and mefloquine (resochin); chloroquine was a later product (Ibid.; NA/IM, 2004). Total synthesis, which has been carried out at the laboratory level, is considered impractical. Recent efforts might be grouped in terms of semi-synthetic artemisinins and synthetic peroxides (Tilly, et al., 2012). Current programs involve (1) microbe-based production, (2) synthetic trioxolanes, (3) spiroindolones, and (4) mimic synthetics.

• **Microbe-Based Production.** In late 2004 The Bill & Melinda Gates Foundation contributed $42.6 million to a nonprofit drug company, the Institute of One World Health (IOWH), to develop a new process ("metabolic engineering") that uses bacteria to synthesize a precursor of artemisinin, and was projected to be much lower in cost (Anonymous, 2004b; Daviss, 2005; Hale et al., 2007); a second grant was made in 2010 (Nguyen, 2010). For the penultimate step, the conversion of the artemisinic acid into artemisinin, the plan was to use chemistry developed much earlier by Roth and Acton (1989) and by Haynes and Vonwiller (1990) as described in the transformation of artemisinic acid below.

A key initial phase of the research involved the isolation of a "cDNA encoding amorphadiene oxidase (CYP71AV1)" that allowed the engineering of artemisinic acid in both E. *coli* (Chang et al., 2007) and yeast (Ro et al., 2006; Covello, 2008). This work was largely done at the University of California, Berkeley. Other research at the Plant Biology Institute (PBI) in Saskatoon, Canada led to the identification of genes encoding other enzymes in the artemisinin pathway (Zhang et al., 2008; Teoh et al., 2009) that have potential for use in genetically-modified microbial and plant production systems (Zhang et al., 2011).

Initial 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, 2007; IOWH, 2007). The Institute partnered with (i) the University of California, Berkeley which - under the leadership of Prof. Jay Keasling – had been conducting research to develop 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; McNeil, 2005; Bower, 2005; and Shore, 2010).

Amyris further developed the bacterial and yeast strains from Prof.

Keasling's lab and found that yeast was the most suitable organism for the production of artemisininic acid. Inclusion of additional Artemisia genes identified by the Canadian group led to generation of yeast strains capable of achieving the levels of artemisinin needed for commercial production (pers. comm. from Chris Paddon, Amyris, May 2011). However "the synthetic chemistry involved in moving from artemisinic acid to artemisinin is not trivial. Sanofi-aventis developed a novel photochemistry process for this step" (Tue Nguyen, OWH, May 2011).

In early 2008, Sanofi-Aventis was named as a partner with plans to build a bioreactor in Europe by 2010 (IOWH, 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 reached the pilot scale-up stage, which proved complex and "longer than standard chemistry"; on the other hand the production cycle proved to be very short, less than a week (Farret, 2010). By April 2011 it had "successfully entered the production and distribution stage" (IOWH, 2011; also see Specter, 2009; Nguyn, 2009, 2010; Perkel, 2011). One observer termed it "…the most complicated genetic engineering feat to date" (Perkel, 2011). It "will be used to smooth out the cycle of boom and bust in crop-based artemisinin supply" (Van Noorden 2010). Production is expected to expand from 20 tons in 2012 to 40 in 2013, about half the world's supply, with an expected price of about $350/kilo (Miller, 2011; see Nguyen and Goldenberg 2011 for further details).

As of November 2011, the construction and installation of the final facility was underway and scheduled to be finished by the middle of 2013. Production of "validation batches" of of artemisinin of about 2.5 tons would begin in the third quarter of 2012. "Ramp-up" of production would begin in the last quarter of 2012 and the first quantities of the final product – ssArte – would be made available to "qualified buyers for development and regulatory purposes" in the fourth quarter of 2012. Production is projected to be 10 tons by the end of 2012, 40-45 in 2013, and 50-60 by 2014 (Nguyen and Goldenberg, 2011). Related research has focused on an approach to developing a supply of semi-synthetic artemisinin based on "production of the artemisinin precursor amorpha-4.11-diene by fermentation from engineered Saccharomyces cerevisae and its chemical conversion to dihydroartemisinic acid, which can be

subsequently converted to artemisinin" (Westfall et al., 2012).

• **Synthetic Trioxolanes.** The Medicines for Malaria Venture (MMV), with several research teams, initially sponsored the development of two related synthetics that could be alternatives to artemisinin. The first, OZ277, initially appeared very promising (e.g., Osorio, et al., 2007), but stage IIA trials demonstrated some pharmaceutical problems and was taken over by Ranbaxy [see Box 2b, p. 84]. A second generation variant, OZ439, which is more stable, active and long-lived (MMV, 2007b, 2009a; Bathurst, 2008; Möhrle, 2009) has successfully completed Phase I trials and is currently in Phase IIa trials (Charman et al., 2011).

• **Spiroindolones.** These represent a new class of malarial drugs, along with artemisinins, and were termed MMV Project of the Year 1999. They are synthetics. NITD609, involving many groups (primarly Novartis and the Swiss Tropical Institute) and identified through a 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 regular tablet formulation. It has completed Phase I trials and is ready for testing in patients (Rottmann et al., 2010; Wells, 2010, 2012; NIH, 2010b; Novartis, 2010; Kotz, 2010; Tse, 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). 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 Section 1.6.2.1.

1.4.1.3.1.4. *Transformation of artemisinic acid.* In 1988, during a visit by Richard Haynes to the Chinese Academy of Science Shanghai Institute of Organic Chemistry, Zhou-Wei Shan, one of the Project 523 investigators, explained aspects of his work that showed artemisinic acid to be a

biosynthetic precursor of artemisinin. Thereafter, Vonwiller and Haynes at the University of Sydney mapped a possible biosynthetic pathway from artemisinic acid to artemisinin which was realized in the laboratory. First, artemisinic acid was reduced to dihydroartemisinic acid. Then singlet oxygen was used to produce an intermediate hydroperoxide that in the presence of an acid catalyst and oxygen was transformed into artemisinin (pers. comms. from Haynes, Feb. 2012). The process was patented in a number of countries and published (Haynes and Vonwiller, 1990).

Roth and Acton at the Walter Reed Army Institute of Research independently developed a similar approach that differed in the last step whereby a different catalyst, trifluoracetic acid, was used to transform the intermediate hydroperoxide into artemisinin (Roth and Acton, 1989,1991; Acton and Roth, 1992). The nature of this remarkable transformation was subsequently mapped out by Haynes and Vonwiller (1995). The work was extended by structurally modifying artemisinic acid to directly prepare artemether and new artemisinin derivatives (Haynes and Vonwiller, 1992; Haynes, Vonwiiller and Wang, 1995). The overall work was published in a review (Haynes and Vonwiller, 1997). Because of the evident importance of artemisinic acid, Haynes and Vonwiller also improved the extaction process for obtaining artemisinic acid from artemisinin (Vonwiller, et al., 1993, 1994).

Haynes had observed in 1990 that "The conversion of artemisinic acid, which also occurs in A. annua into artemisinin will augment supplies of artemisinin obtained by direct extraction from the plant." In 2006, in recognition of the importance of the biotechnical approach, he also indicated the significance of conversion into artemisinin.

In 2012, two German researchers, F. Lévesque and P.H. Seeberger (2012; also see Kupferschmidt 2012) rendered a substantial improvement to the engineering aspects of converting dihydroartemisinic acid into artemisinin. They developed a process that involves photochemistry and "flow chemistry" and utilizes a relatively small and simple reactor. The procedure is quick (4½ minutes) and output can be increased by simply adding more reactors - a different form of scaling up from lab to commercial level. While A*rtemisia annua* is usually the source of artemisinic acid, it can also be produced from yeast, the basis of the Amyris microbe-based process noted above. The aremisinic acid is chemically reduced to dihydroartemisinic acid. Needless to

say, this process has drawn widespread attention. It awaits further developments and assessment.

These varied approaches – to the degree they prove commercially viable - 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 and scaling up 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. Time will tell.

1.4.1.3.2. *Need for a different type of drug action.* 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, it is not possible to tell in advance whether a potential drug has the same or different mechanism (pers. comm. from Ian Bathurst, MMV, Oct. 2008). 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).

Subsequently, (1) Hartwig et al. (2008) proposed that they "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. comm. from Warhurst, 2009). Recent research by Wang et al (2010) indicated that artemisinin and OZ209 kill by "…direct disruption of mitochondrial functions" (also see O'Neill et al., 2010).

In the view of Haynes, "There is now clear evidence that artemisinins may also act as antimalarials by interfering with reduced flavin cofactors associated with the action of flavin disulfide reductases in the malaria parasite that are critical for surmounting the greatly enhanced oxidative stress experienced by the malaria parasite as it metabolizes hemoglobin required for its growth in the red blood cell. The implications of the co-factor mechanism is that it accounts for cytotoxicity of artemisinins against other parasitic and non-parasitic pathogens, and against cancer cell lines" (pers. comm. from H.K. Haynes, Feb. 2012, citing Hayes, et al., 2010, 2011a, 2011b).

As noted earlier, MMV, in cooperation with other groups, is constantly testing other new drugs (see Möhrle 2009 for a recent graphic summary). An

innovative screening effort has recently identified many potential compounds (Cammack, 2011, Yuan et al., 2011). One of the most promising characteristics of NIDT609 is that it is derived from a new class of compounds, spiroindolones, which 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). Even so, Andrea Bosman of WHO's malaria program stated, "there is no possible replacement of artemisinin until 2016" (Samarasekera, 2008). 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.

1.4.1.3.3. *Improved methods of prevention: 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 methods of prevention 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) and 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/IM 2004; Arnot, 2005; 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), but then have faded from view. This led to a critical response by scientists in Africa who were concerned with its likely cost ($10-20 per 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 "It's not either this or that – it's both" (Enserink, 2004; Snow, and White, 2004; also see: Stern and Markel, 2005, and Phelps, 2003, 2010). Once developed, licensing of vaccines can typically take many years (Moorthy et al., 2004). 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 candidates, RTS,S, also

known as Mosquirix, was first developed over 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). All the infants were in homes that had received indoor residual spraying and insecticide-treated bed nets. 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." 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 of RTS,S, the first for any malaria vaccine, was initiated in Tanzania to eventually involve 16,000 children in diverse transmission settings in 11 sites in seven African nations. Each site was to include a research partner from Europe or the U.S. It was hoped that RTS,S would have about 50% protective capacity for several years. An initial report for two nations indicated sustained efficacy for at least 15 months (Oluto et al., 2011). Phase II trials in three nations showed that three doses of the vaccine cut the number of eposodes between 35% and 50% for 12 months after vaccination. The first report for the Phase III trials (RTS,S Clinical Trials Partnership, 2011) indicated that three doses of the vaccine reduced episodes by in toddlers (5-17 months) by about half, the figure varying by population group and type of malaria (clinical and severe); infants will be reported later. This is not high when compared with other vaccines, but "there has never been a successful vaccine against a human parasite" (Stein, 2011). A *Science* article headlined that this "Meets Modest Expectations, Bouys Hopes" (Vogel and Roberts, 2011). It appears to be as safe as other vaccines (Stein, 2011), but cost effectiveness is uncertain (Ibid.: Kelland and Hirshler, 2011). It is hoped to use the results "to win regulatory approval...and make it available as soon as 2015," but there are no plans to try to develop a vaccine for adults (Stein, 2011). (For a sampling of earlier accounts, see 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, 2010a; MVI, 2011; Cookson, 2011; McNeil 2011; Vogel and Roberts, 2011.)

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 trial 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).

Other types of vaccines and approaches are under development. One, 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, 2010a). Further approaches, including that of Sanaria (Shore, 2010), are also under study. Some 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).

1.4.1.4. Implications for Artemisia and artemisinin

Even when suitable alternate sources of artemisinin or vaccines are developed, other key steps remain such as the development of appropriate ACT combinations, conduct clinical trials, and secure appropriate approvals of national authorities. While predictions of success often 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 in terms of relative stability and quality of supply and in this sense may better

serve society, but have yet to be achieved.

Industry's demand for artemisinin, however, may be further influenced by a diverse array of other technical factors. It could be diminished by (1) the build-up of parasite resistance to the drug, (2) increased use of diagnostic tools which reduce unneeded drug use, and (3) various preventative measures which reduce the global malaria burden and the need for drugs. On the other hand the demand could be stabilized or expanded if (1) the development of resistance to pyrethroids should reduce the gains made through the use insecticide-treated bed nets and perhaps house spraying, or less likely, (2) increasing chloroquine resistance occurred (e.g., Ketema, et al., 2011) making it necessary to use ACTs for vivax malaria.

These technically-related uncertainties and others provide longer-term challenges to both the task of equating supply and demand on one hand and maintaining continued funding to subsidize public purchases in developing countries on the other. Shorter-term, year-to-year challenges of a biological (quantity and quality) and economic nature complicate the task of better aligning supply and demand and are taken up in Section 1.5.2.2 (for one early example, see Kindermans, et al., 2007).

1.4.2. National policy and international 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 and international assistance programs.

1.4.2.1. 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). Within Africa, out of 45 nations, 43 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, 2009b; WHO, 2010b, 2010g). There is usually a delay between adoption and implementation of 12 to 24 months.

As noted earlier (Section 1.3.3.5), WHO presently recommends five types of ACTs: (1) AL; (2) AS+AQ; (3) AL+SP; (4) AS+MQ; (5) and DHR+PPQ (recently 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). 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). It would be useful to have regular annual breakdowns (some recent data are provided in Section 1.5.2.2.

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 5, 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). In 2007-08, in 11 of the 13 countries surveyed, the figure was less than 15% (WHO, 2009b).

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 treatment discourage its use in the home. It is also a monotherapy. Instead, increased use of another ACT is proposed (Yeka et al., 2009).

1.4.2.2. *International 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; O'Connell, et al., 2011). It was anticipated that "the financial resources to meet the needs of

ACTs in most African nations" would be "huge" and that between $1.6 and $3.4 billion per year "must be found to give Africa the chance to consider a drug policy based on ACT" (Snow et al., 2003b). The need for a subsidy program had arisen earlier for quinine in India [see Box 3] and was a main focus of the Institute of Medicine study (NA/IM, 2004). The overall goals were facilitated by the establishment of the Global Fund and an "Affordable Medicines Facility for Malaria" as well as a USAID program. They share some similar programmatic constraints.

Box 3. An early subsidy: quinine in India.

In the late 1800s, Clement 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 attected province (Hobhouse, 2005). The program was extended to other provinces between 1890 and 1893 (Webb, 2009a). Corresponding steps taken to develop "poor man's quinine" employing government plantations – "a philanthropic proposition" are vividly described by Duran-Reynals (1946) - but "the quantities of quinine were tiny in comparison with the need" (James, 1911, cited by Webb, 2009a, 139, fn. 27). In southern India, the quinine manufactured in the Nilgiri Hills was not sold to the general public, but rather "at cost to the governmental medical departments of Madras, Bombay and Colombo for distribution to government employees, including the army and to private planters (Brockway, 1979, 121). "Quinization" of various forms continued in India until the early 1900s (Bhattacharya (2011).

1.4.2.2.1. *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. 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). As of November 2009, the U.S. had pledged of $21.8 billion to the Fund for the 2001 to 2011 period and paid $17.0 billion (Kaiser Foundation 2010b); in October 2010 it pledged another $4 billion over a three-year period, subject to Congressional approval (McNeil, 2010b). While the totals are very substantial, goals and needs are inevitably even larger (McNeil, 2007c). Proposals are evaluated through independent review processes (Global Fund, 2007b) [see Box 4]. As of 2006, nearly 30% of total funding went for malaria and composed 64% of overall funding for malaria (Komatsu, et al., 2007; by 2009 the former figure was about the same (29%) and the latter had risen to about 75% (LaFranchi, 2009; Kaiser Foundation, 2010c).

Readily available data on commitments and expenditures for ACTs are suprisingly limited and vary somewhat. Bate (2007a) reported that "After a somewhat slow start, the Global Fund has 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 and Hanson, 2005). In 2006 about 85% of the ACTs were procured with GF funding (Dugue, 2007a). Recent expenditures have been (in millions): 2009, $152.7; 2010, $185.7; and 2011, $161.6 (est.) (Jouberton, 2010).

A recent report on the first decade of Roll Back Malaria indicates that (1) of Fund expenditures in Africa in 2008 on malaria, about 36% was for drugs and (2) while the Fund "does not disaggregate their "pharmaceutical category by drug type," the vast majority is for ACTs (WHO, 2010c). 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). The Fund clearly continued to play the major role in funding purchases of ACTs.

The Global Fund data on ACTs, where found, refer to approved funding

Box 4. Early operating difficulties of the Global Fund

The Global Fund's mode of operation was not without some initial difficulties for African nations. One was the process of application. In 2006, only just over 25% of all the malaria control proposals were considered worthy of financing by the Technical Review Panel. A Harmonization Working Group was set up in early 2007 to help improve the quality of the proposals (RBM, 2007b) and by rounds 7 and 8 approvals rose to 41% and 51% retrospectively (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 (Nahlen and Low-Beer, 2007). A 2006 report stated 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" to do so (Donnelly 2006). Third, while the recipient countries are supposed to buy from WHO-qualified manufacturers, this was not always done and the fund was considering adopting central purchasing (McNeil, 2007a). Other criticisms of the process were provided by Bate, 2007a/b.

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, Oct. 2008). Actual and projected disbursements were reported 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 were 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).

The implementation of these treatments, at least in terms of reaching goals, has evidently been more difficult than for the other Fund activities. 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 bed nets (the third lowest). Also the malaria programs had the fewest A-rated grants

(Global Fund, 2009a). 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; also see Global Fund, 2010a). Country level fraud has occurred and international competitive bidding is needed (Usher, 2010, Tren et al., 2009). Further criticisms by a review panel led to a decision to undertake major modifications in management and operations (Jack, 2011).

While initial funding expanded at an impressive manner, the Fund began to feel the effects of the global financial crisis and some operating difficulties in 2011, characterized in a new study as the year of "Innocence Lost" (Morrison and Summers, 2012). One outcome was the decision that the Fund would "only be able to finance essential services for on-going programs that come to their conclusion in 2014 by making savings in the existing grant portfolio…[and by] further limiting funding to some middle-income countries" (Global Fund, 2011). Given previous criticisms, 2012 could well bring even more change.

1.4.2.2.2. *The Affordable* Medicines *Facility for* Malaria. The Institutes of Medicine report noted earlier (NA/IM, 2004), headed by noted economist Kenneth Arrow, gave considerable attention to the need for a subsidy program which subsequently received further study by Laxminarayan individually (2004) and then with others (2006a, 2006b). In September 2005 the RBM Finance and Resources Working Group asked World Bank to develop a detailed proposal for the design and operation of a global ACT subsidy (RBM 2007a). It contracted with a consulting firm (Dalberg), and the resulting proposal was for an annual subsidy of at least $100 million to encourage production by drug companies (Jack, 2005b).

1.4.2.2.2.1. *Phases in* Establishment. The initial steps took three years. In January 2007 a group of health experts proposed the establishment of a fund to subsidize the purchase of ACTs for Africa (ACT Subsidy, 2007). 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 manufacturers would invoice the global fund for the remaining amount.

As initially outlined by Seiter and Andreasen (2007), the process provided "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 early AMFm materials referred only to "retailers" and do not appear to distinguish between the two categories; Bate (2008b) suggests the former. This seems an important point, particularly since ACTs are a prescription-only medicine in many African nations (Abuya et al., 2009).

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, 2007b; AP, 2007). In February 2007, 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 (RBM, 2007a). 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 2007, 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). 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" (APPMG, 2007b). 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. 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? 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). The Clinton Foundation tested "the practicality of subsidizing ACT drugs" in two areas in central Tanzania (Kwitema, 2007; Kerr, 2007).

Events accelerated in 2008. As of April, progress appeared promising (Samarasekera, 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, 2008a). 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). During an AMFm forum in September in Washington, the United

Kingdom (DFID) announced a pledge of £40 million for the first stage (Enserink, 2008a; 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 (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 Kingdom, 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. Following a technical review, decisions were made by the Fund Board in November 2009. The Pilot phase involved grants of $216 million from the UK, UNITAID and the Gates Foundation to cover the subsidies. Another grant $167 million from the Global Fund covered "supporting interventions." It was initially implemented in Cambodia, Gambia, Kenya, Madagascar, Nigeria, Niger, Tanzania and Uganda – and was to run for two years (Global Fund, 2009c; Adeyi and Atun, 2010). UNITAID "wound down" under a curious financial cloud in early 2012 (Jack, 2012).

Eligible products included AL, AS+AQ, ASAQ, and DHP+PQP, and had to comply with the Fund's quality assurance policy. Manufacturers must commit not to sell oral artemisinin-based monotherapie or above "maximum prices". Co-blistered ACTs were initially allowed but became a source of some controversy (Anonymous 2009a). Fund co-payments will be specific to each formulation and pack size and uniform across all suppliers. The Fund has the right to perform random quality control testing before shipment and monitor manufacturing performance. The program was 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 were Ajanta Pharma, Cipla and Ipca (India), Guilin (China), Novartis and Sanofi-aventus (for the initial views of Cipla, see Sisoda, 2010). 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 producers who could end up as, in the words of a Nigerian writer, "mere sales agents of foreign companies" (Anonymous, 2010d).

1.4.2.2.2.2. *Participation and* Performance. USAID did not participate initially (Jack, 2008a), pending further evidence of the effectiveness of the program – a position mandated by Congress (McNeil, 2009a&b; Gumbel, 2009). Similar concerns have been expressed, along with others such as misprescribing, stockouts and high opportunity costs (Moon et al., 2009; Kamil-Yanni, 2010; Bate and Hess, 2009). Doctors Without Borders noted 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).

Preliminary evidence on performance subsequently 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 population 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 total ACT purchases rose from nearly negligible levels to nearly half the total antimalarial sales…considerable geographic variation in stocking and sales persisted and was related to a variety of socio-spatial matters" (Cohen et al.,

2010). Similar results were obtained in Uganda (Talisuna et al., 2009; MMV, 2010; also see Patouillard et al., 2010). Other surveys provide more data on recent performance by country (AMFm, 2011); some reveal that the availability, market share and use of ACTs remained low (E2Pi, 2011a and 2011b).

The managers of the program foresaw four major challenges to implementation: (1) passing the subsidy on to patients at the retail level, (2) learning the most effective ways to expand the diagnostic tests for malaria, (3) reaching poor and remote populations, and (4) finding the appropriate approach to evaluation and benchmarking of phase one (Adeyi and Atrun, 2010). In response to the skeptics, the Board of the Fund set December 2012 as a target date to review progress and determine "whether to continue, accelerate, expand or terminate the facility." As of mid-2011, Sabot et al., concerned that "the duration of the pilot study is too short," forsee that "the results will…present a mixed and nuanced picture that will require careful interpretation. They argued that "the dialogue should be redirected from the question "if" the AMF should continue, to "ones of how, when and where it should be used" (p. 411).

1.4.2.2.3. *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. For example, Brown (2008b) 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).

• **Distribution and Funding.** Drugs intended for free distribution through public clinics may be stolen and sold through the private sector (Bate, 2010; Cheng, 2010b). Similarly, AMFm purchases or practices may evolve in unintended ways. A survey conducted in July 2011 in urban areas in four countries in West Africa – Ghana, Kenya, Nigeria and Tanzania – revealed that (1) some drugs were diversted into a non-particiating country (Togo), (2)

orders were principally (70%) for adult dosages whereas the main malaria burden is for children, and (3) orders were placed for one country (Zanzibar) which has almost no malaria. Also, less surprisingy, AMFm demand was overwhelming the global market (Tren, et al., 2011).

Moreover, initial enthusiasm for their funding may fade over time or be pushed aside by other emerging priorities. And as noted (Section 1.4.2.2.1), the global financial crisis of 2011 led to considerable financial difficulties for the Fund, which has constrained its grant distribution. Moreover, some donors, reportedly fatigued by the high and continuing cost of AIDs 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 …announced plans to shift its focus to mother and child health." The same was said to be true for the British government and the Gates Foundation (McNeil, 2010a), though they may have subsequently relented.

• **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 bed nets, and (3) the over-diagnosis of malaria - which can lead to a wasteful use of expensive ACTs - could be reduced.

While there has been general agreement on the extent of these 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 they 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). 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; Bastiaens et al., 2011). The subject is discussed in greater detail in Section 1.5.2.

Whether such steps would be sufficient to eliminate the need for subsidies is uncertain. The funding problem will be particularly serious for Africa where it will be difficult to increase domestic financing appreciably: one 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). If malaria becomes rarer in African countries, (1) the burden on affected households may remain unchanged, but (2) as the burden at the national level is lessened, perhaps more of the expenses could be shouldered by domestic resources.

• **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 (cellphones) 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; Van Erps, 2010). There are, however, other aspects of access and "pharmaco-vigilance" (safety) 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 even 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.

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 and Wiseman, et al., 2005. Since the AMF operates at the retail level, the nature of marketing margins and price and income elasticity of demand become relevant (some data on the size of margins in Uganda is provided in Annex 5). Preliminary data have been gathered by Bitrán (2008).

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 to rural consumers" (Goodman et al., 2009). The latter turned out to be the case in one recent survey in Nairobi (Esipisu, 2011): subsidized adult doses of ACTs meant to be sold for the equivalent of 50 cents were being priced at two to five times that amount, the difference being additional profit to the retailer.

The determination of subsidy levels under these varied conditions may merit additional study. A recent analysis by Laxminarayan et al. (2010) indicated that large subsidies "are warranted on externality ground across many scenarios…due to large efficiency gains…" "However, at extremely high infection 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."

1.4.2.3. The World Bank Malaria Booster Program

The World Bank initiated a "Booster Program for Malaria Control in Africa" in 2005, including provision of ACTs (World Bank, 2007, 2009). The Program evidently related back to the "Abuja Summit" meeting in 2000 when the Roll Back Malaria Initiative was established and certain indications of financial support made (ESPD 2005). During the next five years, the Bank spent around $50 million on malaria control efforts/programs.

This came to be viewed as quite inadequate, and in 2005 the Bank initiated the Booster Program to "assist African governments in scaling up effective interventions to bring malaria under control on the continent" (World Bank, 2007). This involved a "substantial increase in funding from the International Development Association, the arm of the World Bank that provides interest-free loans and grants to the world's poorest countries." The program was launched in September with a ten-year horizon. A target of $500

million in IDA resources was set for Phase I, from July 2005 to June 2008 for about 20 nations. Phase II was also set for a three-year period, from July 2008 to June 2011.

The Program had five key components and four types of interventions. The former were: (1) participating countries had to reallocate part of their resources in their IDA envelopes, (2) the scale-up of both control mechanisms and the strengthening of health systems, (3) it was to operate through partnerships, (4) flexible cross-border and multi-sector funding was to be involved, and (5) there was to be monitoring on monies spent. Interventions include (1) insecticide-treated bed nets, (2) access to anti-malaria treatment for children, (3) intermittent preventative treatment for pregnant women, and (4) indoor residual spraying.

Initially, it was expected that 15 million doses of ACTs would be distributed by the end of 2007 and 42 million during Phase I (World Bank, 2007). Deliveries to 16 nations were identified, ranging from a high of over 16 million treatments to D.R. Congo, followed by Benin, Burkina Faso, and Nigeria in the 6–8 million range. But difficulties in introducing ACTS, now familiar, were noted. By the end of 2008, the effects of these constraints were quite evident: only $15.2 million, 6.6% of total disbursements, had gone for ACTs (nothing was said about number of treatments), while nearly 88% went for bed nets, 2.2% for RDTs (rapid diagnostic tests), 2.5% for IRS and 0.7% for lab work. The continuing difficulties in introducing ACTs were noted (2009).

As of October 2010, eight African nations had Booster projects and seven of them were "on track" for additional funding, but largely for bed nets. ACTs were not mentioned, but the situation may change with the introduction of the AMFm subsidy program. Total commitments have been $763 million since 2005 (World Bank, 2010b) and 25.3 million doses of "malaria medication" have been financed (World Bank, 2011).

1.4.2.4. Specialized global and African programs

Malaria has long attracted international attention and more recently advocacy groups (Bates and Herrington, 2007). This has taken a variety of forms, but all have either been focused on, or of relevance to, Africa. They and others have been conveniently summarized in a document prepared for the UN Millenium Project (2005). Four will be briefly noted here, two of which

have played key roles to artemisinin and ACTs.

• **World Health Assembly.** This group is the decision-making body of WHO. Malaria has been a topic of intense discussion since 1990, when the group attributed the global resurgence of malaria to increasing resistance to increasing resistance to the drugs then in use, the lack of a clear control strategy, and an acute shortage of financial resources. It recommended that an appropriate strategy be developed and that a coordinated effort be taken to intensify control efforts. This was followed by the Ministerial Conference on Malaria in Amsterdam in 1992 which developed a global control strategy that was endorsed by the U.N. General Assembly in 1993. The four basic technical elements were (1) provision of early diagnosis and prompt treatment, (2) use of selective preventive measures, (3) early detection and containment of epidemics, and (4) strengthening of local capacities in basic and applied research. While well received, "the donor community failed to mobilize the resources necessary for undertaking nationwide control efforts."

• **African declarations and initiatives.** A Summit meeting of the Organization of African Unity in 1997 unanimously passed a Declaration on Malaria Prevention and Control and approved a comprehensive intervention plan involving member states, UN agencies and the World Bank. "This potentially powerful commitment…faltered due to lack of international support." Also in 1997, "key scientific and donor agencies convened in Dakar, Senegal, to discuss collaborative efforts to address collaborative efforts to address pressing health problems in Africa. Malaria was selected as the initial focus of this effort. Subsequently, the Multilateral Initiative on Malaria (MIM) was created with the aim of maximizing the impact of scientific research on malaria in Africa." A major meeting was held in Durban, South Africa in March 1999 (MIM, 1999). As of 2005 it had "culminated in several effective partnerships between scientists from developed countries and their African counterparts" and is still in operation (see www.mimalaria.org/eng/about.asp).

• **Roll Back Malaria Initiative.** This program was "conceived by WHO in 1998 in response to a call by ministers of health in malaria-endemic countries to reduce the malaria burden, with a special focus on Africa. Subsequently, the global RBM partnership was formed under the auspices of the WHO, comprising the United Nations Development Program, the United Nations Children's Fund and the World Bank." "It adopted the malaria control strategies

that were accepted…in the Amsterdam Ministerial Conference of 1992."

• **TDR, a Special Program for Research and Training in Tropical Diseases.** This group was organized in 1975 and is based at WHO and is sponsored by UNICEF, UNDP, the World Bank and WHO. It conducts a program of scientific collaboration to combat a portfolio of major diseases. As noted earlier, it played a key initial role in supporting early western contacts with China about artemisinin through its Scientific Group on the Chemotherapy of Malaria (see TDR, 1987). TDR received the 2011 Gates Award for Global Health.

• **Medicines for Malaria Venture.** This group was established as a non-profit foundation in 1999 in response to discussions between WHO (chiefly TDR), RBM, and the International Federation of Pharmaceutical Manufacturers. It uses the public-private partnership model, with funding from philanthropic organizations to facilitate discovery, development, and the delivery of new, affordable antimalarial medicines. All known drugs under development as of late 2010 have been noted in Section 1.3.4.1.2. Further information is readily found in its annual reports and other publications which are available in electronic form (www.mmv.org).

1.4.3. Donor assistance and research programs

Since WW II, malaria has increasingly attracted the involvement of some national foreign assistance programs. Initial efforts involved support of international malaria eradication efforts (noted in Section I) and were followed by a variety of multilateral and bilateral activities. These have not been well recorded or reported. Some such information is available for the U.S. and may be illustrative.

1.4.3.1. Agencies of the U. S. Government

The first international 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 global eradication efforts built around DDT (Shuler, 1985; Cowper, 1987; NA/IM, 1991; 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, 1985; Spielman and D'Antino, 2001; Packard. 1998), and then generally not for development of new drugs. The Agency was familiar with the Chinese work with qinghaosu (artemisinin) but did not pursue it then (Shuler, 1985).

A vaccine development program was, however, initiated in 1965 (Shuler, 1985) and continues. A review of the program though 1991 is provided in Diggs (1991) and further developments are summarized in USAID annual reports on the President's Malaria Initiative The early program faced tribulations (Marshall, 1990; Diggs, 1991; Hilts, 1994) and criticism (Desowitz, 1991; Spielman and D'Antonio, 2001). A detailed and well-informed overview has recently been provided by Sherman, 2009.

Other government agencies more heavily involved with malaria research include the Centers for Disease Control (CDC), the Department of Defense (WRAIR), and the National Institutes of Health (NIH, specifically the National Institute of Allergy and Infectious Diseases). In 2009, the latter two represented 26.1% of total global malaria research funding (26.4% including USAID). Overall, the U.S. provided 55.7% of total government funding. Two thirds of the NIH funding goes to external researchers, of which three quarters goes to basic research, including discovery and preclinical testing; a much smaller role is played in clinical trials in developing countries (PATH, 2011).

In 1995, the Fogary International Center of the National Institutes of Health, building on some programs underway in Africa including a malaria research Center in Bamako, Mali, sponsored an international meeting to promote biomedical science in Africa. Of the various topics discussed, one stood out: malaria. Harold Varmus, then director of NIH, as noted, proposed that the group focus on it and arranged an international meeting of relevant partners in January 1997 with the idea of proposing a research consortium to be called the "Multilateral Initiative on Malaria" (MIM). But it proved to be easier to propose than fund, both in Europe and within the US government (in the latter case he found to his "astonishment" that "the agency [USAID] had no senior experts on malaria and was unable to contribute intellectually or financially to our efforts"). Still, MIM "survived as a convener of meetings and a provider of small grants" (Butler, 1997; Nantulya et al., 2007; Varmus, 2000; also see www.mimalaria.org/).

1.4.3.2. Expansion of USAID programs

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 developing 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; WHO 2005e). 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., 2000). 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).

In 2002, USAID and the Gates Foundation sponsored the study by the Institute of Medicine of the National Academies (NA, 2004) cited frequently in this paper and in 2005 funded the "Implementation Guide" for ACTs (RPMP, 2005). 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).

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. (see Figure 9). 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.

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 bed nets, intermittent preventative treatment, and indoor residual spraying (Dugger, 2006; Lowenberg, 2007). Considerable emphasis, as with other donors (Anonymous, 2008g), has been given to commodity delivery [see Box 5]. A summary of activites through 2009 is provided in Korde (2009).

Numerical results in terms of ACTs have been as follows. FY 2006: PMI allocated almost $2.4 million for ACTs (not all necessarily C*oartem*) and to

Box 5. USAID emphasis on commodity delivery.

In USAID's case this at least partly reflects the wishes of Congress and other groups. It 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 (pers. conv. 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 and therapeutic research and development" (also noted by Brainard, 2007). 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.

other malaria drugs out of a total budget of $30 million in three countries: Uganda, Tanzania, and Angola. 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). 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). FY 2009: ACT treatments increased to 29.6 million, plus 8.9 million procured by other partners and distributed by PMI to the 15 focus countries. Over 41,000 health workers were trained in the use of ACTs. Also, 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, 2010a; the report also goes on to review PMI operations research activities, vaccine development and drug development, and relations with U.S. government research organizations). FY2010: ACT procurements increased to 22.1 million treatments (est.) (Dickerson, 2010). In FY2011 they nearly doubled to 41.0 million (USAID, 2011).

While these numbers clearly reflect an increase in quantitative terms, they do not reflect an important ongoing change in qualitative terms. As the 2010 AID report puts it: "With increasing use of diagnostic testing for patients with suspected malaria, the ACT coverage indicator (proportion 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." ACT treatments are and will be increasingly selective. This means that simple comparisons of time series data may increasingly understate what has been accomplished.

In carrying out its programs, the Agency is heavily involved in (1) partnerships and (2) interacting with other U.S. government malarial research and other assistance programs. The former includes multilateral and bilateral collaboration with the Global Fund, Roll Back Malaria and WHO. The latter includes U.S, government malaria research activities noted earlier, such as the Center for Disease Control (CDC), the National Institutes of Health (NIH), the Naval Medical Research Center, and the Walter Reed Army Institute of Research (WRAIR). Areas covered include vaccine and, drug development, the latter particularly involving WRAIR. All are noted in the

annual PMI reports to Congress.

Earlier plans for the 2009-2014 period included, 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-standard drugs, distribution, storage and inventory management, and post-marketing surveillance" (USAID, 2010b). 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 (Anonymous, 2008c; Barber, 2008; Kaiser Foundation, 2009a). The actual amount appropriated depends on annual Congressional action. Subsequent 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). In recent years, the PMI has focused mainly on bilateral programs with African nations, while as noted earlier, multilateral funding for the Global Fund was shifted to the State Department in FY 2008.

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, 2010a).

A comprehensive external review of the performance of the Initiative over its first five years was conducted in 2011, with positive results. The ACT

component did not come in for particular comment, though the Technical Recommendations did include two of relevance: (1) "Strengthen resistance monitoring for both insecticides and antimalarial (artemisinin) drugs" and (2) "Expand PMI's operations research component and advocate for and advocate for an expanded global malaria research agenda" (p. x). One of the Policy Recommendations sagely observed that "The history of malaria control has been one of temporary success followed by failure. PMI has helped create a success in this latest attempt at malaria control; figuring out a strategy for sustaining these advances and adapting to biologic, political, and financial challenges is essential for keeping history from repeating itself" (p. 68).

Thus the US effort in malaria control 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 - about 86% over the past decade. "As a result, some have called for increased multilateral engagement given the global nature of the health challenges…" (Kaiser Foundation, 2010b). This appears to have been reflected in the Obama administration budget proposals for 2013 which call for a decrease of 4.8% ($32 million) in USAID funding for malaria, which is largely bilateral, and a striking increase of 27% ($350 million) for the multilateral Global Fund which has spent about 29% of its funding on malaria, 70% of which has gone to Africa (Kaiser Foundation, 2012; Global Fund, 2012). Due to a change in budget category (to non-security) and the dynamics of an election year, the "budget and the priorities it sets out may look far different by the time the budget process concludes" (Veillette, 2012).

1.4.3.3. Other national donor programs

Only limited information has been found on two programs and one primarily concerns intentions. It would be useful to have a clearer picture of overall malaria activities by other countries and national assistance agencies.

• **The United Kingdom** has long supported international malaria control efforts, presently through the Dept. of International Development (DFID). While no major reviews of past programs have yet been identified, background information may be found at: [http://www.dfid.gov.uk/pubs/files/mdg-factsheets/malariafactsheet.pdf] and [www.dfid.gov.uk/Global-Isues/Emerging-

policy/Malaria/].

The current situation is quite different. An All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases (www.appmg-malaria.org.uk) has been active for a number of years (2007a, 2007b , 2010a. 2010b), and evidently not without effect. On September 27, 2010 Deputy Prime Minister Clegg announced that the UK/DFID contribution to malaria control will increase from about £150 million ($237 million) per year to as much as £500 million ($790 million) per year by 2014 (DFID, 2010a), and $800 m. by 2015 (WHO, 2011, vii). This was followed by an extensive public consultation and the preparation and release of two substantial documents in late 2010, one presenting a "Framework for Results" (DFID, 2010a) and the other a vast and quite remarkable "Evidence Review" (DFID, 2010b). Foreign assistance is one of the areas not slated for cuts by the new government and the DFID efforts in malaria bear watching.

• **China** established contact with some African nations, particularly Nigeria, about artemether as early as 1987 with an eye to sales (Jiafing/Zhang, 2005, Chp. VIII/2) but little more is known about more recent years. China provides various forms of assistance, but this is a mixed package. 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 repaid in oil or other resources (Brautigam, 2009; French, 2010). It has also invested in pharmaceutical firms in Nigeria and Tanzania that produce artemisinin. 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 (Jia, 2006a/b, Anonymous, 2009d; Cyranoski, 2010).

1.4.3.4. Relative contributions of major donors.

While the general pattern has been apparent, perhaps the most detailed comparison has been provided by Snow et al. (2010b). Their analysis indicated that 75.6% of the funding for global malaria control by the end of 2009 was provided by the Global Fund (since 2002), 14.2% by the U.S. (12.8% from PMI since 2004 and 1.4% from USAID), 4.9% by the WBBP (since 2006), and 5.3% by others.

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Programs for deploying antimalarial medicines 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 next.

1.5 Policy Issues: *Public, Public/Private, Social and Program*

Clearly Artemisia/artemisinin is currently playing a critical, but not sole, role in the control of malaria caused by P. falciparum. How long it will continue to do so is uncertain. But while it does, it can make an important contribution to public health in Africa and in other developing regions. Moreover, this is a situation where a key role has been 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.

1.5.1. 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 public "bads" their control requires public action and the utilization of public goods. Pure public goods are freely available to all and are not diminished by use. Scientific knowledge has long been considered a classic example (Dalrymple, 2003, 2005). The general relationship between global public goods and health is well accepted (see; Chen et al., 1999; Kaul and Faust, 2001; Arhin-Tenkorang and Conceic ao, 2003; Smith et al., 2003; Fisman and Luaplant, 2009). In the 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).

1.5.1.1. Public needs and public goods: health and malaria.

In 1927, the Second General Report of the Malaria Commission of the League of Nations (Malaria Commission, 1927) made two comments that are remarkably relevant to the current situation. The first, undoubtedly building

on the experience of Italy [see Box 6], 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." 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…could most profitably be spent."

Box 6. Early use of quinine for civil purposes, Italy

Italy passed a series of laws between 1900 and 1907 that attempeted to control malaria through the use of quinine and sanitary legislation. As described by Snowden (2006), "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 with the certaintly 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 a price fixed by Royal decree (Bowden et al., 2008).

Seventy four years later, another commission (Sachs, 2001) similarly concluded that "An effective assault on diseases of the poor will…require substantial investments in global public goods [GPGs], including…research and development into diseases that are concentrated in poor countries." This report, by the Commission on Macroeconomics and Health for WHO, noted that "GPGs are public goods that are underprovided by local and national governments, since the benefits accrue beyond a country's borders." Another study of global health problems concluded that treatment options for malaria were, in relative terms, "highly cost effective" (Laximinarayan et al, 2006). Even so, "the R&D for diseases specific to poor countries – such as

malaria or other tropical parasitic diseases – tends to be grossly underfinanced" (Sachs). Funding for research on malaria, however, 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. The public good 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" (Onwujekwe et al., 2004; also see NA/IM, 2004 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 (Sachs and Malaney, 2002; Shulman and Dorman, 2003; Snow, et al., 2004; NA/IM, 2004; WHO, 2005b).

These effects are *positive externalities* in economic terms. The social value of medical services can be far larger than the private marginal value (Mushkin, 1958). Pigou, in his classic E*conomics of* W*elfare* (1932), 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" (precursors are cited in Medema, 2009; also cited in Coase, 1960 and Backhouse, 1985). Externalities in medicine and health are important but relatively neglected in the literature.

Coast et al. (1998) propose a series of three equations for negative and positive externalities and net benefits in health (see Box 11, p. 170). Smith et al. (2003) and Smith (2004/2005) have provided useful introductions. Stewart and Ghani (1991) offer 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."

The traditional treatments for malaria through the early 1900s were not usually the result of any formal research process and have long been in the public sector; they are clearly public goods. This was, however, only intermittently the case for quinine: "Throughout the history of quinine, the word 'monopoly' keeps recurring at every step" (Duran-Reynals, 1946). 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). In 1857 he wrote that it was the "government'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." This was subsequently done (also see Jarco, 1993; Philip, 1995; and Jardine, 1999). A similar pattern was followed for Chinese tea (Rose, 2010).

In the case of ACTs, however, we are clearly dealing with *impure public goods*, ones that incorporate both public and private dimensions. As scientific knowledge gets entangled in property rights and embodied in commercial products, it becomes more impure (Dalrymple, 2003). This is not uncommon. Musgrove (2004), 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. Impure public goods are reviewed in [i] an *agricultural* context by Dalrymple (2006a); [ii] a *health* context by Musgrove (2004), Sandler and Arce (2002), Smith, et al. (2003), and Sandler (2004), [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. (2008, 2009, 2010).

Such goods are difficult to map in theoretical terms and, as in this case, can be even more complex to design and execute in short order, especially at the international/global level. In some cases, however, private firms or universities holding patents may differentiate their markets and allow their use in the case of developing countries. This has happened in a few cases noted earlier - the two new ACTs developed under the auspices of Drugs for Neglected Diseases (DNDi) and the bacterial synthesis process sponsored by the Gates Foundation in California (Section 1.4.1.3.1.3) - and while not yet common, is receiving more attention. 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). Other universities have similar provisions; see Chokshi (2005) and Brewster et al. (2005).

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).

1.5.1.2. *Allocation of public resources.* There are also complex and long recognized issues associated with the allocation of resources generally (Dalrymple, 2006b) and between and within malaria programs (Barlow, 1967, 1968; Newman, 1967). As one economist stated, "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). Another wrote 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 interventions" (Hanson, 2004). Still, economic analysis can be of some use in defining (i) policies and (ii) relationships among policy instruments (Hammer, 1993; also NA/IM, 1991).

Some of the early allocation decisions were made, as noted in Section 1.1.1., 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" "as much as a problem of public health." 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) and "made it possible to live and work safely on the island" (Logan). Moreover, 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." 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 (Packard, 2007).

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 1.1.1., 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). A recent massive study of disease control priorities in developing countries utilized a cost effectiveness (CE) approach (see Section 1.3.3.2) and

compared several forms of malaria control, including ACTs, with costs for other diseases (Laxminarayan et al, 2006b, 2006d).

Even with this data, it is difficult to determine impact because of the overall interaction between health and wealth (Sen, 1999; Bloom and Canning, 2000; Weil, 2005) and malaria control and improved economic growth (Sachs and Malaney, 2002; Jimoh et al., 2007; Teklehaimanot and Mejia, 2008a; Bowden et al., 2008; Bleakley, 2009; Leys, 2011). One feeds on the other. The presence of a reciprocal effect provides substantial problems in interpreting the results of correlation analyses, such as those cited in Section 1.1.1., 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 terms of the effect of economic development on the ability of individuals and governments to carry out control programs (see Section 1.5.5 and Packard, 2007 for a fuller discussion of the issues).

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). 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). A larger issue is the question of how much should be spent on infectious vs. chronic diseases (see Senok and Botta, 2005).

In the current setting, it should 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. 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, revealing that drug and related costs would have represented 9.5% of the health sector budget and 28.7% of annual expenditures on medical supplies – a six fold increase in the national budget for malaria control. A Global Fund subsidy was not available until December 2006 (Njau, et al., 2007; pers. comm. from Njau, February, 2007). The drug research component thus serves a vital health maintenance function, as noted by Ruttan (1982). 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 2004b, 2008b).

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. A very successful program in South Africa combined an ACT with vector control (Barnes, et al., 2005b). Some more localized efforts, which could have an impact on growth, have been suggested by Spielman and D'Antonio (2001) and Spielman et al. (2002).

1.5.2. Public/private interactions

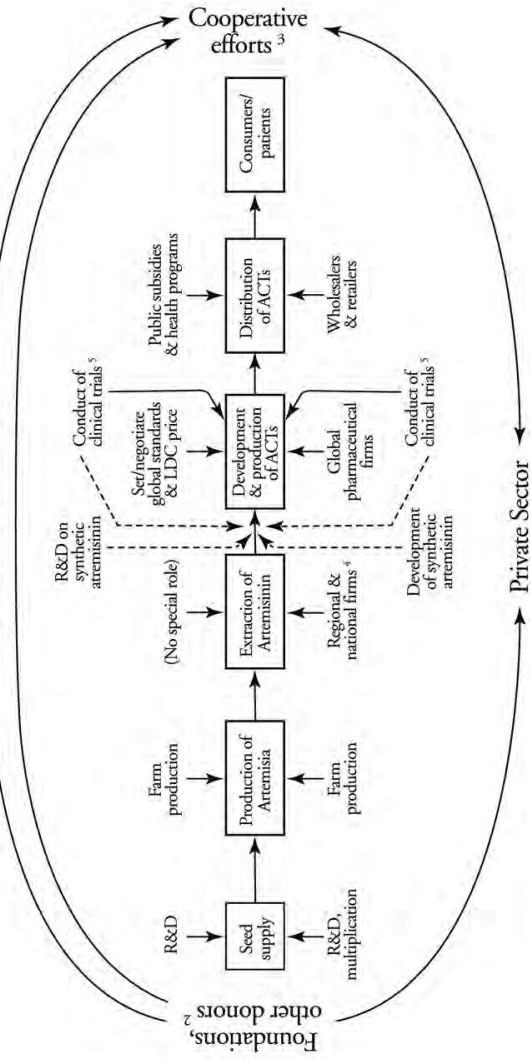
Medicinal plants such as Artemisia are not a common component of agricultural production and processing systems. Nor are linkages to pharmaceutical firms. Medicinal plants differ from agricultural plants such as corn, soybeans, tobacco and rice which might be genetically modified to produce certain drugs, presumably faster and more cheaply – the "pharma" sector in the U.S. (Weiss, 2004; Wisner, 2005; Kaiser, 2008); a recent upstream "pharmer" variant has been noted (Opar, 2011). 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.

1.5.2.1. 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

Figure 10

Generalized Roles of the Public and Private Sectors in the Global Artemisia→Artemisinin→ACT Chain for Developing Nations [1]



[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

Africa; Spector, 2005), other donors, and a series of cooperative efforts. The steps and principal players, from seed to consumer, are depicted in Figure 10. The figure is incomplete in one respect: it does not specifically reflect the preparation of artemisinin derivatives (Section 1.3.2.3). 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). A more general depiction of health innovation systems is provided in Morel et al. (2005). And a related conceptual categorization of the "Typology of Diseases and Incentives and Incentives for R&D" is provided in Section 1.6.3.

1.5.2.1.1. *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 Section 1.3.1.1.2), (2) development of a semi-synthetic artemisinin, and (3) development of a new and quite different set of synthetic drugs (noted in Section 1.4.1.3.1). 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. The 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).

1.5.2.1.2. *Subsidies.* Since the poor in developing nations cannot afford ACTS, subsidies are, as we have seen in Section 1.4.2.2, are necessary. 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/IM (2004) and by Laxminarayan et al. (2005, 2006a/b), Laxminarayan and Gelband (2009), and Laximinarayan, et al. (2010). Effective demand (the ability to purchase) at the government level has been underwritten by the Global Fund. 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.

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 extractors (private firms) in individual countries, 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 that will have a different way of handling payments.

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 in 2005, the whole structure could be threatened (Ahmad, 2005; Anonymous 2005c, Global Fund, 2005). The sustainability of subsidies cannot be taken for granted.

1.5.2.2. Balancing supply and demand

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 that includes a theme on forecasting and quantification of malaria commodities. 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, 2010; also see figure for Novartis in CNAP, 2008). It states that most of the risks fall to suppliers and that there is significant scope for better risk sharing.

1.5.2.2.1. *Artemisia and Artemisinin.* The market situation for these commodities, as suggested earlier (Section 1.4.1.1) has largely been on one of imbalance over the past decade, with short supplies of artemisinin in 2004 (Cyranoski, 2004), prices rising sharply through 2005, declining through 2007, followed by a gradual rise through 2011 (Pilloy, 2010; WHO, 2010f; also pers. comm. from Malcolm Cutler, May 2011).

Beginning in 2007 and 2008, the supply of artemisinin was well in excess of market Demand and was aillustrative of what was to follow. 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). This in turn affected 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. In Uganda in early 2008, farmers were "already feeling the pinch" and "growers are complaining that their produce is rotting away in their stores." Once burned, they may be less likely to resume production of Artemisia.
- **Extractors** of artemisinin and manufacturers of ACTs faced reduced incomes or losses. Since the cost of artemisinin extract reportedly represents 50-70% of the cost of the finished product (Dugue, 2007a; 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 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. One Ugandan firm stated that "We are now a botanical extraction plant (Muhwezi-Bonge, 2008).

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 were 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 were in the $380-$420 range and continued to rise through May 2011. In part, this represented diminished supplies of Artemisia, notably in China and Vietnam where the rise in price for food crops, including rice, made them more profitable than Artemisia (Cutler, 2008; pers. comm., July 2010).

Still, the area under cultivation in China expanded from an estimated 2.000 ha in 2009 to 6,000 in 2010 and 9,000 in 20ll, resulting in production of 132~140 metric tons of artemisin in the latter year (Lin 2011). One unusual feature is the degree to which wild production - as high as 40% in the past - is utilized in the derivation of artemisinin for commercial use. By 2011 this proportion had increased to 67-68% (Lin, 2011). The low level of wild artemisinin makes it less profitable to extract (pers. comms. from Malcolm Butler, Nov. 2008 and May 2011; also see CHAI, 2008). Average yields of cultivated Artemisinin were: 2009, 3.5-4.0 kg.; 2010, 4.0-4.5kg.; and 2011, 3.3-3.5kg. (Lin, 2011).

These variations have been reflected in dramatic form in the global production of artemisinin. One set of estimates, noted earlier (Section 1.4.1.1), 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, 2007-2010; RBM, 2009); and 2010, perhaps 100-110, a shortfall of up to 20 tons (Cutler, pers. comm., 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). 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 traceable in the case of quality

issues. Category 4 was also problematic because of lack of data (CHAI, 2009).

As of November 2009, the situation in China was one of tight supply and increasing prices. Production of Artemisia was far below normal levels in part due to drought (Wang 2010), and low artemisinin extraction levels (about 5%). Wild varieties represented 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, process for Artemisia and artemisinin were increasing rapidly. The need for long-term (12 month) contracts with manufacturers was viewed as very important (these were to be facilitated by the new A2S2 program; see Sect. 1.5.2.2.5). Still, the situation was little better in 2010 when, as noted earlier, less than 2,000 ha. were planted, the weather was bad, and Artemisia continued to face competition with other crops (Li, 2010; Jin, 2010).

1.5.2.2.2. *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 C*oartem* exceeded demand. 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) reported that "The company has long complained that orders for Coartem - currently placed country-by-country - are well below estimates of demand." Further details are provided in Bosman and Mendis (2007).

Part of the problem 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 proposal preparation.

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). 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. Earlier figures are reported in Anonymous, 2005c; Novartis, 2006; Novartis, 2007; and Novartis, 2008a. 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). 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). The latter reductions were attributed to increases in production efficiency in its plants in China and the U.S. (Novartis, 2008a; Wagwau, 2008). The market was viewed 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). 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) and WHO (2009a).

1.5.2.2.3. *Procurement and use of* ACTs. The number of doses of ACTs procured globally is 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). Later data (WHO (2010f, 2010g) differ slightly: ACT courses were placed at 11.2 million in 2005, 76 m. in 2006, and 158 in 2009. Of five ACTs procured by the public sector in 2009, 67% was AL; it was followed by AS+AQ with 23.2 million courses, a sharp increase from 1 million in 2006 (WHO, 2010g). Sales of prequalified ACTs were projected to drop from 2010 to 2011 in the public sector, rise in the private sector due to AMFm (den Beston, 2010), and increase substantially overall (WHO, 2011, xi, 45).

Other earlier sources placed procurements of all ACTs in 2006 at 100 million doses (Enserink, 2007; UNICEF/RBM, 2007). UNICEF's own ACT expenditures, largely funded by the Global Fund and UNITAID, grew from about $4 m. in 2004 and 2005 to $11 m. in 2006, $15 m. in 2007, about $33 m. in 2008, $36 m. in 2009 and over $42 m. in 2010. In 2009, 71.7% was for A+L and 17.6% for AS+AQ (Blasco, 2010).

Global Fund purchases of ACTs (millions of courses) were recently reported in terms of fairly wide ranges as follows: (1) actual deleiveries: 2009, 80-80 million; 2010, 85-105, and (2) estimated deliveries: 2011, 90-105; and 2012-2013, 100+ (Logez, 2011). In 2010 and 2011 (ytd), out of a total product value of $66.9 million, 73% was for A+L, 21% for AS+AQ, and 6% for others (primarily AS+AQ) (Ibid).

There has been an extremely wide variation in use of anti-malarial drug

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 (UNICEF/RBM, 2007). Within this category, between 2006 and 2008 most of the AL was procured for small children (<15 kg) but in 2009 an increasing proportion was for larger children (>35 kg).

1.5.2.2.4. *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, with varying results.

• **The Clinton Foundation** (CHAI) was the first to report their findings (Singh, 2008). 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. The supply projections were 60 metric tons for 2009, which with stocks from storage, was thought to be sufficient, and 90 to 105 metric tons in 2010. In 2011 there was an estimated gap of 25 metric tons because of the shortfall in production, but this depends on stocks and final yields. A change in the sector distribution and formulations is anticipated in 2011 with the implementation of AMFm. The public sector proportion will decline from over 91% and the private proportion will increase correspondingly. AS+AQ declined from 2008 to 2009 and again in 2010 (est.), and then are expected to increase, and that DHA+PQ will increase in 2011 and 2012 (CHAI, 2010).

• **Pilloy/ARTPAL** (Pilloy, 2010) first considered the production of Artemisia which was below expectations 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 noted the important role of inventories of artemisinin, for which public data are scarce. According to his sources they averaged a little below 140 tons from 2006 to 2008 and then dropped to a little less than 120 tons in 2009. They were expected to decline further in 2010 when demand may reach nearly 120 tons and production declines to 50-100

tons. Thus, a sharp increase in plantings was needed in 2010 to cover the needs for artemisinin in 2011.

• **The Boston Consulting Group**, in a study done for the Gates Foundation (BCG, 2009), also considered both short-term needs and longer-term prospects. They also indicated that without some market intervention there would likely be a shortage 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 experience, higher prices for alternative crops, and other problems (BCG, 2009; also see BCG 2010).

Supply and demand estimates for artemisinin and ACTs suggested that there was much uncertainty whether the supply of artemisinin would 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). The situation remained uncertain as of May 2011 (pers. comm. from Malcolm Cutler). By 2015 the gap could begin to narrow as demand declines due to the effect of other prevention and control efforts now underway. There were, however, many variables on the supply and demand side, and much depended on the level and pace of AMFm funding (see Grewal, 2009). In October 2010 it was decided to introduce a new UNITAID-sponsored ACT Forecasting Consortium managed by BCG and including CHAI and MIT-Zaragoza (Ellman & Cutler, 2010; BCG, 2010; WHO, 2011, 45).

The Consortium report in November 2011 (Lamiaux, 2011) projected an increase in global demand for ACTs from about 217 milllion treatments in 2010 to 287 in 2011 (+32%) and 295 in 2012 (+3%). The driving force was/is the surge in AMFm-subsidized treatments in the private sector; the other two sectors (public and premium private) would remain relatively unchanged. The 2011 increase could have stretched the supply of ACTs, possibly cutting into reserve stocks (Pilloy, 2011, 6; Yadav, 2011, 3).

Prospects for 2013 are, as of February 2012, very uncertain, in part for the usual reasons discussed above, as well as the recent uncertainties relating to the completion of the trial period for AMF and the effects of the global economic situation on financing of the Global Fund (RSMWG, 2012).

1.5.2.2.5. *Actions to achieve a better balance.* Several organizational and informational steps of varied nature have been taken toward this important end.

• **Industry-wide global artemisinin conferences.** These began in 2005 and have been held yearly in key production areas. The most recent was in November 2011 in Hanoi, Viet Nam and was sponsored by RBM, UNITAID & WHO (RBM/UNITAID/WHO, 2011). They have focused on a range of industry-wide issues from the supply of Artemisia to the market for ACTs and have led to further interaction between various components, some noted below. Previous meetings were held in Antananarivo, Madagascar (2010), Mumbai, India (2009), Guilin, China (2008), Bangkok, 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 may be obtained from [www.mmv.org/newsroom/events/past-events/past-artemisinin-events].

• **RBM Procurement and Supply Management** Working Group (PSMWG). This group has been studying supply and demand issues. They were given considerable attention at the Artemisinin Conference in Guilin, China in November 2008 (RBM 2008b). Several options were considered and further reviewed in a meeting in Geneva in December 2008 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" (FSC/I+L/Artepal, 2009). 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…" (Ibid., 2009).

• **Assured Artemisinin Supply System (A2S2).** Events moved quickly and this 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 (den Besten, 2009; i+solutions/Tridos, 2009; Boseman, 2010b). In addition, A2S2 provides market intelligence through a newsletter and participation in the annual artemisinin conferences (A2S2, 2011a/b; i+solutions/Tridos, 2009; Boseman, 2010). As of late 2011, loan support had been provided to four extractors representing 36 0tons of artemisin, close to its target of 40 tons for the first phase (van Duijin, 2011).

• **Clinton Foundation.** On another front, the Clinton Foundation announced in July 2008 that it had worked out an agreement with several Chinese and Indian firms that would help stabilize ACT prices. It involved 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 were free to buy elsewhere if they could do so for less than $126 per pound. The Foundation hoped to sign up more suppliers. In 2010 the price negotiating function was shifted to the AEDES/OTECI consortium (Ellman & Cutler, 2010).

• **ACTwatch.** As a further step, this group emerged from a competitive tender issued by the Gates Foundation in 2007. Its focus is on "Evidence for Malaria Medicines Policy" and it gathers 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. The group focuses 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 & Financing Program), and Population Services International. Further information and country data are provided on the group's web page [www.actwatch.info/home/home.asp] and a recent overview of country findings is found in ACTwatch (2010) and O'Connell, et al. (2011). The program is planned to run for five years.

1.5.2.2.6. *The longer run.* There is the strong prospect, alluded to earlier (Sect. 1.3.4.1), of other lower cost forms of artemisinin that may not be dependent on the considerable vagaries of agricultural production. 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). Some of the same factors stimulated the development of synthetic rubber in the United States during WWII (Finlay, 2009).

To the extent that these lower cost forms 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. Artemisia, as noted earlier, was first recommended for *hemorrhoids* in 168 B.C. (Klayman, 1985). It has recently shown promise for cancer (Sect. 1.6.2.1), *bilharzia* (Hepeng, 2005), *leishmaniasis* (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 also shown promise for the treatment of severe *sepsis* in one trial in Kenya (Moore et al., 2009). (By comparison about 60% of quinine production is used as the bitter ingredient in soft drinks; Dagani, 2005.)

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.

1.5.2.3. 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, 2005a; Malenga et al., 2005; Mutabingwa, 2005; Panosian, 2005; Kimani, 2006; Amin et al., 2007; Kouyaté et al., 2007).

A well known underlying issue is over diagnosis 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, including HIV-AIDS in areas of high transmission (Greenwood, et al., 2005). Early practice was to presume that malaria was the cause and treat with inexpensive drugs such as chloroquine. This practice continues for children under five in Africa, but has been questioned and become a source of debate (see English et al., 2009). 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 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). (Also see Section 1.6.2.2.)

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 (0-4yr.) 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 called for expanded microscopy and/or rapid and effective diagnostic tests (RDTs), and individuals trained in their use (Perkins et al., 2008; Whitty et al., 2008; Msellem et al., 2009; Drakeley and Reyburn, 2009; Scavetta, 2010). Such an RDT 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 (sensitive) under high temperature and humidity (Murray, 2010). WHO has recommended "diagnostic testing in all cases of suspected malaria" including children under 5 (WHO, 2010b; WHO, 2010f, 2010g).

Their use has been shown to reduce the number of prescriptions and since the tests are cheaper than ACTs, the cost is likely to be lower than the cost of treating all suspected cases (Kyabayinze et al., 2010; D'Acremont et al., 2011). Still, scale-up of diagnostic testing might need financing mechanisms similar to those being used to subsidize the costs of ACTs and the economics are more complicated than they may first appear (Anonymous, 2010a; Yukich et al., 2010; Gresser, 2011). There are also concerns about their accuracy in high-transmission areas (Graz et al., 2011) and that in cases where patients tested negative for malaria may lead to a widespread and unneeded/unjustified increase in the use of antibiotics (Axt, 2011). At yet, there does not sem to be a clear-cut answer to the question of "How do we best diagnose malaria in Africa?" (Rosenthal, 2012).

1.5.3. Social/individual interactions

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

1.5.3.1. Development of drug resistance

While some individuals have naturally acquired immunity to P. *falciparum* (Hviid, 2005; Langhorne, et al., 2008), our concern here is the speed and degree to which resistance builds up more generally to artemisinin and ACTs. The issue, which does not occur with barriers to transmission, is discussed in terms of antimicrobial resistance by Coast, Smith, and Millar, 1998; Smith and Coast, 2003; and Smith, et al., 2005. There were, as noted earlier (Sect.1.3.3.3), signs that this was happening in several areas (French Guinea and Senegal) where there had been "uncontrolled use" of artemisinins (Jambou et al., 2005). This was defined as "monotherapy or in conjunction with ineffective partner drugs" (Duffy and Sibley, 2005). Jambou et al. (2005) 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."

Even the prospect of *triple combinations*, discussed earlier (Section 1.3.2.5), is of mixed 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 appearance of resistance to the individual components." Such prognoses have implications for subsidy programs. 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." This theme was later 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, et al., 2008).

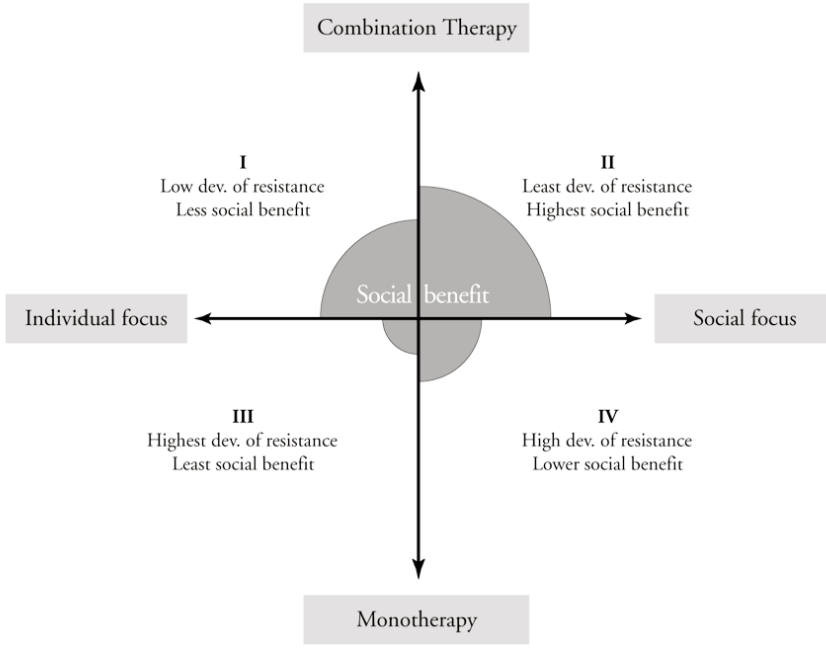
The key ingredients in the development of resistance might be viewed as (i) the relative degree of use of monotherapies and combination therapies, (ii) the likely pace of development of resistance to each, (iii) time, and (iv) individual and social benefits. The latter are important because what is true 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 development of resistance, the lower the degree of social benefits.
- The same, however, may not be true in terms of *individual* benefits: while combination therapies are better for the individual, some - especially those who do not have access to, or cannot afford, combination therapies - may benefit from monotherapies in the short run. 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

Figure 11

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.

in terms of a quadrant model as in Figure 11, or algebraically as done by Coast et al. in Box 11 (p. 170). 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, although this may not be so evident at the margin, and need to be considered in an appropriate blend of public policies.

1.5.3.2. Policy conundrums

The development of biological resistance to artemisinin-based drugs may lead into several important but sensitive policy issues, as illustrated by the following examples. (i) When the point is reached when the demand for Artemisia for pharmaceutical use in ACTs diminishes, continuing excess

Box 7. Early Use of quinine for military and colonial purposes.

Carlson (1977) indicates that Thomas Syndenham had used quinine for 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 prophylaxix had obtained excellent results" for crews of ships in West Africa (Carlson, 1977). Curtin (1998), who focused on military siturations, 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." An Indian example is cited by Fraser (1935), a tea planter in Assam from 1984-1907. 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" In 1903 on home leave, he visited Ronald Ross in Liverpool and was advised to "take ten grams of hydrochloride twice a week, so long as I was in region of intense malaria. And…I never suffered from malaria again." Also see Hedrick (1981) and Webb (2009a, "Bitter Medicines").

supplies could find their way to a more informal market for use in monotherapies and thus accelerate the development of resistance. (ii) Encouraging individual farm production that is not part of a larger program to provide artemisinin for the production of ACTs could facilitate a similar outcome. (iii) Encouraging local manufacture of artemisinin and ACTs in nations with weak regulatory programs may lead to continued use of monotherapies or lower quality ACTs than registered imported drugs (e.g. Sabartova et al., 2010). (iv) Promoting the use of low dosage Artemisinin teas, which are essentially monotherapies in nature or below recommended levels (as noted in Section 1.1.4.1.) when ACTs are available, can also increase resistance. Some of these challenges are the same as faced in the case of HIV/AIDS, TB and some other infectious diseases where cheaper but less effective treatments are available along with combination therapies (pers. comm. from Jack Killen, NIH, Sept. 2008). There may well be a need for more policy analysis centered about the consequences of present activities and/or inaction on resistance.

1.5.3.3. Prevention and cure?

This is one of the oldest issues in malaria policy (e.g. Litsios 2006). Quinine and Artemisia/artemisinin, blended with some liquid - famously, tonic 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 [see Box 7]. Following the isolation of quinine in 1817, the ranks of those conducting trials to deterimine is efficacy and safety included the medical office of the the Madras Presidency. William Geddes was perhaps the most notable and in 1846 wrote that it heralds "a new era" in the medical practices of this and other tropical climates (Harrison, 2010, 197).

Amazingly, quinine continues in use. It is utilized both as an oral drug and as an injection for severe (cerebral) forms of malaria (NA/IM, 2004; Kyu and Fernandez, 2009) – though recently artesunate was shown to be more effective for children (Dondorp et al., 2010). 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). It must, however, be taken three times daily for seven days and has other disadvantages such as a bitter taste and side effects.

Three other approaches to prevention, outlined earlier (Figure 1), can reduce the need for ACTs and lessen the development of resistance.

- **Improved diagnosis.** Its importance has been noted (Section 1.5.2.3).
- **Intermittent preventative treatment (IPT)**. Use of a lower cost drug therapy (such as sulfadoxine-pyrimethamine, SP) as an IPT 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; Gosling et al., 2009; Aponte et al., 2009; Vinetz, 2010; Schellenberg et al., 2010; WHO, 2010f). While SP has been used, in this case as a preventative with promising results and may also lead to other beneficial effects (ter Kuile et al., 2007). By the end of 2009, 33 of 43 endemic countries in Africa had adopted IPT as national policy (WHO, 2011g).
- **Insecticide treated bednets** (ITNs and long-lasting forms, LLINs). These are used during pregnancy and for children (Menendez et al., 2007; WHO, 2007c; UNICEF/RBM, 2007; Brentlinger et al., 2007; Noor et al., 2009). LLINs are an attractive preventative: they are effective (WHO, 2007c), relatively low cost, easily disseminated in a variety of ways (Webster et al., 2007), and generally last at least three years (WHO, 2007c). But they can be (i) uncomfortable and current designs not well suited for young children (Odora, 2007; Kaplan, 2008), (ii) used for other purposes (Minakawa et al., 2008), (iii) mosquitoes may develop resistance to the insecticide used, generally pyrethroids (Kulkarni et al., 2007), and (iv) getting them distributed to the right people can be a substantial challenge (Jack, 2010b; Butler, 2011). 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). They have been the principal focus of some major programs (see Perry, 2011).

These and other preventative measures, such as indoor residual spraying (IRS) and environmental control (WHO, 2007; 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 study (WHO 2010d). However, as Hay et al. (2008) state, the question of how to how to optimize their combination is "largely unknown." 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).

Application of both *preventive* and *curative* tools, 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 be greatest in areas of high transmission, "and require aggressive control with suites of additional and complementary interventions" (Hay et al., 2009).

There are also two intermediate cases where *curative* actions may have *preventative* effects. The first arises from "the effects of malaria during pregnancy on nutrition and hematological influence" (Snow and Omumbo, 2006). 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. The second 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 (Ogutu et al., 2010). 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. Pilot studies would clearly be needed to determine the feasibility and cost-effectiveness of this approach, which might well find a place in comprehensive elimination programs.

Finally, a new class of experimental drugs (imidazole-piperaquines) attack the prasites that cause malaria much earlier and may be useful in both treating malaria and protecting against it (Meister, et al., 2011) .

Clearly the question of how best to balance the allocation of resources between prevention and cure of malaria, which has long been with us, is growing in importance and is not getting any easier to resolve, except, perhaps, for the availability of quantitative tools. It is also not exclusive to malaria: HIV/AIDs presents a somewhat similar, but more extreme, variant (see: Over, 2008, 2010; Bogaarts and Over, 2010a&b; Anonymous, 2010e;

Timberg and Halpern, 2012). Greater involvement of economists and other analysts may be called for.

1.5.4. Program implementation

Although A*rtemisia 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) wrote in N*ature* 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. As Jack (2010a) has stated: "the big challenges ahead are threefold: deepening, broadening, and sustaining the response."

1.5.4.1. 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).

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): "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 subsequently 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). In reviewing the experience of Zambia from 2001 to 2006, another study stated "the choice of drug is only one component

of a successful program strategy" (Steketee et al., 2008). 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; 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, not a simple task [see Box 8].

Further, there is a continuing need to develop new and improved control

Box 8. Illustrative allocation of resources for malaria control in Africa.

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. com. 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 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 et al., 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).

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 such research, it does not appear to be a prominent part of many bilateral or multilateral assistance programs. As Greenwood, et al. (2008) stated: "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; Grabowsky, 2008; Ekland and Fidock, 2008). 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, Watkins and White, 2008). WWARN was launched in December 2008 (Enserink, 2008b) and received a £12.5 million grant from the Gates Foundation in June 2009 (Hindi, 2009). (For details, see [http://www.wwarn.org/home])

These and other steps have been pulled together in a *Global Plan for Artemisinin Resistance Containment* (WHO, 2011) developed in consultation with over 100 malaria specialists (and drawing on WHO, 2010e). Along with more general steps it recommends a combination of increased monitoring and surveillance and investing more in several types of research, including (1) laboratory research to improve the understanding of resistance including molecular markers, (2) research and development including non-artemisinin-based combinations, (3) applied and field research including transmission reduction tools, and (5) mathematical modeling. Also, countries would be divided into three tiers, one being P. *falciparum* and endemic areas, notably Africa, where scaling-up of control measures would be emphasized. In all, a logical and appropriate package of steps.

More generally, 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; also see Hammer, 1993). 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).

Beyond these steps, there is a need to consider *disease interactions* (section 1.5.1.2). 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. Hence a more holistic disease perspective may be called for at the regional and national level.

But even these actions could reflect, as Packard has put it, a focus on malaria as simply "a disease of malaria and mosquitoes," a vector borne disease (2007). 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. "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."

Curiously, less attention may be given to these matters now than in the past. In 2003, for instance, TDR/WHO issued a USAID-funded review of T*he behavioural and social aspects of malaria and its control*; A*n introduction and annotated bibliography* (see Heggenhougen et al., 2003). Yet no references have been seen to it and it was only noted while 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. Efforts to control malaria, in Packard's words (2007) "seldom mirrored these broader views" but rather "relied increasingly on narrow biomedical solutions."

1.5.4.2. Proposals for elimination and eradication

Views differ on the prospects for achieving either. On one hand, Litsios (1996) has stated that "It would be foolhardy of anyone to predict when and how malaria will be conquered." Yet the prospect of control of malaria, at least in

certain areas for a while, has led to greater attention to elimination and eradication. E*limination* 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." Hence, in short, elimination may be transient and eradication virtually permanent (Roberts and Enserink, 2007). Previous experiences with the troubled attempts to eradicate malaria were noted in Sections 1.1.2.1 and 1.5.1.2. (the program in Sardinia is reviewed in Tognotti, 2008). The "global" effort did, however, provide some lessons that proved helpful for the smallpox eradication program which closely followed [see Box 9].

Box 9. Some lessons from the WHO Global Malaria Control Program.

According to Henderson it (1) set precedents in WHO in establishing a global program that 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). Dr. Henderson was leader of WHO's program for smallpox eradication from 1967-1977 and later a principal author of a detailed account of it (Fenner, Henderson et al. 1988 [1,460 pp.]), including Africa (Chps. 17-22) and "Lessons and Benefits" (Chp. 31). The latter noted: "For all countries the economic benefits on the programme were substantial as it became possible to stop all preventative measures and to close treatment facilities." Henderson subsequently included some comments on the malaria program in a more personal retrospective on the smallpox eradication program, which again concludes with a useful chapter on "Lessons and Legacies" (2009).

Hay et al. (2009), noting that "efficient allocation of resources to intervene against malaria rick requires a detailed understanding of the contemporary spatial distribution of malaria risk," concluded that there are "significant opportunities for malaria *control* in Africa and for malaria *elimination* elsewhere" (italics added). In recent years the most significant effects of 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, and Zanzibar). "These countries have used prevention and cure in rapid sequence or in combination…" (WHO, 2008). The situation is much less certain 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). 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. While there

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

1.5.4.2.1. *Elimination.* Proposals for elimination 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 stated that "unless Africa can end both its poverty and its civic strife, 'eradication is just a pipe dream'" (McNeil, 2008b). For other views, see Lines, et al., 2008; Tanner and de Savigny, 2008; and Okie, 2008.

The WHO Global Malaria Program states that elimination requires "the complete interruption of mosquito-borne malaria transmission in a defined geographical area." This involves four phases: (1) control, (2) pre-elimination, (3) elimination, and (4) the prevention of re-introduction (WHO, 2008). Implications for research were reviewed by Greenwood (2008).

A Global Malaria Action Plan (GMAP) was announced in late September 2008 (RBM 2008a), including ACTs, 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). It was projected that 228 million treatments of ACTs would be needed by 2010. An initial strategy towards

eradication was suggested by Feachem and Sabot (2008). A Malaria Elimination Working Group (MEG) composed of donors and scientists was to develop a research and development plan for eradication (Roberts, 2008; 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., 2009a) and contains a number of references to artemisinin and ACTs (also see Feachem et al., 2010). A companion report is subtitled *A Guide on Malaria Elimination for Policy Makers* (Feachem et al., 2009b). 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).

A coordinated series of studies were initiated and published in *The Lancet* (Oct. 29, 2010; see Das and Horton, 2010 and Feachem, et al., 2010). Two were of special relevance here. One examined the "Ranking of elimination feasibility between malaria-epidemic countries" and found that, perhaps not surprisingly, they are lowest in central and West Africa (Tatem et al., 2010). Another examined the "Costs and financial feasibility of malaria elimination" in Swaziland, Tanzania (Zanzibar), Mauritis and two provinces in China (Sabot et al., 2010). It focused on the relative actual or estimated costs of maintaining control and achieving and sustaining elimination over 25 to 50 years and concluded that "elimination [is] unlikely to be warranted on its financial returns alone" but that "elimination might still be a worthy investment it total benefits are sufficient to outweigh marginal costs." A key factor is "the need to continue interventions to prevent reintroduction of malaria and thus were outweighed in most countries by the initial spending increases needed to achieve elimination." It also stated that "The poorest and most vulnerable members of society are typically the last to benefit from public services as malaria control and will thus be the primary beneficiaries of an elimination campaign."

Subsequently, the editor of *The Lancet*, Richard Horton (2011), in a review of Shore (2010) put the issue more sharply: "eliminating malaria is least feasible (most observers would say impossible) in sub-Saharan Africa." "If limited financial resources for malaria are switched away from control in Africa to elimination elsewhere, the regions here the most deaths occur – will be cruelly harmed." "Elimination is not the answer where malaria exerts its

most lethal effects…it is Africa that deserves our special attention."

Further insights have recently been provided in (1) a trial in Zanzibar of "A framework for assessing the feasibility of malaria elimination" (Moonen et al, 2010) and (2) an innovative quantitative modeling assessment of the prospects for controlling P. *falciparum* in Africa (Griffin et al., 2010). The latter, couched in terms of cutting parasite prevalence to 1%, a pre-eradication level, casts useful light on the nature of the task in six nations with varying transmission levels. The four stages of treatment were: (1) ACTs and long-lasting insecticide treated bed nets (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. Others have also reviewed the many challenges faced (e.g., Voelker, 2010; Kelland and Hirschler, 2010).

1.5.4.2.2. E*radication*. Robert Koch, the German bacteriologist, was an early proponent of eradication through the use of quinine prophylaxis, "a method he believed 'could make every malarial place free or almost free of malaria' within nine months" and "outlined a four point plan" for doing so in 1901 (Honingsbaum, 2001; also see Webb, 2009).

A recent multi-year international effort to develop a Malaria Eradication Research Agenda (malERA) focused on identifying knowledge gaps and tools needed for eradication. Its report was published in early 2011 and covered 12 topics, one of which concerned drugs (Alonso, et al., 2011). That revived an earlier notion of thinking about their "impact on infection and transmission." ACTs, while not emphasized, are mentioned at several points in the report on drugs: under "Current Drug Indications" and "Key Knowledge Gaps and Research Priorities." The latter includes a entry on "Tests that can detect resistance to artemisinins and ACT partner drugs" (malERA: Drugs, 2011).

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) and Webb (2009). 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.

1.5.4.2.3. *Maintaining financial support.* In any case, "keeping up the [donor] commitment will be difficult" (Roberts and Enserink, 2007), in part because of the immense cost. In 2007 it was estimated, for instance, that the cost of comprehensive malaria control in Africa would be about $3 billion or around $4.00 per African at risk (Tekleklhaimanot, et al., 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. In supporting AIDs treatments since 2003, for instance, the U.S. has assumed what economists have termed a "treatment mortage" – obligations that can't be ended without catastrophic consequences (Gerson, 2011). Uncertainty can also influence actions by health workers: one of several reasons that ACTs were not prescribed by some in a study in Kenya was "concern whether the government would sustain the supply of artemether-lumefantrine" (Wasunna et al., 2008).

Donor fatigue, changing priorities - some for good reason, some for political reasons, and some of a more quixotic nature - are a general characteristic of foreign assistance programs.

A current example is provided in the case of meningitis: an effective and low cost vaccine has been developed that could eliminate it in a belt across central Africa at a cost of about $570 million. But as of 2010 only $95 million had been raised and the global financial crisis "has pinched foreign aid spending, leaving the remainder in doubt" (Dugger, 2010; also see Antony, 2010 and Jack, 2010d).

As for the Gates Foundation, there were indications (Doughton, 2010) 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."

1.5.5. 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 (Section 1.1.1) commonly viewed as largely a disease of poverty and rural areas (e.g. Carter and Mendis, 2002; Hopkin, 2008; Grabowsky, 2008). This would suggest, among other things, that efforts to help reduce poverty, particularly in rural Africa, might well play a role.

There is some precedent for this view. 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; also see Russell, 1955). In 1928, 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."

Similarly, 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, reported that "economic improvement [of the peasantry] is the matter to which attention should first be given" (1929a). 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" (1929b). In short, as viewed by Malowany (2000), "improvements in health conditions would indirectly reduce malaria incidence."

Subsequently, Packard suggested that long-term sustainability requires higher levels of economic development and economic status of the population (2007). "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?" [see Box 10].

Two economic historians (McGuire and Coelho, 2011) after assessing the relationship between diseases and long-run economic growth posited a virtuous economic growth cycle offset by a vicious biological cycle" (37) that led to "the spread of diseases and lowered income." "These pathogenic infections had significant effects on history, economic development and the well-being of humanity" (38).

The relationship between economic growth and malaria control is, as noted earlier (Section 1.5.1.2), 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 stated: "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). A study of the effect of nutrition on malaria and vice versa 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 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 focus on the overall role of health in economic growth (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 (Ijumba and Lindsay, 2001; Klinkenberg, et al., 2003). 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 forth in graphic form by Weil (2005). Other factors such as gobal climate changes, may counteract the positive effect of socio-economic development (Béguin, et al., 2011).

Box 10. Social and economic effects of malaria in the early United States.

The importance of considering the tangible effects of malaria control on older children and adults has 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). Among other things, it led to malnutrition, immune disorders, and economic costs. L. O. Howard, a USDA entomologist and mosquito expert (Sutter, 2007; Patterson, 2009), 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). 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." 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."

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…." (also see Fogel and Grotte, 2011a). 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; 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 (Couteur and Burreson, 2003; NA/IM, 2004; Webb, 2009a) or (2) was built up due to previous exposure to malaria. Also, it could have been difficult to distinguish between yellow fever and malaria.

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.

1.5.6. Strengthening the overall malaria policy-setting process

Given the large array and complexity of programs to control, let alone eliminate, malaria, there has been a corresponding need to develop a more comprehensive, evidence-based and analytical approach to policy setting. In January 2012, the Global Malaria Program of the World Health Organization, noting the need for a "stronger and more agile policy-settting process to keep pace with the evidence being generated," announced the establishment of a Malaria Policy Advisory Committee (D'Souza, B.J., Newman, R.D., 2012). The group is composed of 15 world-renouned malaria experts and will meet twice a year, with the first meeting scheduled late in the month. All the initial members are medical doctors or biological scientists. Policy recommendations, with supporting evidence, will be published within two months of each meeting as part of of a Malaria Journal series. This is an important and welcome broader development which bears close attention.

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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, the same cannot 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. The humanities have, however, 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. 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 has been initially explored elsewhere (Dalrymple, 2008a, 2008b, fn. 51).

1.6 Externalities: *Malaria, Medicines and Macroeconomics*

The use of artemisinin in drug control of malaria is, as the previous chapter has suggested, clearly carried out in a much larger and multi-dimensional social, political and economic setting. The focus of this paper has largely been, to this point, disease- and drug-centric. Here we move to several more general medical and economic areas and issues that also might well be considered in policy analysis and setting.

1.6.1. Malaria mortality, disease control and externalities

Many factors contribute to malaria mortality, ranging from the well-known (e.g. under-nutrition: Caufield, et al., 2004; Zeba, et al., 2008) to the more exotic. As Prof. Peter Newman, a noted econometrician, stated: "it is a "well established fact that malaria tends to reduce greatly the general health and resistance to disease of any affected population. Therefore deaths from many causes may be affected and not those just from malaria alone" (Newman, 1977). Similarly, Dr. D.A. Henderson of smallpox renown (2009) observed that: "The cause for a death for a disease seldom results from a single causal factor, particularly…in third world countries." "The long-term effects of one disease…may play out in more serious manifestations of another disease occurring months later" (pers. comms. March, Nov., 2010).

1.6.1.1. Epidemiology, interventions and externalities

In the view of Nájera (2001), "perhaps the most important contribution" of malaria control programs during the first half of the 20th century "was the development of malaria epidemiology, including the study of the genesis of epidemics and their possible forecasting and preservation."

In 1997, epidemiologist Louis Molineaux, having participated in a WHO/World Bank study to estimate the global burden of disease, noted that the "sum of the deaths attributed by disease experts to their respective

diseases was much larger…than the total number of deaths available." This led to an important article in which he suggested that "this discrepancy points again to the importance of indirect (multiple cause) mortality."

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 "direct" (unconditionally lethal) and "indirect" (conditionally lethal) mortality.

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), 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).

Interventions, as noted by Molineux, included (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." "If indirect mortality…is important, the other disease control programs could significantly reduce malaria-specific mortality."

The latter, as noted previously (Section 1.5.1.1), is termed a *positive externality* by economists. The inverse, *negative externalities*, represent an unwelcome counterpart. 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; citing Coase, 1960, also see Fisman and Laupland, 2009).

Positive externalities may also be viewed as "spillovers." This is often the case of public agricultural research performed in one area or jurisdiction that is of benefit to other areas. As Alston (2002) noted, "…medical research

spillovers might have a spatial dimension akin to that in agricultural research, when geoclimatic factors play a significant role in the incidence of diseases." Public research is a public good and the rationale behind the Consultative Group on International Research (CGIAR) (Dalrymple, 2008b) and several international health research centers (Ibid, and Dalrymple, 2008a).

The same reasoning can be applied at the program level for malaria control. As Smith, et al. (2011) recently observed, "Reducing malaria creates a benefit for neighbors that did not pay for it." Hence the logic of scaling up malaria "interventions in regionally coordinated programs such as those implemented in Southern Africa and southeast Asia…."

1.6.1.2. Drug-disease interactions

Significant examples of indirect mortality category are provided by drug-disease interactions with HIV/AIDs and other diseases, and possible use of the drug on multiple diseases.

1.6.1.2.1. *Malaria and* HIV/AIDS. This issue was perhaps first taken up in terms of Africa in a WHO/RBM technical consultation held at the Kenya Medical Research Center in 1988 to bring together experts on AIDs and the major tropical diseases in order to review what was known about the interrelationships, to draw up a list of priorities for research, and to outline study designs (WHO/TDR; Smith, et al., 1988; also see Corbett et al., 2002).

A subsequent WHO 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 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." "Moreover, among adult men and non-pregnant women, HIV/AIDS may augment the risk of malarial illness" (WHO, 2004d; also see WHO/UNICEF, 2005) - a *negative externality*. It affects the immune response to malaria, "leading to different patterns of disease…including "increased prevalence and severity of clinical malaria and impaired response to antimalarial treatment" (Flateau, et al., 2011).

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*, spread by involuntary routes (malaria). But since a continuum is involved, they use *communicable* to denote both. Hence the strategies for approaching each might arguably differ somewhat, with more attention being given to behavior in the case of HIV/AIDS and biomedical approaches for malaria (the former was not the case in the view of Timberg and Halpern, 2012).

The two diseases have the greatest degree of overlap in Sub- Saharan Africa, especially in regions of unstable malaria transmission where adults are affected by both diseases, as in Southern Africa (Korenromp et al., 2005; Hewitt et al., 2006). In non-pregnant adults the "interaction is apparently driven by substantial immune compromise" and that "more severe malaria disease and death are seen specifically among persons with little or no acquired immunity [where] the effect of malaria on HIV is less clear" (Hewitt et al.). A study by Muema et al. (2011) suggests that "HIV-infected children have impaired ability to respond to multiple antigens." Another concluded that "The HIV-I epidemic by increasing the malaria parasite biomass in sub-Saharan Africa may also increase the emergence of antimalarial drug resistance" (van Geertruyden, et al., 2008).

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, Anonymous 2006b; 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, co-infection may have also have "facilitated the geographic expansion of malaria in areas where HIV prevalence is high." A subsequent study covering three African nations (Kenya, Malawi, Tanzania), utilizing data from 2003-04 national health surveys, indicated that "individuals who live in areas with high P. *falciparum* parasite rate have about twice the risk of being HIV positive compared with individuals who live in areas "with low rates" (Cuadros et al., 2011). "Reducing malaria transmission becomes even more important to address in the context of HIV." However, "the causes and implications of this co-infection at the population level are unclear."

There can also be more positive externalities. 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 Kamya et al, 2007 and 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, 2010a). Reductions in anaemia have also been reported in Zanzibar (Aregawi, 2011) and are noted more generally in a recent study of the impact of preventative measures in Africa (WHO, 2010d). Moreover, a study by Indian investigators showed that two HIV protease inhibitors (indinavir or nelfinavir) "augment the antimalarial activity of artemisinin against P. *falciparum* in vitro" (Mishra et al., 2010).

Another related dimension concerns the influence of resource allocation. A new study indicates that increased funding for HIV/AIDs has come at the expense of funding ("dollar displacement") for malaria control in developing nations (Lordan et al., 2011). While the above discussion suggested a degree of complementarity in terms of control, the study found that a 1% increase in funds devoted to HIV/AIDS in one year "leads to an 11% decrease in funds devoted to malaria" in the following year. And when the analysis was limited to countries with at least 1% prevalence of malaria, the displacement effect almost doubled. In comparison, there were no discernable replacement effects for TB. While this suggests more year-to-year flexibility in allocation of funding than might have been expected, there appears to be a significant opportunity, and perhaps social, cost in favoring HIV/AIDS over malaria.

1.6.1.2.2. *Interactions with other diseases.* These have also been noted. A recent long term study in Kenya indicated that "interventions to control malaria will have a major additional benefit by reducing the burden of invasive bacterial disease" (Scott, et al., 2011). Similar results have been found in Tanzania (Mtove, et al., 2010). Moreover, a study in Ghana revealed that adult patients with type 2 diabetes had a 46% increased risk of infection with P. *falciparum* (Danquah et al., 2010). While children, who lack semi-immunity, were not included in the study, they may be at greater risk. Treatment with metformin lowered P. *falciparum* prevalence, but the reasons for this overall relationship, which is apparently one-way, are unclear. Other such interactions appear to exist, such as with tuberculosis (Colombatti et al.,

2011), helminthic infection (Thigpen et al., 2011), salmonella (Cunnington, 2011; LSHTM, 2011), and Epstein-Barr virus in promoting Burkett's lymphoma, a form of paedetric cancer in equatorial Africa (Anonymous, 2011d; Chêne et al., 2007). The biological bases for some of these relationships do not appear to be well known.

1.6.1.2.3. E*ffect of drugs on multiple diseases*. A further externality of positive nature is introduced when a drug proves to be effective in treating more than one disease. A remarkable example is provided by dapsone (diamino-diphenyl-sulfone) (Barr, 2011). "From 1936 to 1996 [it] treated a diverse array of diseases including tuberculosis, leprosy, malaria and AIDs-related pneumonia." It was an example of a "clinic-as-laboratory" approach. First noted in the 1930s, it was picked up again during the 1950s when it began its "reinvention as an antimalarial drug" (435), a process which was accelerated when resistance to chloroquine developed in the late 1950s and 1960s, an provided a major threat in Vietnam (443-460). The first first dapsone was received in December 1965 and prevented malaria in about 50% of the cases and became a standary issue for combat troops, despite some concern about side effects. While not a panacea, when combined chloroquie-piperaquine it did lower the malaria rate dramatically" (458). It was replaced by mefloquine in 1972 in 1972. Its next use came in the 1980s as a treatment for HIV/AIDs and remains in use today. More generally it presaged the current interest in searching for new use of "already approved components" which "may be a lnew mode of drug innovation" (466-467).

1.6.1.3. Relative roles of epidemiology and economics

Phillipson and Posner (1999/2000) state that "most research on the public control of infectious diseases is conducted outside economics in the field of epidemiology, the study of occurrence of disease in a population." However, the evaluation of public health measures from an economic perspective is important since it "separates the health effects of public policies from those of private decision-making. In doing so, one study by Gerovitz and Hammer (2004) suggested 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 attempted to (1) "dissect the externalities involved in infectious diseases when there are options of both prevention and cures…" and (2) "examine a typology of infectious diseases" that are spread from person to person and by…vectors such as mosquitos."

Clearly, *positive externalities* stemming from a given form of investment in disease control such as an ACT add to the rate of return from that action, while negative externalities would subtract from them. The former are often public goods and the latter public "bads" (Smith 2004/05). These, however, may be difficult to anticipate, measure, value, and would necessarily be of an ex-post nature. 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 help in developing and controlling diseases associated with poverty in Africa" (Troy-Blomberg and Berzins, 2008). But to the extent that the balance is positive it will contribute to improved health among those involved, and if of more widespread nature even to economic development. Another complex dimension is the extent that other pathogens "modulate the immune responses already at birth and/or throughout early life." Hence externalities appear to be worthy of further consideration, both at the scientific and policy levels [Box 11].

Although this discussion has largely been cast in terms of the *physiological* effect of control efforts for one disease on another, in the case of a versatile medicinal plant such as Artemisia there is the possibility that it might, when suitably formulated, play a role in the treatment of other diseases. There also might be a broader *economic* and *psychological* effect in that progress on one disease could help free financial, human, and institutional resources to improve other aspects of the health system and for other diseases. While it may uncertain how efforts that strengthen one sector – such as the relatively greater involvement of the private sector in the AMFm program –affect spillovers to other sectors or diseases (Bongaarts and Over, 2010b; pers. comm. from Over, Oct. 2010), the possibilities could merit additional study.

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. The same might be said of the drugs involved, particularly artemisinin and its derivatives and synthetic forms.

Box 11. Expressing malaria externalities in quantitative terms.

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). 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 incorporate as many variables.

1.6.2. Other medical uses and linkages

Medicinal extracts such as artemisinin and quinine may 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.

1.6.2.1. 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 (e.g., Berdelle, et al., 2011). If born out in further and more extensive trials, one or more 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; Chaturvedi et al., 2010).

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; Nakase et al. 2008; Singh and Lai, 2004). 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; also see Berger et al., 2005).

Prof. Gary Posner of Johns University (noted in Section 1.4.1.3.1.3) has long been aware of the cancer dimension and his group has "discovered 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. These were 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 their work in the School of Medicine (www.jhu.edu/~chem/posner/ [Research; also see Publications]; accessed 11/8/11; pers. comm. from Posner, Feb. 2010).

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; Singh, et al., 2011). 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; Lai and Singh, 2006; Singh and Panwar, 2006). Other reviews and studies have been reported by by Krishna et al., 2008; O'Neill et al., 2010;

Ferreira et. al., 2010; and Berdelle, et al., 2011. While promising, these results are only a start and the best need to be subjected to clinical trials.

• **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/IM, 2004; 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. comm. from Ian Bauthurst, MMV, Jan. 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 may face the development of resistance

.

1.6.2.2. Artemisinin, antibiotics and combinations

The use of a combination of artesunate and an antibiotic - azithromycin - in malaria control in Asia and Africa is an intriguing combination that is both under development and field study.

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."

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 suggested that that the combinations "are safe

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

Noedl (2009) 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 co-infections, but rather as antimalarials… simultaneously covering numerous pathogens commonly encountered in co-infections or that cause syndromes which are clinically indistinguishable from severe malaria.

Pradel and Schlitzer (2010) 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 towards a needle-free, whole-organism vaccination strategy." Friesen (2010) and Dondorp et al. (2011) echo this view.

Sykes et al. (2009), noting that "Malaria and bacterial disease are difficult to differentiate with limited diagnostic facilities," went on to test azithromycin plus artesunate versus artemether-lumfantrine in children in Tanzania, but the findings did "not support its use in areas "with high levels of existing antimalarial drug resistance." The degree to which other such studies have since been conducted has not been ascertained.

WHO's 2006 "Guidelines for the treatment of malaria" (WHO, 2006b) "included useful advice on the use of antimicrobials in severe malaria," but this section was removed in the 2010 guidelines (WHO, 2010b). In the view of Reyburn (2010), this left "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."

1.6.2.3. Malaria control and other afflictions

Malaria has long been associated with other diseases, particularly schistosomiasis and hookworm (see McGuire and Coelho, 2011 and the many studies by Stephenson, et al. listed in their Reference section), blackwater

fever, and splenomegaly. The former is associated with both malaria and quinine and is characterized by bloody urine. The latter is manifested by enlargement of the spleen (NA/IM, 2004; Eamon, 2010).

Blackwater fever is more relevant in the context of this paper, but while important over a century ago, is now virtually forgotten. It is known, in technical terms as "intra vascular hemolysis, hemoglolbinuria and acute renal failure" (Bruneel, 2001). Quinine is thought to have played some role in both triggering and alleviating it in numerous countries or regions around the world in the mid-1880s through the mid-1900s. It was the most common cause of deaths of Europeans in West Africa and in some cases the mortality was as high as 25%.

This seemed to be particularly true of individuals who had been living in endemic areas for several months [and] had a history of irregular chemophylaxis with quinine" (Bruce-Chwatt, 1987; also see Macgraith, 1948 and Russell, 1952). Ross wrote one sufferer that that it "is usually precipitated…by a sudden dose of quinine, general sulphate of quinine" (Fraser, 1935). Christophers (1937) later noted its puzzling nature, as did Bruce-Chwatt (1987).

Quinine had been pursued during the colonial period in India as a preventative measure over other programs in irrigation projects – a "quinine policy" which was not altogether altruistic (Watts cited by Bhattacharya, 2011) and was viewed by others as a practice to be avoided (Salako, 1987; Bruneel, et al., 2001; NA/IM, 2004; Shah, 2010). With the relative decline in the use of quinine in malaria control, Blackwater fever has also faded in frequency, though occasional reports have appeared (Tran, et al., 1996; Bruneel, et al., 2001; Rogier, et al., 2003).

1.6.3. 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 of economics 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"

Box 12. 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

(the note went on to say "See Lanjou 2001 [cited here] for a useful analysis along these lines"). These relationships are tentatively outlined here in matrix form (in Box 12) and then described in more detail.

• **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 situation 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, they are usually serendipitous, 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. The report added 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." 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.

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The broader epidemiological, medicinal, and macroeconomic issues considered here may well merit further consideration in assessing policy issues related to malaria control. This, however, will require individuals with, or representing, a more comprehensive view of malaria control. At present virtually all of the biological scientists and the relatively few social scientists involved in malaria control are specialists. A wider view is obtained only on the rare occasions when they are brought together on a study or a meeting. In this sense this paper ends up not far from where it started, but hopefully has helped point the need for, and in some sense the way in terms of issues, toward a better balance in the policy arena.

1.7 Concluding Remarks: *The Wisdom of the Red Queen*

Artemisia (*Artemisia annua*) is a seemingly simple, though uncommonly versatile, medicinal plant that has drawn wide 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 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 The Special Programme for Research and Training for Tropical Diseases of the World Health Organization 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). They go on to note that "By 1990, about 80% of drugs were either natural products or analogs inspired by them but that "many pharmaceutical forms have eliminated their natural

products research in the past decade." Others have found this disquieting: Bond (2004) stated 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 and other modes of action. A principal approach involves the development of synthetic chemical substitutes that are equally effective, safe, and significantly lower in cost. 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. 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 alter the balance between agricultural sources and the various forms of chemical and biological synthesis (which so far have not provided a lower cost product but may offer other advantages) in 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).

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 in the case of malaria "The best we can hope to do probably is to keep one jump ahead of Nature" (1970/1987) and Deutsch (2011) in commenting on antibiotics in a broader context stated that "all triumphs are temporary." Thus, as Markel (2004) observed in viewing 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), require even more effort.

Annexes

Annex 1. *Artemisia*: *Discovery and Role in Traditional Chinese Medicine*

As noted in Section 1.2.2., *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. 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."

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; 2006b; 2009). Li Shizen made a similar recommendation in 1596 (in addition to the references cited earlier, see Harper, 1998 and Unschuld, 1986).

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). 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, 2001a).

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) "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 botanists have generally identified the former as A. *apiacea*, now little known, and the latter

as A. *annua* (Yu and Zhong, 2002).

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

Therefore, on the basis of these sources, (1) Q*ing* H*ao* (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 (2) *qinghaosu* was an extract which probably included what is now known as artemisinin.

Whatever the designation, Artemisia was - and still is (Yu and Zhong, 2002) - 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. Saburo, 1979). Also, other plants, particularly Changshjan (D*ichroa 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, 2010a; Wright et al, 2010b).

(*Source: This Box has drawn from a stimulating interaction with: Donald Harper, University of Chicago; Elisabeth Hsu, University of Oxford; John Moffett, Needham Research Institute, Cambridge, and Wallace Peters, and David Warhurst, both formerly with the London School of Hygiene and Tropical Medicine.*)

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Annex 2. A *Kenyan Grower's Perspective*, 2007

[*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.*]

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 F1 but F2 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 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 mechanization 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 that 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.

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 have been grown at the expense of cereal crops that people feed on and when there is crop failure, they go hungry. Artemisia could go the same way.

Annex 3. *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 metric 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 t
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
(assumes 70/30 split between AL & AS/AQ & AL=0.5g artemisinin & AS/AQ=0.34g artemisinin)

1 treatment = 0.5g artemisinin
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)
(see source concerning use of wastage in conversion & definition of treatments)

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

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Annex 4. *Artemisinin: Phytochemical Extraction*

The normal extraction process mentioned 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. Bilia 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 only recently true for the third.

Simon, et al. (undated) 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. comm. 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. comm. from Rezelman, Oct., 2009). Extraction efficiency with ethanol has been 95% and a group at the University of Ghent managed by Arne Heyerick is studying the optimal extract level for cancer treatment (pers. comm. from Rezelman, June 2010; also see [http://artemisia-for-all.org]). 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.

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Annex 5. 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 (Section. 1.4.2) and bilateral programs (1.4.3). 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 of ACTs in Uganda 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 intermittent 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. Surprisingly, 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. This 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 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). 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), Moszynski (2010), and Epstein (2011) provide more recent commentaries on the supply situation

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Annex 6. *The Early Role of Ciba-Geigy in* ACT *Development*

As noted in the text (p. 22), the rights to sell Artemether plus Benflumetol (Co-Artemether) outside of China were purchased by Ciba-Geigy, which was merged with Sandoz Laboratories - both international Swiss pharmaceutical companies - in December 1996 to form Novartis Ltd. The Ciba-Geigy role in the early development of this ACT has been little known and is briefly outlined here based on materials recently provided (Aug. and Sept., 2012) by Dr. A.A. Poltera of Switzerland who served as a project leader for clinical development of anti-parasitic agents for the firm from 1982 to 1994.

In 1987, according to his account, China first offered injectable Artemether for licensing to Pharma International, Ltd., an arm of Ciba-Geigy. He assessed their Clinical Dossier favorably and a "re-launch" was made in 1989. In April 1990 he and a delegation from the firm went to China with the goal of licensing Artemether for the international market. The delegation, however, rejected the first offer for a number of reasons.

Dr. Poltera then asked if "they had something else to offer which we do not know." After further discussion, Prof. Zhou Keding, a member of Project 523 and head of the Chinese Steering Committee of Qinghaosu Research (CSCQR), replied "Yes, we have a combination drug." This was of interest and potentially patentable. As later reported by Chinese authorities to Dr. Poltera (pers. coms., Sept. 2012), a decision was made in October 1982 to support research on combinations, headed by Zhou Yiqing (previously head of Project

523). It initially focused on four combinations and then on two: SP (sulfadoxine-pyrimethamine) and benflumetol (lumefantrine, first synthesized in 1976). The latter was subsequently emphasized and a fixed combination of 1:6 was proposed in 1986 by Prof. Ning Dianxi, a colleague of Prof. Zhou Yiqing, and later registered as Co-Artemether in China (1992).

In August 1990, after a confidentiality agreement had been developed, the two parties met again in Beijing and Prof. Yiqing revealed the composition of Co-Artemether. The following November, Prof. W.H. Wernsdorfer, a member of the 1981 CHEMAL team (see Figure 3), was engaged as a consultant and "coordinated the claim of synergism of Artemether and Benflumetol by in vitro tests." The positive results were central for the patent application for Co-Artemether filed with the World Intellectual Property Organization (A61 K31/335) in June 1991 and approved in February 1992.

This period was followed by several years of (1) interaction within the firm, in part involving Jean Heimgartner who was initially head of licensing for Pharma International Ltd (2011) and then manager of special projects, to complete arrangements and a "Risk Phase" investigation, and (2) conduct of Phase III clinical trials on Hainan Island, which proved successful. The rest of the story, after 1996 and conducted under the auspices of Novartis, is summarized in Section 1.2.4.3., pp. 31-32 and Annex 7.

In retrospect, Dr. Poltera thinks that the combination of a semi-synthetic plant extract with a synthetic combining schizonticidal and gametocytocidal activity was of particular importance (pers. comm., Sept. 2012).

Anonymous, 1995. Adventure in China, PHO News, Pharma Overseas Information Bulletin, Ciba-Geigy, Basle, Feb.

Heimgartner, J, 2011. Coartem Report on Initial Assessment, in *Journey from Co-Artemether to Coartem* [1951-2011], Institute of Microbiology and Epidemiology, Academy of Military and Medical Sciences (IME/AMMS), pp. 112-114. (The book was dedicated to the 60th anniversary of AMMS and written for the 20th anniversary of the Chinese-Swiss link, starting with the 1991 patent filing. It is primarily in Chinese but has a dozen sections fully or partially in English).

Poltera, A.A., 1997. The Chinese-Swiss link for the oral antimalarial drug combination Co-Artemether (Artemether + Benflumetol=A+B): A Personal Experience, Annual Congress of the Swiss Society of Tropical Medicine and Parasitology, Neuchâtel, poster, text in *Schweizerische Medizinische Wochenschrift* (Swiss Medical Weekly), 127 (39), Sept. 1997, 1632.

Poltera, A.A., 1998. Optimizing the effect of Co-Artemether by possible postprandial administration: From Pharmacokinetics to cure and control of Malaria, 2nd European Congress on Tropical Medicine, Liverpool, Sept. 14-18, Poster P46, Congress Abstract Book, 133.

Poltera, A.A., 2011. Early Co-Development of Artemether plus Benflumetol between AMMS and Ciba Geigy, Limited, in *Journey from Co-Artemether to Coartem* [1951-2011], IME/AMMS, 102-109.

Annex 7. *The Early Role of Novartis in ACT Development*

While Novartis played a major and well-known role in the further development of ACTs, relatively limited information has been available about its initial early internal operations from 1996 to 1999.

Two previously little known reports recently came to my attention and are summarized here. The first was provided in a Harvard Business School Case Study by Deborah Spar and Brian Delacey titled "The Coartem Challenge" (first issued in June 2008). The second was a section prepared by Klaus Leisinger for a book commemorating the Silver Jubilee of the Novartis Foundation (2004). They overlap in some respects the events reported in Annex 6 concerning Ciba-Geigy. In addition, Dr. Daniel Vasella provided some additional information on its role in their Access to Medicines Program.

Further information was provided in a Chinese book, *Journey from Co-Artemether to Coartem* (2011), the proceedings of a commemorative meeting with some involvement and participation by Novartis, previously cited in Annex 6 (see Heimgartner, 2011). About two thirds of the text is in Chinese and the remainder in English; a fully translated version in English is expected in 2014.

• Harvard Business School Case Study

The Spar and Delacey study reviewed the series of internal events that initially took place after the formation of Novartis in 1996 and reflects uncommon awareness of the internal operations of the firm.

It notes that one of the first steps of the new firm was to "rationalize its product portfolio." The firm had concentrated its pharmaceutical operations into five key areas, and "Coartem was not an obvious candidate for inclusion in this group." However "it was precisely the type of operation" that the energetic new president, Daniel Vasella, a physician "loved and felt very committed to."

Two phases were involved. The first from 1996 to 1999 included design of clinical trials to investigate the safety of Coartem in pregnant women and the development of a more friendly formulation for children. The

second phase from 1999 to 2004 moved on to clinical studies and activities, regulatory activities and marketing programs to bring Coartem to patients. There was also an urgent need to search for additional sources of artemisinin and secure additional manufacturing capacity.

On May 23, 2001, "Novartis and WHO signed a confidential memorandum of understanding, specifying guidelines by which Novartis would manufacture and deliver Coartem, at cost, to regions where malaria was endemic." One of the first tasks was to search for additional sources of artemisinin. This was done at East Africa Botanicals [drawing on a variety developed by Mediplant in Switzerland [see p. 40] and by a sourcing center in China. Then arrangements were made for additional manufacturing capacity at its Suffern, N.Y. plant. Later in May 2001 (the 28th), it introduced Riamet®, an artemether/lumefantrine combination, on the European market as a stand-by treatment for malaria contacted elsewhere. Large-scale tests in Africa had shown a cure rate of 95% (van Vught et al., 1998).

The first country to respond to the Coartem program was Zambia in 2003 and the first shipment left Basle in November 2003 accompanied by training and educational material.

- **Additional Comments by Former Staff Scientist of Ciba Geigy and Novartis**

Dr. Anton A. Poltera subsequently noted (pers. comms., Feb. 2013) that Pharma International Ltd., a sub group of the Pharma Division of Ciba-Geigy, marketed pharmaceutical products in developing nations. It also had a small unit for clinical research in tropical medicine which he belonged to from 1982 -1994. In May 1994, Ciba Ltd. signed a formal agreement with their Chinese partners to fully develop Coartem with the support of the Ciba Pharma Division, including a "two-figured sum for upgrading facilities in China." The Risk Fund contribution from 1990-1994 was essential before it became an official project with the support of the Ciba Pharma Division (1994-1996)." The agreement to sell at cost for the first ten years was initiated by Gro Harlem Bruntland (the former Director General of WHO). This agreement started on May 23, 2001 and ended ten years later.

• Additional Comments by Former Head of the Novartis Foundation

According to Klaus Leisinger (pers. comms. Jan. & Feb. 2013), there was a vigorous tug-of-war over the project for a long time. The Pharma Division management had different priorities about where best to allocate scarce funds. But there were high-level personalities, among them the Chief Executive Officer, Dr. Alex Krauer, who saw the medical necessity for combatting the poverty disease malaria. It was he who proposed using $1 million from the Ciba-Geigy Foundation's "Risk Fund" to get involved. The "Ausschuss Dritte Welt" (Third World Committee) debated the proposal and decided that the risk fund would pay seeding money to get the project underway. This decision and the perceived "blessing" from Dr. Krauer facilitated the decision of the Pharma Division to take over the development costs of 21 million francs.

• Additional Comments by former CEO and Chairman of Novartis Board

Dr. Daniel Vasella (pers. comm., Feb. 2013), who retired in late February 2013, kindly provided some remarks on the role of Coartem® in their "Access to Medicines Program," a topic not heretofore noted here in these terms.

In 1997 he "committed to making the fight against malaria a key part of this program. It initially involved (1) investigating the safety of Coartem® in pregnant women, the first study by a healthcare company for this patient population. It was followed a few years later by (2) the development of the first pediatric formulation of ACTs for babies and children."

"Today the Novartis Malaria Healthcare Initiative is one of the largest access-to-medicine programs in the healthcare industry. It focuses not only on providing therapies but on improving access to treatment, helping communities deliver better healthcare and investing in research and development."

"For example, the Novartis-led SMS [Short Message Systems] for Life program is a tracking system that has helped improve access to treatment in rural Africa. The system uses SMS messages to track weekly stock levels of medicines at public health facilities. During the first six-month pilot program covering a population of 1.2 million in Tanzania, stock-outs were

reduced from 79% to 26% in three districts. Today, SMS for Life reaches all 5,000 public health facilities across Tanzania and the program is preparing to additional roll outs in Ghana, Kenya, and Cameroon."

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Addendum

Jianfang, Z., 2013 (editor). *A Detailed Chronological Record of Project 523 and Discovery and Development of Qinghaosu* (*Artemisinin*). Translated from the Chinese by Muoi and Keith Arnold, Strategic Book Publishing and Rights Co., Houston, Texas. Contains rare photographs on pp. 100-105.

Dana G. Dalrymple is an agricultural economist by vocation and a historian by avocation. He spent most of his career with the U.S. government in international agricultural development and research, first with the Dept. of Agriculture (USDA) and then on detail to the Agency for Intl. Development (USAID). He received B.S. and M.S. degrees in pomology (horticulture) and agricultural economics from Cornell University, and a Ph.D. in the latter from Michigan State University.

The key ingredient in the most effective treatments for malaria in Africa - artemisinin - comes not from high-tech research, but is an extract of an ancient Chinese 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 interplay 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, and 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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