Malaria Treatment in Sub-Saharan Africa: Drug Development and Cost-Effectiveness Strategies

Master of Arts Thesis
Submitted by Michael Kemmer
MA/MD Candidate
April 25th, 2014
# TABLE OF CONTENTS

Abstract ................................................................................................................................. 1

Chapter 1 - Origins of the Malaria Disease and Initial Treatments ....................................... 3
  1.1 Biological Basis of Malaria .......................................................................................... 3
  1.2 Life cycle of the *Plasmodium* protozoan .................................................................... 4
  1.3 History of anti-malarial drugs ...................................................................................... 6
  1.4 The development of Artemisinin-based compounds .................................................... 8
  1.5 The rise of Artemisinin combination therapies ............................................................ 9

Chapter 2 - Current Treatment Environment and Creative solutions.................................... 11
  2.1 The current state of antimalarial drug use in Africa .................................................... 11
  2.2 Recent Evidence of Efficacy of ACT’s .......................................................................... 12
  2.3 Problems with ACT Treatment: Adherence ................................................................. 13
  2.4 Problems with ACT Treatment: Cost and Access ....................................................... 14
  2.4.1 Affordable Medicines Facility for Malaria ............................................................. 16
  2.4.2 Institute for One World Health ............................................................................. 17
  2.4.3 Drugs for Neglected Diseases Initiative (DNDi) .................................................... 18
  2.5 Contributions of private pharmaceuticals ..................................................................... 19

Chapter 3 - Funding: Current and Future............................................................................ 22
  3.1 Introduction .................................................................................................................... 22
  3.2 Key findings .................................................................................................................. 22
  3.3 Future considerations and goals .................................................................................... 23

Chapter 4 - Evaluation of Cost Effective Studies ................................................................ 25
  4.1 The importance of cost-benefit ................................................................................... 25
  4.2 Primary and secondary treatment ................................................................................ 25
    4.2.1 Primary forms of treatment: Cost-Effectiveness of ITN’s ....................................... 26
    4.2.2 Primary forms of treatment: Cost-Effectiveness of IRS ....................................... 27
    4.2.3 Secondary forms of treatment: Cost-Effectiveness of RDT’s .................................. 28
    4.2.4 Secondary forms of treatment: Cost-Effectiveness of Artesunate .......................... 31
  4.3 Cost-effectiveness of home management of malaria .................................................... 32

Chapter 5 - Recommendations and Conclusion .................................................................. 34
  5.1 ACT’s Administration and drug development: Recommendations ............................ 34
  5.2 Funding: Recommendations ....................................................................................... 35
  5.3 Cost Effectiveness: Recommendations ....................................................................... 36
  5.3 Conclusion ..................................................................................................................... 38

Appendices ............................................................................................................................ 39

Bibliography .......................................................................................................................... 47
Abstract

Healthcare is costly. Even in the United States, the struggles to control costs, while retaining access and quality, are extraordinary. Consider then, trying to eradicate an easily communicable and devastating illness, using drugs and resources from many of the same companies that first world western nations work with and buy from, in a region of the world where the average annual income is as little as 1/50 of those living in America. In essence, that is the situation in sub-Saharan Africa\(^1\) as it attempts to treat malaria.

Malaria remains one of the most devastating – but preventable and treatable – diseases, particularly in children under five. Nowhere is its effect more widely felt than in Sub-Saharan Africa, where 85% and 90% of all malaria cases and deaths occur, respectively.\(^2\) According to recent World Health Organization estimates, there were roughly 660,000 deaths due to malaria in 2010, 85% of which occurred in children under the age of five.\(^3\)

Africa has seen a modest reduction over-all in deaths in recent years (Appendix 1), which has come at a price. Estimates placed the total global R&D funding around US$600m in 2009\(^4\), (Appendix 2) with an estimated US$2.3b available for prevention control. However, that $2.3b figure is less than half of the $5.1b estimated to be required to

\(^1\) http://data.worldbank.org/region/sub-saharan-africa
ensure universal access,\textsuperscript{5} and the figure of $600m in fact demonstrates \textit{under}-attention of the present and impending concerns regarding treatment-resistant forms of malaria.

Acknowledging the impressive yet sub-optimal global financial attention that malaria receives, it would only seem logical to review and assess:

1. A history of antimalarial drug medication, with an evaluation of the pros and cons regarding access and cost of current therapies.

2. A review of some creative solutions to overcoming intellectual-property rights and markets based incentives in a capitalistic economy that may not be naturally inclined to invest in antimalarial medications.

3. The status of global funding for the cause of eradicating malaria, with predictions and expectations for what is needed to sustain and elevate R&D funding over the next decade.

4. How well that funding is being spent, by reviewing studies on cost-effectiveness and outlining a summary of recommendations on how to best utilize the limited financial resources to make the most economical health impact.

This paper, submitted on World Malaria Day (April 25), will address these four topics, in an effort to give a comprehensive evaluation of the state of malaria treatment in sub-Saharan Africa.

\footnote{ibid (www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_factsheet.pdf)}
Chapter 1 – Origins of the Malaria Disease and Initial Treatments

1.1 Biological Basis of Malaria

While bacteria or viruses cause the majority of infections, malaria comes from an infection of a eukaryotic unicellular organism known as a protozoan. As a eukaryote, protozoans have a more complicated internal cell organization than prokaryotes, with membrane bound organelles such as mitochondria and chloroplasts. Bacteria are considered prokaryotes, and are believed to have been on earth millions of years because before eukaryotes evolved.\(^6\) Human beings are scientifically categorized as eukaryotes.

Malaria is also a vector borne disease; a term commonly used to describe an illness caused by an infectious organism transmitted to people by blood-sucking arthropods such as mosquitoes, fleas, tics, or biting bugs. The infectious microbe in this case is a protozoan of the genus \textit{plasmodium}, of which there are dozens of species. Four of those species are capable of causing malaria in humans, which include \textit{Plasmodium falciparum}, \textit{P. vivax}, \textit{P. malariae}, and \textit{P. ovale}.\(^7\)

\textit{Plasmodium falciparum} is found worldwide in tropical and subtropical areas (though predominantly in Africa), and is estimated to kill approximately 1 million people a year. \textit{P. falciparum} multiplies rapidly in the blood, resulting in anemia (due to severe blood loss), and severe malaria. \textit{P. vivax} is primarily found in Asia and Latin America, as well as parts of Africa. It is well known to reactivate in the liver and invade the blood several


\(^7\) [http://www.biotopics.co.uk/malaria/malaria.html](http://www.biotopics.co.uk/malaria/malaria.html)
months after the infecting mosquito bite. \textit{P. ovale} is also known to reactivate, and is found mostly in Africa, particularly affecting the sub-Saharan region, while \textit{P. malariae} is found worldwide. If untreated, it can cause a long lasting, chronic infection that in some cases can last a lifetime.\textsuperscript{8} As this paper focuses on the greatest malarial threat to humanity in sub-Saharan Africa, the \textit{falciparum} species will be primarily considered.

The \textit{Plasmodium} survives within two separate hosts, which include a definitive host (a female \textit{Anopheles} mosquito), and a secondary host (a vertebrate such as a human).\textsuperscript{9} Mosquitoes are not “born” infected with malaria; rather the mosquito itself is infected after feeding on an infected secondary host. A symbiotic relationship between mosquito and \textit{Plasmodium} had been assumed to evolve over tens of thousands of years. Recent research has shown however, that infection with plasmodium organelles causes mosquito to fly less vigorously and lay fewer eggs. Its immune system may be weakened as well.\textsuperscript{10}

\subsection*{1.2 Life cycle of the \textit{Plasmodium} protozoan}

The life cycle begins when a female \textit{Anopheles} mosquito carrying a malaria-causing \textit{Plasmodium} feeds on a secondary host. While feeding, the mosquito injects saliva which helps clot the blood. The saliva also contains the infectious form of the \textit{Plasmodium} parasite known as sporozoites, which are released into the bloodstream. The sporozoites travel to the liver and invade liver cells. Over the next 1-2 weeks, the sporozoites grow, divide, and – in each liver cell - produce tens of thousands smaller forms, called

\textsuperscript{8} http://www.cdc.gov/malaria/about/biology/parasites.html
\textsuperscript{9} http://www.netdoctor.co.uk/travel/diseases/life_cycle_of_the_malarial_parasite.htm
\textsuperscript{10} http://www.nytimes.com/2006/04/28/science/28malaria.html?_r=3&
merozoites. When relapses occur weeks or even months later, they can be attributed to dormant merozoites that have remained in the liver. Only *P. vivax* and *P. ovale* are capable of this, however.

The merozoites then exit the liver cells and re-enter the bloodstream, invading red blood cells. These merozoites then undergo asexual replication, and re-release newly formed merozoites from the red blood cells over the next 24-72 hours. The red blood cells burst at this time, and it is the destruction of thousands of *Plasmodium*-infected cells in the secondary host bloodstream that leads to the symptoms and complications of malaria.

While the vast majority of these merozoites will remain in a constant intracellular cycle of asexual reproduction, some will develop into sexual forms of the parasite, called male and female gametocytes. Like the merozoites, gametocytes will invade red blood cells and circulate in the bloodstream. When a mosquito bites an infected human, it ingests the gametocytes, which are released when the infected blood cells burst inside the mosquito intestine. These develop further into mature sex cells called gametes, which fuse to form zygotes. The zygotes develop into ookinetes that burrow into the gut wall and form oocysts. Growth and division of each oocyst produces thousands of sporozoites (the same infective form as described above). Like before, after 1 to 2 weeks the oocyst bursts, releasing sporozoites into the body cavity of the mosquito, which travel to and invade the salivary glands. The cycle continues when the mosquito injects the sporozoites from its salivary glands into the human bloodstream.\(^\text{11}\) See appendix 3 for a visual representation.

\(^{11}\) http://www.niaid.nih.gov/topics/malaria/pages/lifecycle.aspx
1.3 History of anti-malarial drugs

Traditionally, antimalarials are classified by the stage of the malaria life cycle targeted by the drug. Blood schizonticides act on infected red blood cells. Tissue schizonticides kill merozoites within the liver cell, preventing the invasion of red blood cells. Hypnozoiticides kill persistent \textit{P. vivax} and \textit{P. ovale} that have sequestered within the liver, thus preventing relapses from these dormant stages. Gametocytocides destroy the gamete forms within red blood cells, preventing transmission from human to mosquito.\(^{12}\)

Like many treatments for diseases, the first malarial drugs were discovered mostly by accident. In the late 1880s future Nobel prize-winning German scientist Paul Ehrlich found that methylene blue was particularly effective in staining malaria parasites. In 1891, Ehrlich cured two malaria patients with methylene blue, and soon after the first anti-malarial drug was born. Over the next 50 years, several chemical modifications were made to the methylene blue structure. One derivative, Mepacrine, was mass-produced as an antimalarial drug for American troops in the Pacific war campaigns. At the same time, German scientists were testing and developing a drug with a very similar structure named sontoquin. When sontoquin was released by the Germans to the Allied troops at the end of World War II, it was re-evaluated and renamed chloroquine. Chloroquine would become the foundation of malaria therapy for the next 20-30 years.\(^{13}\)

Chloroquine is tolerated with some rare but serious side effects. However, there is a narrow therapeutic window of dosage. Ingestion of two to three times the recommended


\(^{13}\) Ibid (Schlitzer)
dosage is potentially lethal. With a mechanism of action that was and is still debated to this day, it is believed that Chloroquine interferes with the parasites actions within the red blood cell – categorizing it as a ‘blood schizonticide’. Unfortunately, overuse, combined with mutations within the *Plasmodium* genome, caused resistance to develop in the 1960s and 70s. Today more than 80% of malaria strains are resistant to Chloroquine.\(^\text{14}\)

Predictably, the scientific community’s response to resistance was to modify the chemical structure of the drug. Drugs with a related structure such as Amodiaquine (discovered in the 1950’s), Pyronaridine (first synthesized in 1970 and in clinical use in China since the 1980s), and Naphthoquine (registered in China in 1993) entered the market.\(^\text{15}\) The back-and-forth between resistance and scientific response simultaneously went on in parallel lines of therapeutic agents. Mefloquine was originally synthesized during World War II, redeveloped in the early 60s at the Walter Reed Army Institute of Research, and used therapeutically beginning in 1985. Halofantrine was also developed at Walter Reed. Its antimalarial activity had been discovered during World War II, was first described in 1972 and was introduced into therapy in 1988.\(^\text{16}\)

Chimeric molecules, anti-folates, electron transport chain blockers, even antibiotics have been studied, developed and tried in an effort to combat malaria-causing protozoans at various stages of its lifecycle.\(^\text{17}\) It becomes apparent when reviewing the history of antimalarial therapeutic agents, that much of the Western world’s original involvement

---


\(^{15}\) Ibid (Schlitzer)


\(^{17}\) Ibid (Schlitzer)
stems from a motivation to protect its own (often the military) against the disease. With less and less evidence of this devastating disease on the front doors of most first-world nations, reduced incentive for the purpose of R&D of antimalarial drugs could certainly be reasoned.

It is also apparent that a considerable amount of malaria drug development has taken place in China. Consider that Pyronaridine was developed in China in the 1980s, and Lumefantrine (a drug structurally similar to Halofantrine) was developed in the 1970s by the Academy of Military Sciences in Beijing, China.18 The Chinese were clearly effective in programs to eradicate malaria, as the annual incidence had been reduced from 24 million at the beginning of the 1970s, to tens of thousands by the end of 1990s.19

1.4 The development of Artemisinin-based compounds

Without question, the most important products to come from China in the field of malaria research were artemisinin-based treatments. In the 1960s China began a research program named ‘Project 523’, with the purpose of finding an adequate treatment for its decimated army following exposure to malaria during the Vietnam War. In 1971, using an herb known as ‘sweet wormwood’, researcher Tu Youyou discovered the active ingredient artemisinin. It was found to be fast and effective. Eventually, in the 1980’s the results were published.

18 Ibid (Schlitzer)
19 http://www.wpro.who.int/china/mediacentre/factsheets/malaria/en/
It is widely recognized that Artemisinins are able to kill, within minutes, *Plasmodium* organisms in both asexual and sexual stages of the life cycle. The only other class of compound consistently used to treat severe malaria are Quinines, which will be discussed in part 4 in regards to their cost-effectiveness compared to Artemisinins. Despite their speed in eliminating malaria parasites in all red blood cell stages, Artemisinins have a half-life of less than one hour, which makes them a very poor candidate for malaria prophylaxis. In addition, the short half-life can also contribute to poor cure rates and high rates of reinfection for treatment courses not finished completely. Despite tremendous research efforts on Artemisinin since its discovery, there is still considerable debate concerning its mode of action on malaria parasites.

1.5 The rise of Artemisinin combination therapies

Combination drug treatments are common in treating many infectious diseases, most notably HIV. This principle is also applicable to malaria. The rationale behind ACT is that the chance of a parasite developing resistance as a result of genetic mutations to two different drugs at the same time is considerably lower than developing resistance to only one. Not long after their initial discoveries in the late 1970s, Chinese researchers began to consider the potential for resistance – and initiated studies on possible combination therapies. Artemether (an artemisinin derivative) and the aforementioned Lumefantrine (from a different class) were shown to be an effective combination.

African countries had begun transitioning from Chloroquine to ACTs as a first-line

---

treatment for malaria in the early 2000’s. For some countries, the drug they left behind was Sulphadoxine-Pyrimethamine, which had been introduced in many countries to replace Chloroquine as early as the 1970’s. Malawi, for example, had transitioned from Chloroquine to Sulphadoxine-Pyrimethamine in 1993. 21

In collaboration with Novartis, the first ACT was registered in Switzerland in 1999 as Coartem. It was included in the WHO Essential Medicines List in 2001. In 2001, South Africa became the first country to recommend ACT’s, while in 2007 Malawi and Botswana were the last countries to switch. 22 (Appendix 4)

By 2006, Artemisinin had become the foundation treatment of choice for malaria, and the WHO called for an end to single-drug preparations in favor of combinations of Artemisinin (ACT’s) with other malaria drugs to reduce the risk of resistance. As of 2007, with funding from the Global Fund, ACT had been adopted in 67 malaria-endemic countries (including 41 in Africa) as first-line recommended treatment for the *falciparum* species of malaria. 23 (Appendix 5)

21 Ibid (Cui)
2.1 The current state of antimalarial drug use in Africa

Today, the malaria treatment policy of every major country in sub-Saharan Africa designates ACT as first-line treatment. (Appendix B) What is designated, and what actually takes place however, can be two very different scenarios. Recent time sensitive data models on Chloroquine, sulphadoxine-pyrimethamine and ACT’s have shown a time lag between the adoption of a treatment policy and the following of it. It would take roughly 2 ½ years before researchers found a 50% reduction in the use of Chloroquine after a treatment policy change, and a 1.3-year lag for Sulphadoxine-Pyrimethamine respectively.

In addition, Chloroquine is still used very often today. As much as 50% of those seeking treatment for potential malaria will do so in the private sector, where ACT drugs are as much as 25 times more expensive. Chloroquine may be seen as an appealing alternative. In fact, Chloroquine and Sulphadoxine-Pyrimethamine are still registered and available in many sub-Saharan malaria endemic countries.

It is also important to note is that countrywide treatment policies are often decentralized at the level of the district or province. In South Africa, for example, this resulted in three different policies within three different malaria endemic provinces at the same time.24 (Appendix 13) Inconsistent and unstandardized drug administration is more likely to lead

---

to resistance. The development of resistance to Artemisinin and ACT’s could have disastrous implications, and it has begun to develop in some the secondary drugs such as Mefloquine. The use of these ACTs in this was will surely lead to the inevitable development of resistance to Artemisinins. In addition, countries or districts with continual use of Artemisinin mono-therapies will also diminish the utility of ACT’s.

2.2 Recent Evidence of Efficacy of ACT’s

In order to have full appreciation of the importance of correct administration of ACT’s, some scientific evidence of the current efficacy of these medications must be recognized. Recent results support that belief that ACT treatment works extraordinarily well. In an article published in January 2014, a collaborative effort between researchers in Uganda, Kenya, and at UCSF and the CDC, monitored, over 14 months, the effects of ACT combination drugs Artemether-Lumefantrine (AL) and Dihydroartemisinin-Piperaquine (DP) in three-day time periods for 202 Ugandan four and five-year-old children suffering from uncomplicated *P. falciparum* malaria (nearly 800 cases of malaria total). Measuring prevalence of parasitemia (an index percentage of parasites in the blood) using blood smears evaluated by multiple trained independent technicians,25 “the prevalence….on days 1, 2, and 3 following initiation of therapy was 67.6, 5.6 and 0% in those treated with AL, and 52.2, 5.7 and 0.3% in those treated with DP.”26 Only one of 752 cases tested positively after three days of treatment. (Appendix 7) The only risk factors found to increase the length of time before parasite elimination were elevated temperature, co-infection with HIV, and greatly elevated initial parasitemia.

---


26 Ibid (Muhindo)
These results are consistent with what researchers found in a study published in 2012, where 1346 cases of *P. falciparum* malaria in children under 5 in the Benin Republic were evaluated using Coartem (the trade name for Artemether-Lumefantrine). In only 32 cases, (2.83%), treatment success had not occurred by day three, and an only six cases of success not occur by two weeks.\(^{27}\) It is encouraging to note that Artemether/Lumefantrine could be so successful in such an important population in different parts of the continent.

### 2.3 Problems with ACT treatment: Adherence

Adherence is a major issue in any environment, and in any disease – be it diabetes, mental illness, and certainly malaria. Have both medications packaged together into one blister pack can reduce resistance resulting from patients only taking one drug. Patients may still avoid one particular drug however, with concerns about side effects and cost. Several Artemisinin-based combinations have thus been combined together into one pill. Artemether–Lumefantrine (AL), as well new co-formulated versions of Amodiaquine-Artesunate (AQAS) and Artesunate-Mefloquine (ASMQ) are three examples.

Historically, adherence has been evaluated through patient interviews, simple pill counts, and biological levels assessed through laboratory measurements. Medical event monitoring systems (known his MEMS), electronically track the time and frequency that a pill container was opened. Unfortunately, MEMS and laboratory measurements are often costly. In addition, laboratory measurements of Lumefantrine are often affected by

---

fat intake, thus a patient with low fat absorption at the time of ingestion of the medication could have a severely under reported laboratory value. A study in 2005 looking at short-term 3-day adherence showed an increase in adherence from 78% (in Zambia) to 93% (in Uganda) when ACT combinations went from a 2-pill formulation (Artesunate plus Sulphadoxine-Pyrimethamine) to a single pill (Artemether-Lumefantrine).28

Last April, researchers at the London School of Hygiene and Tropical Medicine conducted a systemic search of all studies on a ACT adherence in sub-Saharan Africa over the last 20 years. In total, 37 studies satisfied criteria, which included involvement of an ACT drug, had specific data on adherence, and was written in English. The study noted a wide range of adherence rates, from as low as 38% in Ethiopia, to 96% in South Africa. This figures were for the same drug (Artemether-Lumefantrine). A study in Malawi noted only a mild discrepancy between patient reporting (100%) of Artemether-lumefantrine, and MEMS cross-checking (92%). In general researchers found there was mild indication that younger patients (particularly younger than 15) were less likely to adhere, while education levels and literacy were found to have a positive correlation with adherence.Ultimately, however, researchers expressed disappointment at the lack of consistency in how adherence was monitored from study to study.29

2.4 Problems with ACT Treatment: Cost and Access

Perhaps the most concerning barrier to the use of ACT treatments is cost. ACT’s cost as

---

much is 30 times that of the older classes of drugs such as Chloroquine and Sulphadoxine-pyrimethamine. International funds such as the Global Fund to Fight AIDS, Tuberculosis and Malaria have reduced this cost, by purchasing ACT in the public sector and providing them free of charge for some patients. However, for most of the population ACT’s are still unaffordable. In Uganda, for example, where most malaria patients live in rural areas with very little income, many have to purchase medicines through the private sector. This of course, involves spending their own money. Research conducted in 2007 by the Ugandan Ministry of Health found the following:

- When the supply chain was working – down to the local level – the medicine was still often of poor quality.
- For even the lower-priced, poor quality medication, only 50% of patients were able to purchase a full course.
- The ACT supply chain was failing, as in some districts only half the public health facilities were at regular supplies.
- Medicines may have been provided free, yet the research found that only 16% of outlets that provided medicines were offering public sector care.
- As many as 45% of outlets selling medicines were not legally permitted to do so.
- In some districts, as few as 4% of private sector outlets stocked ACTs.
- On average, 11 days of household income would be needed to purchase a single course of ACT for a five-year-old child

The realization that a typical family would have to choose between food and education and purchasing medicines for the treatment of malaria is a humbling one. On a positive note, these results provide evidence and justification for policy-makers hoping to
expanding access to effective, affordable, high-quality ACTs in malaria-endemic countries, such as Uganda. More specifically, the study could inform the design of potential international financing mechanisms to subsidize the manufacturers’ price of ACTs, thus reducing the costs to patients.30

2.4 Solutions to reducing costs

There is a fundamental dilemma faced by pharmaceutical companies in the development and manufacturing of medications for diseases such as malaria: When the cost of R&D is high and there is insufficient potential for profit to justify the investment, there can be very little incentive to invest. In regards to malaria drugs, a pharmaceutical companies effort in maintaining a profit and viable business leads to cost far in excess of what patients can afford under the standard of living in sub-Saharan Africa. A number of creative and successful solutions have been developed to overcome these barriers in an attempt to level the playing field.

2.4.1 Affordable Medicines Facility for Malaria

In April 2009, the Global Fund to Fight AIDS, Tuberculosis and Malaria, in conjunction with Rollback Malaria Partnership, as well as the governments of Norway, Great Britain, and the Netherlands, unveiled a new program entitled the Affordable Medicines Facility for Malaria (AMFm).31 Along with the Global Fund, the AMFm first negotiates with pharmaceutical manufacturers to require that sales prices for ACT’s be the same for both public and private first time buyers. Original prices for these drugs may have been as

much is $4. The goal of the AMFm was to produce this to as low as $1. Next, a subsidy managed by the Global Fund further reduces the cost by providing a 'buyer copayment’ directly to manufacturers. This further reduces the cost of the drug down to as little as $.14. In appendix 8, an excerpt of the official fact sheet on ACT prices is shown. Values are consistent and support what has been a very successful program thus far. In October 2012, an evaluation of the program published in the Lancet noted “in the six pilots where the programme was implemented to a substantial degree, AMFm met or exceeded benchmarks for availability, price, and market share of quality-assured ACTs.”32 In November 2012, the Global Fund voted to integrate AMFm into its core grand processes.33

2.4.2 Institute for One World Health

Artemisinin is usually grown organically, though in 2004 researchers at Berkeley were rapidly developing the ability to produce a synthetic form of the drug. This held enormous potential to reduce the cost of ACT’s, though basic research at Berkeley needed to be scaled up, manufactured, and commercialized and managed through the regulatory process. Under a $42 million grant provided by the Gates foundation, Berkeley received $8 million for the support of the basic research, while Amyris Technologies (a for-profit renewable energies company headquartered in California) received $12 million for research on the fermentation and chemical processes, as well as optimizing the synthesis of the drug. The Institute for One World Health, (iOWH), a nonprofit

33 http://www.theglobalfund.org/en/mediacenter/newsreleases/2012-11-15_Board_Approves_Integration_of_AMFm_into_Core_Global_Fund_Grant_Processes/
pharmaceutical company, received the final $22 million for overall product development and market entry strategies.\textsuperscript{34}

Certain details of the collaboration are particularly interesting. Under the terms of the agreement, Berkeley licensed Amyris to have the ability to profit from production of Artemisinin products (such as flavors and fragrances) in the developed world. No profit was allowed for any revenue off its use in malaria drugs. Between Berkeley and the iOWH, the license only allowed to drug to be sold at cost in the developing world.\textsuperscript{35} The agreement basically eliminates the uncertainty in finding the next partner, or the uncertainty in a future contract term. Overall, there were no major gaps between stages of development, as time, expertise, and transactions were supported from start to finish. On April 11, 2013 global pharmaceutical giant Sanofi began large-scale production of a partially synthetic version of artemisinin for the purpose of incorporating it into its ACT medications.\textsuperscript{36}

\textbf{2.4.3 Drugs for Neglected Diseases Initiative}

Established in 2003 from a global consortium of seven health organizations, the Drugs for Neglected Diseases Initiative (DNDi) is a nonprofit R&D organization that develops drugs for neglected diseases, particularly malaria.\textsuperscript{37} DNDi does not perform research in hospitals or laboratories, but rather manages and uses partners, existing resources and expertise to develop drugs in a way that minimizes costs, redundancy, and failure. As has

\textsuperscript{34} http://www.iphandbook.org/handbook/case_studies/cs20/
\textsuperscript{35} http://pt.slideshare.net/egiegerich/public-private-partnerships-that-promote-global-health
\textsuperscript{36} http://newscenter.berkeley.edu/2013/04/11/launch-of-antimalarial-drug-a-triumph-for-uc-berkeley-synthetic-biology/
\textsuperscript{37} http://www.dndi.org/about-us/overview-dndi.html
been mentioned, adherence to anti-malarial drugs is greatly improved when combination drugs come in a single formulation.

As one of the 4 Artemisinin-based combination therapies recommended by the WHO for the treatment of malaria, Artesunate and Amodiaquine (ASAQ) was unavailable in a fixed dose combination until 2007. DNDi coordinated the development of one while keeping ownership of the related intellectual property. DNDi then licensed the intellectual property to Sanofi for manufacturing and distribution of the fixed dose combination to sub-Saharan Africa. Under the terms, Sanofi can sell the drug there at a maximum price of $1. In the private sector, Sanofi can sell the fixed dose combination of market price, of which a small royalty is returned to DNDi. The two agreed not to file a patent on the drug so other pharmaceutical companies can manufacture it. By April 2013, more than 200 million treatments of ASAQ had been distributed in Africa since the agreement and drug became available in 2007.

2.5 Contributions of private pharmaceuticals

Perhaps beyond the perception-heavy concept of corporate responsibility, major pharmaceutical corporations have demonstrated an altruistic and perhaps even sound business making decision in contributing to finding solutions to the malaria problem in sub-Saharan Africa. While the pharmaceutical field is sometimes criticized for a lack of transparency in releasing studies that show failure, in this situation it is the information

---

38 Hotez, Peter. Strengthening Mechanisms to Prioritize, Coordinate, Finance, and Execute R&D to Meet Health Needs in Developing Countries. Institute of Medicine January 15, 2013
that has shown success and replicability that is so vital for others profit from. With support from the Medicines for Malaria Venture, “Glaxo-Smith-Kline released the chemical structures and assay data for 13,500 compounds it had identified as having antimalarial activity against *P. falciparum.*” The information is freely available in the European Bioinformatics Institute’s ChEMBL database and the NIH PubChem database.\(^40\)

Glaxo-Smith-Kline, which has been spending hundreds of millions of dollars in developing a malaria vaccine, has also stated it intends to provide robust support to the national pharmaceutical programs in the countries where it’s product will be providing the most benefit. The company also is involved with a number of partnerships, including Save The Children, Planned Parenthood of Nigeria, AMREF Health Africa, and the African Malaria Partnership. Johnson & Johnson has engaged in several R&D partnerships, including The Medicines for Malaria Venture.

Novartis is also involved with AMFm, and works with purchasers who have signed a ‘first-line buyer’ previously discussed in section 2.4.1. Novartis tracks price levels across several countries using ACTwatch, a research group that measures accessibility and affordability of anti-malarials. The company also holds National Malaria Control Program seminars on an annual basis, bringing together all contributors and players in the production and distribution chain to examine ways that the procurement of malaria treatments can be improved.

\(^{40}\) So, Anthony. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards. BMJ 2012; 344:e1782 doi: 10.1136/bmj.e1782 (Published 3 April 2012)
Novartis’ SMS for Life program enables messaging between dispensing health clinics to communicate with pharmaceutical district managers who are able to bring medicine to districts that need them. While 26% of facilities had no anti-malarials when the program began, within two years this number was reduced to less than 1%. Since April 2011, SMS for Life has covered all 5,009 health facilities across Tanzania.41

---

3.1 Introduction

Funding, of course, is fundamentally crucial to all operations involving eradication of malaria. *Policy Cures* is a well-respected independent research and strategic analysis group that provides information and decision-making tools for the purpose of creating pharmaceuticals for neglected diseases such as malaria, HIV, tuberculosis, and many others. In December 2013, the group released a comprehensive 64-page report entitled *From Pipeline to Product: Malaria R&D Funding Needs Into the Next Decade*, which also functioned as an update to its 2011 report; *Staying the Course*.

3.2 Key findings

A number of key findings are reported:

- Since 1993 annual funding for malaria R&D has increased from US$131 million in 1993 to $610 million in 2011.

- The average annual total global investment in malaria R&D between 2007 and 2011 was roughly $600 million.

- This amount has been consistent and stable; though the group projects that funding requirements over the next decade must average at least $700 million annually to meet needs and expectations.

- While the philanthropic sector contributed roughly a third (32%) of that figure (public funding provided 51%, and industry 17%), 90% of the funding was

---

42 http://policycures.org/whoweare.html
concentrated within the top 12 organizations. (Appendix 9)

- 99% of all philanthropic funding comes from the Gates foundation (84%), and the Wellcome Trust (15%).

- Nearly half of all malaria R&D funding (48%) comes from the Gates foundation and the NIH.

- Changes in circumstances and interactions with other drugs can greatly impact costs and timelines, though the development of one drug can cost from $150-$250 million over 7 to 10 years.

- Drug R&D has received between $190 and $250 million annually since 2007. Perhaps burdened by the global financial crisis, public funding for drug R&D has dropped over that time while private industry funding has been steadily increasing (from $62 million in 2007 to $92 million in 2011).

3.3 Expectations

Researchers set a fairly lofty outlook for projecting malaria funding over the next decade. The goals range from $5.5 to $8.3 billion, at an average of over $700 million a year. These R&D investments are critical, given the emergence of drug resistance in the malaria parasite and insecticide resistance in the mosquito. However, if drugs, diagnostics, vaccines, and insecticides are successfully developed, manufactured, and implemented, funding needs will naturally decrease as goals and exit points defined by the Global Malaria Action Plan are attained. It should be recognized that the R&D

---

43 Policy Cures. *From Pipeline to Product, Malaria R&D Funding Needs into the Next Decade* Copyright 2013, Program for Appropriate Technology in Health
pipeline that has never been healthier, with nearly 90 products in development. This pipeline includes almost 40 drugs, ten of which are in late-stage clinical trials, including the first vaccine candidate to reach late-stage testing. In a notable change from the 2011 report *Staying The Course*, the most recent publication notes that despite earlier projections that funding needs may decline after 2017, the latest projections confirm that funding must be stable through at least 2022.\textsuperscript{44}

\textsuperscript{44}http://www.malariaavaccine.org/pr2013Dec6-RD-report.php
Chapter 4 – Evaluation of Cost Effective Studies

4.1 The importance of cost-benefit

Until relatively recently, no study had evaluated – on a macro scale - how effective the previously mentioned funding was, particularly considering the priorities of limitation vs. null state vs. total elimination that a national malaria program might set as goals. A 2010 study in the Lancet evaluated 6 separate cities/communities (all >1m people) – 2 of which were African (Swaziland and Zanzibar) - and concluded; “The decision facing policy makers, however, is how to best allocate limited resources in the short term.” Furthermore, in particular, “Zanzibar will need to allocate nearly a fifth of estimated public health resources, whereas Swaziland will need to consider increased malaria spending in the context of its massive HIV/AIDS burden.” Ultimately, the paper states: “cost–benefit analysis, which enables broader benefits to be translated into a common monetary metric, is a more effective means to inform strategic decision.”

4.2 Primary and secondary treatment

As mentioned, malaria is preventable and treatable. Primary treatment includes insecticide treated nets (ITN’s) and indoor residual spray (IRS), while secondary treatment involves testing and treatment, and includes anti-malarial medication, as well as rapid diagnostic tests (RDT’s). Both must be implemented prudently and efficiently to maximize health outcomes.

4.2.1 **Primary forms of treatment: Cost-effectiveness of ITN’s**

Long-lasting insecticide treated nets (those which last three years or more) have long been recommended by the WHO, particularly when they are free or highly subsidized through public health services.\(^{46}\) However, many countries are still far behind the goals established by Roll Back Malaria. A suitable mechanism for distribution is still up for debate, and a study in Burkina Faso in 2009 compared the effectiveness of using subsidized sales supported by social marketing versus free distribution to pregnant women through antenatal care (ANC).\(^{47}\) Contrary to prior studies that attempted to evaluate this question, this data here was gathered in the same setting, using the same methodological approaches. The researchers developed both a financial analysis (using the providers perspective), and an economic analysis (using the societal perspective). Using the framework of a community-based cluster-randomized controlled trial, rural districts were divided up into 24 rural clusters, each which received WHO-approved ITN’s.

The well-known NGO Population Services International (PSI) managed the social marketing arm of the study, with the costs incurred by PSI, the wholesalers, and the shopkeepers accounting for the data considered in the financial analysis. The local health district managed the antenatal care/free distribution arm of the study, with costs incurred by the Ministry of Health through the NHD. While fewer nets were distributed through the ANC (5,227<15,000), the total cost for the ANC distribution system was slightly less ($7.21<$8.08). Economic costs were calculated by discounting the capital costs,

---

\(^{46}\) [www.who.int/malaria/publications/atoz/itnspospaperfinal.pdf](http://www.who.int/malaria/publications/atoz/itnspospaperfinal.pdf)

incorporating users contributions (excluded from the financial analysis), and by considering the opportunity cost for the existing resources (from both arms of the study). Remarkably, the analysis found the same cost per net distributed ($4.81) for both arms of the study.\textsuperscript{48} It should be considered that the social marketing campaign entailed by PSI involved additional temporary staff, while distributing ITNs through the ANC entailed primarily increasing and/or modifying the workload of already employed staff. This opportunity cost accounted for 54\% of the ANC economic costs. Overall, the paper concluded that the economic costs of providing free ITNs were not higher than providing ITNs through sales supported by social marketing. Furthermore, when there is an ability to rely on underutilized existing resources, (as may be common in sub-Saharan Africa) the financial intervention cost per ITN distributed is likely to be much lower for free distribution through an ANC.

\textbf{4.2.2 Primary forms of treatment: Cost-effectiveness of IRS}

Along with ITN’s, indoor residual spraying (IRS) is recommended by the WHO as a standard means of malaria control. It is currently used in 44 countries.\textsuperscript{49} Perhaps motivated by a Cochrane review in 2010, which concluded that there was insufficient data whether IRS or ITN provides better protection of malaria\textsuperscript{50}, a recent paper discussed a nonrandomized prospective cohort study in Kenya to determine the efficacy of a combination of ITN’s and IRS, in comparison to ITN by itself. While the researchers found that the combination provided significantly greater protection, they noted that “to

\textsuperscript{48} Ibid (www.who.int/malaria/publications/atoz/itnspospaperfinal.pdf)
\textsuperscript{49} World Health Organization, World Malaria Report 2009
help determine the best use of finite resources, a cost-effectiveness analysis would be useful and should explore the benefit of providing more protection to a limited number of homes through the combination of IRS and ITNs and less protection with ITNs alone to a larger number of homes.”\textsuperscript{51} Unfortunately, a cost-benefit analysis of this type could not be found in the literature, though this highlights the continual need to evaluate malaria interventions for cost-effectiveness at this primarily preventive level, in an effort to best allocate resources.

4.2.3 Secondary forms of treatment: Cost-effectiveness of RDT’s

Rapid diagnostic test for malaria have been in use since as early as 1999, and with or without conventional microscopy, can be extremely reliable in diagnosing malaria. Used alone, an RDT has a sensitivity of approximately 95\%,\textsuperscript{52} and can commonly be used in a rural setting where there is a lack of trained technicians and equipment. This may initially appeared to be particularly useful, as malaria is often diagnosed on clinical grounds (generally a fever), and even if present microscopy equipment is usually quite poor. However, an RDT cannot measure parasite load or treatment success.\textsuperscript{53} It would seem logical to then assess the cost-effectiveness of an RDT, which may be particularly unique based on the population and endemicity.

A study published in 2010 evaluated the economic ramifications of implementing RDT’s

\textsuperscript{51} Ibid (www.who.int/malaria/publications/atoz/itnspospaperfinal.pdf)
\textsuperscript{52} http://www.wpro.who.int/malaria/sites/rdt/whatis/action.html
\textsuperscript{53} http://www.rapid-diagnostics.org/rti-malaria-diag.htm
in public health facilities in Dar es Salaam.\textsuperscript{54} Researchers evaluated the \textit{replacement} of microscopy with RDT in four healthcare centers, comparing with two healthcare center controls (RCT not introduced). A pre-and post intervention survey was conducted on both providers and patients, which evaluated the costs involved for patients as opportunity costs such as lost to work and travel time, and costs for providers as all outpatient service costs, including overhead and all costs associated with the training and implementation of RDT’s. From the patient point of view, the study found that those in the RDT group had a statistically significant reduced user fee for pharmaceuticals. While opportunity cost for patients was similar in both groups, it was far larger then a patient’s direct healthcare costs. RDT clinics were noted to have a 42-minute shorter appointment time. While pharmaceutical costs were also decreased for providers, facility costs (which include overhead, equipment, and staff costs) were notably higher for the RDT group. Overall, patient costs decreased by $.36 per visit to an RDT clinic, while provider costs \textit{increased} $1.31 in RDT clinics – notably $1.87 for patients under five years of age.\textsuperscript{55}

What is concerning here is that a reduced user fee for patients in RDT clinics may counter incentivize providers to go that route in diagnosis. On a positive note, researchers found lower false positive test results and evidence of improved physician compliance in the RDT group. In addition, more reliable malaria testing can provide more useful real-time data on the advancement and progress of the disease from a public health standpoint. Nevertheless, a number of questions and possible implications remain concerning the usefulness, long-term benefit and generalizability of the use of RDTs.


\textsuperscript{55} Ibid (Yucich)
That being said, a trial in Ghana in 2010 gave encouraging results on the fundamental benefits of RDT’s. Both under and over-diagnosis of malaria can have significant financial and public health effects, particularly when malaria incidence is decreasing, thus resulting in an increasing proportion of serious non-malarial fevers. Researchers evaluated the provider habits in four clinics in southern Ghana, three of which were introduced to RDT’s. Unlike the last paper, in this case an RDT replaced simple clinical evaluation, and not only microscopy, using a randomized, controlled, open-label clinical trial.\(^{56}\)

This involved healthcare settings where microscopy was replaced with RDT and compared to previous behavior, and where simple clinical diagnosis was replaced with RDT and compared to previous behavior. In a result that is likely consistent with the study above, in the microscopy group, both providers who remained users of microscopy and those who were replaced with the use of an RDT continue to prescribe anti-malarials to patients with a negative test results over 50% of the time. However, concerning those providers where clinical diagnosis was made without the aid of a test, addition of an RDT in the absence of microscopy reduced antimalarial prescription rate in patients with a negative test results from 90% to 54% of the time.\(^{57}\) Unfortunately, the study did not include a specific cost value analysis, though a two-day training class for all providers on the instruction of an RDT would have been an important component of that. Nevertheless, the cost of irrational drug prescription is significant, and in cases where no

\(^{56}\) Ansah, Evelin. Rapid testing for malaria where microscopy is available and clinics where only presumptive treatment is available: a randomized controlled trial in Ghana. BMJ 2010;340:c930

\(^{57}\) Ibid (Ansah)
current test is utilized, addition of an RDT may lead to significant reductions in pharmaceutical costs.

4.2.4 Secondary forms of treatment: Cost-effectiveness of Artesunate

As discussed, Artesunate had been an effective anti-malaria drug the treatment of malaria, until concern for resistance developed and Artesunate combination therapies (ACT) became the standard of care. As discussed above, a number of creative partnership solutions - including others that make use of tiered pricing and changes in intellectual property – have resulted in a downward trend in ACT prices over the last 10 years (Appendix 10). While this may complicate the long-term validity of a cost-benefit analysis on antimalarial therapy, at the moment inpatient care for malaria can exceed the annual per capita health spending in sub-Saharan Africa ($34).

Furthermore, considering that 85% of all malaria deaths are children under the age of five, the recent (July 2011) study by the WHO on comparing parental (infusion or injection – not by mouth) Artesunate (an Artesunate derivative) with an alternative – Quinine (which has been a mainstay treatment), should be reviewed and discussed.58

Nested within The African Quinine Artesunate Malaria Treatment (AQUAMAT) trial – an 11 site, 9-country trial carried out across Sub-Saharan Africa – researchers at the WHO conducted an economic analysis on the cost-effectiveness of Artesunate. Drawing from a diverse group of sites throughout sub-Saharan Africa, the evaluation framework

utilized incorporated cost for disability-adjusted life years (DALY) averted and cost of
death averted as measures of cost-effectiveness. Drug costs, laboratory costs, and general
inpatient fees were standardized according to WHO guidelines, with parameters of
mortality, severe neurological sequel, and DALY’s evaluated for both drugs. The sample
size totaled over 5400 patients, and mortality was slightly lower (8.5%) in the Artesunate
arm compared with the Quinine arm (10.9%). Of note, was that an additional .7 DALY’s
avoided in the Artesunate group (2.3 vs. 3.0). Both drugs cost roughly $66 per course,
and statistical analysis showed that Artesunate would be cost-effective over Quinone at a
price up to roughly $105. The cost per DALY avoided was only $4, with a cost per life
saved of $123.59 It should be noted that since this study was published, new modes of
Artesunate administration have been recommended and prioritized in the WHO
prequalification process.60

4.3 Cost-effectiveness of home management of malaria

Of course, malaria treatment, particularly in sub-Saharan Africa, does not always occur
as an inpatient. Home management of malaria (HMM) is a form of treatment promoted
by the WHO, and is accepted as policy in 18 sub-Saharan countries – particularly those
with limited infrastructure. HMM is, as can be expected, fraught with many of the
complications and unfortunate outcomes previously addressed in this paper, which may
include unnecessary exposure to malarial medications, wasting valuable drugs, and a
general misuse of resources.61

59 Ibid (Lubell)
tolerability of combo-antimalarial therapies for uncomplicated malaria in Ugandan children. Malar J 7: 106.
HHM however, will not be going anywhere anytime soon – so a cost-effective evaluation of it can be crucial to contributing to solutions to these very problems. In a recent study headed by scientists at the London School of Hygiene and Tropical Medicine, researchers applied a Markov model (generally used to model systems that behave randomly) to a number of different diagnostic and treatment outcomes in the many possible disease courses that a child under the age of five with a fever suspected as malaria may undergo. Using Uganda’s Ministry of Health cost figures as a standard, a hypothetical cohort of 1,000 children was repeatedly cycled through the model.\textsuperscript{62} While detailed evaluation and description of the studies statistical analysis is beyond the scope of this paper, particular outcomes can be drawn, which, despite not having specific numerical values included, deserve consideration.

The analysis showed that HMM and can be particularly cost-effective when transmission rates are very high and the likelihood of appropriate medical care is well. In addition, using the ACT artemether-lumefantrine instead of chloroquine “expands the range of beneficial coverage”\textsuperscript{63} to the point where HMM becomes under high transmission rate at all levels of access to health facilities (Appendices 11, 12).


\textsuperscript{63} Ibid (Lubell)
Chapter 5 – Recommendations and Conclusion

5.1 ACT administration and drug development: Recommendations

The extraordinary amount of funding that is anticipated to be necessary is unfortunately built off the premise that resistance will develop to even the impressively effective ACT drugs currently in use. In fact, resistance has already been shown to develop in parts of East Asia. The populations at risk and currently affected by malaria can make an extraordinary difference in reducing the likelihood of these unfortunate consequences.

- The first, most prevalent, and perhaps most rewarding point of intervention in the process of drug delivery is between provider and patient. Providing clear instructions on drug adherence is essential. Visual aids, in addition to written instructions have shown to be helpful and would be essential and improving malaria medication adherence.

- Communication and ideally, standardization, is essential to ensure that best practices are followed routinely and consistently. Situations such as the one in South Africa where even districts have inconsistent policy measures are unacceptable.

- Standardizing definition and adherence tools would also be extremely helpful for assessing adherence on a macro level.

- It may seem simple and perhaps obvious to recommend vigilant enforcement on the restriction of selling outdated medications that resistance has developed toward, though the implications of this not being handled is arguably far greater than the financial cost of strict regulation.
• The prime mover behind the recruitment of pharmaceutical companies cooperation are the well-established philanthropic/nonprofit frameworks and organizations with the resources, reputation, and credibility for facilitating for a successful drug development and delivery process.

• Initiatives and partnerships such as Medicines for Malaria Ventures, the Gates Foundation, and Rollback Malaria are the backbone of malaria treatment, and a successful contribution towards the cause will almost certainly have involvement with one of these organizations.

• Furthermore, utilizing such resources to reduce the risk involved with a for-profit companies entry into the antimalarial drug market has been shown to be and will continue to be an effective avenue to engage large-scale pharmaceutical research and production.

• It is crucial to recognize however, that these partnerships are run in a business-like fashion, not not-for-profit. Pharmaceutical companies are not interested in engaging in an indefinite number of such agreements.

5.2 Funding: Recommendations

Funding will be continually needed to close the translational gap between a patient’s resources and the market price. As has been discussed, the emergence of public private partnerships and the like between charities, large pharmaceutical companies, and small biotech firms has made an enormous impact.
• The lack of diversity and overall funding (concentrated contributions from 12 major donors), particularly in drug R&D is concerning. Fundraisers should pursue opportunities outside of U.S. to other western nations, particularly in Europe.

• In general, the global malaria funding community must be diligent in making a concerted effort to maintain support from established donors, while recruiting and developing new ones.

• To gain the trust and support of new funders, fundraisers should demonstrate how basic research could be better aligned with product development and distribution.

• Concepts of coordination and measurable outcome need to be apparent and demonstrable to ensure the commitment that fundraisers are seen as necessary over the next decade.

• Ultimately, it would be best to avoid a ‘selling’ of this cause to fundraisers and for-profit businesses as a ‘lost leader’. Policymakers and others in a position of influence should be assured that Malaria R&D funding is a wise investment and will bring value for their money.

5.3 Cost Effectiveness: Recommendations

There are many other locations of intervention in the disease course of malaria that have been left unaddressed in this paper. However, many of the most fundamental and important points for analysis and/or change have been discussed, with a theoretical goal to provide the authors of the 2010 Lancet paper described above some particular pieces of advice on how to develop a more strategically cost-effective malaria treatment delivery process. The following recommendations are provided:
• There appears to be no clear superior distribution model for efficient distribution of ITN’s. What can be recommended is to utilize a free distribution model (such as the antenatal care) when there are unused resources in the community, as the financial intervention cost per ITN distributed will be lower.

• While evidence suggests that a combination of ITN’s and IRS is superior, a cost benefit analysis should be carried out on the monetary value of this combination.

• From a patient point of view, the opportunity costs lost from a visit to a healthcare provider are considerable. If a cost-effective analysis is to include a greater cost to overall economic output (as it should), medical interventions should greatly consider this aspect of patient care.

• It appears that replacing clinical evaluation of potential malaria with an RDT holds great potential in the reduction of wasted resources and unnecessary exposure to anti-malarials. However, more specific cost-benefit analyses should be done to obtain a monetary value for this possible gain.

• Replacing microscopy with RDT is likely to be much less cost-effective; however training for providers to learn how to use RDT’s is in fact not very high per RDT.

• Artesunate holds a clear advantage over Quinine in the parenteral treatment of severe malaria and children. In fact, providers should favor Artesunate financially until it reaches a course cost of $105

• In perhaps what symbolizes the unfortunate limitations of health infrastructure, home management of malaria should still be considered a cost-effective solution under circumstances of high transmission and low access to health facilities, a solution more attractive under drug therapies such as Artemether-Lumefantrine.
5.3 Conclusion
With help and support from the rest of the world, the sub-Saharan African region has
made great progress in the challenge of the eradication of malaria. The agreements
brokered among parties from a vast variety of backgrounds and interests is indicative of
the cooperative human spirit intent on overcoming illness and death. It is fair to say that
public attention has indeed been drawn to this problem, and has resulted in an
extraordinary amount of financial and intellectual assistance. There is of course, a
discrete and limited amount of money and resources to implement. As a result, making
the right choice on resource allocations based on these limited finances is of paramount
importance. The use of cost-effective analysis thus becomes crucial to making these
decisions, and a significant amount of research has been carried out to obtain this
information. Ultimately, overcoming this challenge requires the teamwork of all of those
affected and involved. From patients and providers, to ministers of health and CEOs of
private pharmaceutical corporations, to basic science researchers and philanthropists,
each can and must make a viable effort and impact if the eradication of malaria is to
eventually take place.
Appendices

Appendix 1: Deaths due to malaria broken down by region since 1980

Appendix 2: Global malaria deaths and R&D funding

Source: http://www.economist.com/blogs/dailychart/2011/10/malaria

Appendix 3: Life Cycle of plasmodium protozoa

Source: http://www.nature.com/nrg/journal/v8/n7/images/nrg2126-f1.jpg
Appendix 4: Changes in national malarial treatment policy from 2003 to 2007

Appendix 5: Treatment policy timelines for sub-Saharan African nations for the treatment of *P. falciform* malaria

![Timeline of antimalarial drug policy changes in Africa](image)


Appendix 6: Differences in malaria treatment policy by province within South Africa.

<table>
<thead>
<tr>
<th>Province</th>
<th>CQ Year</th>
<th>SP Year</th>
<th>Artesunate-SP Year</th>
<th>AL Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>KwaZulu-Natal</td>
<td>1940s</td>
<td>1988</td>
<td>-</td>
<td>2001</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>1940s</td>
<td>1997</td>
<td>2001</td>
<td>2006</td>
</tr>
<tr>
<td>Limpopo</td>
<td>1940s</td>
<td>1998</td>
<td>-</td>
<td>2004</td>
</tr>
</tbody>
</table>

*CQ = chloroquine; SP = sulphadoxine-pyrimethamine; AL = artesunate-lumefantrine.*

Appendix 7: Results of study measuring efficacy of AL and DP antimalarial medication combinations.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AL (n = 416)</td>
<td>DP (n = 354)</td>
</tr>
<tr>
<td>Parasite persistence, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive blood smear day 1</td>
<td>269 (67.6%)</td>
<td>181 (52.2%)</td>
</tr>
<tr>
<td>Positive blood smear day 2</td>
<td>23 (5.6%)</td>
<td>20 (5.7%)</td>
</tr>
<tr>
<td>Positive blood smear day 3</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Fever persistence, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile* day 1</td>
<td>124 (30.0%)</td>
<td>65 (18.4%)</td>
</tr>
<tr>
<td>Febrile* day 2</td>
<td>8 (1.9%)</td>
<td>11 (3.1%)</td>
</tr>
<tr>
<td>Febrile* day 3</td>
<td>7 (1.7%)</td>
<td>7 (2.0%)</td>
</tr>
<tr>
<td>28-day WHO treatment outcome, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>16 (3.9%)</td>
<td>13 (3.7%)</td>
</tr>
<tr>
<td>Early treatment failure</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Late parasitological failure</td>
<td>137 (32.9%)</td>
<td>22 (6.2%)</td>
</tr>
<tr>
<td>Late clinical failure</td>
<td>74 (17.8%)</td>
<td>7 (2.0%)</td>
</tr>
<tr>
<td>Adequate clinical and parasitological response</td>
<td>189 (45.4%)</td>
<td>311 (87.9%)</td>
</tr>
</tbody>
</table>


| Country: Ghana                         |
| Manufacturer: any (except Novartis)    |
| Product (Individual Packs)             |
|                                      | Maximum Price (A) | Manufacturer Sales Price (B) | Co-payment percent (C) | Co-payment (D) | First-Line Buyer price (E) |
| AL 6X4                                 | 1.54              | 1.53                          | 91%                    | 1.39 (B*C)     | 0.14 (B-D)               |
| AL 6xi (non-dispersible)               | 0.43              | 0.42                          | 97%                    | 0.41 (B*C)     | 0.01 (B-D)               |

| Country: Ghana                         |
| Manufacturer: Novartis                 |
| Product (Hospital Packs)               |
|                                      | Maximum Price (A) | Manufacturer Sales Price (B) | Co-payment percent (C) | Co-payment (D) | First-Line Buyer price (E) |
| AL 6X4                                 | 1.59              | 1.59                          | 91%                    | 1.45 (B*C)     | 0.14 (B-D)               |
| AL 6xi (dispersible)                   | 0.54              | 0.54                          | 98%                    | 0.53 (B*C)     | 0.01 (B-D)               |

| Country: Kenya                         |
| Manufacturer: any (except Novartis)    |
| Product (Individual Packs)             |
|                                      | Maximum Price (A) | Manufacturer Sales Price (B) | Co-payment percent (C) | Co-payment (D) | First-Line Buyer price (E) |
| AL 6X4                                 | 1.22              | 1.21                          | 70%                    | 0.85 (B*C)     | 0.36 (B-D)               |
| AL 6X4 (non-dispersible)               | 0.83              | 0.82                          | 70%                    | 0.57 (B*C)     | 0.25 (B-D)               |
Appendix 9: Top 12 malaria R&D funders from 2007-2011

<table>
<thead>
<tr>
<th>Funding organisation</th>
<th>Average annual funding (US$) 2007-2011**</th>
<th>Average % of total</th>
<th>2007*</th>
<th>2008*</th>
<th>2009*</th>
<th>2010*</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gates Foundation</td>
<td>155,302,965</td>
<td>25.7%</td>
<td>134,823,644</td>
<td>138,972,244</td>
<td>199,315,338</td>
<td>95,297,069</td>
<td>157,033,439</td>
</tr>
<tr>
<td>US NIH</td>
<td>121,466,665</td>
<td>20.1%</td>
<td>91,449,280</td>
<td>113,515,618</td>
<td>125,658,629</td>
<td>143,980,486</td>
<td>132,729,353</td>
</tr>
<tr>
<td>Aggregate Industry</td>
<td>105,875,944</td>
<td>17.5%</td>
<td>94,304,511</td>
<td>97,323,316</td>
<td>106,222,381</td>
<td>128,434,867</td>
<td>103,082,744</td>
</tr>
<tr>
<td>European Commission</td>
<td>34,423,344</td>
<td>5.7%</td>
<td>41,771,327</td>
<td>39,235,678</td>
<td>33,342,713</td>
<td>277,44,251</td>
<td>30,022,549</td>
</tr>
<tr>
<td>US DOD</td>
<td>30,765,281</td>
<td>5.1%</td>
<td>33,552,928</td>
<td>33,322,812</td>
<td>40,710,817</td>
<td>24,522,851</td>
<td>19,582,000</td>
</tr>
<tr>
<td>Welcome Trust</td>
<td>27,521,000</td>
<td>4.6%</td>
<td>25,875,226</td>
<td>25,332,606</td>
<td>26,263,035</td>
<td>31,155,023</td>
<td>26,979,111</td>
</tr>
<tr>
<td>UK MRC</td>
<td>19,070,062</td>
<td>3.2%</td>
<td>17,023,345</td>
<td>17,991,100</td>
<td>19,320,065</td>
<td>22,155,835</td>
<td>18,616,027</td>
</tr>
<tr>
<td>UK DFID</td>
<td>13,362,716</td>
<td>2.2%</td>
<td>5,809,546</td>
<td>4,623,527</td>
<td>8,475,485</td>
<td>26,875,413</td>
<td>21,026,609</td>
</tr>
<tr>
<td>Australian NHMRC</td>
<td>13,382,180</td>
<td>2.2%</td>
<td>10,715,548</td>
<td>12,470,421</td>
<td>14,067,835</td>
<td>13,405,355</td>
<td>16,151,742</td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>9,702,558</td>
<td>1.6%</td>
<td>14,759,525</td>
<td>8,787,35</td>
<td>7,925,364</td>
<td>9,952,886</td>
<td>7,047,880</td>
</tr>
<tr>
<td>USAID</td>
<td>9,211,746</td>
<td>1.5%</td>
<td>10,019,784</td>
<td>9,267,054</td>
<td>8,945,663</td>
<td>9,456,998</td>
<td>8,439,233</td>
</tr>
<tr>
<td>Indian ICRR</td>
<td>7,033,715</td>
<td>1.2%</td>
<td>10,862,268</td>
<td>7,152,667</td>
<td>5,045,301</td>
<td>5,026,891</td>
<td>548,499,307</td>
</tr>
<tr>
<td>Top 12 subtotal**</td>
<td>530,590,904</td>
<td></td>
<td>616,805,359</td>
<td>664,498,130</td>
<td>596,945,190</td>
<td>602,577,790</td>
<td></td>
</tr>
<tr>
<td>Grand total</td>
<td>530,590,904</td>
<td></td>
<td>616,805,359</td>
<td>664,498,130</td>
<td>596,945,190</td>
<td>602,577,790</td>
<td></td>
</tr>
</tbody>
</table>

Source: Policy Cures. From Pipeline to Product, Malaria R&D Funding Needs into the Next Decade Copyright 2013, Program for Appropriate Technology in Health

Appendix 10: Price per adult treatment of ACT’s since 2001

Appendix 11: Utility of HMM using Chloroquine

**Figure 3.** Model output for the Uganda HMM programme using CQ+SP from a provider perspective. The model suggests that HMM will only be efficient in areas of medium and high transmission, where the probability of appropriate care is low. In low transmission areas HMM is more effective but too costly, and is not cost-effective. CQ+SP = chloroquine + sulfadoxine-pyrimethamine.


Appendix 12: Utility of HHM using AL

**Figure 4.** Model output for the Uganda HMM programme using AL from a provider perspective. Introducing AL into HMM appears to be efficient in most medium to high transmission areas, unless the probability that a child will receive appropriate care from a health facility is 100%. AL = artemether-lumefantrine.

Appendix 13: RTS,S Vaccine Milestones since 1984

RTS,S key milestones

- **GSK and WRAIR initiate collaboration**
- **First clinical tests in humans begin in adults in US**
- **First trials in Africa begin in the Gambia**
- **GSK-MVI partnership initiated**
- **Phase II results in African children and infants published in *Lancet***
- **Phase III study ends**
- **Final results over 32 months of follow-up**

**Phase III study starts**

**Phase III study second set of results**

**Phase III study first results**

**Key PoC study in adults in the Gambia**

**Key PoC study in children in Mozambique**

**Key phase II efficacy results in African children and infants published in *Lancet*** and *NEJM***

---

www.worldmalaria-day.org/download/partners/Updated_RTSS_FactSheet_21_April_2010.pdf
Bibliography


7. Centers for Disease Control and Prevention Malaria Parasites. (www.cdc.gov/malaria/about/biology/parasites.html)


18. IPH Handbook of Best Practices. Improved Production of a Natural Product Treatment for Malaria: One World Health, Amyris, and the University of California at Berkeley (www.iphandbook.org/handbook/case_studies/cs20/)


21. Malaria (www.biotopics.co.uk/malaria/malaria.html)


27. Policy Cures. From Pipeline to Product, Malaria R&D Funding Needs into the Next Decade Copyright 2013, Program for Appropriate Technology in Health


36. The Global Fund. Board Approves Integration of AMFm into Core Global Fund Grant Processes 15 November 2012

37. World Health Organization: Malaria In China (www.wpro.who.int/china/mediacentre/factsheets/malaria/en/)


