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The limitations of current malaria treatments in sub-Saharan Africa

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Thesis

THE LIMITATIONS OF CURRENT MALARIA TREATMENTS
IN SUB-SAHARAN AFRICA

by

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DEDICATION

I would like to dedicate this work to all individuals and communities who suffer from malaria.
THE LIMITATIONS OF CURRENT MALARIA TREATMENTS
IN SUB-SAHARAN AFRICA

IVY EUNICE WANJIRU GODANA

ABSTRACT

Current malaria treatments are ineffective in sub-Saharan Africa due to problems beyond the disease. Approximately 90% of malaria mortalities occur in sub-Saharan Africa, and 77% percent of these are children under the age of five. At the same time, sub-Saharan Africa is also the recipient of 80% of international aid. With international malaria funding increasing in recent years, there must be an analysis on the practicability of funded interventions as malaria continues to be a tremendous burden in the region.

This review highlights the complexity of malaria pathology and its association with poverty that makes treatments ineffective. Available, frontline antimalarial drugs and insecticides have shown increased resistance that has spread throughout many malaria endemic regions. This resistance aggravates the disease as the parasite and the vector evolve, resulting in increased transmission, increased severity of symptoms, and a high risk of mortality. In addition, the heavily funded malaria vaccine under development by GlaxoSmithKline and PATH shows partial efficacy that languishes over time, putting to question the practicability of such heavily funded interventions. The
limitations of available treatments necessitates a holistic approach that responds to the economic state of endemic regions in order to effectively alleviate the burden of disease.

An example of a holistic approach is the Multisectoral Action Framework for Malaria. This approach considers the socioeconomic development and fragile markets of endemic nations to encourage partnerships between governments and healthcare sectors in eradicating malaria. Although it will take years to demonstrate results, the burden of malaria calls for sustained efforts to alleviate the burden of the disease along with the poverty that perpetuates it.
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<td>piperonyl butoxide</td>
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<td>Roll Back Malaria</td>
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**Introduction**

**Malaria Biology**

Malaria begins with a female anopheles mosquito bite. During a blood meal, the malaria parasites are injected from the salivary glands of the mosquito, and into the blood stream of the human host (CDC (a), n.d.). Once in the blood stream, the parasites, known as sporozites mature and infect two hosts: the liver cells (hepatocytes) and the red blood cells (erythrocytes). In the liver cell, the parasites mature into schizonts. The schizonts then grow within the hepatocyte and eventually the cell bursts releasing merozoites. These merozoites then enter the blood stream, infecting the red blood cells. Some merozoites differentiate into sexual erythrocytic stages (gametocytes), which are responsible for infecting another mosquito that takes a blood meal from the infected host. Other merozoites, mature into trophozites then into schizonts, and eventually rupture releasing more merozoites that infect other red blood cells and the cycle continues (Miller, Ackerman, Su, & Wellems, 2013). This rupture is also known as schizogony (“Impact Malaria” n.d.). The parasites also undergo a maturation cycle within the mosquito that is not affected by their presence.

After infection, the host individual may be asymptomatic for a period of time depending on the particular species of the parasite. The plasmodium parasite is the cause of human malaria and exists as four species: *P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax* (CDC (a), n.d.). Following the parasites
incubation period within the host, symptoms such as cough, fatigue, malaise, shaking chills, arthralgia, and myalgia begin to manifest (Medscape, n.d.). Patients will typically clinically present with a simple headache. The most common symptom of malarial infection, however, is intermittent fever which coincides with schizogony or erythrocytic rupture (Medscape, n.d.). The periodicity of the fevers, or malaria paroxysms, also depends on the particular species of the parasite. Tertian fever intermittently occurs every 48 hours due to \textit{P. falciparum, P. vivax, and P. ovale} infection. Quartan fever intermittently occurs every 72 hours and is due to \textit{P. malariae} infection. Usually, it is the patients with longer standing, constant malaria infections that present with this classic symptom. However, the periodicity of the intermittent fevers, is not reliable in malaria diagnosis. Considering there are numerous other illnesses and infections that cause reoccurring fevers, differential diagnosis is perhaps the cause of the inaccuracy of reported values of malaria morbidities and mortalities (Medscape, n.d.).

The most aggressive of the malaria parasite species is the \textit{P. falciparum} that is responsible for the most severe malaria cases as well as 90% of all malaria mortality (Snow & Omumbo, 2006). Malaria paroxysms for this particular strain rapidly escalate into severe disease complications such as cerebral malaria or severe anemia (“Impact Malaria” n.d.). Other complications of severe malaria affect the nervous, respiratory, renal, and hematopoietic systems (Trampuz, Jereb, Muzlovic, & Prabhu, 2003). The complications of severe
malaria usually occur between 3-7 days of fever onset. Thus, early and accurate diagnosis and treatment are extremely important for this particular infection.

The Vector:

The primary purpose of the female anopheles’ bite, or blood meal, is for the successful production of eggs. Blood meals, therefore, are important in the survival of the anopheles mosquito populations. Male anopheles never bite mammals as they lack a proboscis to piece the skin in order to take a blood meal. In consequence, they primarily feed on fruit and vegetable juices. The females have proboscis so they are able to select their mammalian hosts as some are zoophilic, preferring animals, and others are anthrophilic, preferring human blood. It is the anthrophilic female anopheles mosquitoes that are responsible for malaria transmission (Snow & Omumbo, 2006). Taking a look at the life stages of the anopheles, like all mosquitoes there are four stages of life. The first is the egg, then the larva, and then the pupa. These first three stages must take place in climate appropriate water (Tusting et al., 2013). Before reaching the adult stage, the water temperature and salinity is crucial to proper development. Standing water is ideal for almost all species of mosquitoes (CDC (a), n.d.). The anopholes larvae, in particular, are known to prefer water that is exposed to the sun (Urban Malaria Control Program, n.d.). Thus ideal breeding places for malarial mosquitoes include mangrove swamps, rice fields, grassy ditches, the edges of streams and rivers, sewages, and small, temporary rain
pools. Habitats with vegetation are also ideal (CDC (a), n.d.). The fourth and final stage of life is the adult stage that naturally lasts about 2 weeks. This is the mosquito’s reproductive stage as well as the period of time that it is capable of acting as a malaria vector. The adult female anopheles can lay up to 200 eggs directly on water. The eggs distinctively float on either side of the mosquito. The eggs hatch after 2-3 days and the cycle of life continues. In colder climates, this development process may take up to 3 weeks or even longer. It is important to note that the eggs are not resistant to drying (Tusting et al., 2013). Thus the aquatic or humid environment is important for its survival.

The connection between the life cycle of the mosquito and the parasite is dependent on the life-span of the mosquito in its adult stage. The parasite completes its life cycle (gametocyte stage to sporozite stage) in the mosquito throughout a span of 10-18 days. If the mosquito, in its adult life lives long enough then it will be a successful vector. There are specific conditions to ensure successful development of the parasite. The most crucial conditions are temperature and humidity. Higher temperatures are known to accelerate parasite growth, increasing the likelihood of maturation within the mosquito lifespan (CDC (a), n.d.). Thus tropical climates, which are generally hot and humid, are ideal for both the parasite and the vector to thrive.

**Immune System:**

The human immune system is critical for the protection of humans from malaria, in malaria immunopathology, and in the development of clinical immunity
against malaria. Upon infection and as the result of an erythrocytic rupture, the presence of the parasites induce an immune response causing the release of cytokines which activate the hosts monocytes, neutrophils, T cells, and natural killer cells. These cells also respond to parasites in the liver and red blood cells. During hepatic infection, antigens brought along with the sporozite are presented on hepatocyte surfaces together with MHC (Major Histocompatibility Complex) Class I. The cytotoxic T lymphocytes recognize the antigens and kill the infected hepatocytes (Ho et al., 1986). Alternatively, natural killer cells and CD4+ T cells produce interferon gamma which causes an immune reaction cascade resulting in the death of an intracellular parasite. Thus, the parasite developing within the hepatocyte is a major target of protective immunity at the extra-erythrocytic stage (Perlmann & Troye-Blomberg, 2002).

Malaria immunopathology has shown the role the immune system plays in disease progression. Early malaria research determined that tumor necrosis factor (TNF) is released upon malaria infection. There is also an increased rate of secretion of TNF during schizogony (Kwiatkowski et al., 1989). Studies also show that anti-TNF therapy inhibits the manifestation of fever in malaria (Kwiatkowski et al., 1993). TNF, is thus associated with the characteristic intermittent fevers. Fever is also caused by the parasitic invasion of macrophages and monocytes which also secrete TNF as well as other endogenous pyrogens. Pyrogens are also partially responsible for the characteristic fevers through their action on the hypothalamus causing an increase in body temperature (“Impact Malaria” n.d.).
The primary cause of the intermittent fevers, however, is the TNF as demonstrated by studies that show all the symptoms of malarial paroxysm by the injection of TNF into humans (“Impact Malaria” n.d.). The immune system, thus, has a role in the progression of disease.

Protective immunity against malaria is acquired throughout life. In the first year of life, the newborn of an immune mother in a malaria endemic region has acquired immunity. This immunity is due to the passive transfer of IgG across the placenta, naturally protecting the newborn from infection (“Impact Malaria” n.d.). This protection, however, only lasts for the first 6 months of life. After these first 6 months, the child then begins to build immunity as exposure to the disease is frequent, and the immune system responds appropriately (Artavanis-Tsakonas, Tongren, & Riley, 2003). By the time the child is of school age, greater than 6, the child then reaches clinical tolerance, or a stage of anti-disease immunity. The child may have high levels of parasitaemia but may only manifest mild malarial symptoms or may even be asymptomatic. Throughout the child's life, if there is frequent re-infection and consistent or increased exposure, the child will eventually enter a state of premonition where there is significantly less parasitaemia and shorter episodes of infection (Artavanis-Tsakonas, Tongren, & Riley, 2003). This highlights the significance of a robust and active immune system not only in survival but in the development of sound immunity against malaria infection and re-infection.
**Vulnerable Groups:**

Within populations, the burden of malaria is heaviest for certain groups who are vulnerable to infection, severe disease, and mortality. High risk groups include pregnant women, infants whose passive immunity has begun to wane, children under the age of five, HIV/AIDS (Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome) patients, and migrants or mobile populations whose immune systems are unfamiliar with the parasite (WHO (d)). For pregnant women, much of the complications arise from the immunocompromised state of pregnancy and the sequestering of infected red blood cells around the placenta. Although the parasites do not harm the fetus, babies born to infected mothers are more than twice likely to be underweight at birth (Schantz-Dunn & Nour, 2009). A majority of the malaria mortality befalls on children under the age of five, due to their underdeveloped state of immunity along with malnourishment and lack of medical attention. For migrants and mobile populations, the lack of immunity makes them highly susceptible to infection as many reach adult age without building protective immunity (CDC (b), n.d.).

There is evidence that in regions of malaria and HIV infection, there is a debilitating interaction between the two. HIV infection, is known to suppress the immune system increasing the likelihood of malarial infection. HIV also increases the severity of malaria. As aforementioned, malaria increases CD4+ T cell
activation and increases the up-regulation of cytokines. This provides an ideal
microenvironment for the HIV virus to spread among the CD4+ T cells and also
for the rapid replication of the HIV virus (Alemu, Shiferaw, Addis, Mathewos, &
Birhan, 2013). Therefore, malaria aggravates HIV and HIV increases the burden
of malaria ("UNICEF," n.d.). This is particularly important due to the heavy
geographic co-infection of both diseases in Sub-Saharan Africa. Figure 1 shows
regions of HIV prevalence indicated in darker colors. Most of the darkest shaded
countries lie exclusively in sub-Saharan Africa similar to the regions in Malaria
transmission as shown in Figure 2.

Figure 1: Global Distribution of HIV infection
Source: (Incidence, n.d.)
Prevalence:

High malaria prevalence is confined to sub-Saharan Africa. According to WHO's World Malaria Report, in 2012 there were 97 countries still combating malaria transmission (WHO (d), n.d.). Of those 97 countries, a majority were in sub-Saharan Africa. Approximately 90% of malaria mortalities occur in sub-Saharan Africa and 77% occur in children less than 5 years old (WHO(d), n.d.). This prevalence is consistent with the climate conditions. Considering the warmer and tropical regions are along the equator, malaria parasites thrive in these areas. Thus, transmission is more intense, and year-round (CDC (b), n.d.). The interesting thing to note about the distribution of malaria within the tropics is that prevalence is not as high in tropical regions of South America. Reasons for this disparity will be addressed in later chapters. However, as shown in the map in Figure 2, high malaria prevalence is within tropical regions near the equator.
Figure 2: Global Distribution of Malaria  
Source: (CDC (e), n.d.)

Malaria Burden

For over a century malaria has been a global burden. Currently, this burden is perhaps the heaviest for Sub-Saharan African countries that bear the disease in addition to numerous other infectious disease and fragile economies. There are approximately 97 countries, most in Sub-Saharan Africa, that still have ongoing malaria transmission according to WHO’s 2013 World Malaria Report. In 2012, there were about 207 million cases of malaria and about 627,000 mortalities (WHO (d), n.d). The *P. Falciparum* parasite is responsible for almost all malaria mortality and it is estimated that the Sub-Saharan region bears about 90% of its burden (Harrison, 1978). Thus the mortalities are mostly attributed to this particular strain of malarial parasite. It is important to note that these
numbers are estimates rather than approximations because of the incompleteness and inconsistency in diagnosis and assessments over time (WHO (d), n.d.).

Although there has been much progress in vector control and in the eradication of malaria, there are still millions of people who suffer the burden of the disease at the expense of their lives. According to WHO, there are 219 million new cases of malaria each year. Malaria is still a major public health urgency that warrants a more holistic approach to eradication.
Current Treatments and The History of Malaria

The 19th and 20th centuries saw much discovery in the etiology and pathology of malaria as well as in malaria treatment. Although malaria treatment is determined by a myriad of factors, the most important is the species of malaria that caused infection and the part of the world in which the infection was acquired. These characteristics help in determining the extent of drug resistance and also in projecting the severity of disease (CDC (a), n.d.). Considering the prevalence of *P. Falciparum* in Sub-Saharan Africa, this species will be the focus of analysis in this chapter.

Antimalarial Drugs

As early as the 1600s, a quinolone containing substance, quinine, was extracted from the bark of a cinchona tree in South America and used in the treatment of fevers (Foley & Tilley, 1998; Sullivan, 2012). This symptomatic management long preceded the discovery of the malaria etiology and pathology by about 250 years. As a cinchona alkaloid, Quinine is basic so it is usually presented as a salt (Achan et al., 2011). Although the exact mechanism of action is unknown, research has identified that Quinine exerts its antimalarial effects primarily through the erythrocytic stage of infection. Targeting intra-erythrocytic malaria parasites, quinine is rapidly absorbed. Its chemistry, as a weak base, allows it to enter the food vacuole of the intra-erythrocytic parasite. Quinine then
works by inhibiting hemozoin bio-crystallization causing cytotoxic heme to accumulate, which is lethal to the parasite, inhibiting shizogony (Sullivan, 2012; Achan et al., 2011). Therefore, quinine is a schizonticide, because it is selectively destructive of the schizont of a parasite.

The pharmacokinetics of quinine varies for the host and the severity of malaria. Quinine is rapidly absorbed orally as well as parentally. Binding to alpha-1 acid glycoprotein, it is distributed within the body. Peak concentrations are reached between 1-3 hours. Through hepatic biotransformation, 80% is eliminated and the remaining 20% is excreted by the kidney. Its half-life is 11-18 hours (Achan et al., 2011). For patients that are infected with malaria, high concentrations of alpha-1 acid glycoprotein causes increased binding to quinine which results in a decrease in quinine’s volume of distribution and a decrease in elimination time (Achan et al., 2011). Therefore, malaria patients generally sustain high levels of quinine. Due to its low therapeutic index, physiological dangers of its use are referred to as cinchoism. This includes headache, nausea, hearing impairment, vomiting, and diarrhea (Sullivan, 2012). Despite its negative side effects, quinine was the most widely used and the only thoroughly effective anti-malarial treatment in its time. By the 1920s, other synthetic anti-malarial drugs became available and most were more effective with less severe side effects. By World War II, research produced a myriad of drugs that almost replaced quinine (Encyclopedia Britannica, n.d.). Perhaps the most notable is the drug chloroquine which was extremely widely used by the 1940s (Achan et al.,
Investigators of six countries worked on chloroquine from 1934 to 1946 from initial discovery, rejection, re-discovery, evaluation and finally its acceptance in 1946. By the 1950s and 1960s, chloroquine was the main antimalarial drug choice for WHO's Global Eradication Programme for malaria (Meshnick, 2002).

Chloroquine is also a weak base and a quinolone, synthesized to mimic the schizonticidal effects of quinine. Thus, its mechanism of action is the same. Chloroquine was shown to be more effective than quinine in slowing parasite growth (Encyclopedia Britannica, n.d.). Moreover, its wider therapeutic index made it safer to use than (Achan et al., 2011). Chloroquine achieved much success worldwide that in the 1950s, a Brazilian named Marco Pinotti introduced an idea of inserting the drug into cooking salt. The idea was well accepted and employed in South America, Asia, and Africa. Beginning in the 1960s, chloroquine use was halted due to increased cases of parasite resistance to the drug (Meshnick, 2002). Chloroquine's acceptance, wide-spread and heavy use marked the beginning of malarial drug resistance. By the 1980s, most areas with *P. falciparum* malaria saw chloroquine resistance. This then brought quinine back to the forefront of antimalarial drugs, as the parasite still remained sensitive to it (Achan et al., 2011).

By definition, antimalarial drug resistance is the ability of the parasite to survive and continue to multiply despite drug administration of doses equal and higher of that recommended within tolerance of the subject (Bloland, P., 2001). *P. falciparum* resistance to chloroquine is due to the parasite's ability to expel
chloroquine from its food vacuole fast enough before it exerts its schizonticidal effects. So before chloroquine can reach levels of heme polymerization, it is removed from the parasites food vacuole resulting in a decrease in the schizonticidal effects (Bloland, P., 2001). Chloroquine efflux can occur at a rate 40 to 50 times faster among parasites that are resistant compared to those that are not (Krogstad et al., 1987). This mechanism of resistance was verified with drugs such as verapamil that reversed the action of the efflux system, allowing chloroquine to accumulate and exert its effects (Martin, Oduola, & Milhous, 1987). Presently, the *P. falciparum* species has developed resistance to almost all antimalarial drugs, only varying in geographical distribution of the resistance (Bloland, P., 2001). In all regions of high *P. falciparum* infections, resistance to all antimalarial drugs has developed (CDC (a), n.d.). This evolution of resistance against affordable drugs, such as chloroquine, causes a tremendous societal and economic cost in combating malaria.

- **Artemisinin Drugs and Political Involvement:**

  For almost 2,000 years, Chinese herbal medicine practitioners have been using *Artemisia annua* to treat hemorrhoids. The history of the drug Artemisinin began in the Cultural Revolution in China in efforts to assist North Vietnam in the war against the United States. *P. falciparum* malaria was a burden to the Chinese Army and by this time, the parasite had already developed resistance to chloroquine. Vietnam then turned to China for help. This began Project 523
which was coded for the first meeting in 1967 to discuss the problem of chloroquine-resistant *P. falciparum*. By 1972, the active ingredient of *Artemisia annua*, *Qinghaosu*, was purified (Meshnick and Dobson, 2011). Concurrently with the Cultural Revolution occurring in China came clinical trials that showed *Qinghaosu* to be effective in rapid clearance of malarial symptoms, primarily parasites and fevers (Tu, 2011). As the research was a military secret, results and findings of the efficacy of *Qinghaosu* were not shared with the outside world before the revolution. After the revolution, results were published in the late 1970s and early 1980s (Meshnick and Dobson, 2011). In October 1981, a WHO Chemotherapy of Malaria group visited Beijing and Professor Youyou Tu presented the work of Project 523 (Miller & Su, 2011). Shortly after, a publication of the description of Artemisinin was made available. This information revealed artemisinin’s structure as a sesquiterpene lactone with an endoperoxide. The endoperoxide was revealed to be responsible for its antimalarial activity. Unfortunately, although the chemistry of the substance was available, the Chinese scientists wouldn’t share the method of crystallization and purification of the substance from the plant (Milhous & Weina, 2010). Arnold, a malaria researcher with the Walter Reed Army Institute, went to Hong Kong in 1979 to test the Army’s newly developed drug mefloquine, another antimalarial. After trying out his drug against artemisinin, it was clear that artemisinin was a front-runner in malarial treatment and this brought much attention to the Chinese drug (New York Times (a)). WHO took notice but political hesitation from both China
and the West resulted in no action. In 1984, Klayman, also with the Walter Reed Army Institute of Research in the United States, determined that *Artemisinin Annua*, in same structure, could be isolated from sweet wormwood, which grew along the shores of the Potomac River (Klayman et al., 1984). Unfortunately, Klayman’s compound, in drug form, was found to not be as effective as the *Qinghaosu* extracted by the Chinese.

Shown to be highly effective, artemisinin wasn’t used in regions of dire need due to political conflict. Aid agencies were unable to buy drugs that were not endorsed by WHO. By the 1990s, the international conflicts stalled efforts to collaborate with China to get artemisinin into the drug market. Dr. Arnold called WHO’s indecisiveness “genocidal” as nearly 1 million children in sub-Saharan Africa died from malaria while political dissention continued. In 2000, WHO finally endorsed artemisinin although it wasn’t available until 2006. Before its availability, in 2002 the Médecins Sans Frontières (MSF) demanded access to artemisinin but an adviser to the US Agency for International Development, Dennis Caroll, claimed that it “was not ready for prime time” (New York Times (b), n.d.). The political discord muddled the health efforts delaying endorsement, distribution, and usage. Chloroquine and other cheap drugs continued to be used despite the wide-spread resistance.

In China, patent law disappeared under communism. Western patents were not removed so major drug companies were unable to monopolize and profit from artemisinin. In 1994, a neutral, Swiss company, Novartis, bought a
new patent on a mix of artemether, which is an artemisinin derivative, and another Chinese drug, lumefantrine (New York Times (b), n.d.). Novartis planned to sell the mix under the name Riamet to militaries and tourists at a very high price tag but in 2001 agreed to sell it to WHO under the name Coartem. Coartem was sold at a price of $1.57 per treatment but much lower for children who were most vulnerable to malaria’s morbidity and mortality (Lefèvre, Marrast, & Grueninger, 2011). The price was still relatively expensive for many of the populations in Sub-Saharan Africa. It wasn’t until the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002 and President Bush’s Administrations President’s Malaria Initiative in 2005 that the drug became available to populations in developing countries.

These organizations bought out the drugs to deliver them to the world’s most endemic regions. Created in 2005, President’s Malaria Initiative, sought to expand government resources of $1.2 billion to reduce the intolerable burden of malaria and help relieve poverty on the African continent. The four strategies used include insecticide-treated mosquito nets (ITNs), indoor residual spraying (IRS), intermittent preventive treatment for pregnant women (IPTp), and artemisinin-based combination therapies (ACTs) (Presidents Malaria Initiative (PMI), n.d.). Provision of Novartis was a part of the deal. In 2002, The Global Fund to Fight AIDS, Tuberculosis and Malaria was founded to increase resources for the fight against malaria, tuberculosis, and AIDS. By creating and spurring partnerships between government, civil society, the private sector and
communities living with the diseases, the Global Fund drives remarkable progress in alleviating the burden of all three diseases in sub-Saharan Africa. For malaria, the Global Fund funds approximately 50% of all international funding to support the anti-disease efforts in prevention and eradication (Global Fund (a)). Therefore, these organizations were pivotal in the availability of antimalarial drugs in the world’s most endemic regions.

The highly effective and controversial artemisinin is a sesquiterpene lactone bearing a peroxide grouping. Different from other antimalarials, it lacks a nitrogen-containing heterocyclic ring system (Klayman et al., 1984). The mechanism of action involves the heme-mediated decomposition of the Endoperoxide Bridge producing carbon centered free radicals (Meshnick, 2002). Its selectivity to heme explains why it is toxic to malaria parasites. The exact mechanism of action is still under research however studies have shown, for example, that artemisinins directly impair mitochondrial functions of the malaria parasite (Vijverberg & vanden Bercken, 1990).

Comparative studies looking at the efficacy of artemisinin and mefloquine spurred suggestions that a combination therapy would prevent re-occurrence of malarial symptoms as well as the development of resistance. Mefloquine was found to work more slowly than artemisinin in parasite clearance. Artemisinin’s very short half-life requires use of a slow clearance antimalarial to prevent reoccurrence (Li, Arnold, Guo, Jian, & Fu, 1984). There was a growing fear in endemic regions of China that parasite resistance to artemisinin would arise as
many patients who took the drug as a standalone wouldn’t continue treatment after symptoms were cleared. Ultimately, they were not cured, and incomplete treatment would mark the beginning of drug resistance (Li, Arnold, Guo, Jian, & Fu, 1984). In later years, White, working in Thailand, confirmed artemisinin’s rapid activity and the need for a partner drug to effectively clear the malarial parasite (New York Times (a), n.d.). This then became the centerpiece of the use of artemisinin derivatives in combination therapy.

Artemisinin-based combination therapy is currently recommended for *P. falciparum* treatment. Fast acting Artemisinin compounds and derivatives such as Dihydroartemisinin, Artesunate and Artemether are used in combination with slower acting drugs such as Lumefantrine, Mefloquine, Amodiaquine, Sulfadoxine/Pyrimethamine, Piperaquine and Chlorproguanil/Dapsone (Malaria Consortium, n.d.). According to the CDC, *P. falciparum* has also developed resistance to drugs such as Quinine, Mefloquine, Halofantrine, and Sulfadoxine. The resistance to these drugs is less widespread. Currently, there have been an increase in the number of cases of decreased efficacy of ACT treatments in Southeast Asia (Dondorp et al., 2009; Meshnick, 2002). One of the greatest challenges in the next few years will be to maintain efficacy of these top line treatments by preventing resistance. This will require thorough drug monitoring as well as patient compliance.

**Public Health Interventions:**
Non-clinical malaria interventions are targeted to preventing the infectious bite of the mosquito, thereby reducing transmission. One of the most heavily funded preventative measures is Insecticide Treated Nets (ITNs). According to the CDC, ITNs reduce the malaria mortality of children by 20% (CDC (d), n.d.). Treated with pyrethroid insecticide, ITNs are bed nets forming a protective barrier around people sleeping under them. The insecticide repels and kills mosquitoes as well as other insects. By acting on the insect’s nervous system’s voltage gated sodium channels, pyrethroid causes prolonged membrane depolarization and enhanced neurotransmitter release. This is followed by a block of excitation leading to eventual death (Vijverberg & vanden Bercken, 1990). In a study assessing the impact of pyrethroid-treated bed nets among children and adults living in malaria endemic regions, pyrethroid treated nets or curtains were shown to decrease malaria mortality, severity, parasitaemia, anemia, and spleen rates (Lengeler, 1996). The pyrethroid insecticide has shown to pose a low risk for humans and mammals but is very toxic to insects even at low doses. Therefore, pyrethroid has high potency and selectivity for insects. Part of the reason for this selectivity is the fact that pyrethroid depends on negative temperatures to exert its action, which is impossible within the mammalian body. Nevertheless, independent of temperature, mammalian sodium channels have demonstrated to be at least 1000 times less sensitive to pyrethroids in comparison to insect counterparts (Vais, Williamson, Devonshire, & Usherwood, 2001). Thus, pyrethroid is widely accepted for use in bed nets. If washed or exposed to
sunlight, pyrethroid can break down and devoid the bed nets of the protective effects. As a result, bed nets must be retreated every 6-12 months with the same insecticide (CDC (e), n.d.). This need for re-treatment poses an additional cost for maintenance. On the other hand, the lack of re-treatment poses a risk of the development of pyrethroid resistance. In order to manage resistance some companies began to include piperonyl butoxide (PBO) along with pyrethroid in ITNs. WHO, however, does not consider PBO treated nets as a tools to manage rising pyrethroid (CDC (e), n.d.). A limitation of pyrethroid treated bed nets is also resistance. The first reported case of pyrethroid resistance was in Cote d’Ivore in 1993 and has spread to almost all regions in Sub-Saharan Africa with the exception of Southern Africa (Ranson et al., 2011; Corbel et al., 2007; Santolamazza et al., 2008; Abdalla et al., 2008).

Recently, a number of companies have developed Long-Lasting Insecticide-treated Nets (LLINs). These nets are capable of withstanding washing and sunlight for up to 3 years. From 2008 to 2010, 294 million LLIN nets were distributed in sub-Saharan Africa. WHO has currently approved or given interim approval to the use of 13 LLINs (WHO (a), n.d.) LLINs are distinct from other ITNs in that they are made with a netting material that includes insecticide within and around the material fibers. The standard ITNs are treated simply by dipping into insecticides so this new concept removes the need for nets to be retreated annually (Malaria Consortium (b), n.d.). Insecticides used in this method include
Deltamethrin, PBO, polyethylenes, Alpha-cypermethrin, and many others in combination or as standalone treatments (WHO (a), n.d.).

Another non-clinical method of malaria prevention includes Indoor Residual Spraying (IRS). This method involves spraying or coating walls of a house with a residual insecticide such as dichloro-diphenyl-trichloroethane, also known as DDT, indirectly preventing the mosquito bite, the insecticide kills the mosquitoes after a blood meal when they usually rest in an indoor surface (CDC (a), n.d.). This is when the parasite develops and matures within the mosquito enabling transmission. Thus the goal of IRS is to prevent malaria by killing the mosquito before it bites another host, reducing transmission.

The history behind IRS began in 1946. During the Global Malaria Eradication Campaign from 1955-1969, IRS and Chloroquine were the main malaria control interventions (Africa Indoor Residual Spraying Program, n.d.). The campaign unfortunately did not reach its intended objective however it did eliminate malaria from some endemic areas, reducing the burden of the disease (CDC (d), n.d.). In 1962, following Rachel Carson's book *Silent Spring*, environmental concerns as well as increased DDT resistance of mosquitoes caused the campaign to end (Africa Indoor Residual Spraying Program, n.d.). DDT environmental concerns also led to the introduction of more synthetic insecticides. As many of the endemic countries could not bear the financial burden of purchasing DDT, the campaign collapsed (Africa Indoor Residual Spraying Program, n.d.; CDC (f), n.d.). IRS programs were consequently
disbanded. In South Africa, DDT was replaced with alternative chemicals for IRS. The region then saw an increase in malaria mortality and DDT was quickly re-employed (Bouwman, van den Berg, & Kylin, 2011). Recent success in reducing malaria mortality in South Africa revived interests in IRS (CDC (d), n.d.). IRS DDT programs were consequentially re-introduced to Sub-Saharan Africa. According to WHO, DDT has long lasting efficacy of more than 6 months, making it a good candidate for sustained use as IRS (WHO (a), n.d.). If resistance is to be avoided in the long run, use and maintenance must be consistent and well monitored.

Vulnerable groups to malaria are very sensitive to transmission. Proper interventions must be tailored for these preventative efforts to be effective. In addition to ITNs, LLINs, and IRS, pregnant women, especially those living in high transmission areas, are recommended to take Intermittent Preventive Treatment (IPTp). IPTp encompasses administration of an antimalarial, regardless of the presence of infection, during each antenatal care visit (Greenwood, 2006). The antimalarial is Sulfadoxine-Pyrimethamine. This differs from standard chemoprophylaxis in that it produces protective drug concentrations for short periods of time separated by periods of concentrations below that necessary to inhibit parasite growth (Kayentao et al., 2005). Currently, it is the only antimalarial for which there is clinical efficacy and safety data for IPTp (Peters, Thigpen, Parise, & Newman, 2007). WHO recommends that two doses of Sulfadoxine-Pyrimethamine should be given during the antenatal visits and should begin
during the second trimester (WHO (b), n.d.). Additional studies of Sulfadoxine-
Pyrimethamine has shown efficacy in preventing placental accumulation of
parasites among pregnant women in Kenya (Parise et al., 1998). In addition, a
study of Mozambican infants showed that intermittent Sulfadoxine-
Pyrimethamine treatment reduced the incidence of clinical malaria by 22.2%
(Macete et al., 2006). Although not an overwhelming percentage, this reduction is
useful. WHO recommends that Intermittent Preventive Treatment (IPTp) is
administered 3 times within an infant’s first year of life (WHO (c), n.d.). This
intervention, however, is only helpful for women and infants who have sustained
means of accessing healthcare.

The Vaccine

With many problematic and failed efforts, the malaria community is now
focusing on a new vaccine currently being developed by companies
GlaxoSmithKline and PATH. Beginning in the 1980s, the vaccine has undergone
changes and modifications and is finally in the phase 3 clinical trial stage which
The Vaccine, RTS,S ASO1, is developed as a hybrid antigen containing the
HepB surface antigen and the sporozite protein antigen. It also includes an
adjuvant, AS01, which acts as an immunostimulant. The biological rationale for
this vaccine is that it elicits a strong humoral response directed against the
sporozite before it enters and infects the red blood cells, via opsonization or
macrophage destruction (PATH Malaria Vaccine Initiative, n.d.). Moreover, because the sporozites are in the blood stream for less than 30 minutes (some enter the liver cells and remain dormant), the vaccine must also be effective in combating infected liver cells. The hybrid antigen plays a role in eliciting cell mediated immune response via CD8+ and CD4T cells to recognize parasite peptides that are expressed on infected liver cells. T lymphocytes then lyse infected cells (PATH Malaria Vaccine Initiative, n.d.). Much of the success in the preclinical and clinical stages has set up high expectations for this vaccine. Phase 3 clinical studies in various African countries show that the vaccine confers some protection against severe malaria among infants and children. In one of the trials, the RTS,S/AS01 vaccine co-administered with EPI vaccines, showed to provide some protection against clinical and severe malaria in young infants. Infants were 6-12 weeks of age and the vaccine showed efficacy in protecting against malaria in 31.3% of the infants, efficacy against severe malaria in 26.0%, and 99.7% of the all infants who received the vaccine were positive for anti-circumsporozoite antibodies (Agnandji et al., 2012). Perhaps the low numbers in protective efficacy are due to the fact that infants already have passive immunity conferred from their mothers in the first 6 months of life. In a similar study among children 5-17 months of age, vaccine efficacy against malaria was 50.4% and efficacy against severe malaria was 45.1%. Data also shows that three doses of the vaccine provided partial protection 18 months after inoculation however the efficacy appears to decrease over time (Agnandji et al.,
2011). Considering that the vaccine is now in the last phase of clinical trials before it is marketed, these results indicate partial and insubstantial efficacy that may cost more to develop and obtain than it assuages the burden of the disease. Although this vaccine has shown some efficacy, it is important to note that its long term efficacy has yet to be evaluated.

Currently, there hasn’t been a successful vaccine against parasitic infection. There have been many successful vaccines against worldwide pandemics such as polio however the life cycle of the parasite and the complex etiology and pathology of malaria makes finding an effective vaccine complicated. One of the reasons is that the parasites are genetically and biologically complex. Their life cycles are elaborate and can quickly master immune system evasion (Tarleton, 2005). In a recent article, the authors also contend that the complex life cycle and the parasite’s ability to evade host immune response is one of the major challenges preventing a successful vaccine. The author contends that a vaccine that enables complete resistance to infection is probably not feasible however attention should be directed to create an antitoxic vaccine that prevents the pathological complications of malaria (Playfair, Taverne, Bate, & Brian de Souza, 1990). Given the ability of the parasite to evade and evolve, one of the most difficult challenges will be ensuring that increased parasitic virulence does not ensue. A recent study points out that partially effective vaccines, such as those for malaria, may do more harm than good. In this study, the impact of various partially effective vaccines was
assessed in relation to pathogen virulence marked by host mortality. Evidence from the study proves that partially effective vaccines languish the natural selection against highly virulent pathogens. This results in a more severe form of the disease in those individuals whom are not vaccinated (Gandon et al., 2001). This information is extremely vital in dealing with a case such as malaria where previous interventions have been imperfect and not thorough in coverage due to problems beyond that of the actual disease. Even more so, it is important considering the fact that virtually all interventions have seen resistance.

Parasite and Vector

Although the parasite is highly virulent and fatal to humans, it seems to have little to no effect on the mosquito vector. It is unknown how the relationship between the parasite and the mosquito evolved. Recent studies have attempted to elucidate this relationship showing that the parasite does have some effect on the behavior of the mosquito. In a recent study by Smallengange et al. (2013), *P. Falciparum* infected *Anopheles Gambiae* (main mosquito species carrying the *P. Falciparum* parasite), were more attracted to human odors than non-infected mosquitoes. In this blind study, when the mosquitoes were exposed to a sock emanating human odor, significantly more of the infected mosquitoes landed on the substrate. Smallengange et al (2013) suggest that this demonstrates a change in the mosquito’s response to olfactory stimuli when infected with the parasite (Smallegange et al., 2013). This means that infected mosquitoes are
more likely to bite a human host increasing the chance of transmission. It is important to note that this behavior suggested by literature is more detrimental to humans than to the mosquito. As most interventions focus on controlling the disease by killing the mosquito, new survival mechanisms evolve as seen with increased resistance to almost all drug and insecticide interventions as aforementioned. A recent study on the M and S forms of the *Anopholes Gambiae* found that the two have diverged in larval ecology as well as in reproductive behaviors. These changes are through unknown genetic mechanisms that suggest a speciation process taking place (Lawniczak et al., 2010). The *P. Falciparum* parasite is also undergoing genetic changes as demonstrated by Jeffares et al (2006). In the study, genetic variation and mutation is clearly demonstrated within the parasite and its species. Thus, both the parasite and the vector are rapidly evolving to be better suited for survival. Interventions must re-focus on means to eradicate the disease once it has entered the human body, as other external interventions seem to aggravate the problem by spurring natural selection.

**History of Malaria**

In order to create new and effective means of controlling and eradicating malaria, it is important to assess the history to understand how to best move forward. Although discovery took place within the past 200 years, malaria symptoms were recorded as early as 2700 BC in China in the *Nei Ching*, which
was the Canon of Medicine. By the second century BCE, the *Qinghao* plant, was used in treating the symptoms (CDC (b), n.d.). In 340 CE, its anti-fever properties were discovered and recorded. Today, the plant’s active ingredient, *Qinghaosu*, is used in antimalarial drugs. In Greece, around the fourth century, malaria was recognized as the cause in the decline of populations. Hippocrates was responsible for noting the main symptoms of it (CDC (b), n.d.).

The discovery of malaria etiology and pathology began with colonialism and war. During the scramble for Africa, the battle against malaria began as colonials, armies, and settlers began suffering from symptoms (Harrison, 1978). Mortality rates rose warranting investigation on the identification and cause of the disease. In 1880, a French army surgeon, Charles Laveran, living in Algeria discovered parasites in the blood of a patient who suffered from malaria. Laveran, however, did not arrive to this conclusion on his own. A forerunner of Laveran, Achille Kelsh, noted that in patients who died of malaria, there were small, black particles in certain organs that eventually lead to their discoloration (Harrison, 1978). Speculation the causative substance continued until Laveran’s discovery. What made Laveran’s discovery significant was his keen observance in asking the right questions. Laveran sought to identify what happens in malaria that doesn’t happen in any other disease. After observing fresh blood, he discovered motile elements, which were the protozoan parasite, as the cause of malaria (CDC (b), n.d.; Harrison, 1978). Like many other discoveries, Laveran’s parasite was met with much skepticism as many continued to insist on a bacterial
cause. By 1890, Laveran’s parasite was accepted as the cause of malaria. In 1886, Golgi, an Italian neurophysiologist, discovered that there were 2 forms of the disease, distinguishing between tertian and quarternary fever (CDC (b), n.d.). In his observation, he found that the forms had differing numbers of merozoites produced upon maturity. Golgi also observed that the intermittent fevers coincided with the rupture of erythrocytes and the release of merozoites, or schizogony. In 1890, Grassi and Filetti, also Italians, introduced the names *P. vivax* and *P. malariae* for two of the malaria parasites that affect humans. In 1897, Welch named a tertian parasite *P. falciparum*, and in 1922, Stephens named the fourth human malaria parasite *P. ovale* (CDC (b), n.d.).

During the 1870s in China, while studying elephantitis, Manson demonstrated that mosquitoes might be vectors of disease. He discovered that the filariae that cause elephantitis mature in mosquitoes. However, his curiosity didn’t quite peer into how infection takes place (Harrison, 1978). He did, however, pave the way for discovery of mosquitoes as vectors of disease. In 1897, a British officer, by the name of Ronald Ross who working for the Indian Medical Service, demonstrated that mosquitoes are responsible for transmitting the malaria parasites among infected patients (CDC (b), n.d.). In efforts to prove the hypothesis of Laveran and Manson connecting the mosquitoes and malaria, Ross closely recorded his work investigating the role the mosquito plays in infection. Finally, in August 20th 1897, Ross discovered the malaria parasite in the stomach tissue of a female anopholes mosquito that fed on a malarious
patient (Harrison, 1978). Ross also further proved his finding in July of 1898 when he showed that mosquitoes were responsible for transmitting the malarious parasite among birds. Ross’ observation also revealed that parasites, once developed in the mosquito, migrate to the insects’ salivary glands linking parasite transmission to the mosquito (CDC (b), n.d.; Harrison, 1978).

Perhaps the most important aspect of malaria history is the history of its epidemiology and interventions. As the scramble for Africa led to term many regions “the White Man’s grave”, yellow fever and malaria began to take a toll on political and economic interests in these heavily endemic regions. In the year following his discovery, Ronald Ross initiated the first anti-larval measures to control malaria in Freetown, Sierra Leone (Bockarie, Gbakima, & Barnish, 1999). In 1901, Sierra Leone was also battling yellow fever whose vector was also known to be a species of mosquito, *Aedes Aegypti*. So after Ross discovered the mosquito as the vector, he also speculated that it picked up the parasite germ from puddles where they feed. He concluded that the puddles had to be eliminated as a means of eliminating mosquitoes. In 1901, 70 employees led by Ross, began anti-larval efforts by cleaning the pestilential parts of Freetown, Sierra Leone (Harrison, 1978). The city organized removal of garbage, began to sweep, drain, and oil puddled streets and yards. Unfortunately, the cleanup was not maintained after Ross left Freetown and all efforts were abandoned (CDC (b), n.d.; Harrison, 1978).
Anti-larval efforts were also attempted during the construction of the Panama Canal from 1905-1910. The hot, wet climate of Panama saw about 85-90% of 26,000 workers hospitalized for yellow fever and malaria (PBS, n.d.). Yellow fever was particularly gruesome as death rates were extremely higher than malaria. Early symptoms were headaches, fever, and myalgia and progression of the disease eventually led to a dark, bloody vomit indicative of internal bleeding. The end result was organ failure and death. Malaria, although not as disastrous, caused relapse and recrudescence resulting in frequent and expensive hospital stays (Harrison, 1978). The symptoms of both diseases are similar although the pathophysiology of yellow fever is very different. The high fatality rates were mortifying enough to send workers fleeing from the site, abandoning the building of the canal. At the time, the only treatment widely accepted and available was quinine. It was given to assuage the fevers but that didn’t decrease the mortality rates. Moreover, high doses caused cinchoism among many (CDC (b), n.d.; Harrison, 1978).

Through the leadership of physician, William Crawford Gorgas in Panama, launched one of the largest sanitary campaigns in malaria history. In 1905, fumigators with cleaning agents, insecticides, and protective screens visited private homes in Panama. They sprayed drains and cesspools, with oil (Harrison, 1978; PBS, n.d.). The resources to carry out this order were not cheap and required substantial funding and government support to carry out. Political pressure to complete the canal, as reported by PBS, finally pushed President
Roosevelt to back Gorgas’ efforts (PBS, n.d.). In 1912, the antilarval clean-up led to a victory in Panama as the number of hospitalized workers fell to 5,600 (CDC, b, n.d.) Cases of yellow fever were easier to decrease however, malaria would take much longer to eliminate. The burden of disease was relieved and the canal was complete. Panama serves as an example of effective malaria control with government support and integration in alleviating the burden of disease.

In Italy, Malaria was an endemic disease with cases up to 2 million towards the end of the 19th century. Tertian malaria was endemic in central and southern regions of Italy as well as the Islands (Majori, 2012). Dr. Angelo Celli, an intellectual historian, saw malaria as a social problem. He believed that fever was a cause and result of the impoverished lifestyles of those in the central and southern provinces. Moreover, Celli believed that the war on malaria would best be fought by the defending people rather than fighting against mosquito populations (Harrison, 1978). However, as mosquito control at that time proved to formidably be successful and reform seemed too long term of an action to be taken, Celli concluded that quinine was the best antimalarial treatment at hand (Harrison, 1978). The early Antimalarial campaign in Italy focused on therapeutic quinine. It was made widely available, free of charge, and the government ensured supplies were widely distributed especially among the more endemic regions. Moreover, the parliament approved laws to promote measures aiming to reduce larval breeding places of vectors in draining and oiling methods as previously mentioned (Majori, 2012). Although it began as a campaign against
malaria, lack of literacy and adherence to the program among endemic populations resulted in a social melioration. Malaria morbidity did, however, fall to a low of about 2,000 in 1914 before the beginning of World War I (Harrison, 1978).

The role of the Great War (World War I) in malaria history highlighted the inadequacies of current treatments. During the war, many war zones became encouraging or permissive to malaria epidemics as infected soldiers recruited for war were introduced to a region capable of housing the disease. Non-immune soldiers were consequently infected with the disease. When the Great War ended and soldiers returned to their homes, they in turn introduced the disease to a region that was capable of housing it, and the disease spread in regions that were previously non-malarious. From 1914-1918, the only effective drug used was Quinine. However, its limitations laid in its unwanted side-effects, crippling military efforts during a crucial time. Malaria control measures were employed such as drainage schemes to eliminate the mosquito breeding places, use of bed nets, and application of insecticides (CDC (b), n.d.). The German army served as an example of how the use of malaria immune troops, good hygiene, and appropriate medication makes a difference between success and failure (Gachelin & Opinel, 2011). Nevertheless, antimalarial work was back to the starting point as non-endemic regions saw increased malarial infection.

The Great War highlighted the need for access to quinine and more comprehensive preventative methods for malaria. By the time World War II
began, there was a need to develop new antimalarial drugs. Germany, Great Britain, and America, by their engagement in the war and by suffering the morbidity and mortality of malaria, were the main countries involved in the development of synthetic antimalarials (Schlaugenhauf, Patricia, 2004). Some of the antimalarial drugs synthesized were DDT, Chloroquine, and Abatrine (Hays, 2000). These new tools brought back optimism in fighting malaria and led to developments of numerous organizations and campaigns in the post-war years. DDT proved to be successful and the newly synthesized antimalarial drugs proved to be less toxic and more effective than quinine. In 1955, WHO proposed a program to eradicate malaria worldwide with the newly discovered drugs. The efforts began and focused on IRS, antimalarial drug treatment, surveillance and maintenance (CDC (d), n.d.). Some highly endemic, colonized nations saw significant reduction such as India and Sri Lanka. Other nations, mostly in Sub-Saharan Africa, were completely excluded from the eradication campaign. The main reasons were attributed to challenges of executing the eradication methods and strategies within the region (WHO (a), n.d.). Globally, the emergence of drug resistance to antimalarial drugs and insecticides began making the maintenance untenable. Efforts in the regions ceased and malaria made a resurgence (CDC (f), n.d.). In other non-endemic regions malaria cases waned and the regions eventually became malaria free. One such is the United States.

Taking a comprehensive look at Malaria in the United States, malaria cases were observed as early as the 1800s long before the discoveries of Ross
and Laveran. Before the turn of the century, malaria developed to a climax and diminished. Due to climate, southern regions were highly malarious and the north was only malarious during the warmer months when the parasite and mosquito could thrive. Decline in malaria was seen around the 1860s however the civil war caused an increase in morbidity and mortality (Faust, 1951). It was in the 1920s that malaria efforts began in the United States. Between 1900 and 1920s, malaria declined as a result of efforts such as those utilized by Gorgas, particularly that of drainage. Although record keeping wasn’t extensive, records show that there was a peak in malaria cases between 1933 and 1936, presumable as a result of the economic depression that halted eradication efforts. Nevertheless, within the 20th century malaria became virtually extinct in the United States. Factors contributing to this include improvement in agriculture and improvement in drainage eliminating breeding grounds for the mosquito. The life cycle of the parasite waned and fewer mosquitoes picked up the parasite. Over time, this translated into fewer infections and a decline in cases. Even before the Great War, malaria control was successful through public health, economic, and sociologic programs. Better housing, better screening, availability and extensive use of insecticides resulted in improvement of the population health (Faust, 1951). The Southern States still witnessed malaria, however. So during WWII, when Northern soldiers were being trained in the malarious south, and as many returned home from endemic regions throughout the world, malaria cases increased. On July 1, 1947, the National Malaria Eradication Program
began work. DDT application of all homes and premises of malarious regions was ordered. By 1949, about 4.6 million homes had been sprayed. Drainage, and other methods of removing the breeding site of larva were also ordered and eradication looked close (Faust, 1951). In 1949, malaria was no longer a public health problem in the United States, and by 1952, CDC participation within the country ceased (CDC (a), n.d.). Even in the face of relapse, the US no longer saw an epidemic. Most cases of malaria today are usually the result of travelers coming in from malarious regions. Nevertheless, the eradication of malaria in the US shows how efforts can be successful wherein multi-sectoral programs are employed to effectively control and eliminate the burden of malaria.

The history of malaria is important because it gives insight into the best measures that can be taken moving forward. It is clear that clinical and public health interventions have significantly helped to reduce the burden of malaria however these efforts have been successful and enduring in developed nations. The little success seen in endemic, developing regions waned over time and currently, the burden is much heavier as resistance to interventions is on the rise. Although much has been done in health efforts, there is a need for government and economic efforts to effectively ameliorate the burden of malaria by spurring development.
The Economic Case for Malaria

International Funding

International funding for malaria increased from $100 million to $1.94 billion between 2000 and 2013. The inception of the Global Fund to Fight AIDS, Tuberculosis, and Malaria in 2002 caused a sharp increase in funding (RBM, n.d.). Currently, the United States annually pours $522 million, contributing a little over 50% of the total international aid. According to WHO, a total of $5.1 billion is needed annually to provide interventions globally, however, the total funds for malaria do not reach this value (WHO(d), n.d.). The Global Malaria Action Plan also estimated that $5-6 billion is needed annually to maintain malaria control and work towards eradicating malaria as shown in the figure below. Current funding barely reaches $2 billion, thus malaria funding is inadequate.

Perhaps the biggest player in the international funds for malaria is the Global Fund to Fight AIDS, Tuberculosis, and Malaria. By forging partnerships between governments, civil societies, private sectors and communities, the Global Fund does a great deal of work in combating disease. According to their website, the Global Fund has helped 6.1 million people get access to antiretroviral therapies, 11.2 million tests and treatments provided for tuberculosis, and 360 million ITNs distributed for malaria prevention (Global Fund (b), n.d.). Malaria monetary spending is distributed to a few efforts.
Approximately 51% goes to preventative efforts such as ITNs, 25% goes to treatment such as ACTs, 13% to health system training, and 11% to engendering a supportive environment (Pigott et al, 2012).

![Figure 3: Inadequate Funds for Malaria](source)

According to Roll Back Malaria, as 90% of the global malaria burden falls in Sub-Saharan Africa, it is the recipient of 80% of international aid (RBM, n.d.). Funding is generally allocated to regions that suffer the highest morbidity and mortality of malaria. A study conducted by Pigott et al (2012) observed that most Sub-Saharan Africa countries rely on international aid, whereas malaria endemic countries in the Americas generally rely on domestic governments for support.
(Pigott et al., 2012). During the study period, malaria endemic countries in Central America received 11.47% of external aid in compared to 86.89% for Sub-Saharan Africa (Pigott et al., 2012). Of course, these results are indicative of the fact that wealthier countries are more capable and willing to pay for malaria support. And as many Sub-Saharan countries continue to struggle with staying afloat in the world economy, malaria continues to be a burden.

In comparison to Sub-Saharan Africa, the malaria endemic regions of South America do not experience the heavy morbidity and mortality. Malaria cases generally fall in the Amazon Basin in Brazil, Colombia, Bolivia, Peru and small region in Ecuador. In 2010, 240 malaria deaths were reported comprising only 0.085% of the global mortality total (Cruz et al., 2013). This low number is caused by a myriad of factors. First, the parasite prevalent in South America is the *P. vivax* (Oliveira-Ferreira et al., 2010). This strain is less virulent and causes milder forms of malaria compared to the *P. falciparum* prevalent in Sub-Saharan Africa. Also, *P. vivax* is still sensitive to Chloroquine and insecticides that *P. falciparum* has become resistant to. Second, the biodiversity in the region is home to the cinchona bark tree that quinine is extracted from. This has opened up a good clinical basis to support discovery and development of new antimalarial drugs. Moreover, this has also opened up good development in the region. Finally, and perhaps most importantly, South America has developed a quality health care system that thoroughly responds to epidemics (Cruz et al., 2013). It is a clear contrast with Sub-Saharan Africa in that although both
regions are endemic to malaria, there are a myriad of development factors that differentiate how the disease affects both regions.

Looking back at the history of malaria, increased methods of interventions have proved that the parasite mutates, and as a consequence the virulence increases at the cost of higher morbidities and mortalities. Thus, malaria endemic countries, generally developing nations, are forced to rely on external aid because of failed interventions. It is a cycle of need that lands many nations in dependence and Sub-Saharan Africa is a prime example. A recent publication looking at the political implications of aid shows that in aid recipient countries, there is a disconnection between the government and the people (Moss & Van de Walle, 2006). Because national governments may not be directly accountable to its people, in the case of foreign aid, it may not feel that it needs to maintain popular legitimacy. Governments are also unlikely to establish institutions to assuage problems at hand (Moss & Van de Walle, 2006). Thus if we apply this idea to the case for malaria, countries receiving external aid fall into a cycle of dependence. This dependence causes governing institutions to take their hands off of working to alleviate the burden of malaria. In addition, this also leaves room for mal-governance and political corruption as governments may not feel the need to maintain popularity with the people as their needs are met by international efforts. Of course, discrediting the work done by international aid is unfair as millions of lives have been saved by external aid. It is, however, important to bring to light the damaging effects of too much money being pumped
into aid efforts. If the goal is to alleviate the burden of disease while enhancing development, then perhaps increasing outflow of money into these regions may not be the best solution.

**Complexity of Malaria – Poverty and Disease.**

Currently, there is no one solution that can treat malaria in all endemic regions. The complexity of malaria is due to its partnership with poverty. Where there is poverty there is disease, as illustrated in Figure 4. Disease and poverty constitute a viscous, self-perpetuating cycle that makes treatment complicated.

![Geographical Distribution of Malaria and Poverty](image)

**Figure 4: Geographical Distribution of Malaria and Poverty**
Source: (Dunavan, 2005)
Poverty is a cause of disease. In the case for malaria, poverty exposes people to infection (Teklehaimanot & Paola Mejia, 2008). Impoverished dwellings are generally favorable for mosquito breeding and are also areas of infection. Preventative measures, such as ACTs and LLINs may not be affordable to each household leaving many exposed to the infectious bite of the mosquito. Healthcare access is also too expensive leaving many untreated and increasing the risk of transmission. Migration from urban to rural areas is also a cause of disease as it is associated with poverty. Studies show that people who generally migrate from rural to urban areas settle in poorly constructed homes in densely populated areas also creating an environment favoring mosquito breeding (Robert et al., 2003). For example, malaria risk is relatively low in the urban city of Nairobi, Kenya. However, within the city is the densely populated slum of Kibera. Kibera is teeming with high rates of malaria as living conditions accommodate mosquito and parasite breeding (Kasili et al., 2009). Malaria transmission and infection rates in Kibera are consequently high. A recent study validated the association between poverty and disease showing that causality between the two may run in the opposite direction. In this multi-regional study, higher incomes showed to increase prevention and treatment of malaria, contributing to the correlation between poverty and disease (Datta & Reimer, 2013).

Poverty is also a cause of poor nutritional status. It is well known that poor nutrition contributes to disease. As Shankar et al (2000) demonstrated, less food
consumption leads to protein energy malnutrition which increases the morbidity and mortality of malaria. There are numerous nutritional studies that highlight the importance of specific vitamins and minerals that play a role in reducing severity of disease. Trials of vitamin A and Zinc supplementation show that these nutrients can reduce clinical malaria attacks and reduce the severity of disease. A recent study conducted in Ghana among children demonstrated that the group given Vitamin A supplementation had 27% less infection of malaria than the control group (Owusu-Agyei et al., 2013). A study conducted in 2008 in Burkina Faso also showed that Vitamin A supplementation, along with Zinc, reduced risk of fever and severe clinical malaria among children (Zeba et al., 2008). Nutrition clearly plays a role in alleviating the burden of disease. The exact mechanism was shown in a study by Serghides et al. demonstrating that Vitamin A helps in the up-regulation of CD36 expression, which aids in phagocytosis and may activate substances that which inhibit the inflammatory responses that are associated with severe and cerebral malaria (Serghides & Kain, 2002). A study by Anuraj Shankar (2000) et al also showed that Zinc deficiency exacerbates diseases that rely on macrophage killing of infected cells. Malaria, as aforementioned in Chapter 1, is such a disease. Statistical data shows that children from poorer households in urban areas are more likely to be malnourished compared to children from poorer households in rural areas (Fotso & Kuate-Defo, 2006). This hold true as rural households obtain food through subsistence farming whereas households in urban areas depend on an income
to purchase food. As many economically disadvantaged populations are disposed to be undernourished, predisposition to malaria infection is a consequence.

Malaria is a cause of poverty. In many rural regions in Sub-Saharan Africa, malaria infection means time lost to work and resulting in less food consumption (Teklehaimanot & Paola Mejia, 2008). In urban areas, this is also true as less money is earned and less food is purchased. The general idea is that households suffer when a productive member falls ill with malaria. If we look at the context of the disease in a typical household in sub-Saharan Africa, if a productive member falls ill then household labor is diverted from activities that generate income and placed into caregiving if healthcare is unavailable. It is also common that children are withdrawn from school as no income results in no tuition thus reducing the chance of a proper future income (Purdy, Robinson, Wei, & Rublin, 2013). Reduced income follows perpetuating the economic disposition of such a household.

The cycle of poverty and disease is felt most by vulnerable groups. As most malaria mortalities are among children, their first five years are crucial in survival and development. Immune development against malaria is also crucial in this stage. Malnutrition as a result of poverty is highly associated with child mortality. Pelletier et al. found that mild to moderate malnutrition increased the likelihood of mortality and there is also an epidemiologic synergism between disease morbidity and malnutrition (Pelletier, Frongillo, & Habicht, 1993). This is
consistent with current data that shows malaria mortality is mostly among children under the age of five as aforementioned. As for pregnant women, malaria has detrimental effects on both the mother and the unborn child. As mentioned in previous chapters, pregnancy increases the likelihood of malarial infection as the immune system is slightly depressed. Pregnant women suffering from malaria experience severe symptoms, they have higher rates of miscarriage and premature delivery, and their unborn children typically become low-birth-weight neonates (Schantz-Dunn & Nour, 2009). The result of low-birth-weight babies also feeds into the cycle of poverty and disease as it is associated with infant mortality, morbidity, growth retardation, poor cognitive development, and chronic diseases (Mmbando et al., 2008). Children who suffer repeated episodes of malaria are also found to demonstrate reduced learning. This also leads to lower levels of human capital among households in malaria-endemic communities, perpetuating the cycle of poverty and disease (Malaney, Spielman, & Sachs, 2004).

This complex cycle of disease and poverty may be the reason that there have been numerous malaria eradication and control programs that have not reached their objectives in sub-Saharan Africa. Malaria is not a stand-alone disease. There are numerous causative factors and confounding factors that lead to infection. The figure below illustrates the self-perpetuating cycle.
Why previous programs failed

Since the discovery of the etiology and pathology of malaria there have been numerous programs to eradicate the disease. As mentioned in the History of Malaria Section, the Global Malaria Eradication Program established in 1955 eventually collapsed when the goal of eradication wasn’t achieved in many areas. Although many regions saw malaria eradication, other regions like India saw a heavy resurgence as economic and financial crises impeded maintenance and control declined. Due to unclear reasons, the Sub-Saharan region, heaviest in morbidity and mortality, was virtually untouched with the eradication efforts. As Nájera et al (2011) concludes, the failure of this effort highlights that there is no single strategy that will be applicable everywhere. In addition, long term commitment includes community involvement, health systems integration, and
development of reliable and effective surveillance systems along with sustained interventions. Malaria must be approached with a holistic solution to assuage the burden of the disease while also spurring development. Poverty must be relieved together with disease.

**Funding the vaccine**

One of the most heavily funded interventions is the malaria vaccine being developed by GSK and PATH. To date, the Bill and Melinda Gates foundation has donated $1 billion to the development of the RTS,S vaccine (Malaria Vaccine Initiative, n.d.). As aforementioned, the complex cycle of disease and poverty will not be eradicated simply by a vaccine. The amount of money pumped into its development is more than enough to implement programs that focus on alleviating the burden of poverty, decreasing the likelihood of disease. This money could be better used to build homes so families do not have to sleep in breeding places of mosquito larvae. The money could also be used to fund drainage programs, city cleanups, and malaria education so that the burden of malaria can be alleviated as seen throughout history.

Copious funds for the vaccine are also not justified by the small percentage of protective effect the phase III trials have reported. Although it is intended to be used in addition to already established efforts, trial results don’t warrant the heavy funds. As previous efforts have shown, killing the vector will not help and new means of inhibiting the parasite leaves room for mutations. It is
also important to establish clear vaccine efficacy before introducing it to endemic regions. There shouldn’t be an imperfect vaccine as it may interfere with the already present immunity acquired by populations in endemic regions, and also poses a risk for the emergence of new resistance, contributing to the resistance of almost all anti-malarial interventions.

Financing Malaria

There is supporting evidence that more funding results in better outcomes for malaria control. A study conducted by Purdy et al. (2013) attempts to create incentives to increase funding by projecting that malaria reduction and elimination will save about $208.6 billion, globally, between 2013 and 2035. The study aimed to show that attaining funding required to meet international targets would generate economic improvements by eliminating the disease. Another study in Gambia noted a decline in malaria with increased interventions and recommended an intensification of control interventions by increasing funding (Ceesay et al., 2010). The reality of these conclusions is that they are simply theories projected by known factors. A recent study assessed the association between program funding, per person at risk, ITN coverage, and declines in malaria morbidity and mortality (Korenromp et al., 2013). It concluded that the solution would be to maximize donor funding and properly allocate it to countries with highest continued need. It is important to realize the complexity of the disease as well as understand that there are limitations in analyzing numbers as
accuracy of case reporting may not be reliable in certain regions for various reasons. Moreover, associations don’t necessarily mean causality. There are numerous factors that define the efficacy of these heavily funded interventions. According to Gething et al (2014), more systematic, timely, and empirical approaches are needed to track the transmission, morbidity, and mortality of the disease as heavily funded malaria control activities increase in sub-Saharan Africa.

Antimalarial drugs are heavily funded to support endemic sub-Saharan regions. Since 2002 when WHO endorsed ACTs, the drugs were met with a very high demand. However, over the years this demand has been unstable due to financing and programmatic uncertainties (Shretta & Yadav, 2012). Within the ACT market, grants in the public sector from the Global Fund contributes to about 1/3 of the entire market (Maxmen, 2012). For sub-Saharan African regions, the need for external aid aggravates the malaria burden by creating new avenues for more roadblocks. Financing uncertainties, particularly with the Global Fund, include lengthy cycles of review of grants, approvals, and disbursements (Maxmen, 2012). These issues also bleed into other malaria control markets. In Ghana, a delay in the receipt of funds resulted in a 12 month delay for IRS and LLIN programs (Shretta & Yadav, 2012). Unfortunately the malaria parasite and the mosquitoes do not pause for these processes to take place. The result is continued morbidities and mortalities while funds await disbursements. The
reality is that these economic processes must take place for action to be sustained.

The question that must be repeatedly asked is what problem is the malaria community ultimately trying to solve? These external aid impediments wouldn’t exist if endemic countries were able to self-finance their own malaria efforts. Unfortunately, this is not so, and companies that create malaria interventions must receive profit for their products, bought by organizations such as the Global Fund. If we want to establish a global economy where developed drugs can be priced as asking value then investing in developing the “underdeveloped” nations comes first. The issue is that the regions in most need are not able to play in the global world economy. Unless malaria efforts do not come with a price tag then there will be confounding factors impeding the global eradication goal. Moreover, as funding never seems to be adequate, there needs to be a review and analysis on the efficacy and practicability of the current interventions that billions of dollars are spent on.
Discussion and conclusion:

In September 2013, the Multisectoral Action Framework for Malaria was launched in New York. This program is a collaboration between the Roll Back Malaria Partnership and the United Nations Development Programme that aims to coordinate action among various development sectors to combat malaria. The Framework urges policymakers and healthcare practitioners to increase partnerships to speed up the socio-economic development and current malaria controls. By working from the premise that malaria is associated with poor socio-economic development, marginalization, and exploitation of fragile markets, the program aims to combat malaria and poverty simultaneously. The history of malaria demonstrates that eradication was successful in regions where efforts were targeted on broad socio-economic determinants such as living conditions, education, and protecting the environment. With this in mind, an integration of a multisectoral dimension, as proposed by the Roll Back partnership to combating malaria means added value to the outcome as there are a wide range of stakeholders engaged. (RBM, n.d.). The available data on malaria burden and its relation to poverty, must translate into action. Malaney et al (2004) demonstrates that macroeconomic studies find that in endemic regions, malaria is responsible for reducing economic growth by more than 1% each year. One the other hand, microeconomic studies, aggregating the cost per case, finds that economic
growth is reduced by less than 1%. The gap between these estimates, as concluded by Malaney et al (2004), suggests that other malaria associated factors make the burden greater than just the sum of individual cases. The study asserts that these results must be taken into consideration by governments and healthcare policymakers. There are numerous studies that continue to assert that the complexity of malaria warrants a comprehensive approach to eradication. As previously discussed, already known data must be translated into action. This action can only be fully taken with a partnership between various sectors aiming to reduce the burden of disease by also alleviating the burden of poverty.

The limitations of current malaria treatments in Sub-Saharan Africa are beyond clinical interventions and call for economic development. In comparison to South America, it is clear that development is a key factor preventing thorough malaria eradication. Likewise, malaria eradication in developed nations such as the United States serves as an example of the potential efficacy of interventions if development in endemic regions was achieved first. The Multisectoral Action Framework for Malaria is currently a prime example of a holistic approach to treat malaria in the integration of healthcare efforts, economic efforts, and government efforts in theory. Looking back throughout history, multisectoral efforts take years to demonstrate effectiveness. With the myriad of independent global aid organizations and the efforts already producing results, the additional concept of a holistic and multisectoral approach should result in significant reduction of malaria morbidity and mortality over the next few years. Of course, only time will
tell. Nevertheless, the complexity and the burden of the disease warrants continued monitoring and sustained global effort in eradication by employing efforts to aid in developing malaria endemic regions.
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EDUCATION

Candidate for Masters of Science in Medical Sciences 2012-2014
Boston University Sch. Of Medicine/Graduate Medical School, Boston, MA

Bachelor of Science – Biology; Honors College 2008-2012
Baylor University, Waco, TX

RESEARCH PROJECTS

- Malaria –Undergraduate Honors Thesis: The Impact of Nutrition and BMI on Malaria in Rural Western Kenya
- Malaria –Master’s Thesis: The Limitations of Current Malaria Treatments in Sub-Saharan Africa

WORK EXPERIENCE:

- Student Intern- Research - Veteran’s Affairs – Psychology Department, Waco, TX August - December 2010

Duties: As a student intern at the Waco VA, I got to take part in research by entering baseline research data on SPSS. I also got to sit in during discussions and weekly meetings allowing me to see the daily efforts that go into conducting quality research. Moreover, as part of the internship, I read various articles in medical and psychology journals regarding PTSD and other mental disorders relevant to research at the VA. This opportunity allowed me to view healthcare from a holistic perspective, taking into account the mental and psychological well-being of patients.
- Office Assistant - Baylor University's Poage Legislative Library  Jan2009 – May2010

Duties: As a student worker, most of my job consisted of organizing and preparing documents and other historical articles for display. Over some time, I was in charge of JFK Assassination materials which we used for display in exhibits.

- Office Assistant – Baylor University Language Acquisition Center  Aug2010 – May2012

Duties: Entry position included clerical and administrative work. After 1 year I was promoted to Senior LAC assistant where job entailed working with language professors to enhance learning labs for students, editing language films/text book CDs for online resources, administrating language placement exams and managing the center

COMMUNITY SERVICE – Healthcare Related:

Health Care Volunteer - Collin County Adult Health Clinic, Plano, TX  Jun2009-Aug2009

Duties: As a student volunteer, I assisted nurses and physicians in triaging patients by taking vital signs. I also got the opportunity to shadow a few physicians and the head nurse of the clinic. This experience allowed me to see the healthcare needs of those who cannot afford it.

Baylor University Straw to Bread Medical Mission Trip  May 15th 2012-May 31st2012

Duties: In the most remote and rural cities in Kenya, 54 students, teachers, and doctors set up a clinic, much like every year, to provide free healthcare and other needs of the communities in the city of Kisumu. There were 3 physicians, 4 nurses, and eager students and volunteers who ran the clinic. We saw patients with various common and rare diseases and did what we could at the clinic to stabilize and treat their illnesses. However, for patients whom we could not treat, we accompanied to the nearest hospital, and paid for their care.

SKILLS

- SPSS
- Clinical Trial Design
- MsWord/Excel/Powerpoint
- Additional Languages: Swahili (fluent)

EXTRACURRICULAR:

- Romania Mission trip – 07/2008
- Baylor Women’s Lacrosse Team (Part of the Texas Women’s Lacrosse League) - 08/2008-05/2009
- Bolivia Mission trip – 07/2009
- American Medical Student Association Baylor University - 08/2009-05/2010
- Ethiopian Student Association – Baylor University Chapter - August 2010-May 2012
- Dominican Republic Mission trip – 05/2013