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Malarial Therapy: The Impact of Resistance and the Future of Anti-Malarial Drugs

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Malaria, one of the most debilitating illnesses of all time, is the most common parasitic disease in sub-Saharan Africa. The disease is the leading cause of illness and death in sub-Saharan Africa, killing a child roughly every 40 seconds. In 2004, the World Health Organization estimated that 300 million cases of malaria occur annually and that nearly one million people die from malaria every year (Mandell, 2009). Furthermore, almost half of the world's population is at serious risk for malarial infection. Malaria has an extremely negative impact on the social and economic productivity of nations around the world (Pampana, 1969). Thus, it is a disease that deserves necessary scientific research and financial support to ensure that this tremendous problem is solved. It is vital that there be a global effort to eradicate this parasitic disease in the public health sector.

Although often considered a single disease, malaria is more accurately viewed as an umbrella term for many diseases, each shaped by the subtle interactions of biologic, ecologic, social, and economic factors of the disease (National Research Council, 1991). Furthermore, the species of parasite, the behavior of the mosquito host, the individual's health, the environment, and access to health services all play important roles in determining the intensity of disease transmission (National Research Council, 1991). Malariologists recognize that malaria is a local phenomenon that differs greatly from area to area and even from village to village. Consequently, a single global plan for malaria control is of little use for specific conditions. Many countries do not even have the human or financial resources to carry out any social or economic effort to control the disease (Pampana, 1969).

Currently, the best way to treat malaria is highly debated and not yet known. However, scientists do agree that the foundation of malaria control relies on early and effective treatment. Only a handful of drugs are available to prevent or treat malaria, and the spread of drug-resistant strains of the malaria parasite threatens to reduce further the already limited pool of effective drugs (National Research Council, 1991). Further complicating the situation, many societies do not even believe in modern medicine, or have access to any advanced treatment at all. The debate over

which medicine is the most effective is both complex and widespread. However, making a successful treatment available is not enough to reduce malaria mortality because the treatment also must be used correctly and optimally. If not used correctly, even the most efficacious treatment can fail to cure the disease and may facilitate the development of drug resistance (Oaks, 1991).

Fortunately, malarial therapies exist and are continually being improved upon. These drugs, such as the pills chloroquine and artemisinin, decrease the death rate of malaria and increase the economic and social productivity of those affected by allowing them to return to work and normal life sooner than untreated individuals. Chloroquine and artemisinin both have individual benefits and disadvantages, and understanding these differences is crucial to understanding malaria.

Chloroquine is the less expensive and older of the two, and it was the drug of choice throughout most of the 1900s until worldwide malaria resistance rendered it ineffective. It is not recommended in today's medical fields for various reasons. This is primarily because over time, the parasite adapted to the drug, rendering it ineffective. The current drug of choice is artemisinin, which is perhaps more effective but is more expensive than chloroquine-based therapies. However, price is not the only issue with artemisinin-based therapies. Just like in chloroquine, resistance in artemisinin is beginning to develop across the world; and thus, the drug is becoming more and more ineffective in treating malaria. Scientists and researchers are desperate to find ways to stop the resistance so that there can be a solution to the malaria crisis. Currently, malarial drug researchers are focusing their efforts on the containment of artemisinin resistance, as artemisinin is the recommended drug by the World Health Organization and the best medication today to fight malaria.

This essay will outline the history of chloroquine and artemisinin therapies as part of the fight against malaria, in an attempt to provide the necessary background information to understand the current issue of growing artemisinin drug resistance around the world. This issue is crucial to understanding public health on a global level, and its interactions with economics, politics, and the social realm. It represents a concerted effort between drug companies, researchers, and policy makers to implement new and helpful therapies, while at the same time regulating and limiting less-effective and potentially risky treatments.

Impact of Malaria

Malaria affects the health, safety and welfare of nations globally, having significant measurable direct and indirect costs as well as constraining economic and social development. This constraint over time increases the gap of prosperity between countries infected with malaria and countries without malaria. Malaria poses a serious risk to a given country's economy: for example, it forces the tourist and hospitality industries into recessions due to the reluctance of tourists to travel abroad. Tourism and

trade industries account for a large part of a given country's revenue and when people are afraid to travel abroad, that country's economy can be directly affected. When people fear a disease, they stop travelling and therefore the economy suffers.

Additional direct costs include supplies for preventing and treating malaria. Many governments and citizens spend money on buying insecticide-treated mosquito nets and insecticide sprays in the hope of avoiding the disease. These remedies are preventative and not therapeutic, and should be considered an effective first line of defense against the disease. Additionally, governments inject massive streams of capital for the purpose of maintaining health infrastructure and educating the community on the prevention of malaria. This is a major source of malarial prevention that is continuing to grow in the twenty-first century. Doctors, drug companies, and small businesses also fund programs and foundations that educate, treat, and cure victims of the disease. Malaria can be overwhelming to a nation's healthcare infrastructure, as malaria patients can flood the public health system. Malaria patients account for as much as 40% of public health expenditure, 30-50% of inpatient admissions, and up to 50% of outpatient visits in some African countries (World Health Organization, 2002).

While the direct burdens of malaria are evident, the indirect costs of malaria are not as apparent. Indirect costs include lost economic and social productivity associated with illness or death. Loss of workdays, school absenteeism, and permanent neurological or physical damage associated with severe episodes of malaria are indirect burdens placed on a country, government, and individual. In the extreme case of death, indirect costs can also include the discounted potential lifetime earnings that a person can earn for himself or his family. In the case of a head of household, this burden can be devastating.

Chloroquine & Resistance

Chloroquine is one of the most prescribed anti-malarial drugs in the world, and was discovered in 1934 by Hans Andersag at Bayer laboratories in Germany. It would go on to become the first-line drug for malaria treatment in the twentieth century ("Saving Lives," 2004). Part of what makes this drug's impact so massive is that it is safe for use in infants as well as pregnant women. Its affordability also means that it is the go-to drug for travelers in heavily populated malarious areas. It is most effective primarily against the blood-born asexual stages of the disease, although it also works against the bloodstream stage. Chloroquine was initially very effective and inexpensive, as the majority of the population could purchase it at 10 cents per retail course of pills, even in the poorest areas of the world. The drug was used all over the world and was the primary source of care even outside of organized healthcare systems because of its affordability. As of 2006, chloroquine remained the primary source of therapy throughout Africa because of this affordability factor. It was, and

still is, distributed mainly through private economic channels, eventually reaching consumers through local stores and drug sellers that are ubiquitous in poor countries ("Saving Lives," 2004).

The first case of chloroquine resistance was documented in 1956 and, before long, resistance developed worldwide. Various factors contributing to drug resistance are the "dosing, duration, adherence, quality, availability, and distribution patterns of drug use, and the immunity profile of the community" ("Saving Lives," 2004). It is now well established that chloroquine does not work against the majority of cases of life-threatening malaria. The impending loss of this principal drug in the fight against malaria has hampered malaria control efforts and placed greater responsibility on policymakers to rapidly change their guidelines on antimalarial treatments, keeping in mind the possibility that alternatives to chloroquine could also be rendered obsolete by drug resistance.

Drug resistance affects global malaria control through economic cost, changes in distribution of the malaria species, and access to high-quality treatment. In Africa, for instance, the appearance of chloroquine resistance led to an increase in hospital admissions ("Global Report," 2010). Given the limitations on financial resources in most malaria-endemic countries, there has been considerable difficulty in deciding on an alternative treatment that is both affordable as well as sound from a long-term perspective. The key to eradication is to successfully balance the costs of the drugs with the effectiveness of the drugs over time so that resistance to the drugs does not occur. Artemisinin-based combination treatments (ACTs) are the current standard in malarial treatment. ACTs are different types of anti-malaria pills that, taken in combination, decrease the likelihood of resistance developing. Combination therapy holds considerable promise of both increased efficacy and decreased development of parasite resistance. Thus, ACT combination therapy is the most promising drug in the fight against malaria.

Artemisinin-based Combination Treatments (ACT)

Artemisinins are antimalarial drugs that clear the parasites from the blood more efficiently and quickly than any other antimalarial agent (Arnold, 2013). They are derived from *Artemisia annua*, a Chinese wormwood herb. The World Health Organization recommends artemisinins as the primary therapy for P. falciparum malaria. Researchers have stated that, "Combinations are effective because the artemisinin opponent kills the majority of parasites at the start of the treatment, while the more slowly eliminated partner drug clears the remaining parasites" (White, 2004). Partnering artemisinins with a second drug confers better protection against the development of resistance. Over the past few years, artemisinin derivatives have proved highly effective and successful in many Asian countries while no resistance has occurred (Arnold, 2013).

ACT's are a very expensive option for malarial therapy, and the price for artemisinin has fluctuated between $120 and $1200 per kilogram from

2005 to 2008 (Roll Back Malaria, 2008). The market price for this drug is an economic hardship for many people around the globe. At present, a full course of ACT drugs cost about two USD, roughly 20 times the price of the equivalent chloroquine course (Amponsah, 2013). ACT would cost the global malaria community an additional estimated 500 million dollars annually, significantly impacting poor individuals afflicted with the disease. Furthermore, this estimation indicates that it may be an unmanageable cost for countries with per capita incomes of less than two thousand dollars a year. Thus, the economic burdens of the costs are direct, visible issues for many underdeveloped countries battling the malaria crisis.

The malaria crisis is both economic and biomedical in nature. Economically, the era of inexpensive and effective antimalarial treatment may have ended, but poverty has not ("Saving Lives," 2004). Though spending only two dollars seems insignificant for most Americans, in most malaria-endemic countries governments or consumers cannot afford the cost. This financial burden has created a dangerous situation for countries struggling with malaria.

At present, artemisinins are the only antimalarial drugs completely appropriate for global use that are still effective against all chloroquine-resistant malarial parasites. Malaria's toll could rise even higher if the resistance to artemisinins is allowed to develop and spread before other options (drugs) are invented and approved. The long-term goal of public health experts is to contain the resistance of artemisinins—preserving their effectiveness and price for as long as possible.

The World Health Organization prequalified the first fixed-dose artemisinin combination therapy called Coartem and recommended it as the first-line malaria treatment in 2001. Three years later, in 2004, it approved Coartem for use in infants and young children. Finally, in 2008, the first-ever high quality pediatric formulation of an ACT, Coartem Dispersible, launched with the aim of preventing malaria in children. Although scientists and doctors are hopeful that Coartem will continue to help in the treatment of malaria, they are also cautious as they are beginning to find resistance to this medication in various countries (Thanh, Trung, & Phong, 2012).

In addition to combination drug therapies, malarial control requires many other preventative measures to eliminate the disease, including bed nets, environmental measures limiting mosquito breeding, and other preventative treatment for high-risk asymptomatic individuals. Therefore, a cost-benefit analysis is a large part of the economic debate on malaria. By measuring the benefits of curing a case of malaria against the increased costs of treatment, economists and researchers alike can reach an agreement regarding this problem. Artemisnins, when taken in combination, serve to avoid the emergence of resistance worldwide, saving lives in future generations.

Artemisinin Resistance

Artemisinin resistance has been detected in Cambodia, Myanmar, Thailand, and Vietnam. This resistance has occurred because of poor treatment practices, inadequate patient adherence to prescribed drugs, widespread availability of oral artemisinin monotherapies, and substandard forms of the drugs. This situation is dangerous as the population in Asia is ever increasing, and the spread of resistance to India or sub-Saharan Africa is impending and very possible, as are the possible public health consequences (World Health Organization, 2013).

The World Health Organization defines resistance in a very specific way. There are two types of resistance: suspected and confirmed. The definition of artemisinin resistance is based on "clinical and parasitological outcomes" observed during studies of ACT and trials of artesunate monotherapy:

> An increase in parasite clearance time, as evidenced by greater than ten percent of cases with parasites detectable on day three after treatment with an ACT (suspected resistance) or treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for seven days, or the presence of parasites at day three and recrudescence within twenty eight out of forty two days. (World Health Organization, 2012).

The World Health Organization definition helps people regulate and monitor resistance. The definition allows people to understand what resistance means and how to eventually monitor it within different countries.

Factors affecting the development of artemisinin resistance include uncontrolled use of artemisinin-based combination therapy, artemisinin monotherapy, substandard and counterfeit drugs, and high treatment costs. Many companies try to sell counterfeit drugs and mix low-cost drugs in the hopes of making a profit. In addition to medical drugs, herbal and homeopathic treatments are also used in fighting malaria. Promising herbal alternatives are appearing, but the only long-term solution for eradicating malaria would be the development of a successful vaccine paired with preventative efforts and vector control.

The World Health Assembly asked for all malaria-endemic countries to cease the provision of monotherapies in 2007, and then four years later the World Health Organization released the *Global Plan for Artemisinin Resistance Containment.* This plan outlines how to contain resistance and prevent it from spreading around the world (World Health Organization, 2013). Clinical evidence for artemisinin resistance was first reported in the 2008 study, and subsequently was confirmed by a detailed study from western Cambodia. Resistance in nearby Thailand was reported later in 2012. In April 2011, the World Health Organization stated that resistance to the most effective antimalarial drug, artemisinin, could unravel national (India) malaria control programs, which have achieved significant progress in the last decade. The World Health Organization advocates the

correct use of antimalarial drugs and acknowledges the crucial role of community health workers in reducing malaria in the region. It is vital that nations monitor the effectiveness of their ACTs so that in the case of resistance, they can change to a different ACT and partner drug. Monitoring should include watching if the rate of treatment failure exceeds 10%, and also if the proportion of patients still has the parasite on day three of the clinical study.

One of the World Bank's long-term primary goals has been to subsidize cheap antimalarial therapies. The selling points are the promise of increased access to life-saving drugs and the delay of resistance. The only question was whether a massive release of ACTs into the market would lead to drug resistance. The World Bank commissioned an analysis on the potential of expanding the use of ACTs and whether reducing or stalling the use of monotherapies would delay resistance, or whether it would create greater opportunities for resistant parasites to spread. They found that the use of ACTs could greatly increase with the subsidy and the risk of resistance would still be lower than it would be without the subsidy.

The World Bank ultimately came to the conclusions that ACT subsidies were worthwhile if more than two ACTs were funded. They determined these findings based on the following conclusions:

> 1) The global ACT subsidy would likely extend the therapeutic life of artemisinin drugs because the benefits of crowding out monotherapies outweighed increased resistance that would result from greater ACT use. 2) Even a partial subsidy that was able to crowd out artemisinin monotherapies would be preferable to a delay in implementation. Use of artemisinin monotherapy was almost a guarantee for resistance. 3) Subsidizing two or more ACTs, compared with subsidizing just one, was likely to be more cost-effective and further delay the time when artemisinin resistance would become an obstacle to malaria control. (Laxminarayan, 2009).

These conclusions are consistent with the scientific findings because the use of more than two artemisinins delays resistance the most, and also the use of monotherapies speeds up resistance the fastest.

As seen in this portion of the paper, ACT resistance can be a misleading term. There is a vast array of artemisinins, and if a few specific artemisinins are resistant in an area, it does not mean the area is "ACT resistant" since other artemisinins in combination could and would be effective. Despite the observed changes in parasite sensitivity to artemisinins, the treatment failure rates with ACTs remain low (< 10%), provided that partner drugs that are effective in the region are selected and used. High treatment failure rates with ACTs have been observed only in those areas where resistance to a partner drug has been confirmed (World Health Organization, 2012). In those settings, changing to an ACT with a different partner drug resulted in high treatment efficacy. Therefore, when an ACT appears to be ineffective in a particular region, reference should be made to that specific ACT and not to ACTs as a whole.

The Future of Artemisinin Resistance

The World Health Organization's 2012 Malaria Report discussed artemisinin resistance and its plan to address it and move forward with the eradication of malaria worldwide. The plan is one of containment: it seeks to control and eliminate the spread of resistant parasites. The four nations with suspected or confirmed artemisinin resistance (Cambodia, Myanmar, Thailand, and Vietnam) all have containment plans. These higher transmission areas will "focus on limiting the risk of spread by lowering the malaria burden through intensified malaria control, by increasing access to diagnosis and appropriate treatment, and by scaling up provision of health-care services to migrant and mobile populations" (World Health Organization, 2012). Lower transmission areas are working on the elimination of *P. falciparum* parasites.

The World Health Organization stresses the need for financial resources, long-term political commitment, and a stronger cross-border effort and cooperation in order to succeed with the goal of containment (World Health Organization, 2013). The World Health Organization's Malaria Report of 2013 states that the efforts have been effective, but still need to be expanded and supported. On April 25, 2013, The World Health Organization published an *Emergency Response to Artemisinin Resistance in the Greater Mekong sub region, "*with the purpose of informing and guiding an emergency scale-up of containment efforts in affected countries" (World Health Organization, 2013).

The addition of a partner drug (e.g., chloroquine, sulfadoxine-pyrimethamine, or mefloquine) to a 3-day course of an artemisinin derivative was shown to substantially reduce resistance. For this reason, and to reduce the risk that clinically significant resistance to artemisinin derivatives will emerge, the World Health Organization recommends use of artemisinin derivatives only in combination with partner drugs (artemisinin-based combination therapy).

The future of artemisinin resistance is unclear. The spread is difficult to predict based on the past and the previous patterns of resistance (World Health Organization, 2012). The World Health Organization stresses the need for more tests, studies, and further research on artemisinin resistance. More research and studies, however, mean that countries will need more money and resources. Many foundations and private entities can be tapped for the funding needed to implement such necessary studies.

In the meantime, the prohibition of oral artemisinin monotherapies and the expansion of antimalarial drug effectiveness monitoring are still being implemented. According to the World Health Organization, in 2012, eight more countries withdrew marketing authorization of oral artemisinin-based monotherapies. The number of nations running antimalarial drug effectiveness studies is increasing, especially in Africa, where the reliance on ACTs is high. Despite some resistance around the world, ACTs remain effective in curing patients as long as the partner drug still works effectively. In regions where resistance to both

components of multiple ACTs is present, such as in the Pailin province of Cambodia, special provisions for "directly observed therapy using a non-artemisinin-based combination have been put in place" (World Health Organization, 2012). These special requirements as well as containment efforts to reduce the incidence of *P. falciparum* malaria will help to halt the spread of resistant parasites.

After negotiations with the World Health Organization, pharmaceutical companies such as Novartis and Sanofi-Aventis provide ACT drugs at cost on a nonprofit basis; however, these drugs are still more expensive than other malaria treatments (Roll Back Malaria, 2008). Artemisinin drugs are being produced under the World Health Organization's standards of quality at the Guilin Factory in China, The University of York, the World Agroforestry Center, and Sanofi in Garessio, Italy. A scientist named Jay Keasling, of the University of Berkeley, designed a biosynthetic process for artesiminic acid in order to manufacture the drug on a large scale. Sanofi expects to produce 25 tons of artemisinin in 2013, and up to 60 tons in 2014 (Roll Back Malaria, 2008). The price per kilogram is approximately three hundred dollars, roughly the same as the natural source. Despite concerns that this new Sanofi source would lead to the termination of companies that produce artemisinin, an increased supply of the drug would likely lead to lower prices and therefore increase availability of the drug.

ACT drugs need to earn a place in all government-sanctioned or sponsored malarial programs. The number of developing countries adopting ACTs has grown to 77 as of 2008, but the high price of ACTs compared to other treatments like chloroquine causes economic hardships amongst the poorer regions of the world.

Current research focuses on developing patterns of resistance to partner drugs, thereby determining which ACT should be used in a given geographic location. In the few places where chloroquine is still effective, it is the drug of choice because of its practical price. However, when dealing with artemisinins, some types can be resistant in a specific geographic area while others are still effective, causing the need for drug monitoring. For example, ACT regimens that contain sulfadoxine-pyrimethamine, lumefantrine, or amodiaquine are used primarily in Africa, where they are not resistant yet ("Treatment of Malaria", 2012). Due to declining efficacy of mefloquine along the Thailand-Cambodia border, artemisinin is increasingly being recommended for use in Southeast Asia (Thanh, 2012). The need for specific artemisinin combinations in specific geographic locations should be taken very seriously, because if overlooked (a resistant Artemesinin taken in combination with effective Artemisnins), it could lead to even more resistance worldwide.

Conclusion

The battle with Artemesinin resistance requires a global committed

response. The containment efforts are expensive and complicated, creating a need for financial support and international cooperation. The World Health Organization is currently working with affected countries and their surrounding partners to guarantee a scale-up of malarial interventions.

The Bill and Melinda Gates Foundation, AusAID, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria support the World Health Organization's efforts. While these organizations offer steps in the right direction, the World Health Organization estimates that the organization still needs about 350 million dollars of additional funding by the year 2015 in order to pursue the various avenues that need to be examined. There are other challenges that need to be addressed, such as strengthening the pharmaceutical market regulation in Africa and Asia, and completely removing monotherapies from the global market (World Health Organization, 2013).

Unfortunately, there is no all-encompassing solution to the world's deteriorating malaria situation. No specific malaria control strategy will be applicable in all areas or epidemiologic situations. With the lacking financial resources and a small group of effective antimalarial drugs, the current conditions are headed toward deterioration unless something is done quickly. Ideally, education and prevention methods would allow us to live in a world where all malarious individuals would be prevented from becoming severely infected and dying. A better education and a better drug supply will reduce the incidence of morbidity and mortality with malaria. Direct prevention methods such as bed nets, screens, and other personal protection measures must be taken seriously in malarious areas. Preventative actions are just as important to the fight against malaria as the drugs themselves. Vector control is also very necessary. Low-cost vector control measures designed to reduce the prevalence of infective mosquitos in the environment should be prioritized, such as filling in small bodies of water where larvae can develop. Higher cost vector control measures need to be explored, such as large-scale source reduction or spraying of residual insecticides. By preventing the disease, the fight against malaria can be efficiently controlled by people using common sense and staying away from contaminated waters and mosquito infested areas.

A radical global effort is necessary to end malaria. Drugs, bed nets, vector control, social reform, and education are among the long list of things that need to be mandated in order for malaria to be controlled and contained. Despite the observed changes in parasite sensitivity to artemisnins, ACTs remain efficacious in curing patients, provided the partner drug is still efficacious. Containment efforts in the Mekong sub region have shown that incidence of malaria can be decreased, which is a key component of the overall containment plan to halt the spread of resistant parasites. Greater use of diagnostic tests to better target antimalarial treatment will contribute to this effort. Historically, the knowledge learned about the resistance mechanisms of chloroquine has helped the World Health Organization and public health leaders of today

shape the plan to fight Artemesinin resistance, and ultimately eliminate malaria all over the world.

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