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Malaria:
The Global Challenge

Diploma Thesis

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Introduction

Malaria is a life-threatening disease caused by parasites of the species *Plasmodium* which are transmitted to humans through the bites of infected anopheline mosquitoes. One century ago, malaria was endemic across every continent except Antarctica. Public health measures based on the use of insecticides and changes in land use have eradicated malaria in most developed countries including Australia, Europe and the USA. Never the less the potential for malaria transmission remains. Those of us travelling from malaria-free areas to disease "hot spots" are especially vulnerable to the disease. This vulnerability was seen in the United States in 2002 where there were 1,337 cases of malaria and of those all but five were imported. [1] Between 1957 and 2003, in the United States, 63 outbreaks of locally transmitted mosquito-borne malaria have occurred; in such outbreaks, local mosquitoes become infected by biting persons carrying malaria parasites (acquired in endemic areas) and then transmit malaria to local residents. [1] Disease still remains endemic in some 100 countries in Africa, the Americas, the Eastern Mediterranean Region, the South-East Asia Region, and the Western Pacific Region. (Figure 1)

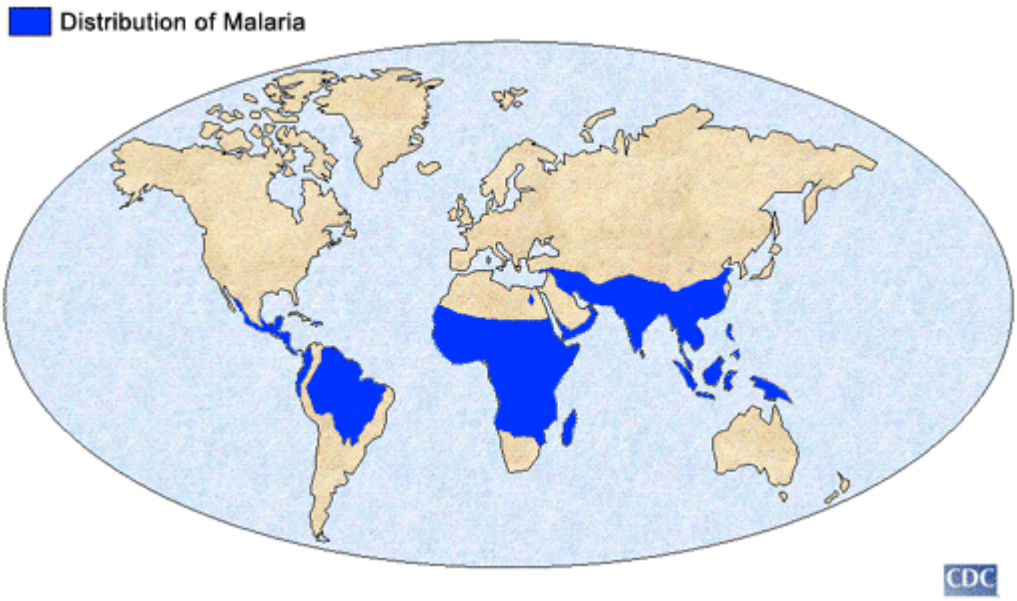


Figure 1. Distribution of Malaria

Taken from the CDC (Center for Disease Control and Prevention). Available from http://www.cdc.gov/Malaria/

It is proposed that half of the world's population is at risk of malaria, especially those residing in lower-income countries. World wide there are 350–500 million cases of malaria each year and over one million people die, most of them being children in sub-Saharan Africa. [2] This means that there are two malaria related deaths every minute and that a child dies from malaria every 30 seconds. Furthermore, malaria is the fourth most common cause of death in children under 5 years of age in developing countries, after perinatal conditions (conditions occurring

around the time of birth), lower respiratory infections (pneumonias), and diarrheal diseases. (Table 1)

Leading Causes of Death in Children Under Five Years of Age, Estimates for 2000-2003 (Source: World Health Organization, The World Health Report 2005)			
Rank	**Cause**	**Numbers (thousands per year)**	**% of all deaths**
1	Neonatal causes	3,910	37
2	Acute respiratory infections	2,027	19
3	Diarrheal diseases	1,762	17
4	Malaria	853	8
5	Measles	395	4
6	HIV/AIDS	321	3
7	Injuries	305	3
	Other causes	1,022	10
	Total	10,596	100.0

Table 1. Leading Causes of Death in Children Under Five Years of Age

Taken from the WHO (World Health Organization): Health Topics - Malaria. Available from http://www.who.int/topics/malaria/en/

It is important to note that not all people go to hospitals when sick or when having a baby, and many die at home. Thus the true statistics of morbidity and mortality due to malaria are likely much higher than reported. The global spread of malaria is a direct result of human migration and therefore it concerns us all. Malaria is a preventable and curable disease and more needs to be done globally in order to win the fight against it. This review will focus on the global impact of malaria and on the current prevention and treatment strategies used to defend against this killer.

1. Parasitology

There are four types of human malaria, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*. All of which are transmitted by female Anopheles mosquitoes. *Plasmodium falciparum* and *Plasmodium vivax* are the most common types while *Plasmodium falciparum* is the most deadly.

1.1. Malaria Life Cycle

The whole process of infection begins with the female mosquito becoming infected after taking a blood meal containing gametocytes. The developmental cycle of the mosquito generally takes 7-20 days (depending on temperature), finishing with sporozoites migrating to the insect's salivary glands. All strains of *Plasmodium* have a complex life cycle that begins when a female mosquito injects sporozoites into the human host when taking a blood meal. (Figure 2)

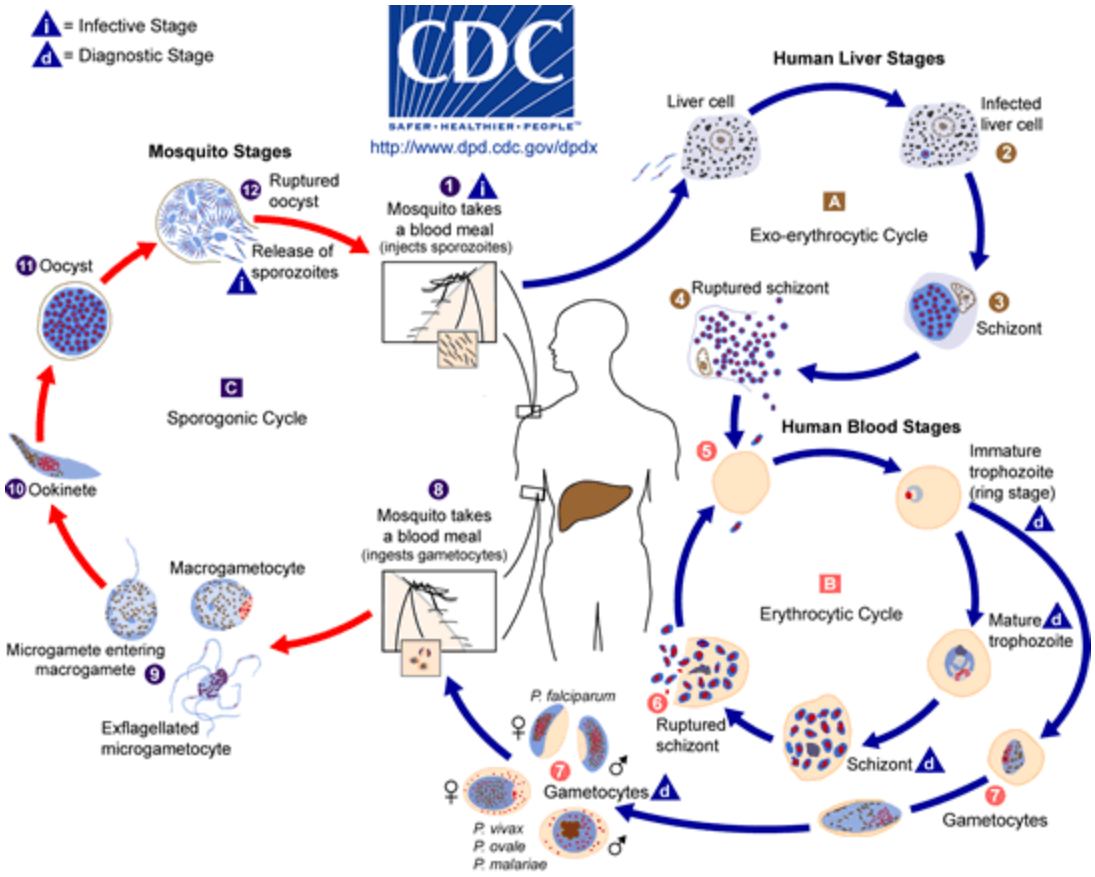


Figure 2. Malaria Life Cycle

Taken from the CDC (Center for Disease Control and Prevention). Available from http://www.cdc.gov/Malaria/

The sporozoites enter the bloodstream and rapidly migrate to the liver and invade hepatocytes. Here they give rise to tens of thousands of merozoites over a period of 6–16 days. In the case of *P. vivax* and *P.*

ovale, a few parasites will remain dormant in the liver and may reactivate at any time causing a relapsing infection. Merozoites then erupt into the bloodstream and invade erythrocytes where they multiply and mature over a period of 24–72 hours. Infected red blood cells (RBC) then lyse and liberate the merozoites which immediately invade new RBCs to repeat the whole cycle. The classical signs of malaria, acute febrile episodes and rigors that occur every 48 to 72 hours, coincide with the lysis of infected RBCs releasing the matured merozoites. A few of the merozoites develop not into trophozoites but into gametocytes, which are not immediately released from the red cells but can sexually combine and develop into new sporozoites when taken up by an anopheline mosquito, thus completing the life cycle.

2. Transmission

Malaria transmission rates differ from region to region. Some regions have a relatively constant number of cases throughout the year and are thus termed malaria endemic regions, while other areas are called malaria seasonal regions due to their coinciding with the rainy season. Transmission depends on local factors such as patterns of rainfall, types of mosquito species in the area and the proximity of mosquito breeding sites to humans.

Rainfall can create collections of water which serve as "breeding sites" for the *Anopheles* eggs which develop into larvae, pupae and eventually adults. In order to transmit malaria, female *Anopheles* must survive long enough after they have become infected to allow the parasites they harbor to complete their growth cycle (extrinsic growth cycle). This process takes approximately 9-12 days in tropical areas. The "breeding sites" may either dry up prematurely in the absence of further rainfall, or conversely they may be flushed out by excessive rains. The ambient temperature and humidity will also determine chances of survival. Warmer ambient temperatures will shorten the duration of the extrinsic growth cycle, thus increasing the chances of transmission. This explains in part why malaria transmission is greater in tropical and semitropical areas and lower altitudes, particularly for *P. falciparum*. Having said this, transmission will not occur even in tropical and

subtropical areas under adverse conditions such as high altitude, desert areas and on some islands in the Pacific Ocean which have no local *Anopheles* species capable of transmitting malaria and in countries where transmission has been stopped due to eradication. Perhaps the trend of global warming may increase the geographic range of malaria and may be responsible for future malaria epidemics.

At lower temperatures (less than 15°C for *P. vivax* and less then 20°C for *P. falciparum*) the extrinsic cycle will falter and malaria transmission will be less intense and more seasonal. [1] In cooler regions *P. vivax* might be more prevalent because it is more tolerant of lower ambient temperatures. In Western Europe and the United States, economic development and public health measures have succeeded in eliminating malaria. [1] However, *Anopheles* mosquitoes still live in these areas and can transmit malaria. Thus, reintroduction of the disease is a constant threat.

Climate may also influences human behaviors which in turn may increase contact with *Anopheles* mosquitoes especially between dusk and dawn, when the mosquitoes are most active. Behaviors such as camping or sleeping outdoors in hot weather conditions without appropriate protection against mosquitoes will surely increase the risk of transmission.

Epidemics can also occur when the mosquito-borne parasite is introduced into areas where people have had little prior contact with infectious species of mosquito and have poor or no immunity to malaria. In areas where malaria cases are constant, epidemics can occur when people with low immunity migrate into these regions. Triggers of epidemics include wet weather conditions, floods, or mass population movements due to conflict. Therefore special measures must be taken to prevent the possible spread of malaria in disaster situations.

3. Treatment

3.1. Chemoprophylaxis

Current chemoprophylactic first-line strategies were designed to prevent death due to severe *falciparum* malaria. The drugs also largely prevent primary attacks due to non-falciparum species, although the later relapses that can occur with *P. vivax* and *P. ovale* are not affected. As mentioned above the resistance of *P. falciparum* to chloroquine is wide spread. Therefore in areas where malaria is endemic, atovaquone–proguanil, mefloquine, or doxycycline is recommended by the CDC and WHO. [3] All the above mentioned agents have been shown to have more than 95% efficacy in preventing malaria due to *P. falciparum*. Mefloquine resistance is quite rare and occurs in limited rural areas of Southeast Asia. (Figure 3)

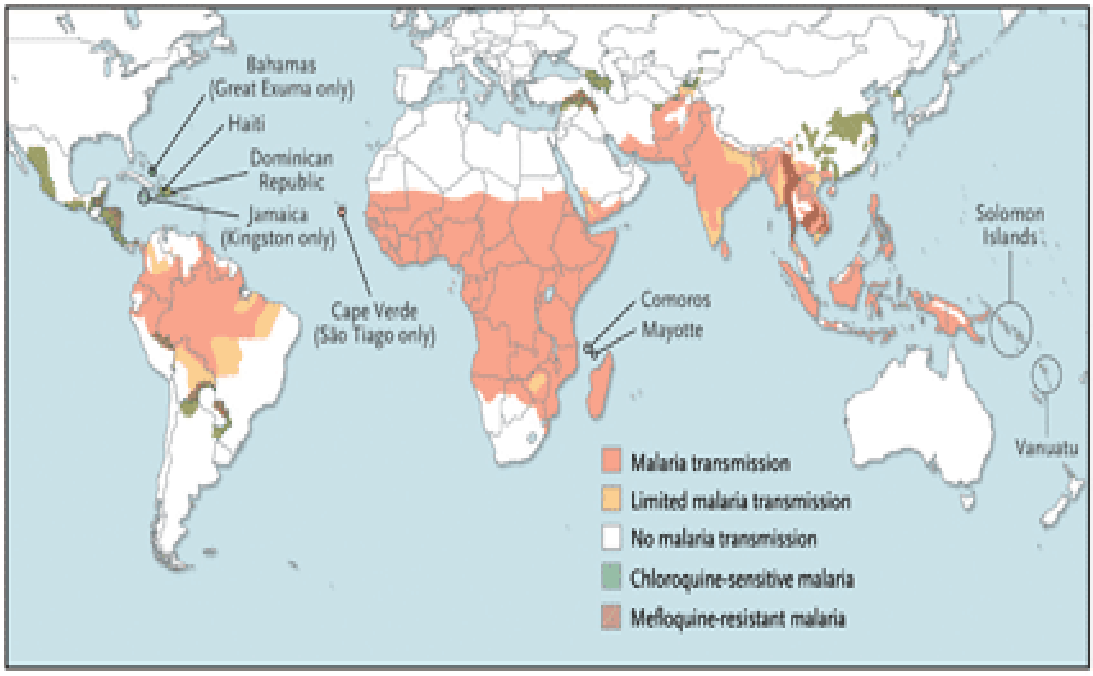


Figure 3. Areas of Mefloquine-resistant malaria

Data are from the World Health Organization and from the Centers for Disease Control and Prevention. [22], [23]

An interesting common miss-perception among antimalarial agents such as chloroquine, mefloquine, and doxycycline is that they prevent initial malaria infection in humans. They in fact act much later, on parasites that infect red blood cells once they have been released from the initial maturation phase in the liver. Therefore, these drugs must be continued for 4 weeks following the last exposure to infective mosquitoes in order to eradicate any parasites that may still be released from the

liver. The drug atovaquone–proguanil acts both on blood-stage parasites and also interferes with the development of actively replicating parasites in the liver. Thus, it does not need to be continued for 4 weeks but can be discontinued 1 week after the exposure ends. [10] Chemoprophylaxis with atovaquone–proguanil and doxycycline should ideally begin 1 to 2 days before travel to endemic malaria areas, and chemoprophylaxis with chloroquine should begin 1 week before travel. Mefloquine treatment should be started preferably 3 weeks before travel. This allows for the assessment of possible adverse effects that may result in discontinuation and change to an alternative drug. Unexplained acute anxiety, depression, restlessness, and confusion are indications for discontinuation and alternative drug switching.

The drug choice for travelers to areas where there is chloroquine-resistant malaria will depend on factors related to the traveler. Factors would include the duration of the trip, the person's age and medical history, whether the person is pregnant, and whether there has been previous drug intolerance, as well as economic considerations. Overall the best-tolerated drug is Atovaquone–proguanil, but with extended trips the cost considerations significantly increase. It is also important to give clear instructions on adherence to prescribed drugs.

3.2. Treatment Following Malaria Infection

Malaria can be classified as uncomplicated or severe. Severe malaria is generally defined as acute malaria with major signs of organ dysfunction or high levels of parasitemia. [3] It is these severe cases where fatal outcomes of disease do occur. In areas where malaria is endemic, young children are at high risk for severe malaria. In older children and adults partial immunity develops after repeated infections, and they are thus at relatively low risk for severe disease. Pregnant women are also at increased risk for severe malaria. [4]

In cases of severe malaria the treatment should be initiated as soon as possible and in endemic areas, the WHO recommends that treatment be started within 24 hours after the first symptoms appear. Early treatment of malaria will shorten its duration, prevent complications and help to avoid the majority of deaths. In areas where malaria is not endemic, all patients with malaria (uncomplicated or severe) should be kept under clinical observation if possible. Malaria places a considerable drag on health in developing countries, therefore malaria disease management is an essential part of global health development. Treatment must aim to cure patients of the disease rather than to diminish the number of parasites carried by an infected person. Such treatment will keep the spread of malaria in check.

Most drugs used in treatment are active against the parasite forms of malaria in the blood and include, chloroquine, sulfadoxine-pyrimethamine (Fansidar®), mefloquine (Lariam®),atovaquone-proguanil (Malarone®), quinine, doxycycline and artemisin derivatives. In addition, primaquine is active against the dormant parasite liver forms (hypnozoites) and prevents relapses of disease. However, primaquine should not be taken by pregnant women or by people who are deficient in G6PD (glucose-6-phosphate dehydrogenase) because of the serious health risks associated. Of the above mentioned drugs two exist, both of which are derived from plants whose medicinal values had been noted for centuries. They are artemisinin and quinine each derived from the Qinghao plant (*Artemisia annua* L, China, 4th century) and the cinchona tree (South America, 17th century) respectively. [5] How to treat a patient depends on the species of infecting parasite, the area where the infection was acquired and its drug resistance status, the clinical status of the patient, any co-morbidities, pregnancy, drug allergies or other medications taken by the patient. Approved therapies for treatment of uncomplicated *falciparum* malaria in the United States include atovaquone–proguanil, quinine (a 3-day course plus a 1-week course of doxycycline or, in children, clindamycin), and mefloquine. [6] The current recommendations for severe malaria are to administer quinidine as a loading dose followed by continuous infusion; the loading dose may be omitted only if mefloquine or quinine were recently administered. [7]

Quinidine does have a major drawback and that is its cardiac toxic effects. With emerging evidence of the superiority of artesunate over quinine or quinidine it appears that the best available treatment, particularly for *P. falciparum* malaria, is a combination of drugs known as artemisinin-based combination therapies (ACTs). The advantage of artemisinins is rapid action against all of the erythrocytic stages of the parasite, including transmissible gametocytes. [6] ACTs incur a rapid clinical response and a decrease in the transmission of malaria. In addition, there is currently limited, if any, resistance to artemisinins in malaria parasites. Currently in the United States artemisinin-based drugs are not approved by the Food and Drug Administration (FDA), however it is possible to use these drugs with an investigational-new-drug (IND) application. This allows investigational use of intravenous artesunate when treating severe malaria.

Malaria control efforts are proving to be problematic as parasite resistance to some medicines is developing. The reason for this resistance is linked to the inappropriate use of antimalarial drugs over the past century. Of considerable note is the extent of chloroquine resistance *falciparum* which is nearly universal and extends over most of the endemic regions, (Figure 3)

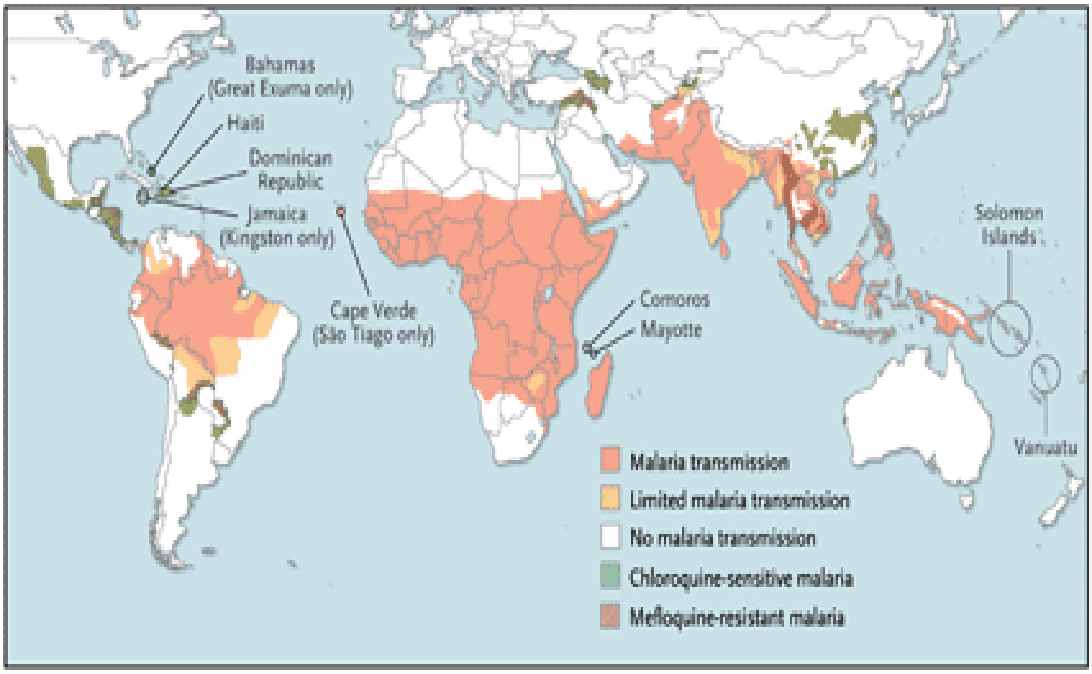


Figure 3. Areas of chloroquine-sensitive *P. falciparum*

Data are from the World Health Organization and from the Centers for Disease Control and Prevention. [22], [23]

excluding only Mexico, areas of Central America that are west of the Panama Canal, the Caribbean, East Asia, and a few Middle Eastern countries. [3] In order to combat resistance, combined drug therapies are being employed on a more regular basis. To assure combined drug therapy success the individual drugs must have separate mechanisms of action against the same stage of the parasite. Combined antimalarial therapies include old and new drugs — old drugs in new combinations

(eg. chloroquine and sulfadoxine–pyrimethamine), an old drug combined with a new drug (eg. amodiaquine and artesunate), and new drugs in combination (eg. lumefantrine and artemether). [8] It appears that combination therapy that includes artemisinin is potent and thus useful in endemic areas. To date there are no effective alternatives to artemisinins for the treatment of malaria either on the market or nearing the end of the drug development process. With the emergence of drug resistance and the lack of new drugs on the market the emphasis should then shift from treatment of malaria to prevention and elimination of this disease.

4. Prevention and Elimination

4.1. Vector Control

All travelers to regions where malaria is endemic should be educated regarding personal and environmental measures to provide protection against mosquito bites. These measures include a mosquito repellent containing *N,N*-diethyl-3-methylbenzamide (DEET), the use of long sleeves, pants and footwear that provides full coverage, and the use of properly screened and/or air-conditioned sleeping areas. [9]

The core of prevention focuses on transmission reduction of malaria. This is done by controlling the malaria-bearing mosquito. There are two main interventions for vector control and they include the use of mosquito nets treated with long-lasting insecticides (a cost effective method) and indoor residual spraying of insecticides. The nets are used to provide protection to risk groups, especially young children and pregnant women in high transmission areas. This provides personal protection for 3-5 years depending on conditions of use. Also indoor spraying if used effectively can protect for 3-6 months. DDT is effective for longer periods, up to 12 months in some cases. These interventions can be locally complemented by other mosquito vector control methods, for example reducing standing water habitats (insect breeding grounds). Efforts to control mosquitoes are improving in many areas, however there are significant challenges. These challenges include, increasing mosquito

resistance to key insecticides DDT and pyrethroids, especially in Africa; a lack of effective alternate insecticides, and changing behaviors of local malaria-carrying mosquitoes (result of vector control forcing movement of mosquitoes to more hospitable areas). Since there are no equally effective and efficient insecticide alternatives to DDT and pyrethroids, and given the fact that developing new pesticides is very costly and time consuming, it is therefore essential to enforce vector management practices with sound management of insecticides. National control efforts should include routine insect resistance detection in order to ensure that the most effective vector control methods are being used. Recent data has shown that large-scale use of WHO recommended strategies could rapidly reduce malaria, especially in areas of high transmission. For example, the Maldives, Tunisia and the United Arab Emirates have implemented WHO recommended strategies and have been able to eliminate malaria. These country successes are due to intense national commitments and coordinated efforts with partners.

4.2. Vaccines

There is currently no vaccine that will prevent malaria, but they are currently under development. There are several lines of evidence suggesting that a prophylactic malaria vaccine for humans is feasible. The first promising studies demonstrating the potential for a malaria vaccine were performed in 1967 by immunizing mice with live, radiation-

attenuated sporozoites, providing protection to about 60% of the mice upon subsequent injection with normal, viable sporozoites. [11] Humans however are not mice and the road to developing an effective vaccine is long and difficult. Presently, there are a massive variety of vaccine candidates on the table. Pre-erythrocytic vaccines (vaccines that target the parasite before it reaches the blood), in particular vaccines based on a vaccine candidate derived from the circumsporozoite protein (CSP) that is found at the surface of the sporozoite and of the infected hepatocyte. This vaccine aims to generate an antibody response that will neutralize sporozoites and prevent them from invading the hepatocyte, and/or to elicit a cell-mediated immune response that will inhibit intra-hepatic parasites. These comprise the largest and most promising group of research for the malaria vaccine at this time. This type of vaccine would be ideal for travelers as it would prevent the onset of clinical disease. Of this type of vaccine the candidate RTS,S/AS02A is the furthest along in vaccine trials. It's being developed by a partnership between the PATH Malaria Vaccine Initiative, the pharmaceutical company, GlaxoSmithKline, and the Walter Reed Army Institute of Research. [12] In October 2004, the researchers of RTS,S/AS02A announced results of a Phase IIb trial which indicated that the vaccine reduced infection risk by approximately 30% and severity of infection by over 50%. The study included more than 2,000 children from Mozambique. [13] More recent tests in October 2007, involved the RTS,S/AS02A vaccine and the focus

was on the safety and efficacy of administering it earlier in infancy. The researchers announced results of a phase I/IIb trial conducted on some 214 Mozambican infants with ages ranging from 10 and 18 months in which the full three-dose course of the vaccine led to a 62% reduction of infection with no serious side-effects apart from minor pain at the site of injection. [14] Further research is being done and will delay this vaccine from commercial release until approximately 2011. [15]

Other vaccine candidates include: those that seek to induce immunity to the blood stages of the infection (asexual blood-stage vaccines); those that seek to avoid more severe pathologies of malaria by preventing adherence of the parasite to blood venules and placenta; and transmission-blocking vaccines that would stop the development of the parasite in the mosquito right after the mosquito has taken a blood meal from an infected person. [16] It is hoped that the sequencing of the *P. falciparum* genome will provide targets for new drugs or vaccines. [17] Asexual blood-stage vaccine strategies aim to elicit antibodies that will inactivate merozoites and/or target malarial antigens expressed on the RBC surface. Induction of antibody-dependent cellular cytotoxicity and complement lysis are the goals; they also are meant to elicit T-cell responses there-by inhibiting the development of the parasite in red blood cells. This type of vaccine would mostly serve as a disease-reduction vaccine and would be most effective in endemic areas.

There are however some important obstacles in the development of a vaccine including the lack of immune correlates of protection, the lack of reliable and predictive animal models, and the developmental and antigenic diversity and variability of the parasite.

4.3. Biological Warfare

Recent research coming from a team at the University of Queensland in Australia and the Central China Normal University in Wuhan has uncovered a hidden potential in the bacteria called Wolbachia, which halves the life span if its insect host, the fruit fly. [18] These researchers have been able to successfully introduce Wolbachia into an entirely new host, the mosquito Aedes aegypti. This mosquito spreads the virus causing dengue fever, but what is exciting is its potential implication in the fight against malaria. These scientists have shown that the life shortening effects of this bacteria do not interfere with A. aegypti reproduction, in fact, it is advantageous to the infected female by killing the eggs of uninfected females fertilized by an infected male. Wolbachia however, can be disastrous for the dengue virus and for malaria, both of which have a relatively long incubation period: it takes up to two weeks to invade the mosquito, replicate, and enter the salivary glands of the mosquito before being spread to a new host. [18] Therefore, the mosquito may not live long enough to pass on disease.

Researchers uncovered another exciting and unexpected side effect of Wolbachia infected mosquitoes. It turns out that infected mosquitoes attempted to bite humans frequently but were unable to draw blood. On further inspection it was revealed that the mosquitoes' proboscises (the tubular feeding and sucking organ) had become "bendy" and could not penetrate human skin. [18] The infected mosquito would therefore be "dead" for all intensive purposes. The next step is to test whether the laboratory success will translate into success in the field. Currently field trials are being set up.

5. Economic Impact

Beyond the human toll, malaria wreaks substantial economic havoc in high-rate areas, decreasing Gross Domestic Product (GDP) by as much as 1.3% in countries with high rates of transmission. [19] Health costs due to malaria include personal and public expenditures on prevention and treatment. Costs to individuals and their families include: purchase of drugs for treating at home; expenses for travel to, and treatment at, dispensaries and clinics; lost days of work; absence from school; expenses for preventive measures; expenses for burial in case of deaths. Costs to the public (governments) include: maintenance of health facilities; purchase of drugs and supplies; public health interventions against malaria, such as insecticide spraying or distribution of insecticide-treated bed nets; lost days of work with resulting loss of income; and lost opportunities for joint economic ventures and tourism. The CDC estimates that the cost for potentially life-saving treatments of malaria are estimated to be US$0.13 for chloroquine, US$0.14 for sulfadoxine-pyrimethamine, and US$2.68 for a 7-day course of quinine. [20] It is proposed that in some heavily burdened countries the disease accounts for up to 40% of public health expenditures, between 30% and 50% of inpatient hospital admissions and as much as 60% of outpatient health clinic visits. [20] It is clear that malaria disproportionately affects poor people who cannot afford treatment or have limited access to health care. It essentially traps families and communities in a downward spiral

of poverty. The key to breaking this downward spiral of poverty is increased assistance from rich countries to enable the poorest countries to put the basic infrastructure and human capital in place. This means increased donor funding to help fight disease, establish a network of primary health care posts, improve and extend educational institutions and schooling, and build the networks of roads, power, and telecommunications on which a modern economy depends. Global investment in malaria control has been surprisingly low, hovering around $100 to $200 million per year. [21] The UN Millennium Project's Working Group on Malaria, headed by Prof. Burton Singer of Princeton University and Prof. Awash Teklehaimonot of Columbia University, discovered that figures of $2 to $3 billion each year are needed to enable poor African countries to achieve substantial control over the disease. The is equivalent to annual investments amounting to $2 to $3 for each of the roughly 1 billion people in the developed world. These sums are therefore tiny for rich countries, but they are out of reach for the impoverished individuals and governments in sub-Saharan Africa.

6. Methods

This scientific review paper focused on the global impact of malaria and prevention of this disease. The research included information provided by the World Health Organization (WHO), Center for Disease Control and Prevention (CDC) and many journal articles such as the Lancet, New England Journal of Medicine (NEJM) and Nature; just to name a few. The data, current research and statistics were compiled and presented as a review paper.

7. Results

7.1. Imported Malaria

As discussed, malaria has been eradicated from many areas where previously it was endemic. Despite transmission being interrupted in these areas, there is a constant risk for the reintroduction of the parasite. Given human migration and travel patterns this risk will likely remain since there are still active mosquito vectors. Of those malaria cases in malaria-free areas the vast majority are credited to persons returning to the country from endemic areas ("imported" malaria). (Figure 4)

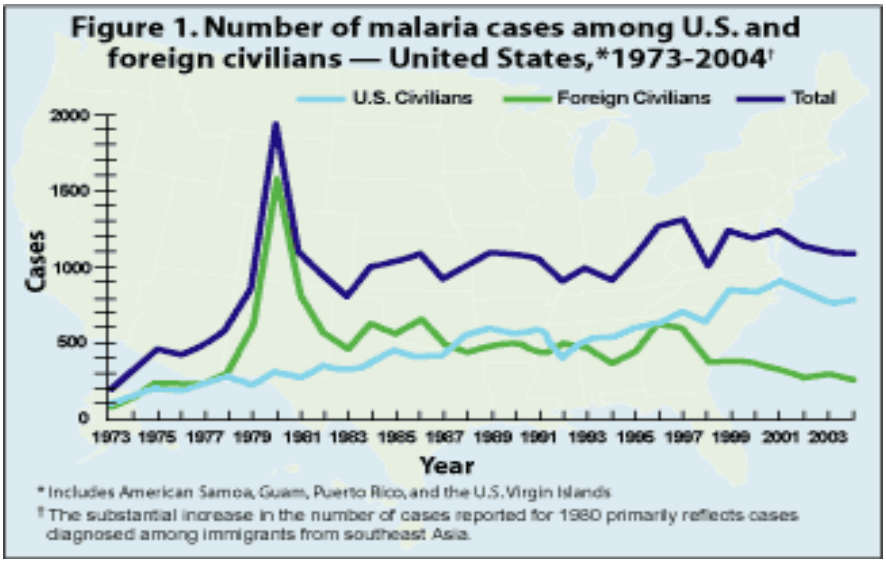
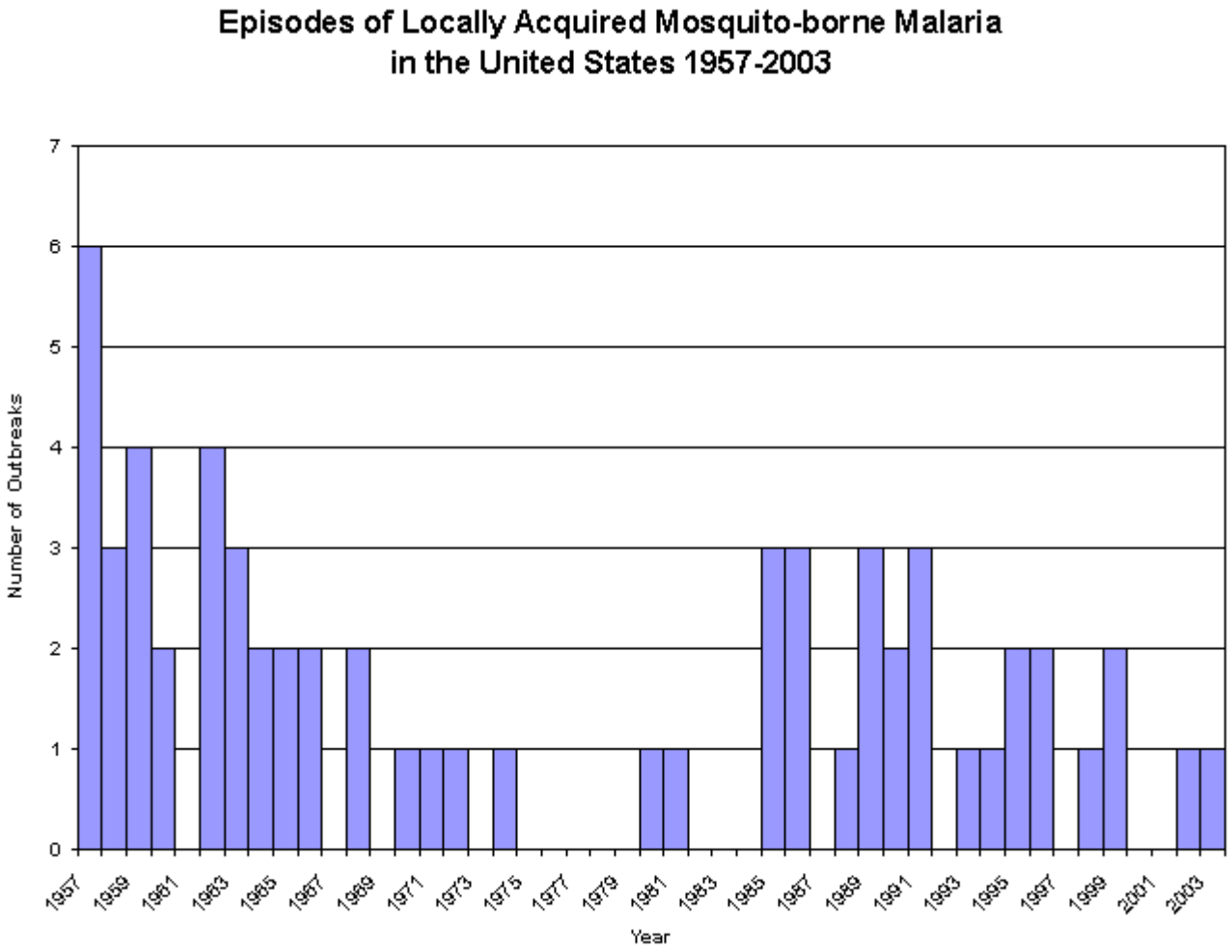


Figure 4. Number of malaria cases in the United States

Taken from the CDC (Center for Disease Control and Prevention). Available from http://www.cdc.gov/Malaria/

In the United States, approximately 1,200 malaria cases are reported annually of which the majority are due to imported malaria. It therefore is very rare for malaria to occur locally in non-endemic regions. Outbreaks of locally transmitted cases of malaria in the United States have been small and relatively isolated to date. This graphical presentation clearly shows how rare it is, with only one case in 2003. (Graph 1)



Graph 1. Locally acquired Malaria in the United States 1957-2003

Taken from the CDC (Center for Disease Control and Prevention). Available from http://www.cdc.gov/Malaria/

Usually travelers or immigrants coming from malaria endemic areas will develop signs of malaria after arriving in the United States and therefore the cases will be reported. Prompt reporting of patients with malaria and adequate assessment of risk factors for malaria allows initiation of an

appropriate public health response to prevent reestablishment of malaria transmission. It is vital that continued domestic surveillance and prompt diagnosis and treatment are carried out in order to prevent the reintroduction of malaria into areas that are currently malaria-free. However, other mechanisms exist for cases to occur and they include "airport" malaria.

7.2. "Airport" Malaria

"Airport" malaria is described as malaria caused by a bite from infected anopheline mosquitoes that are transported by aircraft from a malaria-endemic country to a non-endemic country. [24] If the local conditions are appropriate for survival, then local residents can be bitten and thus can acquire malaria without having traveled abroad. In temperate climates, temperature and humidity can be favorable in the summer for the mosquito not only to survive but also to move around and perhaps lay eggs. It was found during random searches of airplanes at Gatwick Airport (London) that 12 of 67 airplanes from tropical countries contained mosquitoes. [25] In fact there are a number of reported cases of airport malaria.

For example, six cases were identified in and around Roissy-Charles-de-Gaulle Airport in 1994 [26], two cases of *P. falciparum* malaria were identified in Italy in two persons who lived in Geneva in 1989 [27] and another five cases of airport malaria were reported in Geneva in the summer of 1989. [28] With the enormous and continuing increase in air traffic, we can expect cases of airport malaria to increase.

8. Discussion

A very real global public health threat due to the resurgence of malaria exists. This threat stems from a general collapse of vector-control operations and from resistance to chemoprophylactic drugs such as chloroquine and sulfadoxine–pyrimethamine. Recent surveys show rates of treatment failure which are higher than 50 percent for chloroquine in most affected regions, as well as poor efficacy of sulfadoxine–pyrimethamine in sub-Saharan Africa and Southeast Asia. The drugs quinine and mefloquine remain effective therapies in most parts of the globe except in some regions bordering Thailand. Resistance to the drug primaquine (the only drug for preventing relapses of malaria) has not been documented, however it is suspected that resistance does occur. New drugs should be effective among the poor, self-treating rural populations in regions of endemic disease and should be provided through programs that address issues of availability and cost, convenience and adherence, safety and tolerability, and quality assurance. The combination therapies with artemisinin derivatives represent the current best efforts toward providing such therapeutic agents. When compared with traditional monotherapies, these drugs deliver an inhibitory effect that substantially reduces the probability of selection for resistant parasites. However, widespread distribution without complementary effective delivery of health care places the clinical

usefulness of these critical drugs in doubt. If we want to effectively combat malaria a scaled-up control effort would have to include the free distribution of bed nets and effective medicines to impoverished rural Africans, who cannot afford to buy the nets even at highly subsidized prices. Insecticide-impregnated bed nets have proved highly effective in reducing morbidity and mortality, especially when an entire village uses the nets. At this point in time these are the best available strategies in the fight to control malaria.

There are however exciting finding coming from the area of vaccine development with the pre-erythrocytic vaccine candidate RTS,S/AS02A being the most promising. It is currently undergoing further testing and no vaccine will be ready for commercial use until at least 2011. Researchers are also investigating the effects of a bacteria called Wolbachia on mosquitoes. Wolbachia has been introduced into mosquitoes in a clinical setting with good results. Wolbachia shortens the mosquitoes life span enough so that the parasite within will not be able to mature before the death of the mosquito, thereby stopping the transmission of malaria. Furthermore, it appears that the mosquitos' proboscises becomes weakened and will not penetrate skin. Thus rendering the mosquito dead before its time. Currently, field studies are being set up.

It is clear that there should be a global initiative focused on malaria control in developing countries. The costs of fighting malaria seem high from a single country point of view, however it is apparent that it is a disease that affects the global community. Relatively small amounts of money are currently being set aside for malaria control. This is simply not enough and richer countries need to invest in this fight before this deadly disease comes knocking on our door. Evidence of this threat is seen in the cases of traveler's malaria and "airport" malaria. Although the numbers are not significant in non-endemic areas the threat of an outbreak is of constant concern.

9. Conclusion

Malaria is a global killer which claims more lives annually than many other diseases. The keys in the fight against it are prompt treatment of severe malaria, anti-malarial prophylactic drugs for travelers and prevention strategies focusing on vector control, vaccine development and biologicals that work against the spread of malaria. The global distribution of malaria clearly shows a predilection for developing and thus poor countries. If we are to succeed in this global battle the richer countries must help with the costs associated with drug treatment, mosquito net distribution and insecticide spraying protocols. Also of utmost importance is the continuation of research and development of vaccines and potential biological substances which combat malaria. Furthermore, it is essential that there be a partnership of countries and organizations to ensure national commitments in order to gain an upper hand in this fight against malaria.

10. Summary

More than half the world's population is at risk from malaria, with up to 500 million cases each year and more than one million deaths directly resulting from the disease. Those at highest risk from the disease are people living in endemic areas, travelers to endemic areas, small children and pregnant women. Malaria is a constant risk to the overall health of the global population.

There are four types of human malaria, with P. Falciparum being the most deadly. All types have a complex life cycle which begins with the female mosquito becoming infected after taking a blood meal containing gametocytes. The developmental cycle of the mosquito takes about 1-2 weeks and finishes with sporozoites migrating to the insect's salivary glands. The female mosquito then injects sporozoites into the human host when taking another blood meal. The sporozoites enter the bloodstream, migrate to the liver. Here they give rise to merozoites which erupt into the bloodstream and invade RBCs. They multiply and mature then lyse and expel the merozoites which reinvade and the cycle begins again. The classical signs of malaria coincide with the lysis of infected RBCs.

Transmission of malaria depends on local factors such as patterns of rainfall, types of mosquito species, mosquito proximity to humans, human behavior and temperature.

Treatment of malaria depends on the species of infecting parasite, the area where the infection was acquired and its drug resistance status, the clinical status of the patient, any co-morbidities, pregnancy, drug allergies or other medications taken by the patient. Proper treatment of malaria will shorten its duration, prevent complications and help to avoid the majority of deaths. Currently the best available treatment is a combination of drugs known as artemisinin-based combination therapies (ACTs). This therapy works rapidly and has little or no resistance to date. In order to protect against the development we must combine drugs with different mechanisms of action against the same stages of the parasite.

Malaria prevention includes vector control, chemoprophylaxis use and the future possibility of vaccine use. Vector control is achieved with the use of insecticide treated mosquito nets and indoor residual spraying of insecticides. Education is essential for the traveler and they must be fully versed in the use of long sleeves, pants and footwear that provides full coverage. Chemo prophylactic drugs are very effective in preventing disease with the exception of chloroquine and sulfadoxine–pyrimethamine which have high rates of resistance. Thus mefloquine is the most commonly used drug by travelers in recent times. There are no vaccines currently available to prevent malaria but there are many under development with the pre-erythrocytic candidate RTS,S/AS0 being the most ready for commercial release.

The economic tolls of malaria as thrown some developing countries into a downward spiral of poverty. The disease has caused a drop in GDP by as much as 1.3% and has accounted for up to 40% of public health expenditures.

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