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A Compendium on Malaria in Tropical Africa

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Abstract

Malaria is an endemic disease in tropical Africa. Its transmission is initiated by the bite of an infected female *Anopheles gambiae* of mosquito. It has been estimated that more than 300 million people are infected each year, with a child dying of the disease every 40 seconds, and over 1 million die annually of malaria in Africa alone. There are approximately 200 million to 500 million new cases of malaria each year in the world, with about 90% of them in Africa. In tropical Africa alone, malaria is responsible each year for the deaths of more than a million children under the age of 14. Of the four species of malaria parasites known to infect man, *Plasmodium ovale, Plasmodium malariae* and *Plasmodium vivax* undoubtedly cause major morbidity, but do usually result to low mortality. *Plasmodium falciparum* by contrast is responsible for over one million deaths in Africa each year, accounting for up to 80% of malaria in Africa. Drugs currently used for chemoprophylaxis are chloroquine, halofantrine (Halfan), doxycycline, tafenoquine, primaquine, amodiaquine, quinine, quinidine, mefloquine (Lariam), proguanil (Paludrine), quinghaosu (Artemisin), pyrimethamine – sulfadoxine (Fansidar) and Atovaquone. Susceptibility to malaria infection and disease is regulated by hereditary and acquired factors. However insecticide treatment of bed nets is the most promising form and effective way of preventing malaria. Efforts to develop an effective malaria vaccine are under way.

Key Words: Malaria, Chemotherapy, vaccine, Africa, Tropics.

Introduction

Malaria is an ancient scourge, as evidenced by early Chinese and Hindu writings. During the fourth century B.C. the Greeks noticed its association with exposure to swamps and began drainage projects to control the disease. The Italians gave the disease its name, *Malaria*, which means "bad air," in the seventeenth century because of its association with the ill – smelling vapours from the swamps near Rome (Nester *et al.*, 2004, Prescott *et al.*, 2005).

Malaria is a serious acute and chronic relapsing infection in human, characterized by periodic paroxysms of chill and fever, varying degree of anemia, splenomegaly, hepatomegaly and various syndromes resulting from involvement of individual organs (Lucas and Gills, 1990, Prescott *et al.*, 2005). It is a disease of the tropical and sub – tropical zones and may also occur in temperate regions. Its dissemination diminishes with distance from the equator (Werner and Friedrich, 1987).

Malaria presents enormous health problems in Africa and it is possible that over 90% of the 200 million estimated malaria infected people in the world are in Africa. Of the estimated 300 – 400 million acute attacks per year, world-wide, about 80% of the cases (including deaths) occur in tropical Africa (WHO, 1990). Because of drug and insecticide resistance, malaria is now on the increase globally particularly in Africa, India, the Far East and South America. About 35% of the world's population is estimated to be infected, with some 10 million new cases annually and perhaps two million deaths. It has been estimated that more than 300 million people are infected each year, and over one million die annually of malaria in Africa alone. There are over 150 million cases of malaria in the world each year. In tropical Africa alone, malaria is responsible each year for the deaths of about a million children under the age of 14. About 1,000 cases are reported each year in the United States, divided between returning U.S. travelers and non – U.S citizens (Prescott *et al.*, 2005).

According to WHO (1990), 270 million people currently have malaria, and each year 1 to 2 million of these infected people die of the disease (Mekane and Kandel, 1996). Today there are 300 to 500 million people infected annually worldwide, with

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about 3 million deaths and also with a child dying of the disease every 40 seconds. More people are dying of the disease (Nester *et al.*, 2004). Similarly, Baron (1996) reported that there are approximately 200 million to 500 million new cases each year in the world, and the disease is the direct cause of 1 million to 2.5million deaths per year.

According to Talaro (2005), throughout human history, including prehistoric times, malaria has been one of the greatest afflictions in the same ranks as influenza and tuberculosis. Even now, as the dominant protozoan disease, it threatens 40% of the world's population every year and approximately 300 million to 500 million new cases are still reported each year, with about 90% of them in Africa. The most frequent victims are children and young adults, of whom at least 2 million die annually. The total case rate in the United States is about 1,000 to 2000 new case a year, most of which occur in immigrants.

Each year, over a million people world-wide die of malaria and more than 100 million new cases are discovered, with children more particularly affected. It is estimated that in rural areas in tropical Africa, one child out of every 20 die of malaria before the age of 5 (UNICEF, 1993).

The 110 million clinical cases of malaria reported annually, more than 90 million are in Africa, south of the Sahara. An estimated 280 million people are carriers of the malaria parasite in the region (Mahmoud, 1987, Benzerrong and Elom, 1991). According to a United Nations Population Division report in 1990, malaria is the only disease today, apart from acquired immunodeficiency syndrome (AIDS) that shows a significant raising tendency. The fight against malaria remains one of the biggest challenges of public health (Okara and Khalil, 1993).

The economic cost of this disease is enormous and the estimated cumulative cost in 1997 for fighting malaria in Africa was $2.2 billion. Successful eradication can therefore save very large sums, for example an estimate of $20 billion from eradicating smallpox (Mims *et al.*, 2005).

Malaria is one of the most prevalent and devastating tropical parasitic diseases causing great suffering and also loss of life today in the world. It is a common disease in tropical Africa caused by a parasitic protozoan of the genus *Plasmodium* transmitted in nature through the bite of an infected female *anopheline* mosquito called *Anopheles gambiae*. The world wide prevalence of malaria, its great impact upon the health of the population of warm climate and its tolls in mortality and morbidity have made it the outstanding single global health problem (WHO, 1985).

Malaria parasites belong to the subphylum–*Sporozoa*, subclass-*Haemosporidiae*, family-*Plasmodiidae* and genus-*Plasmodium*. There are several species of *Plasmodium*, but among them, only four (4) are known to cause malaria with symptoms in human. These are *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium vivax* and *Plasmodium falciparum* (Roger and Miller, 1989).

Types of malaria

Malaria in humans is caused by four species of protozoa parasites of the genus *Plasmodium* which include:-

Plasmodium malariae: *P. malariae* causes quartan malaria. It is found in tropical and sub – tropical Africa regions; India and the Far East.

Plasmodium falciparum: Of all the species of *Plasmodium*, *P. falciparum* is the most highly pathogenic and it causes malignant tertian (or quotidian) malaria. It is the most serious form of malaria and the most widespread, accounting for up to 80% of malaria found mainly in the hotter and more humid regions of the world; the tropical and sub – tropical Africa regions, Middle East, Far East and South America.

Plasmodium vivax: This species of malaria parasite of human occurs throughout most

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of the temperate regions. It is much less common in tropical Africa, especially in West Africa. This is because *P. vivax* can infect only red blood cells possessing surface membrane receptors related to Duffy blood group antigens (FyFy). These antigens are found rarely in Negroes, a probable reason for the infrequent occurrence of *Plasmodium vivax* malaria in West Africa. It causes benign tertian malaria and is mainly found in India, North and East Africa, South America and Far East.

Plasmodium ovale: Also causes benign tertian malaria or *ovale* tertian malaria similar to that of *vivax* malaria. It was described by Stephen in 1922 who saw it in the blood of a soldier who had returned from East Africa. It is found in the tropical Africa regions, mostly common in West Africa (Miller, 1977, Mims *et al.*, 2005).

Infection with *Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale* occurs throughout most of the tropical Africa. *Plasmodium vivax* infection is rare in West and Central Africa. Only three species – *Plasmodium falciparum*, *Plasmodium malariae* and *Plasmodium ovale* are known in Nigeria (Alaribe, 1994). This is probably due to the mechanism of erythrocyte invasion by malaria merozoites (Miller, 1977).

Malaria is holoendemic in Nigeria with *Plasmodium falciparum* as the dominant strain (Moluneaix and Cramicara, 1980). It is the most common cause of out – patient visits to health facilities and is consistently reported as one of the five leading causes of death (Salako *et al.*, 1981).

Pathogenesis, pathology and clinical findings of malaria infection

Malaria is a disease to which one quarter of the world's population remains at risk with an estimated 250 million clinical cases annually. At any given time, part of the population living in an endemic area are infected with malaria parasite; but remain asymptomatic. Only a minority develop symptomatic disease and even fewer progress to combinations of the three major manifestations of severe disease, namely; anaemia, cerebral malaria and respiratory distress (Marsh *et al.*, 1995).

Periodic paroxysms of malaria are closely related to events in the blood stream. An initial chill, lasting from 15 minutes to one hour, begins as a synchronously dividing generation of parasites rupture their host red cells and escape into the blood. Nausea, vomiting and headache are common at this time (Adelberg *et al.*, 1995, Talaro, 2005).

The symptoms of the disease are caused by the merozoites, which reproduce asexually within the red blood cells of their human host. Periodically, they all break out of the cells together and when they do so, they bring on the chill and fever characteristics of the disease, including vomiting, headache, paroxysms etc. This occurs approximately every 48 hours with *P. vivax, P. ovale P. falciparum* and every 72 hours for *P. malariae* (John, 1977, Mckane and Kandel, 1996).

The succeeding febrile stage, lasting several hours, is characterized by a spiking fever that may reach 40^0C or more. During this stage, the parasites presumably invade new red cells. The third, or sweating stage, concludes the episode. The fever subsides, and the patient falls asleep and later awakes feeling relatively well. In the early stages of infection, the cycles are frequently asynchronous and the fever pattern irregular; later, paroxysms may recur at regular 48 or 72 hour intervals, although *P. falciparum* pyrexia may last 8 hours or longer and may exceed 41^0C. As the disease progresses, splenomegaly and, to a lesser extent, hepatomegaly appears. A normocytic anaemia also develops, particularly in *P. falciparum* infections (Adelberg *et al.*, 1995, Prescott *et al.*, 2005).

According to McGregor (1984) malaria is about twelve times more common in pregnant women compared with their non – pregnant counterparts. The infection is

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associated with increases in spontaneous abortion, still births and low birth weights (Brabin, 1983). In area of intense transmission, these adverse effects of *falciparum* malaria are largely confined to first pregnancies. Moreover, pregnant women in these areas tend to have more severe malarial infections (McGregor, 1984).

Rasheed *et al.* (1993) reported that *in-vitro*, there is impaired proliferative responses of peripheral and placental lymphocytes to malaria antigens; consistent with a general decrease in cellular immunity during pregnancy (Weinberg, 1984).

The adverse effects of *falciparum* malaria on pregnancy have been attributed to the metabolic consequences of the infection (White *et al.*, 1983), as well as to the immuno suppressive effects of increased corticosteroid and progesterone production (Vleugels *et al.*, 1987, Szekeres *et al.*, 1990).

Immunity/Host Defenses

In parts of Africa where malaria is highly endemic people are infected and re-infected so frequently that they develop a degree of acquired immunity. These subjects may become asymptomatic or mild symptomatic carriers. The population develops and maintains a high degree of immune response while at the same time there is nearly, a permanent presence of very small numbers of malaria parasite in many subjects, mostly adults (WHO, 1990). Bruce-Chwatt (1988) had described resistance which builds up in previously infected host in the presence of asymptomatic parasitaemia as premonition.

According to Adelberg *et al.* (1995), an acquired strain – specific immunity has been observed that appears to depend upon the presence of a low-level parasitemia that somehow inhibits new infections or maintains the infection at a nonsymptomatic level. This so-called premonition, or concomitant immunity, is soon lost after the parasites disappear from the blood.

In endemic areas, infants are protected from infection up to the age of 6 months presumably due to the protective effect of maternal antibodies and the less favourable intracellular environment for parasite development (Baron, 1996). Thereafter, the pattern of clinical disease and development of immunity is to a large extent determined by the level of malarial transmission. In hyper-endemic areas, clinical malaria occurs mainly in children less than one year of age, and the major manifestation is anaemia (Brewster *et al.*, 1990). There is a rapid decline in the rate of disease after the first year of life, as antimalarial immunity is acquired. Where transmission is less intense or seasonal, exposure is insufficient to induce significant immunity. As a result, individuals of all ages are susceptible to severe infection, but complications are especially evident in children from one to four years of age (Greenwood *et al.*, 1987).

Natural genetically determined partial immunity to malaria occurs in some populations, notably in Africa. Therefore, susceptibility to malaria infection and disease is regulated by hereditary and acquired factors. It now seems clear that the sickle cell trait (which is the cause of sickle cell anemia) developed as a balanced polymorphism to protect against serious *P. falciparum* disease. Although individuals with hemoglobin S (sickle cell anemia) or the sickle cell trait are as easily infected with malaria parasites as normal individuals, they rarely exhibit malaria disease because their erythrocytes have a low binding capacity for oxygen; therefore the malarial parasite which has a very active aerobic metabolism cannot grow and reproduce within these erythrocytes so *P. falciparum* develops poorly in their erythrocytes (Baron, 1996, Prescott *et al.*, 2005).

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The virtual absence of *P. vivax* infections in many areas of Africa is explained by the fact that most blacks do not have Duffy blood-group antigens (FyFy), which apparently function as erythrocyte surface receptors for *P. vivax* merozoites; without the Duffy antigen, the parasites cannot invade erythracytes. *P. ovale* frequently replaces *P. vivax* in this region (Adelberg *et al.*, 1995). Malaria parasites do not develop well in ovalocytes, and it has been suggested that ovalocytosis, which is quite common in some malarious areas, such as New Guinea, may reduce the incidence of malaria. Glucose-6-phosphate dehydrogenase deficiency, as well as a number of other hemoglobinopathies (including the β-thalassemias and hemoglobin E), also protect against malaria infection (Baron, 1996).

Acquired immunity can also protect against malaria infection and the development of malaria disease. In malarious areas, both the prevalence and severity of malaria infections decrease with age. However, in contrast to many viral infections, multiple infections with malaria do not confer long-lasting, sterile protective immunity. Virtually all adults in malarious areas suffer repeated malaria infections. Individuals who are repeatedly exposed to malaria develop antibodies against many sporozoites, liver–stage, blood–stage, and sexual–stage malaria antigens. It is thought that antibodies acting against sporozoites, liver–stage and blood–stage organisms are responsible for the decreased susceptibility to malaria infection and disease observed in adults in malarious areas, and that antibodies against the sexual stages of plasmodia may reduce malaria transmission (Miller *at el.*, 1986).

Additional work also suggests that the naturally acquired immunity includes the release of cytokines that act against all stages of the parasite, and also a cytotoxic T – cell response directed at liver stages of the parasite. Acquired antibody – mediated immunity is apparently transferred from mother to fetus across the placenta. This passively transferred immunity is lost within 6 to 9 months, as is the immunity in adults if they leave a malarious area and are no longer exposed to plasmodia. Pregnant women, particularly primigravidas, are more susceptible to malaria infections and serious disease (Baron, 1996).

Immunity to malaria develops in stages, and in endemic areas children who survive early attacks become resistant to severe disease by about 5 years. Parasite levels fall progressively until adulthood when they are low or absent most of the time. However, 1year spent away from exposure is sufficient for most of this immunity to wane, i.e. repeated boosting is needed to maintain it. The actual mechanisms seem to involve both antibody and cell-mediated immunity as presented in Table 1.

Table 1: Immunity to malaria

Stage	Mechanism
Sporozoites	Antibody
Liver stage	Cytotoxic T cells, TNF, IFN - α, IL-1
Merozoites	Antibody
Asexual erythrocyte stage	Antibody, ROI, RNI, ECP, TNF
Gametocytes	Antibody, ? Cytokines
Gametes	Antibody

Source: Mims *et al.* (2005)

The principal mechanisms thought to be responsible for immunity at each stage of the cycle. (IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; ROI, reactive

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oxygen intermediates; RNI, reactive nitrogen intermediates; ECP, eosinophil cationic proteins).

Epidemiology

Malaria today is generally limited to the tropics and subtropics, although outbreaks in Turkey attest to the capacity of this disease to reappear in areas cleared of the agent. Malaria in the temperate zones is relatively uncommon, although severe epidemic outbreaks may occur when the largely nonimmune populations of these areas are exposed; it is usually unstable and relatively easy to control or eradicate. Tropical malaria is usually more stable, difficult to control, and far harder to eradicate. In the tropics, malaria generally disappears at altitudes above 6000 feet. *P. vivax* and *P. falciparum*, the most common species, are found throughout the malaria belt. *P. malariae* is also broadly distributed but considerably less common. *P. ovale* is rare except in West Africa, where it seems to replace *P. vivax* (Adelberg *et al.*, 1995).

All forms of malaria can be transmitted transplacentally or by blood transfusion or by needles (syringes) shared among addicts when one is infected. Malaria contracted in this manner is easier to treat since it involves only red blood cells and not the liver or do not develop a liver or exoerythrocytic infection; thus, relapse does not occur; only sporozoites from mosquitoes can infect the liver. Natural infection (other than transplacental transmission) takes place only through the bite of an infected female anopheline mosquito called *Anopheles gambiae;* the mosquito that most efficiently transmits this parasite to humans in Africa. Since suitable vectors are abundant in North America, the potential exists for the spread of malaria whenever it is introduced. Infected mosquitoes and humans constitute the reservoir for malaria (Nester *et al.*, 2004).

Parasitized blood transfusion as a source of malaria infection was confirmed by Arafa (1992) when two Saudi patients underwent cardiac surgery developed fever after being discharged from hospital. Both received blood transfusion during the operation. The cause of fever was found to be malaria parasites acquired from the transfused blood.

The disease is still widely transmitted in the tropics and subtropics. In these areas malaria transmission may be endemic, occurring predictably every year, or it may be epidemic, occurring sporadically when conditions are correct. Endemic transmission of malaria may be year-round or seasonal. In some areas of Africa, 90 to 100 percent of children less than 5 years old have malaria parasites circulating in their blood all the time. Because naturally acquired immunity develops with increasing exposure, in endemic areas malaria disease is primarily found in children. In epidemic areas, on the other hand, naturally acquired immunity falls off between epidemics, and malaria therefore affects all age groups during epidemics (Baron, 1996).

Approximately 1,000 cases of malaria are reported each year in the United States in returning travelers. Of the 1016 imported cases reported in 1991, the majority were acquired in Africa (466 cases) and India (221 cases). *P. vivax* accounted for 43% of the cases and *P. falciparum* for 39%. The risk to travelers of acquiring *P. falciparum* is greatest in Africa. This is because it is the most prevalent species there, malaria transmission is much more intense there than in other parts of the world, and there is significant risk in urban areas. *Anopheles* mosquitoes capable of transmitting malaria are found in a number of areas of the United States. Local transmission may therefore occur when these mosquitoes feed upon malaria-infected individuals, generally immigrants from malaria-endemic areas. Local transmission has recently occurred in Southern California, New Jersey, New York City, and Houston, Texas. Malaria may also occur when infected mosquitoes

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are transported into non-endemic areas, such as by airplanes or ships (Baron, 1996).

Chemo Therapy Of Malaria

Drug resistant malaria is common, with some 19.5 million infections in 1998. Children younger than 5 years are most at risk. Whereas in 1999 there were 475000 deaths in this age group in the developed world, there were more than 12 million deaths in the developing world, 60% of which were due to infection (Mims *et al.*, 2005).

Generally, the fight against malaria is geared toward stages of the malaria parasite's life cycles, hence, there are four (4) classes of such drugs named after each of the four stages. These are:

The Primary Tissue Schizonticides

These are drugs such as paludrine and pyrimethamine-sulfadoxine (fansidar), that blocks the first multiplication phase (pre-exoerythrocytic schizogony) in the liver.

The Secondary Tissue Schizonticides

They are anti-relapse drugs, these are drugs such as primaquine which act to prevent the production of second generation liver merozoites.

The Blood Schizonticides

These are anti-malaria drugs that prevent multiplication of the first generation liver merozoites in the blood cells and could also kill them. Examples of such drugs include chloroquine, quinicrine, etc.

The Gametocides (Gametocytocidal Drugs)

These are drugs that kill the gametrocytes in the blood. Examples of such drugs include primaquine, pyrimethamine-sulfadoxine (fansidar) etc (Miller *et al.*, 1986, Baron, 1996).

Drugs currently used for chemoprophylaxis are chloroquine, proguanil (Paludrine), mefloquine and doxycycline. On the thai-Burmese border, 100mg doxycycline has been used successfully against *falciparum* malaria in adolescent school children (Pang *et al.*, 1987). Tetracycline, a slow blood schizonticide may also be used with quinine in treating drug-resistant *falciparum* malaria. Tetracycline should not be administered to children less than nine years of age or to pregnant women due to staining of immature teeth and bone. Adult women should not be on doxycycline treatment for long terms. They may develop *Candida vaginitis*. As a result, such women are advised to discontinue with the antibiotic (Shanks, 1995).

In the near future, the following drugs might be used for prophylaxis. They are, WR 238605, WR 250417, Atovaquone, Halofantrine and Azithromycin. Heisey *et al.*, (1988) reported that primaquine analoque (WR238605)- a US Army primaquine was more potent and less toxic than primaquine when tested in *P. cynomolgi* rhesus (Macaca mulatta) monkey model.

Another drug, WR 250417, is a new biguanide related to proguanil. It is a prodrug of an earlier compound WR 99210 and extremely active against multiple-drug-resistant *Plasmodium falciparum*. Now, it is no longer administered because it causes significant gastrointestinal intolerance (Shanks, 1995).

There is also Atovaquone, originally called BW 566C80. It is an hydroxynaphthoquinone that blocks the electrone transport chain of mitochondrial respiration (Fry and Pudney, 1992). Halofantrine has also been used successfully for malaria treatment, although it has no role in prophylaxis. Its variable bioavailability suggests that its prophylactic use will require a new and better absorbed formulation (Gillespie *et al.*, 1993).

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Another variation of malaria prevention that has been tried was post exposure treatment with halofantrine. It was given to people who have been heavily exposed to malaria, but were not yet symptomatic. This specialized use of halofantrine for treatment has been found successful in French soliders returning from African (Baudon *et al.*, 1990) and in Papua New Guinea Copper Miners (Shanks *et al.*, 1993).

Kuschner *et al.* (1994) reported that Azithromycin is a new antimicrobial agent of the azalide class, which is related to macrolide antibiotics like erythromycin. Azithromycin is known for its antimalaria activity and favourable pharmacokinetics profile which suggests it might be a useful chemoprophylactic agent.

A newer derivative, tafenoquine or primaquine, is generally effective against the exoerythrocytic stage and the *P. falciparum* gametocytes. Strains of chloroquine-resistant *P. falciparum* are now common in many parts of the world, and resistant strains of *P. vivax* have appeared in some areas. Promising new medications such as a combination, atovaquone and proguanil, may help with this problem. Some patients infected with chloroquine-resistant strains respond to intravenous quinine or quinidine together with an oral medication such as tetracycline or a sulfa drug (Nester *et al.*, 2004).

Quinine remains the drug of choice for life-threatening malaria. Complications of quinine treatment include massive intravascular hemolysis (blackwater fever). Other major drugs are chloroquine (to which *P. falciparum* is increasingly resistant) and the Chinese drug quinghaosu (artemisin) with primaquine for preventing relapses (Mims *et al.*, 2005).

Herbal Remedy

Herbal remedy for malaria is important considering parasite resistance to existing drugs. Plants are the major source of most drugs against a variety of ailments. Quinine, the original antimalarial including over 35 other alkaloids are derived from the bark of *Cinchona ledgeriana*, an indigenous peruvian plant (Foster, 1994). *Azadirachta indica* (neem) extract is used in treating malaria and other febrile illnesses. It contains nimbolides, gedunin, quereetin, rutin, etc as the bioactive components (Fujioka *et al.*, 1989). Artemisinin, a sesquiterpene lactone is derived from the Chinese antipyretic plant, *Artemisia annua L.* and it produces the most rapid resolution of fever and parasitaemia. It is hence presently the drug of choice either alone or in combination therapy with other antimalarials (Hien and White, 1993). Prevailing parasite resistivity to chloroquine and other common drugs, the presence of high morbidity and mortality attributable to malaria and the absence of relevant vaccines necessitates the investigatioh of local plant species for novel alternative pharmacophores (Jigam, 2005).

Other pure compounds of plant origin with antimalarial activity include *Corialstonine* and *Corialstonidine*, indole alkaloids isolated from *Alstonia coriaceae* (Wright *et al.*, 1993), *Crypotolepine* from *Criptolepis sanguinolenta* (Kirby *et al.*, 1989), *ancistrocladine, dioncopeltine A* and *dioncopeltine C* from species of *Ancistrocladaceae* and *Dioncophyllaceae* (Francoise *et al.*, 1994; 1995; 1997). A *Bisbenzylsoquinaline alkaloid* isolated from *Triclisia patens* was shown to have an antimalarial to mammalian cell cytotoxicity ratio equivalent to that of chloroquine (Phillipson, 1994).

Other include *Isoquinoline alkaloids* such as *Berberine* that have antimalarial (Venners and Klyanman, 1988) and anti-amoebic activity. *Ataphillinine* is an *acridone* alkaloid from the *Rutaceae* family with activity against *Plasmodium berghei* in mice (Fujioka *et al.*, 1989) and a number of limonoids such as gedunin,

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nimbolide and rutin with antiplasmodial activity have been isolated from the neem tree and other members of the *Meliaceae* family.

Other compounds including *gossypol*, a polyphenolic compound from cottonseed oil, have been shown to be active against *Plasmodium falciparum*, *Trypanosoma Cruzi* and *Entamoeba histolytica* (GonZalez-Garza and Said-Fernandez, 1988).

Current approaches to malaria control and prevention

Malaria control depends upon elimination of mosquito breeding places, personal protection against mosquitoes (screens, pyrethrin-treated netting, repellents), suppressive drug therapy for exposed persons, and adequate treatment of cases and carriers. Eradication requires prevention of biting contact between *Anopheles* mosquitoes and humans long enough to prevent transmission, with elimination of all active cases by treatment and by spontaneous cure (Adelberg *et al.*, 1995).

Bed nets impregnated with pyrethroid insecticides, have an advantage over simple bed nets in that in the presence of a hole or somewhat defective use, mosquitoes would still not gain access or would die if they did, while the amount of insecticide needed is far less than residual spraying of houses. Additionally, the impregnated net acts as a baited trap at night, as mosquitoes are attracted to the net by the carbon dioxide from sleeping persons and may then take up a lethal dose of insecticide. In controlled trials in highly endemic areas it was found that use of impregnated bed nets substantially reduced morbidity and clinical attacks due to malaria, while having a much smaller effect on the prevalence of parasitaemia. This pattern has been found in several regions of Africa. Even in the forest zone of West Africa with perennial transmission at high level, the frequency of clinical malaria attacks in young children was reduced by 50% when impregnated bed nets were used. A national programme has been carried out in the Gambia and the method is being widely applied following successful trials in several countries of Asia, Africa and Oceania (Bradley, 1995).

The anopheline mosquitoes responsible for malaria is typically most active in the early evening and during the night. Prevention of malaria is possible when the sleeping place is protected from mosquitoes. In a tropical home, bed nets are good adjunct where screens are impracticable. Common mistakes associated with bed nets include failure to mend holes and allowing one's body to touch the net while sleeping. Thoroughly tucking in the nets lower edges is also important as it protects the sleeper from mosquitoes.

Insecticide 'treatment of bed nets is the most effective way of preventing mosquitoes. The nets are soaked in a permethrin solution every few months (Alonso *et al.*, 1991). To ensure control, stagnant water in the surrounding environment including those in containers, pits and swamps should not be found very close to the living quarters, since they are veritable breeding places for mosquitoes. Most importantly a clean environment should be maintained.

Most cases of malaria in Americans can be prevented by chemoprophylaxis and by avoiding the mosquito vector. Prophylaxis with chloroquine or mefloquine should begin 2 weeks before entering the malarious area (to ensure tolerance to the drug and to provide adequate blood levels) and should continue throughout the stay in the area and for 4 weeks after leaving. Doxycycline should be started 1 to 2 days before travelling to a malarious area and should continue throughout the stay in the area for 4 weeks after leaving. Chloroquine is the recommended chemoprophylactic for those travelling to areas where plasmodia are still chloroquine sensitive (Mexico, Central America, Haiti, The Dominican Republic, and the Middle East) (Baron, 1996).

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Nester *et al.* (2004) also reported that after leaving malarious areas, people take primaquine to eliminate possible exoerythrocytic infection, which if untreated could cause recurrence of the disease.

Current global programmes and initiatives geared towards malaria eradication (1998-2015)

Unfortunately, the malaria problem is likely to worsen unless effective control is achieved soon. The world population is about 6 billion, with 250 new births occurring every minute. Moreover, various computer models project the climate to warm significantly, resulting in an increase in the areas where malaria is likely to occur. The combination of increasing population, expanding areas where malaria can be easily transmitted, and the development of medication-resistant plasmodia and insecticide-resistant mosquitoes underscores the need for an effective control programme (Nester *et al.*, 2004).

In 1998, a new initiative called Roll Back Malaria was begun, linking the World Health Organization (WHO), the United Nations Childrens Fund (UNICEF), the United Nations Development Programme (UNDP), and the World Bank in the fight against malaria. Their goal is to halve malaria deaths by the year 2010, and halve deaths again by 2015. The initial focus is on detailed mapping of malarious areas using satellite imagery and climate information, and documenting the level of malaria treatment and prevention at the village level. The aim is to organize and fund a sustained effort to improve access to medical care, strengthen local health facilities, and promote the delivery of medications and insecticide impregnated mosquito netting. Besides Roll Back Malaria, other initiatives under way are designed to spur development of new antimalarial medications and to better fund vaccine and other research. In contrast to initiatives in the past, there is now better understanding that malaria control must be part of overall economic development, since it is difficult for one to move forward without the other (Nester *et al.*, 2004).

Prospects of an effective malaria vaccine

The search for malaria vaccine started in 1950. After the expense and demoralizing failure of malaria eradication programmes (using D.D.T) in the 1950's, no one felt the need for vaccine more keenly than the World Health Organization (WHO), but today the quest for a vaccine against malaria has reached an exciting stage.

In 1971, David Clyde at the University of Maryland, School of Medicine, Baltimore, USA, repeated in human, including himself an experimental techniques using attenuated malaria parasite previously preformed in chicken and mice. The technique was an attempt at immunization using weakened or attenuated malaria parasites which had been irradiated in the mosquito host before the insects were allowed to bite. Once in the blood stream of humans, the parasites were unable to continue their life cycle and so could not cause disease.

Earlier results on bird and mice show that they develop immunity to malaria after repeated exposure to the irradiated sporozoites (Johnstone, 1987). To find out if humans could develop the same immunity, Clyde (1971) moved on using attenuated malaria parasite previously performed in chicken and mice and he finally found out that humans could develop immunity to the natural malaria sporozoites after repeated exposure to irradiated sporozoites.

Current vaccine practice, vaccine strategy, and vaccine development for malaria infection

Obviously, the development of vaccine is the area of greatest interest in the application of recombinant DNA technology to the control of malaria parasites. The stages in the life cycle of

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malaria parasite, which are potential targets of malaria parasite vaccine, are presented in Table 2.

Table 2: Malaria vaccine strategies

Stage	Vaccine Strategy
Sporozoites	Sporozoite vaccine to induce blocking antibody, already field-tested in humans. Antibody produce in response to these vaccines may block sporozoite attachment.
Liver Stage	Sporozoite vaccine to induce cell-mediated immunity to liver stage, already tested in humans. Subsequent development of the sporozoite in the hepatocytes will be blocked.
Merozoites	Merozoite (antigen) vaccine to induce invasion inhibitory antibody. Antibody produced by vaccination against merozoite antigen may block invasion of the red cell.
Asexual erythrocyte stage	Asexual stage (antigen) vaccine to induce other responses to red cell stage, and against toxic products ("anti-disease" vaccine)
Gametocytes and Gametes	Vaccines to interrupt sexual stages-"transmission blocking" vaccine. Transmission blocking antibodies, bound to gametocytes may interfere with sexual reproduction in the insect vector preventing the production of new infective sporozoites and terminating the life cycle.

Source: Mims *et al.* (2005)

To produce an efficacious vaccine against malaria, the recombinant DNA technique also known as gene splicing is a procedure that may be used. This is a procedure whereby segment of genetic material from one organism is transferred to another. It could also be used to integrate one DNA or part of it into another DNA which carries the foreign DNA. Using the recombinant DNA techniques in producing a potent vaccine, parasite antigen is identified, especially the immunodominant epitope that specifically stimulates protective B-cell and T-cell immune response and clone their genes (Nwagu, 1993).

Several vaccines are currently undergoing evaluation in clinical trials. Noteworthy is SPf66, a synthetic tripeptide vaccine which contains peptides from the organism's blood and sporozoite stages developed by Patarroyo and colleagues, has been tested in Colombia and found to be partially effective (<50%) (Tanner *et al*., 1995). Although initial results were promising, subsequent clinical trials have reported protective efficacies of only about 30% against first clinical episodes of *P. falciparum* (Baron, 1996). A complete prophylactic vaccine would have to be active against both sporozoites and merozoites of the target species, with an antigametocyticidic effect to curb transmission (Adelberg *et al*., 1995).

Scientists have been trying to perfect a vaccine against malaria for many years. The first major breakthrough was reported in 1976 from the laboratory of Dr. William Trager at the Rockefeller University, USA. Trager described a method for the continuous *in vitro* cultivation of *P. falciparum*, allowing for the production of antigens from different stages of the organism's life cycle. Later on, other

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scientists using genetic engineering techniques cloned the genes responsible for these antigens and identified which antigens were potential vaccine candidates (Nester *et al.*, 2004).

Current progress on malaria vaccine and the way forward towards vaccines development

At present, there are human trials under way with several different DNA Vaccines against malaria. DNA vaccine is a more complicated genetic vaccine to emerge in recent years. A DNA vaccine elicits protective immunity against a microbial pathogen by activating both branches of the immune system: humoral and cellular. Long-lasting memory cells also are generated (Prescott *et al.*, 2005).

Much interest has been generated by the surprising discovery that intramuscular injection of microbial DNA itself, with a suitable promoter, can immunize laboratory animals against infection such as malaria. It is thought that the corresponding antigen is expressed and presented on muscle cells. DNA vaccines tend to promote cell-mediated immunity, but conditions have been found to encourage antibody production (Mims *et al.*, 2005).

DNA Vaccines are being hailed as the most promising of all of the newer approaches to immunization. The two most promising malaria vaccines currently under development are a recombinant DNA version of the sporozoite surface antigens and one that contains the parasite's DNA. DNA-based vaccines are segments of naked DNA from infectious organisms that can be introduced directly into muscle tissue. The host tissue actually expresses the DNA for a short time, producing the microbial antigens encoded by the DNA, which induces an immune responses (Talaro, 2005).

A number of different vaccines are currently under development, including recombinant protein vaccines and a 15-gene naked DNA vaccine. Novel types of vaccines being actively studied also include peptide vaccines, edible vaccines, and DNA-based vaccines. Because none of these relies on whole cells, the procedures eliminate the possibility of infection with the immunizing agent, however, some of these vaccines are weakly immunogenic. Peptide vaccines are composed of key antigenic peptides from disease –causing organisms. They are stable to heat and do not contain extraneous materials to cause unwanted reactions or side effects (Nester *et al.*, 2004).

The vaccines of the future may use totally new means of delivering the antigen. In edible plant vaccines, a novel approach to vaccination is to express the genes for bacterial or viral antigens in edible plant tissues. Edible vaccines are also created by transferring genes encoding key antigens from infectious agents into plants. This could be a much cheaper way of making vaccines than the existing fermentation or cell culture methods, as the transgenic plant will make the vaccine antigen as it grows. The plant will also deliver the vaccine, as the vaccinee only has to eat some of the transgenic plant to get immunized. Potatoes, tomatoes, and tobacco plants have been used in experiments to make edible vaccines, with promising results. May be one day eating a transgenic banana will protect us against a battery of human pathogens, since the plant could be engineered to express multiple genes (International Travel and Health, 2002, Mims *et al.*, 2005).

Conclusion

Malaria represents by far the most important parasitic disease in man. The World Health Organisation has estimated that 5% of the world population is infected annually (Kolberg, 1994). Malaria remains as much scourge as ever, threatening primarily about two billion people who live in endemic areas and also travellers (Winstanley, 1995).

The current and very important problem with chemoprophylaxis is not drug

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resistance, but compliance with drug regimens. The expectation for new means of prevention such as malaria vaccines that will replace the need for chemoprophylaxis in the near future is yet cloudy (Adomeh, 1998).

The failure of vector elimination to control malaria and the emergence of drug-resistant parasites underscores the need for an effective malaria vaccine. While the world await the development of an effective malaria vaccine, preventive and control measures should depend upon elimination of mosquito breeding places, personal protection against mosquitoes by using bed nets impregnated with insecticides, mosquito repellents, suppressive drug therapy for exposed persons, and adequate treatment of cases and carriers since efforts to develop an effective malaria vaccine are under way.

With the worldwide research made possible by recombinant DNA technology, biotechnology, and genetic engineering towards the quest for an effective malaria vaccine and drug, it is hoped that the menace of malaria especially in tropical Africa would be history in the near future.

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