

Review

Current trends in malarial chemotherapy

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Malaria is a tropical disease caused by the genus *Plasmodium*. The sexual stage of the plasmodium is carried by mosquito while the asexual stage is carried by man. Transmission from the mosquito to man is through mosquito bite. Commonly presented symptoms of malarial attack include fever, weakness, anorexia, and anaemia. Some complications such as convulsion (in children) and acute pulmonary edema are common. The conventional drugs used in malarial chemotherapy include, chloroquin, sulfadoxine/pyramethamine, quinine and primaquine. Newer drugs in use include artemisine and its derivatives (such as dihydroartemisinin, artesunate, artemether), halofantrine, atovaquone, malaria vaccines, and artemisinin combinations (such as artemether/lumefantrine, artesunate/mefloquine). These newer drugs were developed based on some shortcomings of the conventional drugs such as drug resistance and unbearable side effects. Of all the drugs available for the first line treatment of malaria, the artemisinin combinations are the drugs of choice as they possess reduced recrudescence and relapse when given for 3 days. Some new combinations are still on trial and include fosmidomycin/clindamycin. Malaria vaccines which show some promising features are also still undergoing more trials.

Key words: malaria, chemotherapy, combination therapy, artemisinin, resistance.

INTRODUCTION

Malaria is an acute or chronic mosquito-borne disease of man, which is usually characterised by chills, anemia, fever, splenomegaly and damage to organs like brain and liver (Ukwe, 2003). Malaria, caused specifically by the anopheles mosquito, is responsible for about 1 million deaths globally every year and currently, 40% of the world's population, live in malaria endemic areas. Various species of plasmodia such as *P. falciparum*, *P. ovale*, and *P. malariae* cause quartan malaria while *P. vivax* causes benign tertian malaria. Epidemiologically, the transmission of malaria occurs all year round but has greater intensity during the wet season (WHO, 1997).

The life cycle of the plasmodium is divided into the sexual and asexual phases, with the sexual phase taking place in the female mosquito and the asexual taking place in man. When man is infected through the saliva from the bite of a mosquito, the sporozoites (fertilised zygote) leaves the blood stream of man after 30–60 min and enters the liver cell. At the hepatocyte, the parasite

undergoes asexual replication in a stage often called exoerythrocytic schizont stage. These replicated cells are released into the circulatory system as merozoites following rupture of the host hepatocyte.

The clinical manifestations seen in malaria attack are exclusively due to the asexual erythrocytic stage parasite. Tissue schizonts and gametocyte do not have any obvious or prominent pathology, but in the erythrocytic stage the most notable is an acute fever which is mainly due to erythrocytic cell bursting which reduces the number of circulatory red blood cell and may lead to anorexia in very severe cases due to low haemoglobin in blood (Wongsrichanalai et al., 2002; Molyneux, 1977; Obiaga, 1998). The most common complications of malaria are seen during pregnancy (Goldsmith, 1998).

The control of malaria involves control of living cells as well as the environment. This involves the use of insecticides to control the vector mosquito and the eggs as well as larvae. Other preventive measures include use of nets, closing of doors/windows against mosquitoes and use of mosquito repellents. These are generally referred to as vector control measures.

Prophylaxis on the other hand is the use of drugs to prevent the occurrence of malaria. Drugs such as pyri-

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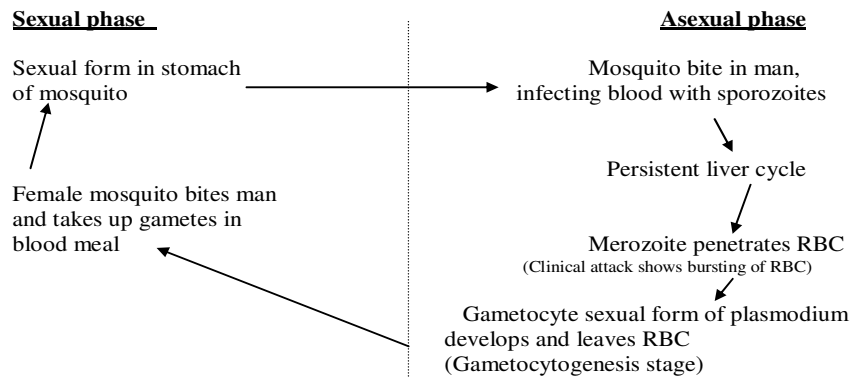


Figure 1. Life cycle of the plasmodium causing malaria.

methamine are commonly used. Chemotherapy is the use of drugs to treat malarial attack and is a very effective way of treating malaria attack, once a person is infected. Chemotherapeutic agents can be classified as tissue schizonts, sporontocides, blood schizonticides and gametocytocides, based on chemotherapeutic considerations (Tracy and Webster, 1996). Based however on the stage of the parasite on which they act, they can be classified as causal prophylactic, suppressive treatment, clinical cure, radical cure, and miscellaneous.

The major problem with the use of conventional antimalarial drugs like chloroquine and sulphonamide combinations is the resistance developed by the parasite (Boland, 2001). Many factors are responsible for the development of resistance but all lead to decreased sensitivity of the parasites to the normal dose of the drugs. The factors include self-treatment, poor compliance, mass administration, long half-life and high level of transmission intensity. Other problems associated with the conventional antimalarial drugs include adverse effects of like rashes, Erythema multiform and Erythema nodosum; adulteration, and substandard formulations. The current antimalarials, which are gradually replacing the conventional ones as drugs of first choice do not have the above attendant problems and include artemisinin with its derivatives and combinations. Others are halofantrine, and atovaquone.

TRANSMISSION OF MALARIA

World over, malaria has ranked as one of the greatest threats to mankind, due to its high mortality rate especially among children in endemic areas such as Africa (Kwatkwski and Arsh, 1997; Maurice, 1996). As a result, the World Health Organisation has tried to put up laudable programmes aimed at eradicating it. Most recent of these measures include the Roll-back-Malaria programme aimed at global malarial eradication (WHO,

1997).

The female anopheles mosquito is responsible for the transmission of malaria in man. The adult plasmodium grows much in areas where there is stagnant water, with a particular temperature and high population. In recent times, transmission has been found to be more in children and this is likely due to their low level of immunity. Some adults are susceptible to the infection while some have acquired immunity against the attack due to increased exposure. It has also been found that it can also be transmitted via blood transfusion or sharing of syringes. Mechanical transmission via infected blood transfusion will result in shorter incubation period since there will be no liver stage and there is an increased risk of fatality with mechanically transmitted *P. falciparum*. Congenital transmission has also been documented, but is believed to be relatively rare despite the heavy infection of the placenta (Wongsrichanalai et al., 2002).

Life cycle of causative plasmodia

The life cycle of the plasmodia causing malaria is divided into the sexual and asexual phases. The sexual phase takes place in the female mosquitoes while the asexual phase occurs in man. When man is infected with the sporozoite from the saliva of the mosquito, the sporozoite leaves the blood stream after 30–60 min and enters the liver cell. After invading the hepatocyte, the parasite undergoes asexual replication. This replicative stage is often called exoerythrocytic schizont stage. The replicated cells are then released into the circulatory system as merozoites following rupture of the host hepatocyte (Figure 1).

The merozoite released recognizes specific proteins on the surface of the erythrocyte and actively invades the cell. After entering the erythrocyte, the parasite undergoes a trophic period followed by an asexual replication. The young trophozoite is often called a ring form. As the

parasite increases in size, the ring morphology disappears. During the trophic period, the parasite ingests the host cell cytoplasm and breaks down the haemoglobin into amino acids. A by-product of the haemoglobin digestion is the malaria pigment or hemozoin.

The gametocytes stage, when it occurs does not cause pathology in the human host and when the gametocyte is ingested by the mosquito, it tends to initiate the sexual stage of the plasmodia life cycle. The two phases of the gametocytic stage are gametocytogenesis, occurring in the blood stream of the host (man) and the gametogenesis taking place in the mosquito gut. For *P. vivax* and *P. falciparum*, the exoerythrocytic stage lasts for 10-14 days, while for *P. malariae*, it lasts for 18 days to 6 weeks. The erythrocytic stage on the other hand lasts for 48 h in *P. falciparum*, *P. vivax* and *P. ovale* and 72 h in *P. malariae*.

Mode of attack

The female anopheles mosquito usually attacks by piercing and sucking using its proboscis, with which it introduces an enzyme from the saliva into the blood stream, in order to inhibit blood clotting while sucking. In the process, the protozoa, is introduced into the blood. From the blood, it goes into the liver for cell division and multiplication before being released into the blood again as merozoites, which then cause reduced immunity and the symptoms that usually manifest.

Clinical manifestations

The clinical manifestations seen in malaria attack are exclusively due to the asexual erythrocytic stage parasite. Tissue schizonts and gametocyte do not have any obvious or prominent pathology, but in the erythrocytic stage, the most notable is an acute fever, which is mainly due to erythrocytic cell bursting which reduces the number of circulatory RBC and may lead to anorexia in very severe cases due to low haemoglobin in blood (Obiaga, 1998). In some individuals, it manifests as severe headache and in some, they start having sores on the lips with slight fever. All these depend on the immunity state of the individual i.e. the general health and nutritional status of the infected individual. The disease has a tendency to relapse or recrudescence over month, or even years.

Prevention and control of malaria

The control of malaria involves control of three living and their environment. Man, the host is a moving target and

can take the disease with him to far and wide places. Mosquitoes are also moving, highly adaptable and has shown resistance to insecticides. It is therefore important to target non-flying eggs and larvae. The parasite also is highly adaptable, hides in humans and mosquitoes and has also developed resistance to drugs. The strategy broadly suggested by WHO lays emphasis on vector control and renewed emphasis on treatment and they are early diagnosis and treatment, epidemic forecasting, monitoring, evaluation and operative research and integration of activity in primary health centers.

Man plays the major role in malaria control. This can be achieved by educating the people about the disease, and its control so that they can effectively contribute in controlling it. Other preventive methods include closing of doors and windows in the evenings to prevent entry of mosquitoes into human dwellings, insecticide spray, mosquito repellent lotions and coils.

CONVENTIONAL ANTIMALARIAL DRUGS

These include chloroquine, mefloquine, primaquine, proguanil, pyrimethamine, sulfonamide derivatives, and antibiotics. They are generally classified either based on chemotherapeutic considerations or on the stage of the parasite they act on.

Classification based on chemotherapeutic considerations

On the basis of the above, antimalarials are classified as tissue schizonticides, sporonticides, blood schizonticides and gametocytocides.

Tissue schizonticides eliminate developing tissue schizonts or latent hypnozoites in the liver (Tracy and Webster, 1996). They are active on the parasitic forms of plasmodia prior to invasion of the RBC or the secondary exoerythrocytic forms, thereby preventing recurrences typical of infections with *P. vivax* and *P. ovale*. Drugs that classified under this include primaquine, proguanil and pyrimethamine.

Sporonticides render gametocytes non-infective by inhibiting the formation of oocyst and sporozoites in infected mosquito. None of the conventional antimalarial agents is used clinically for this purpose.

Blood schizonticides act on the asexual form of the parasite in the blood. Majority of the drugs commonly used in malaria treatment fall into this category and they include chloroquine, mefloquine, pyrimethamine, amodiaquine, proguanil and quinine.

Gametocytocides can be subdivided into those that act only on the immature form and those that act on all stages of maturation. Commonly, they act on the sexual form of the parasite by destroying gametocytes in the

blood. Examples of drugs in this class are primaquine and chloroquine. None of the drugs in this class prevents infection except pyrimethamine and proguanil, which prevents maturation of the early *P. falciparum* hepatic schizonts. Also blood schizonticides cure *P. falciparum* and *P. malariae* attacks when used for sufficient time, i.e. for at least 4 weeks. Primaquine on its part destroys liver hypnozoites of *P. vivax* and *P. ovale*.

Classification based on the stage of parasite

In this classification, we have drugs used for causal prophylaxis, suppressive treatment, clinical cure, radical cure and miscellaneous treatment.

Causal prophylactics are agents used in the exoerythrocytic stage of the mosquito life cycle i.e. the first stage where the sporozoites multiply in the liver to form tissue schizonts. These agents act by impeding the development of the schizonts; before they are released into the blood stream as merozoites. *P. falciparum* is most susceptible to prophylactic treatment and drugs used at this stage are mainly pyrimethamine and primaquine but primaquine is presently rarely used for this purpose due to its serious side effects. Other drugs used are proguanil which is effective against *P. falciparum* malaria but not fully effective against *P. vivax*. Proguanil is not usually employed in acute malarial attacks because of its slow onset of action.

Drugs used in *suppressive treatment* suppress the plasmodium of the erythrocytic stage thereby suppressing the symptoms but do not eradicate the infection as is seen in the exoerythrocytic stage. When the drugs used at this stage are withdrawn, the symptoms may return, as a result of the underlying persistence of the plasmodium in the liver. Drugs used as suppressive agents include pyrimethamine.

Drugs used for *clinical cure* act on the asexual erythrocytic stages of the *P. malariae* and automatically prevent the development of the schizonts. Examples of some drugs used here are chloroquine and amodiaquine. When used, they are effective against gametocytes of *P. vivax*, *P. ovale*, *P. falciparum* and *P. malariae*. In *P. falciparum*, chloroquine is very sensitive and can be used alone in acute attacks. In the cure of *P. vivax* and *P. ovale* attacks, primaquine can be given concurrently with chloroquine in order to eradicate the persistent liver stages. Normally, when chloroquine is given in acute malaria attack, it clears the fever in 24 – 48 h while the clearing of the parasite in the blood stream is within 48 – 72 h.

Drugs used in *radical cure* are those, which are found to eradicate both the exoerythrocytic and erythrocytic stages of malarial infection. They have also been found to have a profound gametocytocidal effect against all four species of plasmodium. The drugs include primaquine and pamaquine.

The *miscellaneous drugs* include quinine, which are the oldest antimalarial and a principal alkaloid. Due to its severe side effects, its use has been stopped. Recently however, due to the increasing resistance of the plasmodia to sulfadoxine/pyrimethamine combinations and to chloroquine, the use of quinine has returned in very severe malaria attacks and in the treatment of cerebral malaria. Other drugs in this category are quinacrine—an acridine derivative, the antibiotics—doxycycline and minocycline, used mainly in combination with chloroquine for the eradication of malarial parasites in pregnant adults and children.

CURRENT TRENDS IN ANTIMALARIAL TREATMENTS

The major problem or set back to the use of conventional antimalarial drugs is resistance developed by the parasite to the drugs (Warhust, 2001). Drug resistance, especially chloroquine resistance is a major public health problem in the control of malaria. By drug resistance, we mean, a treatment failure graded into different levels depending on the timing of the recrudescence following treatment. Traditionally, these levels of drug resistance have been outlined as sensitive (no recrudescence), RI (delayed recrudescence), RII (early recrudescence) and RIII (minimal or anti-parasite) (Wellems and Phowe, 2001). A modified protocol based on clinical outcome was introduced by WHO in 1996. In this protocol, the level of resistance is expressed as adequate clinical response (ACR), late treatment failure (LTF) or early treatment failure (ETF) (Boland, 2001). ACR is characterized by absence of parasitemia (irrespective) of fever or absence of clinical symptoms (irrespective of parasitemia) on day 14 of follow-up. LTF is characterized by reappearance of symptoms in the presence of parasitemia during days 4 – 14 of follow-up, while ETF is indicated by persistence of clinical symptoms in the presence of parasitemia during the first 3 days of follow-up.

Major factors in the development of drug resistance are the use of sub-therapeutic doses of drugs or not completing; the treatment regimen. Others are self-treatment, poor compliance, mass administration, use of drugs with long half-life, and high transmission intensity.

The current antimalarial drugs being recommended for use today include artemisinin and its derivatives. This drug has found very effective use in a short period of time and one advantage they have is that they have short half-life, which counters one of the major factors that lead to drug resistance. Besides, there has not been any reported case of severe side effects in their use. In pregnancy, artemisinin has been approved to be safe in the second and third trimesters but their use in the first trimester is not recommended. Another advantage of artemisinin over quinine, for instance, is its lower risk of hypoglycemia.

Artemisinin and its derivatives have an essential role

to play in malaria control and are of an acceptable quality. They are used rationally and are protected for as long as possible against the development of acquired drug resistance by the parasite.

Other recent antimalarial drugs are halofantrine (Halfan[®]), atovaquone, artemisinin combinations with drugs like amodiaquine and mefloquine. The non-artesunate combinations are chlorproguanil/dapsone and atovaquone/proguanil. New combinations that are currently on trials are fosmidomycin/clindamycin and piperazine / dihydroartemisinin in trimethoprim.

Artemisinin and its derivatives

Artemisinin or qinghaosu is a sesquiterpene lactone endoperoxide whose antimalarial principle is extracted from the herb *Artemisia annua* L, first discovered in China (Wayman, 1995). It is a 15-C atom structure with a trioxane ring and a lactone ring and has a molecular weight of 282 (Webster and Lehnert, 1994). Over 2000 years ago, it was discovered and used as an antipyretic. In 1972, however, the antimalarial component of it was discovered and was found to produce more rapid resolution of fever and parasitaemia than all known antimalarial agents and found to be a more potent schizontocides (Luo and Shen, 1987; DeVries and Dien, 1996).

Artemisinin is sparingly soluble in water and oils, leading to the search for and discovery of its derivatives, which are more water-soluble. Dihydroartemisinin is an intermediate compound formed after breakdown of artemisinin, by the reduction of the lactone to a lactol and other active derivatives (Looareesuwan et al., 1996).

The artemisinin derivatives can be grouped as water-soluble and lipid soluble, the water solubles include artesunate and artelinic acid and are currently available as tablets, IV injections and suppositories. The lipid soluble types include artemether and arteether (Basco and Lebras, 1997). Artenilic acid is still undergoing trials for transdermal administration. Artemisinin and its derivatives have clinically been used in the treatment of uncomplicated malaria. In general, the oral formulation of these drugs is rapidly incompletely absorbed and their bioavailability is low (Bethel et al., 1997). There is good evidence that they undergo extensive first pass metabolism in the liver. Both artesunate and artemether are rapidly transformed into dihydroartemisinin so that the metabolite is generally present at higher levels than the parent compound (Teja et al., 1997).

The major mechanism of action of all artemisinin drugs is the prevention of the development of ring stage parasites to the more mature pathogenic stages that rosette and cytoadhere in the capillaries (Watkins and Masobo, 1993). They act essentially as blood schizonticides, and the presence of the Endoperoxide Bridge appears to be essential for antimalarial activity. It is also suggested that they cause a marked diminution of nucleic

acid synthesis. The artemisinin derivatives have equally been observed to produce a faster relief of clinical symptoms and clearance of parasites from the blood than other antimalarial drugs (DeVries and Dien, 1996). The only problem encountered in the use of artemisinin drug is that when used as monotherapy within a short period, i.e. less than 5 days, clearance of parasitemia from the blood is only temporary in up to 50% of patients. This has been attributed to the short time it takes for artemisinin drugs to be eliminated from the body.

Artemisinin has been widely employed in the treatment of uncomplicated multidrug resistant falciparum infections (Price et al., 1997). Compared to quinine in the treatment of severe malaria however, patients treated with artemether had a least an equal chance of survival as a patient treated with quinine, while parenteral artemether and artesunate are easier to use than quinine, and did not induce hypoglycemia (VanHensbroek et al., 1996; Mcintosh and Olliaro, 1998).

Artemisinin and its derivatives have a significant effect on gametocytogenesis (Peters et al., 1986; Price et al., 1998). Most common side effects of artemisinin drugs are headache, nausea, abdominal pain, vomiting and occasionally diarrhoea (Brewer et al., 1998). Resistance to artemisinin drugs so far, has not been reported, although some resistant strains of *P. falciparum* have been developed in the laboratory (Chawira et al., 1997).

Dihydroartemisinin

This is the active metabolite of artemisinin and its derivatives and is the most potent antimalarial of this group of compounds, though the least stable. Its mode of action or pharmacodynamics is the same with that of artemisinin but they are found to have peroxide bond essential for antimalarial activity. When this bond breaks up, it generates singlet oxygen and free radicals and studies have shown that the presence of free radicals has resulted in morphological changes of the parasitic membranes and this shows that the site of action of dihydroartemisinin could be the membranous structure.

Oral dihydroartemisinin has been shown to be effective in the treatment of multidrug resistant uncomplicated *P. falciparum* infection. Dihydroartemisinin does not have activity against hypnozoites, so such cannot be used in eradication from the liver but it has an effect on gametocytocytic stage. It has a half-life of more than 10 h. It has currently been discovered that dihydroartemisinin appears to offer no advantage in the treatment of uncomplicated malaria or severe malaria. It is not also recommended for the treatment of malaria caused by *P. vivax*, *P. ovale* and *P. malariae*.

Artesunate

This is a water-soluble hemisuccinate derivative of dihydroartemisinin. It is the most widely used member of

this family of drugs. Artesunate has been found not to have hypnozoiticidal activity and is effective against *P. falciparum*, which may be resistant to all other conventionally used ant malarial drugs. The essential part of the mechanism of action of artesunate which explains its rapid effect as well as its efficacy is the presence of a peroxide bond which breaks inside the parasite forming singlet oxygen as well as free radicals, thereby exerting a direct cytotoxic effect on the cells and the sub-cellular membranes.

Following oral administration, artesunate is rapidly absorbed and reaches maximum plasma concentration within 45–90 min. It is metabolized in the liver and by simple hydrolysis or by esterases in the plasma which gives rise to dihydroartemisinin which acts against malaria by the same mechanism. The drug has a mean plasma half-life of 2–3 h and is 50% bound to plasma protein. The plasma concentration is more erratic following administration by suppository compared to the intravenous route, but inadequate absorption is unusual (Alin et al., 1996). Artesunate use as monotherapy should be limited to specific indications such as in patients with a history of adverse reactions to the combination drugs. It is not recommended for the treatment of malaria caused by *P. vivax*, *P. ovale* and *P. malariae*.

Artesunate does not affect the cardiovascular system but a slight slowing of sinus frequency has been noticed (Benkis et al., 1993). Appearance of skin rash has been observed when it was used in combination with sulfamethoxypyrazine and an adequate diuresis should be maintained in order to prevent crystalluria provoked by urinary excretion of sulfamethoxypyrazine and its metabolite.

Artemeter

It is an oil-soluble methyl ether derivative of dihydroartemisinin effective against *P. falciparum* that is resistant to all other operationally used antimalarial drugs. It is not hypnozoiticidal but reduces gametocyte carriage. The pharmacodynamic action is the same as with artemisinin. It is metabolized in the liver to the dimethylated dihydroartemisinin. Its pharmacokinetics following oral administration appears to be similar to those for artemisinin, but plasma ant malarial activity is significantly higher with intramuscular administration than with oral use. Its half-life is the same as artemisinin.

Halofantrine

This is a phenanthrene methanol antimalarial drug, which is effective against sexual form of *P. falciparum*. It is metabolized in the liver and has an elimination half-life of 1 to 2 days. It has been found to be more active than mefloquine and is administered in three doses of 500 mg each at 6-hourly intervals. It has been shown that when halofantrine is taken with food, it may increase the risk of irregular heartbeat, hence it is advised that it be taken

one hour before meal or two hours after meal. In rare cases, halofantrine may affect the heart, causing irregular heartbeats that could result in death. It is contraindicated in patients with a history of irregular heartbeat. Caution is to be taken in patients with liver and kidney diseases but if it must be given, special monitoring is necessary.

Some side effects associated with the drug includes allergic reaction, swelling of lips, tongue, face, shortness of breath and choking of throat. Others are light-headedness, chest pain, seizures, dizziness, headache, cough, abdominal pain, itching, and muscle aches.

Miscellaneous drugs

Other new drugs classified under this heading include *atovoquone* – a hydroxyl-naphthioquinone which is highly lipophilic and an analog of ubiquinol. Atovoquone is not significantly metabolised and its bioavailability is increased three fold when administered with meals. It undergoes enterohepatic cycling and is primarily excreted in faeces. It has a half-life of 2.2–2.9 days. Common side effects include diarrhoea, vomiting, insomnia, headache, nausea, cough and rashes.

Other drugs in this category include the *combination drugs* and the *vaccines*, most of which have not yet been approved for use but trial results are very promising. Significant progress has been made in the development of the malaria vaccine during the past 20 years. An ideal frequency of administration, dose and mode of action are areas of concern. Because vaccines based on a single antigen have a limited role to play in malaria due to the fact that not all people respond to the same antigen, efforts have been directed towards the development of multi-stage, multi-component vaccines, incorporating multi-antigenic sequences from different asexual and sexual stages of plasmodia. About nine different malaria antigens have so far been identified. The Indo-US researchers have combined the coding sequences for these key portions, called epitopes into one synthetic gene as the basis for the new vaccine named CDC/NII Malvac-1 (Playpair, 1999). The monkey trials will be followed by human trials. Other vaccines so far developed include: CSP Vaccine, NYVAC-Pf-7, GameteVaccine, DNA Vaccine, and Recombinant Vaccine (D'Alessandro et al., 1999).

The combination drugs include artesunate/mefloquine and artemether/benflumetol, which have both been shown to be highly active against multidrug resistant *falciparum* infections. There is indication that the combination of artesunate and mefloquine may have played a role in both slowing down the development of resistance to mefloquine as well as reducing malaria transmission in an area of high mefloquine resistance (Price et al., 1997). Again, this combination ensures high cure rates since the residuum of parasites remaining after the action of artesunate treatment of three days is exposed to maximum concentrations of them. Besides,

artesunate reduces gametocytaemiarates and therefore transmission, so reducing the selection pressure for the spread of resistance (Watkins and Masoba, 1998).

Some artemisinin based combinations include artesunate/chloroquine, artesunate/amodiaquine, artesunate/sulfadoxine/ pyrimethamine, piperazine/ dihydroartemisinin/trimethoprim, piperazine/dihydroartemisinin/ trimethoprim/ primaquine and artemeter/humefantrine. The non-artemisinin based combinations include: chloroquine/dapsone, atovaquone/proguanil, sulfadoxine/ pyrimethamine/chloroquine, sulfadoxine/ pyrimethamine/ quinine, sulfadoxine/ pyrimethamine/ mefloquine, quinine/tetracycline, quinine/clindamycin and fosmidomycin/clindamycin. Combining drugs may obviously increase the direct cost of treatment. For example, the addition of artesunate to mefloquine increases the cost by around 50% whereas the combination of an artemisinin derivative with chloroquine or sulfadoxine/pyrimethamine would increase costs by 10 – 20 fold (White, 1998). These costs however, would be offset against the potential indirect savings from both reduced morbidity and the costs of treating recrudescence (Boland et al., 1998).

CONCLUSION

Malaria has continued to pose a major threat to the lives of millions of persons worldwide, especially those in the tropics. Several programmes have been evolved to both prevent the incidence and control the attack of the disease. Some of the preventive measures include vector control programmes like use of insecticide treated nets/curtains, and proper environmental cleanliness. Drugs have continued to play key role in both malarial prevention and treatment. Conventional drugs like chloroquine, which used to be first line drugs for treatment are now being replaced by newer drugs as a result of development of resistance by the plasmodium parasite responsible for malaria and due to some undesirable side effects. Artemisinin and its derivatives/combinations are the most rapidly acting ant malarial drugs are now preferred as first line drugs in the treatment of malaria due to their short half life and rapid onset of action. Cost however, is a major constraint as they are not easily affordable by the majority of the populace. The use of vaccine for malarial treatment is currently undergoing clinical trials and holds a big prospect to antimalarial therapy.

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