Introduction to Malaria
Malaria is very common disease of the tropical regions. It is a very old disease and prehistoric man is thought to have suffered from malaria. It probably originated in Africa and accompanied human migration to the Mediterranean shores, India and South East Asia. In the past it used to be common in the marshy areas around Rome and the name is derived from the Italian, (malaria) or "bad air"; it was also known as Roman fever. Today some five hundred million people in Africa, India, South East Asia and South America are exposed to endemic malaria and it is estimated to cause two and a half million deaths annually, one million of which are children.

Malaria is a protozoal infection in man, caused by infection of any of the four species of Plasmodium: P. falciparum, P. vivax, P. malariae, and P. ovale. It is transmitted by the bite of Anopheles mosquito, and it infects human and insect hosts alternatively. P. falciparum causes falciparum/malignant/tertian malaria, which is the most serious form of malaria and can be fatal in individuals who are not immune, if not treated promptly. P. vivax causes vivax/benign tertian malaria, which is widespread. Although symptoms during the primary attack can be severe but rarely are fatal. P. malariae causes quartan malaria, which is generally mild but can cause fatal nephrosis; and P. ovale causes ovale/ovale tertian malaria which is the least common type of malaria, and produces clinical symptoms similar to P. vivax. The multiplying parasite causes fever and other symptoms of malaria which if not treated in time may be fatal especially by P. falciparum.

The life cycle of Plasmodium occurs in two stages: one in mosquito and other in humans. The reproductive stage (sporogony) occurs in mosquito (vector) and human act as the host or the carrier where the parasite multiplies (schizogony). In P.
vivax, *P. ovale* and probably *P. malariae*, all stages of development subsequent to the liver cycle can be observed in the peripheral blood. However, in the case of *P. falciparum* only ring forms and gametocytes are usually present in the peripheral blood. Developing forms appear to stick in the blood vessels of the large organs such as the brain and restrict the blood flow with serious consequences. The parasites of *P. falciparum* multiply very rapidly and may occupy 30% or more of the red blood cells causing a very significant level of haemolysis. One reason for this is that *P. falciparum* invades red cells of all ages whereas *P. vivax* and *P. ovale* prefer younger red cells, while *P. malariae* seeks mature red cells.

The spread of malaria and occurrence of drug resistant strains of *Plasmodium* has made malaria prophylaxis difficult. Prevention is provided by tissue Schizontocides that destroy the exoerythrocytic forms of the parasites. Blood Schizontocides produce suppression or clinical prophylaxis, which, if continued until all exoerythrocytic forms of the parasite are destroyed, will ultimately produce a suppressive cure. In *P. falciparum* infections this would be achieved by about a month after the last infected bite, but infections with *P. vivax* and *P. ovale* may still reoccur after standard clinical prophylactic regimens due to the presence of latent exoerythrocytic forms.

**Quinine salts**

| 8–Aminoquinolines | e.g. Primaquine and Quinocide. |
| 9–Aminoacridines | e.g. Mepacrine. |
| 4-Aminoquinolines | e.g. Chloroquine and Amodiaquine. |
| Biguinides | e.g. Proguanil. |
| Diaminopyrimidines | e.g. Pyrimethamine. |
| Sesquiterpene lactones | e.g. artemisinin derivatives. |
Anti-malarial drugs: Chemical Classification

Antimalarial drugs fall into several chemical groups and it is useful to have some knowledge of their chemistry. Anti-malarial drugs can be classified on the basis of chemical structure into several categories. Some of them are as under:

1. **Quinine**: Quinine has been used for more than three centuries and until the 1930's it was the only effective agent for the treatment of malaria. It is one of the four main alkaloids isolated from the bark of the Cinchona tree and is the only drug which over a long period of time has remained largely effective for treating the disease. It is now only used for treating severe falciparum malaria partly because of its undesirable side effects like, acute massive intravascular haemolysis and haemoglobinuria i.e. black water fever.

2. **Atebrin** (mepacrine): This drug is a 9-amino-acridine developed in the early 1930's. It was used as a prophylactic on a large scale during the II world war. It is now considered to have too many undesirable side effects and is no longer used.

3. **Proguanil**: This drug was first synthesized in 1946. It has a biguanide chain attached at one end to a chlorophenyl ring and it is very close in structure to pyrimethamine. The drug is a folate antagonist and destroys the malarial parasite by binding to the enzyme dihydrofolate reductase. It is still used as a prophylactic in some countries.

4. **Malarone**: In 1998 a new drug combination was released in Australia called Malarone. This is a combination of proguanil and atovaquone. Atovaquone became available 1992 and was used with success for the treatment of *Pneumocystis carinii*. When combined with proguanil there is a synergistic effect and the combination is at the present time a very effective treatment. The drug
combination has undergone clinical trials and has been found to be 95% effective in otherwise drug resistant falciparum malaria, and claimed to be largely free from undesirable side effects.

5. **Maloprim:** It is also a combination of two drugs- dapsone and pyrimethamine. Its use is no longer recommended for the treatment of malaria due to development of resistant plasmodium to this drug.

6. **Fansidar:** This is a combination drug, each tablet containing sulphadoxine 500mg. and pyrimethamine 25mg. It acts by interfering with folate metabolism. Resistance to Fansidar is now widespread and serious side effects have been reported. It is no longer recommended.

7. **Mefloquine (Lariam):** First introduced in 1971, is structurally related to quinine. The compound has a long half life, therefore it is a good prophylactic, but widespread resistance and undesirable side effects have resulted in a decline in its use.

8. **Halofantrin (Halfan):** This belongs to a class of compound called the phenanthrene-methanols and is not related to quinine. It is an effective antimalarial introduced in the 1980s, but due to its short half life of 1 to 2 days, is therefore not suitable for use as a prophylactic. Unfortunately resistant forms are increasingly being reported and there is some concern about side effects.

9. **Artemisinine Derivatives:** These are derived from a Chinese herbal remedy Artemisia annua and covers a group of products. The two most widely used are artesunate and artemether. These are widely used in southeast Asia. A high rate of treatment failures has been reported and it is now being combined with other drugs for the treatment of falciparum malaria.
10. **Chloroquine**: (7-Chloro-4- (4-diethylamino-1-methylbutylamino) quinoline) A very effective 4-amino-quinoline both for treatment and prophylaxis. It was first used in the 1940s shortly after the Second World War and was effective in curing all forms of malaria, with few side effects when taken in the dose prescribed for malaria and it was low in cost. It is rapidly acting blood schizontocide with some gametocytidal activity against *P. ovale*, *P. vivax*, *P. malariae* and immature gametocytes of *P. falciparum*. Chloroquine has also been used in rheumatoid arthritis but its usefulness is limited by its toxicity, particularly when it is given for long periods. Unfortunately most strains of falciparum malaria have now become resistant to chloroquine and more recently chloroquine resistant vivax malaria has also been reported in Papua New Guinea, Indonesia, Thailand and India. This drug will clear the erythrocyte stages of the parasite but it has no effect on the exo-erythrocytic liver stage and a course of primaquine (an 8-aminoquinoline) is required for radical cure.

11. **Primaquine Phosphate**- [8-(4-Amino-1-methylbutylamino)-6-methoxy quinoline phosphate]. It is a tissue schizontocide effective against exoerythrocytic forms of the plasmodia parasite and is a gametociticide. It also has activity against pre-erythrocytic forms, oocyst, and blood schizonts, although this latter activity is too slow to be of clinical use. It is used to produce radical cure and to prevent relapse of *P. vivax* and *P. ovale* malaria, and will also destroy gametocytes in falciparum malaria. A course of treatment with a schizontocide such as chloroquine is given and this is given with or followed by a course of 14 daily doses of primaquine phosphate to kill the tissue forms. Some *P. vivax* infections acquired in south west pacific may have some resistance to primaquine, and course of treatment for up to