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# A Review On Antimalarial Drugs

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## ***Abstract***

Malaria is an infectious disease caused by a parasite *Plasmodium*, which infects red blood cells. Malaria is a major global health problem, continues to affect a large number of people each year, especially those in developing countries. The therapeutic options are scare and massively challenged by the emergence of resistant parasite strains, which causes a major obstacle to malaria control. Antimalarial drugs play a central role in the control and elimination of malaria, but in most circumstances they cannot do the job alone. Antimalarial drugs act principally to eliminate the erythrocytic stages of malaria parasites that are responsible for human illness. Great progress has been made in recent years to reduce the high level of suffering caused by malaria worldwide. The five identified *Plasmodium* species responsible for inflicting malaria in humans are *P. vivax, P. knowlesi, P. ovale, P. malariae* and *P. falciparum.* Of these, *P. falciparum* is the most virulent and prevalent *Plasmodium* species. Antimalarial drugs have been used in various ways to prevent malaria in the resident populations of endemic areas for nearly 100 years. This article provides an overview of antimalarial drugs with causes of malaria, prevention, treatment, symptoms, side effects of drugs and mainly the medications of malaria.

**Keywords:** *Plasmodium*, medications, parasite, malaria, quinine.

## ***INTRODUCTION:-***

Antimalarial drugs or simply antimalarials are type of antiparasitic chemical agent, often naturally derived, that can be used to treat or to prevent malaria, in the latter case, most often aiming at two susceptible target groups, young children and pregnant women. As of 2018, modern treatments, including for severe malaria, continued to depend on therapies deriving historically from quinine and artesunate, both parentral drugs, expanding from there into the many classes of available modern drugs. Incidence and distribution of the disease is expected to remain high, globally, for many years to come; moreover, known antimalarial drugs have repeatedly been observed to elict resistance in the malaria parasite- including for combination therapies featuring artemisinin, a drug of last resort, where resistance has now been observed in Southeast Asia. As such, the needs for new antimalarial agents and new strategies of treatment (e.g. new combination

therapies) remain important priorities in tropical medicine. As well, despite very positive outcomes from many modern treatments, serious side effects can impact some individuals taking standard doses.[2]

Malaria is an infectious disease caused by a parasite, *Plasmodium*, which infects red blood cells. Malaria has infected humans since the beginning of mankind. The name "mal aria" (meaning "bad air" in Italian) was first used in 1740 by H. Wapole. The term was shortened to "malaria" in the 20th century. C. Laveran in 1880 was the first to identify the parasites in human blood. The five species that cause malaria are:

- *Plasmodium falciparu*m: The most serious type, can be life-threatening.
- *Plasmodium vivax:* Generally less serious and are usually not life-threatening.
- *Plasmodium malariae:* Generally less serious and are usually not life-threatening.
- *Plasmodium ovale:* Generally less serious and are usually not life-threatening.
- *Plasmodium knowlesi:* Dangerous, found only in long-tailed and pigtail macaque monkeys, can be life threatening.[1]

Specifically, antimalarial drugs may be used to treat malaria in three categories of individuals, (1) those with suspected or confirmed infection, (2) those visiting a malaria-endemic regions who have no immunity, to prevent infection via malaria prophylaxis, and (3) or in broader groups of individuals, in routine but intermittent preventative treatment in regions where malaria is endemic via intermittent preventive therapy. Practice in treating cases of malaria is most often based on the concept of combination therapy (e.g.-using agents such as artemether and lumefantrine against chloroquine-resistant Plasmodium falciparum infection), since this offers advantages including reduced risk of treatment failure, reduced risk of developed resistance, as well as the possibility of reduced side-effects. Prompt parasitological confirmation by microscopy, or alternatively by rapid diagnostic tests, is recommended in all patients suspected of malaria before treatment is started. Treatment solely on the basis of clinical suspicion is considered when a parasitological diagnosis is not possible.[13]

Malaria is still considered as a major global health problem, affecting a large population of the world. According to World Health Organization (WHO), there were about 216 million malaria cases globally and 445,000 deaths in 2016. Most of the cases and the deaths occurred in the WHO African region and affected primarily children and pregnant women.[7]

Currently, there is no commercially available malaria vaccine, though efforts to develop vaccines are still ongoing. The most promising vaccine candidate is RTS, S/ AS01, which is in clinical trials for treatment of malaria caused by P. falciparum. Several medications are available to prevent malaria for travellers in malaria-endemic countries and a number of drugs are available for treatment of those who have the disease.[18]

The risk of disease can be reduced by preventing mosquito bites through the use of mosquito nets and insect repellents or with mosquito-control measures such as spraying insecticides and draining standing water. Several medications are available to prevent malaria for travellers in areas where the disease is common. Occasional doses of the combination medication

sulfadoxine/pyrimethamine are recommended in infants and after the first trimester of pregnancy in areas with high rates of malaria. As of 2020, there is one vaccine which has been shown to reduce the risk of malaria by about 40% in children in Africa. A pre-print study of another vaccine has shown 77% vaccine efficacy, but this study has not yet passed peer review. Efforts to develop more effective vaccines are ongoing. The recommended treatment for malaria is a combination of antimalarial medications that includes artemisinin. The second medication may be either mefloquine, lumefantrine, or sulfadoxine/pyrimethamine. Quinine, along with doxycycline, may be used if artemisinin is not available. It is recommended that in areas where the disease is common, malaria is confirmed if possible before treatment is started due to concerns of increasing drug resistance. Resistance among the parasites has developed to several antimalarial medications; for example, chloroquine-resistant P. falciparum has spread to most malarial areas, and resistance to artemisinin has become a problem in some parts of Southeast Asia.[4]

Malaria has afflicted mankind since ancient times and refuses to perish. In 2015 alone, there were an estimated 214 million new cases of malaria worldwide and 438,000 deaths. Concerted efforts world over have substantially decreased the malaria burden over the past decade, but it still threatens the lives of millions of children especially in the tropics. India too has witnessed a significant fall in the number of malaria cases from 2 million in 2000 to 1.1 million in 2015. Consistent upscaling of National vector borne disease control programme (NVBDCP), introduction of Rapid diagnostic tests (RDTs), use of Artemisinin based combination therapy (ACT) and long lasting insecticide nets have contributed to this improvement. However, there is a long way to go as India still accounts for 70% of the malaria burden of the South East Asian Region of WHO. In India, about 91% of malaria cases and 99% of malarial deaths are reported from high disease burden states namely Northeastern (NE) states, Andhra Pradesh, Chhattisgarh, Gujarat, Jharkhand, Karnataka, Madhya Pradesh, Maharashtra, Odisha, Rajasthan and West Bengal. However, other states are also vulnerable and have local and focal upsurge. Moreover, the emergence of drug resistance of plasmodium and increased insecticide resistance of its vector threaten to undo the progress made so far.[11]

Antimalarial drugs are used in the prophylaxis and treatment of malarial infection. Single antimalarial drug is not effective against all four species. Quinine was the first known antimalarial drug. Currently there are 4 major drug classes were used to treat malaria which includes quinolone-related compounds, antifolates, artemisinin derivatives and antimicrobials but no drug has been discovered yet which eradicate in all forms of the parasite's life cycle individually rather than combination of those drugs. Quinolines target the erythrocytic stage of malarial infection.[6]

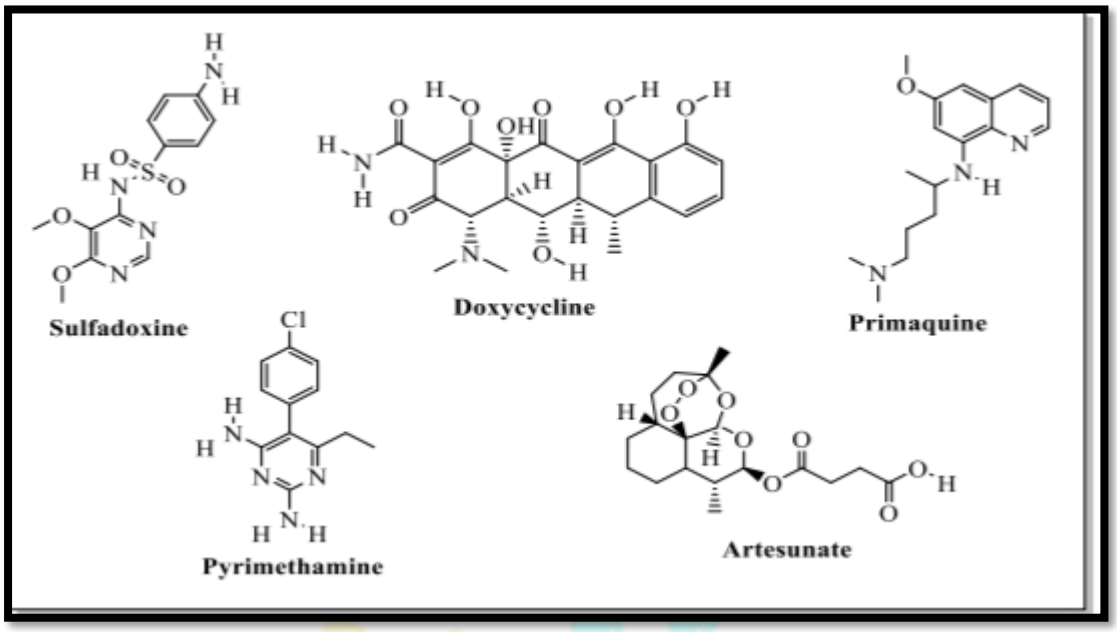


Fig. 1: Structure of some antimalarial drugs

The control and eventual eradication of malaria depend on a small set of tools. For control of anopheles mosquito vectors the values of insecticide-impregnated bednets and indoor residual spraying of insecticides have been clearly demonstrated, but their efficacy will be limited without coincident efforts directed against malaria parasites. An effective vaccine against malaria would be extremely valuable. Unfortunately, although the RTS, S vaccine, which has offered modest protection against malaria in African children, may be available in a few years, no highly effective vaccine is on the horizon. Thus, appropriate use of antimalarial drugs remains a cornerstone of malaria control. Drugs have two key roles for malaria control. First, prompt and effective treatment of malaria prevents progression to severe disease and limits the development of gametocytes, thus blocking transmission to mosquitoes. Second, drugs can be used to prevent malaria in endemic populations, including various strategies of chemoprophylaxis, intermittent preventive therapy, and mass drug administration. Anti-malaria aid campaigns have a globally positive impact for health outcomes and beyond.[21]

## ***SIGN AND SYMPTOMS:-***

1. Flulike illness with systemic fever.
2. Chills, Sweating.
3. Muscle aches (Fatigue, Pain)
4. Central headache.
5. Nausea.
6. Vomiting.
7. Dry Cough.
8. Diarrhea.
9. Spleen Enlargement.
10. Tiredness.
11. Rapid breathing.

The classic symptom of malaria is paroxysm—a cyclical occurrence of sudden coldness followed by shivering and then fever and sweating, occurring every two days (tertian fever) in P. vivax and P. ovale infections, and every three days (quartan fever) for P. malariae. P. falciparum infection can cause recurrent fever every 36–48 hours or a less pronounced and almost continuous fever.[2]

Sometimes symptoms may occur later in those individuals who have taken antimalarial medications. Initial propagation are similar to flu-like symptoms, septicemia, gastroenteritis and viral diseases. They also may include headache, fever, shivering, joint pain, vomiting, jaundice, haemoglobin urea, retinal damage, convulsions and hemolytic anemia.

Majorly malaria shows symptoms for affected persons as fever (>92% of cases), chills (79%), headaches (70%) and diaphoresis (64%) with common symptoms includes dizziness, malaise, nausea, vomiting, mild diarrhea, and dry cough. Physical signs include tachycardia, jaundice, orthostatic hypotension, hepatomegaly and splenomegaly. Symptoms typically begin 10-15 days after the initial mosquito bite, but can occur as late as several months after infection with some P. vivax strains. Travellers taking preventative malaria medications may develop symptoms once they stop taking the drugs. Children tend to have more general symptoms: fever, cough, vomiting and diarrhea.[20]

## ***COMPLICATIONS*:-**

The main complication is the development of respiratory distress, due to respiratory compensation of metabolic acidosis, Concomitant pneumonia, noncardiogenic pulmonary oedema and severe anemia. Acute respiratory distress syndrome occurs in 5-25% of adults and up to 29% of pregnant women. Infection of HIV with malaria increases the chances of death. Due to infection with *P. falciparum* cerebral malaria may occur. Which is associated with retinal whitening (a useful clinical sign in distinguishing malaria from other causes of fever). Splenomegaly, liver enlargement, hypoglycemia, severe headache and hemoglobin urea with renal failure may occur.[1]

Malaria has several serious complications. Among these is the development of respiratory distress, which occurs in up to 25% of adults and 40% of children with severe *P. falciparum* malaria. Possible causes include respiratory compensation of metabolic acidosis, noncardiogenic pulmonary oedema, concomitant pneumonia and severe anemia. Although rare in young children with severe malaria, acute respiratory distress syndrome occurs in 5-25% of adults and up to 29% of pregnant women. Coinfection of HIV with malaria increases mortality. Kidney failure is a feature of blackwater fever, where haemoglobin from lysed red blood cells leaks into the urine.[3]

Community participation and health education strategies promoting awareness of malaria and the importance of control measures have been successfully used to reduce the incidence of malaria in some areas of the developing world. Recognising the disease in the early stages can prevent it from becoming fatal. Education can also inform people to cover over areas of stagnant, still water such as water tanks that are ideal breeding grounds for the parasite and mosquito, thus cutting down the risk of the transmission between people. This is generally used in urban areas

where there are large centers of population in a confined space and transmission would be most likely in these areas. Intermittent preventive therapy is another intervention that has been used successfully to control malaria in pregnant women and infants and in preschool children where transmission is seasonal. To reduce malaria infections, world health programs distribute preventive drugs and insecticide treated bets nets to protect people from mosquito bites.[11]

## ***CAUSES OF MALARIA*:-**

Malaria is caused by infection with parasites in the genus *Plasmodium.* In humans, malaria is caused by six *Plasmodium* species: *P. falciparum, P. malariae, P. ovale curtisi, P. ovale wallikeri, P. vivax* and *P. knowlesi.* Among those infected, *P. falciparum* is the most common species identified (~75%) followed by *P. vivax* (~20%). Although *P. falciparum* traditionally accounts for the majority of deaths, recent evidence suggests that *P. vivax* malaria is associated with potentially life-threatening conditions about as often as with a diagnosis of *P. falciparum* infection. *P. vivax* proportionally is more common outside Africa. There have been documented human infections with several species of *Plasmodium* from higher apes; however, except for *P. knowlesi*—a zoonotic species that causes malaria in macaques—these are mostly of limited public health importance.[18]

Parasites are typically introduced by the bite of an infected *Anopheles* mosquito. What these inoculated parasites, called "sporozoites", do in the skin and lymphatics, exactly, has yet to be accurately determined. They grow and divide in the liver for 2-10 days with each infected hepatocyte eventually harboring up to 40,000 parasites. The infected hepatocytes break down, releasing this invasive form of Plasmodium cells, called "merozoites" into the bloodstream. The liver infection causes no symptoms, all symptoms of malaria result from the infection of red blood cells. Symptoms develop once there are more than around 100,000 parasites per milliliter of blood. The five species that cause malaria are as follows:-

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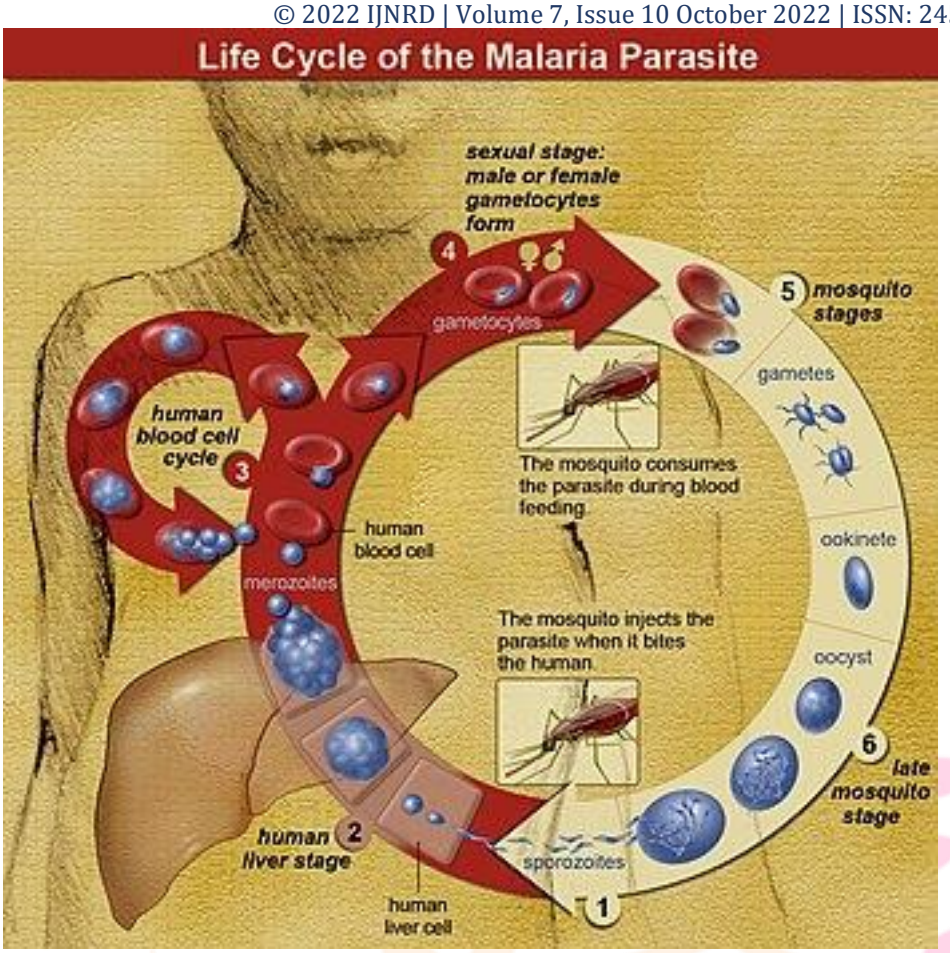


Fig. 2: The life cycle of malaria parasites

***Plasmodium falciparum:*** *Plasmodium falciparum* is a unicellular protozoan parasite of humans and the deadliest species of *Plasmodium* that causes malaria in humans. The parasite is transmitted through the bite of a female *Anopheles* mosquito and causes the disease's most dangerous form, falciparum malaria. It is responsible for around 50% of all malaria cases. *P. falciparum* is therefore regarded as the deadliest parasite in humans. It is also associated with the development of blood cancer and is classified as a Group 2A carcinogen. As of the World Health Organization *World Malaria Report 2021*, there were 241 million cases of malaria worldwide in 2020, resulting in an estimated 627,000 deaths. Nearly all malarial deaths are caused by *P. falciparum* and 95% of such cases occur in Africa. Children under five years of age are most affected, accounting for 80% of the total deaths. In Sub-Saharan Africa, almost 100% of cases were due to *P. falciparum*, whereas in most other malarial countries, other less virulent plasmodial species predominate.[23]

***Plasmodium malariae:*** *Plasmodium malariae* is a parasitic protozoan that causes malaria in humans. It is one of several species of *Plasmodium* parasites that infect other organisms as pathogens, also including *Plasmodium falciparum* and *Plasmodium vivax*, responsible for most malarial infection. Found worldwide, it causes a called "benign malaria", not nearly as dangerous as that produced by *P. falciparum* or *P. vivax*. The signs include fevers that recur at approximately three day intervals – a *quartan fever* or *quartan malaria* – longer than the two days intervals of the other malarial parasites.[26]

*P. malariae* is the one of the least studied of the six species that infect humans, in part because of its low prevalence and milder clinical manifestations compared to the other species. It

is widespread throughout Sub-Saharan Africa, much of Southeast Asia, Indonesia, on many of the islands of the western Pacific and in areas of the Amazon Basin of South America. In endemic regions, prevalence ranges from less than 4% to more than 20%, but there is evidence that *P. malariae* infections are vastly underreported.

***Plasmodium ovale:*** *Plasmodium ovale* is a species of parasitic protozoan that causes tertian malaria in humans. It is one of several species of *Plasmodium* parasites that infect humans, including *Plasmodium falciparum* and *Plasmodium vivax* which are responsible for most cases of malaria in the world. *P. ovale* is rare compared to these two parasites and substantially less dangerous than *P. falciparum. P. ovale* has recently been shown by genetic methods to consist of what is considered to be two species, namely *P. ovale curtisi* and *P. ovale wallikeri.* This species was first described in 1914 by John William Watson Stephens in a blood sample taken in the autumn of 1913 from a patient in the sanitarium of Pachmari in central India and sent by Major W. H. Kenrick to Stephens. However *P. ovale* has also been reported in the Philippines, eastern Indonesia and Papua New Guinea, as well as in Bangladesh, Cambodia, India, Myanmar, Thailand and Vietnam. It has been estimated that there are about 15 million cases of infection each year with this parasite.[24]

***Plasmodium vivax:*** *Plasmodium vivax* is a protozoal parasite and a human pathogen. This parasite is the most frequent and widely distributed cause of recurring malaria. Although it is less virulent than *Plasmodium falciparum,* the deadliest of the five human malaria parasites. *P. vivax* malaria infections can lead to severe disease and death, often due to splenomegaly. *P. vivax* is carried by the female *Anopheles* mosquito, the males do not bite. Plasmodium vivax is found mainly in Asia, Latin America and in some parts of Africa. The findings indicate that human *P. vivax* is of African origin. *Plasmodium vivax* accounts for 65% of malaria cases in Asia and South America. It has been estimated that 2.5 billion people are at risk of infection with this organism. P. vivax is carried by at least 71 mosquito species. It contributes 3.5% of global population at risk.[25]

***Plasmodium knowlesi:*** *Plasmodium knowlesi* is a parasite that causes malaria in humans and other primates. It is found throughout Southeast Asia and is the most common cause of human malaria in Malaysia. Like other *Plasmodium* species, *P. knowlesi* has a life cycle that requires infection of both a mosquito and a warm-blooded host. While the natural warm-blooded hosts of P. knowlesi are likely various Old World monkeys, humans can be infected by *P. knowlesi* if they are fed upon by infected mosquitoes. *P. knowlesi* is a eukaryote in the phylum Apicomplexa, genus *Plasmodium* and subgenus *Plasmodium.* It is most closely related to the human parasite *Plasmodium vivax* as well as other *Plasmodium* species that infect non-human primates. Humans infected with *P. knowlesi* can develop uncomplicated or severe malaria similar to that caused by Plasmodium falciparum. *P. knowlesi* malaria is an emerging disease previously thought to be rare in humans but increasingly recognized as a major health burden in Southeast Asia. *P. knowlesi* was first described as a distinct species and as a potential cause of human malaria in 1932.[28]

## ***DIAGNOSIS OF MALARIA:-***

Diagnosis of malaria in non-endemic areas requires a high degree of suspicion which might be elicited by any of the following; recent travel history, enlarged spleen, fever, low number of platelets in the blood and higher than normal levels of bilirubin in the blood combined with a normal level of white blood cells. Malaria is usually confirmed by the microscopic examination of blood films or by antigen based rapid diagnostic tests (RDT).[12]

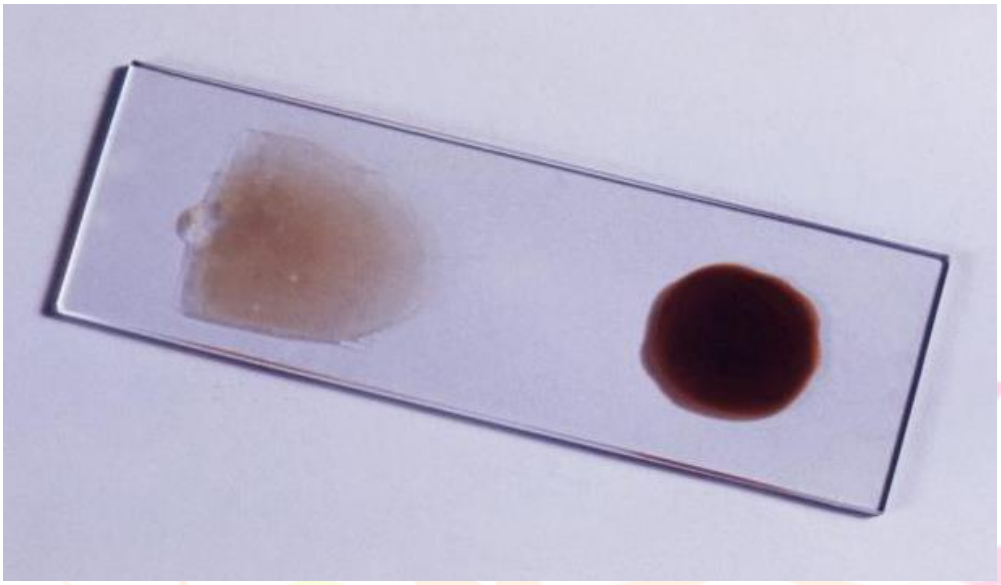

Fig. 3: The blood film is the gold standard for malaria diagnosis

## ***LIFE CYCLE OF THE MALARIA PARASITE:-***

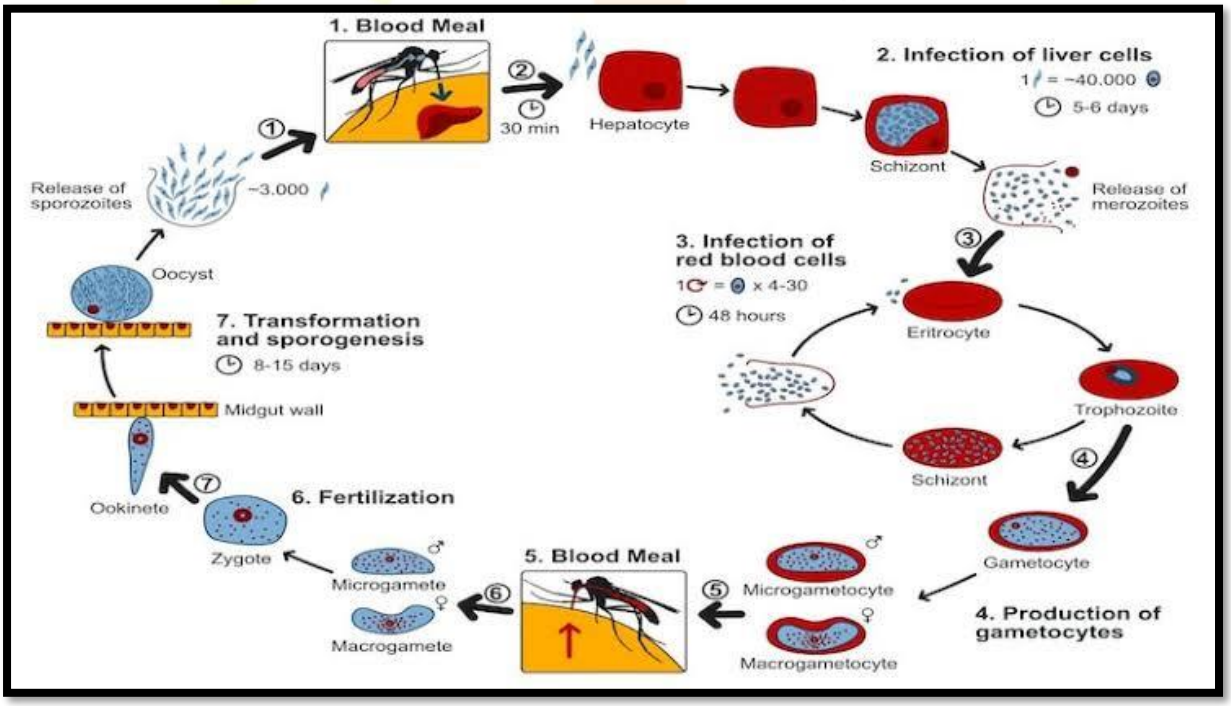


Fig. 4: Life cycle of malaria

The life cycle of the malaria parasite (Plasmodium) is complicated and involves two hosts, humans and Anopheles mosquitoes. The disease is transmitted to humans when an infected *Anopheles mosquito* bites a person and injects the malaria parasite (sporozoites) into the blood.

Sporozoites travel through the bloodstream to the liver, mature and eventually infect the human red blood cells. While in red blood cells, the parasites again develop until a mosquito takes a blood meal from an infected human and ingests human red blood cells containing the parasites. Then the parasites reach the *Anopheles mosquito's* stomach and eventually invade the mosquito salivary glands. When an *Anopheles mosquito* bites a human, these sporozoites complete and repeat the complex *Plasmodium* life cycle. *P. ovale* and *P. vivax* can further complicate the cycle by producing dormant stages (hypnozoites) that may not develop for weeks to years. Currently, most antimalarial agents are targeting the asexual phase of malaria infection that causes symptomatic illness. The pre-erythrocytic (hepatic) stage remains unattractive because clinical symptoms not generated. Antimalarial drugs exhibit considerable stage selectively of action.[6]

## ***CLASSIFICATION OF MALARIA:-***

Malaria is classified into either "severe" or "uncomplicated" by the World Health Organization (WHO). The severe malaria is declared when any of the following criteria are present, otherwise it is considered as uncomplicated malaria.

1. Decreased consciousness
2. Significant weakness such that the person is unable to walk
3. Inability to feed
4. Two or more convulsions
5. Low blood pressure (less than 70 mmHg in adults and 50 mmHg in children)
6. Breathing problems
7. Circulatory shock
8. Kidney failure or hemoglobin in the urine
9. Bleeding problems or hemoglobin less than 50 g/L
10. Pulmonary oedema
11. Blood glucose less than 2.2 mmol/L
12. Acidosis or lactate levels of greater than 5 mmol/L
13. A parasite level in the blood of greater than 100,000 per microliter in low-intensity transmission areas.[22]

## ***CEREBRAL MALARIA:-***

Cerebral malaria is defined as a severe *P. falciparum* malaria presenting with neurological symptoms, including coma or with a coma that lasts longer than 30 minutes after a seizure. According to the World Health Organization (WHO), cerebral malaria is defined as severe form of *P. falciparum* malaria that causes cerebral manifestations. Typically, patients with cerebral malaria will experience a coma that persists for more than 30 minutes after a seizure occurs. While this may be true, patients with any degree of altered consciousness and other signs of cerebral dysfunction should be treated for severe malaria. It is estimated that about 1% of children who have been infected with *P. falciparum* will develop cerebral malaria, with the incidence in adults being highly rare. However, low transmission areas will often find that cerebral malaria occurs more commonly in older children and adults. Studies have shown that younger children

may be partly protected from cerebral malaria as a result of a process known as premonition, during which maternal immunity is transferred to the child in utero.[32]

## ***ANOPHELES MOSQUITO:-***

*Anopheles* is a genus of mosquito first described and named by J. W. Meigen in 1818. About 460 species are recognized; while over 100 can transmit human malaria, only 30-40 commonly transmit parasites of the genus *Plasmodium*, which causes malaria in humans in endemic areas. *Anopheles gambiae* is one of the best known, because of its predominant role in the transmission of the most dangerous malaria parasite species (to humans) – *Plasmodium falciparum.*[17]

Only female mosquitoes feed on blood, male mosquitoes feed on plant nectar and do not transmit the disease. Females of the mosquito genus *Anopheles* prefer to feed at night. They usually start searching for a meal at dusk and continue through the night until they succeed. Malaria parasites can also be transmitted by blood transfusions, although this is rare.[34]

Fig. 5: An *Anopheles stephensi* mosquito shortly after obtaining blood from a human

## ***METHODS OF MALARIA PREVENTION:-***

There are various methods used to prevent malaria which are such as:

- Medications
- Mosquito elimination
- Prevention of bites.

As of 2020, there is one vaccine for malaria (known as RTS/S) which is licensed for use. At present there is no vaccine available for malaria. Malaria occurs in an area where the combination of high human population density, high anopheles mosquito population density and high rates of transmission from humans to mosquitoes and from mosquitoes to humans available. If any of these is lowered sufficiently, the parasite will eventually disappear from that area. However, unless the parasite is eliminated from the whole world, it could become re-established if conditions revert to a combination that favours the parasite's reproduction. Furthermore, the

cost per person of eliminating anopheles mosquitoes rises with decreasing population density, making it economically possible in some areas.[29]

Prevention of malaria may be more cost-effective than treatment of the disease in the long run, but the initial costs required are out of reach of many of the world's poorest people. There is a wide difference in the costs of control and elimination programs between countries. China government announced a strategy to pursue malaria elimination which required small proportion of investment of public expenditure on health. Whereas a similar program in Tanzania would cost an estimated one-fifth of the public health budget. In areas where malaria is common, children under five years old often have anemia, which is sometimes due to malaria.[15]

Fig. 6: Child with malaria in Ethiopia

## ***MEDICATIONS/DRUGS OF MALARIA:-***

There are a number of medications that can help prevent or interrupt malaria in travellers to places where infection is common. Many of these medications are also used in treatment. In places where *Plasmodium* is resistant to one or more medications, three medications—mefloquine, doxycycline or the combination of atovaquone/proguanil (*Malarone*)—are frequently used for prevention. Antimalarial mass drug administration to an entire population at the same time may reduce the risk of contracting malaria in the population, however the effectiveness of mass drug administration may vary depending on the prevalence of malaria in the area. The use of preventive drugs is often not practical for those who live in areas where malaria exists, and their use is usually given only to pregnant women and short-term visitors. This is due to the cost of the drugs, side effects from long-term use and the difficulty in obtaining antimalarial drugs outside of wealthy nations.[10]

Giving antimalarial drugs to infants through intermittent preventive therapy can reduce the risk of having malaria infection, hospital admission and anemia. During pregnancy, medication

to prevent malaria has been found to improve the weight of the baby at birth and decrease the risk of anemia in the mother. The use of preventive drugs where malaria-bearing mosquitoes are present may encourage the development of partial resistance. Areas of the world with chloroquine-sensitive malaria are uncommon. The protective effect does not begin immediately. Each antimalarial drug is considered by chemical structure and mechanism of action.[14]

## *Quinine and related agents:*

Quinine has a long history stretching from Peru and the discovery of the cinchona tree and the potential uses of its bark, to the current day and a collection of derivatives that are still frequently used in the prevention and treatment of malaria. Quinine is a medication used to treat malaria and babesiosis. This includes the treatment of malaria due to *Plasmodium falciparum* that is resistant to chloroquine when artesunate is not available. Quinine is an alkaloid obtained from cinchona acts as a blood schizonticidal and weak gametocide against *Plasmodium vivax* and *Plasmodium malariae*. Quinine is very effective and widely used in the treatment of acute cases of severe *P. falciparum* but it is less effective and more toxic than chloroquine. Mostly useful in areas where high level of resistance to chloroquine, mefloquine and sulfa drug combinations with pyrimethamine. The World Health Organization recommendation for quinine by oral, intravenous or intramuscular routes is 20 mg/kg first times and 10 mg/kg every eight hours for five days where as in quinine sensitivity quinine may combined with doxycycline, tetracycline or clindamycin. Use of quinine is characterized by a frequently experienced syndrome called cinchonism. Quinimax and quinidine are the two most commonly used alkaloids related to quinine in the treatment or prevention of malaria.[16]

## *Chloroquine:*

Chloroquine is a medication primarily used to prevent and treat malaria in areas where malaria remains sensitive to its effects. Chloroquine was least expensive, best tested, safest and the most widely used anti-malarial. It is taken by mouth. Chloroquine is a 4-aminoquinolone compound with a complicated and still unclear mechanism of action. Now chloroquine is suggested to use in combination with other antimalarial drugs to extend its effective usage. Children and adults should receive 25mg of chloroquine per kg given over three days. Recommended by the WHO, involves giving an initial dose of 10 mg/kg followed 6-8 hours later by 5 mg/kg then 5 mg/kg on the following 2 days. Chloroquine has been used in the treatment of malaria for many years and no abortifacient or teratogenic effects have been reported during this time.[16]

## *Hydroxychloroquine:*

Hydroxychloroquine is a medication used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. It is taken by mouth, often in the form of hydroxychloroquine sulfate. Hydroxychloroquine is in the antimalarial and 4-aminoquinoline

families of medication. Hydroxychloroquine was derived in the 1950s by adding a hydroxy group to existing Chloroquine making it more tolerable than Chloroquine by itself.[16]

### *Amodiaquine:*

Amodiaquine is a 4-aminoquinolone anti-malarial drug similar in structure and mechanism of action to chloroquine. Amodiaquine (ADQ) is a medication used to treat malaria, including *Plasmodium falciparum* malaria when uncomplicated. Amodiaquine is now available in a combined formulation with artesunate (ASAQ) and is among the artemisinin-combination therapies recommended by the World Health Organisation. Amodiaquine has become an important drug in the combination therapy for malaria treatment in Africa. Amodiaquine was first made in 1948. The drug should be given in doses between 25 mg/kg and 35 mg/kg over three days in a similar method to that used in chloroquine administration.[3]

### *Pyrimethamine:*

Pyrimethamine is used in the treatment of uncomplicated malaria. It is particularly useful in cases of chloroquine-resistant *P. falciparum* strains when combined with sulfadoxine. It acts by inhibiting dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, thereby halting the processes of DNA replication, cell division and reproduction. It should not be used by people with folate deficiency that has resulted in anemia. Pyrimethamine was discovered in 1952 and came into medical use in 1953. It is taken by mouth.[23]

### *Proguanil:*

Proguanil also known as chlorguanide is a synthetic derivative of pyrimidine. It is a medication used to treat and prevent malaria. It is often used together with chloroquine or atovaquone. It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil. This inhibits the malarial dihydrofolate reductase enzyme. It was developed in 1945 by a British Antimalarial research group. 3mg/kg is the advised dosage per day by WHO. It is taken by mouth. Proguanil hydrochloride is marketed as Paludrine by AstraZeneca.[16]

### *Sulfonamides:*

Sulfadoxine and sulfamethoxypyridazine are specific inhibitors of the enzyme dihydropteroate synthetase in the tetrahydrofolate synthesis pathway of malaria parasites. They are structural analogs of p-aminobenzoic acid (PABA) and compete with PABA to block its conversion to dihydrofolic acid. When sulfonamides are co-administration with the antifolate pyrimethamine, most commonly as fixed-dose sulfadoxine-pyrimethamine (Fansidar), produces synergistic effects sufficient to cure sensitive strains of malaria. Allergies to sulfonamides are common.[16]

## *Mefloquine:*

Mefloquine is a medication used to prevent or treat malaria. Mefloquine was developed during the Vietnam War and is chemically related to quinine. It was developed to protect American troops against multi-drug resistant *P. falciparum.* It is now used solely for the prevention of resistant strains of *P. falciparum* despite being effective against *P. vivax, P. ovale and P. malariae.* Mefloquine is effective in prophylaxis and for acute therapy. A dose of 15-25 mg/kg is recommended, depending on the prevalence of mefloquine resistance. Mefloquine was developed by the United States Army in the 1970s and came into use in the mid-1980s. It is taken by mouth. Mefloquine can only be taken for a period up to six months due to side effects. After this, other drugs again need to be taken.[10]

## *Atovaquone:*

Atovaquone is available in combination with proguanil under the name Malarone. It is commonly used in prophylaxis by travellers and used to treat *falciparum malaria* in developed countries. Atovaquone is a chemical compound that belongs to the class of naphthoquinones.[30]

## *Primaquine:*

Primaquine is a highly active 8-aminoquinolone that is effective against *P. falciparum* gametocytes but also acts on merozoites in the bloodstream and on hypnozoites. Specifically it is used for malaria due to *Plasmodium vivax* and *Plasmodium ovale* along with other medications and for prevention if other options cannot be used. It is the only known drug to cure both relapsing malaria infections and acute cases. The mechanism of action is not fully understood but it is thought to block oxidative metabolism in Plasmodia. It is taken by mouth. Primaquine was first made in 1946. For the prevention of relapse in *P. vivax* and *P. ovale* 0.15 mg/kg should be given for 14 days. As a gametocytocidal drug in *P. falciparum* infections a single dose of 0.75 mg/kg repeated seven days later is sufficient.[30]

## *Halofantrine:*

Halofantrine is a drug used to treat malaria. Halofantrine is a relatively new drug developed by the Walter Reed Army Institute of Research in the 1960s. It is a phenanthrene methanol, chemically related to Quinine. Its mechanism of action is similar to other antimalarials. Despite being effective against drug resistant parasites, halofantrine is not commonly used in the treatment or therapy of malaria due to its high cost. A dose of 8 mg/kg of halofantrine is advised to be given in three doses at six-hour intervals for the duration of the clinical episode. It is not recommended for children under 10 kg despite data supporting the use and demonstrating that it is well tolerated. Halofantrine is not recommended for use in pregnancy and lactation, in small children or in patients that have taken mefloquine previously. A popular drug based on halofantrine is Halfan. A popular drug based on halofantrine is Halfan. The level of governmental control and the prescription-only basis on which it can be used contributes to the cost, thus halofantrine is not frequently used.[30]

### *Lumefantrine*

Lumefantrine also known as benflumetol is an antimalarial drug. It is a relative of halofantrine that is used in some combination antimalarial regimens.

### *Artemisinin:*

Artemisinin is a Chinese herb that has been used in the treatment of fevers for over 1,000 years, thus predating the use of Quinine in the western world. It is derived from the plant *Artemisia annua*, with the first documentation as a successful therapeutic agent in the treatment of malaria is in 340 AD by Ge Hong in his book Zhou Hou Bei Ji Fang (A Handbook of Prescriptions for Emergencies). Ge Hong extracted the artemisinin using a simple macerate, and this method is still in use today. The active compound was isolated first in 1971 and named artemisinin. Artemisinin has a very rapid action and the vast majority of acute patients treated show significant improvement within 1–3 days of receiving treatment. On the first day of treatment 20 mg/kg is often given and the dose then reduced to 10 mg/kg per day for the six following days. It is also only given in combination with other antimalarials.[27][6]

### *Doxycycline:*

Doxycycline is a tetracycline compound derived from oxytetracycline. It is a bacteriostatic agent that acts to inhibit the process of protein synthesis by binding to the 30S ribosomal subunit thus preventing the 50s and 30s units from bonding. It is also used to prevent malaria in combination with quinine. When treating acute cases and given in combination with quinine; 100 mg of doxycycline should be given per day for seven days. In prophylactic therapy, 100 mg (adult dose) of doxycycline should be given every day during exposure to malaria. Doxycycline may be taken by mouth or by injection into a vein. It kills malaria by targeting a plastid organelle, the apicoplast. Doxycycline was patented in 1957 and came into commercial use in 1967. Due to its effect of bone and tooth growth it is not used in children under 8, pregnant or lactating women and those with a known hepatic dysfunction.[9]

### *Clindamycin:*

Clindamycin was first made in 1966 from lincomycin. It is only used in combination with quinine in the treatment of acute cases of resistant *P. falciparum* infections and not as a prophylactic. Clindamycin should be given in conjunction with quinine as a 300 mg dose (in adults) four times a day for five days. It appears to be generally safe in pregnancy. It is taken or available by mouth or by injection into a vein.[31]

## ***SIDE EFFECTS OF ANTIMALARIALS DRUGS:-***

The most common side effects of antimalarial drugs are diarrhea, nausea and vomiting, stomach cramps or pain, loss of appetite, headache, itching, difficulty concentrating, dizziness and lightheadedness and sleep problems. These problems usually go away as the body adjusts to the drug and do not require medical treatment. Less common side effects such as hair loss or loss

of color in the hair, skin rash or blue-black discoloration of the skin, fingernails or inside of the mouth also may occur and do not need medical attention unless they are long-lasting.

More serious side effects are not common, but may occur:

- Blurred vision or any other vision changes
- Convulsions (seizures)
- Mood or mental changes
- Hallucinations
- Anxiety
- Confusion
- Weakness or unusual tiredness
- Unusual bruising or bleeding
- Hearing loss or ringing or buzzing in the years
- Fever with or without sore throat
- Slow heartbeat
- Pain in the back or legs
- Dark urine
- Pale skin
- Taste changes
- Soreness, swelling or burning sensation in the tongue
- Liver and kidney failure
- Chest pain
- Abdominal pain
- Insomnia
- Anorexia
- Anaphylaxis (life-threatening allergic reactions)
- Changes in blood sugar
- Anemia
- Thrombocytopenia
- Malaise (feeling of discomfort).[8]

## ***ANTIMALARIAL RESISTANCE:-***

Antimalarial drug resistance has been defined as: “the ability of a parasite to survive or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject. The drug in question must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action.” The antimalarial drugs resistance is common. The drug in question must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action. In most instances this refers to parasites that remain following on from an observed treatment, thus it excludes all cases where antimalarial prophylaxis has failed. In order for a case to be defined as resistant, the patient in question must have received a known and observed anti-

malarial therapy while the blood drug and metabolite concentrations are monitored concurrently.[2]

Drug resistance may lead to treatment failure, but treatment failure is not necessarily caused by drug resistance despite assisting with its development. A multitude of factors can be involved in the processes including problems with non-compliance and adherence, poor drug quality, interactions with other pharmaceuticals, poor absorption, misdiagnosis and incorrect doses being given. The majority of these factors also contribute to the development of drug resistance.

Drug resistant parasites are often used to explain malaria treatment failure. However, they are two potentially very different clinical scenarios. The generation of resistance can be complicated and varies between *Plasmodium* species. This can be caused by a single point mutation or multiple mutations. In most instances a mutation will be fatal for the parasite or the drug pressure will remove parasites that remain susceptible, however some resistant parasites will survive. Resistance can become firmly established within a parasite population, existing for long periods of time.[19]

The first type of resistance to be acknowledged was to chloroquine in Thailand in 1957. The resistance of other quinolone antimalarials such as amiodiaquine, mefloquine, halofantrine and quinine are thought to have occurred by similar mechanisms. *Plasmodium* have developed resistance against antifolate combination drugs. The most commonly used being sulfadoxine and pyrimethamine.[16]

## ***PREVENTION:-***

The prevention of antimalarial drug resistance is of enormous public health importance. It can be assumed that no therapy currently under development or to be developed in the foreseeable future will be totally protective against malaria. In accordance with this, there is the possibility of resistance developing to any given therapy that is developed. This is a serious concern, as the rate at which new drugs are produced by no means matches the rate of the development of resistance.[5]

In addition, the most newly developed therapeutics tend to be the most expensive and are required in the largest quantities by some of the poorest areas of the world. Provisions essential to this process include the delivery of fast primary care where staff are well trained and supported with the necessary supplies for efficient treatment. This in itself is inadequate in large areas where malaria is endemic thus presenting an initial problem.[19]

There are two general approaches to preventing the spread of resistance: preventing malaria infections and preventing the transmission of resistant parasites. Preventing malaria infections developing has a substantial effect on the potential rate of development of resistance, by directly reducing the number of cases of malaria thus decreasing the need for anti-malarial therapy. Preventing the transmission of resistant parasites limits the risk of resistant malarial infections becoming endemic and can be controlled by a variety of non-medical methods including

insecticide-treated bed nets, indoor residual spraying, environmental controls and personal protective methods such as using mosquito repellent.[33]

A hope for future of antimalarial therapy is the development of an effective malaria vaccine. This could have enormous public health benefits, providing a cost-effective and easily applicable approach to preventing not only the onset of malaria but the transmission of gametocytes, thus reducing the risk of resistance developing.

## ***WHO RELEASES NEW MALARIA GUIDELINES FOR TREATMENT AND PROCUREMENT OF MEDICINES:-***

The World Health Organization (WHO) is releasing new guidelines for the treatment of malaria and the first ever guidance on procuring safe and efficacious antimalarial medicines.[15]

## ***CONCLUSION:-***

Malaria is a life threatening disease and it is preventable and curable and common place in tropical countries. Malaria is a major global health problem that causes significant mortality and morbidity annually. Effective antimalarial drug treatment reduces malaria transmission. The only way to get malaria is to be bitten by a certain type of mosquito that has bitten someone who has the disease. Antimalarial drugs are available only with a physician's prescription. They come in tablet, capsule and injectable forms. Available antimalarial drugs can be divided into multiple classes. According to WHO's latest World malaria report, there were an estimated 241 million malaria cases and 627,000 malaria deaths worldwide in 2020. This review aims to summarize the past, present and future of compounds used to treat malaria. As a result, the world urgently requires new, safe and efficient antimalarial medications and other preventions, as well as vaccinations to combat the present resistance problem. The drugs or medications includes artemisinin, mefloquine, lumefantrine, sulfadoxine, doxycycline, chloroquine, primaquine, etc.

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