



**TRAINING MODULE
ON
CLINICAL MANAGEMENT OF MALARIA
FOR
MEDICAL OFFICERS**



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Learning Unit 1. Introduction to malaria and Life Cycle of Malarial Parasite

1.1 What is Malaria?

Malaria is a disease transmitted by the female anopheles mosquito. The parasite which causes malaria is the plasmodium (a unicellular organism). Malaria is a global health problem; worldwide 300-500 million people develop malaria every year. In India the number of recorded cases is about 1.5 million per year, but it is estimated that the real number may be much higher. About thousand deaths due to malaria are reported every year by NVBDCP, but as many hospitals do not report malaria cases to the programme, the real number is thought to be much higher.

1.2 Malaria Control programme in India

Malaria has been a problem in India for centuries. Details of this disease can be found in the ancient Indian Medical Literature like the "*Charaka Samhita*". In the 1930s there was no aspect of life in the country that was not affected by malaria. The annual incidence of malaria was estimated at around 75 million cases in 1953, with about 8 lakh deaths. To combat this menace, the Govt. of India launched the National Malaria Control Programme (NMCP) in April 1953. The programme was highly successful and within 5 years, the incidence dropped to 2 million cases. Encouraged by this, the programme was changed to a more ambitious National Malaria Eradication Programme (NMEP) in 1958. By 1961 the incidence dropped to a mere 50,000 cases a year. But since then the programme suffered repeated setbacks due to technical, operational and administrative problems, and cases started rising again. In the late 1960's malaria cases in urban areas started to increase and surges of malaria in rural areas were also widespread. As a result in 1976, 6.47 million cases were recorded by the malaria control programme, the highest since resurgence began. In the year 1995 Malaria Action Programme (MAP) was taken up in high risk areas. The National Malaria Eradication programme was renamed as National Anti Malaria Programme (NAMP) in 1999 covering the concept of effective control. In 2004 the programme was integrated with other vector borne diseases control and was named as the National Vector Borne Disease Control Programme (NVBDCP).

The reported malaria incidence is now about 1.5 million cases per year. Over the last few decades, the proportion of falciparum malaria has increased; and the drug resistance of *P.falciparum* and insecticide resistance of vectors threaten to cause setbacks. Malaria therefore remains one of the most important public health problems of India, despite continuous efforts at its control.

The Strategy of malaria control in India is three pronged comprising of Early Diagnosis and Prompt Treatment (EDPT), Integrated Vector Management (IVM) and Supportive interventions like Training for capacity building, Behaviour

Change Communication (BCC), intersectoral coordination, Public Private Partnerships (PPP), community participation and legislation.

1.3 Types of Malarial Parasite

In India two types of plasmodia are responsible for most human malaria.—They are *Plasmodium vivax* (*P. vivax*, PV) and *Plasmodium falciparum* (*P. falciparum*, PF). There are two other plasmodia (*Plasmodium malariae* and *Plasmodium ovale*) that cause malaria in humans, but they are rare and of practicably no public health importance in India. *P.falciparum* is the variety which is responsible for almost all the deaths due to malaria. *P. vivax* causes debilitating illness, but vivax malaria is rarely fatal, unless accompanied by some other problem like malnutrition. In many states of India, particularly the North Eastern states, Orissa and Chhattisgarh, a very high proportion of malaria cases are due to *P. falciparum*.

1.4 Life Cycle of the Malarial Parasite

The malarial parasite undergoes 2 cycles of development – the human cycle (asexual cycle) and the mosquito cycle (sexual cycle). Man is the intermediate host and mosquito the definitive host.

1.4.1 Asexual cycle in human being

The asexual cycle begins when an infected anopheles mosquito bites a person and injects sporozoites. There are 3 phases in the human cycle.

1.4.1.1 Hepatic Phase

The sporozoites disappear within 60 minutes from the peripheral circulation. Many of them are destroyed by phagocytes, but some reach the liver cells. After 1-2 weeks of development (depending upon the species), they become hepatic schizonts, which eventually burst releasing a shower of merozoites. The number of merozoites produced from a single sporozoite varies – as many as 40,000 in *P. falciparum*, whereas only 200 – 15,000 in other species. In *P. falciparum*, the intrahepatic schizonts rupture almost simultaneously and there is no persistent tissue phase (exo-erythrocytic phase). In other species, the hepatic forms may remain dormant (hypnozoites) for long periods, liberating merozoites at various intervals, causing relapses of malaria.

1.4.1.2 Erythrocytic Phase

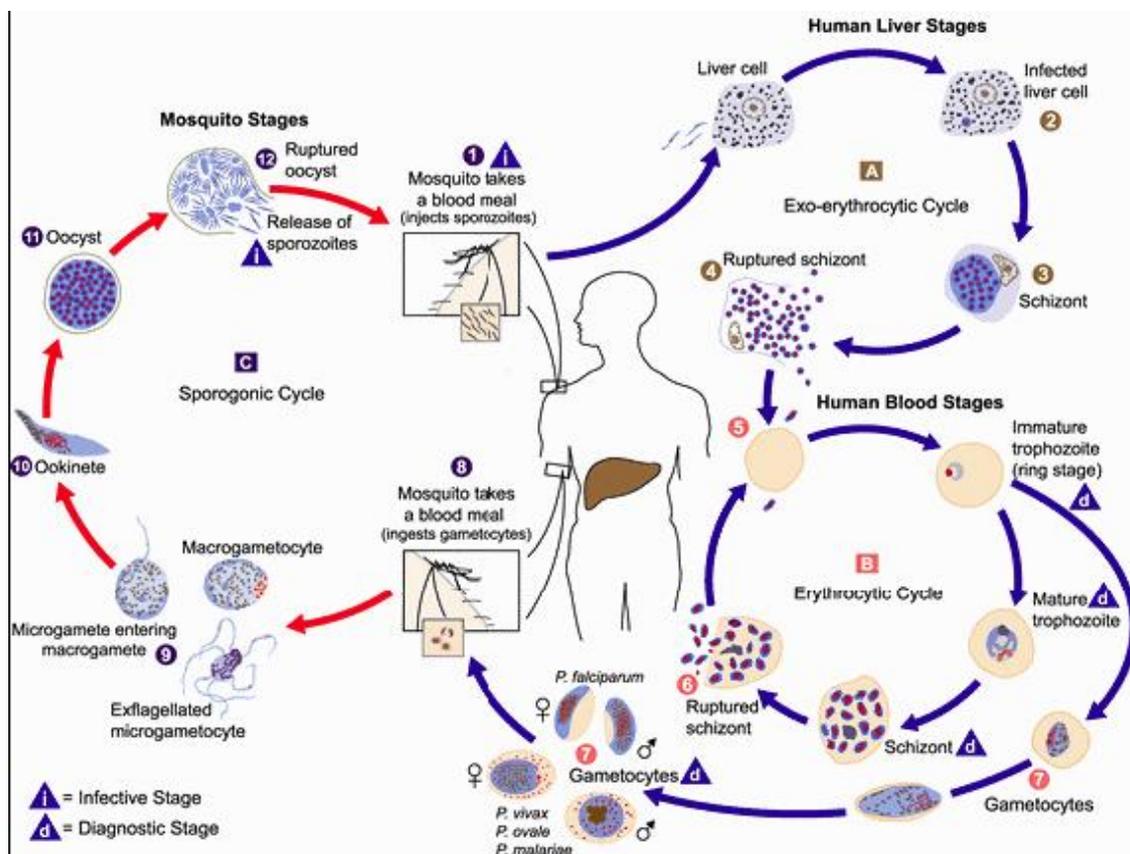
Many of the merozoites released from the liver cells are quickly destroyed, but a significant number attach themselves to specific receptor sites on the RBCs, penetrate them and pass through various stages of trophozoite and schizont. The erythrocytic phase ends with the liberation of merozoites, which infect fresh RBCs. The clinical feature of fever with chills coincides generally with the rupture of RBCs. The cycle is repeated over and over again until the condition worsens

or when it may be slowed down by the immune response of the host. The duration of each erythrocytic cycle varies between species – 48 hours for *P. falciparum*, *P. vivax* and *P. ovale*; and 72 hours for *P. malariae*.

1.4.1.3 Gametogony

Some of the erythrocytic forms of plasmodia do not divide further but develop into male and female gametocytes. Not all **infected** persons are **infectious** (can infect anopheline mosquitoes). The blood of the person has to have mature male and female gametocytes and the density should be minimum 12/ cumm of blood to be infective. These gametocytes take over a week to appear in the blood. Gametocytes do not cause any symptoms in humans. Most drugs like chloroquine kill the asexual forms that cause the fever but leave intact the sexual forms that are infective especially in case of *P. falciparum*. Thus an apparently normal person may harbour the disease and contribute to its spread.

Figure 1. Life Cycle of *Plasmodium* species in man and the mosquito



1.5 Spread of malaria

The plasmodia spread from person to person by the bite of mosquitoes. This process is called the **transmission** of the disease, and the mosquitoes are the **vectors** of malaria. However, not all mosquitoes can act as malaria vectors. It is only mosquitoes belonging to the genus *Anopheles* - and that too the female of the species which can carry the parasite and infect. Male *Anopheles* mosquitoes only feed on plant juices and nectar and cannot transmit malaria.

1.5.1 Sexual Cycle in Mosquito

The mosquito cycle (sporogony) begins when gametocytes are ingested by the vector mosquito while feeding on an infected person. The male gametocytes, after reaching the stomach of the mosquito and develop into 4-8 filaments called "microgametes". The female gametocyte undergoes maturation to become a "macrogamete". The microgametes get attracted to the macrogamete, and one of the microgametes fertilizes the macrogamete. The resulting zygote is at first motionless, but within 18-24 hours, becomes a motile ookinete, which penetrates the stomach wall of the mosquito and develops into an oocyst on the outer surface of the stomach. The oocyst further develops into numerous sporozoites, when the oocyst ruptures and releases the sporozoites into the body cavity of the mosquito. Many of the sporozoites migrate to the salivary glands and the mosquito becomes infective to man. The period required for the development of the parasite from the gametocyte stage to sporozoite stage is about 10-20 days depending on atmospheric temperature and humidity. This period is known as the "extrinsic incubation period". The sporozoites (the infective stage of *Plasmodium*) are injected with saliva when the mosquito next feeds.

In falciparum malaria, there may be involvement of the brain and coma in addition to life threatening complications including kidney or liver failure. With early and effective treatment, the case fatality rates in *P.falciparum* malaria can be brought down from above 5% to close to zero. Malaria cases can be classified according to the parasite species causing them and according to the severity of the disease, as either uncomplicated or severe malaria. It should be understood that severe vivax malaria is very rare.

1.6 Immunity to malaria

Repeated infections with malaria parasites lead to the acquisition of antibodies directed against various antigens of various stages of malaria parasites as well as cell-mediated immunity. The immunity is to a large extent, but not completely, specific to the species of malaria parasite. It is also to some extent strain-specific, meaning that a person, who has been exposed to malaria in a certain part of the world (or part of a large country like India) will have a higher degree of immunity to local malaria parasites than to those from a distant location. There is no perfect immunity to malaria: nobody acquires such a high level of protective antibodies that he or she can be certain not to contract malaria. Also, in contrast to many other communicable diseases, the immunity to malaria is time-limited: the person who has acquired a certain degree of immunity through repeated malaria attacks will lose that immunity in a few years, if the exposure is not

maintained. For this reason, sometimes the terms semi-immunity or premunition are preferred to immunity.

Typically in areas with very intense transmission, persons who are heavily exposed, acquire some immunity in childhood. Then as adults, they get ill relatively rarely and when they do, the disease is mild and of short duration. It seems that in old age, immunity is lost again, but it is not clear whether this is a result of ageing processes or of old people being less exposed to malaria or both. Typically, people with a certain degree of immunity still harbour parasites: They are **asymptomatic carriers**. It can be difficult to detect such cases and this can have implications for malaria control. If a certain population is heavily exposed to malaria, so that some people have some immunity to the disease and exposure is reduced for some years as a result of control measures, the immunity will largely be lost. If control is then relaxed, malaria may return with occurrence of large number of cases. For this reason, sustainability is important in malaria control.

Scientific work to develop a **malaria vaccine** has taken place for decades. One or two vaccines may well be marketed within the coming 5 years, but they are likely to have only a limited degree of effectiveness and would, at best, only be a supplement to other malaria control tools.

Malaria is a serious disease, which has affected human populations for many thousands of years. It has therefore exerted a selective pressure, favouring certain genotypes in humans with some innate (in contrast to acquired, as described above) immunity to malaria. Among these conditions are sickle cell disease, thalassaemia and glucose-6-phosphate dehydrogenase deficiency, all of which are common in India, especially in populations which are or have in the past been heavily exposed to malaria.

1.8 Malaria Control

Malaria control comprises all activities undertaken to reduce the burden of malaria in a given population. It includes the diagnosis and treatment of malaria cases and prevention. Surveillance of the disease, prevention and control of epidemics and field studies to regularly assess the malaria situation and its determinants are essential components in a malaria control programme. The main methods of prevention aim to reduce the risk of humans being bitten by infected anopheline mosquitoes. The aim of malaria control is to reduce morbidity and mortality of malaria to the lowest possible levels locally. In some cases, the aim may be elimination, i.e. the interruption of transmission, where no new cases occur.

1.8.1 Diagnosis and treatment

Uncomplicated malaria can become severe malaria within 1-2 days (shorter for young children) of onset of symptoms. Early and effective treatment will halt the progression of the disease, thereby preventing deaths from occurring. This could

be achieved by treating everybody with a fever as malaria, and this was in fact done until recently as “presumptive treatment”. Nowadays, because of drug resistance, it is necessary to use more expensive and differentiated treatment regimens. The strategy of presumptive treatment has therefore been replaced by early diagnosis (through RDTs or microscopy) followed by prompt, effective treatment. Early effective treatment benefits not only the individual patient, but also has the following advantages:

a) Lowering the infectivity of infected persons to the mosquito vector will contribute to reducing malaria transmission, and eventually the incidence of malaria.

b) Early diagnosis is important because in the early stages the infected persons have only asexual forms of plasmodia in the blood, which are not infective to mosquitoes. It takes about 4 - 5 days after the person has developed fever to develop the sexual forms of *P. vivax* in the blood; for *P. falciparum* it takes 8 -10 days. If the blood is cleared of the parasites during this time, then the transmission from that person is prevented.

c) In low transmission areas, where most infective people are symptomatic, treating all cases within the first week could cut transmission dramatically. In high transmission areas, where there are many asymptomatic carriers, case management alone has relatively little role in transmission control.

d) Most antimalarial medicines have no significant action on the gametocytes, whereas primaquine can effectively destroy them. Artemisinin derivatives have some effect on gametocytes, but it is not as constant as that of primaquine. Therefore, primaquine is included in the treatment of falciparum malaria, because some patients only report after they have developed gametocytes.

1.8.2 Measures directed against the transmission by mosquitoes

1.8.2.1 Transmission dynamics

It is important to have a basic knowledge of the transmission dynamics to understand malaria control. The intensity of malaria transmission in an area is the rate at which people are inoculated with malarial parasites by mosquitoes. It is expressed as the annual Entomological Inoculation Rate (EIR) i.e. the average number of infectious bites by malaria-infective mosquitoes delivered to an individual human resident in that area per year. Annual EIRs range from 500 to 1000 in certain parts of Africa to about 10 to 100 in places where there are seasonal peaks. At levels of about 0.01 or less, malaria transmission is barely and rarely sustained.

The EIR can go down, if:

- a) There are fewer people, who have gametocytes in their blood; so that the probability of a mosquito becoming infected upon biting a human being is reduced.
- b) Total population of mosquitoes has decreased.
- c) People have taken measures to avoid mosquito bites.
- d) More animals are available as sources of blood meals, provided the vectors are zoophilic.
- e) Average life-span of vectors has been reduced, so that only a few of those infected become infective for human beings.

Field studies and mathematical models have shown that in most situations the most effective vector control methods are the ones, which include reduction of life-span of vectors. The explanation is that the average life-span of a female anopheline is only a little longer than the extrinsic incubation period. Thus, a 20% reduction of the average life-span of female anophelines may lead to a situation, where no or very little transmission takes place. In contrast, even if the density of anophelines is reduced by, for example 80%, the remaining 20% will be able to maintain some transmission. In practice, methods which reduce the life-span of anophelines may also reduce their density and the frequency with which they bite humans.

1.8.3 Behaviour Change Communication (BCC)

The NVBDCP envisages strong community participation and behavior change components in the malaria control program to meet the challenges in malaria control. Three interventions of proven value are now being introduced at a large scale into the program, each of which has benefits tangible even to the lay person, and thus having high likelihood of acceptability and utilization:

1.8.3.1 Diagnosis. In the place of slide tests which involved delay in getting results, rapid diagnostic tests (RDT) for *P. falciparum* are now available. These tests can be conducted at the most peripheral levels by any one with simple training.

1.8.3.2 Treatment. In place of Chloroquine which was associated with treatment failure due to drug resistance, ACT is now available which is nearly 100% effective and is not associated with any major side effects.

1.8.3.3 Bed nets. In place of Insecticide impregnated Bednets which required periodic reimpregnation, soon we will have Long lasting bed nets which do not require reimpregnation, remaining effective even after 20-25 washes and lasting for 3-5 years.

A fourth component of the program having high acceptance potential is the establishment of trained ASHAs at village level, known as ASHAs. The malaria control program offers considerable scope for communities to participate in and own the program.

1.9 Vulnerable groups

Certain groups are particularly vulnerable to malaria:

Pregnancy increases vulnerability of women to severe malaria, by lowering immunity. Malaria can cause abortion, stillbirth, low birth weight and severe anaemia in pregnant woman. Early and complete treatment of malaria is therefore of the greatest importance in pregnant women.

Young children are at highest risk in those populations, which are exposed to very intense transmission, where older people develop immunity. Even in areas with less intense transmission, severe disease may develop particularly rapidly in young children. Diagnosis may be difficult, as young children can have fever from a number of different causes.

People who do not live in malaria-endemic areas have no immunity. The problem of immigrants may be a lack of knowledge of malaria and about where to go for treatment if they fall ill. Travellers, tourists and immigrants need information on protective measures against malaria in various locations and situations.

1.10 Malaria and gender

Women are more likely to delay visits to qualified health care providers and more likely to visit traditional healers for their sickness and for their children because of their lesser control over resources and decision-making process in the household. There may be a gender bias towards the male child, who gets preferential attention in getting health care. Studies have shown that women in many situations do not have control over decision making about accessing quality health care. Malaria in pregnant women is associated with more serious complications.

When men have malaria the household becomes severely affected economically. Women's work days become longer and the work load becomes heavier as they have to take care of the ill apart from their routine activities. There may also be times when they have to go for work to compensate for the wage loss of the male members. In households without any male earning member, the economic consequence can be very severe on the entire family.

There is a need to promote women's active participation in leadership and decision-making. It is critical that people at every level come together to create awareness of the magnitude of the problem and on the way gender inequalities lead to a greater impact on women and the girl child in case of sickness due to malaria.

Learning Unit 2. Malaria Entomology

2.1 Malaria entomology is the study of biology and ecology of the mosquitoes that transmit malaria. There are more than 4000 species of mosquitoes in the world of which about 424 belong to Anopheline group, and about 70 are considered to be the main vectors of malaria. In India there are about 53 species of anopheline mosquitoes and of these nine are vectors for malaria; only six of them being important primary vectors. The other three can contribute to spread of malaria but by themselves cannot initiate or sustain transmission (secondary vectors).

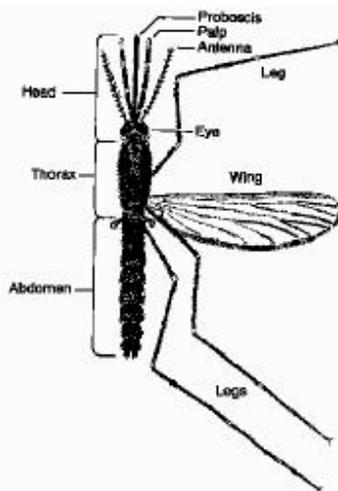
2.2 Distinguishing mosquitoes from other insects

Mosquitoes belong to the **class Insecta** – having the following characteristics:

- the body is divided into three sections—head, thorax and abdomen
- the head has one pair of antenna, and a pair of compound eyes
- the thorax has three pairs of legs

The main parts of the adult mosquito are shown in Figure 3.1 below. Four characteristics can be used to describe adult mosquitoes: only one pair of wings; a long proboscis; the body is covered with scales; and wings have **veins** that show a defined pattern

Figure 3.1 Main parts of the adult mosquito



2.3 Distinguishing anophelines from culicines

Distinguishing characteristics of anophelines and culicines are illustrated in Figs. 2.2 and 2.3.

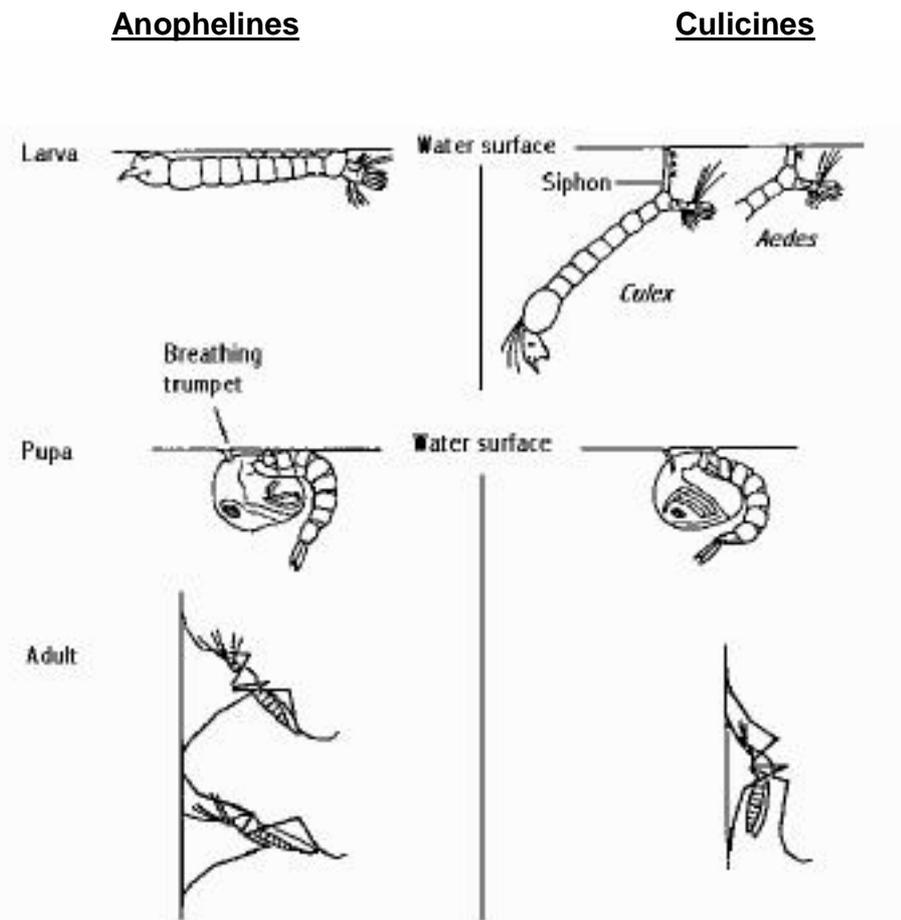


Figure 2.2 Comparison between anopheline and culicine mosquitoes

2.3.1 Eggs

Culicine eggs clump together in a "raft" (*Culex*) or float separately (*Aedes*); anopheline eggs float separately and each of them has "floats".

2.3.2 Larvae

The **culicine** larva has a breathing tube (**siphon**) which it also uses to hang down from the water surface, whereas the **anopheline** larva has **no siphon** and rests parallel to and immediately below the surface.

2.3.3 Pupae

Pupae of both anophelines and culicines are comma-shaped and hang just below the water surface. They swim when disturbed. The breathing trumpet of

the anopheline pupa is short and has a wide opening, whereas that of the culicine pupa is long and slender with a narrow opening. However, it is difficult to distinguish anopheline from culicine pupae in the field.

2.3.4 Adults

Live adult anopheline and culicine mosquitoes, can easily be distinguished by observing their resting postures. Anophelines rest at an angle between 50° and 90° to the surface whereas culicines rest more or less parallel to the surface. Anopheline mosquitoes can also be distinguished from culicines by the length and shape of the palps. The differences (Fig. 2.3) are:

- In female anophelines, palps are as long as proboscis; in female culicines, palps are very much shorter than proboscis.
- In male anophelines, palps are as long as proboscis and club-shaped at tip; in male culicines, palps are longer than proboscis, with tapered tips.

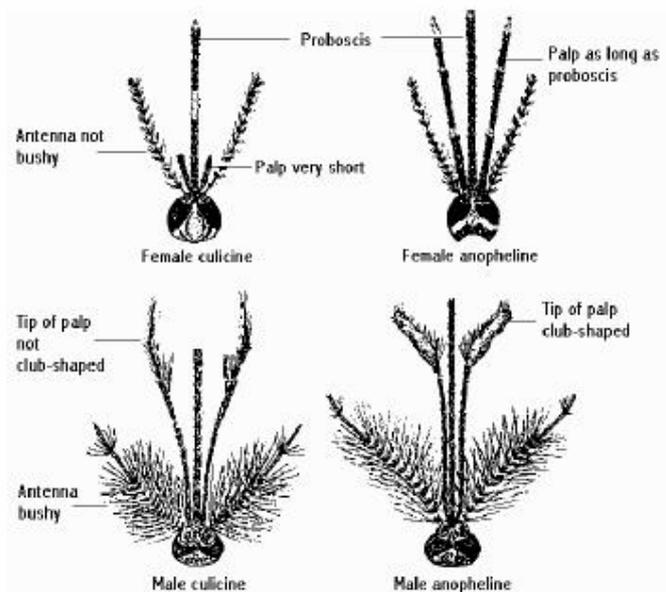


Figure 2.3 Heads of male and female anopheline and culicine mosquitoes

2.4 Distinguishing female *Anopheles* from males

It is important to distinguish females from males because only the female *Anopheles* takes blood meals and transmits malaria; on the antennae of the female the hairs are few in number and short (Fig. 2.3). The male has very long hairs on the antennae, which consequently have a bushy appearance.

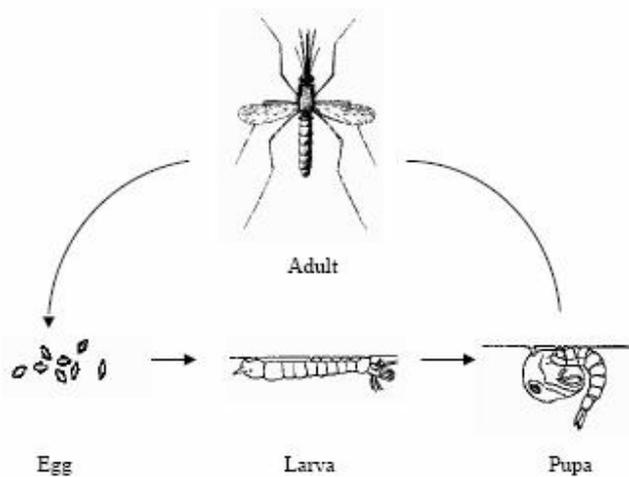
2.5 Life cycle of anopheline mosquitoes

All mosquitoes have four different stages in their life cycle: the **egg**, **larva**, **pupa** and **adult**.

2.5.1. Eggs

A female anopheline mosquito normally mates only once in her lifetime. She usually requires a blood meal after mating for development of eggs. Blood meals are generally taken every 2-3 days before the next batch of eggs is laid. About 100-150 eggs are laid on the water surface during oviposition. Oviposition sites vary from small hoof prints and rain pools to streams, swamps, canals, rivers, ponds, lakes and rice fields. The average lifespan of female anopheline mosquitoes is about 3-4 weeks.

Figure 3.3 Life cycle of an *Anopheles* mosquito



2.5.2 Larva

A larva hatches from the egg after about 1-2 days. The anopheles larva floats parallel under the water surface, since it needs to breathe air. It feeds by taking up food from the water. When disturbed, the larva quickly swims towards the bottom but soon needs to return to the surface to breathe. There are four larval stages or **instars**. The total time spent in the larval stage is generally 8-10 days at normal tropical water temperatures. At lower temperatures, the aquatic stages take longer to develop.

2.5.3 Pupa

The pupa is shaped like a comma and it's a non feeding stage. It stays under the surface and swims down when disturbed. The pupal stage lasts for two to three days after which the skin of the pupa splits. Then the adult mosquito emerges and rests temporarily on the water's surface until it is able to fly.

2.5.4 Adult

Mating takes place soon after the adult emerges from the pupa. The first batch of eggs develops after one or two blood meals, while successive batches usually require only one blood meal. The feeding and resting habits of mosquitoes are of great importance in control programmes and for this reason they must be well understood. Most anopheline mosquitoes bite at night. Some bite shortly after sunset while others bite later, around midnight or the early morning. Some mosquitoes enter houses to bite and are described as being **endophagic**; others bite mostly outside and are called **exophagic**.

After the mosquito takes a blood meal she usually rests for a short period. Mosquitoes that enter a house usually rest on a wall, under furniture or on clothes hanging in the house after they bite and are said to be **endophilic**. Mosquitoes that bite outside usually rest on plants, in tree holes, on the ground or in other cool dark places and are called **exophilic**.

Host preferences are different for different species of mosquitoes. Some mosquitoes prefer to take blood from humans rather than animals and are described as being **anthropophagic/anthropophilic** while others only take animal blood and are known as **zoophagic/zoophilic**. Clearly, those who prefer to take human blood are the most dangerous as they are more likely to transmit malaria from person to person.

2.6 Malaria vectors of India

The important malaria vectors in India are:

- a. *Anopheles culicifacies*: The most common vector in India, especially in rural areas and is widely distributed in India. Occurs sporadically in N.E. India. Not reported in Andaman & Nicobar Islands and Lakshadweep.
- b. *Anopheles fluviatilis*: Important vector in hilly and forested areas. Widely distributed in the foothill areas including both peninsular and North East India
- c. *Anopheles stephensi*: Distributed throughout India except at higher altitudes. Found only sporadically in the North East. Almost all urban malaria is due to this species.
- d. *Anopheles sondaicus*: Typical of seashores; low importance except on islands. Responsible for malaria transmission in Andaman & Nicobar islands only.
- e. *Anopheles minimus*: Of great importance in the north east India, breeding in slow- moving streams with grassy margins, mainly in foothills.

- f. *Anopheles dirus*: Vector in forested and forest fringe area in the north-east. Highly exophilic and exophagic and difficult to). Breed in small, transient, partly shaded pools in forest areas (eg. Elephant footprints)
- g. *Anopheles annularis*: Mainly a secondary vector, which is common in central India and Orissa.
- h. *Anopheles philippinensis*: It is incriminated as a vector in deltaic West Bengal and N.E. India. Breeds mainly in paddy fields.
- i. *Anopheles varuna*: Secondary vector in Andhra Pradesh, Jharkhand and Orissa.

2.7 Bionomics of important vector species. The behaviour of the four important vector species is given below:

	<i>An. culicifacies</i>	<i>An. stephensi</i>	<i>An. fluviatilis</i>	<i>An. minimus</i>	<i>An. dirus</i>
Site of breeding	Water in paddy fields, wells, irrigation wells, step wells, ponds, cattle water storages, cattle foot prints	Clean water in water tanks, water logged in trenches, large clean water puddles, upturned cans, etc	Rock pools, hilly streams, ponds	Shaded slow flowing streams with grassy margins, swamps, ditches, channels	small, transient, partly shaded pools in forest areas (eg. Elephant footprints)
Zoophilic/anthropophilic	Zoophilic; Occasionally anthropophilic	Zoophilic/Anthropophilic according to availability	Anthropophilic	Highly anthropophilic	Highly anthropophilic
Seasonality	Peaks during monsoon months	Rainy months	Peaks in late monsoons and early winter months	Perennial	Rainy months
Peak Time of biting	Varies – (1900 to 0400)	Varies- (2200 to midnight)	Late night (2300 to 0300)	1800 to 1900 (Outdoors); Midnight to 0200 (Indoors)	2100 – 03:00 Hrs

	<i>An. culicifacies</i>	<i>An. stephensi</i>	<i>An. fluviatilis</i>	<i>An. minimus</i>	<i>An. dirus</i>
Preferred place of biting	Endophagic	Endophagic	Endophagic & exophagic	Endophagic & Exophagic	Primarily Exophagic & Endophagic as well
Resting behaviour	Endophilic	Endophilic	Endophilic/ Exophilic	Endophilic/ Exophilic	Exclusively Exophilic
Biological efficiency as vector	Low	Low	High	High	High

Learning Unit 3. Case detection, case management and chemoprophylaxis

The objectives of malaria case management are:

- To prevent severe disease and death in patients presenting with uncomplicated malaria
- To shorten the duration of symptoms
- To reduce malaria transmission
- To prevent relapses of vivax malaria

3.1 Recognition of malaria

People living in malaria-endemic areas need to be informed that any febrile disease might be malaria and that malaria can rapidly become a very dangerous disease. They also need to be informed about where they can obtain qualified care for malaria. This is particularly important for migrants to endemic areas (for example temporary labour), who may be ignorant both of what malaria is and where treatment is available.

3.2 Diagnosis of malaria

A patient with fever and no other obvious cause is considered a case of *suspected malaria*. A more elaborate definition is presented in the table *Case definitions applied in NVBDCP*. In practice the ascertainment of an “obvious cause” can only be expected from well-trained and experienced health staff. A volunteer or health activist working in a high-risk area should be taught to consider any fever case in the absence of specified symptoms as suspected malaria.

Any volunteer, health worker or health professional observing a case of suspected malaria must immediately initiate a diagnostic test by

1. Microscopy of blood for malarial parasites and/or
2. Rapid Diagnostic Test¹ for *Pf*

If a microscopy result can be made available to the provider managing the patient within 24 hours (in practice on the day, when the patient presents or the day after), only microscopy is done. Antimalarial treatment is given only on the basis of a positive slide-result.

If a microscopy result cannot be available within 24 hours, the procedure depends on the risk of *P.falciparum*. RDTs are to be supplied and used for diagnosis in villages (or subcenter areas, where village data is not available) where

- Pf % > 30 and SfR > 2%:
- Consistently high API and deaths are reported
- Inaccessible areas - cut off during transmission season
- Limited road and public transportation facility for treatment of severe and complicated malaria requiring immediate medical attention

An RDT is done in front of the patient and a slide is taken. If the RDT is negative, the slide is sent for microscopy. If it is positive, the patient is treated for falciparum malaria,

¹ Currently, the program uses HRP2 based rapid diagnostic tests

and the slide is discarded in order to reduce the load on the microscopy services. Mixed infection cannot be ruled out in such cases, but the risk is low. The ACT treatment for *P.falciparum* is also effective for the blood stages of *P.vivax*. If the patient should have a *P.vivax* relapse later, he or she is expected to return and then be diagnosed and treated with primaquine.

[STATE RATIONALE FOR CRITERIA: TO MINIMIZE WASTAGE ALSO]

Wherever a microscopy result **can** be made available within 24 hours, microscopy should be maintained as the only routine method. RDTs should be used in PHC and other health facilities only in emergencies in the absence of the laboratory technician (LT).

Techniques of RDTs and microscopy are described in annex ..., which also describes precautions with storage and handling of RDTs.

It should be noted that these tests have a shelf-life of only 12 months and that they may deteriorate at high ambient temperatures.

Interpretation of rapid diagnostic tests

HRP2-based tests for *P.falciparum* detect a circulating antigen excreted by asexual plasmodia. The tests have a sensitivity of about 95%, when the asexual parasite density is above 100/ μ l. Malaria patients are rarely symptomatic at lower densities. If a suspected malaria patient has a negative RDT, it can therefore be assumed that the patient does not have malaria and another cause of the symptoms should be sought. If no other cause can be found and the clinical suspicion is high (e.g. intermittent fever with rigors and sweats), the test should be repeated after about 24 hours and special efforts should be made to obtain the microscopy result rapidly.

HRP2 antigen can persist for up to 4 weeks after clearance of asexual parasitaemia through treatment. False positive tests are therefore common, especially in patients with a recent history of treatment. RDTs should therefore **not** be used for following up patients after treatment. They are not useful to monitor prognosis. If a patient, who has been treated, is febrile within one month after the treatment and the RDT is positive, the patient **may** have malaria. If possible, the diagnosis should then be confirmed by microscopy.

The above rules for use of diagnostics should be applied at all levels of care and in passive as well as active case detection.

Quality microscopy remains the best method of diagnosis. Functional microscopy facility should therefore be strategically positioned in all PHCs, especially in high risk areas. If needed, laboratory staff under NRHM & RNTCP should be trained on malaria microscopy. Where an LT position is vacant, contractual recruitment should be undertaken.

3.3 Treatment

3.4.1 Antimalarial drugs used in public health in India

1. Schizonticidal drugs

Chloroquine, quinine, sulfadoxine-pyrimethamine, artemisinin derivatives: artesunate, arte-mether and arte-ether.

- 2) Gametocytocidal and anti-relapse drug
Primaquine.

3.4.2 Selection of drugs

All fever cases diagnosed positive by either RDT or microscopy need to be promptly started on effective treatment. The treatment will depend upon the species of *Plasmodium* diagnosed.

Treatment of uncomplicated falciparum malaria

Artesunate 4mg/kg daily for 3 days plus sulfadoxine-pyrimethamine 25mg/kg + 1.25 mg/kg as a single dose on the first day (ACT) plus primaquine (PQ) in a single dose on the first day.

In low-risk areas with PV predominance and Pf is sensitive to chloroquine resistance, the Pf cases will be treated with chloroquine and primaquine. Similarly, the clinical cases (unconfirmed cases) will also be treated with chloroquine in situations where diagnosis is not possible within reasonable time, no later than the day after fever is reported to the health facility.

Contra-indications

Primaquine is contraindicated in pregnancy, children under one year and persons with a history of haemolysis following primaquine treatment. Patients belonging to these categories should not receive primaquine.

Precautions

Sulfadoxine-pyrimethamine can, in rare cases cause serious cutaneous or mucocutaneous eruptions and/or agranulocytosis. Any patients with a cutaneous or mucocutaneous reaction within a month after taking sulfadoxine-pyrimethamine should, if there is not an obvious alternative explanation be considered allergic to sulphonamides and not be given sulfonamide treatment again.

Suspected cases of ACT side effects should be reported to NVBDCP with individual case reports.

Artemisinin derivative monotherapy must not be given under any circumstance for uncomplicated malaria, as there is great concern that use of such monotherapy could lead to artemisinin resistance.

Treatment failures

Treatment failures are expected to be very rare with ACT. Most cases of apparent treatment failures will probably be caused by inadequate patient compliance. Therefore, apparent treatment failures should be re-treated with ACT, if they occur at least 14 days after initial treatment. Earlier treatment failures should be treated with quinine to minimize the risk of side-effects from repeated treatment with sulfadoxine-pyrimethamine.

NVBDCP and NIMR jointly monitor the susceptibility to ACT in sentinel sites.

Treatment of uncomplicated vivax malaria

Chloroquine (CQ) for 3 days (Day 1: 10mg/kg + Day 2: 10mg/kg + Day 3: 5mg/kg) plus primaquine 0.25mg/kg daily for 14 days as per prescribed guidelines

Primaquine contra-indications: See above.

Explanation

P. vivax in India remains fully sensitive to chloroquine. This is monitored by NIMR. In recent years, controlled trials have failed to demonstrate any anti-hypnozoite (anti-relapse) effect of primaquine, when given for 5 days. NVBDCP has therefore adopted the 14 day regimen recommended by WHO.

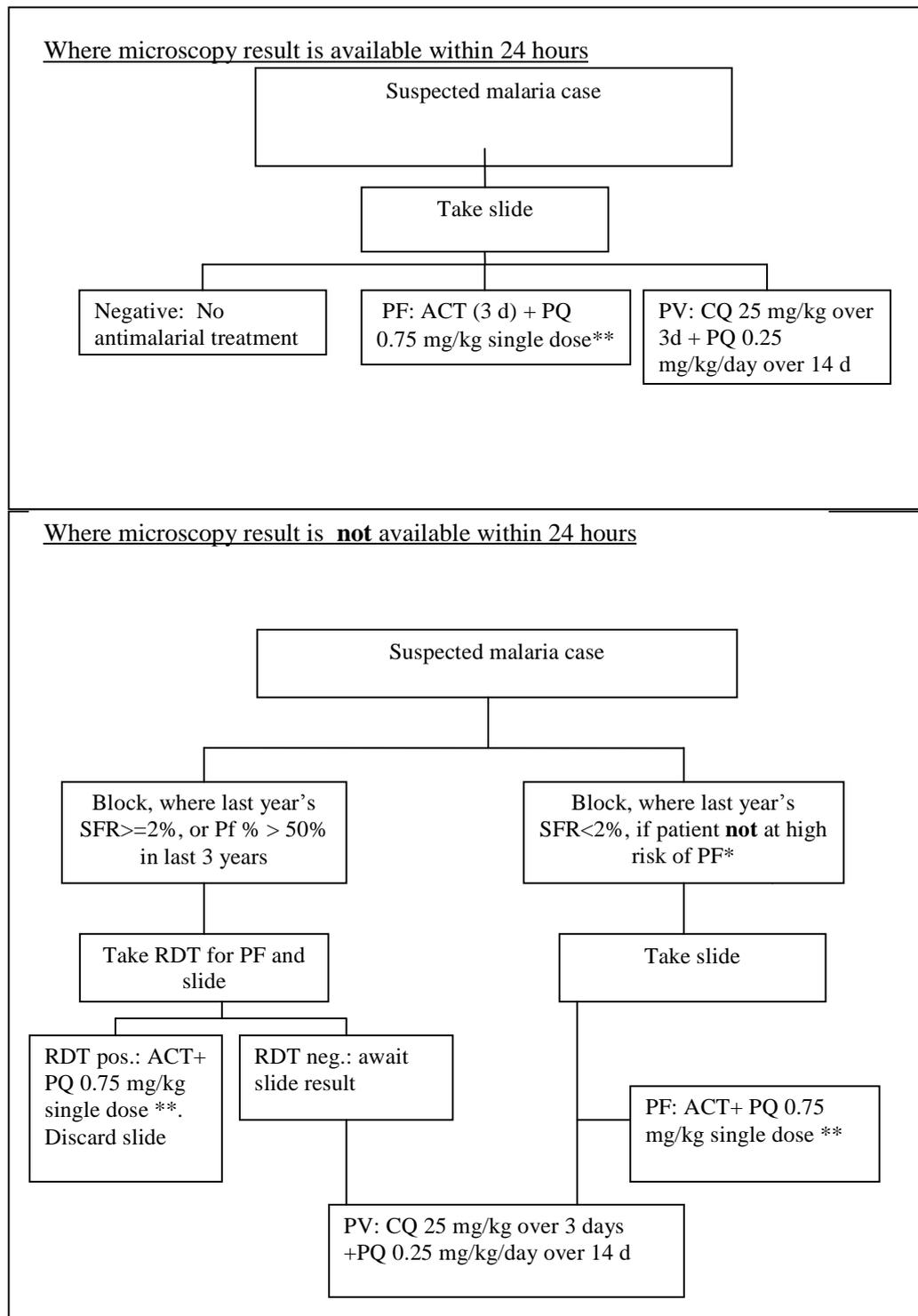
Treatment of uncomplicated mixed infections (of PF and PV)

Artesunate for 3 days plus sulfadoxine-pyrimethamine in a single dose on the first day plus primaquine for 14 days

Contra-indications: See above.

An algorithm for the diagnosis and treatment of fever cases for malaria is given in Figure 3.1.

Fig 3.1: Fever Diagnosis and Treatment Algorithm



ACT= artemisinin-based combination therapy (artesunate + sulfadoxine-pyrimethamine); CQ= chloroquine; PQ=primaquine

Note that PQ is contra-indicated in pregnancy and in children under 1 years.

Age-specific Drug Schedules

1. Chloroquine tablets of 150 mg chloroquine base

Age in years	Day 1	Day 2	Day -3
	Tab. chloroquine	Tab. Chloroquine	Tab. Chloroquine
<1	½	½	¼
1-4	1	1	½
5-8	2	2	1
9-14	3	3	1½
15 & above	4	4	2

2. Primaquine tablets of 7.5 or 2.5 mg base

Age (in years)	<i>P. falciparum</i>		<i>P. vivax</i>	
	Primaquine 0.75 mg/kg on day 1		Primaquine 0.25 mg/kg daily dose for 14 days*	
	mg base	No. of Tablets (7.5 mg base)	mg base	No. of Tablets (2.5 mg base)
<1	Nil	0	Nil	Nil
1-4	7.5	1	2.5	1
5-8	15	2	5.0	2
9-14	30	4	10.0	4
15 & above	45	6	15.0	6

* Primaquine is contraindicated in children under one year and pregnant women.

3. Artesunate 50 mg tablets + sulfadoxine-pyrimethamine 500 + 25 mg tablets (ACT) combination

Age		1 st Day (number of tabs)*	2 nd Day (number of tabs)	3 rd Day (numbers of tabs)
<1 Year	AS	½	½	½
	SP	¼	Nil	Nil
1-4 Yeas	AS	1	1	1
	SP	1	Nil	Nil
5-8 Year	AS	2	2	2
	SP	1 ½	Nil	Nil
9-14 Year	AS	3	3	3
	SP	2	Nil	Nil
15 and above	AS	4	4	4
	SP	3	Nil	Nil

* Artemisinin group of drugs is not recommended in pregnancy

3.4.3 Initiation of treatment and advice to the patient/caretaker

Once a suspected case is diagnosed positive by RDT or microscopy, treatment is started. The first dose is always taken in the presence of the health volunteer/worker. If the patient is a child under 5 years or pregnant, ask her or him to wait for 15 minutes after taking the first dose. If it is vomited within this period, let the patient rest for 15

minutes, then give a first dose again (i.e. open a new blister-pack and discard what remains of the old. If the patient vomits the first dose again, it is considered a case of severe malaria (see below).

The remaining part of the treatment is given to the patient/caretaker to take home with clear instructions.

Explain to the patient/caretaker

- That if the treatment is not completed as prescribed, the disease may recur, possibly being more serious and more difficult to treat.
- To come back immediately, if there is no improvement after 24 hours, if the situation gets worse or the fever comes back.
- That regular use of a mosquito net is the best way to prevent malaria.

3.4.4. Recording of treatment

The result of RDT or slide should be entered by ASHA/ Health Worker/ MO in column 12 & 14 of M1. In case of Blood slide the date of receipt of result is to be entered in column 11. This will indicate the time lapse between the date of slide collection and receipt of results. If RDT has not been performed simply mark a cross (X). Now depending upon the species, ASHA/ Health worker/ MO will decide the anti-malarials to be administered. These will be entered in column 15 or 16 of M1. Suppose ACT has been selected then the entry will be made in column 16 while a cross (X) will be put in column 15. The date of starting and completing the treatment will be entered in column 17 and 18. During supervisory visits the time lag between slide collection or RDT and initiation of treatment should be identified.

3.5 Severe and complicated malaria

A case of uncomplicated malaria usually presents with fever, rigors, headache, bodyache, fatigue, anorexia and nausea.

Serious complications can arise in *P.falciparum* infection. They may sometimes develop suddenly over a span of time as short as 12 -24 hours and may lead to death, if not treated promptly and adequately. These complications are:

- Cerebral malaria with convulsions, lethargia, coma, paralyses and other neurologic manifestations
- Severe anaemia
- Renal failure, which may be combined with severe haemolytic anaemia in the syndrome of black water fever
- Adult respiratory distress syndrome, which may progress to pulmonary edema
- Liver failure with jaundice and haemorrhagic tendency
- Septicaemia
- Bacterial pneumonia
- Hyperpyrexia
- Dehydration
- Hypoglycaemia (often caused more by quinine than by malaria)
- Circulatory shock (rarely with disseminated intravascular coagulation)

In children, febrile convulsions, repeated vomiting and dehydration are common if the temperature is high from any cause. Therefore, these symptoms are not necessarily indicative of severe malaria. However, children with such symptoms should be managed as severe malaria in routine program situations, and a diagnosis of malaria should be confirmed at the earliest.

In pregnancy, malaria, specially *P.falciparum* is a serious disease because with each bout of malaria, there is a reduction in haemoglobin and profound anaemia may develop rapidly. They are also at high risk of abortions or intrauterine growth retardation because sequestration of parasites in placenta restricts oxygen and nutrients flow to the fetus. [PREMATURITY, STILLBIRTHS? TO CHECK]

The management of severe malaria requires immediate administration of life saving drugs. Therefore availability of the following is essential

- Antimalarials which can be given parenterally.
- Intravenous infusion equipment
- Special nursing for patients in coma
- Facilities for blood transfusion
- Well equipped laboratory
- Oxygen respirator

Often these items are not available at the PHC level. Under such circumstances, the Medical Officer, PHC and paramedical staff should be able to administer emergency treatment and refer the case without delay to other institutions where such facilities are available.

The DVBD/CO/ DMO should list all facilities in the district where emergency care for severe malaria is available and this list should be available in PHCs and with all Community Workers like ASHA. MO-PHC should develop links with these institutions. For timely referral of severe cases, transportation should be provided from untied funds available under NRHM.

3.5.1 The role of peripheral workers

The community comes in contact with ASHA and MPW (M&F) as a routine. They depend on these persons for advice and treatment of different diseases, malaria being one of them. Therefore, Medical Officers **while training these workers should emphasize the need to recognize a serious case of malaria before it is too late.** These workers should be conversant with the signs and symptoms of malaria and those which are likely to indicate serious complications.

They should be **instructed that if the patient does not get relief from symptoms of malaria within 24 hours, and/or headache/fever continues to increase, the patient should report to the nearest PHC/CHC/Hospital.**

Criteria for immediate referral to Primary Health Centre

- a) Persistence of fever after 48 hours of initial treatment.
- b) Continuous vomiting and inability to retain oral drugs.
- c) Headache continues to increase
- d) Severe dehydration – dry, parched skin, sunken face
- e) Too weak to walk in the absence of any other obvious reason

- f) Change in sensorium e.g. confusion, drowsiness, blurring of vision, photophobia, disorientation
- g) Convulsions or muscle twitchings
- h) Bleeding and clotting disorders
- i) Suspicion of severe anaemia
- j) Jaundice
- k) Hypothermia

3.5.2 Role of MO - PHC

The PHC Medical Officer should be capable of performing a full clinical assessment and ensure that the following facilities are available:

- A person trained in nursing serious cases
- Blood smear examination & parasite count with result within one hour
- Routine examination of urine, haemoglobin, blood glucose
- Parenteral antimalarials: Artesunate, arte-ether, arte-mether or quinine
- Saline/dextrose for intravenous transfusion
- Oxygen
- Antipyretics, anticonvulsants, diuretics, antibiotics

If any one of these is not available, administer intravenous or intramuscular antimalarial and refer to a higher level facility.

Criteria for referral to District Hospital

- a) Cerebral malaria patients not responding to initial antimalarial treatment.
- b) Severe anaemia warranting blood transfusion
- c) Bleeding and clotting disorder
- d) Haemoglobinuria
- e) Pulmonary oedema
- f) Cerebral malaria complicating pregnancy
- g) Oliguria not responding after correction of fluid deficit and diuretics
- h) Fluid, electrolyte and acid base disturbance.

3.5.3 Diagnosis

All attempts should be made to confirm the diagnosis using microscopy or RDTs. At PHCs & District level hospitals RDTs should be used in emergency hours only in the absence of technician/microscopist. Wherever possible, treatment should be guided by microscopy. High degree of parasitaemia and presence of stages of the parasite other than ring and gametocyte indicate poor prognosis. Severe malaria in the absence of microscopical evidence of asexual *Plasmodium falciparum* (or *P.vivax*. see below) is exceedingly rare. In such cases, all efforts should be done to identify an alternative cause. If microscopy is negative and RDT is positive for *P.falciparum*, it is possible that the explanation is that antigen is persisting from an earlier infection. However, if the symptoms clearly point to severe malaria and there is no alternative explanation, such a case can be recorded as having severe malaria. Such occurrences are possibly more common in patients, who have started an ACT treatment a few days before. Severe malaria with negative RDT is possible, but extremely rare. A patient with negative microscopy and negative RDT should not be recorded as severe malaria, but may be treated as such, if the responsible clinician deems it necessary.

3.5.4 Treatment

In severe malaria cases, a parenteral artemisinin derivative **or** quinine is the drug of choice.

It has been shown that intravenous artesunate is the most effective treatment for severe malaria in adults in Asia. It is presently being investigated whether this is so for young children also, but there is no reason to assume a priori that it is inferior. If injectable artesunate and the facilities for IV administration are available, this should therefore be the preferred treatment in all patients.

Dosage regimens

Artesunate: 2.4 mg/kg IV/ IM followed by 2.4 mg/kg after 12 and 24 hours then once daily.

Arte-mether: 3.2 mg/kg IM followed by 1.6 mg/kg once daily.

Arte-ether: 150 mg daily IM in adults only for 3 days

Artesunate is dispensed as a powder of artesunic acid. This is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 ml of 5% dextrose and given by intravenous injection or by intramuscular injection to the anterior thigh. The solution should be prepared freshly for each administration and should not be stored.

Parenteral treatment should continue until the patient is able to take oral treatment. When that is the case, full course of ACT should be administered to patients treated with artemisinin derivatives.

Quinine: 20 mg salt/kg as a loading dose, then 10mg salt /kg 8 hourly in 5% dextrose or dextrose saline. The infusion rate should not exceed 5 mg salt/kg per hour. Loading dose may not be given if the patient has already received quinine or if Clinician feels inappropriate. As soon as the patient is able to take orally, oral quinine should be given. The total duration of treatment should be 7 days including parenteral dose.

Pregnant women with severe malaria should be treated like any other adult patient. In these patients, the benefits of the artemisinin derivatives outweigh the theoretical hazards. Particular attention should be given to the high risk of hypoglycaemia in pregnancy.

3.6 Chemoprophylaxis

As chloroquine is no longer considered an effective treatment for falciparum malaria in India, it is no longer used for chemoprophylaxis. In pregnant women, there is no safe and effective alternative to chloroquine, which has been tested in India. Therefore, chemoprophylaxis is no longer recommended as a routine method of prevention in pregnancy. Personal protection should be used in children under 8 years, pregnant women and long term travelers and will now be based on the use of insecticide-treated nets

Use of chemoprophylaxis is limited to following situations:

- *a). Short term travelers/Tourists (less than 6 weeks) from non-malarious areas to malarious areas. Drug of choice is Doxycycline 100 mg daily in adults and

1.5mg / kg daily in Children; beginning 2 days before travel – 4 weeks after leaving a malarious area.

*b). Long term travelers where appropriate eg. Military & Paramilitary Troops on night patrol duty etc in malarious areas. The decision of Medical Authority is to be followed. Drug of choice is Mefloquine 250 mg weekly for adults & 5 mg/kg for children once a week; beginning 1 week before - 4 weeks after exposure