Global strategy for dengue prevention and control 2012-2020 *(11)*

Dengue is a global threat that requires a global response involving all possible partners. The global strategy promotes co-ordination and collaboration among multisectoral partners on integrated vector management approach and sustained control measures at all levels. The goals are :

a. to reduce dengue mortality by at least 50 per cent by 2020;
b. to reduce dengue morbidity by at least 25 per cent by 2020; and
c. to estimate the true burden of the disease by 2015.

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MALARIA

Malaria is a protozoal disease caused by infection with parasites of the genus **Plasmodium** and transmitted to man by certain species of infected female Anopheline mosquito. A typical attack comprises three distinct stages : cold stage, hot stage and sweating stage. The clinical features of malaria vary from mild to severe, and complicated, according to the species of parasite present, the patient's state of immunity, the intensity of the infection and also the presence of concomitant conditions such as malnutrition or other diseases. The febrile paroxysms occur with definite intermittent periodicity repeating every third or fourth day depending upon the species of the parasite involved.

Problem statement

WORLD

According to the latest estimates, there were about 198 million (124-283 million) cases of malaria in the year 2013 and an estimated 584,000 deaths (367,000-755,000). Malaria mortality rates have fallen by 47 per cent globally since year 2000, and by 54 per cent in the WHO African Region. Most deaths occur among children living in Africa, where a child dies every minute from malaria *(1A)*.

Approximately half of the world's population is at risk of malaria. Most malaria cases and deaths occur in sub-Saharan Africa. However, Asia, Latin America, and to a lesser extent the Middle East and parts of Europe are also affected. In 2013, 97 countries and territories had ongoing malaria transmission.

The specific risk groups for malaria includes the following population *(1)* :

1. young children in stable transmission areas who have not yet developed protective immunity against the most severe forms of the disease;
2. non-immune pregnant women as malaria causes high rates of miscarriage and can lead to maternal death;
3. semi-immune pregnant women in areas of high transmission. Malaria can result in miscarriage and low birth weight, especially during first and second pregnancies;
4. semi-immune HIV-infected pregnant women in stable transmission areas, during all pregnancies. Women with malaria infection of the placenta also have a higher risk of passing HIV infection to their newborns;
5. people with HIV/AIDS;
6. international travellers from non-endemic areas because they lack immunity.
7. immigrants and their children living in non-endemic areas and returning to their home countries to visit friends and relatives are similarly at risk because of waning or absent immunity.

Malaria affects mainly poor, underserved and marginalized populations in remote rural areas which are characterized by inadequate control measures and limited access to health care. Higher malaria prevalence has been reported among ethnic and tribal groups living in remote forested and border areas, as well as among mobile and migrant populations.

The childhood deaths result mainly from cerebral malaria and anaemia. Fatality rates of 10-30 per cent have been reported among children referred to hospital with severe malaria. However, these rates are even higher in rural and remote areas where patients have restricted access to adequate treatment. Malaria also contributes indirectly to illness and deaths from respiratory infections, diarrhoeal disease and malnutrition. Deaths from malaria in countries outside Sub-Saharan Africa occur principally in non-immune people who become infected with *P. falciparum*.

Underreporting of malaria cases and deaths remain a major challenge. Drug-resistant parasites, poor treatment-seeking behaviour and the presence of counterfeit antimalarial drugs further hinder control efforts. Resistance of *P. falciparum* to the 4-aminoquinolines and sulfadoxine-pyrimethamine is widespread in almost all countries of SEAR, with varying levels of severity. Resistance to mafloquine was reported from Myanmar and Thailand. Quinine has reduced susceptibility in Thailand. With progress from mono-to-multidrug resistance, all malaria-endemic countries that have *falciparum* malaria adopted the highly effective artemisinin - based combination therapy (ACT).

The coverage of indoor residual spraying with insecticides (IRS) remains low (42 per cent). Insecticide-treated nets have been introduced in almost all countries to supplement IRS efforts, but the coverage remains extremely low.

INDIA

Malaria continues to pose a major public health threat in India, particularly due to *Plasmodium falciparum* which is prone to complications. In India about 21.98 per cent population lives in malaria high transmission

(≥ 1 case/1000 population) areas and about 67 per cent in low transmission (0-1 case/1000 population) areas *(2)*. About 92 per cent of malaria cases and 97 per cent of deaths due to malaria is reported from North-eastern states, Chhattisgarh, Jharkhand, Madhya Pradesh, Orissa, Andhra Pradesh, Maharashtra, Gujarat, Rajasthan, West Bengal and Karnataka. However, the other states are also vulnerable with local and focal outbreaks of malaria. Much of these areas are remote and inaccessible, forest or forest fringed with operation difficulties and predominantly inhabited by tribal population *(3)*.

The countrywide malaria surveillance data for the period from 1995 to 2013 is as shown in Table 1.

The API has been steadily declining in India from 3.29 in 1995 to 0.88 in 2012. When interpreting API, it is important to evaluate the level of surveillance activity indicated by the Annual Blood Examination Rate (ABER). At low levels of surveillance, the Slide Positivity Rate (SPR) is a better indicator. The SPR has also shown a decline in the country from 3.51 in 1995 to 0.51 in 2013. The *Pf* cases have declined from 1.14 million in 1995 to 0.44 million cases in 2013. However *Pf* % has gradually increased from 38.8% in 1995 to nearly 66.9% in 2013, which may indicate increasing resistance to chloroquine *(4)*.

India is predominantly characterized by unstable malaria transmission. Transmission is seasonal with increased intensity related to rains. Due to the low and unstable transmission dynamics, most of the population has no or little immunity toward malaria. As a result, the majority of Indians living in malarious areas are at risk of infection with all age groups affected. However, surveys have shown that in some foci, mainly in forested areas, transmission is intense and the disease burden is to a large extent concentrated in children.

There are six primary vectors of malaria in India : (1) *An. culicifacies* is the main vector of rural and peri-urban areas and is widespread in peninsular India. It is found in a variety of natural and man-made breeding sites. It is highly zoophilic. Species A is an established vector for *P. Vivax* and *P. falciparum*, whereas species B is completely refractory to *P. Vivax* and partially refractory to *P. falciparum*. It has been demonstrated that species B, however, may play a role as a vector of *P. falciparum* in areas where the cattle population is very low or absent; (2) *An. stephensi* is responsible for malaria in urban and industrial areas. The type form is found in urban areas; intermediate form in urban and semi-urban localities and *mysorensis* form is present in rural areas (it is not a vector); (3) *An. fluviatilis* is the main vector in hilly areas, forests and forest fringes in many states, especially in the east; (4) *An. minimus* is the vector in the foot hills of North-Eastern states; (5) *An. dirus* is an important forest vector in the North-East; and (6) *An. epiroticus* is now restricted to the Andaman and Nicobar Islands *(5)*.

Prevalent major epidemiological types of malaria in India *(6)*

In the course of the stratification exercise, various problems and constraints responsible for the slow progress of malaria control have been identified. An analysis of these factors has resulted in the identification of malaria priority areas.

TRIBAL MALARIA : The population of tribal areas are contributing about 50 per cent of *P. falciparum* cases of the country *(5)*. Infants, young children and pregnant women have been identified as malaria high risk groups followed by mobile tribal population engaged in forest-related activities. Limited health infrastructure and lack of drugs at village level are the factors responsible for high morbidity and mortality due to malaria.

RURAL MALARIA : These include irrigated areas of arid and semiarid plains. Malaria is of moderate to low endemicity. *An. culicifacies* is the main vector and *P.vivax* is predominant during lean period and *P.falciparum* during periodic exacerbation. In these the health infrastructure is moderately developed.

URBAN MALARIA : 15 major cities including 4 metropolitans account for nearly 80 per cent of malaria cases covered under urban malaria control scheme. The health infrastructure is well developed. In peri-urban areas malaria situation is influenced by poor sanitary conditions and low socio-economic groups living in unplanned settlements prone to periodical epidemics.

MALARIA IN PROJECT AREAS : Project areas are those areas where construction and developmental activities are taken up and temporary tropical aggregation of labourers takes place bringing in different strains of malaria parasite and non-immune population. This results in disturbance in eco-system, prolific increase in vector breeding places and increased man-mosquito contact favouring high malaria transmission. These pockets contribute a large number of malaria cases which are highly disproportionate to the

TABLE 1
Countrywide malaria surveillance data (1995-April 2014)

Year	Population (in thousands)	BSE (in millions)	Total malaria cases (in millions)	*P. falciparum* cases (in millions)	Pf%	API	SPR	SFR	Deaths due to malaria
1995	888,143		2.93	1.14	38.84	3.29	3.51		1,151
2008	1,119,624	9.73	1.52	0.77	50.81	1.36	1.57	0.80	1,055
2009	1,150,113	10.33	1.56	0.84	53.72	1.36	1.51	0.81	1,144
2010	1,151,788	10.60	1.60	0.83	52.12	1.37	1.41	0.74	1,023
2011	1,210,000	10.93	1.31	0.66	50.30	1.10	1.20	0.61	754
2012	1,211,509	10.89	1.06	0.53	50.01	0.88	0.98	0.49	516
March 2013 to April 2014	–	23.40	0.8	0.44	66.93	–	0.51	0.34	379

Pf – Plasmodium falciparum
API – Annual Parasite Incidence
SPR – Slide Positivity Rate
BSE – Blood Smear Examined
SFR – Slide Falciparum Rate

Source : *(4)*

relatively small population groups inhabitating the area. One or more major vectors are involved in malaria transmission. Limited health facilities for prompt treatment is invariably associated with chloroquine resistant malaria parasite. Hence specific control strategy is required for such areas.

BORDER MALARIA : These are the high malaria transmission belts along the international borders and state borders. These areas have their own problems in regard to malaria control because of mixing of population and poor administrative control.

Some definitions (2)

Malaria control : reducing the malaria disease burden to a level at which it is no longer a public health problem.

Malaria elimination : the interruption of local mosquito-borne malaria transmission; reduction to 'zero' of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required.

Certification of malaria elimination : can be granted by WHO after it has been proven beyond reasonable doubt that the chain of local human malaria transmission by *Anopheles* mosquitoes has been fully interrupted in an entire country for at least 3 consecutive years.

Malaria eradication : permanent reduction to 'zero' of the worldwide incidence of infection caused by a specific agent; applies to a particular malaria parasite species. Intervention measures are no longer needed once eradication has been achieved.

Epidemiological determinants

Agent factors

(a) AGENT

Malaria in man is caused by four distinct species of the malaria parasite – *P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale*. *Plasmodium vivax* has the widest geographic distribution throughout the world. In India, about 50 per cent of the infections are reported to be due to *P. falciparum* and 4–8 per cent due to mixed infection and rest due to *P. vivax*. *P. malariae* has a restricted distribution and is said to be responsible for less than 1 per cent of the infections in India. The largest focus of *P. malariae* in India is reported to be in Tumkur and Hassan districts in Karnataka. *P. ovale* is a very rare parasite of man, mostly confined to tropical Africa. It has also been reported in Vietnam. The severity of malaria is related to the species of the parasite.

Life history

The malaria 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 (Fig. 1).

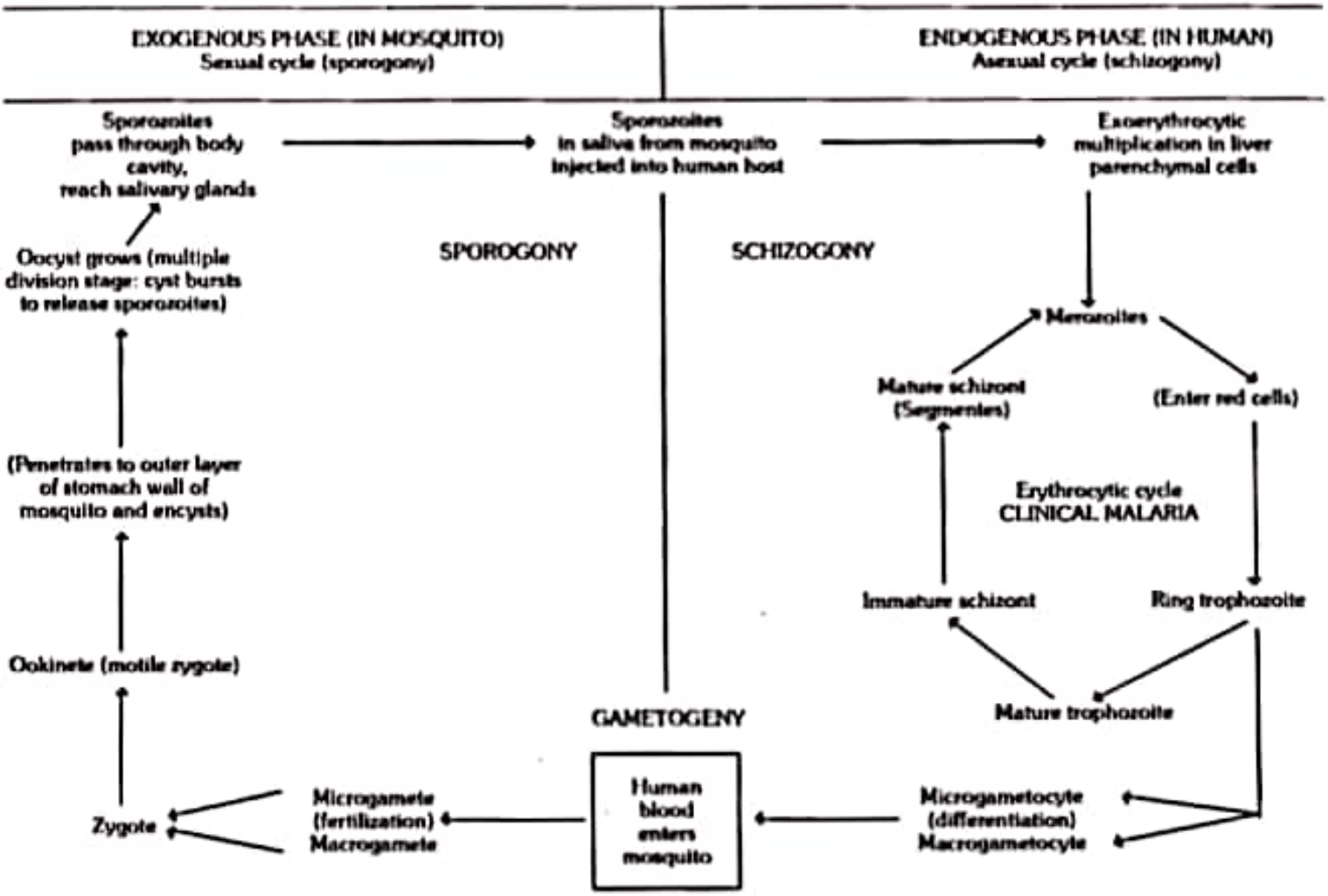


FIG. 1

Lifecycle of the malaria parasite.

Source : *(10)*

(i) *Asexual cycle*: The asexual cycle begins when an infected mosquito bites a person and injects sporozoites. A considerable amount of new knowledge about the parasite's life cycle has become available in recent years, concerning almost all phases of the cycle *(7)*. A brief description is as follows – four phases are described in the human cycle: (a) HEPATIC PHASE: The sporozoites disappear within 60 minutes from the peripheral circulation *(8)*. 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 considerably with the infecting species. A single *P. falciparum* sporozoite may form as many as 40,000 merozoites, whereas sporozoites from other species of plasmodia produce only 2,000 to 15,000 merozoites *(8)*. In the case of *P. falciparum*, the intrahepatic schizonts rupture almost simultaneously and there is no persistent tissue phase (the so-called exo-erythrocytic phase). On the contrary, the intrahepatic schizonts of the other plasmodia do not burst all at the same time. Some hepatic forms persist and remain dormant in the hepatocytes for considerable periods before they begin to grow and undergo pre-erythrocytic schizogony, thus liberating merozoites into the blood stream causing relapses of these infections. *P. vivax* and *P. ovale* may continue to relapse for 2 to 3 years and *P. malariae* may persist for 10 to 20 years or more. Once the parasites enter the RBC, they do not reinvade the liver. (b) ERYTHROCYTIC PHASE: Many of the merozoites are quickly destroyed, but a significant number attach to specific receptor sites on the RBC. The merozoites then penetrate the RBC and pass through the stages of trophozoite and schizont. The erythrocytic phase ends with the liberation of merozoites, which infect fresh red blood cells. The cycle is repeated over and over again until it is slowed down by the immune response of the host *(9)*. The duration of the erythrocytic cycle is constant for each species of malaria parasite- 48 hours for *P. falciparum*, *P. vivax* and *P. ovale*; and 72 hours for *P. malariae*. (c) GAMETOGENY: In all species of malaria some erythrocytic forms do not divide but become male and female gametocytes. These are the sexual forms of the parasite which are infective to mosquito.

(ii) *Sexual cycle*: The mosquito cycle (sporogony) begins when gametocytes are ingested by the vector mosquito when feeding on an infected person. The gametocytes continue further development in the mosquito. The first event to take place in the stomach of the mosquito is exflagellation of the male gametocyte, 4-8 thread-like filaments called "micro-gametes" are developed. The female gametocyte undergoes a process of maturation and becomes a female gamete or "macrogamete". By a process of chemotaxis, microgametes are attracted towards the female gamete, and one of which (microgamete) causes fertilization of the female gamete. The resulting zygote is at first a motionless body, but within 18-24 hours, it becomes motile. This is known as *Ookinete*, which penetrates the stomach wall of the mosquito and develops into an oocyst on the outer surface of the stomach. The oocyst grows rapidly and develops within it numerous sporozoites. When mature, the oocyst bursts and liberates sporozoites into the body cavity of mosquito. Many of the sporozoites migrate to the salivary glands of the mosquito, and the mosquito now becomes infective to man. The period of time required for the development of the parasite from the gametocyte to sporozoite stage in the body of the mosquito is about 10-20 days depending upon favourable conditions of atmospheric temperature and humidity. This period is also referred to as the "extrinsic incubation period".

(b) RESERVOIR OF INFECTION

With the possible exception of chimpanzees in tropical Africa, which may carry the infection with *P. malariae*, no other animal reservoir of human plasmodia is known to exist *(9)*. A human reservoir is one who harbours the sexual forms (gametocytes) of the parasite. A patient can be a carrier of several plasmodial species at the same time. Children are more likely to be gametocyte carriers than adults. The child is thus epidemiologically a better reservoir than the adult. Certain conditions must be met before a person can serve as a reservoir: (i) the person must harbour both the sexes of the gametocyte in his blood. If the person harbours only male or female gametocytes, further development cannot take place in the mosquito vector, (ii) the gametocytes must be mature; immature forms do not undergo further development. It may take 2-4 days for the gametocytes to attain maturity after their appearance in the blood, (iii) the gametocytes must be viable, i.e., if the patient receives an antimalarial drug, the gametocytes lose their viability or infectivity to mosquitoes (iv) the gametocytes must be present in sufficient density to infect mosquitoes. The number of gametocytes necessary to infect mosquitoes is not definitely known, but it is thought by some that there must be at least 12 per cubic mm of blood.

(c) PERIOD OF COMMUNICABILITY

Malaria is communicable as long as mature, viable gametocytes exist in the circulating blood in sufficient density to infect vector mosquitoes. In vivax infections, gametocytes appear in blood 4-5 days after the appearance of the asexual parasites; in falciparum infections, they do not appear until 10-12 days after the first appearance of asexual parasites. Gametocytes are the most numerous during the early stages of the infection when their density may exceed 1,000 per cubic mm of blood. They also tend to occur in waves in peripheral blood.

RELAPSES: It is usual for vivax and ovale malaria to relapse more than 3 years after the patient's first attack. Recurrences of falciparum malaria usually disappear within 1-2 years. *P. malariae* has a tendency to cause prolonged low-level, asymptomatic parasitaemia *(11)*. The infection is known to persist for 40 years or more. It is probable that persons harbouring such infections are at least occasionally infective to mosquitoes.

It is now considered more likely that vivax and ovale relapses are derived from original, sporozoite-induced, liver schizonts which have lain latent long before bursting. In *P. falciparum* and *P. malariae* infections latent liver schizonts do not appear to occur. Relapses in these species, most authorities maintain, are due to a chronic blood infection, i.e., erythrocytic schizogony persisting at a low level.

Host factors

The main variables of the human element that have an influence on malaria epidemiology include the following :

(a) AGE : Malaria affects all ages. Newborn infants have considerable resistance to infection with *P. falciparum*. This has been attributed to the high concentration of foetal haemoglobin during the first few months of life, which suppresses the development of *P. falciparum (12)*. (b) SEX : Males are more frequently exposed to the risk of acquiring malaria than females because of the outdoor life they lead.

Further, females in India are usually better clothed than males. (c) RACE : Individuals with AS haemoglobin (sickle-cell trait) have a milder illness with falciparum infection than do those with normal (AA) haemoglobin *(8)*. Persons whose red blood cells are "Duffy negative" (a genetic trait) are resistant to *P. vivax* infection. (d) PREGNANCY : Pregnancy increases the risk of malaria in women. Malaria during pregnancy may cause intrauterine death of the foetus; it may also cause premature labour or abortion. Primigravid women are at greatest risk *(13)*. (e) SOCIO-ECONOMIC DEVELOPMENT : Malaria has demonstrated the relationship between health and socio-economic development. It is generally accepted that malaria has disappeared from most developed countries as a result of socio-economic development *(13)*. (f) HOUSING: Housing plays an important role in the epidemiology of malaria. The ill-ventilated and ill-lighted houses provide ideal indoor resting places for mosquitoes. Malaria is acquired in most instances by mosquito bites within the houses. The site, type of construction, nature of the walls, etc. influence the selection of control measures *(14)*. (g) POPULATION MOBILITY : People migrate for one reason or other from one country to another or from one part of a country to another. Labourers connected with various engineering, irrigation, agricultural and other projects and periodic migration of nomads and wandering tribes are outstanding examples of internal migration. Some of them may import malaria parasites in their blood and reintroduce malaria into areas where malaria has been controlled or eliminated. Imported malaria has become quite a public health problem in Europe, North America, and other temperate parts of the world, owing to the rising tide of air travel, tourism and migration *(10)*. (h) OCCUPATION : Malaria is predominantly a rural disease and is closely related to agriculture practices. (i) HUMAN HABITS : Habits such as sleeping out of doors, nomadism, refusal to accept spraying of houses, replastering of walls after spraying and not using measures of personal protection (e.g. bed nets) influence man-vector contact, and obviously the choice of control measures. (j) IMMUNITY: The epidemic of malaria is influenced by the immune status of the population. Immunity to malaria in humans is acquired only after repeated exposure over several years. Thus in endemic malarious areas a state of collective immunity becomes established slowly, so that infants, young children, migrants and travellers from non-endemic areas suffer most from the disease. Those, however, who survive to the adult age show less evidence of adverse effects to the attenuated infection. Infants born of immune mothers are generally protected during the first 3-5 months by maternal IgG antibody; infants born of semi-immune mothers are only partially protected. Active immunity is species-specific, that is, immunity against one strain does not protect against another. People living in endemic areas exposed continually to malaria develop considerable degree of resistance to clinical disease, but their partial immunity to malaria declines with time after they leave their endemic countries. Semi-immune individuals may harbour malaria parasites without presenting any symptoms of disease. Both humoral and cellular factors play a role in this protection *(1)*.

Environmental factors

India's geographic position and climatic conditions had been, for long, favourable to the transmission of malaria. (a) SEASON : Malaria is a seasonal disease. In most parts of India, the maximum prevalence is from July to November. (b) TEMPERATURE: Temperature affects the life cycle of the malaria parasite. The optimum temperature for the development of the malaria parasite in the insect vector is between 20 deg. to 30 deg.C (68 deg. to 86 deg.F). The parasite ceases to undergo development in the mosquito if the mean temperature is below 16 deg.C (60.8 deg.F). Temperatures higher than 30 deg.C are lethal to the parasite. (c) HUMIDITY: The atmospheric humidity has a direct effect on the length of life of the mosquito, although it has no effect on the parasite. A relative humidity of 60 per cent is considered necessary for mosquitoes to live their normal span of life. When the relative humidity is high, mosquitoes are more active and they feed more voraciously. If the humidity is low, mosquitoes do not live long. (d) RAINFALL : Rain in general provides opportunities for the breeding of mosquitoes and may give rise to epidemics of malaria. Rain increases the atmospheric humidity which is necessary for the survival of mosquitoes. However, heavy rain may have an adverse affect in flushing out the breeding places. Paradoxically in some areas, (e.g., Sri Lanka) severe epidemics of malaria followed years of drought. It was because, the lesser monsoon rains led to the formation of small pools of water in river beds, which served as active breeding places for malaria vectors. The relationship between rainfall (total and its distribution) and mosquito breeding is of fundamental importance *(15)*. (e) ALTITUDE: As a rule, *Anophelines* are not found at altitudes above 2000-2500 metres, due to unfavourable climatic conditions. (f) MAN-MADE MALARIA: Burrow pits, garden pools, irrigation channels and engineering projects like construction of hydroelectric dams, roads, bridges have led to the breeding of mosquitoes and an increase in malaria. Malaria consequent on such human undertakings is called "man-made malaria".

Vector of malaria

Out of about 45 species of anopheline mosquitoes in India, only a few are regarded as the vectors of primary importance. These are: *An. culicifacies*, *An. fluviatilis*, *An. stephensi*, *An. minimus*, *An. philippinensis*, *An. sundaicus*, and *An. maculatus*. The vectors of major importance are *An culicifacies* in rural areas and *An. stephensi* in urban areas.

In the absence of a vaccine, vector control is the only practical approach to malaria control. A knowledge of anopheline biology is essential for understanding the epidemiology of malaria and its prevention. The main factors which determine the vectorial importance of mosquitoes are: (a) DENSITY : To be an effective vector, a species must be present in adequate density in or near human habitations. A sudden increase in density of vectors, may be a cause of epidemic outbreaks. For each vector, there is what is known as "critical density" below which effective transmission cannot be maintained in a community. This level varies with different species. In the case of *An. culicifacies* a high density is required for the propagation of malaria; in the case of *An. fluviatilis* which is very efficient vector, a much lower density would suffice. (b) LIFE SPAN: The key factor in the transmission of malaria is the life span of the vector. The vector mosquito must live for at least 10-12 days after an infective blood meal to become infective. The strategy in malaria eradication is to shorten the life span of mosquitoes to less than 10 days by insecticides. (c) CHOICE OF HOST : Some mosquitoes prefer human blood, some animal blood, and some show great variation in their feeding habits. The percentage of

human blood feeds in the case of *An. culicifacies*, an important vector in India, has been found to vary from 2–80 per cent *(8)*. In contrast, *An. fluviatilis* is a highly anthrophilic species. The anthrophilic species, i.e., those that have a high preference for human blood are better vectors of malaria than zoophilic species. (d) RESTING HABITS : After a blood meal, some mosquitoes rest indoors on the walls for quite sometime. This behaviour pattern is known as "endophily". But there are some species which rest outdoors (exophily). A knowledge of the resting habits (which must be under constant surveillance) is the basis for organizing rational anti-adult measures. In fact, the concept of malaria eradication is based on endophilism (indoor resting habits) of most malarial vectors. (e) BREEDING HABITS : The breeding habits of mosquitoes vary considerably. Some breed in moving water *(An. fluviatilis)*, some in brackish water *(An. sundaicus)* and some in wells, cisterns, fountains and overhead tanks *(An. stephensi)*. A knowledge of the breeding habits is required for conducting anti-larval operations. (f) TIME OF BITING : The majority of Indian mosquitoes bite at night excepting the Aedes mosquitoes. Anophiline mosquitoes have nocturnal feeding habits, between dusk and dawn. (g) VECTORIAL CAPACITY : The term vectorial capacity refers to the combined effect of the density of the vector population, its susceptibility to infection, life span and probability of feeding on man. It is distinct from physiological capacity to transmit infection. (h) RESISTANCE TO INSECTICIDES : A knowledge of the status of vector resistance to insecticides is also necessary. On this depends the choice of insecticides to be used. When an insect vector is resistant to a given insecticide, alternative insecticides have to be used.

Mode of transmission

(a) VECTOR TRANSMISSION: Malaria is transmitted by the bite of certain species of infected, female, anopheline mosquitoes. A single infected vector, during her life time, may infect several persons. The mosquito is not infective unless the sporozoites are present in its salivary glands. (b) DIRECT TRANSMISSION: Malaria may be induced accidentally by hypodermic intramuscular and intravenous injections of blood or plasma, e.g., blood transfusion, malaria in drug addicts *(16, 17)*. Blood transfusion poses a problem because the parasites keep their infective activity for at least 14 days in blood bottles stored at – 4 deg.C *(16)*. Persons who have lived in an endemic area (including those who have been taking antimalarials prophylactically) and anyone who has had malaria should not be accepted as blood donor until 3 years afterwards *(18)*. (c) CONGENITAL MALARIA: Congenital infection of the newborn from an infected mother may also occur, but it is comparatively rare.

Incubation period

This is the length of time between the infective mosquito bite and the first appearance of clinical signs of which fever is most common. This period is usually not less than 10 days.

The duration of the incubation period varies with the species of the parasite, and in natural infections (in mosquito-transmitted malaria) this is 12 (9–14) days for falciparum malaria, 14 (8–17) days for vivax malaria, 28 (18–40) days for quartan malaria and 17 (16–18) days for ovale malaria. With some strains of *P. vivax*, the incubation period may be delayed for as long as 9 months; this may also occur with other species in persons who have been taking suppressive antimalarial drugs *(8)*.

Clinical features

The primary fever is marked by paroxysms which correspond to the development of the parasites in the red blood cells. The peaks of the fever coincide with the release into the blood stream of successive broods of merozites.

The typical attack comprises three distinct stages, i.e., the cold stage, the hot stage and the sweating stage. These are followed by an afebrile period in which the patient feels greately relieved.

COLD STAGE : The onset is with lassitude, headache, nausea and chilly sensation followed in an hour or so by rigors. The temperature rises rapidly to 39–41°C. Headache is often severe and commonly there is vomiting. In early part of this stage, skin feels cold, later it becomes hot. Parasites are usually demonstrable in the blood. The pulse is rapid and may be weak. This stage lasts for 1/4–1 hour.

HOT STAGE : The patient feels burning hot and casts off his clothes. The skin is hot and dry to touch. Headache is intense but nausea commonly diminishes. The pulse is full and respiration rapid. This stage lasts for 2 to 6 hours.

SWEATING STAGE : Fever comes down with profuse sweating. The temperature drops rapidly to normal and skin is cool and moist. The pulse rate becomes slower, patient feels relieved and often falls asleep. This stage lasts for 2–4 hours.

The febrile paroxysms occur with definite intermittent periodicity repeating every third or fourth day depending upon the species of the parasite involved. The classical 3 stages (cold, hot and sweating) may not always be observed due to maturation of generations of parasite at different times. Periods of latency may last several weeks or months *(8, 19)*. The disease has a tendency to relapse and is characterized by enlargement of the spleen and secondary anaemia. Febrile herpes is common in all malarial patients.

In patients with *P. falciparum* infection the primary fever in its first few days is usually irregular or even continuous and then the classical 48 hour periodicity becomes established or the fever may continue to be irregular and the hot and cold stages, so typical of other malarial infections are less clearly separated from one another. In persons with poor immunity the paroxysms are associated with marked prostration. Headache, nausea and vomiting are usually more severe, and there is greater tendency towards the development of delirium, haemolytic jaundice and anaemia. The mortality is much greater than in other forms of malaria.

With *P. vivax* infection, symptoms are same but are usually milder and more regularly divided into "hot" and "cold" stages than in *P. falciparum* infections.

P. ovale infections differ little from that of *P. vivax*. However, they tend to be milder than *P. vivax* and cease after a few paroxysms even if no treatment is given.

Clinically, *P. malariae* attacks resemble those of *P. vivax* but the cycle is of 72 hours instead of 48 hours. The tendency for long-term relapses to occur is marked.

The complications of *P. falciparum* malaria are cerebral malaria, acute renal failure, liver damage, gastro-intestinal symptoms, dehydration, collapse, anaemia, blackwater fever etc. The complications of *P. vivax*, *P. ovale* and *P. malariae* infections are anaemia, splenomegaly, enlargement of liver, herpes, renal complications etc.

Diagnosis

The diagnosis of malaria depends on demonstration of

the parasite in the blood. Suspicion of the diagnosis is aroused by epidemiological and clinical evidence.

1. Microscopy

Two types of blood films are useful in searching for and identification of malaria parasite. The "thin film" and the "thick film". It is recommended that both types of film be prepared on a single microscope glass slide. The thick film is more reliable in searching for parasite, as large volume of blood is examined under each microscope field. When scanty, parasite may be found about 20 times more rapidly in thick slide than in thin slide. The thin slide is more valuable for identifying the species of the parasite present. In it they are seen more clearly.

The advantage of microscopy are : The sensitivity is high. It is possible to detect malarial parasite at low densities. It also helps to quantify the parasite load; It is possible to distinguish the various species of malaria parasite and their different stages.

2. Serological test

The malarial fluorescent antibody test usually becomes positive two weeks or more after primary infection, by which time the infection may have been cured. A positive test is therefore, not necessarily an indication of current infection. The test is of the greatest value in epidemiological studies and in determining whether a person has had malaria in the past *(20)*.

3. Rapid diagnostic test (RDT)

Rapid Diagnostic Tests are based on the detection of circulating parasite antigens with a simple dipstick format. Several types of RDTs are available. Some of them can only detect *P. falciparum* while others can detect other parasites also. The latter kits are expensive and temperature sensitive. RDTs are produced by different companies, so there may be differences in the contents and in the manner in which the test is done. The users manual should always be read properly to avoid false negative results *(21)*.

Measurement of malaria

PRE-ERADICATION ERA

In the pre-eradication era, the magnitude of the malaria problem in a country used to be determined mostly from the reports of the *clinically diagnosed malaria cases*. The classical malariometric measures are spleen rate, average enlarged spleen, parasite rate etc. In a control programme, the case detection machinery is weak. Therefore, the classical malariometric measures may provide the needed information, i.e. the *trend of the disease*.

(a) SPLEEN RATE : It is defined as the percentage of children between 2 and 10 years of age showing enlargement of spleen. Adults are excluded from spleen surveys, because causes other than malaria frequently operate in causing splenic enlargement in them. The spleen rate is widely used for measuring the endemicity of malaria in a community. (b) AVERAGE ENLARGED SPLEEN : This is a further refinement of spleen rate, denoting the average size of the enlarged spleen *(22)*. It is a useful malariometric index. (c) PARASITE RATE : It is defined as the percentage of children between the ages 2 and 10 years showing malaria parasites in their blood films. (d) PARASITE DENSITY INDEX : It indicates the average degree of parasitaemia in a sample of well-defined group of the population. Only the positive slides are included in the denominator *(8)*. (e) INFANT PARASITE RATE : It is defined as the percentage of infants below the age of one year showing malaria parasites in their blood films. It is regarded as the most sensitive index of recent transmission of malaria in a locality. If the infant parasite rate is zero for 3 consecutive years in a locality, it is regarded as absence of malaria transmission even though, the Anopheline vectors responsible for previous transmission may remain. (f) PROPORTIONAL CASE RATE : Since the morbidity rate is difficult to determine, except in conditions when the diagnosis and reporting of each case is carried to perfection, proportional case rate is used *(8)*. It is defined as the number of cases diagnosed as clinical malaria for every 100 patients attending the hospitals and dispensaries. This is a crude index because the cases are not related to their time/space distribution.

ERADICATION ERA (current incidence levels)

During the eradication era, the *microscopic diagnosis* of malaria cases became the main method of diagnosis. The parameters used for the measurement of malaria were mostly parasitological in nature; the commonly used parameters were API, ABER, SPR and SFR. The same parameters are being used at the present time. These parameters are unlikely to reveal the true epidemiological picture, unless the case detection machinery is fully supervised and very efficient. The following parameters are in use at present :

a. Annual parasite incidence (API)
b. Annual blood examination rate (ABER)
c. Annual falciparum incidence (AFI)
d. Slide positivity rate (SPR)
e. Slide falciparum rate (SFR).

a. Annual parasite incidence (API)

API is given by the formula :

$$\text{API} = \frac{\text{Confirmed cases during one year}}{\text{Population under surveillance}} \times 1000$$

API is a sophisticated measure of malaria incidence in a community. It is based on intensive active and passive surveillance, and cases are confirmed by blood examination. Areas with API ≥ 2 per 1000 population per year have been classified as high risk areas in India, and thereby eligible for vector control.

b. Annual blood examination rate (ABER)

ABER is given by the formula :

$$\text{ABER} = \frac{\text{Number of slides examined}}{\text{Population}} \times 100$$

ABER is an index of operational efficiency. The annual parasite incidence (API) depends upon the annual blood collection and examination rates. A sufficient number of blood slides must be systematically obtained and examined for malaria parasite to work out accurately annual parasite incidence (API).

At present, about 100 million fever cases are screened every year in India. The aim is to screen 10 per cent of the population even though the disease transmission is expected to reduce. The surveillance system has not undergone any change *(5)*.

c. *Annual falciparum incidence*

Since the emergence of *P. falciparum* problem in India, data are collected separately for total malaria cases and *P. falciparum* cases.

d. *Others*

The slide positivity rate and slide falciparum rate are useful parameters. They provide information on the trend of malaria transmission.

Slide positivity rate : slide positivity rate is the percentage of slides found positive for malarial parasite, irrespective of the type of species.

Slide falciparum rate : It is the percentage of slides positive for *P. falciparum* parasite.

VECTOR INDICES

A malaria survey is not complete unless it includes investigations relating to the insect vector. Some of the important vector indices are: (a) HUMAN BLOOD INDEX : It is the proportion of freshly-fed female Anopheline mosquitoes whose stomach contains human blood. It indicates the degree of anthrophilism. (b) SPOROZOITE RATE : It is the percentage of female anophelines with sporozoites in their salivary glands. (c) MOSQUITO DENSITY : It is usually expressed as the number of mosquitoes per man-hour-catch. (d) MAN BITING RATE (Biting density) : It is defined as the average incidence of anopheline bites per day per person. It is determined by standardized vector catches on human bait (e) INOCULATION RATE : The man-biting rate multiplied by the infective sporozoite rate is called the inoculation rate. All these rates are employed in the quantitative assessment of malaria and in building up a composite epidemiological picture of malaria.

APPROACHES AND STRATEGIES OF MALARIA CONTROL

As the concept of control replaces that of eradication in many national programmes, a reordering of priorities in the selection of control methods must occur. These priorities and approaches must be based on epidemiological considerations, adverse effects on health, economy, technical feasibility, functional resources, human resources and community participation. Recently WHO stressed a number of points relevant to future strategy of malaria control. The main emphasis is on the need to base it on an epidemiological approach. These aspects are discussed below.

APPROACHES TO MALARIA CONTROL

Strategic Action Plan for malaria control in India, 2007-2012, and more recently 2012-2017 were developed by Directorate of National Vector Borne Disease Control Programme.

The strategies for prevention and control of malaria and its transmission are *(5)* :

(a) Surveillance and case management
  (1) Case detection (passive and active)
  (2) Early diagnosis and complete treatment
  (3) Sentinel surveillance.

(b) Integrated vector management
  (1) Indoor residual spray (IRS)
  (2) Insecticide treated bed-nets (ITNs) and long lasting insecticidal nets((LLINs)
  (3) Antilarval measures including source reduction.

(c) Epidemic preparedness and early response

(d) Supportive interventions
  (1) Capacity building
  (2) Behavioural change communication
  (3) Intersectoral collaboration
  (4) Monitoring and Evaluation
  (5) Operational research and applied field research.

Early diagnosis and treatment of malaria aims at :

(1) Complete cure;
(2) Prevention of progression of uncomplicated malaria to severe disease;
(3) Prevention of deaths;
(4) Interruption of transmission; and
(5) Minimizing risk of selection and spread of drug resistant malaria parasite.

GUIDELINES FOR DIAGNOSIS AND TREATMENT OF MALARIA IN INDIA-2013 *(23)*

According to the revised drug policy 2013, there is no scope of presumptive treatment in malaria control. The recommended guidelines are as follows :

Treatment of Uncomplicated Malaria

All fever cases diagnosed as malaria by microscopy or RDT should promptly be given effective treatment.

TREATMENT OF P. VIVAX CASES

Positive *P. vivax* cases should be treated with chloroquine in full therapeutic dose of 25 mg/kg divided over three days. Vivax malaria relapses due to the presence of hypnozoites in the liver. The relapse rate in vivax malaria in India is around 30%. For its prevention, primaquine may be given at a dose of 0.25 mg/kg daily for 14 days under supervision. Primaquine is contraindicated in G6PD deficient patients, infants and pregnant women. Caution should be exercised before administering primaquine in areas known to have high prevalence of G6PD deficiency. Primaquine can lead to haemolysis in G6PD deficiency. Patient should be advised to stop primaquine immediately if he develops symptoms like dark coloured urine, yellow conjunctiva, bluish discolouration of lips, abdominal pain, nausea, vomiting etc. and should report to the doctor immediately.

TREATMENT OF P. FALCIPARUM CASES

Artemisinin Combination Therapy (ACT) (Artesunate 3 days + sulphadoxine-pyrimethamine 1 day) should be given to all confirmed *P. falciparum* cases found positive by microscopy or RDT. This is to be accompanied by single dose of primaquine (0.75 mg/kg body weight) on Day 2.

However, considering the reports of resistance to SP drug in North Eastern states, the Technical Advisory Committee has recommended to use the coformulated tablet of Artemether (20 mg) + Lumefantrine (120 mg) as per age-specific dose schedule for the treatment of *Pf* cases in North Eastern states. This drug is not recommended during the first trimester of pregnancy and for children weighing < 5 kg. Production and sale of Artemisinin monotherapy has been banned in India, as it can lead to development of parasite resistance to the drug.

TREATMENT OF MALARIA IN PREGNANCY

ACT should be given for treatment of *P. falciparum*

malaria in second and third trimesters of pregnancy, while quinine is recommended in the first trimester. *P. vivax* malaria can be treated with chloroquine. Primaquine is contraindicated in pregnant woman.

TREATMENT OF MIXED INFECTIONS

Mixed infections with *P. falciparum* should be treated as falciparum malaria.

Resistance should be suspected if inspite of full treatment with no history of vomiting, diarrhoea, patient does not respond within 72 hours, clinically and parasitologically. Such cases not responding to ACT, should be treated with oral quinine with tetracycline/doxicycline. These instances should be reported to concerned District Malaria/State Malaria Officer/ROHFW for initiation of therapeutic efficacy studies.

Diagnosis and treatment of malaria *(23)*

All fever cases diagnosed as malaria by either RDT or microscopy should be promptly given effective treatment. The medicines chosen will depend upon whether the patient has *vivax* malaria or *falciparum* malaria. The flow charts in different settings for diagnosis and drug selection for the treatment of malaria are shown in Fig. 2, 3 and 4.

A. Where microscopy result is available within 24 hours

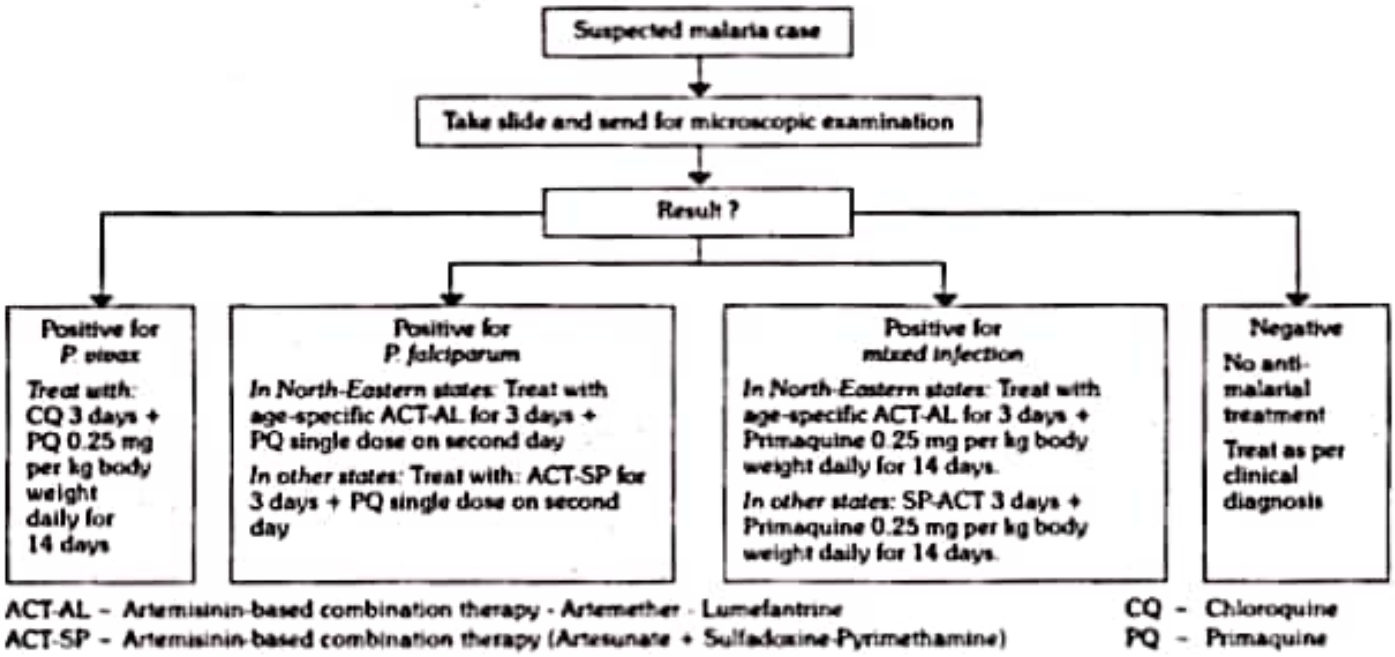
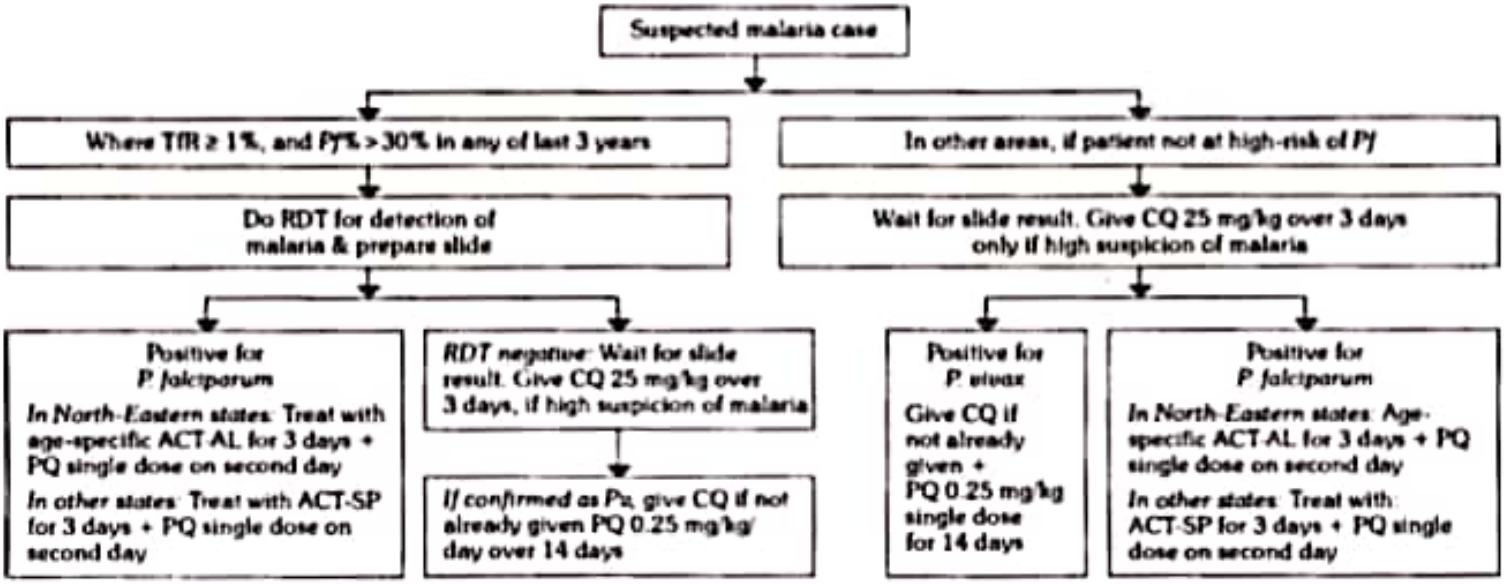


FIG. 2

B. Where microscopy result is not available within 24 hours and monovalent RDT is used

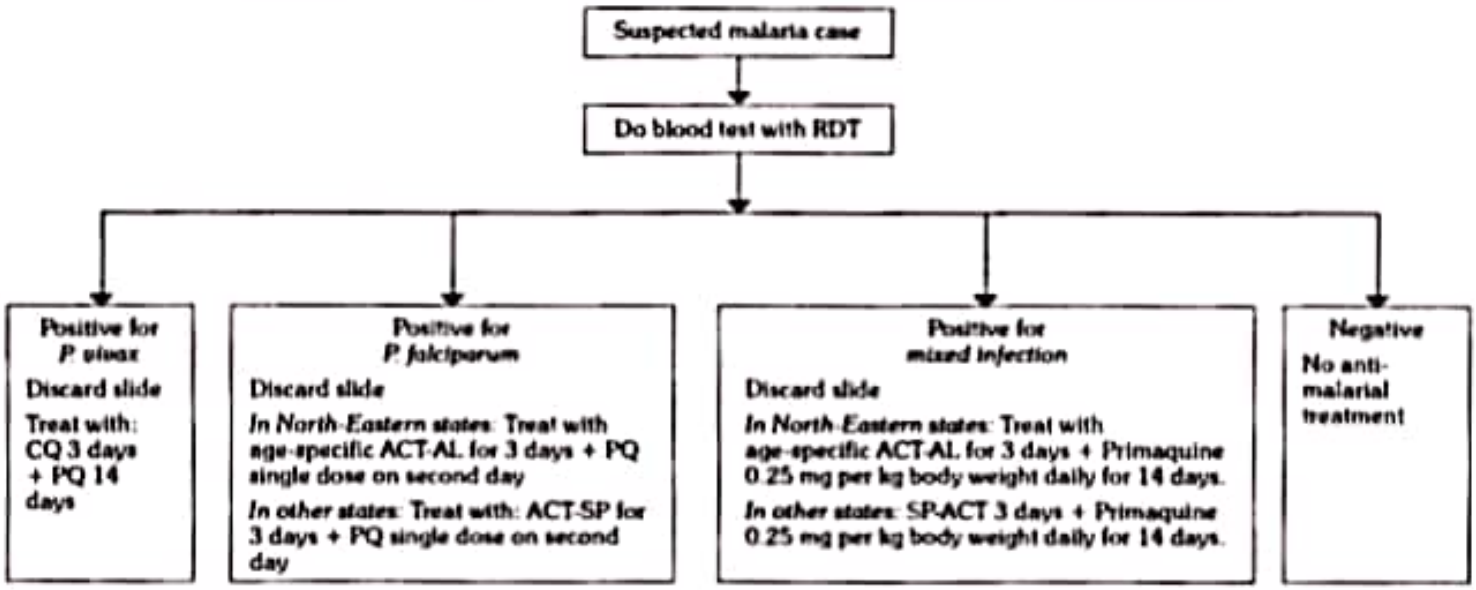


TfR = Test falciparum rate

Note : If a patient has severe symptoms at any stage, then immediately refer to a nearest PHC or other health facility with indoor patient management or a registered medical doctor.

FIG. 3

C. *Where microscopy result is not available within 24 hours and bivalent RDT is used*



Note : (a) If a patient has severe symptoms at any stage, then immediately refer to a nearest PHC or other health facility with indoor patient management or a registered medical doctor.

(b) PQ is contra-indicated in pregnancy and in children under 1 year (Infant).

FIG. 4

Treatment of *vivax* malaria *(23)*

Diagnosis of vivax malaria may be made by the used of RDT (Bivalent) or microscopic examination of the blood smear. On confirmation, following treatment is to be given :

Drug schedule for treatment of P. vivax malaria:

1. *Chloroquine*: 25 mg/kg body weight divided over three days i.e.

   10 mg/kg on day 1,

   10 mg/kg on day 2 and

   5 mg/kg on day 3.

2. *Primaquine*: 0.25 mg/kg body weight daily for 14 days.

   Primaquine is contraindicated in infants, pregnant women and individuals with G6PD deficiency.

   14 day regimen of Primaquine should be given under supervision.

Dosage chart for treatment of *vivax* malaria

Age	Day 1		Day 2		Day 3		Day 4 to 14
	CQ (150 mg base)	PQ (2.5 mg)	CQ (150 mg base)	PQ (2.5 mg)	CQ (150 mg base)	PQ (2.5 mg)	PQ (2.5 mg)
Less than 1 yr	½	0	½	0	¼	0	0
1-4 years	1	1	1	1	½	1	1
5-8 years	2	2	2	2	1	2	2
9-14 years	3	4	3	4	1½	4	4
15 yrs or more*	4	6	4	6	2	6	6
Pregnancy	4	0	4	0	2	0	0

Note : CQ 250 mg tablet is having 150 mg base

Treatment of *falciparum* malaria *(23)*

Diagnosis of falciparum malaria may be made by the use of RDT (monovalent or bivalent) or microscopic examination of the blood smear. It is imperative to start the treatment for falciparum malaria immediately on diagnosis. The treatment for falciparum malaria is as follows:

In other states (other than North-Eastern states):

1. Artemisinin based combination therapy (ACT-SP)*

   Artesunate (AS), available as 50 mg tablets are given for three days, and Sulfadoxine-Pyrimethamine (S-P) tablets, containing 500 mg Sulfadoxine and 25 mg pyrimethamine are given for one day, as shown in the dosage chart below.

   All tablets for a day should be taken together, swallowed with water.

   In addition, Primaquine (PQ large) tablets should be given on the second day.

Dose schedule for treatment of uncomplicated P. falciparum cases:

1. Artemisinin based combination therapy (ACT-SP) *

   Artesunate 4 mg/kg body weight daily for 3 days, plus

   Sulfadoxine (25 mg/kg body weight) – Pyrimethamine (1.25 mg/kg body weight) on first day.

   * ACT is not to be given in 1st trimester of pregnancy.

2. Primaquine * : 0.75 mg/kg body weight on day 2.

   With the introduction of different coloured blister packs for different age groups, treatment by the field level staff has been made easy. The colour code for different age groups for packing of tablet ACT+SP has been given as follows :

Dosage chart for treatment of *falciparum* malaria with ACT-SP

Age group (Years)	1st day		2nd day		3rd day
	AS	SP	AS	PQ	AS
0-1* Pink blister	1 (25 mg)	1 (250 + 12.5 mg)	1 (25 mg)	Nil	1 25 (mg)
1-4 Yellow blister	1 (50 mg)	1 (500 + 25 mg each)	1 (50 mg)	1 (7.5 mg base)	1 (50 mg)
5-8 Green blister	1 (100 mg)	1 (750 + 37.5 mg each)	1 (100 mg)	2 (7.5 mg base each)	1 (100 mg)
9-14 Red blister	1 (150 mg)	2 (500 + 25 mg each)	1 (150 mg)	4 (7.5 mg base each)	1 (150 mg)
15 & above White blister	1 (200 mg)	2 (750 + 37.5 mg each)	1 (200 mg)	6 (7.5 mg base each)	1 (200 mg)

* SP is not to be prescribed for children <5 months of age and should be treated with alternate ACT

* ACT-AL is not to be prescribed for children weighing less than 5 kg.

In North-Eastern states (NE states):

1. ACT-AL co-formulated tablet of Artemether (20 mg) – Lumefantrine (120 mg)

   (Not recommended during the first trimester of pregnancy and for children weighing <5 kg)

Recommended regimen by weight and age group
The packing size for different age groups based on Kg body weight.

Co-formulated tablet ACT-AL	5–14 kg (>5 months to <3 years)	15–24 kg (>3 to 8 years)	25–34 kg (>9 to 14 years)	>34 kg (>14 years)
Total dose of ACT-AL	20 mg/ 120 mg twice daily for 3 days	40 mg/ 240 mg twice daily for 3 days	60 mg/ 360 mg twice daily for 3 days	80 mg/ 480 mg twice daily for 3 days
	Pack size			
No. of tablets in the packing	6	12	18	24
Give	1 tablet twice daily for 3 days	2 tablets twice daily for 3 days	3 tablets twice daily for 3 days	4 tablets twice daily for 3 days
Colour of the pack	Yellow	Green	Red	White

2. Primaquine * : 0.75 mg/kg body weight on day 2

Treatment of uncomplicated P. falciparum cases in pregnancy:

1st trimester : Quinine salt 10 mg/kg 3 times daily for 7 days.

Quinine may induce hypoglycaemia; pregnant women should not start taking quinine on an empty stomach and should eat regularly, while on quinine treatment.

2nd and 3rd trimester : Area-specific ACT as per dosage schedule given above i.e. ACT-AL in North-Eastern states, ACT-SP in other states.

Primaquine (PQ) prevents transmission of falciparum malaria to others by its ability to kill gametocytes. PQ tablets should be taken after a meal; not on an empty stomach. Children less than the age of one year and pregnant women should not be given primaquine. As pregnant women having falciparum malaria require different medicines, they should be directed to go to the nearest PHC or hospital immediately, without delay.

Treatment of mixed infections (*P. vivax* + *P. falciparum*) cases *(23)*

All mixed infections should be treated with full course of ACT and Primaquine 0.25 mg per kg body weight daily for 14 days.

In North-Eastern states: Treat with: Age-specific ACT-AL for 3 days + Primaquine 0.25 mg per kg body weight daily for 14 days.

In other states: ACT-SP 3 days + Primaquine 0.25 mg per kg body weight daily for 14 days.

Dosage chart for treatment of mixed (*vivax* and *falciparum*) malaria with ACT-SP

Age	Day 1			Day 2		Day 3		Day 4-14
	AS tablet (50 mg)	SP tablet	PQ (2.5 mg)	AS tablet (50 mg)	PQ (2.5 mg)	AS tablet (50 mg)	PQ (2.5 mg)	PQ (2.5 mg)
Less than 1 year	½	½	0	½	0	½	0	0
1–4 years	1	1	1	1	1	1	1	1
5–8 years	2	1½	2	2	2	2	2	2
9–14 years	3	2	4	3	4	3	4	4
15 years or more	4	3	6	4	6	4	6	6

Treatment of *P. ovale* and *P. malariae*

In India these species are very rarely found in few places. *P. ovale* should be treated as *P. vivax* and *P. malariae* should be treated as *P. falciparum*.

General recommendations for the management of uncomplicated malaria

1. Avoid starting treatment on an empty stomach. The first dose should be given under observation. Dose should be repeated if vomiting occurs within 15 minutes by opening a new blister pack (discard what remains of old pack). If the patient vomits the first dose again, it is considered a severe case of malaria and refer the patient immediately to the nearest Block PHC/CHC/Hospital. Special precaution should be taken in case of a child under-5 years of age, and in pregnant woman.
2. Explain to the patient or caretaker that : (a) if the treatment is not completed as prescribed, the disease may manifest again with more serious features and more difficult to treat, (b) to come back immediately, if there is no improvement after 24 hours, if the situation gets worse or the fever comes back, and (c) that regular use of a mosquito net (preferably insecticide treated net) is the best way to prevent malaria.
3. Patient should also be examined for concomitant illness.

Resistance to anti-malarial drugs

Resistance can be defined as either the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the patient.

Drug resistance is a complex phenomenon, where, by genetic mutation, a parasite acquires the ability to resist, partly or fully, the effects of one or more anti-malarial drugs. When the resistant parasites are exposed to the drug, they multiply selectively. If parasites are resistant to the drug being used, the patient may not respond to treatment. One of the commonest reasons for the development of drug resistance is that the parasites are exposed to insufficient amount of the drug due to low prescription dosage, lesser amount of drug dispensed, incomplete treatment taken by the patient, drug vomited out or low absorption of drug due to any other reason e.g., diarrhoea, poorly stored drug, poor quality drug when supplied or expiry date medicine. In such cases, most of the sensitive parasites are killed by even these small doses, but resistant parasites survive, multiply and spread to other people by mosquitoes. The new patient then gets infection from the resistant malaria parasites and does not respond to the drug at all, or responds only partly. Meanwhile, the earlier patient may appear cured because most of the parasites were killed by the drug, and the symptoms abated.

It should be kept in mind that the patient might have had a fresh reinfection, or in the case of *vivax* malaria, there might have been a relapse of malaria *(23)*.

Treatment failure *(24)*

After treatment patient is considered cured if he/she does not have fever or parasitaemia till day 28th. Some patients may not respond to treatment which may be due to drug resistance or treatment failure, specially in falciparum malaria. If patient does not respond and presents with following, he/she should be given alternative treatment.

Early treatment failure (ETF) : Development of danger signs or severe malaria on Day 1, 2 or 3, in the presence of parasitaemia, parasitaemia on Day 2 higher than on Day 0, irrespective of axillary temperature, parasitaemia on Day 3 with axillary temperature >37.5°C; and parasitaemia on Day 3, > 25% of count on Day 0.

Late clinical failure (LCF) : Development of danger signs or severe malaria in the presence of parasitaemia on any day between Day 4 and Day 28 in patients who did not previously meet any of the criteria of early treatment failure; and presence of parasitaemia on any day between Day 4 and Day 28 with axillary temperature >37.5°C in patients who did not previously meet any of the criteria of early treatment failure.

Late parasitological failure (LPF) : Presence of parasitaemia on any day between Day 7 and Day 28 with axillary temperature <37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

Such cases of falciparum malaria should be given alternative ACT or quinine with Doxycycline. Doxycycline is contraindicated in pregnancy, lactation and in children upto 8 years. Treatment failure with chloroquine in *P. vivax* malaria is rare in India.

Treatment of severe malaria

CLINICAL FEATURES *(23)*

Severe manifestations can develop in *P. falciparum* infection over a span of time as short as 12-24 hours and may lead to death, if not treated promptly and adequately. Severe malaria is characterized by one or more of the following features:

(1) Impaired consciousness/coma
(2) Repeatd generalized convulsions
(3) Renal failure (Serum Creatinine >3 mg/dl)
(4) Jaundice (Serum Bilirubin >3 mg/dl)
(5) Severe anaemia (Hb <5 g/dl)
(6) Pulmonary oedema/acute respiratory distress syndrome
(7) Hypoglycaemia (Plasma glucose <40 mg/dl)
(8) Metabolic acidosis
(9) Circulatory collapse/shock (Systolic BP<80 mm Hg, < 50 mm Hg in children)
(10) Abnormal bleeding and disseminated intravascular coagulation.
(11) Haemoglobinuria
(12) Hyperthermia (Temperature >106°F or 42°C)
(13) Hyperparasitaemia (<5% parasitized RBCs in low endemic and >10% in hyperendemic areas)

Foetal and maternal complications are more common in pregnancy with severe malaria; therefore, they need prompt attention.

Microscopic evidence may be negative for asexual parasites in patients with severe infections due to sequestration and partial treatment. Efforts should be made to confirm these cases by RDT or repeat microscopy. However, if the symptoms clearly point to severe malaria and there is no alternative explanation, such a case should be treated accordingly.

Criteria for immediate referral are as follows: (a) Persistence of fever after 24 hours of initial treatment; (b) Continuous vomiting and inability to retain oral drug; (c) Headache continues to increase; (d) Severe dehydration (dry, parched skin, sunken eyes etc.); (e) Too weak to walk in the abscence of any other obvious reason; (f) Change in sensorium e.g. confusion, drowsiness, blurring of vision, photophobia, disorientation; (g) Convulsion or muscle twitchings; (h) Bleeding and clotting disorder; (i) Suspicion of severe anaemia; (j) Jaundice; and (k) Hypothermia *(23)*.

Treatment of severe malaria cases *(23)*

Severe malaria is an emergency and treatment should be given as per severity and associated complications which can be best decided by the treating physicians. Before admitting or referring patients, the attending doctor or health worker, whoever is able to do it, should do RDT and take blood smear, give a parenteral dose of artemisinin derivative or quinine in suspected cerebral malaria cases and send case sheet, details of treatment history and blood slide with patient. Parenteral artemisinin derivatives or quinine should be used irrespective of chloroquine resistance status of the area with one of the following options:

Chemotherapy of severe and complicated malaria

Initial parenteral treatment for at least 48 hours: *Choose one of following four options*	Follow-up treatment, when patient can take oral medication following parenteral treatment
Quinine : 20 mg quinine salt/kg body weight on admission (IV infusion or divided IM injection) followed by maintenance dose of 10 mg/kg 8 hourly; infusion rate should not exceed 5 mg/kg per hour. Loading dose of 20 mg/kg should not be given, if the patient has already received quinine.	*Quinine* 10 mg/kg three times a day with: doxycycline 100 mg once a day OR clindamycin in pregnant women and children under 8 years of age. – to complete 7 days of treatment.
Artesunate: 2.4 mg/kg IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day. OR *Artemether*: 3.2 mg/kg bw IM given on admission then 1.6 mg/kg per day. OR *Arteether*: 150 mg daily IM for 3 days in adults only (not recommended for children).	Full oral course of area-specific ACT. *In North-Eastern states*: Age-specific ACT-AL for 3 days + PQ single dose on second day *In other states*: Treat with: ACT-SP for 3 days + PQ single dose on second day

Note : The parenteral treatment in severe malaria cases should be given for minimum of 24 hours once started (irrespective of the patient's ability to tolerate oral medication earlier than 24 hours).

After parenteral artemisinin therapy, patients will receive a full course of area-specific oral ACT for 3 days. Those patients who received parenteral Quinine therapy should receive oral Quinine 10 mg/kg body weight three times a day for 7 days (including the days when parenteral Quinine was administered) plus Doxycycline 3 mg/kg body weight once a day, or Clindamycin 10 mg/kg body weight 12-hourly for 7 days (Doxycycline is contraindicated in pregnant women and children under 8 years of age) or area-specific ACT as described.

Note :

- Pregnant women with severe malaria in any trimester can be treated with artemisinin derivatives, which, in contrast to quinine, do not risk aggravating hypoglycaemia.
- The parenteral treatment should be given for minimum of 24 hours.
- Once the patient can take oral therapy; give:
- Quinine 10 mg/kg three times a day with doxycycline 100 mg once a day or clindamycin in pregnant women and children under 8 years of age, to complete 7 days of treatment, in patients started on parenteral quinine.
- Full course of ACT to patients started on artemisinin derivatives.
- Use of mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications associated with it.

Some don'ts in severe malaria case management

Do not use corticosteroids, do not give intravenous mannitol, do not use heparin as anticoagulant, do not administer adrenaline or do not overhydrate.

Toxic hazards of drugs

Chloroquine has few side-effects. Nausea, vomiting, blurring of vision and headaches may occur, but they are mild and transient. Cases of retinal damage have been reported but only in persons exposed to large cumulative doses over many years. It is important to remember that chloroquine should not be given on empty stomach. Despite reports of teratogenicity in experimental animals, most authorities accept that pyrimethamine can safely be taken alone during pregnancy *(25)*. The teratogenic effect of pyrimethamine in man is not proved. In regard to primaquine, although in recommended doses, no serious toxic manifestations have been encountered so far in India. It is useful to bear in mind the likely toxic symptoms, which may be of three types : *(a) Plasmocid types* : this is a rare toxic manifestation involving the CNS. *(b) Gastrointestinal* : cramps, nausea and vomiting. *(c) Cardiovascular* : This is probably the most serious toxic manifestation which is to be carefully observed during the administration of the drug. Even the first dose may bring about the warning sign of cyanosis. The surveillance worker/MPW must carefully check for all possible toxic symptoms before he administers the daily dose of primaquine. In the case of appearance of any of the toxic symptoms discussed above, primaquine treatment should be stopped immediately *(26)*.

Chemoprophylaxis

Chemoprophylaxis against malaria has, with the development of drug resistance, become unreliable. Experts disagree on whether well-conducted prophylaxis gives an additional benefit if effective treatment is readily available. However, experts feel that it can play a useful role in reducing the risk of fatal disease *(27)*.

Chemoprophylaxis is recommended for travellers from non-endemic areas and, as a short term measure for soldiers, police and labour forces serving in highly endemic areas. Chemoprophylaxis should be complemented by personal protection where feasible and by other methods of vector control *(27)*.

The recommendations for short-term chemoprophylaxis (less than 6 weeks) are as follows *(27)* :

(1) Dosing schedules for the children should be based on body weight.

(2) Antimalarials that have to be taken daily (e.g. Doxycycline) should be started the day before arrival in the risk area.

(3) Weekly chloroquine should be started 1 week before arrival.

(4) Weekly mefloquine should preferably be started 2–3 weeks before departure, to achieve higher pre-travel blood level and to allow side-effects to be detected before travel so that possible alternative can be considered.

(5) All prophylactic drugs should be taken with unfailing regularity for the duration of the stay in the malaria risk area, and should be continued for 4 weeks after the last possible exposure to infection, since parasites may still emerge from the liver during this period.

The recommendations for the long-term chemoprophylaxis (more than 6 weeks) are as follows:

(1) The risk of serious side-effects associated with long-term prohylactic use of chloroquine and proguanil is low. However, anyone who has taken 300 mg of chloroquine weekly for over five years and requires further prophylaxis should be screened twice-yearly for early retinal changes. If daily dose of 100 mg chloroquine have been taken, screening should start after three years *(27)*.

(2) Data indicate no increased risk of serious side-effects with long-term use of mefloquine if the drug is tolerated in the short-term, as mefloquine does not accumulate during long-term intake.

(3) Available data on long-term chemoprophylaxis with doxycycline is limited.

Mefloquine is contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions.

Chemoprophylaxis is still desirable for pregnant women living in areas where transmission is very intense and leads to parasitaemias, causing low birth weight and anaemia, or to a high risk of life-threatening malaria attacks. However, the choice of safe drugs is becoming increasingly narrow, and it may be necessary to replace chemoprophylaxis by prompt treatment of clinical episodes or periodic treatments during pregnancy. While the choice of strategy should be guided by the national malaria control policy, its implementation should normally be part of antenatal care *(28)*.

The recommended regimens for chemoprophylaxis are as given in Table 2.

ACTIVE INTERVENTION MEASURES

Neither chemotherapy nor chemoprophylaxis will be able to reduce significantly the malaria prevalence or transmission. It can be obtained only when proper anti-mosquito measures are introduced.

TABLE 2

Drug regimens for prophylaxis of malaria

Drugs		Usual amount per tablet or capsule	Adult dose for prophylaxis
Generic name	Common trade names		
Chloroquine[a]	Aralen Avlochlor Nivaquine Resochin	100 or 150 mg (base)	300 mg (base) = 3 tablets of 100 mg or 2 tablets of 150 mg once a week, on the same day each week OR 100 mg (base) = 1 tablet of 100 mg daily for six days per week
Proguanil[b]	Paludrine	100 mg	200 mg = 2 tablets once a day
Mefloquine[c]	Lariam Eloquin Mephaquin	250 mg	250 mg = 1 tablet once a week, on the same day each week
Doxycycline[d]	Vibramycin	100 mg	100 mg = 1 capsule once a day

a. Also available as suspension.
b. Recommended only in association with chloroquine.
c. The use of the higher treatment dose regimen is recommended for infections acquired in areas on the Thailand/Cambodia and Thailand / Myanmar borders only.
d. There is relatively little experience with this drug, and knowledge of its efficacy and toxicity is limited.

Source : *(27)*

1. STRATIFICATION OF THE PROBLEM

Malaria is a complex disease, and its distribution and intensity vary from place to place. Stratification of the problem has become an essential feature for the planning and development of a sound control strategy to maximize the utilization of available resources. It can also provide guidelines as to which strategy could be most suited and economical under the existing conditions. For details please refer to page 416 chapter 7.

2. VECTOR CONTROL STRATEGIES

Vector control is still one of the primary weapons to control malaria in endemic areas. The methods used are as shown in Table 3.

TABLE 3

Malaria vector control measures

Action	For individual and family protection	For community protection
Reduction of human-mosquito contact	Insecticide-treated nets, repellents, protective clothing, screening of houses	Insecticide-treated nets zooprophylaxis
Destruction of adult mosquitoes		Insecticide-treated nets, indoor residual spraying, space spraying, ultra low-volume sprays
Destruction of mosquito larvae	Peri-domestic sanitation	Larviciding of water surfaces, intermittent irrigation, sluicing, biological control
Source reduction	Small-scale drainage	Environmental sanitation, water management, drainage
Social participation	Motivation for personal and family protection	Health education, community participation

Source : *(29)*

(a) Anti-adult measures

(i) Residual spraying : The discovery of DDT in 1940s and followed by other insecticides revolutionized malaria control. The spraying of the indoor surfaces of houses with residual insecticides (e.g., DDT, malathion, fenitrothion) is still the most effective measure to kill the adult mosquito. It has been observed that discontinuation of spraying has very often led to the resurgence of malaria. This implies that spraying once applied may need to be continued for an indefinite period. If indoor spraying is to have any effect, then exhaustive coverage is needed. Indoor house spraying reduces the longevity of the vector.

Malathion and fenitrothion are organophosphate insecticides which are being used with increasing frequency for malaria control following the development of vector resistance to DDT *(30)*.

(ii) Space application : This is a major anti-epidemic measure in mosquito-borne diseases. It involves the application of pesticides in the form of fog or mist using special equipment. The ultra-low-volume method of pesticide dispersion by air or by ground equipment has proved to be effective and economical. Outdoor space sprays reduce vector population quickly.

(iii) Individual protection : Man-vector contact can be reduced by other preventive measures such as the use of repellents, protective clothing, bed-nets (preferably impregnated with safe, long-acting repellent insecticides), mosquito coils, screening of houses etc. The methods of personal protection are of great value when properly employed. However, they have rarely been used on a large scale because of cost.

(b) Anti-larval measures

(i) Larvicides : During the first half of the 20th century, anti-larval measures such as oiling the collections of standing water or dusting them with paris green effectively controlled malaria (but the measures were eclipsed at the end of World War II). With the increase in insecticide resistance, the older methods of mosquito control have now become promising. Some modern larvicides such as temephos which confer long effect with low toxicity are more widely used. However larviciding must be repeated at frequent intervals and for this reason it is a comparatively costly operation.

(ii) Source reduction : Techniques to reduce mosquito breeding sites (often called source reduction) which include drainage or filling, deepening or flushing, management of water level, changing the salt content of water and intermittent irrigation are among the classical methods of malaria control to which attention is being paid again *(31)*. Whenever practicable, measures for the improvement of the environment by the permanent reduction of sources should be instituted.

(iii) Integrated control : In order to reduce too much dependance on residual insecticides, increasing emphasis is being put on "integrated" vector control methodology which includes bioenvironmental and personal protection measure *(32)*. This approach is important because there is no single and simple method that would ensure control of transmission.

By mid 1995 all malaria endemic countries in the region had adopted the revised malaria control strategy to reduce morbidity and mortality and to reduce its area of distribution, particularly of multidrug resistant malaria. The use of stratification approach by the majority of anti-malaria programmes in the Region has led to more cost-effective interventions. Vector resistance to insecticides has necessitated the use of more expensive pyrethroid, thereby limiting the coverage. Malaria control added impetus as **Roll Back Malaria** initiative was launched by WHO, UNICEF, UNDP and the World Bank in 1998.

THE GLOBAL POLICY FOR DIAGNOSIS AND TREATMENT OF MALARIA, INCLUDING PREVENTIVE TREATMENT *(33)*

The government of every country affected by malaria has a national malaria control policy covering prevention and case-management.

The objectives of an antimalarial treatment policy are to : ensure rapid cure of the infection; reduce morbidity and mortality, including malaria-related anaemia; prevent the progression of uncomplicated malaria into severe and potentially fatal disease, reduce the impact of malaria infection on the fetus during pregnancy; reduce the reservoir of infection; prevent the emergence and spread of drug resistance; and prevent malaria in travellers.

The launch of Roll Back Back Malaria (RBM) in 1998, the United Nations Millenium Declaration in 2000, the Abuja Declaration by African Heads of State in 2000 (part of the African Summit on Roll Back Malaria), the World Health Assembly in 2005, and the RBM global strategic plan 2005–2015 have all contributed to the establishment of goals, indicators and targets for malaria control.

With the publication in 2005 of the **Roll Back Malaria global strategic plan** for 2005–2015, WHO and RBM set targets to be achieved by the year 2010 and 2015. The goals established by World Health Assembly and the Roll Back Malaria partnership is to reduce the number of malaria cases and deaths recorded in 2000 by 50 per cent or more by the end of 2010 and by 75 per cent or more by 2015. In September 2008, RBM launched the Global Malaria Action Plan that defines the steps required to accelerate achievement of the partnership's 2010 and 2015 targets for malaria control and elimination *(34)*.

Malaria vaccines

Vaccination against malaria is a burning issue today. Over the past decades, there has been significant progress in malaria vaccine development, yet many valid candidate vaccines have been slow to enter clinical trial and an effective vaccine is thought to be still 10 years away. Several vaccine candidates are now being tested in Africa, Asia and the United States.

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