Malaria

CONTENTS

1. Aetiology ................................................................. 4
2. Pathophysiology ............................................................. 7
3. Diagnosis of malaria infection ........................................... 8
4. Treatment ........................................................................ 17
Malaria

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Summary

Malaria is a life-threatening disease caused by protozoan parasites transmitted to people through the vector, the infected mosquitoes. About half the world's population (3.3 billion) lives in areas having some risk of malaria transmission and one fifth (1.2 billion) in areas with a high risk of malaria. The largest populations at risk of malaria are found in the WHO South-East Asia and Western Pacific regions. Africa has the largest number of people living in areas with a high risk of malaria, followed by the South-East Asia Region. India is a major contributor to global malaria incidence. Of the 2.5 million reported cases in the South East Asia, India alone contributes about 70% of the total cases. Data for the year 2008 reveals that the largest numbers of cases in the country were reported by Orissa, followed by Jharkhand, Chhattisgarh, Madhya Pradesh, West Bengal, Uttar Pradesh, Assam, Maharashtra, Rajasthan, Gujarat with largest numbers of deaths from Orissa followed by Maharashtra, West Bengal and Mizoram. Provisional data from the National Vector Borne Disease Control Programme report a total of 1.52 million cases of malaria (including 0.75 million P. falciparum cases) and 935 deaths from the country in 2008. Travelers from malaria-free areas to disease "hot spots" are especially vulnerable to the disease. Existence of four species of malaria parasite in the country is responsible for the above malaria cases and deaths. Emergence of new species in the neighboring countries adds new threat to the existing situation. In addition, there are many vectors of malaria which breed in different locations. Malaria is preventable and curable. Early treatment of malaria shortens its duration, prevents complications and avoids a majority of deaths. In addition, tackling the menace of emerging resistance against the antimalarials is a great challenge. Based on the therapeutic efficacy studies conducted by NIMR and the National Programme, new treatment guidelines for malaria are issued from time to time and adherence to these guidelines contribute in controlling the situation of malaria in country. Vector control also plays an important role in preventing malaria. Malaria takes an economic toll - cutting economic growth rates by as much as 1.3% in countries with high disease rates and because of its great impact on health in low-income countries, malaria disease management is an essential part of global health development. The main objective of this article is to bring all the aforesaid perspectives into discussion and to present the treatment guidelines on malaria as per National Programme.

1. AETIOLOGY

Malaria is caused by protozoan parasites of the genus Plasmodium which is transmitted among humans by female mosquitoes of the genus Anopheles. Of the approximately 430 known species of Anopheles mosquitoes, only 30-50 transmit malaria in nature (CDC). Plasmodium species belongs to the kingdom Animalia, phylum Protozoa, order Haemosporididae and family Plasmodiidae. Five species of the plasmodium parasite can infect humans; the most serious forms of the disease are caused by Plasmodium falciparum. Malaria caused by Plasmodium vivax, Plasmodium ovale and Plasmodium malariae causes milder disease in humans that is not generally fatal. A fifth species, Plasmodium knowlesi, causes malaria in macaques but can also infect humans.
Among all of these P. vivax and P. falciparum are common in India and mainly responsible for the malaria situation in the country. Some states are highly endemic in the country like for example, 65 per cent of all malaria cases in the country are reported from six States - Orissa, Jharkhand, Chhattisgarh, Madhya Pradesh, West Bengal and the States in the North-East. In some of these areas such as Orissa, the situation of malaria is even worse than in sub-Saharan Africa. In addition, over time there has been a dramatic shift from P. vivax malaria to P. falciparum malaria in the country. The ratio of P. falciparum vs. P. vivax malaria was 0.41 in 1985 which has drastically shifted to 1.01 in 2007.

2. LIFE CYCLE OF MALARIA PARASITE

Presence of two hosts is needed to complete the life cycle of malarial parasites. Female anopheline mosquito is the definitive host and humans play as the intermediate host for the malarial parasites. The malaria parasite undergoes two cycles of development- Human cycle (asexual cycle) and Mosquito cycle (sexual cycle). The human cycle starts when an infected female anopheline mosquito bites a person and injects the infected form, sporozoites into the blood stream of the host. The sporozoites in turn infect liver cells and mature into schizonts, which rupture and release merozoites. Merozoites are then attached to the specific receptors on the red blood cell membrane and pass through the stages of trophozoite and schizont. Each cycle of erythrocytic phase lasts 48 to 72 hrs. Erythrocytic phase ends with the release of merozoites, which then infect new red blood cells. Some of the merozoites, instead of developing into trophozoites and schizont give rise to forms which are capable of sexual functions after leaving the host and these forms are called gametocyte. These gametocytes are infective to mosquito. After the blood infection the initial tissue phase disappears completely in P. falciparum but in P. vivax, P. malariae, and P. ovale it persists in the form of a local liver cycle. The presence of this local liver cycle is known as Exo-erythrocytic schizogony. The Exo-erythrocytic schizogony forms are responsible for relapse of vivax, ovale and quartan malaria. The mosquito cycle starts when gametocytes are ingested by the female anopheline mosquito from the blood of the infected host. The gametocytes are further developed in the vector. The first phase of the development occurs in the midgut (stomach) of the mosquito and is termed as exflagellation of the male gametocyte. From one micro gametocyte (male gametocyte), 5-8 thread like filamentous structures are developed (male gamete). The female gametocyte undergoes maturation and develops into a female gamete or macrogamete. Microgametes are attracted towards the female gametes (macrogametes) by a process of chemotaxis. Fusion takes place between male and female pronuclei resulting into a zygote. The zygote lengthens and matures into an ookinete which penetrates the stomach wall of the mosquito and develops into an oocyst on the outer surface of the stomach. Fully mature Oocyst ruptures and releases sporozoites in the body cavity of the mosquito. Many of the sporozoites migrate to the salivary glands of the mosquito. The mosquito at this phase is capable of transmitting infection to man. The time period for the development of the parasite from the gametocyte to sporozoites stage in the mosquito is about 10-20 days depending on the atmospheric temperature and humidity.
2.1 Schematic diagram of the Life Cycle of Malaria Parasite

Fig. 1. The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female Anopheles mosquito inoculates sporozoites into the human host. Sporozoites infect liver cells and mature into schizonts, which rupture and release merozoites. (Of note, in P. vivax and P. ovale a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony). Merozoites infect red blood cells. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites. Some parasites differentiate into sexual erythrocytic stages (gametocytes). Blood stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an Anopheles mosquito during a blood meal. The parasites' multiplication in the mosquito is known as the sporogonic cycle. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes. The zygotes in turn become motile and elongated (ookinetes) which invade the midgut wall of the mosquito where they develop into oocysts. The oocysts grow, rupture, and release sporozoites, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle.
1.2 Pathophysiology

The malarial parasites reside in the red blood cells as well as other tissues of the body. Different stages of the life cycle of malaria parasite exhibit different physiological changes, which are responsible for waxing and waning of different clinical symptoms.

Pre erythrocytic schizogony- the sporozoites enter the subcutaneous tissue, and either through the lymphatic circulation or directly travel to the liver. No major symptoms are shown, (rarely a prodromal illness characterized by vague aches and pain, headache, nausea). The sporozoites enter the hepatocytes and divide into the merozoites.

Erythrocytic schizogony- the schizonts rupture the liver cells and enter the blood infecting the red blood cells. Where they grow in number to form rings, trophozoites and schizont to form merozoites, the mature schizonts rupture the RBC and release the merozoites into blood further affecting more RBCs. The young red blood cells are predominantly infected in P. vivax malaria, while red blood cells of all ages are affected in P. falciparum malaria. Thus the severity of infection and infective load are more in case of P. falciparum malaria.

The growing parasite consumes and degrades intracellular proteins, principally hemoglobin, resulting in the formation of malaria pigment and hemolysis of the infected red cell. This may alter the transport property of red cell membrane and red cell becomes more spherical and less deformable. The rupture of the red cell by merozoites also releases certain factors and toxins, which could directly induce the release of cytokines like TNF and IL-1 from macrophages which may result in chills and high grade fever. There is also the release of malaria pigment at the time of rupture of parasitized RBCs. This leads to a dense pigmentation of organs rich in reticuloendothelial cells.

Severe falciparum malaria may lead to manifestations and complications such as cerebral malaria, malarial anemia, hyperparasitemia, hypoglycemia, DIC (Disseminated intravascular coagulation), thrombocytopenia, renal failure etc.

Severe malaria encompasses three clinical syndromes: severe anemia, cerebral malaria (CM) and malaria associated hyperpnea (increased rate and depth of breathing).

Severe anemia, hypoglycemia, and convulsions are common in children. Acute renal failure, jaundice and pulmonary edema are common in adult patients. Cerebral malaria is a frequent feature of severe stage of malaria in all ages. Metabolic acidosis is a constant feature of severe malaria\textsuperscript{15}, the severity of the accompanying metabolic acidosis, caused by lactic acid is a strong prognostic factor in both adults and children with severe malaria\textsuperscript{16}. This increase in lactate is mainly due to increased anaerobic glycolysis\textsuperscript{16}, which is caused by decreased perfusion at the microcirculatory or tissue level.

Cardiac index is high and systemic resistance is low in severe malaria as a consequence of the increased metabolic demands associated with fever, the systemic inflammatory response, and malaria associated progressive anemia\textsuperscript{17}.

Patients can present with, or develop hypertonic posturing, abnormal respiratory pattern and gaze abnormalities. Seizures are an important feature of CM.
The characteristic physical findings of severe malaria anemia are respiratory distress and a hyperdynamic circulation.

In case of P. vivax malaria; there is, destruction of non-infected RBC, invasion and destruction of reticulocytes, increased fragility of infected and non-infected RBCs, pooling of RBC in the spleen, increased deformability of infected RBCs, asymptomatic infection with Relapse, greater cytokine production relative to P. falciparum, splenic rupture prior to splenic hematoma or thrombocytopenia etc.

P. vivax commonly affects the lung and cough occurs in the majority of patients with vivax malaria. As in acute lung injury in other disease settings, ARDS (acute respiratory distress syndrome) in P. vivax probably results from cytokine-related increases in alveolar permeability and altered alveolar fluid clearance. Rosetting has been described in vitro. Rosetting causes higher microvascular obstruction than cytoadherence and is associated with cerebral malaria (cytoadherence with other vital organ damage).

Thrombocytopenia is common, with multiple mechanisms resulting in the peripheral destruction and splenic sequestration. P. vivax may cause acute microvascular thrombosis, endothelial injury and thrombocytopenia.

3. Diagnosis of Malaria infection

Diagnosis of Malaria involves identification of malaria parasites or its derivatives in the blood of the patient. The accurate and timely diagnosis of malaria infection reduces the possibility of severe complications and mortality and will facilitate early and specific antimalarial treatment. The blood sample is the most frequently used specimen to make a diagnosis, but other samples like saliva and urine also have been investigated as alternatives as these are less invasive specimens. The diagnosis of malaria may involve one or more of the following procedures.

➢ Clinical Diagnosis
➢ Microscopic tests
➢ Non microscopic tests
➢ Other diagnostic methods
➢ Emerging technologies

3.1 Clinical Diagnosis:

Clinical diagnosis is based on the patient's symptoms and on physical findings at the time of examination. Unfortunately, the clinical symptoms of mild to moderate malaria like chills, fever, sweating, headache, muscle pain, nausea and vomiting are not specific and are also found in other diseases. This in turn hampers the diagnostic specificity resulting in indiscriminate use of antimalarials and ultimately the quality of care for patients. Thus, in most cases the early clinical findings in malaria are not typical and need to be confirmed by a laboratory test.

The symptoms of malaria can be non-specific and include fever, rigors, headache, myalgia, arthralgia, anorexia, nausea and vomiting. Malaria should be suspected in patients residing in endemic areas
and presenting with relevant symptoms. As malaria is known to mimic the signs and symptoms of many other diseases like viral infections, enteric fever etc, the other causes should also be suspected and investigated in the presence of listed manifestations:

- Running nose, cough and other signs of respiratory infections
- Diarrhoea/dysentery
- Burning micturition and/or lower abdominal pain
- Skin rash/infections
- Abscess
- Painful swelling of joints
- Ear discharge
- Lymphadenopathy

3.2 Microscopic tests

For nearly hundred years, the direct microscopic visualization of the parasite on the thick and thin blood smears has been the accepted method for the diagnosis of malaria. The microscopic tests involve -

3.2.1 Peripheral smear

The most economic, preferred and reliable diagnosis of malaria is microscopic examination of blood films because each of the four major parasite species can be diagnosed based on their distinguishing characteristics. Two types of blood films are traditionally used. Thin films are similar to usual blood films and allow species identification because the parasite's appearance is best preserved in this preparation. Thick films allow the microscopist to screen a larger volume of blood and are about twelve times more sensitive than the thin film, so picking up low levels of infection is easier on the thick film, however the appearance of the parasite is much more distorted and species identification can be much more difficult. Recently, a study showed that conventional malaria microscopic diagnosis at primary healthcare facilities in Tanzania could reduce the prescription of antimalarial drugs, and also appeared to improve the appropriate management of non-malarial fevers. The methods involved in staining and identification of malaria parasite are labor intensive, time consuming, and require considerable expertise and trained manpower. The major drawback of microscopic examination is its relatively low sensitivity in accurate identification of malaria species at low parasitemia.

3.2.2 Quantitative Buffy Coat

Fluorescent dyes that stain nucleic acids have been used in the detection of blood parasites. In the Quantitative Buffy Coat method, blood samples are collected in a special tube containing acridine orange, an anticoagulant and then are centrifuged in a microhematocrit centrifuge. After centrifugation, the tubes are examined using a fluorescence microscope with a stage adapter. The
resulting colour due to differential staining of nuclear DNA in green colour and cytoplasm RNA in red, allows recognition of the parasites that concentrate below the granulocyte layer in the tube. The parasites are then seen as fluorescent bodies standing at different levels of the sedimentation column depending on the stage and species of the parasite. Recently, it has been shown that acridine orange is the preferred diagnostic method (over light microscopy and immunochromatographic tests) in the context of epidemiologic studies in asymptomatic populations in endemic areas, probably because of increased sensitivity at low parasitemia. Nowadays, portable fluorescent microscopes using light emitting diode (LED) technology, and pre-prepared glass slides with fluorescent reagent to label parasites, are available commercially. Although the QBC technique is simple, reliable, and user-friendly, it requires specialized instrumentation, is more costly than conventional light microscopy, and is poor at determining species and numbers of parasites.

3.3 Non microscopic tests

3.3.1 Antigen Test

A Rapid Diagnostic Test (RDT) is an alternate way of quickly establishing the diagnosis of malaria infection by detecting specific malaria antigens in a patient's blood. At present 86 malaria RDTs are available from 28 different manufacturers. These test kits are available to detect antigens derived from malaria parasites within a short span of time and do not require any equipment. Most RDTs target a P. falciparum-specific protein, e.g. histidine-rich protein II (HRP-II) or lactate dehydrogenase (LDH). In addition, detection of P. falciparum specific and pan-specific antigens (aldolase or pan-malaria pLDH) is used in distinguishing non-P. falciparum infections from mixed malaria infections. Most RDT products are suitable for P. falciparum malaria diagnosis, some can effectively and rapidly diagnose P. vivax malaria. Recently, a new RDT method has been developed for detecting P. knowlesi. RDT extends the benefit of parasite-based diagnosis of malaria particularly for remote malaria-endemic areas. Thus in remote rural settings, e.g. the subcentres attached to primary health centres (PHCs) where electricity and health-facility resources are limited, RDTs are the available options, provided used in conjunction with other methods to confirm the test results. Till date, there were issues related to the quality control of the RDTs but recently the NIMR has launched a Quality Assurance Programme for RDT in collaboration with NVBDCP. This would involve quarterly quality checks besides predispatch quality checks of the RDTs.

3.3.2 Other Immunological tests

The presence of the malaria parasite in the patient elicits the production of a wide range of antibodies, both specific against Plasmodia antigens and non specific against leukocytes, red blood cell, rheumatoid factor, etc. The first serological test to be used for malaria antibodies was immunofluorescence antibody testing (IFAT), which gave quantitative results for both G and M specific immunoglobulin. Its specificity and sensitivity largely rely on the laboratory technician's expertise. This technique is simple and sensitive but is time consuming and often useful in epidemiological surveys and for screening potential blood donors. Other limitations of IFAT are
Malaria

that it cannot be automated, and thus less number of sera can be studied; requires fluorescence microscope, specific reagents and trained manpower. All these factors limit the use of IFA in remote settings. The indirect haemagglutination test (IHA) is simple and suitable for field studies, but its sensitivity and specificity are poor. The enzyme-linked immunosorbent assay (ELISA) has similar sensitivity and specificity characteristics as that of IFA test, but the interpretation of the results may be better standardized. Finally, for research purposes, radioimmunoassay (RIA) is sometimes used but this technique also needs well equipped research laboratories and personnel. Since the presence of specific antibodies only reflects past infection, it is obvious that seroprevalence rate is very high in populations living in malaria endemic areas, where it linearly increases with age. The detection of specific antibodies has therefore little role to play in the individual diagnosis of actual clinically relevant infection in malaria endemic areas.

3.3.3 Molecular Diagnosis:-

Conventional microscopy is the gold standard for malaria diagnosis but has limitations as may be inadequate for very low parasitaemia (below the detection threshold of 10 parasites/ml of blood) and also detecting drug-resistant parasites. The possibility that modern molecular biologic techniques overcome these drawbacks was thus explored. The initial studies in nucleic acid-based malaria diagnosis used the parasite's repetitive DNA found throughout the Plasmodium genome as the diagnostic target\(^\text{31}\). Therefore, after the sequencing of two small subunits (18S) rRNA genes from \(P.\) falciparum and \(P.\) vivax\(^\text{32,33}\), species-specific regions of the rRNA genes have been exploited in developing a sensitive and specific diagnostic procedure. PCR technique was found to be more sensitive than QBC and some RDTs\(^\text{34,35}\). In addition, PCR can help detect drug-resistant parasites, mixed infections, and may be automated to process large numbers of samples \(^\text{36,37}\). Some modified PCR methods are proving reliable, e.g., nested PCR, real-time PCR, and reverse transcription PCR etc. PCR appears to have overcome the two major problems of malaria diagnosis-sensitivity and specificity, but its use is limited by complex methodologies, high cost, and the need of trained manpower.

3.4 Other diagnostic methods

3.4.1 Flowcytometry

Flowcytometry technique is based on detection of hemozoin pigment (a chemically inert crystalline substance produced in the digestive food vacuole of blood stage malaria parasite). Hemozoin is detected by depolarization of laser light, as cells pass through a flowcytometer channel. This method may provide a sensitivity of 49-98%, and a specificity of 82-97% \(^\text{38,39}\) for malarial diagnosis particularly useful for diagnosing clinically unsuspected malaria. However, this technique is time consuming, requires trained manpower, costly equipment. Besides these disadvantages false-positives may occur with other bacterial or viral infections. Hence it should be considered as a screening tool for malaria.

3.4.2 Automated blood cell counters (ACC)

Automated blood cell counter is a practical tool for malaria diagnosis. In cases of malaria, abnormal
cell clusters and small particles with DNA fluoresce, probably free malarial parasites, have been seen on automated hematology analyzers and it is suggested that malaria can be suspected based on the scatter plots produced on the analyzer. This technique shows promising results but needs more validation.

### 3.4.3 Mass spectrometry

A novel method for the in vitro detection of the malarial parasite at a sensitivity of 10 parasites/µl of blood has been reported earlier. It includes a protocol for cleanup of whole blood samples, followed by direct ultraviolet laser desorption time-of-flight mass spectrometry. Many samples could be prepared in parallel and measurement per sample may not take longer than a second. However, rural areas in the country with intermittent electricity are not suitable for existing high-tech mass spectrometers. Improvements in the equipment can be useful.

### 3.5 Emerging techniques

Researchers from the Universities of Exeter and Coventry have developed Magneto-optic technology (MOT) as the first new technique for diagnosing malaria able to challenge the rapid diagnostic tests (RDTs) currently used in the field. Early results, now published in the Biophysical Journal, suggest that the technique could be as effective as RDTs but far faster and cheaper, making it a potentially viable alternative.

Magneto-optic technology (MOT) detects haemozoin, a waste product of the malarial parasite, in the blood. Haemozoin crystals are weakly magnetic and have a distinct rectangular form. They also exhibit optical dichroism, which means that they absorb light more strongly along their length than across their width. When aligned by a magnetic field they behave like a weak polaroid sheet such as used in sunglasses. This new technology takes advantage of these properties to give a precise reading of the presence of haemozoin in a small amount of blood sample. These researchers have created a device, which gives a positive or negative reading for malaria in less than a minute.

### 4. Malaria Vectors and its control

Malaria is transmitted from man to man by female anopheles mosquito, one of the most capable vectors of human disease. There are approximately 430 known species of Anopheles mosquitoes, and out of these some 58 species are found in India. Six of these have been recognized as the main malaria vectors in the country, namely An. culicifacies, An. dirus, An. fluviatilis, An. minimus, An. sundaicus and An. stephensi. Beside these, some vectors of local importance are An. philippinensis-nivipes, An. varuna, An. annularis and An. jeyporiensis. The areas of distribution are different for these mosquitoes. An. fluviatilis, An. minimus are found in the foot-hill regions. An. stepensi, An. sundaicus are found in the coastal regions, An. culicifacies and An. philippinensis are found in the plains. Species like An. stephensi are highly adaptable and are found to be potent vectors of human malaria. An.culicifacies and An. stephensi are vectors of major importance found in rural and in urban areas respectively. Brief information on each species of vector and its distribution within the country will help the readers in deciding the control measures.
Anopheles culicifacies is widely distributed throughout the country and contributes to about 60-65% of all malaria cases in the country especially from rural and peri-urban areas\textsuperscript{45}. All the members of An. culicifacies species rest indoor, mainly in cattle sheds and because of its high density, it acts as a major vector for malaria. The main breeding sites are streams, rice fields, burrow pits, irrigation channels etc.

The An. fluviatilis exists as a species complex comprising of at least three sibling species (S,T and U) distributed throughout the country\textsuperscript{46}. Out of these, species T is the most widely distributed and species S has been recognized as highly efficient malaria vector predominantly found in Orissa\textsuperscript{47,48}.

An. minimus is also recognized as species complex comprising of at least three sibling species and is an efficient malaria vector reported only from northeastern states and adjoining areas\textsuperscript{49-51}, (Singh, O. P. et al., unpublished data).

An. stephensi is a sub-tropical species and is considered an important vector in country. So far there is no description of sibling species available but two races, 'type form' and 'var. mysorensis' have been described \textsuperscript{48,52}. The 'type form' is a malaria vector, inhabitant of urban area with specific breeding sites such as wells, garden ponds, cisterns, overhead tanks, ground level cement tanks, water coolers, building-construction sites etc. The var. mysorensis is a non-vector, found in rural areas.

The An. dirus complex is mainly prevalent in the forest and forest-fringe area and its members are vectors in the country\textsuperscript{53}. It is a complex of at least seven sibling species with only two species, An. baimaii and An. elegans are reported from the country. The former is an efficient malaria vector found in north-eastern states and the latter in Shimoga hills of Karnataka, the vectorial status of which is unknown \textsuperscript{47,54}.

An. sundaicus is an important malaria vector in coastal areas in Southeast Asian region. It is reported from West Bengal, Orissa, the coastal areas of Andhra Pradesh and Andamans\textsuperscript{55}, but its presence is now restricted to Andaman and Nicobar Islands\textsuperscript{56} and Kuch of Gujarat state \textsuperscript{57}. It prefers to breed in saline/brackish water, though it has been reported to breed in freshwater also. Also a new cytotype D from Car Nicobar Island has been reported\textsuperscript{58}. Presence of widely distributed vector species along with sibling species makes the malaria situation complex and control measures become difficult.

**4.1 Vector Control**

Vector control plays an important role in the global malaria control strategy. The aim is to reduce transmission of the disease which in turn reduces the levels of mortality and morbidity. Knowledge of appropriate tools for prevention and control of the disease is required as the gap between the prevention and control through effective vaccine is yet to be filled. Following a number of reasons, vector control has turned ineffective during the past. The reasons could be inappropriate use of alternative control tools, inadequate use of insecticides, lack of evidence based interventions, inadequate resources and infrastructure, and weak management etc.\textsuperscript{59} Changing environmental conditions, the behavioural characteristics of certain vectors and resistance to insecticides have added to the difficulties\textsuperscript{59}. The main options available for vector control are indoor residual spraying
(IRS) of insecticides, personal protection measures, larval control, biological control and environmental managements. The World Health Organization’s Global Malaria Programme recommend the use of IRS as a major means of malaria vector control to reduce and eliminate transmission, and distribution of insecticide-treated nets (ITNs) to achieve full coverage of populations at risk, as primary interventions that must be scaled up in countries to effectively respond towards achieving the Millennium Development Goals for malaria by 201560. Vector control mainly relies on indoor residual spraying of DDT, malathion or synthetic pyrethroids (SPs) in rural areas and source reduction and anti-larval measure in urban areas in the country48. Following the spray of DDT An. minimus s.l. reported earlier from Uttar Pradesh has disappeared from the Terai region of Uttar Pradesh (now in Uttaranchal)61. A number of breeding areas are occupied by An. culicifacies during monsoon season making control measures like anti-larval methods difficult to employ. Control of An. culicifacies is a major concern for vector-control programme in the country as this vector has developed resistance against all commonly used insecticides48.

Man-made urban areas are the major breeding sites for An. stephensi, and thus by involving community, biological control methods and enforcement of legislative measures can be employed to control the breeding of An. Stephensi.

4.2 Vector Control Strategies

As per the guidelines issued by NVBDCP, the vector control strategies include one or more of the available options like the chemical control measures which include use of Indoor Residual Spray (IRS) with insecticides recommended under the programme, use of chemical larvicides like Abate in potable water, aerosol space spray during day time and malathion fogging during outbreaks etc. Besides, chemical control, biological control is environment friendly option which includes use of larvivorous fish in ornamental tanks, fountains etc. and use of biocides. In addition, personal prophylactic measures that individuals / communities can take up include use of mosquito repellent creams, liquids, coils, mats etc. and screening of the houses with wire mesh, use of bednets treated with insecticide and wearing clothes that cover maximum surface area of the body. Also involving the community participation in sensitizing and thereby involving the community in detecting the Anopheles breeding places and their elimination may help in malaria control. NGO schemes involving community in programme strategies and collaboration with CII/ASSOCHAM/FICCI will strengthen the vector control programme. Environmental management & source reduction methods which include source reduction i.e. filling of the breeding places and proper covering of stored water, Channelization of breeding source etc. are environment friendly options.

A brief idea of different vector control strategies will enrich the knowledge of the readers about the available strategies for vector control and these are also implemented throughout the country by the National programme.

4.2.1 Environmental management and Source Reduction

Environmental methods for controlling most of the breeding include source reduction by filling ditches, areas, pits, low lying areas, streamlining, channelising, desilting, deweeding, trimming of drains, water disposal and sanitation, emptying of water container once in a week, etc.
4.2.2 Chemical Control

Recurrent anti-larval measures with approved larvicides to control the vector mosquitoes are recommended. The larvicides like temephos and fenthion are usually used as chemical control measures. Indoor Residual Spray (IRS) with insecticides recommended under the programme is the mainstay of vector control.

IRS has shown excellent result in controlling malaria in many parts of the world in the past. Use of DDT as IRS resulted in bringing down malaria from 75 million cases to an all time low of 0.1 million cases\(^{62}\) in the country in 1966. The spectacular success in malaria control by DDT IRS paved the way for possibility of malaria eradication. However, the malaria control programme received serious setbacks from 1968 onwards due to various factors including insecticide resistance in vectors. The first report of resistance to DDT appeared in An. Culicifacies\(^{63}\) in 1958 and became widespread thereafter. Another insecticide, benzene hexa-chloride (BHC, gamma isomer), was banned for public health use since 1997 owing to health concerns. Besides these insecticides,
malathion and pyrethroids are being used in the public health programme. Resistance against HCH, dieldrin and malathion was also reported quickly after their short use. In spite of the fact that spraying of insecticides in malaria control programme over the last five decades has resulted in resistance to insecticides and behavioural changes in vector population, IRS still remains the main vector-control strategy in India and DDT remains the main choice of insecticide in most situations. The World Health Organization has recently recommended effective implementation of IRS with DDT or other recommended insecticides as a central part of national malaria control strategies where this intervention is appropriate. In the last two decades, synthetic pyrethroids (SPs) such as deltamethrin, cyfluthrin and lambda-cyhalothrin have been introduced into public health programme as residual insecticide and for impregnation on mosquito nets. However, reports on resistance against SPs have already surfaced in areas where SPs are in use. One of the major reasons for the resurgence of malaria in mid-1970s has been insecticide resistance in vector species. Presently, An. culicifacies, has developed resistance to DDT in 286 districts and to DDT and malathion in 182 districts of India. Limited number of chemical groups of effective insecticides is available for vector control. Due to rapid increase in insecticide resistance in vectors and due to non-availability of effective new molecules of insecticides in near future, management of insecticide resistance becomes important. Space spraying of Pyrethrum extract (2%) in 50 houses in and around every malaria positive case to kill the infective mosquitoes during daytime is an effective strategy of vector control. Also, malathion fogging during outbreaks has been shown to be highly effective in controlling the vectors.

4.2.3 Biological Control

Biological control of mosquito breeding is controlled through biological agents especially larvivorous fishes (Gambusia and Guppy) and by larvicides. As part of alternate strategies, the bio-environmental control approach was implemented in the country after successful multi-centric field trials conducted by the National Institute of Malaria Research (formerly Malaria Research Centre). Larvivorous fishes have also been found to be very effective in controlling malaria in certain situations in Karnataka. The National Vector Borne Disease Control Programme is presently implementing this strategy as part of integrated disease control in many states.
Two biocides from the bacterium Bacillus thuringiensis var.israelensis (Bti) and B. sphaericus (Bs) are extensively field tested in India. The Bti is now being used in public health programmes as anti-larval measure in urban areas; however Bs developed resistance soon after its application.

4.2.4 Personal Prophylactic Measures

Personal protection measures are based on insecticide-impregnated materials such as bed nets and curtains mainly, but its implementation is a problem. It has been demonstrated that if they are properly applied they can provide a 30 to 60 percent reduction in malaria morbidity. The use of insecticide-treated nets (ITNs) is being promoted because the application of a residual insecticide greatly enhances the protective efficacy of bed-nets. Pyrethroids are the only insecticides that have been used for impregnation of bed-nets due to very low mammalian toxicity, rapid knock-down effect on vectors at very low doses and high residual effect. Deltamethrin was the first insecticide that was used for impregnation of bed-nets with remarkable success followed by cyfluthrin, lambda-cyhalothrin, bifenthrin and alphacypermethrin. Owing to the success of these ITNs, which require re-treatment at periodic intervals, long-lasting insecticide-treated nets (LLINs) became available, in which insecticide is incorporated into the net fibres. Trials of various brands of LLINs impregnated with permethrin, deltamethrin and alphacypermethrin are underway. These nets are said to have increased activity for longer periods of time (reportedly five years) unlike the earlier treated nets that need re-impregnation generally after six months. The emerging pyrethroid resistance in vectors is a serious threat to the success of pyrethroid-treated nets. Search for alternative insecticides with novel mode of action and use of mosaic or mixture of insecticides to prevent insecticide resistance is being advocated. Use of mosquito repellent creams, liquids, coils, mats etc. and screening of the houses with wire mesh, wearing clothes that cover maximum surface area of the body are some other protection measures.

Management of insecticide resistance can be attempted using insecticide-based approaches in conjunction with other non-insecticidal vector-control methods. The proposed strategies of insecticide management are: (i) rotational strategies based on two or preferably more insecticide classes with different modes of action over time, (ii) the use of mixtures of insecticides, (iii) mosaic approach, i.e. spatially separated applications of different compounds against the same target vector, and (iv) minimal use of insecticides based on the distribution of sibling species and their susceptibility to insecticides.

For effective management of insecticide resistance, thorough understanding about the mode of action of the available insecticide products, update on emerging options and monitoring of resistance should become the integral part of vector control programmes.

5. Treatment

The primary objective of treatment of uncomplicated malaria is to completely cure the infection and to prevent the progression of uncomplicated malaria to severe disease. Another important consideration while treating malaria is to prevent the spread and emergence of resistance to antimalarials.
5.1 Currently available drugs

Based on the mode of action on different stages of life cycle, the biological classification of antimalarial drugs can be as follows-

5.1.1 Sporontocides: These drugs prevent further development of the malarial oocysts and sporozoites in the infected mosquitoes eg. proguanil, pyrimethamine and atovaquone

5.1.2 Hypnozoitocides (For preventing relapse): These drugs kill hypnozoites and are also known as anti relapse drugs. Thus they can cause a radical cure, eliminating all remaining parasites in the body after the primary infection is effectively treated. eg. primaquine and tafenoquine.

5.1.3 Tissue Schizonticides (For casual prophylaxis): These drugs inhibit the growth of the parasite in the pre-erythrocytic stage (i.e in the liver). Thus, they prevent the initiation of the erythrocytic stage of the infection resulting in the prevention from malarial fever and further transmission to mosquito. eg. primaquine, tafenoquine, proguanil and tetracycline.

5.1.4 Blood Schizonticidal (For clinical or suppressive cure): These drugs kill the asexual erythrocytic stage of the malarial parasites and thus terminate the clinical attack of the disease (hence clinical cure). Total elimination of the parasite from the body by repeated suppressive treatment is called suppressive cure eg. most antimalarial drugs except primaquine.

5.1.5 Gametocytocides: These drugs destroy the sexual stages of the parasite in blood, including that of P. falciparum. Therefore, they prevent the transmission of the parasite to the mosquito eg. primaquine and tafenoquine.

5.2 National Drug policy on treatment of malaria

In India, National Vector Borne Disease Control Programme (NVBDCP), the central nodal agency for the prevention and control of vector borne diseases issues guidelines for treatment of malaria. The emphasis for malaria control is on early case detection and prompt treatment (EDPT). All clinical suspected cases should preferably be investigated for malaria by Microscopy or Rapid Diagnostic Kit (RDK). To date, malaria control has relied heavily on comparatively small number of chemically related drugs, belonging to either the quinolone or the antifolate groups. Antimalarial drugs kill malaria parasite, thereby preventing multiplication and leading to their removal from the circulation75.

Chloroquine is the first line treatment for P. vivax malaria in the country. Primaquine is co-administered for 14 days to prevent relapse except in contraindicated patients which include G6PD deficient patients, infants and pregnant women76. Treatment of P. falciparum malaria is based on areas identified as chloroquine sensitive/resistant. In low risk and chloroquine sensitive areas, the prescribed first line drug is chloroquine, for three days. This practice is to be followed at all levels including VHWs like FTDs/ASHA as well in chloroquine sensitive areas. In high risk area in addition to chloroquine, single dose of Primaquine should also be given on first day. Wherever microscopy results are not available within 24 hours or the patient is at high risk of Pf both RDT and slide should be taken. Cases positive for Pf by RDK should be treated with full therapeutic
dose of chloroquine or ACT combination as per prescribed drug in that area. However negative cases showing signs and symptom of malaria without any other obvious causes should be considered as clinical malaria and treated with chloroquine in full therapeutic dose of 25 mg/kg body weight over three days. Such cases if later found positive may be treated accordingly.

ACT is the first line of antimalarials drug for treatment of P.falciparum in chloroquine resistant areas, identified cluster of Blocks surrounding resistant foci, all seven NE states and 50 high Pf endemic districts in the state of Andhra Pradesh, Chhattisgarh, Jharkhand, Madhya Pradesh and Orissa. Artesunate-sulphadoxine pyrimethamine is the recommended ACT in the country. ACT should be given only to confirmed P. falciparum cases, found positive by microscopy or Rapid Diagnostic Test (RDT). Compliance and full intake are to be ensured. Artemisinin based combination therapy is now considered the best therapy for falciparum malaria. Such treatments are effective, work rapidly and have very few adverse effects; they combine unrelated compounds with different molecular targets, thereby delaying the emergence of resistance. Since 2005, most countries where malaria is endemic have adapted treatment policies based on these combination therapies. WHO guidelines recommend that anti malarial treatment policy should be changed when treatment failure proportion exceeds 10%.

As per the guidelines of NVBDCP, the details of treatment based on diagnosis should be as follows:

5.2.1 P. vivax malaria:
Microscopically positive P.vivax cases should be treated with chloroquine in full therapeutic dose of 25 mg/kg body weight divided over three days. Primaquine should be given in dose of 0.25mg/kg bw daily for 14 days.

5.2.2 P. falciparum malaria:
The P.falciparum cases in low risk and chloroquine sensitive areas should be treated with chloroquine in therapeutic dose of 25 mg/kg body weight divided over three days along with single dose of Primaquine 0.75 mg/kg bw (body weight) on first day. ACT combination is recommended for treatment of P.falciparum in chloroquine resistant areas, identified cluster of Blocks surrounding resistant foci, high Pf endemic districts in selected 50 districts of 5 states namely Andhra Pradesh, Chhattisgarh, Jharkhand, Madhya Pradesh and Orissa and 67 districts of N.E states. The dose is 4 mg/kg bw of Artesunate daily for 3 days + 25 mg/ kg bw of sulphadoxine/sulphalene and 1.25 mg per kg bw of pyrimethamine on the first day. Single dose of Primaquine i.e 0.75 mg/kg body weight, may be given with ACT combination as it will be beneficial for gametocyte clearance in P.falciparum and will facilitate effective interruption of transmission.

5.2.3 Malaria in Pregnancy:
In pregnancy, quinine is recommended for treatment of falciparum malaria while chloroquine is the drug of choice for vivax malaria. According to WHO guidelines, ACT should not be used in first trimester due to safety concerns; however, ACT is recommended in the second and third trimester of the pregnancy and monitoring for safety is advised.
5.2.4 Travel Malaria:
In addition, it is recommended that ACT should be given to patients with history of travel to areas listed for use of ACT and also to patients who have no clinical or parasitological response to full dose of chloroquine within 72 hours of starting the therapy.

5.2.5 Resistant malaria:
Resistance should also be suspected if in spite of full treatment with no history of vomiting, diarrhea, patient does not respond within 72 hours parasitologically. Such individual patients should be reported to concerned District Malaria /State Malaria Officer/ROHFW Pf monitoring teams for monitoring of drug sensitivity status. In cases resistant to chloroquine and SP-ACT, oral quinine with tetracycline or doxycycline can be prescribed. Mefloquine should only be given to chloroquine/multi resistant uncomplicated P.falciparum cases.

5.2.5 Severe malaria:
Severe malaria is an emergency and treatment should be given as per severity and associated complications which can best be decided by the treating physicians. Parenteral artemisinin derivatives (for non pregnant women) or quinine should be used irrespective of chloroquine resistance status of the area. However, the guidelines for specific antimalarial therapy as per the WHO recommendation are given below:

- Quinine: 20 mg/kg body weight (bw) on admission (IV infusion or divided IM injection) followed by maintenance dose of 10 mg/kg bw 8 hourly; infusion rate should not exceed 5 mg salt / kg bw per hour.
- Artesunate: 2.4 mg/kg bw i.v. or i.m. given on admission (time=0), then at 12 h and 24h, then once a day, thereafter for maximum 7 days. For children the recommended dose is 1.2 mg/kg/day for 5-7 days.
- Artemether: 3.2 mg/kg bw i.m. given on admission then 1.6 mg/kg bw per day until oral therapy or a maximum of 7 days.
- αβ Arteether: 150 mg daily i.m for 3 days in adults only (not recommended for children).

6. Drug Resistance
Antimalarial drug resistance has emerged as one of the greatest challenges for malaria control today. Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated. Drug resistance has also played a significant role in the occurrence and severity of epidemics in some parts of the world.

Chloroquine has been most important antimalarial drug for the last half century. For the treatment of vivax malaria, Chloroquine remains the first line antimalarial drug in India. 100% cure rate was reported in West Bengal and Orissa during 1998-2001 and in different regions of India. As chloroquine binds extensively to tissues and is eliminated slowly, a large proportion of the population in an areas where malaria was endemic have detectable chloroquine concentration in their blood.
Malaria at any given time. The first report of chloroquine resistance towards P. falciparum emerged from Assam\textsuperscript{80} followed by sporadic reports from various part of the country with wide variation in distribution of resistance\textsuperscript{81}. Map of areas showing Chloroquine Resistant Areas (1978-2008 updated to August) is given as fig 2\textsuperscript{76}. Chloroquine gave us 30 to 40 years of benefit, however, following Chloroquine resistance, Sulfadoxine Pyrimethamine (SP) was introduced as Second line drug for the treatment of Chloroquine resistant falciparum malaria in many districts and PHCs. Unfortunately this successor, Sulfadoxine- Pyrimethamine fell to resistance within 5 years of intensive use. Sulphadoxine and Pyrimethamine inhibit the enzymes dihydropteroate synthase and dihydrofolate reductase, respectively\textsuperscript{82}. Pyrimethamine inhibits the dihydrofolate reductase (DHFR) enzyme of P.falciparum and thus its folate biosynthesis pathway. Sulphadoxine acts as a competitive inhibitor in folate biosynthetic pathway of the parasite. This drug acts by inhibiting the enzyme dihydropteroate synthase (DHPS) thus interfering in the step of conversion of dihydropteridine pyrophosphate to dihydropteroate \textsuperscript{83}. Mutations in some of the key amino acids of this enzyme lead to its reduced binding affinity towards this drug \textsuperscript{84}(Nicholas J. White, 2006). Since SP is given as a combined dose to malaria patients, its resistance is measured by detecting mutations in both DHFR and DHPS enzymes. Higher the number of combined DHFR-DHPS mutations, higher SP resistance is shown by the parasite. However, molecular studies showed that mutations of DHPS gene were less frequent than DHFR gene\textsuperscript{85}. Resistance to other antimalarials was also reported from different parts of the world. Resistance to mefloquine was found mostly in Cambodia, Myanmar, Thailand and Viet Nam. So far no resistance to artemisinin or its derivatives has been reported, although some decreased in vitro sensitivity has been reported in China and Viet Nam\textsuperscript{86}. The prevalence and spread of drug resistance strains of P. falciparum is posing major threat to malaria control programme. P. falciparum strains resistant to various anti malarial drugs are spreading at a faster rate in some areas due to population movement, poor or inadequate health facilities, lack of proper malarial control programmes and improper use of anti malarial drugs\textsuperscript{87}. For the last decade, chloroquine-resistant Plasmodium falciparum has spread explosively in Sub-Saharan Africa, Southeast Asia and South Asia\textsuperscript{88}. In 2001, WHO recommended the use of artemisinin based combinations [artesunate + sulphadoxine - pyrimethamine (AS+SP), artesunate + amodiaquine (AS +AQ), artemether - lumefantrine] as first line treatment for uncomplicated falciparum malaria in response to reduced effectiveness of CQ & SP monotherapies\textsuperscript{86,89}. During the last three years WHO has assisted the studies on therapeutic efficacy of first and second line antimalarials. Based on these results, Artemisinin-based combination therapy (ACT) has been introduced for treatment of falciparum malaria in CQ resistant areas since 2006\textsuperscript{90} and now being implemented in 117 districts (i.e 50 high endemic districts of States namely Andhra Pradesh, Chhatisgarh, Jharkhand, Madhya Pradesh & Orissa + 67 in North Eastern States), in addition to 253 PHCs of 46 districts included on the basis of chloroquine resistance status and its surrounding cluster of Blocks, Table 1\textsuperscript{76}.
Fig-2: Chloroquine Resistant Areas (1978-2008 updated to August)\textsuperscript{76}

Table 1: Districts/Areas identified for use of ACT Combination (AS+SP) for treatment of Pf malaria\textsuperscript{76}

<table>
<thead>
<tr>
<th>S. No.</th>
<th>State/UT</th>
<th>Name of Districts</th>
<th>Name of Chloroquine resistant PHC / surrounding cluster of Block PHCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Andhra Pradesh</td>
<td>Vizianagaram, Vishakapatnam, Srikakulam, East Godavri, Khammam</td>
<td>Entire 5 districts</td>
</tr>
<tr>
<td>2</td>
<td>A&amp;N Islands</td>
<td>Great Nicobar &amp; Little Andaman</td>
<td>20 PHCs</td>
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<tr>
<td></td>
<td>Assam (24 districts)</td>
<td>Dhubri, Kokrajhar, Goalpara, Bongaigaon, Barpeta, Nalbari, Kamrup, Kamrup M, Darrang, Sonitpur, Lakhimpur, Dhemaji, Golaghat, Nagaon, Jorhat, Morigaon, Karbi-Anglong, N.C. Hills, Cachar (Silchar), Haila Kandi, Karimganj, Tinsukhia, Sibsagar, Dibrugarh,</td>
<td>Entire 24 districts</td>
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<tr>
<td>4</td>
<td>Arunachal Pradesh (6 districts)</td>
<td>Changlang, Lohit, East Siang, Papum Pare, East Kameng, West Kameng,</td>
<td>Entire 6 districts</td>
</tr>
<tr>
<td>5</td>
<td>Chhattisgarh (11 districts)</td>
<td>Jagdalpur, Korba, Ambikarpur, Raigarh, Jashpurnagar, Raipur, Dhamteri, Dantewada, Kanker, Bilaspur, Korea</td>
<td>Entire 11 districts</td>
</tr>
<tr>
<td>6</td>
<td>D &amp; N Haveli (6 districts)</td>
<td>D &amp; N Haveli (6 PHCs)</td>
<td>Whole D &amp; N Haveli (6 PHCs)</td>
</tr>
<tr>
<td>7</td>
<td>Goa (2 districts)</td>
<td>North Goa and South Goa (28 PHCs)</td>
<td>Whole state (28 PHCs)</td>
</tr>
<tr>
<td>8</td>
<td>Gujarat (27 PHCs of 7 district)</td>
<td>Panchmahal (4 PHCs) (Kadana, Lunavada, Khanpur, Santarampur)</td>
<td>Kutch Bhuj - (6 PHCs) Kavada, Gorewali, Mundra, Mandavi, Anjar, Nakhatrana</td>
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<td></td>
<td></td>
<td>Anand (2 PHCs)</td>
<td>Pansora, Anand</td>
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<td></td>
<td></td>
<td>Dahod (3 PHCs)</td>
<td>Degawada, Limkheda, Dhanpur</td>
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<td>Patan (5 PHCs)</td>
<td>Lolada, Harij, Radhanpur, Patadi, Rapar</td>
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<td></td>
<td></td>
<td>Surat (4 PHCs)</td>
<td>Surat city, Olpad, Choryasi, Kamrej</td>
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<td></td>
<td></td>
<td>Kheda (3 PHCs)</td>
<td>Matar, Mahudha, Mehmdabad</td>
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<tr>
<td>9</td>
<td>Jharkhand (12 districts)</td>
<td>Gumla, Ranchi, Simdega, Lohardaga, East Singhbhum, West Singhbhum, Saraikela, Sahibganj, Godda, Dumka, Latehar, Pakur</td>
<td>Entire 12 districts</td>
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<tr>
<td>State</td>
<td>PHCs</td>
<td>Districts</td>
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<tr>
<td>Karnataka</td>
<td>53 PHCs of 12 districts</td>
<td>Kolar (7 PHCs), Raichur (20 PHCs), Bellary (2 PHCs), Mandya (1 PHC), Bagalkot (4 PHCs), Chittarajana (1 PHC), Gadag (1 PHC), Chitradurga (6 PHCs), Belgaum (1 PHC), Gulbarga (8 PHCs), Bijapur (1 PHC)</td>
<td></td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>(9 districts)</td>
<td>Jhabua, Dindori, Shahdol, Chhindwara, Shahdol, Mandla, Seoni, Hoshangabad, Guna</td>
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<tr>
<td>Maharashtra</td>
<td>(32 PHCs of 2 districts)</td>
<td>Raigarh, Ghadchiroli (31)</td>
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<tr>
<td>Manipur</td>
<td>(11 districts)</td>
<td>All district (total no.11)</td>
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<tr>
<td>Meghalaya</td>
<td>(7 districts)</td>
<td>All District (total no. 7)</td>
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<tr>
<td>Mizoram</td>
<td>(3 districts)</td>
<td>Lunglei, Kolasib, Mamit</td>
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<tr>
<td>Nagaland</td>
<td>(12 districts)</td>
<td>All District (total no. 12)</td>
<td></td>
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<tr>
<td>State</td>
<td>Districts</td>
<td>PHCs</td>
<td>Malaria Areas</td>
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<tr>
<td>Orissa</td>
<td>(13 districts and 39 PHCs of 11 districts)</td>
<td></td>
<td>Entire 13 districts</td>
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<tr>
<td></td>
<td>Keonjhar, Kandhamal, Sundergarh, Mayurbhanj, Kalahandi, Nuapada, Koraput, Sambalpur, Gajapati, Rayagada, Jharasguda, Malkangiri, Nawarangpura,</td>
<td></td>
<td>Angul (7 PHCs) Bantala, Madhupur/Athamallic, Banarpal, Koshala/Chendipada, Kanhia, Khamar/Palalahda, R.K. Nagar / Kishorenagar</td>
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<td></td>
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<td>Dhenkanal (3 PHCs) Khajurikata, Odapada, Beltikri/Dhenkanal</td>
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<td></td>
<td>Deogarh (3 PHCs) Tileibbani, Chhatabar/Riamal, Bamparda/Barkot</td>
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<td></td>
<td></td>
<td>Bolangir (6 PHCs) Khaprakhol, Bangamunda/Sindheipalli, Guduvella, Ghasian/Patna, Belpada, Tureikela</td>
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<td></td>
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<td></td>
<td>Boudh (3 PHCs) Adenigarh, Manamundu, Baunshini/Boudh</td>
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<td></td>
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<td>Balasore (3 PHCs) Bherampur, Iswarour, Khairah</td>
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<td>Baragarh (2 PHCs) Bukuramunda, Jamla</td>
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<td>Cuttack (2 PHCs) Kanpur, Maniabandha</td>
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<td>Ganjam (4 PHCs) Badagada, Adapada, Bomkei, Dharakot</td>
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<td></td>
<td>Nayagarh (2 PHCs) Gania, Madhyakhand</td>
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<td>Sonepur (4 PHCs) Birmaharajpur, Naikenpali, Tarva, Ullunda</td>
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<tr>
<td>Rajasthan</td>
<td>(11 PHCs of 4 districts)</td>
<td></td>
<td>Dungarpur (4 PHCs) Bicchiwara, Damri, Simalwara, Dungapur</td>
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<td></td>
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<td></td>
<td>Banswara (4 PHCs) Kushalgarh, Chota Dungara, Banswara, Talwara</td>
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<td></td>
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<td></td>
<td>Baran (2 PHCs) Kishanganj, Shahbad</td>
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<td></td>
<td>Udaipur (1 PHC) Kotra</td>
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<tr>
<td>Tamilnadu</td>
<td>(1)</td>
<td></td>
<td>Rameshwaram Island</td>
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<tr>
<td>Tripura</td>
<td>(4 districts)</td>
<td></td>
<td>All District (total no. 4) Whole state</td>
</tr>
<tr>
<td>Uttar</td>
<td>Pradesh (1)</td>
<td></td>
<td>Mirzapur NTPC Project area Mirzapur</td>
</tr>
<tr>
<td>West Bengal</td>
<td>(39 PHCs of 5 districts)</td>
<td></td>
<td>Purulia (11 PHCs) Bagmundi, Sadar, Bandhwan, Sirkabad, Jhalda-II, Balarampur, Jhalda-I, Joypur, Barabazar, Manbazar-II, Manbazar-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Jalpaiguri (13 PHCs) Uttar Latabari, Mal, Kalimpong, Sukna, Falakata, Kumagram, Garubathan, Raigunj, Maynaguri, Matiali, Madarihat Alipurduar-I, Alipurduar-II</td>
</tr>
</tbody>
</table>
## Conclusion

Effective ways are available to manage malaria and efforts are on to eliminate malaria in some countries. The malaria cases in the country in the last three years have also shown downward trend. Prompt and effective diagnostic tools, better control measures for vectors, timely supply of antimalarial medicines etc. are essential component for the management and control of malaria. However, coherent action of all the above components is required to control the menace of malaria in the country.

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GLOSSARY

1. WHO- World Health Organization
2. NVBDCP-National Vector Borne Disease Control Programme
3. NIMR-National Institute of Malaria Research
4. RBC-Red Blood cell
5. TNF-Tumor Necrosis Factor
6. IL-1-Interleukin-1
7. DNA-Deoxyribonucleic acid
8. RNA-Ribonucleic acid
9. PCR-Polymerase Chain Reaction
10. NGO-Non-govermentl organization
11. DDT-dichlorodiphenyltrichloroethane, synthetic pesticide
12. G6PD-Glucose-6-phosphate dehydrogenase
13. VHWs -Voluntary Health Workers
14. FTDs- Fever Treatment Depots
15. ASHA- Accredited Social Health Activist
16. ACT-Artemisinin-based Combination Therapies
17. NE states-North-Eastern states
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