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Update on Malaria

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Abstract

Malaria has been a menace worldwide, existing endemically in some countries one of those being India. A national programme for control of this disease had been launched in India in 1953, which evolved as the present composite programme against several endemic vector borne diseases, as the National Vector Borne Disease Control Programme. The disease is being treated in the country according to the National Drug Policy for Malaria 2013. Presently the National Strategic Plan 2017-2022 has been formulated for achieving malaria elimination by 2030. Preventive measures include integrated vector control, personal protection and chemoprophylaxis. Several candidate vaccines have been under research of which the most promising one i.e. RTS,s is due to be piloted by the World Health Organization in selected areas of 3 African countries, through WHO's Malaria Vaccine Implementation Programme (MVIP) that will begin in 2018.

Keywords: malaria; National Vector Borne Disease Control Programme; malaria treatment; malaria vaccine

Introduction

Malaria is a protozoan disease, caused by infection with parasites of the genus Plasmodium. It is transmitted to man by the bite of certain species of infected female Anopheles mosquitoes [1].

Malaria is one of the most widespread diseases occurring worldwide, being endemic mainly in the tropical regions. It is the most important of the parasitic diseases of the humans, affecting more than hundred endemic countries with a population of over 2.5 billion people and causing an estimated 6.5 lakh deaths each year [1].

Malaria continues to pose a problem in India over centuries to the present. Details of this disease can be found even in the ancient Indian medical literature like the 'Charaka Samhita'. According to the World Malaria Report 2016, India contributes about 89% of the malaria burden in the South East Asian Region. However, there has been considerable reduction in morbidity and mortality due to malaria and the country has achieved the sixth goal of the Millenium Development Goals [2].

National efforts against malaria started in India with the National Malaria Control Programme in 1953, which evolved over the decades to be merged with control strategies of several endemic vector borne diseases and was named as the National Vector Borne Disease Control Programme launched in 2003-04. Presently the National Strategic Plan for Malaria Elimination (2017-22) has been developed based on the National Framework for Malaria Elimination of the National Vector Borne Disease Control Programme [2].

Epidemiology

The disease is endemic in all of India. Currently majority of the malaria cases are reported from the eastern and central parts of the country and from states with large hilly, forest and tribal areas. It is a seasonal disease flaring up mainly during the post monsoon time of the year, the maximum prevalence

being from July to November. Temperature, humidity and rainfall have direct effect on the life cycle of mosquito and thus on the prevalence of the disease. In most parts of the country, periodic epidemics of malaria occur every five to seven years [1,2].

Transmission is mainly by vector i.e. by bite of infected mosquito. Direct transmission may occur by accidental injection of infected blood or plasma. Congenital infection of the newborn of an infected mother may rarely occur [1]. The disease is transmitted by 9 species of anopheles mosquito, out of which 6 most important ones are *A. culicifacies, A. stephensi, A. fluviatilis, A. dirus, A. minimus* and *A. epiroticus* [2].

Malaria is caused by more than 100 species of the parasite *Plasmodium*, of which four have been seen to cause human infection. These are – *P. vivax, P. falciparum, P. malariae and P. ovale*, the first two being main contributors to the disease burden in India [1]. A fifth species named *P. knowlesi*, has been recently identified, which is a zoonotic monkey malaria that infects humans in forest fringe areas of Southeast Asia [3]. Although the total number of cases of malaria in India has reduced, there has been an increase in the number of *P. falciparum* cases, accounting for more than 67% of the total cases in 2015 [1].

The parasite undergoes two cycles of development – the human (asexual) cycle and the mosquito (sexual) cycle. Man is the intermediate host and mosquito the definitive host. The phases in the human cycle are – Hepatic phase, Erythrocytic phase and Gametogony. Within an hour of mosquito bite infusing the parasites, the sporozoites disappear from peripheral circulation. Many are destroyed by phagocytes, but some reach the liver cells, where they become hepatic schizonts, which eventually burst releasing a shower of merozoites. Most of these merozoites penetrate the RBC and pass through the stages of trophozoite and schizont. The erythrocytic phase ends with the release of merozoites, which infect fresh RBC. Duration of the erythrocytic cycle varies between the species and is approximately 42 hours for falciparum, vivax and ovale, and 72 hours in malariae infection. 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 the mosquito, thus contributing to spread of the disease. Some parasites in the hepatic stage known as hypnozoites persist for long, remaining dormant in the hepatocytes, and can activate later causing relapse of the infection. This phenomenon is observed in all species except *P. falciparum* [1].

Malaria affects all ages, though newborn infants have been seen to have considerable resistance to *P. falciparum* infection due to presence of fetal haemoglobin. Males are more frequently exposed to the risk of acquiring malaria because of the outdoor life they lead. Pregnancy increases the risk of malaria in women. The epidemic of malaria is influenced by the immune status of the population, which is acquired after repeated exposure over several years [1].

Clinical Features

The duration of the incubation period of malaria varies with species of the parasite, and in natural infections i.e. in mosquito transmitted malaria this is as follows [1]:

- 12 (9-14) days for falciparum malaria
- 14 (8-17) days for vivax malaria
- 17 (16-18) days for ovale malaria
- 28 (18-40) days for malariae malaria

Uncomplicated Malaria [1]

The illness often starts with a period of several days of continued fever, before the development of classical bouts of fever on alternate days. The typical attack comprises of three distinct stages, i.e. the cold stage lasting for ½-1 hour, the hot stage lasting for 2-6 hours and the sweating stage lasting for 2-4 hours. The temperature may rise up to 40^0C [1,3]. Malaria caused by *P. falciparum* is more dangerous than other forms of malaria, though the onset is often insidious with malaise, headache and vomiting. Cough and mild diarrhea are common. The fever is irregular with no particular pattern and is often continuous. The cold, hot and sweating stages are also not distinctly observed. A patient with falciparum malaria, apparently not seriously ill, may develop serious fatal complications [1].

Severe Malaria [3]

Severe malaria occurs when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. The manifestations of severe malaria include:

- Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities
- Severe anemia due to hemolysis
- Hemoglobinuria due to hemolysis
- Acute respiratory distress syndrome (ARDS)

- Abnormalities in blood coagulation
- Hypotension caused by cardiovascular collapse
- Acute kidney failure
- Hyperparasitemia, where more than 5% of the red blood cells are infected by malaria parasites
- Metabolic acidosis, often in association with hypoglycemia
- Hypoglycemia, which may also occur in pregnant women with uncomplicated malaria, or after treatment with quinine.

Diagnosis [4]

Diagnosis of malaria is done by various methods; most common ones being used are clinical for presumptive diagnosis and direct microscopic examination of intracellular parasites on stained blood films for definitive diagnosis.

- *Clinical Diagnosis:* This is based on the patient's symptoms and on physical findings at examination.
- *Microscopic Tests:* Direct microscopic visualization of the parasite on the thick and/or thin blood smears has been the accepted method for the diagnosis of malaria in most settings, from the clinical laboratory to the field surveys. The microscopic tests involve staining and direct visualization of the parasite under the microscope. Two methods are generally employed.
  - Peripheral smear study with Giemsa stain
  - Quantitative buffy coat which is slightly more sensitive than conventional method
- *Antigen Detection:* Various test kits are available to detect antigens derived from malaria parasites, which use a dipstick or cassette format, and provide results in 2-10 minutes. These Rapid Diagnostic Tests (RDTs) offer a useful alternative to microscopy in situations where reliable microscopic diagnosis is not available and hence are used in national programme.
- *Molecular Diagnosis:* Parasite nucleic acids are detected using polymerase chain reaction (PCR). This technique is more accurate than microscopy. However, it is expensive, and requires a specialized laboratory.
- *Serology:* Serology detects antibodies against malaria parasites, using either indirect immuno fluorescence (IFA) or enzyme-linked immuno sorbent assay (ELISA). Serology does not detect current infection but rather measures past experience.

Additional laboratory findings may include mild anemia, mild decrease in blood platelets (thrombocytopenia), elevation of bilirubin, and elevation of aminotransferases.

Treatment

Drug policy on malaria in India was first formulated in 1982 and has subsequently been reviewed and revised periodically, with the most recent one being the National Drug Policy for Malaria (2013), brought out by the National Vector Borne Disease Control Programme, Government of India.

Table 1: Aims for use of various antimalarials under NVBDCP [6,7]

Aims	Drugs
To destroy the erythocytic forms i.e. schizonts, and alleviate symptoms	Chloroquine, quinine, artemisinin, pyrimethamine/sulphadoxine
To destroy the exo-erythrocytic forms i.e. hypnozoites, and prevent relapse	Primaquine
To destroy the sexual forms i.e. gametocytes, and prevent spread	Primaquine, Chloroquine
To prevent primary infection by erythrocytic stage prophylaxis, mainly in *P. falciparum* and to certain extent in *P. vivax*	Doxycycline Mefloquine

Table 2: Age-Wise Dosage Schedule for Treatment of *P.vivax* Cases

Age (in years)	Tablet Chloroquine (150 mg base)			Tablet Primaquine (2.5 mg base)
	Day-1	Day-2	Day-3	Day 1 to Day 14
< 1	½	½	¼	0
1–4	1	1	½	1
5–8	2	2	1	2
9–14	3	3	1½	4
15 & above	4	4	2	6
Pregnancy	4	4	2	0

Treatment for malaria is currently given according to this all over the country [5]. Several drugs are used with various objectives, as outlined in Table 1.

According to National Drug Policy 2013 the following treatment is given [5].

1. Treatment of P.vivax cases (Table 2)

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

Note: Primaquine is contraindicated in infants, pregnant women and individuals with G6PD deficiency. 14 day regimen of primaquine should be given under supervision. Before giving daily dose of primaquine check for presence of cyanosis or smoky pink coloured urine. In such cases do not give further doses of primaquine.

2. Treatment of uncomplicated P.falciparum cases (Table 3 & 4)

a. In states other than North Eastern states

- Artemisinin based Combination Therapy (ACT)
- *Artesunate* 4 mg/kg body weight daily for 3 days Plus

Table 3: Dosage Chart for treatment of *falciparum malaria* with ACT-SP

Age group (Years)	1st day		2nd day		3rd day
	AS	SP	AS	PQ	AS
<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)	1 (50 mg)	1 (7.5 mg base)	1 (50 mg)
5-8 Green blister	1 (100 mg)	1 (750+37.5 mg)	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)

Table 4: Dosage Chart for treatment of *falciparum* malaria with ACT-AL Co-formulated tablet of Artemether (20 mg) - Lumefantrine (120 mg)
(Not recommended during first trimester of pregnancy and for children weighing < 5 kg)

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

- *Sulfadoxine* (25 mg/kg body weight) - Pyrimethamine (1.25 mg/kg body weight) on first day Plus
- *Primaquin* 0.75 mg/kg body weight in a single dose on day 2.

AS: Artesunate; SP: Sulphadoxine-Pyrimethamine; PQ: Primaquine

Note: SP is not to be prescribed for children <5 months of age and should be treated with alternate ACT. ACT is not to be given in 1st trimester of pregnancy.

b. In North Eastern states

- Co-formulated tablets given according to age group
- *Artemeter* 20 mg
- *Lumefantrine* 120 mg
- *Primaquine*: 0.75 mg/kg body weight on day 2

AL: Artemether-Lumefantrine

3. Treatment of uncomplicated P.falciparum cases in pregnancy

- *1st Trimester:* Quinine salt 10mg/kg 3 times daily for 7 days. ACT is not to be given in 1st trimester of pregnancy.

Note: Quinine may induce hypoglycemia; 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 given above, that is
- ACT-AL in North Eastern states
- ACT-SP in other states

4. Treatment of mixed infections (P.vivax + P.falciparum) Cases (Table 5)*:* 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 wt. daily for 14 days.

5. 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.*

6. Treatment of Severe Malaria: The guidelines for specific antimalarial therapy are as follows:

- *Artesunate:* 2.4 mg/kg body weight IV or IM given on admission (time = 0 h); then at 12 h and 24 h and then once a day. **OR**
- *Artemether:* 3.2 mg/kg body weight IM given on admission and then 1.6 mg/kg body weight per day. **OR**
- *Arteether:* 150 mg IM daily for 3 days in adults only (not recommended for children). **OR**
- *Quinine:* 20 mg/kg body weight on admission (IV infusion or divided IM injection) followed by maintenance dose of 10 mg/kg body weight 8 hourly. The infusion rate should not exceed 5 mg salt/kg body weight per hour. (*loading dose of Quinine i.e. 20mg /kg body weight on admission may not be given if the patient has already received quinine or if the clinician feels inappropriate).

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 oral ACT for 3 days as described in previous section. 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

Table 5: Dosage Chart for treatment of mixed (*vivax* and *falciparum*) malaria with ACT-SP

Age	Day 1			Day 2		Day 3		Days 4-14
	AS (50 mg)	SP	PQ (2.5 mg)	AS (50 mg)	PQ (2.5 mg)	AS (50 mg)	PQ (2.5 mg)	PQ (2.5 mg)
< 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	4	3	6	4	6	4	6	6

Table 6: Different types of treatment failure[1]

	Danger signs/ severe malaria	Parasitaemia		
Early treatment failure (ETF)	On day 1, 2 or 3 in presence of parasitaemia	Parasitaemia on day 2 higher than that on day 0 irrespective of axillary temperature	Parasitaemia on day 3 with axillary temperature >37.5^{0}C	Parasitaemia on day 3 with >25% count than that on day 0
Late clinical failure (LCF)	On any day between 4 and 28 in presence of parasitaemia, and did not meet any criteria of ETF	Parasitaemia on any day between 4 and 28 with axillary temperature > 37.5^{0}C, in patients who did not previously meet any criteria of ETF		
Late parasitological failure (LPF)		Parasitaemia on any day between 7 and 28 with axillary temperature <37.5^{0}C, in patients who did not previously meet any criteria of ETF or LCF		

body weight 12 hourly for 7 days (doxycycline is contraindicated in pregnant women and children under 8 years of age).

Some don'ts in severe malaria case management - DO NOT use corticosteroids, give intravenous mannitol, use heparin as anticoagulant, administer adrenaline or overhydrate.

Anti Malarial Drug Efficacy and Resistance

Antimalarial drug efficacy is assessed through therapeutic efficacy studies (TES), conducted in a controlled environment. These are prospective studies done at regular intervals at the same sites which help in early detection of resistance. However, additional tools are needed to confirm its presence, such as in vitro tests, molecular analysis and measurements of drug concentrations. For infections appearing during follow-up, genotyping must be conducted to distinguish new infections from recrudescence [8].

Resistance to anti malarial drugs has been evident for three of the five species i.e. *P. vivax* and *P. falciparum* and *P. malariae*, of which serious clinical problem is encountered with *P. falciparum*. Resistance and treatment failures to antimalarial medicines have been defined by WHO as follows [8]:

- *Antimalarial resistance* is defined as 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 tolerance of the subject;
- *Artemisinin resistance* is defined as delayed parasite clearance following treatment with an artesunate monotherapy or with an ACT – this represents partial resistance/tolerance;
- *Multidrug resistance* (MDR) requires resistance to more than 2 operational antimalarial compounds of different chemical classes;
- *Treatment failure* is the inability to clear parasites from a patient's blood or to prevent their recrudescence after the administration of an antimalarial drug. Many factors can contribute to treatment failure, including incorrect dosage, poor patient compliance, poor drug quality, and drug interactions and resistance. Most of these factors are addressed by therapeutic efficacy studies. Different types of treatment failure have been defined (Table 6).

Detection of drug resistance is done by drug resistance tests, commonly available ones being as follows [4,8]:

- Therapeutic efficacy Test
- In vivo test
- In vitro tests
- Animal model studies
- Molecular characterization

After treatment the patient is considered to have been cured if s/he does not have parasitaemia till day 28. Treatment failure has been categorized in the following stages, in presence of which the patient is given alternative treatment.

Prevention

1. *Vector control:* This is done through integrated vector management, which includes biological and chemical control as anti-larval and anti-adult measures, along with engineering modifications [1,5,9].
2. *Personal Protection:* This is achieved by mosquito proofing of human dwellings by screening, sleeping under mosquito net preferably insecticide treated net (ITN) and long lasting insecticidal nets (LLIN). These nets are impregnated with deltamethrin, lambdacyhalothrin, or cyfluthrin. Mosquito repellent coils, pellets or cream containing diethyltoluamide 35% *N, N*-diethyl-3-methylbenzamide (DEET) formulations may also be used. In addition people should be advised to wear covered clothing [1,5,7].
3. *Chemoprophylaxis:* Chemoprophylaxis should be administered only in selective groups in high *P.falciparum* endemic areas. Use of personal protection measures including Insecticide Treated bed Nets (ITN)/Long Lasting Insecticidal Nets (LLIN) should be encouraged for pregnant women and other vulnerable population including travellers for longer stay. However, for longer stay of military and para-military forces in high *Pf* endemic areas, the practice of chemoprophylaxis should be followed wherever appropriate e.g. troops on night patrol duty and decisions of their medical administrative authority should be followed [7].

Under the national programme, chemoprophylaxis is administered as follows [5]

- *Short term chemoprophylaxis (up to 6 weeks)* – Doxycycline 100 mg once daily for adults and 1.5 mg/kg once daily for children (contraindicated in children below 8 years). The drug should be started 2 days before travel and continued for 4

weeks after leaving the malaria endemic area. Doxycycline is not recommended for pregnant women and children less than 8 years.

- *Chemoprophylaxis for longer stay (more than 6 weeks)* – Mefloquine: 250 mg weekly for adults and should be administered two weeks before, during and four weeks after exposure. Mefloquine is contraindicated in individuals with history of convulsions, neuropsychiatric problems and cardiac conditions. Therefore, necessary precautions should be taken and all should undergo screening before prescription of the drug.

4. *Vaccine:* There is no licensed vaccine against malaria at present. However efforts have been going on for decades. Malaria parasites have complex life cycles and, thus, distinct developmental stages, each of which has multiple antigens that could serve as targets of an immune response. Candidate vaccines were developed based on various antigens derived from these different stages. The major target species for vaccine development is *P. falciparum* [10].

Most current vaccine candidates target a single stage of the parasite's life cycle, out of which vaccines against the early pre-erythrocytic stages have shown most success. Of these the most promising one is RTS,S which is the world's first malaria vaccine that has been shown to provide partial protection against malaria in young children. The vaccine acts against *Plasmodium falciparum*, which is the most deadly malaria parasite worldwide and the most prevalent in Africa. The vaccine has been recommended by WHO for pilot introduction in selected areas of 3 African countries, through WHO's Malaria Vaccine Implementation Programme (MVIP) that will begin in 2018. MVIP will assess the feasibility of administering the required 4 doses of the vaccine in children; the vaccine's role in reducing childhood deaths; and its safety in the context of routine use. Data and information derived from the MVIP will inform a WHO policy recommendation on the broader use of the vaccine globally [10,11].

National Strategic Plan 2017-2022

The objectives of National Strategic Plan 2017-2022 in India are:

- Achieve universal coverage of case detection and treatment services in endemic districts to ensure 100% parasitological diagnosis of all malaria cases and complete treatment of all confirmed cases.
- Strengthen surveillance system to detect, notify, investigate, classify and respond to all cases
- Near universal coverage of population at risk of malaria by appropriate vector control intervention
- Near universal coverage of population at risk of malaria by appropriate BCC activities
- Effective programme management and coordination at all levels to deliver a combination of targeted interventions for malaria elimination

The strategies adopted for malaria elimination are Diagnosis and case management; Surveillance and epidemic response; Prevention by integrated vector management; Cross-cutting interventions like advocacy, communication and community mobilisation; programme management and co-ordination; monitoring and evaluation; research and development.

Under the Strategic Plan classification based on API has been done for districts as follows:

Category 0: Prevention of re-establishment phase

Category 1: Elimination phase

Category 2: Pre-elimination phase

Category 3: Intensified control phase

Strategies are targeted towards the priority districts.

Aligning with the National Framework for Malaria Elimination, the NSP 2017-22 focusses on strategic policies to provide universal intervention package, paving the way for malaria elimination by 2030.

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