Guidelines for Diagnosis and Treatment of Malaria in India

2009

Government of India

National Institute of Malaria Research

National Vector Borne Disease Control Programme

Preface

Malaria is a major public health problem in India, accounting for sizeable morbidity, mortality and economic loss. Apart from preventive measures, early diagnosis and complete treatment are the important modalities that have been adopted to contain the disease. In view of widespread chloroquine resistance in *Plasmodium falciparum* infection, and other recent developments, the national policy has been revised to meet these challenges.

The guidelines on 'Diagnosis and Treatment of Malaria in India (2009)' have been developed during the brainstorming meeting organized by the National Institute of Malaria Research (NIMR) and sponsored by WHO Country Office in India. These guidelines are the collaborative effort of National Vector Borne Disease Control Programme, National Institute of Malaria Research and experts from different parts of the country. The aim of this endeavour is to guide the medical professionals on the current methods of diagnosis and treatment based on the national drug policy (2008). This manual deals with the treatment of uncomplicated malaria and specific antimalarials for severe disease. The general management should be carried out according to the clinical condition of the patient and judgement of the treating physician. The warning signs of severe malaria have been listed so as to recognize the condition and give the initial treatment correctly before referring them to a higher facility.

It is hoped that these guidelines will be useful for doctors involved in the management of malaria.

Director, NIMR
Director, NVBDCP

Contents

1. Introduction

Malaria is one of the major public health problems of the country. Around 1.5 million confirmed cases are reported annually by the National Vector Borne Disease Control Programme (NVBDCP), of which 40–50% are due to *Plasmodium falciparum.* Malaria is curable if effective treatment is started early. Delay in treatment may lead to serious consequences including death. Prompt and effective treatment is also important for controlling the transmission of malaria.

In the past, chloroquine was effective for treating nearly all cases of malaria. In recent studies, chloroquine-resistant *P. falciparum* malaria has been observed with increasing frequency across the country. The continued treatment of such cases with chloroquine is probably one of the factors responsible for increased proportion of *P. falciparum* relative to *P. vivax.*

A revised *National Drug Policy on Malaria* has been adopted by the Ministry of Health and Family Welfare in 2008 and these guidelines have therefore been prepared for clinicians involved in the treatment of malaria.

2. Clinical features

Fever is the cardinal symptom of malaria. It can be intermittent with or without periodicity or continuous. Many cases have chills and rigors. The fever is often accompanied by headache, myalgia, arthralgia, anorexia, nausea and vomiting. The symptoms of malaria can be non-specific and mimic other diseases like viral infections, enteric fever etc.

Malaria should be suspected in patients residing in endemic areas and presenting with above symptoms. It should also be suspected in those patients who have recently visited an endemic area. Although malaria is known to mimic the signs and symptoms of many common infectious diseases, the other causes should also be suspected and investigated in the presence of following manifestations:

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

All clinically suspected malaria cases should be investigated immediately by microscopy and/or Rapid Diagnostic Test (RDT).

3. Diagnosis

3.1 Microscopy

Microscopy of stained thick and thin blood smears remains the gold standard for confirmation of diagnosis of malaria.

The advantages of microscopy are:

- The sensitivity is high. It is possible to detect malarial parasites 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.

3.2 Rapid Diagnostic Test

Rapid Diagnostic Tests are based on the detection of circulating parasite antigens. Several types of RDTs are available (http://www.wpro.who.int/sites/rdt). Some of them can only detect *P. falciparum*, while others can detect other parasite species also. The latter kits are expensive and temperature sensitive. Presently, NVBDCP supplies RDT kits for detection of *P. falciparum* at locations where microscopy results are not obtainable within 24 hours of sample collection.

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 user's manual should always be read properly and instructions followed meticulously. The results should be read at the specified time. It is the responsibility of the clinician or technician doing a rapid test for malaria to ensure that the kit is within its expiry date and has been transported and stored under recommended conditions. Failure to observe these criteria can lead to false/negative results. It should be noted that *Pf* HRP_2 based kits may show positive result up to three weeks of successful treatment.

Early diagnosis and treatment of cases of malaria aims at:

- Complete cure
- Prevention of progression of uncomplicated malaria to severe disease
- Prevention of deaths
- Interruption of transmission
- Minimizing risk of selection and spread of drug resistant parasites.

4. Treatment of uncomplicated malaria

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

4.1 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, therefore, it should be tested if facilities are available. Primaquine can lead to hemolysis 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.

4.2 Treatment of *P. falciparum* cases

The treatment of *P. falciparum* malaria is based on areas identified as chloroquine resistant/ sensitive as listed in annexure. Artemisinin Combination Therapy (ACT) should be given in resistant areas whereas chloroquine can be used in sensitive areas. ACT should be given only to confirmed *P. falciparum* cases found positive by microscopy or RDT.

4.2.1 What is ACT?

ACT consists of an artemisinin derivative combined with a long acting antimalarial (amodiaquine, lumefantrine, mefloquine or sulfadoxine-pyrimethamine). The ACT used in the national programme in India is artesunate + sulfadoxine-pyrimethamine (SP). Presently, Artemether + Lumefantrine fixed dose combination and blister pack of artesunate + mefloquine are also available in the country. Other ACTs which will be registered and authorized for marketing in India may be used as alternatives.

4.2.2 Should artemisinin derivatives be given alone?

Artemisinin derivatives must never be administered as monotherapy for uncomplicated malaria. These rapidly acting drugs, if used alone, can lead to development of parasite resistance.

4.2.3 Treatment in chloroquine-resistant areas

Areas which qualify for ACT

- High *Pf* endemic districts in seven North-eastern states, Andhra Pradesh, Chhattisgarh, Jharkhand, Madhya Pradesh and Orissa (see annexure).

- Other chloroquine resistant PHCs and clusters of blocks surrounding identified drug resistant foci (see annexure).

Individual cases who qualify for ACT

- Patients with history of travel to listed areas.
- No clinical or parasitological response to full dose of chloroquine within 72 hours of starting the therapy.

4.2.4 Can ACTs be given in pregnancy?

According to current WHO guidelines, ACTs can be given in the second and third trimester of pregnancy. The recommended treatment in the first trimester of pregnancy is quinine.

4.3 Treatment of mixed infections

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

4.4 Treatment based on clinical criteria without laboratory confirmation

All efforts should be made to diagnose malaria either by microscopy or RDT. However, special circumstances should be addressed as mentioned below.

What is the treatment, if RDT is negative and a microscopy result cannot be obtained within 24 hours?

If RDT for only *P. falciparum* is used, negative cases showing signs and symptoms of malaria without any other obvious cause for fever should be considered as 'clinical malaria' and treated with chloroquine in full therapeutic dose of 25 mg/kg body weight over three days. If a slide result is obtained later, the treatment should be adjusted according to species.

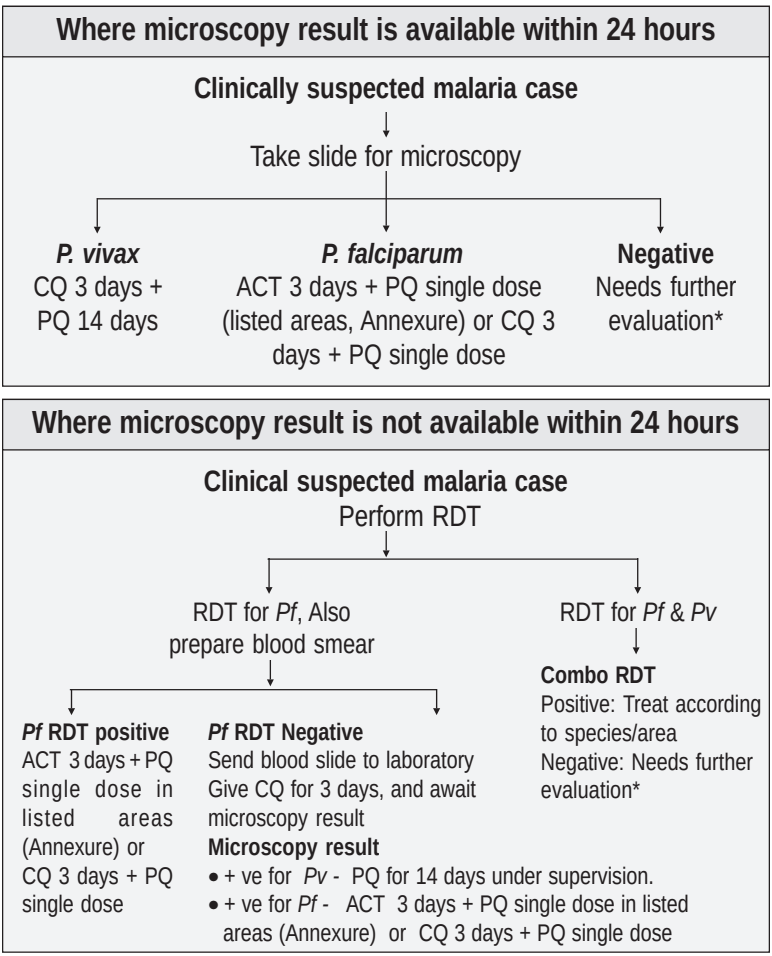
What is the treatment, if neither RDK nor microscopy is available?

'Clinical malaria' cases should be treated with chloroquine in full therapeutic dose.

General recommendations for the management of uncomplicated malaria

- Avoid starting treatment on an empty stomach. The first dose should be given under observation. Dose should be repeated if vomiting occurs within 30 minutes.
- The patient should report back, if there is no improvement after 48 hours or if the situation deteriorates.
- The patient should also be examined for concomitant illnesses.

The algorithm for diagnosis and treatment is as follows:



*Look for other causes of fever; repeat blood slide examination after an appropriate interval

Table 1. Chloroquine for *P. vivax* and *P. falciparum* cases in areas considered to be chloroquine sensitive

Age in years	Number of tablets		
	Day 1 (10 mg/Kg)	Day 2 (10 mg/Kg)	Day 3 (5 mg/Kg)
<1	½	½	¼
1 – 4	1	1	½
5 – 8	2	2	1
9 – 14	3	3	1½
15 & above	4	4	2

Table 2. Primaquine for *P. vivax* (Daily Dosage for 14 days)

Age in years	Daily dosage (in mg base)	No. of tablets (2.5 mg base)
< 1	Nil	Nil
1 – 4	2.5	1
5 – 8	5.0	2
9 – 14	10.0	4
15 & above	15.0	6

Table 3. Primaquine for *P. falciparum* (Single dose on first day)

Age in years	Dosage (in mg base)	No. of tablets (7.5 mg base)
< 1	Nil	0
1 – 4	7.5	1
5 – 8	15	2
9 – 14	30	4
15 & above	45	6

Note: Primaquine should be given for 14 days under supervision.
Do not give Primaquine to pregnant women and infants and G6PD deficiency cases.

Table 4. ACT (Artesunate + SP) dosage schedule for *P. falciparum* cases in chloroquine resistant areas

Age in years		Number of tablets		
		1st Day	2nd Day	3rd Day
< 1	AS SP	½ ¼	½ Nil	½ Nil
1 – 4	AS SP	1 1	1 Nil	1 Nil
5 – 8	AS SP	2 1½	2 Nil	2 Nil
9 – 14	AS SP	3 2	3 Nil	3 Nil
15 and above	AS SP	4 3	4 Nil	4 Nil

AS – Artesunate 50 mg, SP – Sulfadoxine 500 mg + Pyrimethamine 25 mg

5. Severe malaria

5.1 Clinical features

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:

- Impaired consciousness/coma
- Repeated generalized convulsions
- Renal failure (Serum Creatinine >3 mg/dl)
- Jaundice (Serum Bilirubin >3 mg/dl)
- Severe anaemia (Hb <5 g/dl)
- Pulmonary oedema/acute respiratory distress syndrome
- Hypoglycaemia (Plasma Glucose <40 mg/dl)
- Metabolic acidosis
- Circulatory collapse/shock (Systolic BP <80 mm Hg, <70 mm Hg in children)
- Abnormal bleeding and DIC

- Haemoglobinuria
- Hyperthermia (Temperature >104^{o} F)
- 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.

5.2 Can cases of severe malaria be negative on microscopy?

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.

5.3 Requirements for management of complications

For management of severe malaria, health facilities should be equipped with the following:

- Parenteral antimalarials, antibiotics, anticonvulsants, antipyretics
- Intravenous infusion equipment and fluids
- Special nursing for patients in coma
- Blood transfusion
- Well-equipped laboratory
- Oxygen

If these items are not available, the patient must be referred without delay to a facility, where they are available.

5.4 Specific antimalarial treatment of severe malaria

Severe malaria is an emergency and treatment should be given promptly.

Parenteral artemisinin derivatives or quinine should be used irrespective of chloroquine sensitivity

- **Artesunate:** 2.4 mg/kg i.v. or i.m. given on admission (time=0), then at 12 hours and 24 hours, then once a day (Care should be taken to dilute artesunate powder in 5% Sodium bi-carbonate provided in the pack).
- **Quinine:** 20 mg quinine salt/kg on admission (i.v. infusion in 5% dextrose/dextrose saline over a period of 4 hours) 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. NEVER GIVE BOLUS INJECTION OF QUININE. If parenteral quinine therapy needs to be continued beyond 48 hours, dose should be reduced to 7 mg/kg 8 hourly.
- **Artemether:** 3.2 mg/kg i.m. given on admission then 1.6 mg/kg per day.
- αβ **Arteether:** 150 mg daily i.m. for 3 days in adults only (not recommended for children).

Note:

- Once the patient can take oral therapy, the further follow-up treatment should be as below:
  - Patients receiving parenteral quinine should be treated with oral quinine 10 mg/kg three times a day to complete a course of 7 days, along with doxycycline 3 mg/kg per day for 7 days. (Doxycycline is contraindicated in pregnant women and children under 8 years of age; instead, clindamycin 10 mg/kg bw 12 hourly for 7 days should be used).
  - Patients receiving artemisinin derivatives should get full course of oral ACT. However, ACT containing mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications.

- **Intravenous preparations should be preferred over intramuscular preparations**
- **In first trimester of pregnancy, parenteral quinine is the drug of choice.** However, if quinine is not available, artemisinin derivatives may be given to save the life of mother. In second and third trimester, parenteral artemisinin derivatives are preferred.

5.5 Can *P. vivax* lead to severe malaria?

In recent years, increased attention has been drawn to severe malaria caused by *P. vivax.* Some cases have been reported in India, and there is reason to fear that this problem will become more common in the coming years. Severe malaria caused by *P. vivax* should be treated like severe *P. falciparum* malaria.

6. Chemoprophylaxis

Chemoprophylaxis is recommended for travellers, migrant labourers and military personnel exposed to malaria in highly endemic areas. Use of personal protection measures like insecticide-treated bednets should be encouraged for pregnant women and other vulnerable populations.

6.1 For short-term chemoprophylaxis (less than 6 weeks)

Doxycycline: 100 mg daily in adults and 1.5 mg/kg for children more than 8 years old. The drug should be started 2 days before travel and continued for 4 weeks after leaving the malarious area.

Note: Doxycycline is contraindicated in pregnant women and children less than 8 years.

6.2 For long-term chemoprophylaxis (more than 6 weeks)

Mefloquine: 5 mg/kg bw (up to 250 mg) weekly and should be administered two weeks before, during and four weeks after leaving the area.

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

7. Recommended reading

Malaria in India and guidelines for its control including case management

Website of National Vector Borne Disease Control Programme

http://www.nvbdcp.gov.in/malaria-new.html

National Drug Policy on Malaria (2008)

Ministry of Health and Family Welfare/Directorate of National Vector Borne Disease Control Programme, Govt. of India

http://www.nvbdcp.gov.in/Doc/drug-policy-08.pdf

RDTs/RDKs

Website of WHO Regional Office for the Western Pacific

http://www.wpro.who.int/sites/rdt

Treatment of malaria in general, especially ACT

World Health Organization (2006). WHO Guidelines for the Treatment of Malaria. Geneva, World Health Organization

http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf

Severe malaria

Regional guidelines for the management of severe falciparum malaria in small hospitals

World Health Organization, Regional Office for South-East Asia (2006). New Delhi, WHO/SEARO

http://www.searo.who.int/LinkFiles/Tools_&_Guidelines_Smallhospitals.pdf

Regional guidelines for the management of severe falciparum malaria in large hospitals

World Health Organization, Regional Office for South-East Asia (2006). New Delhi, WHO/SEARO.

http://www.searo.who.int/LinkFiles Tools_&_Guidelines_LargelHospitals.pdf

Kochar DK, Das A, Kochar SK *et al*. (2009) Severe *Plasmodium vivax* malaria: A report on serial cases from Bikaner in northwestern India. *Am J Trop Med Hyg* 80 (2): 194 –198.

Annexure

Districts/Areas identified for use of ACT Combination (AS+SP) for treatment of *Pf* malaria

S. No.	State/UT	Name of Districts	Name of Chloroquine resistant PHC / surrounding cluster of Block PHCs
1	**Andhra Pradesh (5 districts)**	Vizianagaram, Visakhapatnam, Srikakulam, East Godavri, Khammam	Entire 5 districts
2	**A&N Islands (2 districts)**	Great Nicobar & Little Andaman	20 PHCs
3	**Assam (24 districts)**	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,	Entire 24 districts
4	**Arunachal Pradesh (6 districts)**	Changlang, Lohit, East Siang, Papum Pare, East Kameng, West Kameng	Entire 6 districts
5	**Chhatisgarh (11 districts)**	Jagdalpur, Korba, Ambikarpur, Raigarh, Jashpurnagar, Raipur, Dhamteri, Dantewada, Kanker, Bilaspur, Korea	Entire 11 districts
6	**D & N Haveli**	D & N Haveli (6 PHCs)	Whole D & N Haveli (6 PHCs)
7	**Goa (2 districts)**	North Goa and South Goa (28 PHCs)	Whole state (28 PHCs)
8	**Gujarat (27 PHCs of 7 districts)**	Panchmahal (4 PHCs)	Kadana, Lunavada, Khanpur, Santarampur

contd...

	Gujarat (27 PHCs of 7 districts)	Kutch Bhuj (6 PHCs)	Kavada, Gorewali, Mundra, Mandavi, Anjar, Nakhatrana
		Anand (2 PHCs)	Pansora, Anand
		Dahod (3 PHCs)	Degawada, Limkheda, Dhanpur
		Patan (5 PHCs)	Lolada, Harij, Radhanpur, Patadi, Rapar
		Surat (4 PHCs)	Surat City, Olpad, Choryasi, Kamrej
		Kheda (3 PHCs)	Matar, Mahudha, Mehmdabad
9	**Jharkhand (12 districts)**	Gumla, Ranchi, Simdega, East Lohardagga, Singhbhum, West Singhbhum, Saraikela, Sahibganj, Godda, Dumka, Latehar, Pakur	Entire 12 districts
10	**Karnataka (53 PHCs of 12 districts)**	Kolar (7 PHCs)	Gulur, Bagepally, Chelur, Pathpalya, Shivpura, Chakavelu, Gudibande
		Raichur (20 PHCs)	Echanal, Hatti, Ramdurga, Nagarala, Anwari, Anehosur, Gurugunta, Mudgal, Maski, Sajjalgudda, Makapur, Mediknal, Santhakallur, Galag, Jalahally, Gabbur, Arkera, Kopper, Masarkal, Hirebuddur
		Bellary (2 PHCs)	Kamalpura, Kamply
		Mandya (1 PHC)	D.K. Halli
		Bagalkot (4 PHCs)	Kamatagi, Nandikeshwar, Hungunda, Pattadkal
		D. Kannada (1 PHC)	Mangalore
		Chemarajanagar (1 PHC)	Sathegala

contd...

	Karnataka (53 PHCs of 12 districts)	Gadag (1 PHC)	Bellati
		Chitradurga (6 PHCs)	Ranganathapura, Betturpalya, Dindawara, Yelladakere, V.V.Pura, J.G.Hally
		Belgaum (1 PHC)	A.K. Hal
		Gulbarga (8 PHCs)	Kakkera, Kembhavi Project, Pettampura, Rajankallur, Kurkunta, N. Pura Project, B.R. Gudi Project, Malkhed
		Bijapur (1 PHC)	Almatti Project
11	**Madhya Pradesh (9 districts)**	Jhabua, Dindori, Shahdol, Chhindwara, Siddhi, Mandla, Seoni, Hoshangabad, Guna	Entire 9 districts
12	**Maharashtra (32 PHCs of 2 districts)**	Raigarh	Washi
		Ghadchiroli (31)	Korchi (2), Dhanora (5), Gadchiroli (2), Etapalli (3), Bhamragad (3), Aheri (3), Sironcha (5), Kurkheda (2) Mulchera (2), Chamorshi (2), Aarmori (2)
13	**Manipur (11 districts)**	All districts (11)	Whole state
14	**Meghalaya (7 districts)**	All districts (7)	Whole state
15	**Mizoram (3 districts)**	Lunglei, Kolasib, Mamit	Entire 3 districts
16	**Nagaland (12 districts)**	All districts (12)	Whole state
17	**Orissa (13 districts and 39 PHCs of 11 districts)**	Keonjhar, Kandhamal, Sundargarh, Mayurbhanj, Kalahandi, Nuapada, Koraput, Sambalpur, Gajapati, Rayagada, Jharasguda, Malkangiri, Nawarangpura	Entire 13 districts

contd...

	Orissa (13 districts and 39 PHCs of 11 districts)	Angul (7 PHCs)	Bantala, Madhapur/ Athamallic, Banarpal, Koshala/ Chendipada, Kanhia, Khamar/ Palalahda, R.K. Nagar/ Kishorenagar
		Dhenkanal (3 PHCs)	Khajurikata, Odapada, Beltikri/Dhenkanal
		Deogarh (3 PHCs)	Tileibbani, Chhatabar/ Riamal, Bamparda/ Barkot
		Bolangir (6 PHCs)	Khaprakhol, Bangamunda/ Sindheipalli, Guduvella, Ghasian/patna, Belpada,Tureikela
		Boudh (3 PHCs)	Adenigarh, Manamunda, Baunshini/Boudh
		Balasore (3 PHCs)	Bherhampur, Iswarour, Khaira
		Baragarh (2 PHCs)	Bukuramunda, Jamla
		Cuttack (2 PHCs)	Kanpur, Maniabandha
		Ganjam (4 PHCs)	Badagada, Adapada, Bomkei, Dharakot
		Nayagarh (2 PHCs)	Gania, Madhyakhand
		Sonepur (4 PHCs)	Birmaharajpur, Naikenpali, Tarva, Ullunda
18	**Rajasthan (11 PHCs of 4 districts)**	Dungarpur (4 PHCs)	Bicchiwara, Damri, Simalwara, Dungurpur
		Banswara (4 PHCs)	Kushalgarh, Chota Dungara, Banswara, Talwara
		Baran (2 PHCs)	Kishanganj, Shahbad
		Udaipur (1 PHC)	Kotra
19	**Tamil Nadu (1)**	Rameshwaram Island	
20	**Tripura (4 districts)**	All districts (4)	Whole state

contd...

21	**Uttar Pradesh (1)**	Mirzapur	NTPC Project area Mirzapur
22	**West Bengal (39 PHCs of 5 districts)**	Purulia (11 PHCs)	Bagmundi, Sadar, Bandhwan, Sirkabad, Jhalda-II, Balarampur, Jhalda-I, Joypur, Barabazar, Manbazar-II, Manbazar-I
		Jalpaiguri (13 PHCs)	Uttar Latabari, Mal, Kalimpong, Sukna, Falakata, Kumargram, Garubathan, Rajgunj, Maynaguri, Matiali, Madarihat, Alipurduar-I, Alipurduar-II
		Bankura (5 PHCs)	Ranibandh, Raipur, Khatra, Belpahari, Hirbandh
		Darjeeling (8 PHCs)	Naxalbari, Sukna, Kurseong, Mirik, K-Phansidewa, Kalimpng-I, Phansidewa, Rajgunj
		Kolkata Municipal Corporation	Ward No. 37 and 43
	Total	**117 districts (50 WBD + 67 NE states + 256 PHCs of 48 districts)**	

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NIMR/TRS-06/APR-2009

Feedback Form

Guidelines for Diagnosis and Treatment of Malaria in India

1. Are these guidelines useful? :
2. Are they user friendly? :
3. Do they give complete information on the subject? :
4. Do they give the message regarding diagnosis and treatment of malaria clearly? :
5. Any suggestion to improve the guidelines? :

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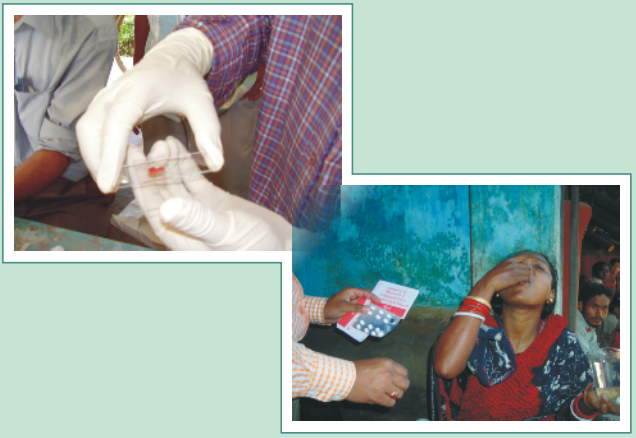

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