

An overview of WHO GUIDELINES
ON THE MANAGEMENT OF
MALARIA

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- Global scenario :

Malaria is the most common parasitic disease of man. Malaria is currently endemic in 109 countries and in territories of tropical and subtropical zones, spanning all continents of the world except Antarctica and Australia. There were an estimated 247 million malaria cases among 3.3 billion people at risk in 2006, causing nearly a million deaths, mostly of children under 5 years. To accelerate progress in malaria control, the 2005 World Health Assembly (WHA) set targets of 80% coverage for four key interventions: insecticide-treated nets for people at risk; appropriate antimalarial drugs for patients with probable or confirmed malaria; indoor residual spraying of insecticide for households at risk; and intermittent preventive treatment in pregnancy.

According to the World Malaria Report 2008 by the WHO; INDIA had an estimated 10.6 million malaria cases in 2006 that accounted for approximately 60% of cases in the WHO South East Asia Region (fig 1). With over 100 million slides examined over every year, all reported cases are confirmed; about half are due to Falciparum malaria. The states most affected are UP, Bihar, Karnataka, Orissa, Rajasthan, Madhya Pradesh & Pondicherry. But the percentage of malaria deaths is lower in India compared to other South-East Asian countries (fig 2).

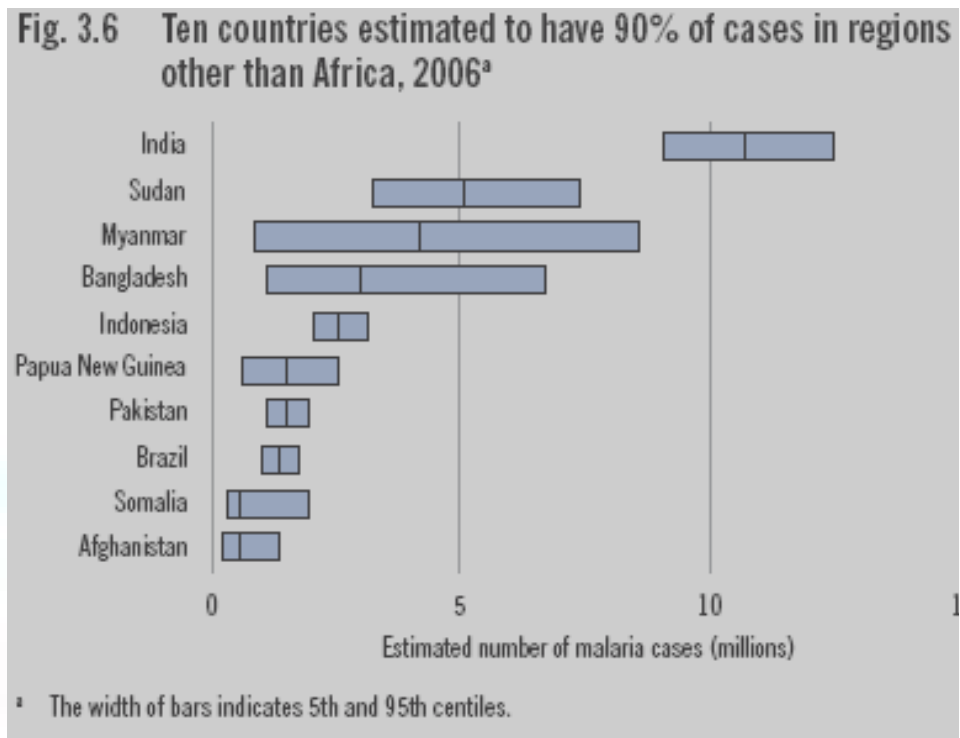


Fig 1(taken from World Malaria Report 2008)

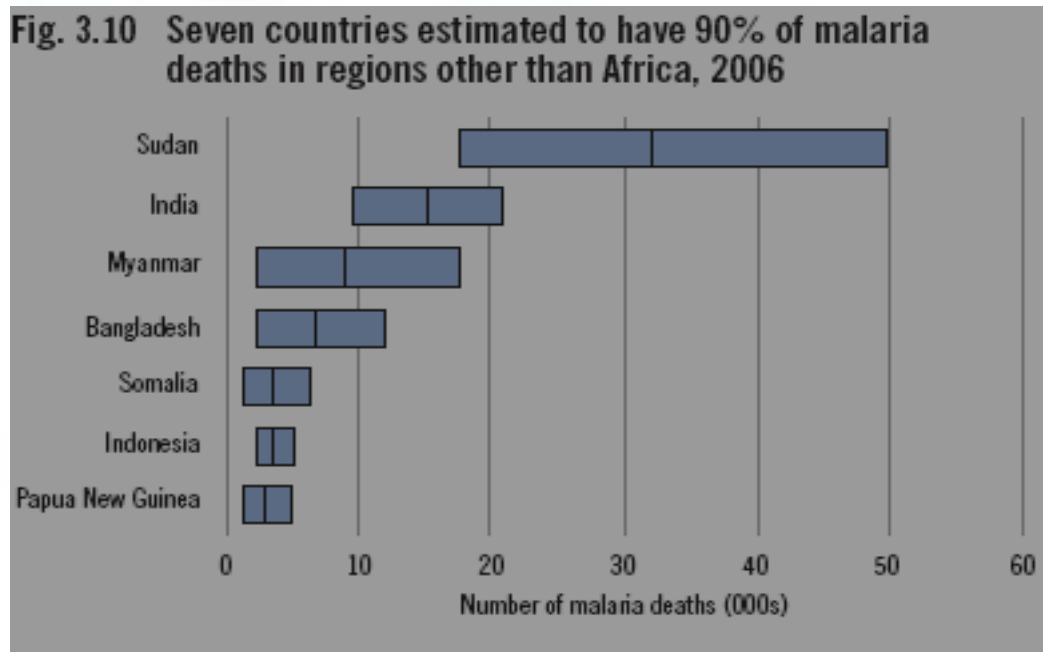


Fig 2(taken from world malaria report, WHO;2008)

- EPIDEMIOLOGICAL PROFILE OF MALARIA IN INDIA

Stratification of burden (reported cases/1000)

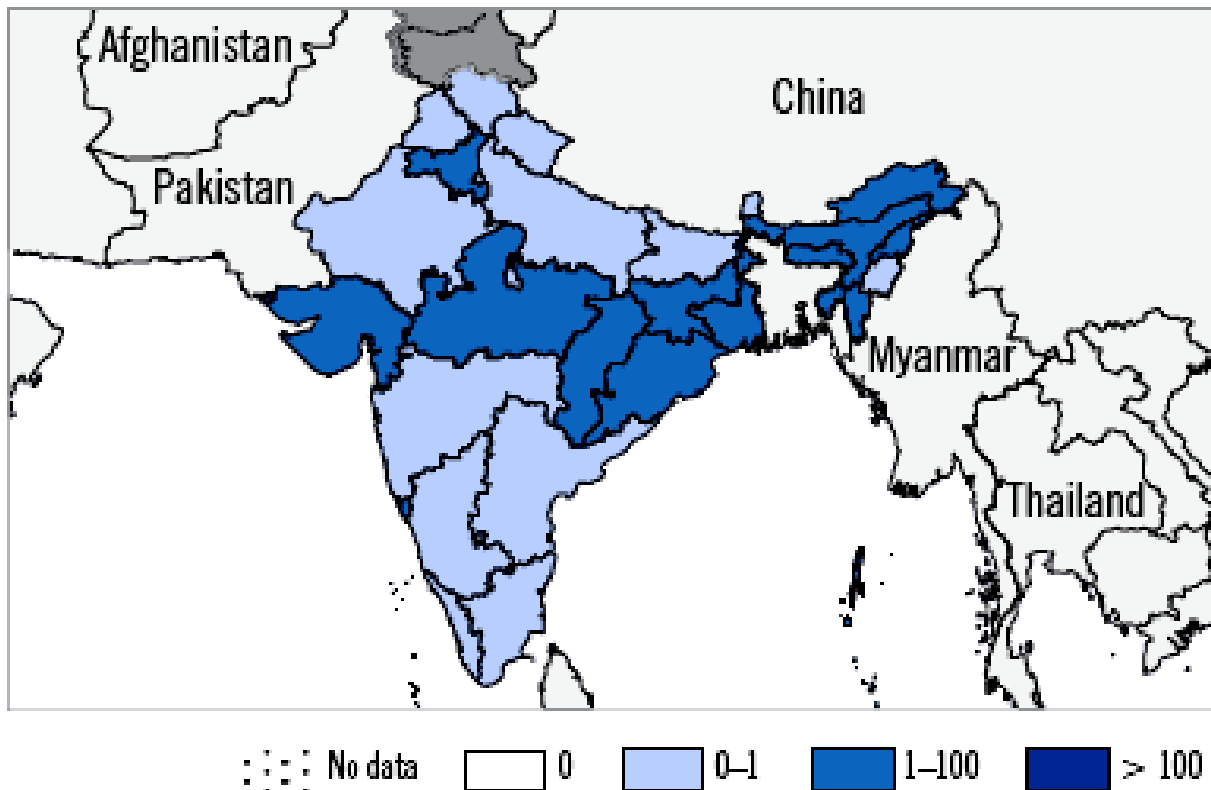


Fig 3

- Population by Malaria endemicity (table 1)

High transmission > 1/1000	27 %
Low transmission 0-1 /1000	58%
Malaria free cases	15%
Rural population	71 %

World Malaria Report 2008; WHO

- Estimated malaria burden (table 2)

Estimated cases and deaths per 1000.

		Per 1000	Lower	Upper
Fever suspected of being malaria	All ages	552	483	767
	< 5 yrs	432	378	599
Malaria cases	All ages	9.0	8.0	11
	<5 yrs	7.0	6.0	8.0
Malaria deaths	All ages	0.01	0.01	0.02
	<5 yrs	0.04	0.02	0.05
Malaria case fatality rate	All ages	—	—	—
	<5 yrs	—	—	—

Based on the above figures 58 % of the Indian population is in low transmission settings. As outlined in table 2, still burden of malaria in under five populations is very high and as equal to all other age groups. As outlined in FIG 4 estimated malaria burden in under 5 age group is the same since 2002 upto 2007.

Reported and estimated malaria cases, per 1000

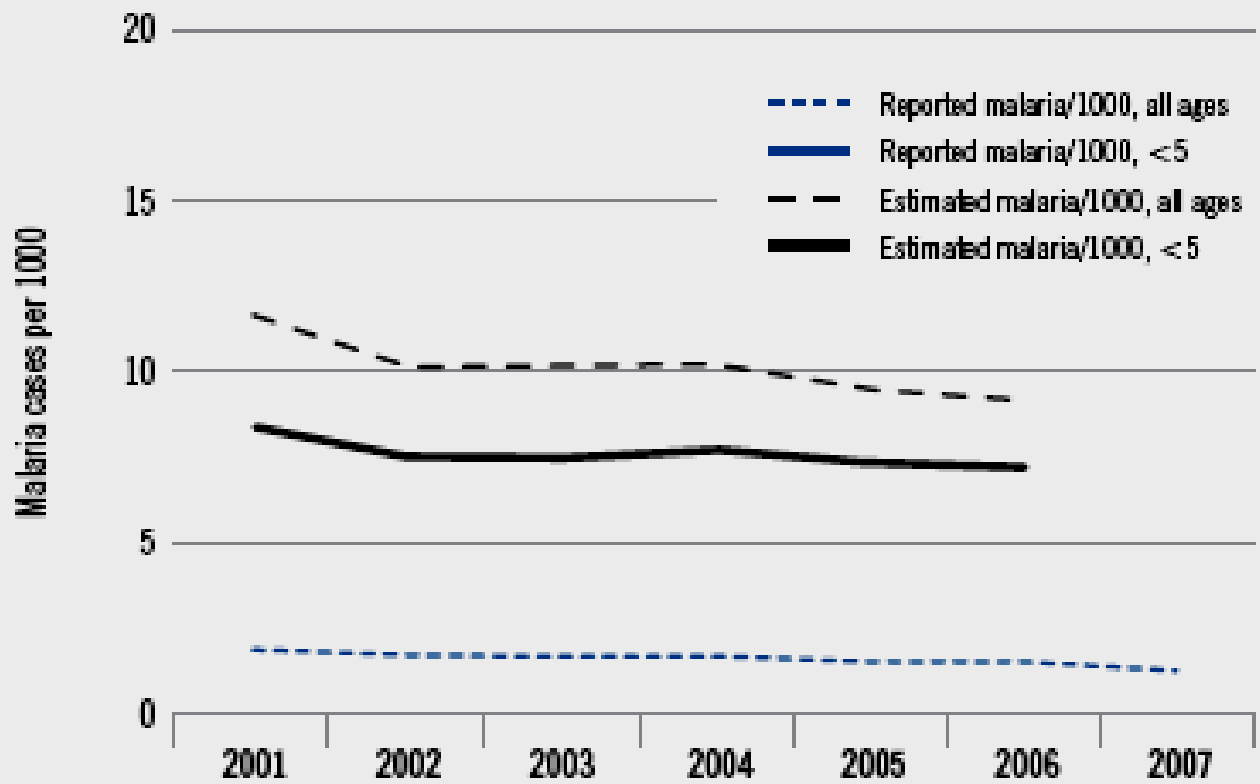
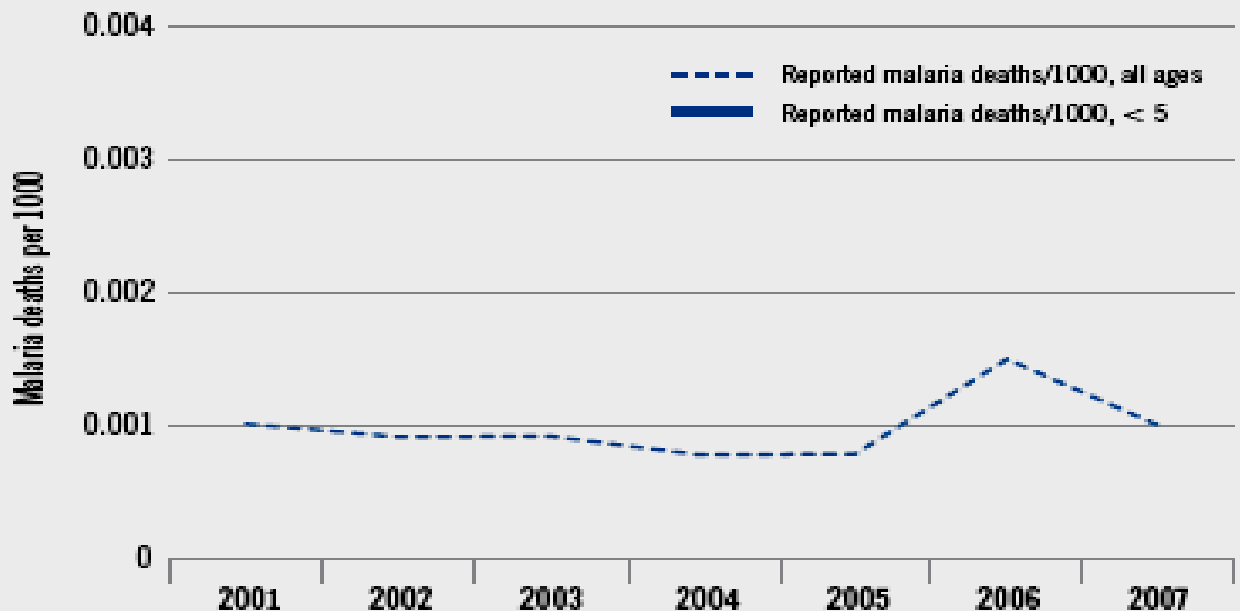


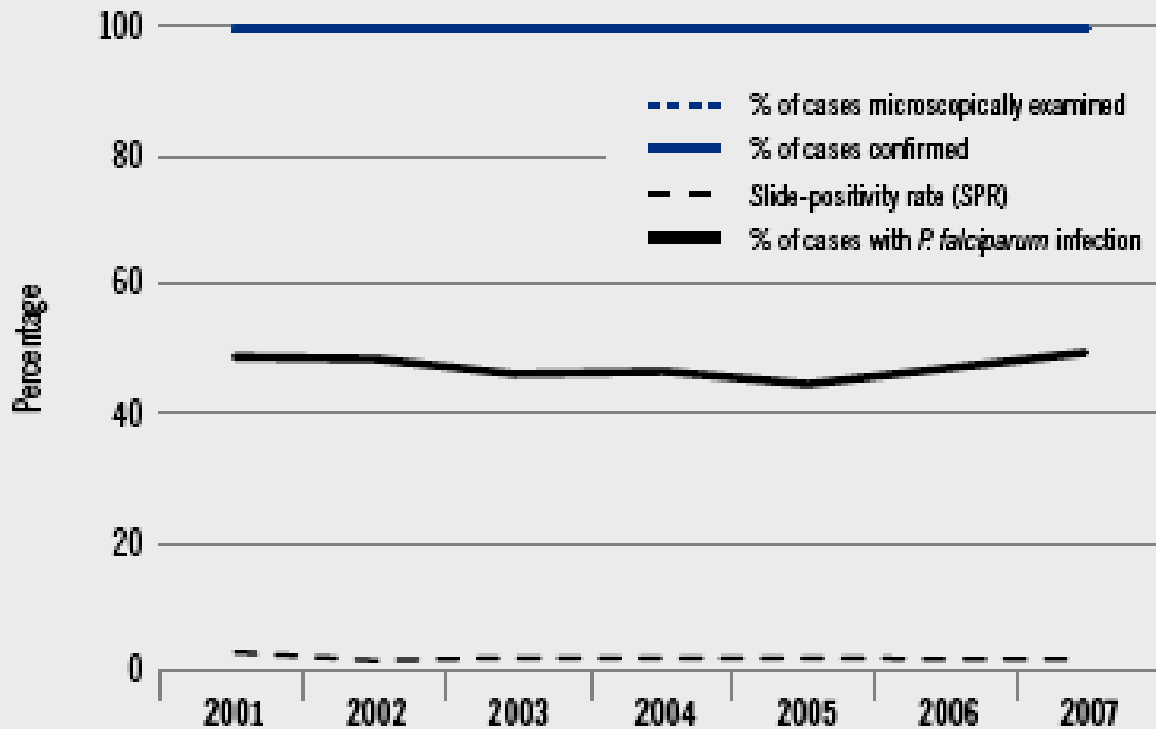
Fig 4(taken from world malaria report, WHO;2008)

Reported malaria deaths, per 1000



(Fig 5 taken from world malaria report, WHO;2008)

Slide examination, case confirmation, *Plasmodium* spp



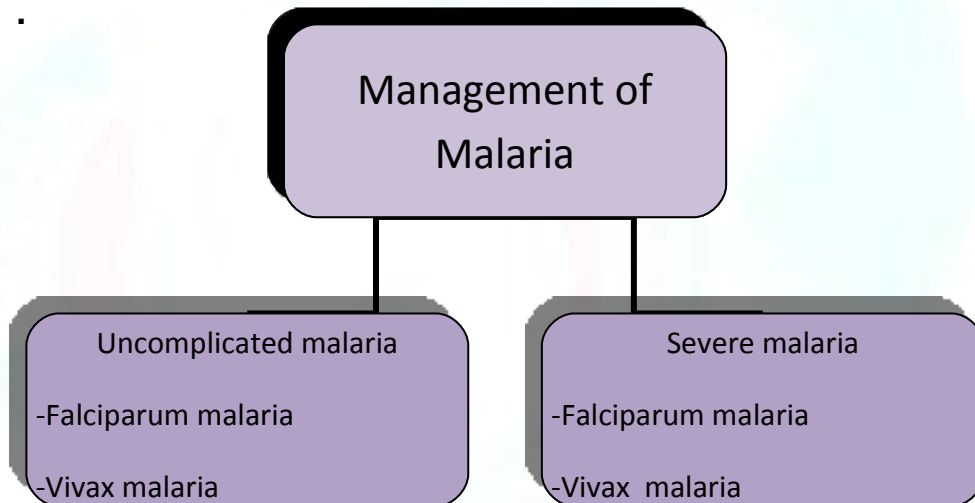
Examined	90 389 019	91 617 725	99 136 143	97 111 526	104 120 792	106 606 703	94 855 005
Positive	2 085 484	1 841 227	1 869 403	1 915 363	1 816 569	1 785 109	1 476 562
<i>P. falciparum</i>	1 005 236	897 446	857 101	890 152	805 077	838 555	725 502

Fig 6(taken from world malaria report, WHO;2008)

But suprisingly as outlined in Fig 5 and 6 , maxium number of malaria deaths are reported in 2006 and as outlined in Fig 6 percentage of Falciparum infection is the same over the past 7 years.

• Management of Malaria:

Management of Malaria can be discussed under the following areas.



UNCOMPLICATED MALARIA

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence of vital organ dysfunction.

- Uncomplicated Falciparum malaria:

Antimalarial combination therapy is recommended by WHO for the management of uncomplicated falciparum malaria.

Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and thus unrelated biochemical targets in the parasite. Rationale for combining two different antimalarial with different mode of action is to counteract resistance and to improve therapeutic efficacy. Antimalarial combination therapy

recommended for Falciparum malaria is Artemisinin based combination therapy.

Rationale behind Artemisinin based combination therapy:

Artemisinin and its derivative produce rapid clearance of parasitaemia (by a factor of approx 10,000 in each asexual cycle), rapid resolution of symptoms and are eliminated rapidly. When given in combination with rapidly eliminated compounds (tetracyclines, clindamycin), a 7-day course of treatment; slowly eliminated antimalarials, shorter courses of treatment (3 days) are effective. The following ACTs are currently recommended (alphabetical order):

Artemether + Lumefantrine

Artesunate + Amodiaquine

Artesunate + Mefloquine

Artesunate + Sulfadoxine–pyrimethamine.

The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination:

In areas of multidrug resistance (South-East Asia):

Artesunate + Mefloquine or Artemether-Lumefantrine

The Artemisinin derivative components of the combination must be given for at least 3 days for an optimum effect.

**ARTEMETHER
+LUMEFANTRINE**

co - formulated tablets containing 20 mg of Artemether and 120 mg of Lumefantrine can be used as a six dose regimen twice a day for 3 days

Dosing interval and no of tablets	5-14 kg	15-24 kg	25-34 kg	>34 kg
0h	1	2	3	4
8h	1	2	3	4
24h	1	2	3	4
36h	1	2	3	4
48h	1	2	3	4
60 h	1	2	3	4

Artemether - Lumefantrine is recommended for children above 5 kg. lumenfantrine absorption are enhanced by co - administration with fat so patients should be advised to take this ACT with milk or fat containing food.(a)

**ARTESUNATE
AMODIAQUINE**

+ Recommended dose :
Artesunate - 4mg/kg/bw and
Amodiaquine-10mg(base)/kg/bw
Once a day for 3 days

Can be used above 5 months

Separate scored tablets ; co- formulated not yet available.(b)

**ARTESUNATE
MEFLOQUINE
ARTESUNATE**

+ 4 mg/kg/bw of Artesunate OD for 3 days and Mefloquine 25 mg/kg bw in two (15 + 10) divided doses on day 2 and 3. (c)

**ARTESUNATE
SULPA-
PYRITHEMANINE**

4 mg/kg bw of Artesunate given once a day for 3 days and

Single administration of SP as 25mg/kg of Sulfadoxine and 1.25 mg/kg of Pyrimethamine on day one.

Available as separately scored tablets (d)

Recommended ACT for management of uncomplicated Falciparum Malaria-
table 3

b- Artesunate- & Amodiaquine combination has been mentioned in WHO (guidelines for treatment for malaria – 2006) , only concerning point mentioned by WHO is that resistance likely to worsen to continued availability of Chloroquine and Amodiaquine monotherapies. This combination has not been mentioned by IAP infectious disease chapter.

C – This combination has been recommended by WHO to be used in South – East Asian countries but currently there are insufficient safety and tolerability data on Mefloquine dosage in children and Mefloquine shares cross resistance with Quinine which is still an effective drug in our country ; so IAP infectious disease chapter do not advocate use of Mefloquine.

d- Under the previous national drug policy, SP was used in areas of chloroquine resistance. Countries where SP was introduced following chloroquine resistance showed its rapid decline in efficacy within few years. WHO recommends that this combination is efficacious only when 28 day cure rates with SP exceeds 80 %; for this reason maybe it has not recommended this combination for South – East Asian region countries.

In correct approaches to treatment- Practical aspects

1. What is not combination therapy?

1. Drug combinations like SP; Sulfalene- pyrimethamine; Proguanil-dapsone; chlorproguanil-dapsone and Atovaquone-proguanil. These compounds rely on synergy, so they are operationally single and are not considered as antimalarial combination therapy.

2. Efficacy of non – ACT?

Non ACT like SP+ Chloroquine or SP + Amodiaquine; due to prevailing high levels of resistance have compromised the efficacy of these combinations. WHO recommends that ACT is not available than Amodiaquine + SP may be used as an interim measure.

2. WHO recommends that a full course of antimalarial treatment should always be given once a decision to give antimalarial treatment has been reached. Partial treatments should not be considered.

3. WHO has also recommended that Artemisinin and partner medicines of ACT should not be available as monotherapies?

Management of Treatment failures with ACT

1. Failure within 14 days:

If fever and parasitaemia fail to resolve or recur within 2 weeks of treatment then this is considered as treatment failure. Whenever possible treatment failure must be confirmed parasitologically. Management is with second line antimalarials.

2. Failure after 14 days:

Recurrence of fever and parasitaemia more than 2 weeks after treatment could be due to recrudescence or new infection. Parasitological confirmation not a precondition. If there is recrudescence first line management is effective in most cases.

Recommended second line antimalarials by WHO; (table 4)

- 1. Alternative ACT known to be effective in that region.**
- 2. Artesunate (2 mg/kg OD) + Tetracycline (4 mg/kg bw qid); >8 yrs**

Or

Doxycycline (3.5 mg/kg bw od) ; > 8yrs

Or

Clindamycin (10 mg/kg bw bd)

Above drugs to be given a combination for a period of 7 days.

- 3. Quinine 10 mg salt/kg/dose 3 times daily for 7 days**

+

Tetracycline or Doxycycline or Clindamycin for 7 days.

MANAGEMENT OF MULTIDRUG RESISTANCE P. FALCIPARUM

Multidrug resistance is generally defined as resistance to three or more antimalarial compounds from different chemical classes. Generally 4-aminoquinolones (chloroquine) and antifolates (SP). Management is combination of

1. Quinine + tetracycline/Doxycycline/Clindamycin for 7 days

(Same dosage as second line antimalarial) plus

Single dose of Primaquine above 1 yr 0.75mg/kg (gametocytocidal action)

Or

2. Artemether -Lumefantrine combination therapy.

MANAGEMENT OF UNCOMPLICATED VIVAX MALARIA

1. Chloroquine sensitive Vivax Malaria:

Chloroquine 10 mg base/kg stat followed by 5 mg/kg at 6, 24 and 48 hrs.

Or

Chloroquine 10 mg base /kg stat followed by 10 mg/kg at 24 hrs and 5 mg/kg at 48 hrs.

2. Chloroquine resistant Vivax malaria:

Relatively few data are available on Chloroquine resistant Vivax malaria. Studies have shown that Mefloquine; Quinine; Artemether-Lumefantrine; Amodiaquine can be used. However clinical data at present is insufficient.

3. Radical cure :

Radical cure is to prevent relapses. P.Vivax forms hypnozoites, parasite stages in the liver that can result in multiple relapses of infection, weeks to months after the primary infection.

Primaquine should be given in the dose of 0.25 mg/kg OD for 14 days. As Primaquine can cause hemolytic anemia in G- 6 PD deficiency, they should be preferably screened for the same prior to starting treatment. As infants are relatively G-6 PD deficient, it is not recommended in this age group. In cases of borderline G6PD deficiency, once weekly dose of Primaquine 0.75 mg/kg is given for 8 weeks. In severe G6PD deficiency Primaquine should not be given.

- Management of severe Falciparum malaria

Definition of severe Falciparum malaria:

In a patient with P. falciparum asexual parasitemia and no other obvious cause of their symptoms, the presence of one or more of the clinical or laboratory features classifies the patient as suffering from severe malaria

Clinical manifestation:

Prostration

Impaired consciousness

Respiratory distress (acidotic breathing)

Multiple convulsions

Circulatory collapse

Pulmonary oedema (radiological)

Abnormal bleeding

Jaundice

Haemoglobinuria

Laboratory:

Severe anemia

hypoglycemia

Acidosis

Renal impairment

Hyperlactataemia

Hyperparasitaemia

Recommendations of treatment of severe Malaria

After rapid clinical assessment and confirmation of the diagnosis, full doses of parental antimalarial treatment should be started without delay with which effective antimalarial is first available.

MANAGEMENT OF SEVERE FALCIPARUM MALARIA

In low transmission areas or outside Malaria endemic areas:

1. Artesunate 2.4 mg/kg bw i.v/i.m on admission then at 12 h and 24 h, then once a day for 7 days (change to oral once patient can tolerate orally. (Plus)

Tetracycline / Doxycycline/Clindamycin is added to Artesunate as soon as patient can swallow and should be continued for 7 days.(dosage as in table 4)

In high transmission areas; the following antimalarials are recommended

1. Artesunate 2.4 mg/kg bw i.v/i.m on admission then at 12 h and 24 h, then once a day for 7 days (change to oral once patient can tolerate orally). (or)
2. Artemether 3.2 mg/kg bw i.m given on admission then 1.6 mg/kg bw per day for 7 days. (or)
3. Quinine 20 mg salt/kg /bw diluted in 10 ml of isotonic fluid/kg by infusion over 4 hrs .Then 12 hrs after the start of loading dose of 10 mg salt/kg over 2hrs.This maintenance dose should be repeated every 8 hrs ,calculated from beginning of infusion ,until patient can swallow , then Quinine tablets 10 mg salt /kg 8hrly to complete a 7 days course (plus)

Tetracycline / Doxycycline/Clindamycin is added to Artesunate as soon as patient can swallow and should be continued for 7 days. (dosage as in table 4)

Management of severe Vivax Malaria

P.Vivax has a very low case fatality rate. Management is same as above.

Some practical aspects of management in relation to Malaria

Role of Blood transfusion in Malaria:

In high transmission settings, blood transfusion is recommended for children with an Hb < 5 gm/dl and in low transmission settings a threshold of 7 g/dl is recommended. These general recommendations need to be tailored to the individual.

Role of concomitant use of Antibiotics:

The threshold for administering antibiotic treatment should be low in severe Malaria. Septicemia and severe Malaria are associated and there is diagnostic overlap particularly in children. Although enteric bacteria (notably salmonella) have predominated in most trials, a variety has been cultured, so broad spectrum antibiotic treatment should be given initially.

Hyperparasitemia;

There is not enough evidence to provide a firm recommendation on the definition of hyperparasitaemia, although $> 5\%$ parasitemia in a low transmission setting and $> 10\%$ in a higher setting are recommended.

Hyperparasitemia patients with no other signs of severe disease should be treated with Artemisinin derivative (oral/parental) based on the child's condition. The optimum duration of treatment for hyperparasitaemia is still unresolved, available data's suggests for a course of seven days.

- WHO recommendations for the diagnosis and treatment of Malaria.
 1. WHO recommends that treatment of Malaria should be based on a laboratory-confirmed diagnosis, with the exception of children under 5 years of age in areas of high transmission in whom treatment may be provided on the basis of a clinical diagnosis.

2. All uncomplicated *P. falciparum* infections should be treated with an artemisinin-based combination therapy and *P. vivax* with chloroquine and primaquine (except where *P. vivax* is resistant to chloroquine, when it should be treated with ACT and primaquine). In Central America, the only remaining region where *P. falciparum* is sensitive to chloroquine, the change to ACT should be made when chloroquine failure rates reach 10%.
3. Four ACTs are currently recommended for use: artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine and artesunate-sulfadoxine-pyrimethamine. The choice of the ACT should be based on the efficacy of the partner medicine in the country or area of intended deployment.
4. Patients suffering from severe malaria presenting at the peripheral levels of the health system should be provided prereferral treatment with quinine or artemisinins, and transferred to a health facility where full parenteral treatment and supportive care can be given.
5. Severe malaria should be treated parenterally with either an artemisinin derivative or quinine until the patient can swallow, when a complete course of ACT must be administered.

Points to ponder in relation to WHO guidelines

1. WHO does not recommends starting antimalarial drugs in children above 5 yrs with no laboratory confirmed diagnosis, how many of us follow it?

2. WHO recommends to start ACT in all *P. Falciparum* cases ; but in the recommendations given by Infectious disease chapter , Indian Academy Pediatrics of IAP in “Management Of Malaria in Children”; Update 2008 has divided management of *Falciparum* Malaria under two headings ; Chloroquine sensitive and Chloroquine resistant *Falciparum* Malaria. More than 80 % of the therapeutic efficacy studies conducted from 2001–07 indicate failure to chloroquine beyond cut off level of 10% in INDIA. WHO in its technical report ‘WORLD MALARIA REPORT’ has outlined that in “Central America; the only remaining region where *P. falciparum* is sensitive to chloroquine, the change to ACT should be made when chloroquine failure rates reach 10%”; based on these facts is it still justified to classify treatment of *Falciparum* malaria into Chloroquine sensitive and Choroquine resistant?

3. WHO clearly recommends the use of either Quinine or Artesunate derivatives & combination of clindamycin/doxycycline/tetracycline for the management of Severe Malaria; how many of us follow this?

• References:

1. World Malaria Report; WHO/HPM/GMP/2008
2. Guidelines for the treatment of Malaria; WHO/HTM/MAL/2006.110
3. <http://www.malaria-journal.com/content/8/1/107>.
4. *Dr Ritabrata Kundu et al: Management of Malaria in Children: Update 2008*. Indian pediatrics 2008; 45:731-735



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