DRUG RESISTANT MALARIA
CURRENT STATUS

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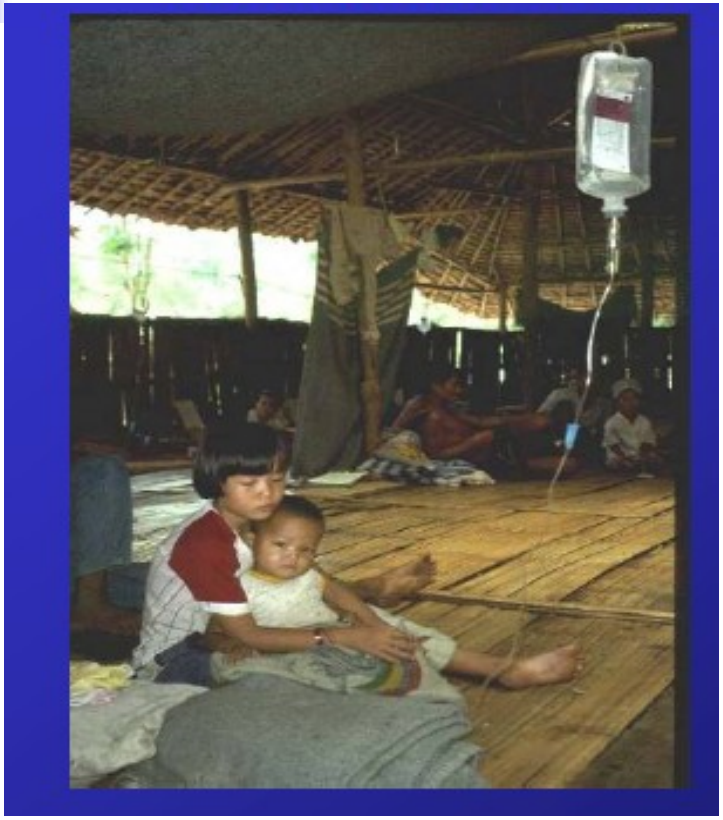
DRUG RESISTANT MALARIA

- Ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal or higher than those usually recommended, but within the limits of tolerance of the patients
- Main obstacle to malaria control
- Resistance to nearly all antimalarials in current use
- Curtails the life-span of antimalarial drugs
- Increases malaria morbidity, mortality and treatment cost

DRUG RESISTANT STRAINS OF MALARIA

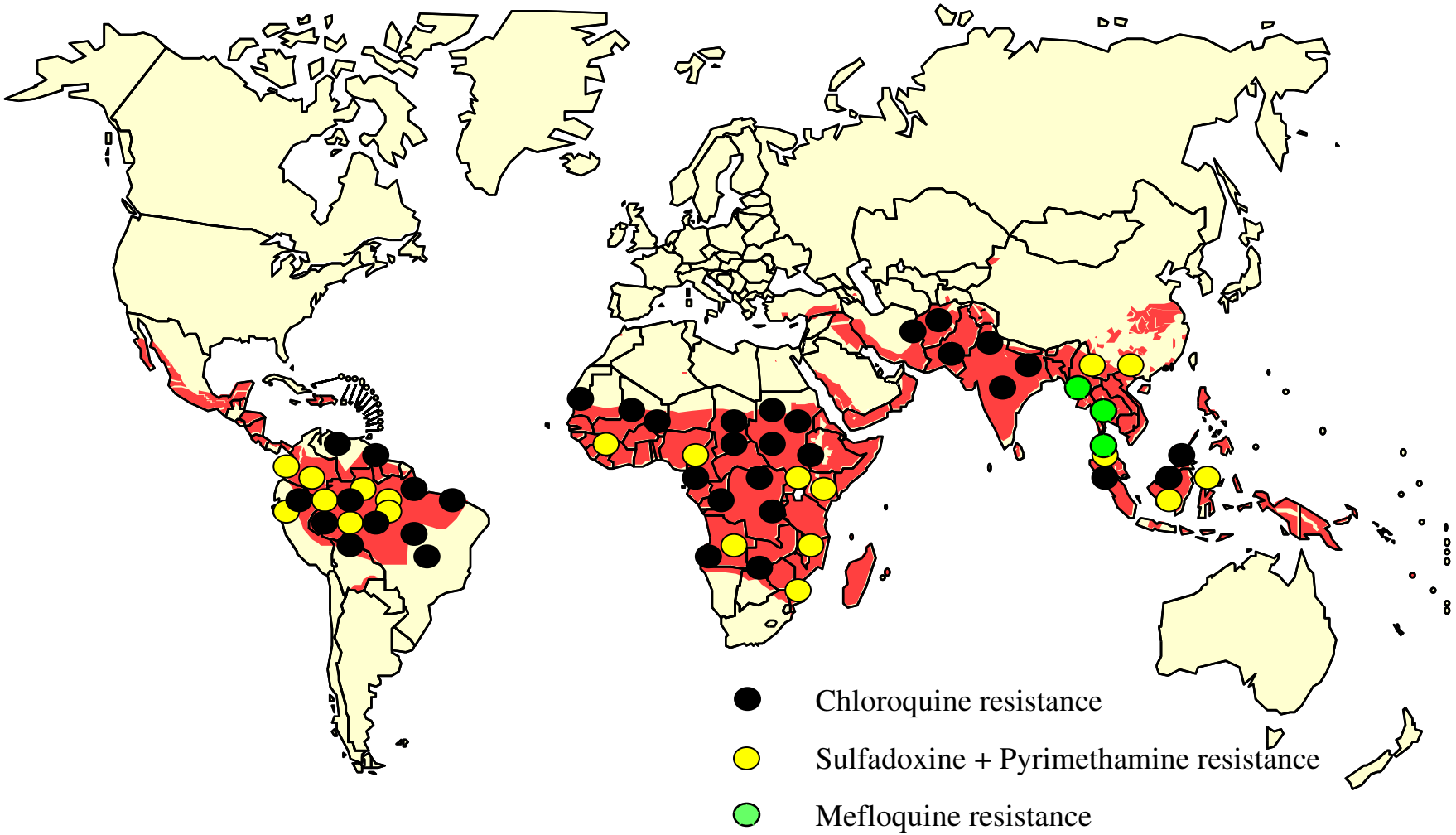
- Predominant – *P. falciparum*
- Recent development – *P. vivax*
- Chloroquine resistant *P. malariae* has been described in Indonesia

BURDEN OF DRUG RESISTANT MALARIA



- Recurrent infections
- More malaria –
  Work/school,
  productivity, anaemia,
  pregnant, birth weight
- Epidemics
- More deaths
- Greater financial costs
  (Health service,
  community, individual)

DISTRIBUTION OF DRUG RESISTANT MALARIA



ETIOLOGY OF DRUG RESISTANT MALARIA

- Naturally occurring genetic mutations in the malaria parasite
- Inadequate treatment (subtherapeutic dose, suboptimal drug) of a high biomass infection – main selective pressure for resistance
- Resistant parasites are transmitted to other individuals by mosquitoes
- Drugs with long half lives

(J Postgrad Med March 2004, Vol. 50, No. 1, p. 41)

DRUG RESISTANT MALARIA

Chloroquine resistance

- Chloroquine is ineffective in almost all malaria endemic countries
- In India chloroquine resistance was first detected in 1973 in Assam.
- Severe in northeast and southeastern regions of India with high morbidity and mortality.

DRUG RESISTANT MALARIA

Sulfadoxine/pyrimethamine resistance

- Resistance to SP was first described from the Thai-Cambodian border in 1960s
- Ineffective in South East Asia and the Amazon Basin for several years
- In Africa, SP resistance was detected in the late 1980s
- In India resistance to sulpha drugs has been reported from northeast states and Orissa
- Resistance in *P. falciparum* to sulphadoxine/ pyrimethamine combination was first detected in Delhi in 1987

(J Vect Borne Dis 41, September & December 2004, pp 45–53)

DRUG RESISTANT MALARIA

Quinine resistance

- The first case of quinine resistance was observed from Thai-Cambodian border in mid 1960s.
- The clinical resistance to quinine therapy has been noticed sporadically in Southeast Asia and western Oceania
- It is less frequent in South America and Africa.
- In India resistance has emerged against quinine in northeastern states and Kolar district in Karnataka.

(J Vect Borne Dis 41, September & December 2004, pp 45–53)

DRUG RESISTANT MALARIA

Mefloquine resistance

- Mefloquine resistance was first observed in late 1980s near the Thai-Cambodian border
- It is frequent in some parts of Southeast Asia and has been reported in the Amazon region of South America and sporadically in Africa
- Resistance in *P. falciparum* to mefloquine in India was detected in Surat district in Gujarat state

(J Vect Borne Dis 41, September & December 2004, pp 45–53)

MECHANISMS OF ANTIMALARIAL DRUG RESISTANCE

Chloroquine resistance

- Increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of heamepolymerization
- This chloroquine efflux occurs at a rate 40 to 50 fold faster among resistant parasites than that in sensitive ones
- Mutations in pfmdr-1 & 2 and pfcrt gene have also been associated with chloroquine resistance.

(J Vect Borne Dis 41, September & December 2004, pp 45–53)

MECHANISMS OF ANTIMALARIAL DRUG RESISTANCE

Sulphadoxine/pyrimethamine resistance

- Specific gene mutations encoding for resistance to dihydrofolate reductase and dihydropteroate synthetase have been identified.
- The dehydrofolate reductase enzymes of resistant strains bind to pyrimethamine 400–800 fold less readily than to the enzymes of drug sensitive strains

Quinine resistance

- *pfmdr-1* mutation associated with chloroquine resistance may also account for reduced susceptibility to quinine.
- The exact mechanism of resistance is not clear

(J Vect Borne Dis 41, September & December 2004, pp 45–53)

MECHANISMS OF ANTIMALARIAL DRUG RESISTANCE

Mefloquine resistance

- Polymorphism of *pfmdr-1* gene is associated with mefloquine resistance.

(J Vect Borne Dis 41, September & December 2004, pp 45–53)

CHLOROQUINE RESISTANT P. VIVAX

- Recent development
- Misperception that P. vivax is benign and easily treated
- Gravity of the threat posed by vivax malaria to public health has been poorly appreciated

(Clin Microbiol Rev. 2009 Jul;22(3):508-34.)

- Severe and fatal disease have been associated with P. vivax infection
- Resistance in *P. vivax* is more serious as hypnozoites will cause relapse of resistant parasites

(J Vect Borne Dis 41, September & December 2004, pp 45–53)

CHLOROQUINE RESISTANT P. VIVAX

- Reported in focal areas of India, Burma, Indonesia, Papua New Guinea, Brazil, Guyana, Colombia and Solomon Islands

- In Papua, chloroquine resistant *P. vivax* constitutes a significant public health problem.

(J Postgrad Med March 2004, Vol. 50, No. 1, p. 41)

ARTEMISININ RESISTANCE

- Artemisinin resistance has been obtained in laboratory models
- Genetically stable and transmissible artemisinin (ART) and artesunate (ATN)-resistant malaria parasites has been selected in the rodent malaria parasite *Plasmodium chabaudi*

(Antimicrob Agents Chemother. 2006 Feb;50(2):480-9)

- Decreased susceptibility to artesunate has been reported in Western Cambodia

(N Engl J Med. 2009 Jul 30;361(5):455-67)

- Resistant parasites have mutations in PfATP6, a Ca^{++} ATPase and putative drug target

WHO CLASSIFICATION OF RESISTANCE

- Traditionally, response to treatment was categorised purely on parasitological ground as sensitive, R-I, R-II and R-III level of resistance
- R-I: (low grade): recrudescence of the infection between 7 and 28 days of completing treatment following initial resolution of symptoms and parasite clearance
- R-II: (high grade): Reduction of parasitaemia by >75% at 48 hours, but failure to clear parasites within 7 days
- R-III: Parasitaemia does not fall by >75% within 48 hours

(Manson's Tropical Diseases, 21st Ed., 2003, p. 1262)

WHO CLASSIFICATION OF RESISTANCE

- Modified based on clinical, parasitological and fever assessment

Early treatment failure (ETF) (If the patient develops one of the following during the first three days of follow-up)

- Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitemia;
- Parasitaemia on Day 2 higher than Day 0 count irrespective of axillary temperature;
- Parasitemia on Day 3 with axillary temperature ≥ 37.5°C;
- Parasitemia on Day 3 ≥ 25 % of count on Day 0.

WHO CLASSIFICATION OF RESISTANCE

Late Clinical Failure (LCF) (If the patient develops one of the following during the follow-up period from day 4 to day 28)

- Development of danger signs or severe malaria after Day 3 in the presence of parasitemia, without previously meeting any of the criteria of *Early Treatment Failure*
- Presence of parasitemia and axillary temperature ≥ 37.5 °C (or history of fever) on any day from Day 4 to Day 28, without previously meeting any of the criteria of *Early Treatment Failure*

WHO CLASSIFICATION OF RESISTANCE

Late Parasitological Failure (LPF) (If the patient develops one of the following during the follow-up period from day 7 to day 28)

- Presence of parasitemia on any day from Day 7 to Day 28 and axillary temperature < 37.5 °C, without previously meeting any of the criteria of *Early Treatment Failure* or *Late Clinical Failure*

Adequate Clinical Response (ACR) *(if the patient shows one of the following during the follow-up period (Up to day 28)*

- *Absence of parasitemia on Day 28 irrespective of axillary temperature without previously meeting any of the criteria of*

Early Treatment Failure or Late Clinical Failure or Late

NEW APPROACHES TO TACKLE DRUG RESISTANCE

- Research into new compounds with novel mechanism of action
- Reversing resistance of existing drugs
- Combination Therapy (Artemisinin Combination Therapy)
- Approach taken from Tuberculosis

LIMITATION OF ARTEMISININ MONOTHERAPY

- High recrudescence rates (10-15%) is reported with artemisinin monotherapy
- Artemisinin compound clears most but not all parasites very rapidly
- 7 day dosage is required with monotherapy

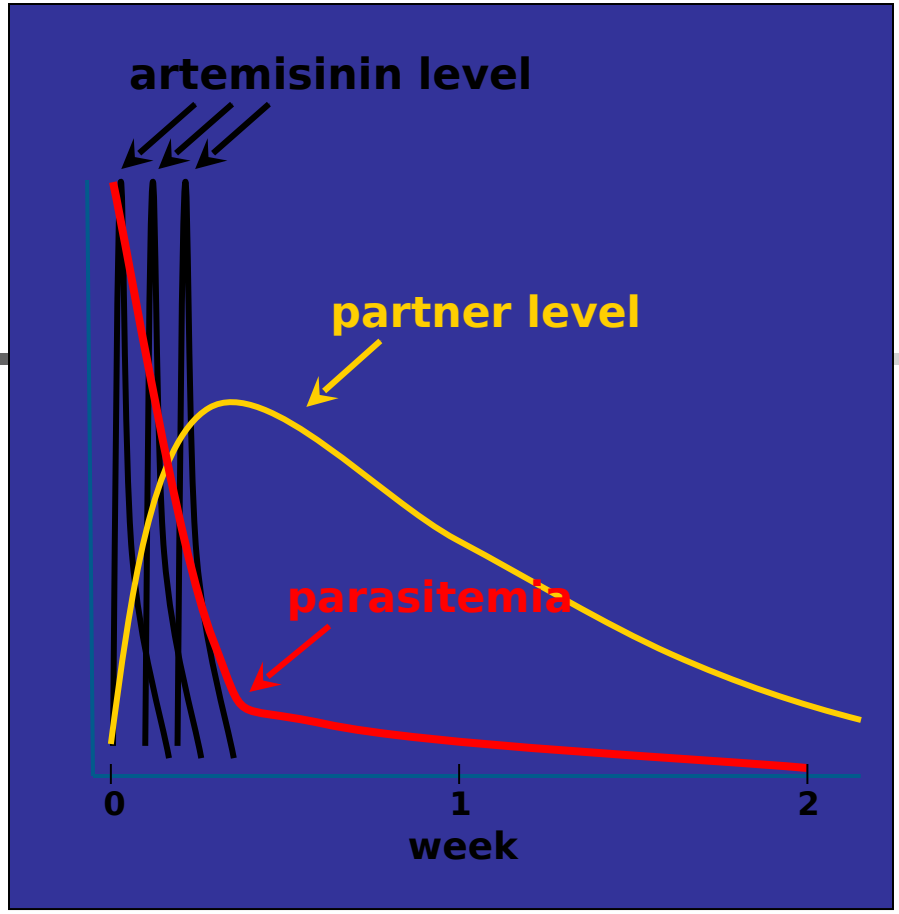
Postgrad. Med. J. 2005;81;71-78

COMBINATION THERAPY IN MALARIA

- Combination therapy with antimalarial drugs is the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite.

- The aim is to improve efficacy and to retard the development of resistance to the individual components of the combination.

ARTEMISININ COMBINATION THERAPY

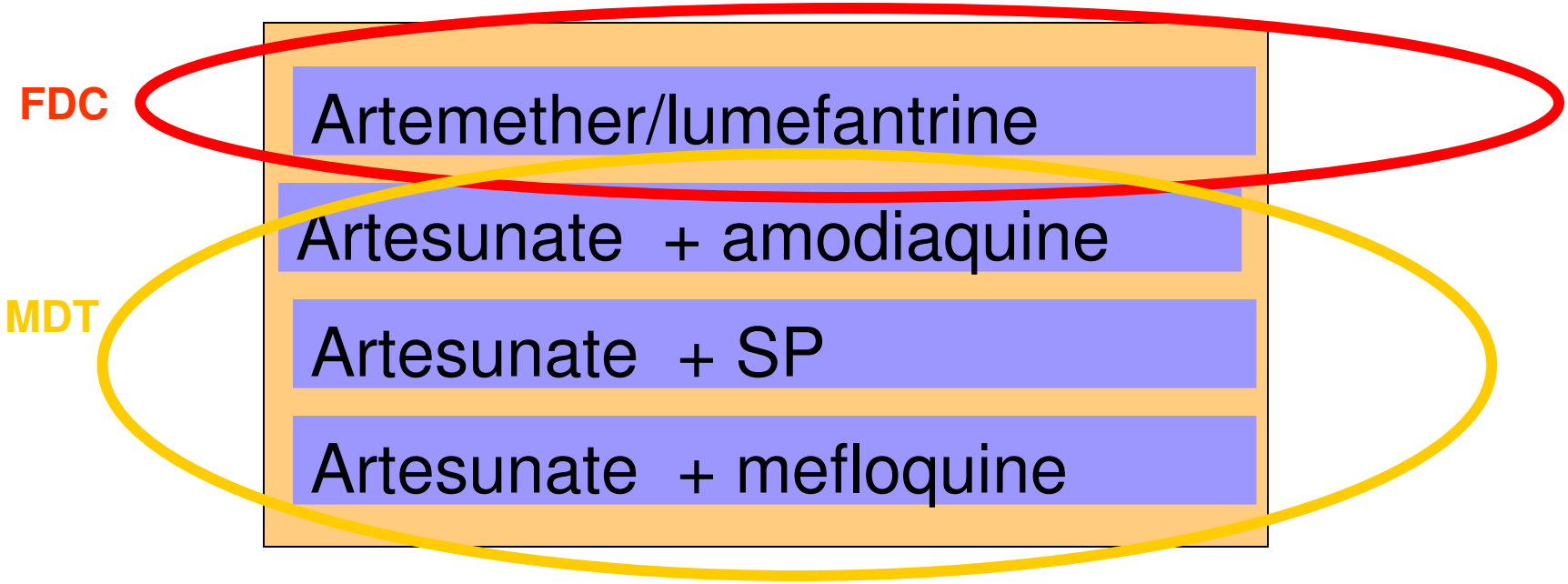


WHO GUIDELINES (2006)

- **WHO has endorsed ACT as first-line treatment for acute uncomplicated malaria, where the potentially life-threatening parasite P. falciparum is the predominant infecting species.**

ACT: Artemisinin-based combination therapy

WHO INITIATIVE



WHO Technical Consultation on
"Antimalarial Combination Therapy" – April 2001

ROLE OF CLINICIANS TO COMBAT DRUG RESISTANT MALARIA

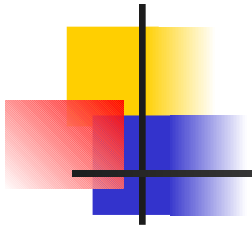
- Clinicians should keep a watch on resistance
- Clinicians should not use Artemisinin and its derivatives as first line agent in malaria
- Artemisinin and its derivatives should not be used in vivax malaria
- Clinicians should use Artemisinin Combination Therapy in uncomplicated falciparum malaria

IPCA'S INITIATIVE FOR RESTRICTION OF DRUG RESISTANT MALARIA

- Development of synthetic trioxane in collaboration with CDRI
- Development of artesunate/curcumin co-package in collaboration with IISc and NIMR
- Stopping the manufacture of single ingredient oral artemisinin derivatives
- CME's on ACT
- CME's by expert Dr. Peter Weina from Walter Reed Institute

CONCLUSIONS

- The emergence and spread of drug resistant malaria represents a considerable challenge to controlling malaria.
- Very few new drugs are in pipeline
- It is essential to ensure rational deployment of the few remaining effective drugs, to maximize their useful therapeutic life
- WHO advocates Artemisinin combination therapy for uncomplicated falciparum malaria
- Clinician play an important role in restricting drug resistant malaria



Thank You