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

- Chloroquine resistance
- Sulfadoxine + Pyrimethamine resistance
- Mefloquine resistance
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

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.
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)*
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)
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)*
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 haemepolymerization
- 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 pfcr1t gene have also been associated with chloroquine resistance.

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

- \textit{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)*
Mefloquine resistance

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

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

*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

*CHLOROQUINE RESISTANT P. VIVAX*

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

(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.

• 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
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 \( \geq 37.5^\circ C \);
- Parasitemia on Day 3 \( \geq 25 \% \) of count on Day 0.
**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 $\geq 37.5 ^\circ C$ (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 Parasitological Failure.
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 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

Diagram showing:
- artemisinin level
- partner level
- parasitemia

Week scale: 0 to 2
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

FDC
Artemether/lumefantrine
Artesunate + amodiaquine
Artesunate + SP
Artesunate + mefloquine

MDT

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
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
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