

# OVERVIEW OF MALARIA

RELATIONSHIPS WITH HIV AND  
AIDS

- Introduction
- Epidemiology
- Life cycle
- Malaria/HIV/AIDS interactions
- Disease burden
  - Pregnant women
  - Children under 5
- Clinical features
- Treatment
- Anti-malarial treatment policy WHO and Nigeria
- Prevention
- Challenges
- Unanswered questions

# Introduction

- Malaria refers to the disease caused by the protozoa Plasmodium species, carried by the female anopheles mosquito
- 4 species of plasmodium cause malaria in humans – *P. falciparum*, *P. malariae* , *P. ovale* and *P. vivax*
- *P. falciparum* is commonest cause of malaria in sub-Saharan Africa and causes severe disease in humans

# Epidemiology

- 300 million cases in the world annually
- 90% of these are in sub Saharan Africa
- 50% of us have at least 1 episode/year and children 4 – 5 episodes
- Significant cause of mortality and morbidity particularly in the under 5 population and pregnant women
- 1 million deaths/year 90% of which occur in children < 5years
- Malaria poses a public health problem which is increasing by the day

# Epidemiology

- Used to be found all over the world, with the exception of a few temperate areas.
- Occurs in areas with conducive atmosphere for the growth of the anopheles mosquito
  - adequate rainfall, poor sanitation and the female anopheles mosquito
- Eradicated in the developed world with improvement in their living conditions and socioeconomic standards

# Epidemiology

- 3 patterns of transmission by mosquitoes
- Stable malaria
  - Intense perennial malaria transmission
  - Some seasonal variation increases in the wet season most marked in (northern Nigeria)
  - High level of immunity in adults
- Seasonal malaria
  - Seasonal transmission with variations
  - Low level of immunity in adults
- Epidemic malaria
  - Affects all age groups

# Malaria Endemicity

- Determined by:
  - Parasitemia Rate
  - Palpable Spleen Rate in 2-9 yrs old

# Endemicity Contd....

1. Hypoendemic <10%
2. Mesoendemic 10 – 50%
3. Hyperendemic 51 – 75%
4. Holoendemic >75%

Nigeria is a malaria holoendemic area.

# How Is Malaria Transmitted?

- Bites from infected female anopheles mosquito
- Transfusion malaria
- Congenital malaria

# Life Cycle

- Man is the only source and reservoir of the human malaria parasites
- Infected female anopheles mosquito injects sporozoites into man during a blood meal
- Sporozoites disappear from the bloodstream into liver parenchymal cell, where they develop into tissue schizonts
- Merozoites are liberated into the blood infecting erythrocytes and starting the erythrocytic phase
- They grow into trophozoites burst the rbc and infect other RBCs
- Some trophozoites develop into gametocytes and continue the sexual lifecycle in the mosquitoes after ingestion

# Disease Burden

- Manifests in various ways
- Affects the individual, community, country
- Affects the health of the population
- Affects the economy of the population
- Affects the productivity of the population

- Disease Burden
- People most at risk of infection are -
  - Child < 5 years old
  - Pregnant women,
  - haemoglobinopathies and
  - non immune

# HIV and malaria

- Both are major global problems
- Both are found in similar geographical areas, diseases of and causes of poverty
- Interactions have major health implications
- Together with TB cause > 4 million deaths/year in sub-Saharan Africa
- Major disease burden and interactions are found in women and children

# Health burden of malaria – pregnant women

- HIV and malaria are major causes of morbidity in pregnancy, and malaria in pregnancy has adverse effects
- Effects differ with the level of malarial transmission and level of immunity in the pregnant woman.
- Effects are worse and life threatening in the non immune or partially immune.

# pregnant women, cont'd

- In areas of stable malaria, although adult women have a high degree of immunity to the disease, this is impaired in the pregnant state, particularly the first
- Recurrent/frequent febrile illness, more severe episodes of uncomplicated and complicated malaria, and maternal deaths
- Anemia, worsening of physiologic anaemia of pregnancy from hemolysis, and its complications in pregnancy

# pregnant women, cont'd

- Placental parasitization limits and reduces nutrients to the fetus amongst others, thereby predisposing to IUGR or fetal death (IUFD).
- Abortions, still births and premature delivery
- Deaths in mother and child

# Health burden of malaria - baby

- Baby – premature delivery/LBW/SGA weight is single imp prognosis for survival and development
- IUGR/ IUFD
- Congenital malaria
- Poorer outcome of babies

# with HIV co infection-pregnant women

- Impaired ability to control malaria parasitaemia
  - More MPs, higher parasite densities, more febrile illness, severe anaemia
  - More adverse birth outcomes – LBW and are more likely to die in infancy
  - This affects all pregnant women not just primips
- Conflicting results if placental malaria is associated with increase MTCT
  - Balance between placental immune responses and increase in stimulation of viral replication

# with HIV co infection-pregnant women

- The effect of HIV on malaria
- . HIV-infected pregnant women are at increased risk of
  - malaria parasitaemia in general, in the placenta, and at the time of delivery
  - higher malaria parasite densities, – clinical malaria.
- . HIV shifts the burden of malaria from women in their first and second pregnancy to all pregnant women.
- . HIV impairs prophylaxis and treatment of malaria among pregnant women: at least three doses of IPT with SP are required to achieve efficacy in areas with high HIV-prevalence.

- **The effect of malaria on HIV**
- . Malaria contributes to increased HIV replication, which is greatest among women with highest parasite density, irrespective of the degree of immunosuppression.
- . Research on the impact of malaria during pregnancy on the risk of mother-to-child transmission of HIV has given conflicting results.

The effect of prophylaxis with both SP and Cotrimoxazole in pregnancy

# The effect of co-infection on pregnancy outcome

- Infection with both malaria and HIV, in particular in individuals with low CD4-cell count, contributes to increased risks of
  - – anaemia, – low birth weight, – preterm birth, IUGR.
- It is not clear whether dual exposure to both placental malaria and HIV increases the risk of infant mortality compared with infants born to HIV-infected women without malaria
- It is not known whether maternal HIV infection results in increased susceptibility to malaria in infants.
- There is a potential risk of increased adverse drug reactions if opportunistic infection prophylaxis with cotrimoxazole and malaria prevention with sulfadoxine-pyrimethamine are taken together.

- The pregnant woman with malaria infection / HIV must be treated both medically and obstetrically, taking care of both maternal and fetal interests.
- Malaria control and prevention during pregnancy
  - Intermittent Preventive treatment with S/P
  - Insecticide treated bed nets
  - Case management of malaria

- IPT involves providing all pregnant women with at least two preventive doses of an effective antimalarial drug – S/|P during routine antenatal visits.
  - Safe, inexpensive and effective (as experiences in Nigeria, Malawi, Kenya IPT reduced placental infection by 30%, LBW babies by 23%; it was also found out that 75% of pregnant women took advantage of IPT when offered.
- ITN involves the use of permethrin treated bed nets to prevent man mosquito contact.
  - From Kenya, 25% less LBW, benefits the infant and others around

- Proper and judicious antimalarial use both for cure and prophylaxis.
  - Benefits both mother and child (improve growth in teenage mothers, increase birth weight and improved outcome)
- The choice of a suitable drug depends on gestational age of fetus, severity of disease, the resistance of the infecting malaria parasites to the antimalarial drugs, cost of medications and the safety profile of the drug in both the mother and the fetus. Ideally, effective care should clear both peripheral and placental parasites. Treat according to treatment guidelines

# Health burden of malaria - child

- Disease burden among children arises from mortality and morbidity associated with malaria
- 90% of all deaths due to malaria occur in this age group and malaria is directly responsible for 20% of deaths among this age group

# Health burden of malaria - child

- Malaria effects in children are mainly due to complications of the disease
- Severe acute malaria
- Complicated malaria
- Repeated episodes of malaria infections causing severe life threatening anaemia, convulsions, coma and deaths

# Health burden of malaria - child

- Malaria makes children more susceptible to other childhood infections, thereby contributing indirectly to mortality and morbidity resulting from these – diarrhoeal diseases, acute respiratory infections and malnutrition
- Single most important contributor to mortality and morbidity in children of affected areas

# Health burden of malaria - child

- Long term consequences of repeated malaria infections in children -
- Chronic anaemia and its effects
- Poor growth and development
- Decreased play and social interactions
- Decreased learning and educational opportunities
- Leads overall to a diminished ability to attain full/maximum potential of child development

# Effect of co infection in the child

- Not much is known about the effects of HIV and malaria on the child.
- Malarial anaemia is associated with blood transfusions, increasing the risk of HIV transmission through blood.
- Similarly, the presence of both infections leads to more illness, increased risk of chronic anaemia, susceptibility to other infections and a diminished survival potential.

# Effect of co infection in the child

- In areas of stable malaria
  - . HIV infection leads to increased rates of malaria fever
  - . Malaria and parasite density are higher in children with advanced immunosuppression.
- – In areas of unstable/epidemic malaria
  - . HIV-infected children are more likely to experience severe disease and coma.

# Principles of care

- Principles of care are
- Prevention through the use of ITN, which has been shown to reduce deaths by 1/3
- Prompt recognition of malaria and effective case management
- Prevention of anaemia through nutrition, iron deficiency and intestinal helminthes
- Prevention of malaria related LBW by pregnant mothers use of ITN

# Health burden of malaria – adults and non pregnant females

- Adults – lose valuable time when incapacitated with malaria
- 3 – 4 days and may be longer especially when 1<sup>st</sup> line drugs fail
- Reduced productivity, school absenteeism, poor economic activity etc
- Premature deaths, disability

# Health burden of malaria – adults and non pregnant females

- HIV may augment the risk/effect of malaria infection especially in the advanced immune suppression.
- HIV infected adults with low CD4 counts may be more susceptible to treatment failures of antimalarial drugs.
- Acute malaria temporarily increases viral replication
- Blood transfusions in malaria may increase risk of further HIV infections

# Health burden of malaria – adults and non pregnant females

- **Non-pregnant adults**
- – In areas of stable malaria
- . **HIV** increases the risk of asymptomatic malaria, clinical malaria and case fatality. The risk of clinical
- malaria increases with advancing HIV-related immunosuppression.
- . **HIV** infection may compromise malaria treatment; the risk increases with advancing HIV-related
- immunosuppression.
- – In areas of unstable malaria
- . **HIV** increases the risk of complicated and severe malaria and death. – **Malaria** contributes to transient rise in viral load among HIV-infected adults.

# Health burden of malaria - others

- Haemoglobinopathies – Sickle Cell Disease
- Malaria is the single most common cause of mortality and morbidity in malaria endemic areas
- Associated with crises-hyperhemolytic, vaso occlusive
- Children <5 years are most affected
- Non immune, immigrants are similarly affected

# Health burden of malaria - poor

- Poor people are most affected
- More at risk of been infected with malaria / HIV
- More at risk of becoming infected more frequently with malaria
- Live in areas that offer little protection
- Unlikely to afford malaria prevention
- Unable to pay for effective malaria treatment +/- transport to health facility for prompt treatments
- Malaria costs are up to 5% of some household incomes and 13% in Nigeria

# Malaria/HIV effects - drugs

- Drug interactions between ARVs and antimalarials given for treatment or prophylaxis may occur
- Pharmacokinetic interactions involve mostly PIs and NNRTIs; thus in patients receiving PIs (or the NNRTI delavirdine) halofantrine should not be given because of excessive risk of toxicity; other NNRTIs should be used with caution.
- A potential interaction between quinine and NNRTI or PI drugs also needs to be investigated.

# Malaria/HIV effects - drugs

- **Pharmacodynamic and pharmacokinetic interactions between antimalarials and antiretrovirals**
- Cotrimoxazole has an antimalarial effect and could accelerate the development of resistance to SP
- Therefore, monitoring drug resistance, in particular in communities where prophylaxis with
- cotrimoxazole is common, is important.
- . More research is urgently required; close monitoring and pharmacovigilance needs to be emphasized
- in the treatment of malaria and HIV.

# Classification of Malaria

## 1. Asymptomatic Infection

- Common among adults in stable malaria zones
- Because of high immunity
- Uncomplicated malaria:
  - Symptomatic malaria without life threatening manifestations.
  - Fever, headache, aches and pains
  - Child irritable, vomiting, refusal to feed
  - Without prompt treatment, clinical picture may deteriorate at an alarming rate

- **Severe malaria:**
  - Patient with *P. falciparum* asexual parasitaemia and presence of one or more of the clinical or laboratory features listed singly or in combination
    - Cerebral malaria, Convulsions, Severe normocytic anaemia, Hypoglycaemia, Metabolic acidosis with respiratory distress, Fluid and Electrolyte disturbances, Acute Renal Failure, Acute pulmonary oedema and ARDS, Circulatory collapse, shock, Abnormal bleeding, Jaundice, haemoglobinuria, High Fever, Hyperparasitaemia

<b>Clinical manifestations</b>	<b>Children</b>	<b>Adults</b>
<b>Prostration</b>	<b>+++</b>	<b>+++</b>
<b>Impaired consciousness</b>	<b>+++</b>	<b>++</b>
<b>Multiple convulsions</b>	<b>+++</b>	<b>+</b>
<b>Respiratory distress (Acidosis)</b>	<b>+++</b>	<b>+</b>
<b>Severe Pallor</b>	<b>+++</b>	<b>+</b>
<b>Abnormal bleeding</b>	<b>+</b>	<b>+++</b>
<b>Circulatory collapse</b>	<b>+/-</b>	<b>+</b>
<b>Pulmonary oedema</b>	<b>+/-</b>	<b>+</b>
<b>Jaundice</b>	<b>+/-</b>	<b>+</b>

<b>Laboratory Findings</b>	<b>Children</b>	<b>Adults</b>
<b>Severe Anaemia</b>	<b>+++</b>	<b>+</b>
<b>Hypoglycaemia</b>	<b>+++</b>	<b>++</b>
<b>Acidosis</b>	<b>+++</b>	<b>++</b>
<b>Hyperlactataemia</b>	<b>+++</b>	<b>++</b>
<b>Hyperparasitaemia</b>	<b>+++</b>	<b>+</b>
<b>Renal impairment</b>	<b>+</b>	<b>+++</b>

# Malaria Treatment Policy

- Reduce morbidity
- Stop the progression of uncomplicated disease into severe and potentially, fatal disease, and reduce mortality
- Reduce the impact of placental malaria infection and maternal malaria associated anemia through IPT
- Minimize the development of drug resistance

# Case Management

- Proper Case management is the goal. It has major impact of reducing morbidity and mortality
- Elements
- Prompt and accurate diagnosis
- Prompt and effective treatment
- Diagnostic capacity and resources
  - Availability of safe, effective, affordable and acceptable antimalarial drug at all levels where it is needed!
  - Management of other manifestations

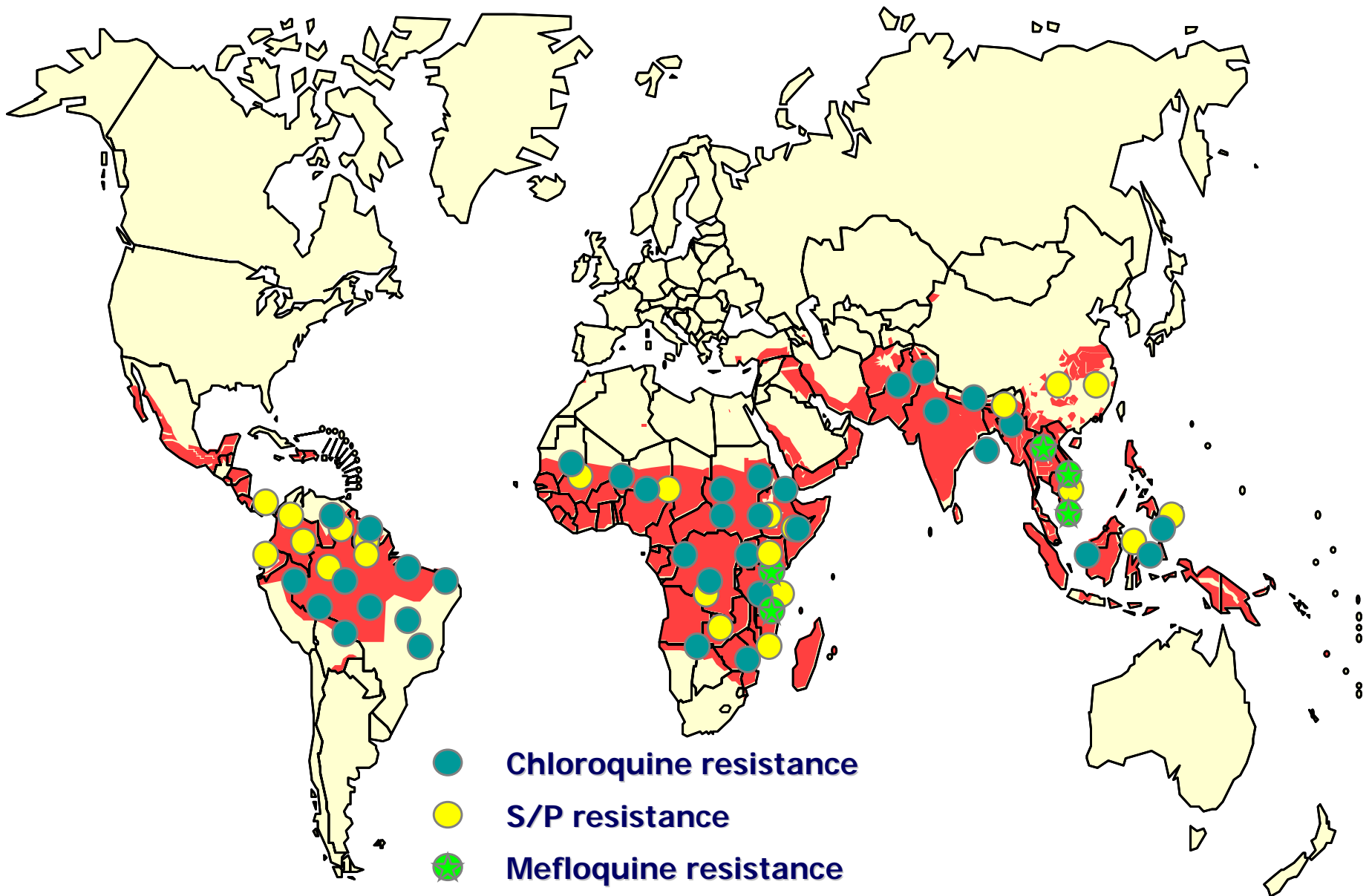
# Uncomplicated Malaria

- Objective of Treatment
  - To cure the infection and prevent mortality and reduce morbidity i.e. Parasite clearance and not clinical cure
    - Thereby prevent both progression to severe disease and
    - Prevent the additional morbidity associated with treatment failure.
  - To reduce transmission
    - This a public health goal of treatment
    - To reduce infectious reservoir and thereby reduce transmission.
  - To prevent the emergence and spread of resistance to the antimalarial drugs.
    - A secondary but important objective

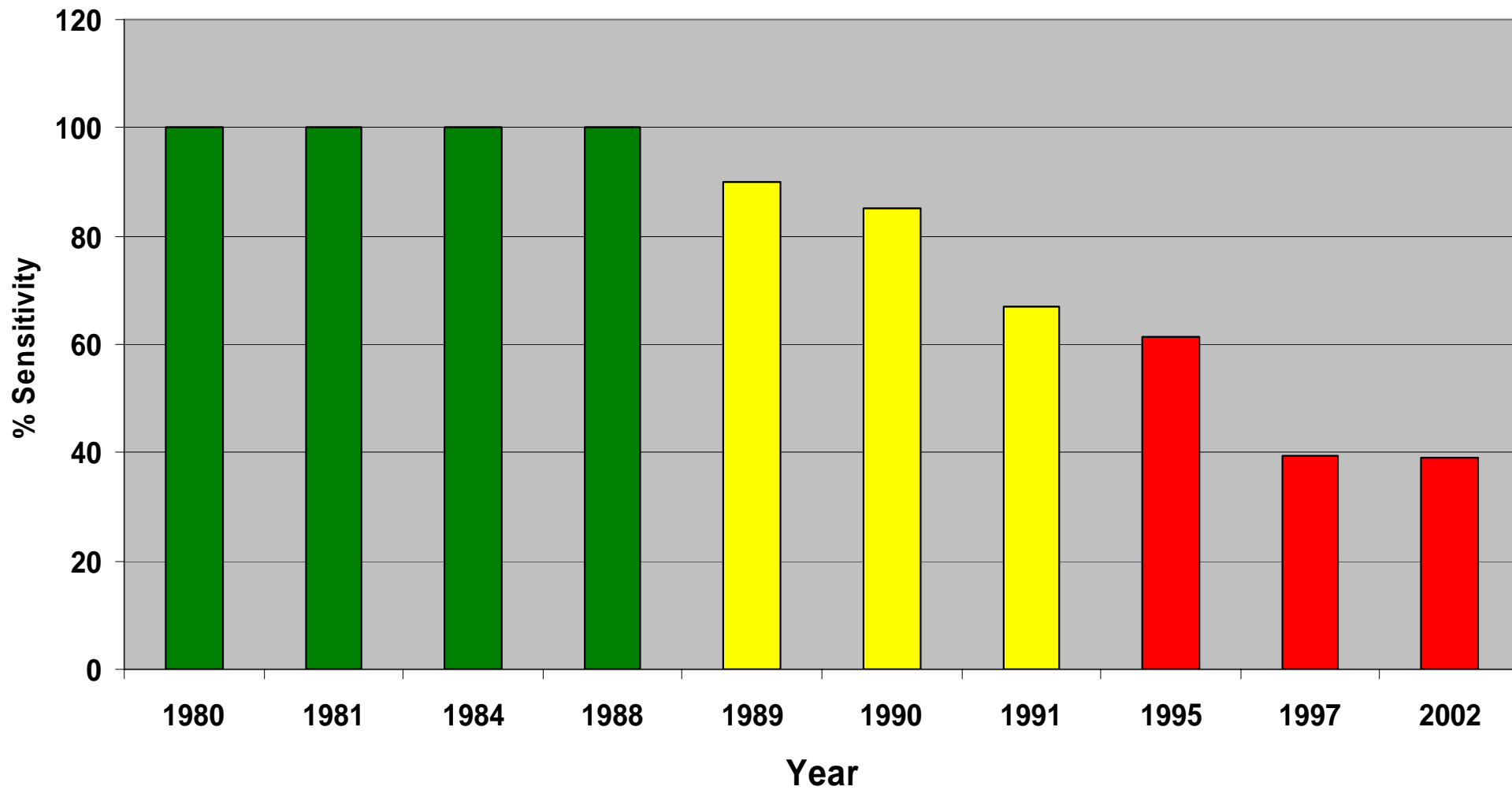
# Anti malarial Drug Situation

- Chemotherapy remains a strategy consistently used in malaria control
- Anti malarial drug resistance has limited the use of available drugs
  - Ability, of a parasite strain to multiply or to survive in the presence of concentrations of a drug that would normally destroy parasites of the same species or prevent their multiplication
- What is the current status of CQ and SP in relation to these objectives?
  - At the global level
  - In Nigeria

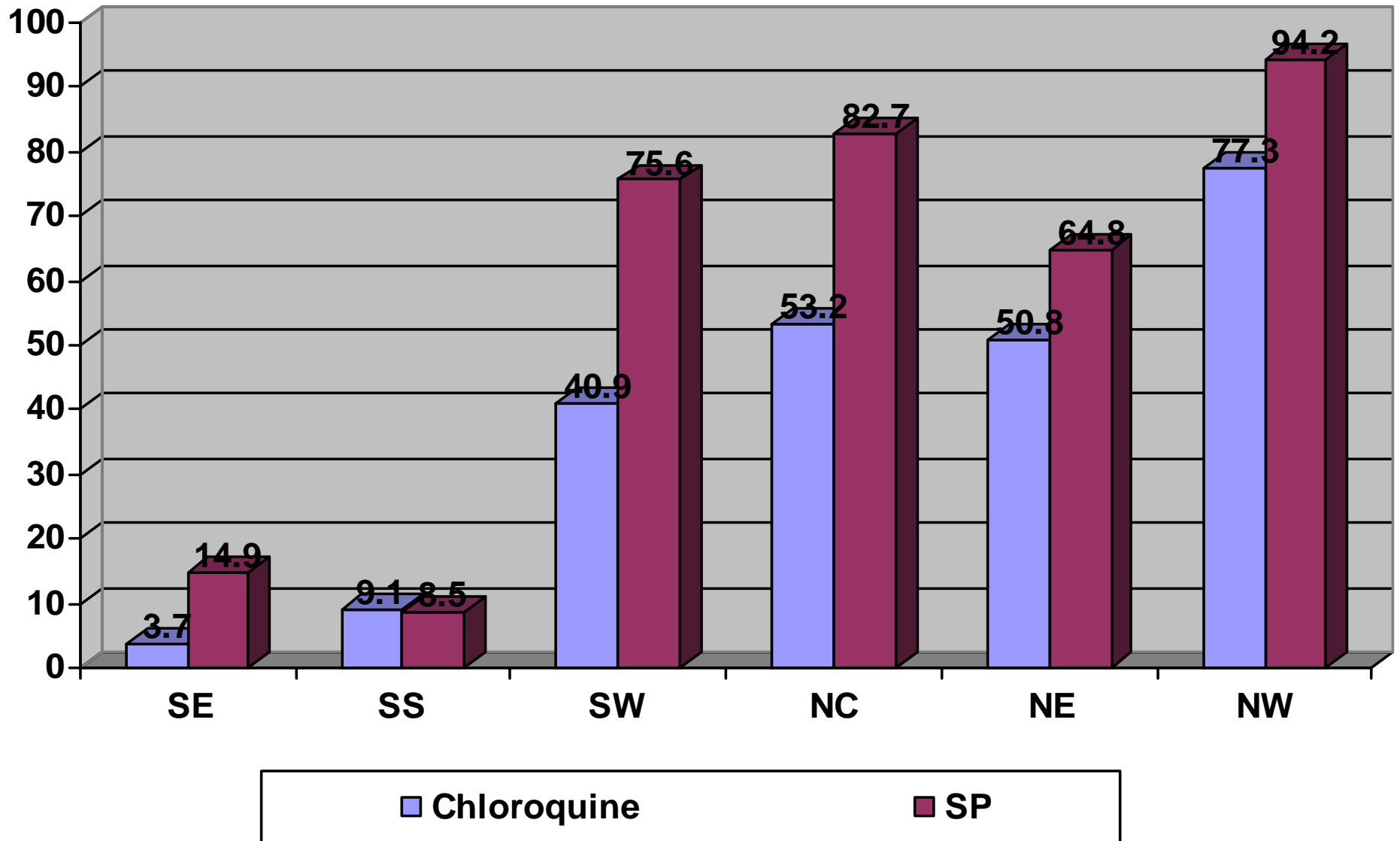
# Status of Antimalarial Drug Resistance 2003



# TREND OF CHLOROQUINE SENSITIVITY IN NIGERIA



*DTET Adequate Clinical & Parasitological Rates*



# SUMMARY OF FINDINGS

- National average of Adequate CPR for CQ and SP were 39% and 57% respectively
- In every zone other than the NW, CQ sensitivity was less than 75%, while sensitivity for SP was less than 75% in the SS, SE and NE zones
- CQ and SP resistance to are so wide spread that they are no longer viable options for effective anti malarial therapy
- Alternative drugs as monotherapies all have limitations in relation to efficacy and safety

# Rationale for Combination Therapy

- Concept is based on the synergistic or additive potential of 2 or more drugs to:
  - improve treatment efficacy, and
  - retard the development of resistance to the individual components of the combination
- Concept already in use in multiple- drug therapy for:
  - Tuberculosis
  - Leprosy
  - Cancer
  - HIV / AIDS
- Benefit to individual patients and society

# Single drug versus Combination Treatment in malaria

- RCTs provide scientific evidence to above change
- There is benefit in adding artesunate to chloroquine, amodiaquine, SP, and mefloquine for treating uncomplicated malaria. The combination treatment resulted in less parasitological failures at day 28 and reduced gametocyte carriage compared with baseline.
- Expert comment:
  - The addition of artesunate to standard monotherapy significantly reduces treatment failure, recrudescence, and gametocyte carriage.

# WHO definition of Antimalarial Combination Therapy

- Simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite: (fixed-dose formulations or co-administrated therapy)

# What is NOT antimalarial combination therapy

- antimalarial drug with a drug that enhances its action
  - (e.g. CQ plus chlorpheniramine)
- use of a blood schizonticidal drug with a gametocidal drug
  - (CQ plus primaquine)
- combinations in which components have no significant schizonticidal effect
  - (e.g. SP, chlorproguanil–dapson)

# Rationale for Artemisinin-based combinations

- Rapidly and reliably effective
- Safe
- Prevent emergence of resistance
- Reduce transmission potential (*reduction of gametocyte carriage*)
- 3 day regimens when in combination
- Broad stage specificity (ring forms, mature and old schizonts)
- Inhibit the production of gametocytes and can reduce transmission
- Rapidity of action enhances the action of partner drug
- No significant resistance so far reported

- Against ACT use
  - Cost, Availability and Accessibility
  - Risk of loss of most valuable anti malaria from drug resistance
  - Address the underlying problems with delivery of the drugs to areas where they are needed.

# WHO Policy on treatment of drug-resistant malaria

- Malaria endemic countries which are experiencing resistance to currently used antimalarial monotherapies (chloroquine, SP or amodiaquine), to change treatment policies to combination therapies, preferably the highly effective artemisinin-based combination therapies – (ACTs)".

# WHO Recommendations

- Artemeter-Lumefantrine
- Artesunate plus amodiaquiune
- Artesunate plus Sulphadoxine/Pyrimetamine (areas where SP efficacy is high)
- Artesunate plus Mefloquine (In areas of moderate transmission)
- Amodiaquiune plus Sulphadoxine/Pyrimetamine (areas where efficacy of both amodiaquiune SP is high, mainly West Africa: This is reserved as an interim option)

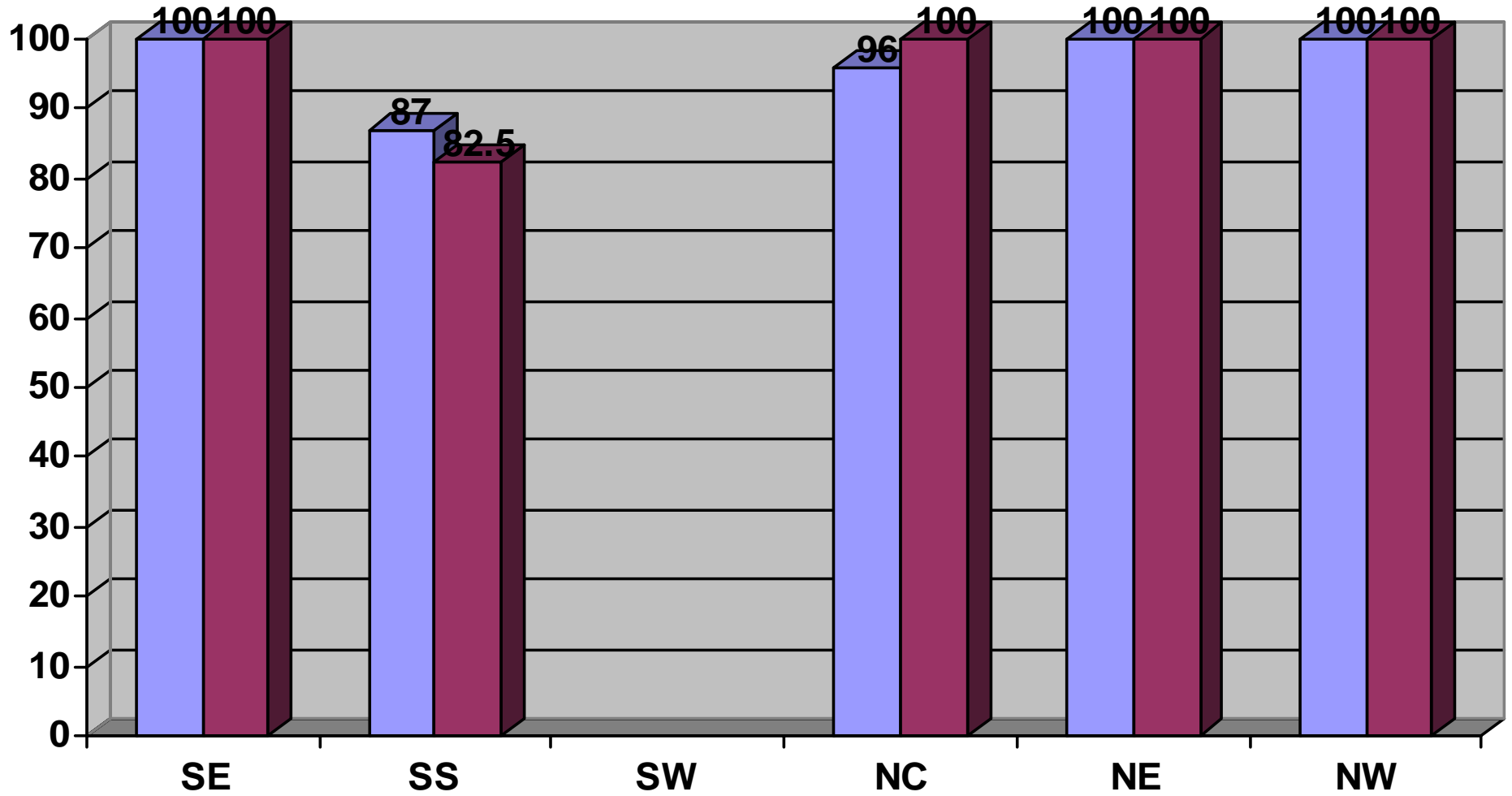
# Nigeria's Policy

- Held a National Consensus in May 2004 to review available global and country based evidence on antimalarial sensitivity pattern and make recommendations on the way forward
    - There is a need to change the current first and second line antimalarial drugs;
    - Studies should be undertaken to select replacement for the failing drugs
    - The following candidate drugs are recommended for the studies
      - Artemether-Lumefantrine
      - Artesunate+Amodiaquine
- The studies should be carried out with adequate national spread

# Result of 2004 ACPR for ACTs in Nigeria

<b>Zones</b>	<b>Artemeter-Lumefantrine</b>	<b>Artesunate+ Amodiaquine</b>
<b>SE</b>	<b>100</b>	<b>100</b>
<b>SS</b>	<b>87</b>	<b>82.5</b>
<b>NC</b>	<b>100</b>	<b>96</b>
<b>NW</b>	<b>100</b>	<b>100</b>
<b>NE</b>	<b>100</b>	<b>100</b>
<b>SW</b>	<b>-</b>	<b>-</b>

*DTET Adequate Clinical & Parasitological Rates*



# Current National Policy

- Nigeria updated Treatment Policy and adopted ACTs for treatment of Uncomplicated malaria in 2005
- AL is the ACT of Choice
- Other ACTs include AA AM
- If the patient shows evidence of inadequate clinical/parasitology response, do the following:
  - Evaluate the patient and review diagnosis
  - Exclude sub optimal dosing or inadequate intake
  - Seek confirmatory test
- In the rare case of all of the above being normal and malaria is unresponsive give oral Quinine.

# Policy Contd.

- Monotherapy with dihydroartemisinin, other artemisinin derivatives and other antimalarial medicines are not recommended.
- Treatment must be used in combination with another effective antimalarial drug.

# Treatment Course

- Artemether-lumefantrine
  - Comes as co-formulated drug
  - 20mg Artemether and 120 mg lumefantrine
  - 1.5/12mg twice daily x 6doses
- Artesunate-Amodiaquine
  - Comes as co blistered package
  - 50mg artesunate and 153 mg amodiaquine
  - Artesunate 4 mg/kg once dly for 3 days +
  - Amodiaquine 10mg base/kg on days 1, 2, & 3.
- Artesunate-mefloquine
  - Artesunate 4 mg/kg once daily for 3 days + mefloquine 25 mg base/kg (15 mg/kg on day 2, 10 mg/kg on day 3) or mefloquine 8.3mg/kg daily for 3 days

## Treatment course AL : 6 dose regimen

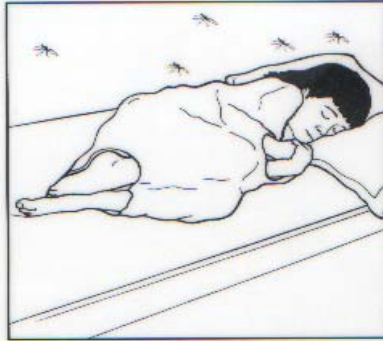
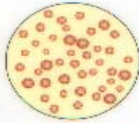
Age group (weight)	Number of tablets / dose
(5) 10-14kg ((6mths)1-3yrs)	1 tab twice dly x3 days
15-24kg (4-8yrs)	2 tabs twice dly x 3days
25-34kg (9-14yrs)	3 tabs twice dly x 3days
>35kg (>14yrs)	4 tabs twice dly x3days
	<i>2<sup>nd</sup> dose should be 8-12 hrs of 1<sup>st</sup> dose</i>



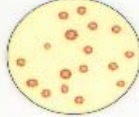
**CORRECT use** [ ] **means**  
**MALARIA IS CURED**

**Day 1**

Dose 1

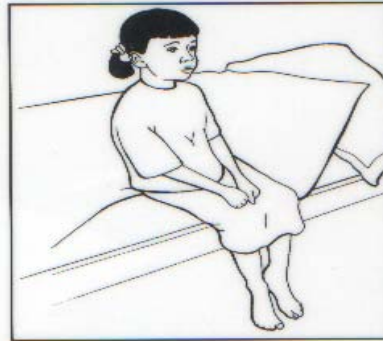
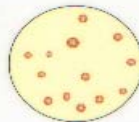


Dose 2

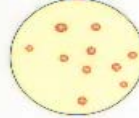


**Day 2**

Dose 3



Dose 4



**Day 3**

Dose 5



Dose 6

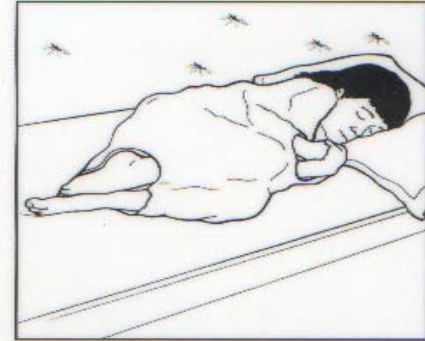
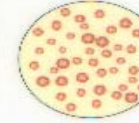


Take all 6 doses in 3 days  
Don't stop taking them because you feel better – finish your pack!

**INCORRECT use** [ ] **means**  
**MALARIA IS NOT CURED**

**Day 1**

Dose 1

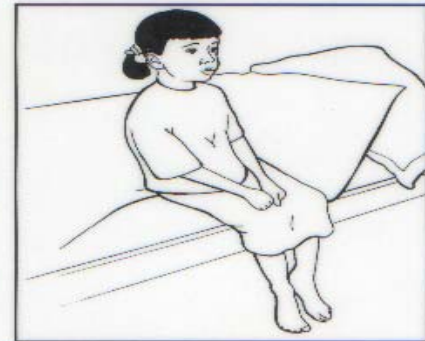
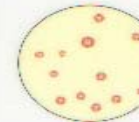


Dose 2

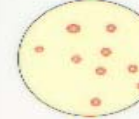
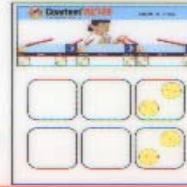


**Day 2**

Dose 3

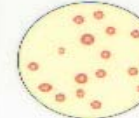


Dose 4

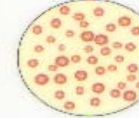


**Day 3 REFUSED TABLETS**

Dose 5



Dose 6



Take all 6 doses in 3 days  
Don't stop taking them because you feel better – finish your pack!

# Treatment of severe malaria

- The primary objective of antimalarial treatment in severe malaria is to save life/ limit disability.
  - Prevention of recrudescence and avoidance of minor adverse effects are secondary.
- Elements of care:
  - clinical assessment of the patient, - prompt evaluation, clinical diagnosis and identify life threatening complications
  - specific antimalarial treatment;
  - Treatment of complications and
  - Supportive care

# Specific Antimalarial Treatment

- Quinine;
  - 20mg salt/kg on admission (i.v. in glucose infusion, or divided i.m. injection) then 10mg/kg 8 hourly. Infusion rate not to exceed 5mg salt/kg/hour.
- Artesunate;
  - 2.4mg/kg i.v. or i.m given on admission (time = 0), then at 12 and 24 hours, then once daily
- Artemether;
  - 3.2mg/kg i.m. given on admission then 1.6mg/kg daily

# Antimalarials in current use in Nigeria

- Artemisinin Derivatives
  - Artemeter, Artemisinin, Artesunate, Dihydroartemisinin
- Quinine
- Amodiaquine
- Halofantrine
- Chloroquine
- Sulphadoxine Pyrimethamine
- Mefloquine
- Proguanil
- Pyrimethamine
- Clindamycin
- Doxycycline

# Prevention

- Rapid diagnosis
- Prompt treatment
- Vector control
  - Self protection
  - Bed nets
  - Insecticide eg DDT
  - ITN
- Chemoprophylaxis
- Vaccine

# Chemoprophylaxis

- Not usually recommended for those living in malaria endemic areas
- Sickle Cell Disease Proguanil lifelong
  - 100mg daily children, 200mg daily adults
- Non immune/travellers
  - Several options – Mefloquine, Doxycycline, Atovaquone-proguanil
  - Commence prior to arrival in Nigeria until at least 2 weeks away from here

# CHALLENGES

- Malaria and HIV are adversely affecting our population, both of which need to be controlled
- Physicians need to update themselves on current developments
- Advocacy and capacity building must be on at all levels to ensure effective case management of both illnesses