MALARIA

INTRODUCTION/EPIDEMIOLOGY

Global burden of malaria

- Most important parasitic disease of humans
- Disease burden: 300 – 500 Mil. Cases; 90% in Africa
- 103 countries in the world are malarious.
- 2 Bil. people exposed to the risk of infection annually.
- Eliminated from north America, Europe and Russia
- Residents of non-endemic areas may also have
  - Travel malaria
  - Airport malaria
  - Mortality very high in this group

Malaria in Africa

- 1.5 – 2.7 million deaths annually world wide
- A child dies every 5 seconds from malaria in Africa.
- 71% of deaths occur in children < 5 years of age.

Malaria in Nigeria

- Transmission - intense and occurs all year round in most parts of Nigeria. Major peak during the rainy season
- Rural dwellers suffer > than urban dwellers
- Most patients suffering from severe malaria die before reaching a health care facility or within 24hrs of hospitalization.
- An estimated >300,000 Nigerian children aged less than 5 years die from malaria annually.

Endemicity and immunity to malaria

Endemicity refers to the amount or severity of malaria in an area or community.

- Measured by parasitaemia or palpable spleen rates:

A. Hypoendemicity - little transmission and the disease has little effect on the population. (<10%)

B. Mesoendemicity - varying intensity of transmission; typically found in rural communities of the sub-tropics. (10-50%)

C. Hyperendemicity - intense but seasonal transmission; immunity is insufficient to prevent the effects of malaria on all age groups. (51-75%)

D. D. Holoendemicity - intense transmission occurs throughout the year. As people are continuously exposed to MPs they gradually develop immunity to the disease. (>75%)

Endemicity and immunity to malaria

Depending on the intensity of transmission, malaria can be stable or unstable, reflecting different epidemic scenarios.

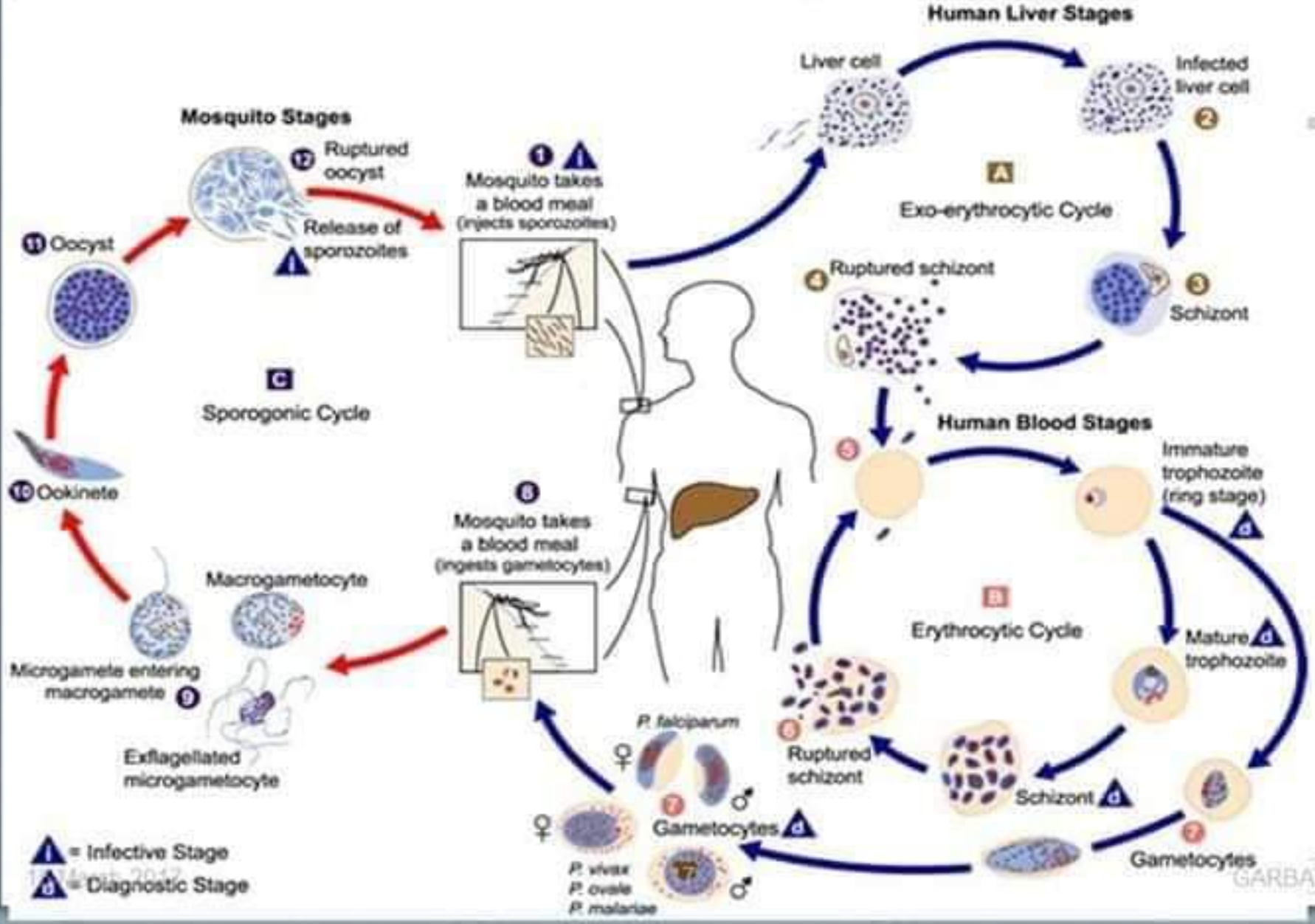
- Stable malaria: Sustained incidence over several years. Seasonal fluctuations in transmission may occur but epidemics are unlikely.
- Unstable malaria: Marked variations in the incidence of malaria over time. Population does not develop immunity and people of all ages are susceptible to severe disease when transmission increases.

Predisposition

- Malaria and hemoglobinopathies
  - Geographical distribution of sickle-cell gene closely follows that of endemic *P. falciparum* malaria
  - Subjects with sickle cell trait (Hb AS) have less severe malaria than individuals with AA genotype
  - Susceptibility to malaria is increased by:
    - Splenectomy
    - Pregnancy (especially primigravidae)
    - Malnutrition

PATHOGENESIS

LIFE-CYCLE OF *P. falciparum*



Pathogenesis

- *P. falciparum causes most severe disease* because it can infect RBCs of any age
- Immunity can be natural or acquired
- Natural:
  - Duffy-negative blood group-*P. vivax* (lacks receptor)
  - Genotype AS
  - Thalassemia
  - G6PD deficiency
  - Pyruvate Kinase deficiency
  - Functional spleen
- Acquired: Following attack of malaria

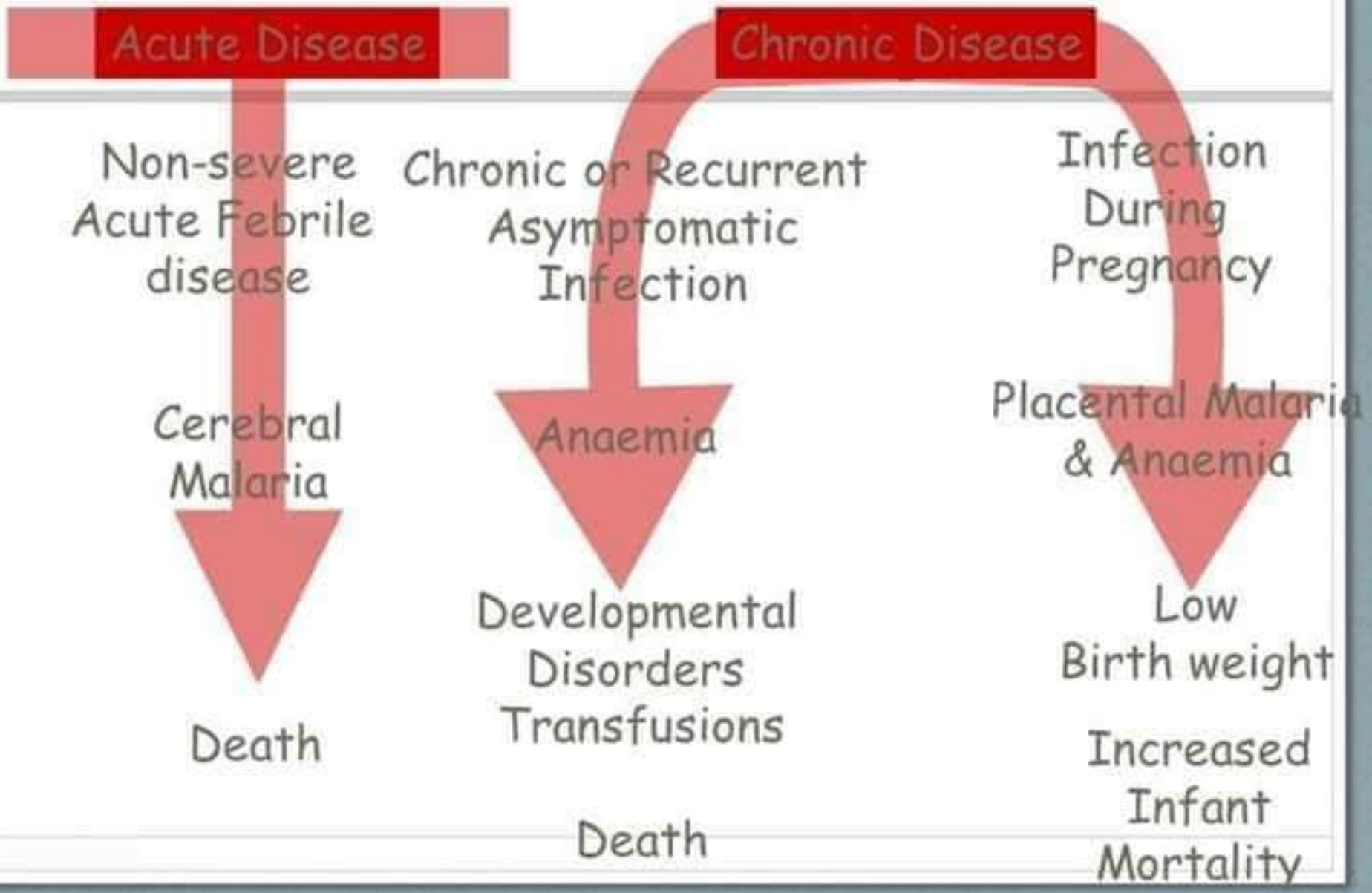
CLINICAL FEATURES

The clinical course of *P. falciparum*

Following a bite by an infected mosquito, many people do not develop any signs of infection. If infection does progress, the outcome is one of three depending on host and parasite factors:

A. Asymptomatic parasitaemia ("clinical immunity")
B. Acute, uncomplicated malaria
C. Severe malaria

MALARIA – Clinical syndromes



Clinical features

- Determined by the immune state of the host and the species of the parasite
- Semi-immune: less severe attacks
- Non-immune:
  - Children in endemic areas
  - Adults entering a malarious area for the 1st time
  - Individuals with a defective immune system
- Incubation period: 10-15 days, can be shorter
- Febrile episodes: 48hr-72hr cycle

Clinical Features (Cont'd)

Severe malaria may present with confusion, or drowsiness with extreme weakness. In addition, the following may develop:

- Cerebral malaria, defined as unrousable coma not attributable to any other cause in a patient with falciparum malaria.
- Generalized convulsions.
- Severe normocytic anaemia.
- Hypoglycaemia.
- Metabolic acidosis with respiratory distress.
- Fluid and electrolyte disturbances.

Clinical Features (Cont'd).

- Acute renal failure.
- Acute pulmonary oedema and adult respiratory distress syndrome (ARDS).
- Circulatory collapse, shock, septicaemia ("algid malaria").
- Abnormal bleeding.
- Jaundice.
- Haemoglobinuria.
- High fever.
- Hyperparasitaemia.

Poor Prognostic symptoms 1

- **Clinical**
  - Marked agitation
  - Hyperventilation (respiratory distress)
  - Hypothermia (<36.5C)
  - Bleeding
  - Deep coma
  - Repeated convulsions
  - Anuria
  - Shock

Poor Prognostic symptoms 2

- **Laboratory**
  - Hypoglycemia (<2.2 mmol/L)
  - Hyperlactatemia (>5 mmol/L)
  - Acidosis (pH <7.3, serum HCO3 <15 mmol/L)
  - Elevated serum creatinine (>265 mol/L)
  - Elevated total bilirubin (>50 mol/L)
  - Elevated liver enzymes (AST/ALT 3 times upper limit of normal, 5-nucleotidase)
  - Elevated muscle enzymes (CPK, myoglobin)
  - Elevated urate (>600 mol/L)

Poor Prognostic symptoms 3

- Haematology
  - Leukocytosis (>12,000/L)
  - Severe anemia (PCV <15%)
- Coagulopathy
  - Decreased platelet count (<50,000/L)
  - Prolonged prothrombin time (>3 s)
  - Prolonged partial thromboplastin time
  - Decreased fibrinogen (<200mg/dL)
- Parasitology
  - Hyperparasitemia
    - Increased mortality at >100,000/L
    - High mortality at >500,000/L
    - >20% of parasites identified as pigment-containing trophozoites and schizonts
    - >5% of neutrophils with visible pigment

DIAGNOSIS

Diagnostic Implications

- Presumptive diagnosis – majority of cases in Nigeria
- Definitive diagnosis – Microscopy is GOLD STANDARD available only in hospitals with laboratory support.
- As cost of treatment rises there will be increased need for definitive diagnosis
  - Rapid diagnostic technique may be the answer
    - pLDH based (OptiMAL®)
    - HRPII based test (ParaSight-F)®

Laboratory Diagnosis Of Malaria: 1

(1) Microscopy based tests

- Microscopic examination of Giemsa stained blood film is the ***Gold standard***

- Others microscopy based tests
  - Quantitative Buffy Coat (QBC)
  - Fluorescence microscopy
  - Benzothiocaboxypurine (BCP) staining procedure

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Laboratory Diagnosis Of Malaria: 2

(2) ***Antigen Detection Based Tests (RDT)***

- Histidine Rich Protein II (HRPII) e.g. ParaSight-F, ICT
- pLDH based tests –OptiMAL

(3) ***Nucleic Acid Methods***

- Rising incidence of drug resistance will influence the choice of diagnostic tools

TREATMENT

Aim Of Treating Malaria

- To fight an established infection, and this includes
  - Elimination of the parasites.
  - Supportive measures to overcome morbidity associated with infection
  - Monitoring to ensure early diagnosis and treatment of complication that can lead to death within hours.

Clinical Case Management & Basic Supportive Care

- Rehydration
- Monitor Blood Sugar
- Anticonvulsants –to control seizures – rectal diazepam.
- Dialysis in renal shut down.
- Blood transfusion for anaemia- PCV < 20%.
- Antibacterial for bacterial infections - aspiration pneumonia and sepsis
- Exchange blood transfusion

Available Antimalarial Drugs

- 4-Aminoquinolines
- 8- Aminoquinolines
- Antifolates
- Cinchona Alkaloids
- Phenantrine methanol
- Antibiotics
- Sesquiterpene lactones
- Quinoline Methanols
- Naphthoquinones
- Pyronaridine

Treatment Of Severe Malaria 1

- Quinine – Prefered drug
  - Continuous iv infusion, intramuscular, rectal.
  - Loading dose 20mg/kg over 4 hours by a rate-controlled iv infusion (infusion pump).
    - Care hypotension or cardiac arrhythmias – ECG monitoring.
    - Hypoglycaemia: monitor blood sugar.
    - Intravascular haemolysis in G6PD deficient patients.

Treatment Of Severe Malaria 2

Artemisinin derivatives

- IV, IM, rectal
- Superior to QN only in areas where QN resistance exists.
- Metabolized to dihydroartemisinin the biologically active metabolite
- Well tolerated

- Artesunate: 2.4mg/kg IV bolus, then 1.2mg/kg iv daily.
- Artemether: 3.2mg/kg IM, then 1.6mg/kg IM daily.
- Dihydroartemisinin suppositories (40mg and 80mg strength)

Treatment Of Severe Malaria 3

Chloroquine

- Parental CQ (iv infusion) in areas where *P. falciparum* is still sensitive
  - e.g. Central America - north of panama canal, Haiti, Dominican republic, Argentina, Egypt, Syria, Turkey, Saudi Arabia, Iraq etc. Rapid parasite lowering affect in sensitive infection.
  - Caution: hypotension prolonged.
  - Loading dose 10mg/kg base over 8 hours. Followed by 15mg/kg base infused over 24 hours.

Treatment Of Severe Malaria 4

- Switch to oral drugs as soon as patient can take orally. Choice of oral drugs guided by sensitivity pattern of plasmodia in the locality.
  - Combination therapy
    - artemether/lumefantrine (Coartem®),
    - atovaquone/proguanil (Malarone®)
    - artemether/amodiaquine,
    - QN/tetracycline or
    - artemether/mefloquine.

Advantages of ACT:

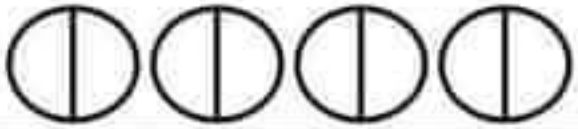
- High efficacy and rapid clearance of parasites
- Artemisinin reduces gametocyte carriage thus reduces malaria transmission
- Artemisinin derivatives – most rapidly schizonticidal antimalarial drugs known to date
- Used for >2 centuries in china and still effective (artemisinin derivatives do not remain in the blood stream for long)
- Relatively good safety profile despite initial anxiety following pre-clinical findings
- Reduction in malaria transmission

Coartem® cummulative dose Tablets in 3 days

≤ 3yrs  Twice daily for 3days = total 6tabs

4 - 8yrs  Twice daily for 3days = total 12tabs

9 - 13yrs  Twice daily for 3days = total 18tabs

≥ 14yrs  **Twice daily for 3 days = total 24tabs**

PREVENTION

Reduce Contact Between Humans And Mosquitoes

WHO Recommendation

- For many years that pregnant women in malaria endemic areas should:
  - receive an initial antimalarial treatment dose on their 1st contact with antenatal services, followed by;
  - Weekly chemoprophylaxis (at less than therapeutic dose) with an effective antimalarial drug—CQ for most countries

WHO Expert Committee on malaria.

Who Should Receive Malaria Chemoprophylaxis?

Travelers to endemic countries

- Non-immune
- Returning immigrants to endemic areas (lost their immunity)

- Residents of endemic countries
  - Targeted segments
    - <5year olds
    - Pregnant women
    - Imunocompromised patients e.g. SCA, HIV/AIDS, Post splenectomy, Cancer, Post organ transplant

Drugs For Chemoprophylaxis

- Pyrimethamine – No longer effective
- Proguanil – 200mg daily
- Doxycycline – Travelers 250mg daily.
  - Not in children or pregnant women
- Malarone (Atovaquone/proguanil) –
  - very effective, good safety margin but expensive ($32 – 35 USD/dose)
- Mefloquine – 250mg weekly
  - ($T_{1/2}$ too long, neuro-psychiatric AE)
- Chloroquine/Amodiaquine
  - Not recommended as it is used in Rx
  - Resistance emerged
  - Bone marrow suppression with amodiaquine

Adverse Events Of Antimalarials

- Cochlear nerve damage-high-dose CQ
- High-dose quinine-Oxytocic to the pregnant uterus, causes frequent meconium emissions during labor, embryo- and feto-toxic and teratogenic.
- Mefloquine-safe and effective, it cleared parasitemia more effectively, did not cause hypoglycemia, caused less tinnitus than quinine