

# **University of Zambia**

## **School of Medicine**

**3<sup>rd</sup> Year MBChB**

**MALARIA**

**Mr. Tembo**

**2024**

# Malaria

Phylum **APICOMPLEXA**

Class **SPOROZOEA**

Subclass **COCCIDA**

Order **EUCOCCIDIIDA**

Suborder **EIMERIINA**

Genus **Cryptosporidium,**  
**Pneumocystis, Sarcocystis, Toxoplasma,**  
**Isospora**

Suborder **HAEMOSPORINA**

Genus **Plasmodium**

# Malaria Epidemiology

- Malaria has been haunting mankind for many years
- Has killed more people than all the wars
- Globally, about 3.2 billion people are at risk of malaria, and 1.2 billion are at high risk
- In 2015, malaria caused 214 million infections and 438000 deaths
- Nearly 90% of these deaths occurred in Africa, and 70% occurred in children <5 years

# Malaria

**Mal = bad**

**aria = air**

## **Aetiological agents**

- *Plasmodium vivax*: Benign Tertian Malaria
- *Plasmodium falciparum*: Malignant Tertian Malaria
- *Plasmodium malariae*: Benign Quartan Malaria
- *Plasmodium ovale*: Benign Tertian Malaria
- *Plasmodium knowlesi* (monkey-derived malaria):  
Quotidian (24 hour cycle)

# Each disease has a distinct course

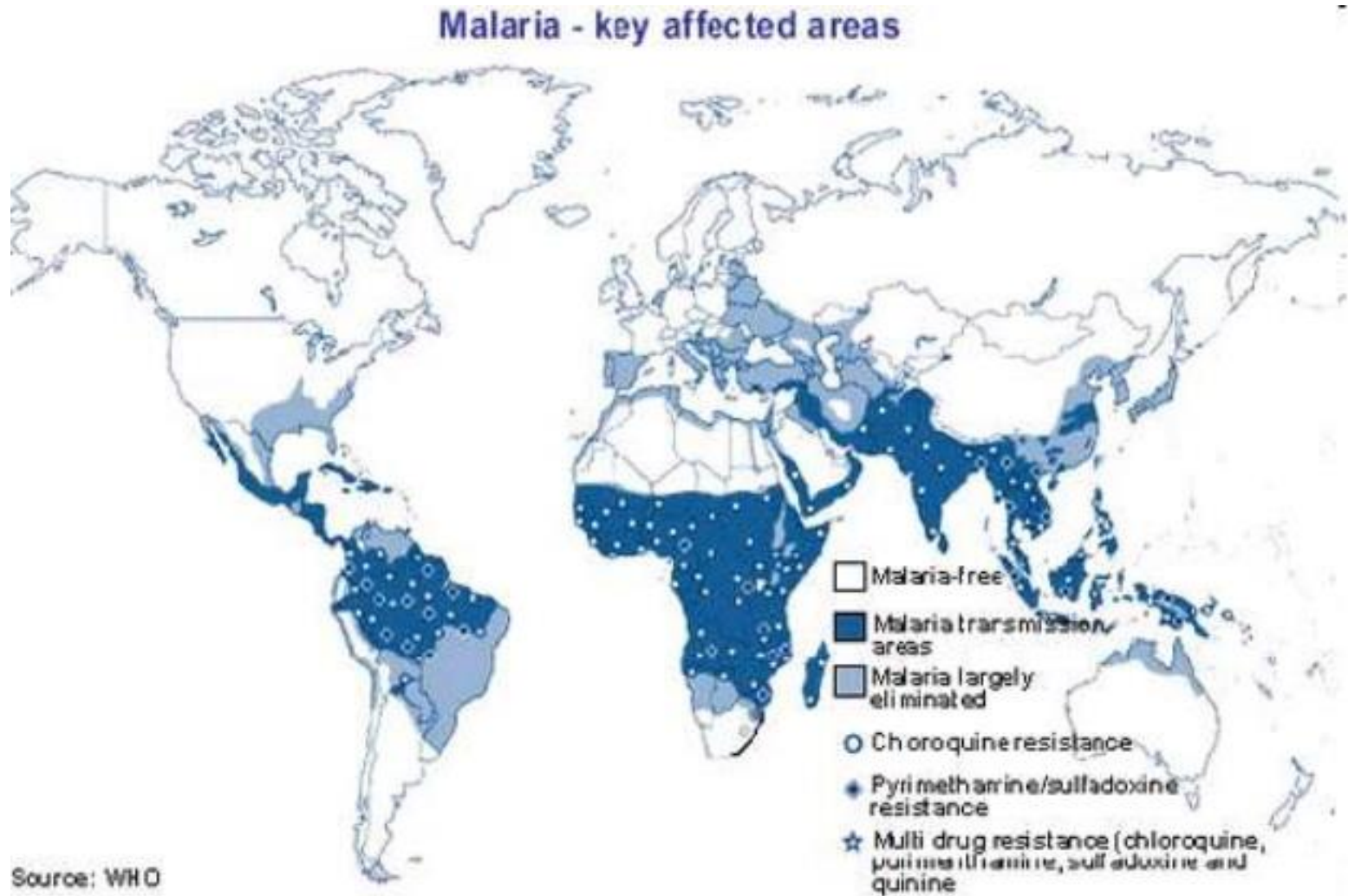
Tertian Malaria” (*P. falciparum*, *P. ovale* and *P. vivax*) fever occurs every third day.

“Quartan Malaria” (*P. malariae*) fever occurs every fourth day.

# Distribution

- *P. vivax* is the most widely distributed in Asia, North Africa, and Central and South America
- *P. falciparum*, the predominant species in Africa, Papua New Guinea, and Haiti, is rapidly spreading in South-east Asia and India
- *P. malariae* is present in most places but is rare, except in Africa
- *P. ovale* is virtually confined to West Africa where it ranks second after *P. falciparum*

# Distribution of Malaria Infection



# Transmission

- Transmitted by female *Anopheles* sp. mosquito; dusk until dawn
- Other forms of transmission
  - blood transfusion, congenitally acquired disease, organ transplantation, and sharing of contaminated needles
- “Airport malaria” → infected mosquitoes can enter a country via airplane thereby transmitting infection

# Transmission Patterns

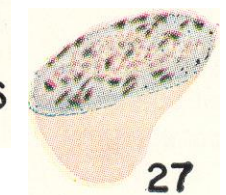
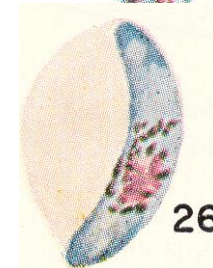
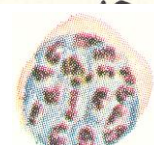
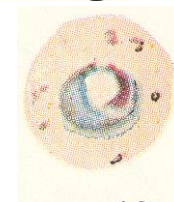
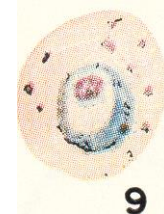
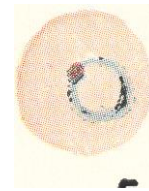
- Malaria may occur in endemic as well as epidemic patterns
  - It is described as **endemic**, when it occurs constantly in an area over a period of several successive years and
  - as **epidemic**, when periodic or occasional sharp rises occur in its incidence

# Transmission Patterns

- Hypoendemic (transmission is low)
- Mesoendemic (transmission is moderate)
- Hyperendemic (transmission is intense but seasonal)
- Holoendemic (transmission of high intensity)

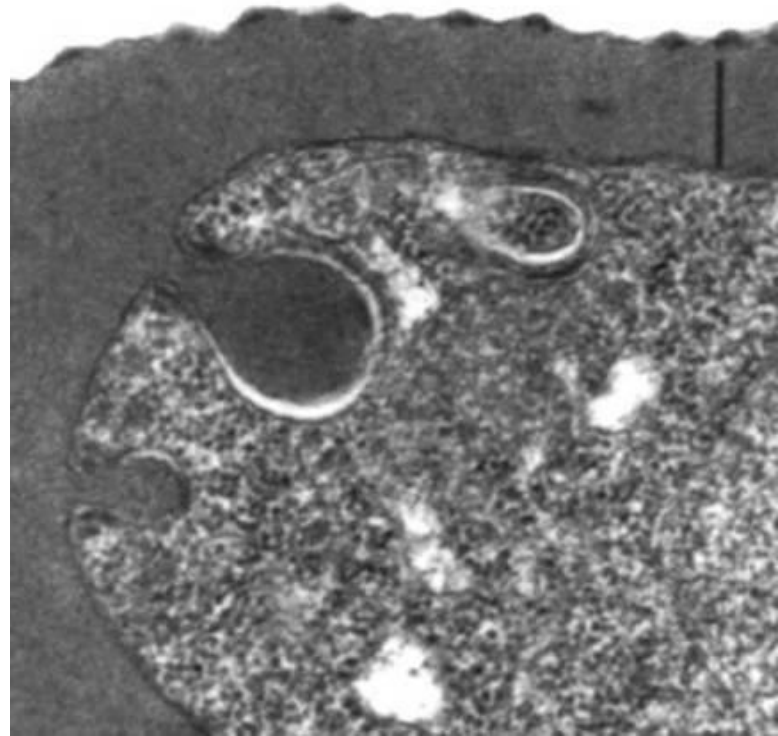
# Plasmodium falciparum

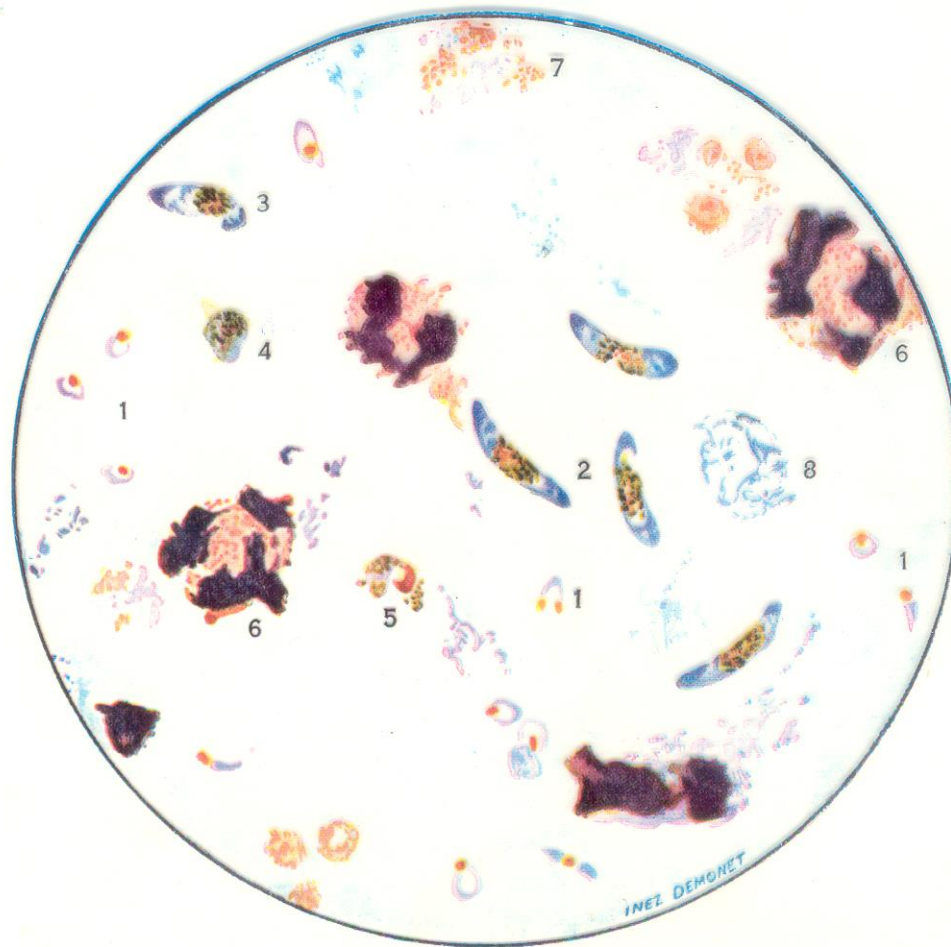
- World wide
- **Habitat:** rbc of all ages
- **Morphology:**
  1. Trophozoite, ring stage. multiple infections, High parasitaemia.
  2. Schizont infected cell ruptures to release up to 32 merozoites, schizogony 48 hourly
  3. Gametocytes: enclosed in rbc membrane  
Banana shaped, called crescents
  4. Zygote, Ookinete, Oocyst, Sporozoites
  5. Infected rbc show stippling on the surface (Maurer's clefts) .



6. Electron microscopy reveal Knobs on surface of parasitised rbc = **Histidine Rich Protein**, explains sequestration
- Knobs - host derived, antigenic
  - attachment points to ICAM-II.
  - Gametocytes no knobs, do not sequester
  - **Kumar** -----Pathology ( cytoadherence, Pathophysiology of fever in malaria)

**7. No hypnozoites in Pf**

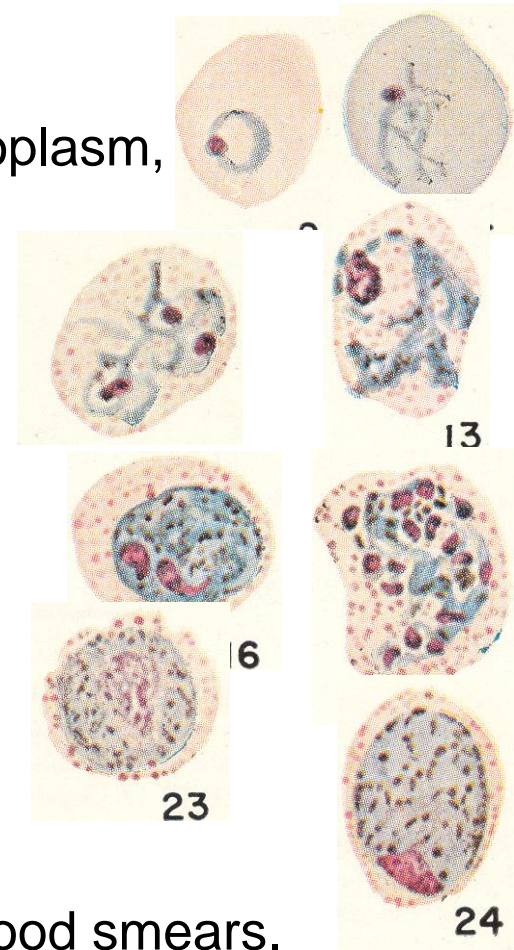




Plasmodium falciparum thick-film preparation The film contains numerous ring-stage trophozoites, five normal gametocytes, one rounded-up and one degenerate gametocyte, leukocytes, blood platelets, and remains of red cell stroma 1, Small trophozoites. 2, Gametocyte-normal. 3, Slightly distorted gametocyte 4, "Rounded-up" gametocyte 5, Disintegrated gametocyte. 6, Nucleus of leukocyte. 7, Blood platelets. 8, Cellular remains of young erythrocyte

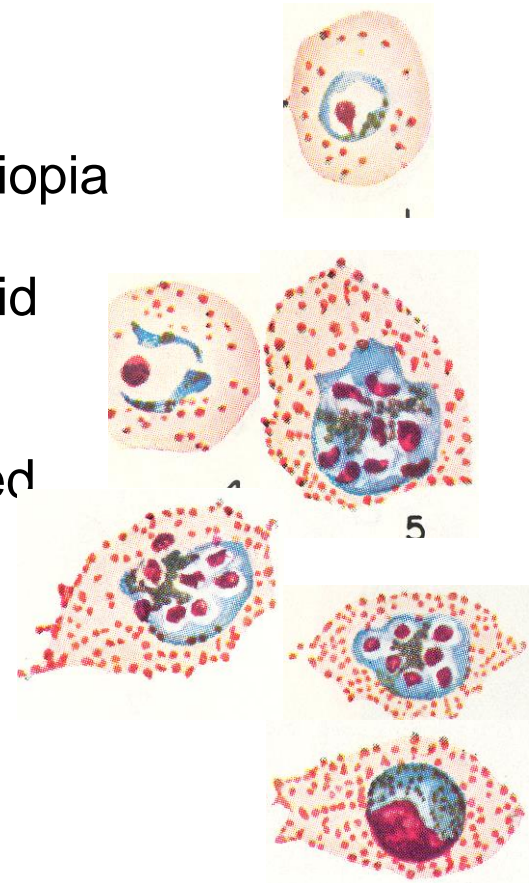
# Plasmodium vivax

- Nearly Worldwide, 16 Degrees North -20 degrees South. **P. vivax rare in West Africa**
- **Habitat – Infects young RBCs**
- 1. Trophozoites- large, fragmented amoeboid cytoplasm,
  - infected rbc enlarged and pale,
  - Schuffner's dots in infected rbc cytoplasm
- 2. Schizonts 8-24 merozoites,
  - schizogony 48hourly
- 3. Gametocytes compact and round,
  - fill rbc without sign of schizogony
- 4. **Hypnozoites**: Latency for several years
  - = Dormant sporozoites in hepatocytes
  - Uninucleate, Explains clinical malaria relapses.
- **Krotoski (1980). Brit. Med J. 1:153-154**
- 5. No Knobs, no sequestration, all stages seen in blood smears.



# Plasmodium ovale

- Least common malaria, Vivax –like
- **Habitat- infects young RBCs**
- Tropics, esp W.Africa, Burma, China, S.E.Asia, Ethiopia
- **Morphology:**
  1. Trophozoites: compact cytoplasm, not amoeboid, large prominent nuclei
  2. Schuffner's dots, infected rbc slightly enlarged
  3. 20-30% parasitised rbc's oval, show fimbria, ragged end, artifact
  4. Low merozoite numbers 8-10, central darker pigment, schizogony 48 hourly
  5. Gametocytes: oval, rbc's fimbriated, show Schuffner's dots.
  6. Hypnozoites present

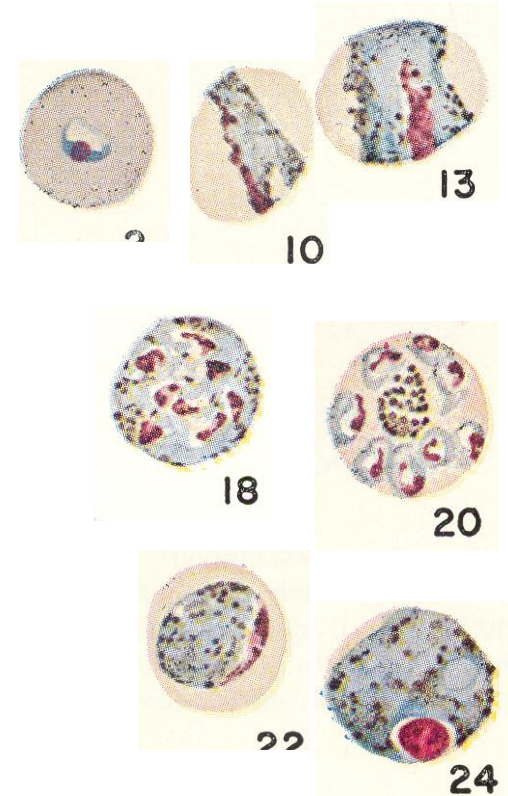


# Plasmodium malariae

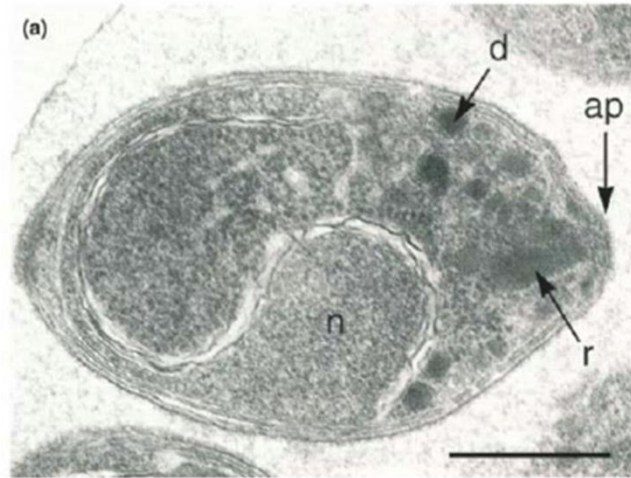
- Tropical Africa, Asia, India, used to
- in Europe and USA, uncommon in S.America
- **Habitat- Infects old RBCs**

## Morphology:

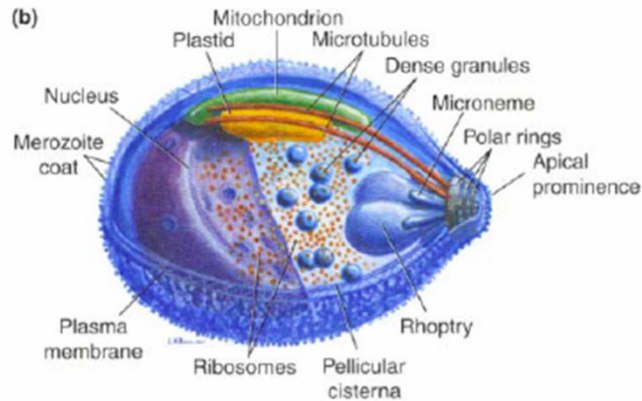
1. Trophozoites form bands around rbc, invades mature cells
2. Schizogony 72 hourly
3. No Schuffner's dots, Ziemann's stippling
4. Schizonts: 6 - 12 merozoites, with malaria pigment at the center forming Daisy heads or marguerites
5. Gametocytes oval
6. No Hypnozoites: 40 year recrudescence



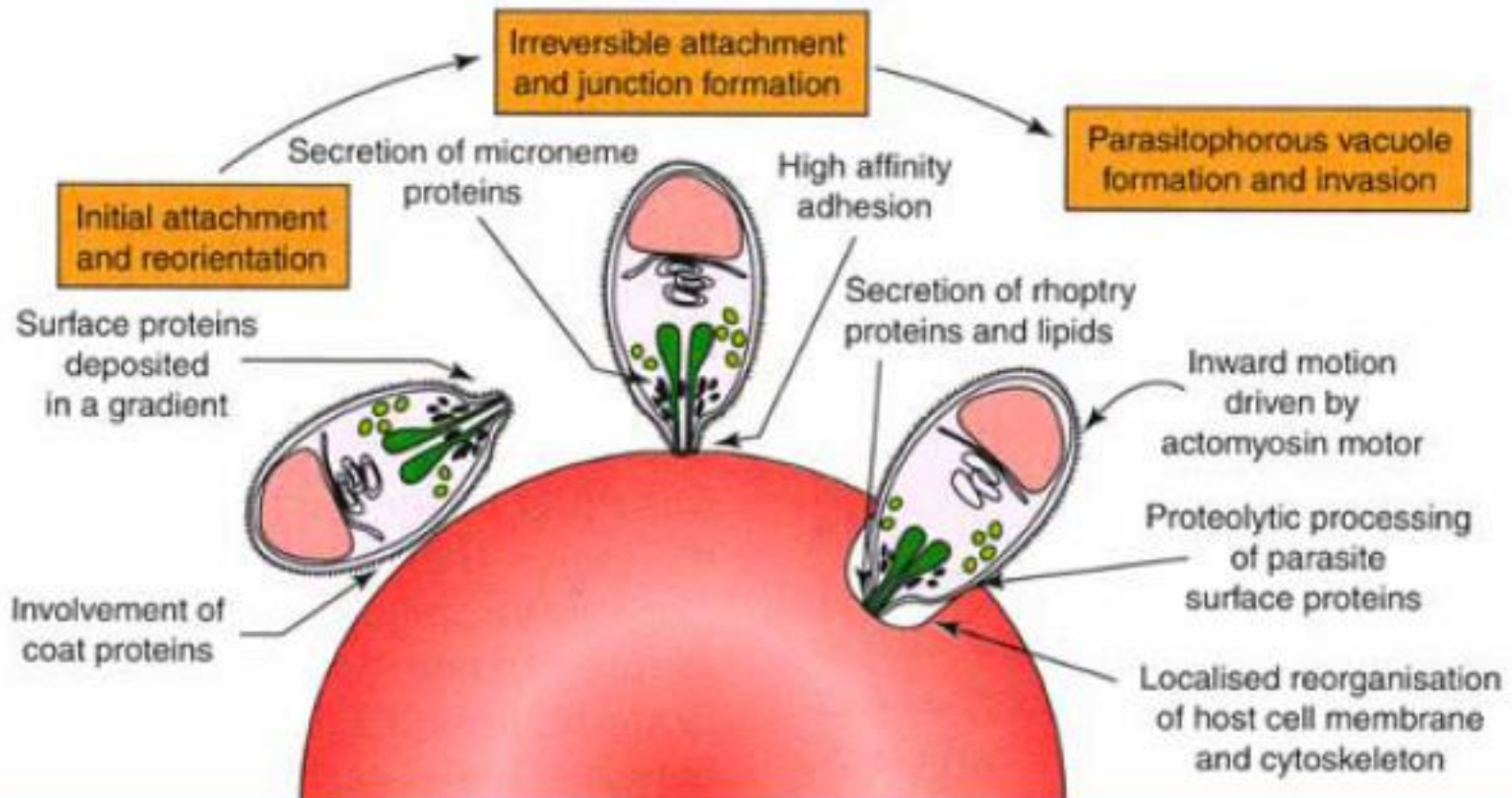
# The Plasmodium parasite that invades



Plasmodium Anatomy



# Mechanisms of Red Cell Invasion By Plasmodium



# Life Cycle

- Malaria parasite passes its life cycle in 2 hosts.
  - **Definitive host:** Female Anopheles mosquito
  - **Intermediate host:** Man
- an asexual phase occurring in humans, which act as the intermediate host and
- a sexual phase occurring in mosquito, which serves as a definitive host for the parasite

# Life Cycle

## Asexual phase:

- Malaria parasite **multiplies** by division or splitting a process designated to as **Schizogony** (from **schizo**: to **split**, and **gone** = **generation**)
- This asexual phase in man, is also called **vertebrate, intrinsic, or endogenous phase**

# Life Cycle

- **In humans, schizogony occurs in 2 locations**
  - **In the red blood cell (erythrocytic schizogony) and**
  - **In the liver cells (exoerythrocytic schizogony or the tissue phase)**
- **Products of schizogony, whether erythrocytic or exoerythrocytic, are called merozoites (meros: a part, zoon: animal)**

# Life Cycle

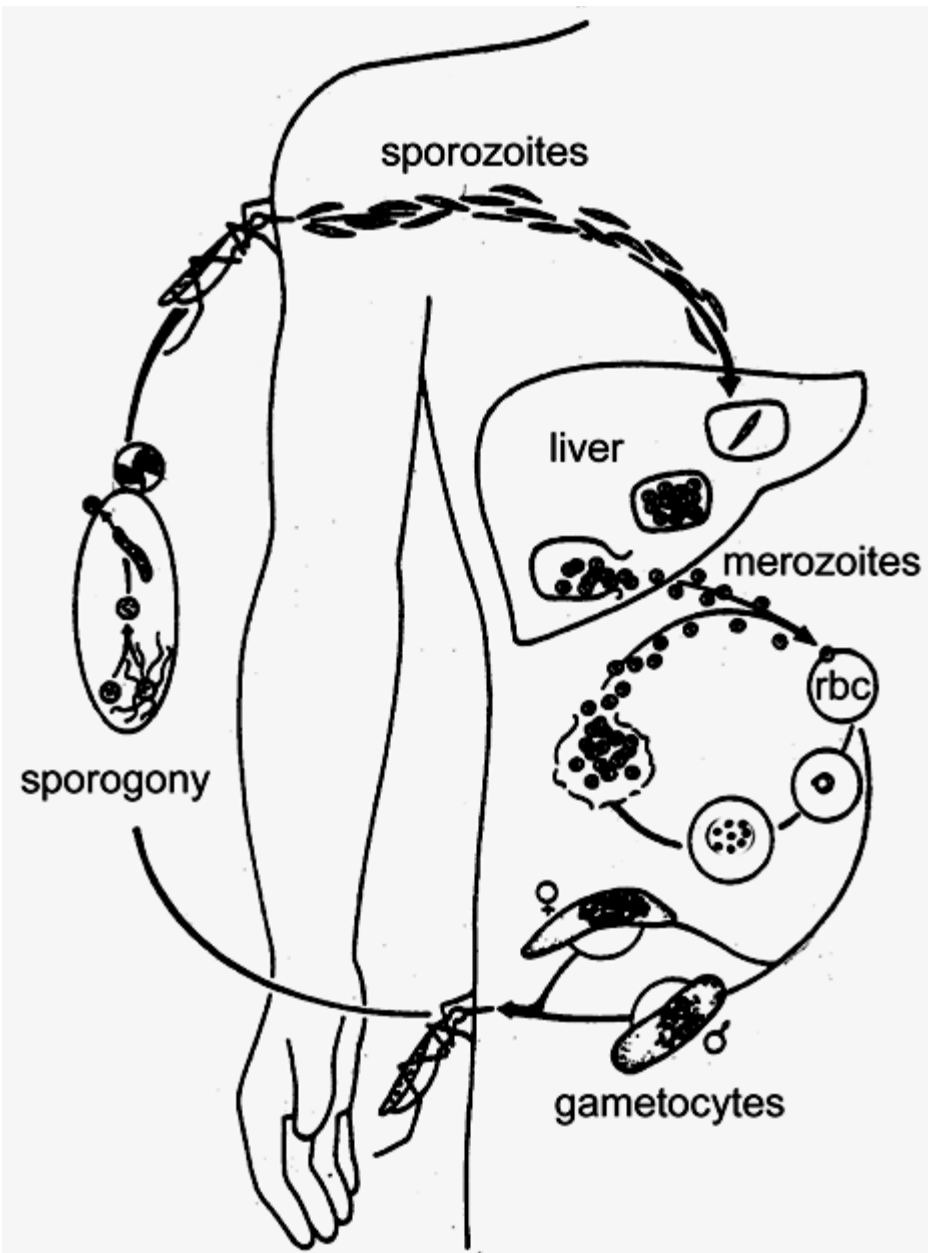
## Sexual phase:

- Takes place in female *Anopheles* mosquitoes
- Maturation and fertilization give rise to a large number of sporozoites (from sporos: seed)
- Phase of sexual multiplication is called **sporogony** or **also called** the invertebrate, extrinsic, or exogenous phase

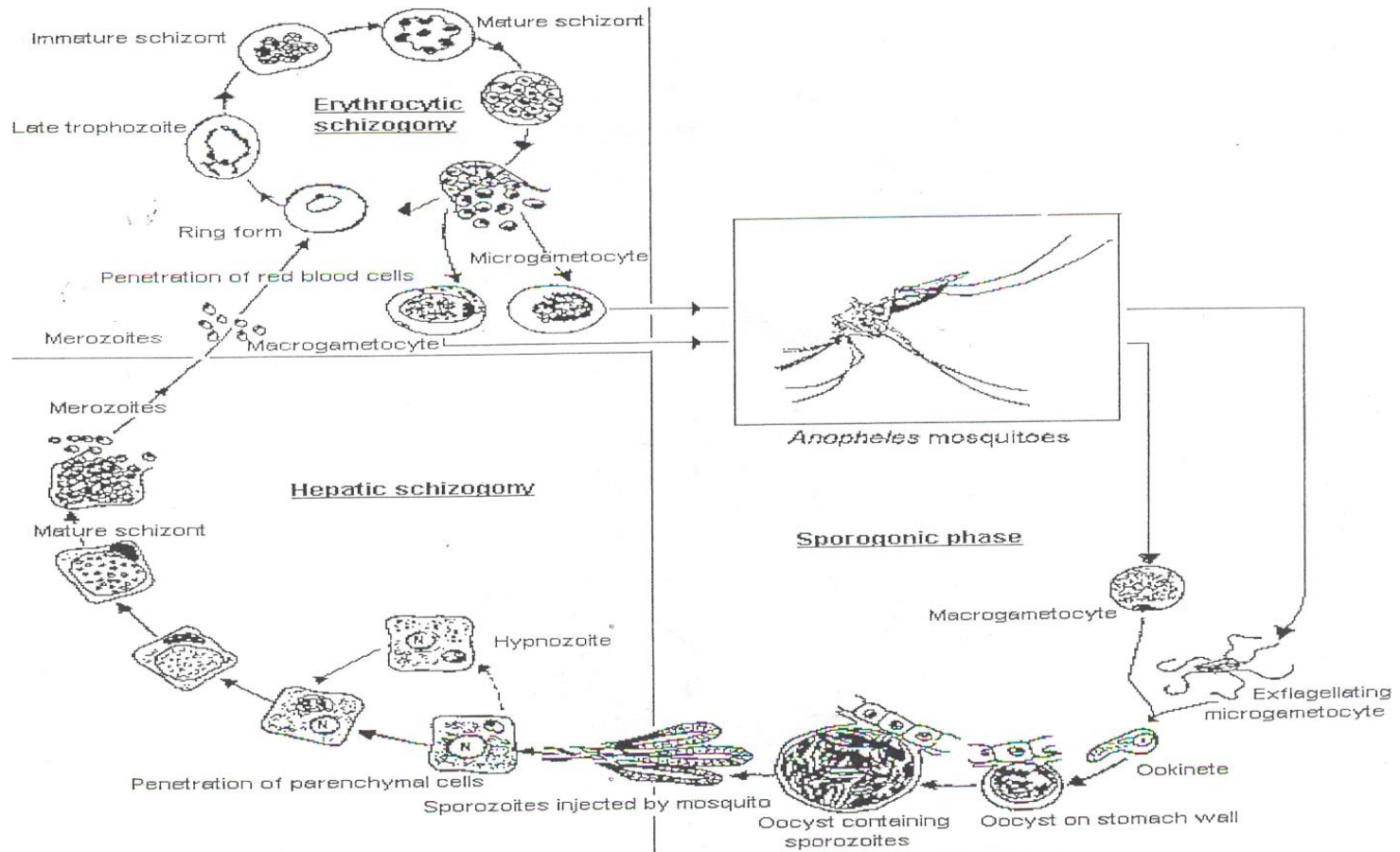
# Life Cycle

## Three phases

1. exoerythrocytic schizogony in liver
2. Erythrocytic schizogony
3. sporogony on gut wall of mosquito



# Life Cycle



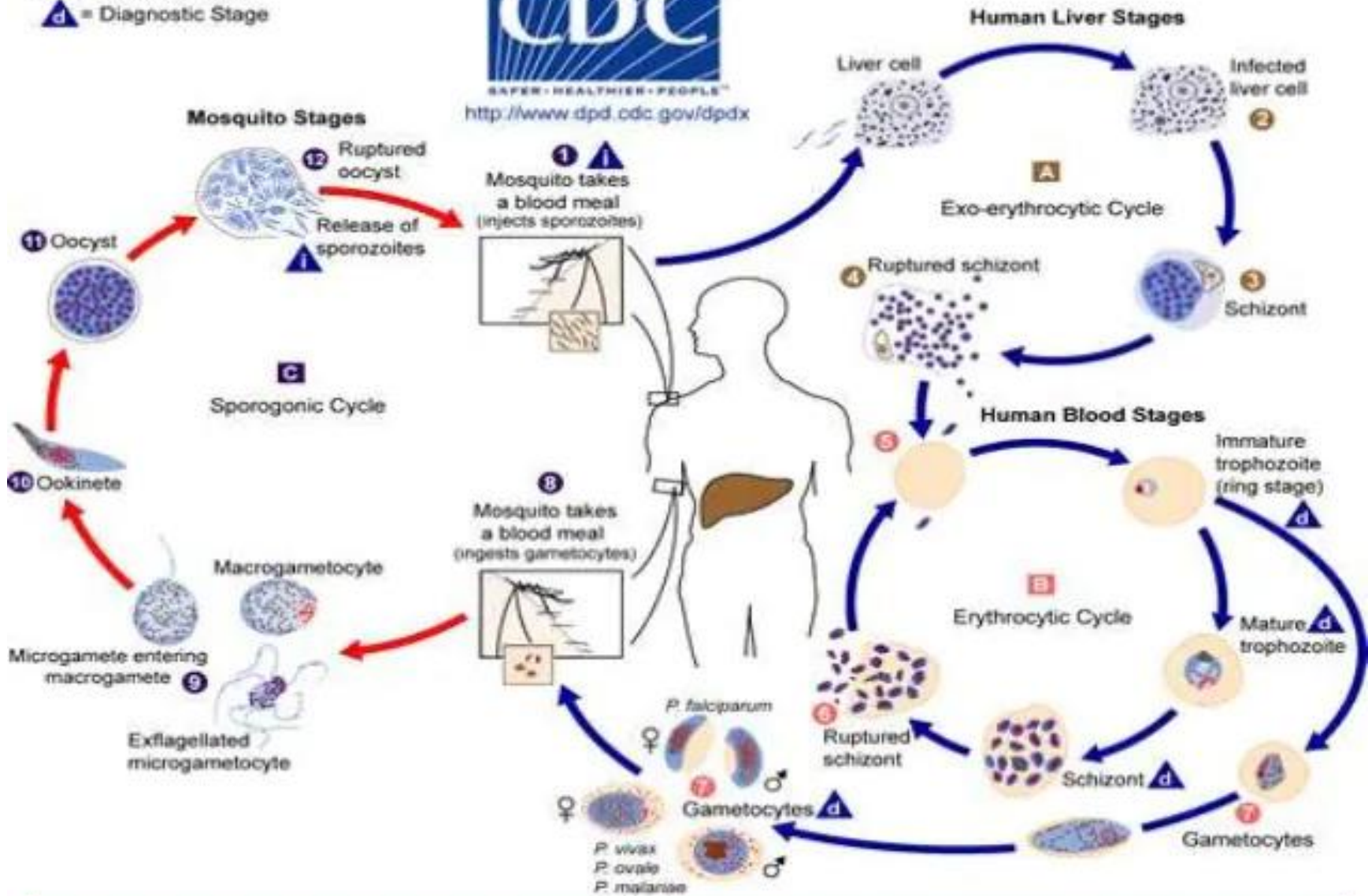
LIFE CYCLE of *PLASMODIUM* spp.

Adapted and redrawn from NCDC

**i** = Infective Stage  
**d** = Diagnostic Stage



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<http://www.dpd.cdc.gov/dpdx>



# Life Cycle-Human Cycle (Schizogony)

- Human infection comes through the bite of the infective female *Anopheles* mosquito
- Sporozoites, which are infective forms of the parasite are present in the salivary gland of the mosquito
- Injected into blood capillaries when the mosquito feeds on blood after piercing the skin
- Usually, 10–15 sporozoites are injected at a time

# Life Cycle-Human Cycle (Schizogony)

- Within an hour of being injected into the body by the mosquito, the sporozoites reach the liver and enter the hepatocytes
  - To initiate the stage of **pre-erythrocytic schizogony or merogony** (tissue) stage or exoerythrocytic stage
- The sporozoites undergo repeated nuclear division to become schizonts

# Life Cycle-Human Cycle (Schizogony)

- Mature liver stage schizonts contain 2000–50,000 **merozoites**
- Mature schizonts rupture in 6–15 days and release thousands of merozoites into the blood stream
- The merozoites infect the erythrocytes

# Life Cycle-Human Cycle (Schizogony)

## Erythrocytic stage

- The merozoites released by pre-erythrocytic schizonts invade the red blood cells
- Transform to become young parasites ‘ the **ring forms or young trophozoites**’
- **Young trophozoites become late (mature) trophozoite and transform into schizonts or meronts**
- Then become mature schizont containing 8–32 merozoites and haemozoin

# Life Cycle-Human Cycle (Schizogony)

- The mature schizont bursts releasing the merozoites into the circulation
- The merozoites invade fresh erythrocytes within which they go through the same process of development (young ringforms – mature trophozoites)
- This cycle of **erythrocytic Schizogony or merogony** is repeated sequentially
  - leading to progressive increase in the parasitaemia, till it is arrested by the development of host immune response

# Life Cycle-Human Cycle (Schizogony)

- Rupture of mature schizont releases large quantities of pyrogens.
- This is responsible for the febrile paroxysms characterizing malaria
- In *P. falciparum*, erythrocytic schizogony always takes place inside the capillaries and vascular beds of internal organs

# Life Cycle-Human Cycle (Schizogony)

- The parasite feeds on the haemoglobin of the erythrocyte
- It does not metabolize haemoglobin completely and
  - therefore, leaves behind a haematin-globin pigment called the **malaria pigment or haemozoin pigment** as residue

# Life Cycle-Human Cycle (Schizogony)

## Gametogony

- After a few erythrocytic cycles
  - some of the merozoites that infect RBC's do not proceed to become trophozoites or schizonts but instead develop into sexually differentiated forms of **gametocytes**
- Development of gametocytes takes place within the internal organs and only the mature forms appear in circulation

# Life Cycle-Human Cycle (Schizogony)

- The mature gametocytes are round in shape, except in *P. falciparum*, in which they are **crescent-shaped**
- In all species, the female gametocyte is larger (**macrogametocyte**)
- In the smaller male gametocyte (**microgametocyte**)
- Female gametocytes are generally more numerous than the male gametocytes

# Life Cycle-Human Cycle (Schizogony)

- Gametocyte appear in circulation
  - 4–5 days after the first appearance of asexual form in case of *P. vivax*
  - and 10–12 days in *P. falciparum*
- A person with gametocytes in blood is a carrier or reservoir
- The gametocytes do not cause any clinical illness in the host, but are essential for transmission of the infection

# Life Cycle-The Mosquito Cycle (Sporogony)

- When a female Anopheles mosquito ingests parasitized erythrocytes along with its blood meal
  - the asexual forms of malaria parasite are digested
  - but the gametocytes are set free in the midgut (stomach) of mosquito and undergo further development
- The nuclear material and cytoplasm of the male gametocytes divides to produce 8 microgametes with long, actively motile, whip-like filaments (**exflagellating male gametocytes**)

# Life Cycle-The Mosquito Cycle (Sporogony)

- The female gametocyte does not divide but
  - undergoes a process of maturation to become the female gamete or macrogamete
  - It is fertilized by one of the microgametes to produce the **zygote**
- The zygote, which is initially a motionless round body, gradually elongates and
  - within 18–24 hours, becomes a **vermicular motile form called the ookinete (travelling vermicule)**

# Life Cycle-The Mosquito Cycle (Sporogony)

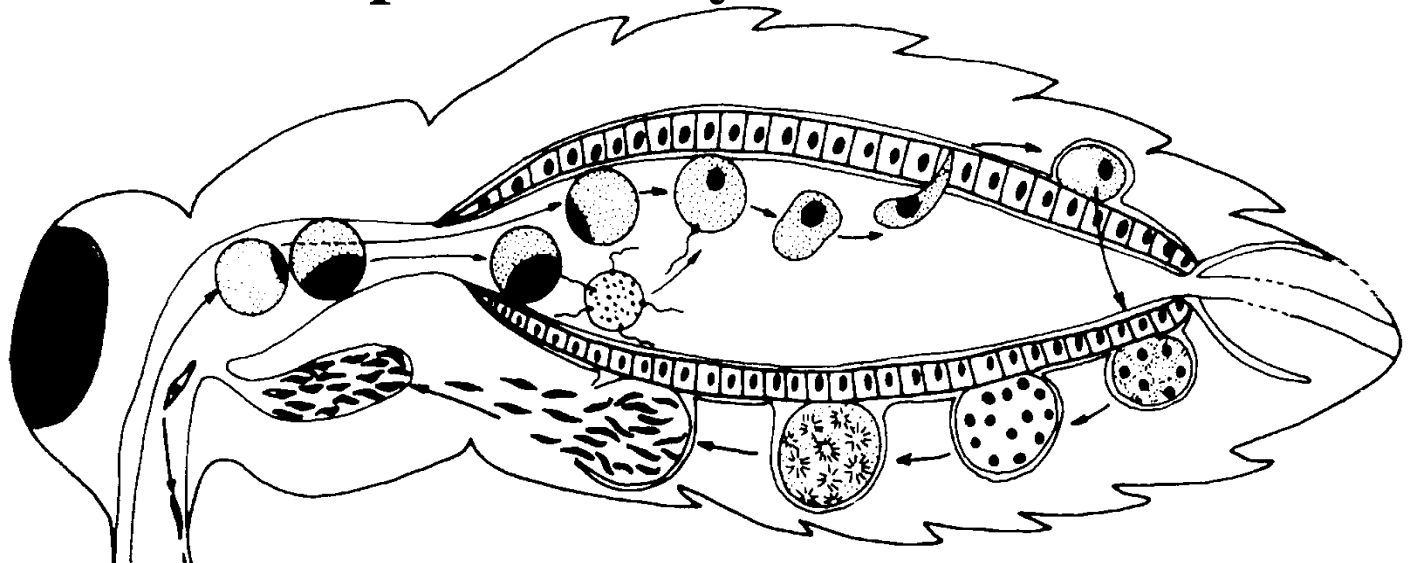
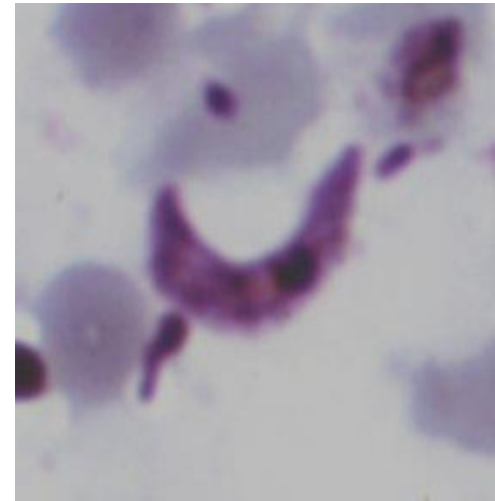
- The **ookinete develops into oocyst**
  - **which is yet** another multiplicative phase, within which numerous **sporozoites are formed**
- The mature oocyst ruptures releasing sporozoites which find their way to the salivary glands

# Sporogony

- occurs in mosquito (9-21 d)
- fusion of micro- and macrogametes
- zygote → ookinete (~24 hr)

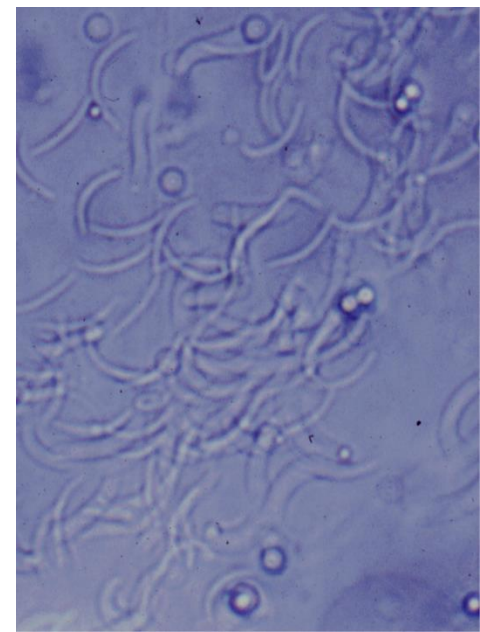
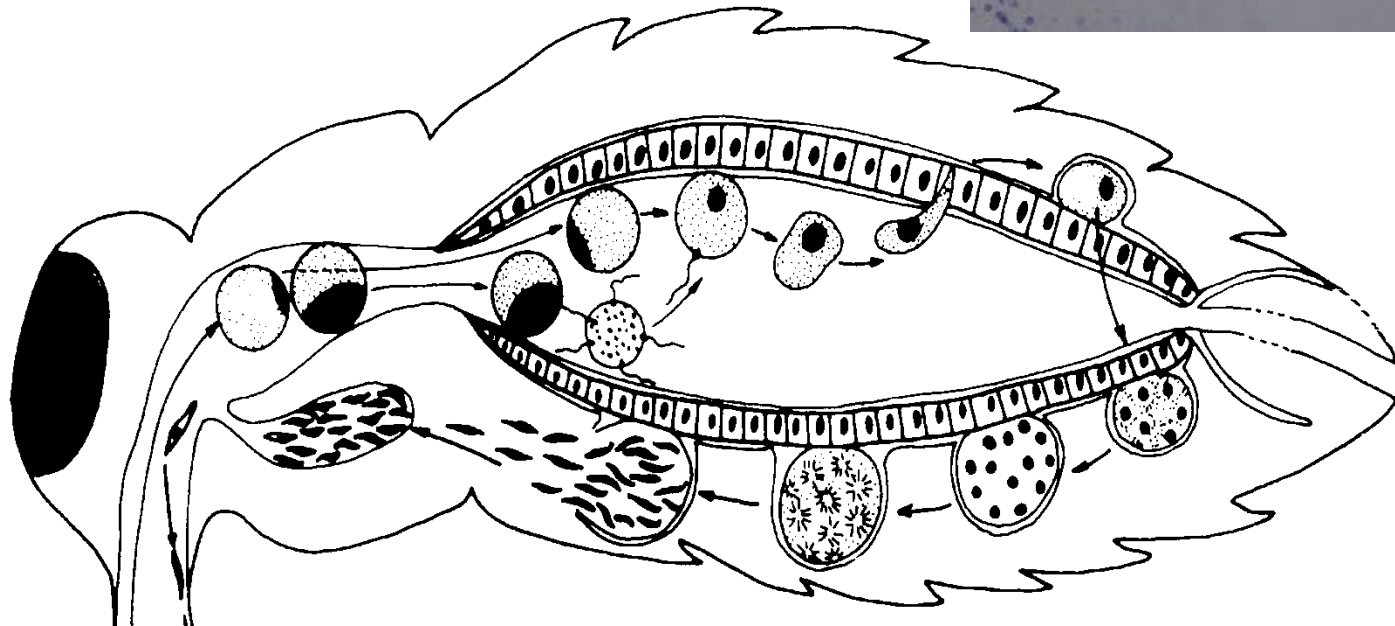
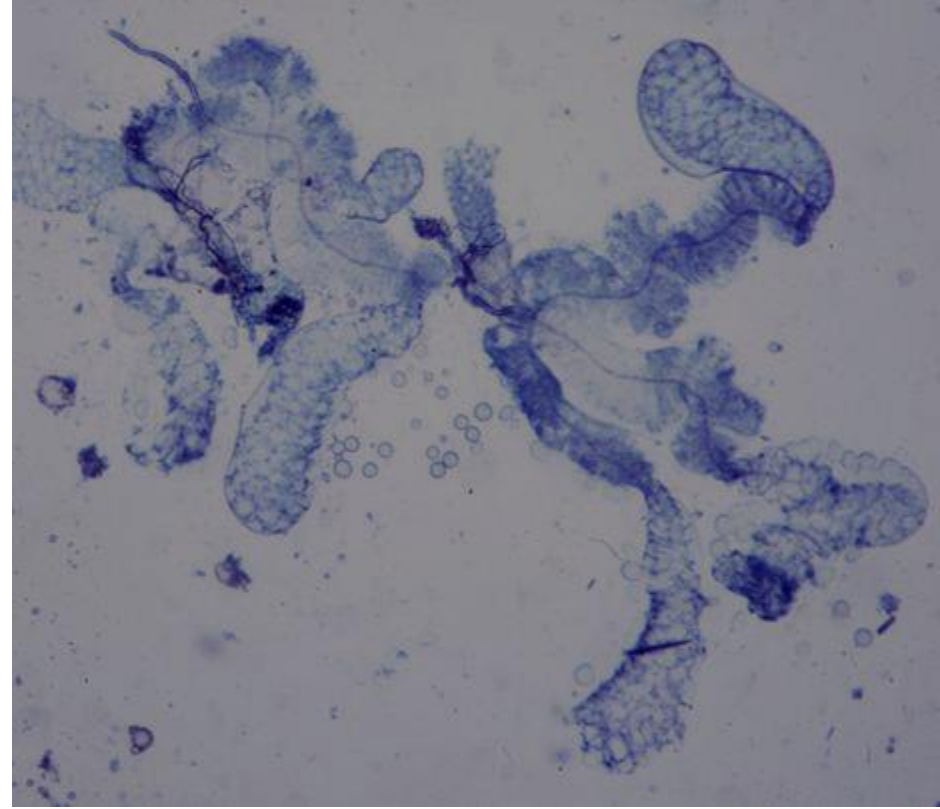
## Vermicule

- ookinete transverses gut epithelium ('trans-invasion')
- Ookinete develops into oocyst



# Sporogony

- sporozoites migrate through hemocoel
- sporozoites 'invade' salivary glands



# Life Cycle-The Mosquito Cycle (Sporogony)

- The mosquito is now infective and when it feeds on humans
  - the sporozoites are injected into skin capillaries to initiate human infection
- The time taken for completion of sporogony in the mosquito is about **1–4 weeks (extrinsic incubation period)**
  - **depending on the environmental temperature and the species**

# Pathogenesis of Malaria

1. Erythrocytic infection
2. Cytoadherence, sequestration and rosetting - P. f
3. Host defense mechanism - immunopathology

# Pathogenesis of Malaria

## 1. Erythrocytic infection

- Particularly in *P. falciparum* infection results in
  - progressive and dramatic structural changes, biochemical and mechanical modifications of the red cells
- Several pathophysiological factors occur:
  - the parasite biomass; 'malaria toxin(s)' and inflammatory response

# Pathogenesis of Malaria

## 1. Erythrocytic infection

**Anaemia:** Normocytic, hemolytic

- a. Erythrocytic infection, Parasite multiplication and survival - Hb digestion
- b. Destruction of parasitized rbc's at end of schizogony
- c. Auto-antibodies specific for unparasitized cells: -  
autoimmune, nonspecific sensitization, rbc's bind  
Ab/Ag complexes that fix complement

# Pathogenesis of Malaria

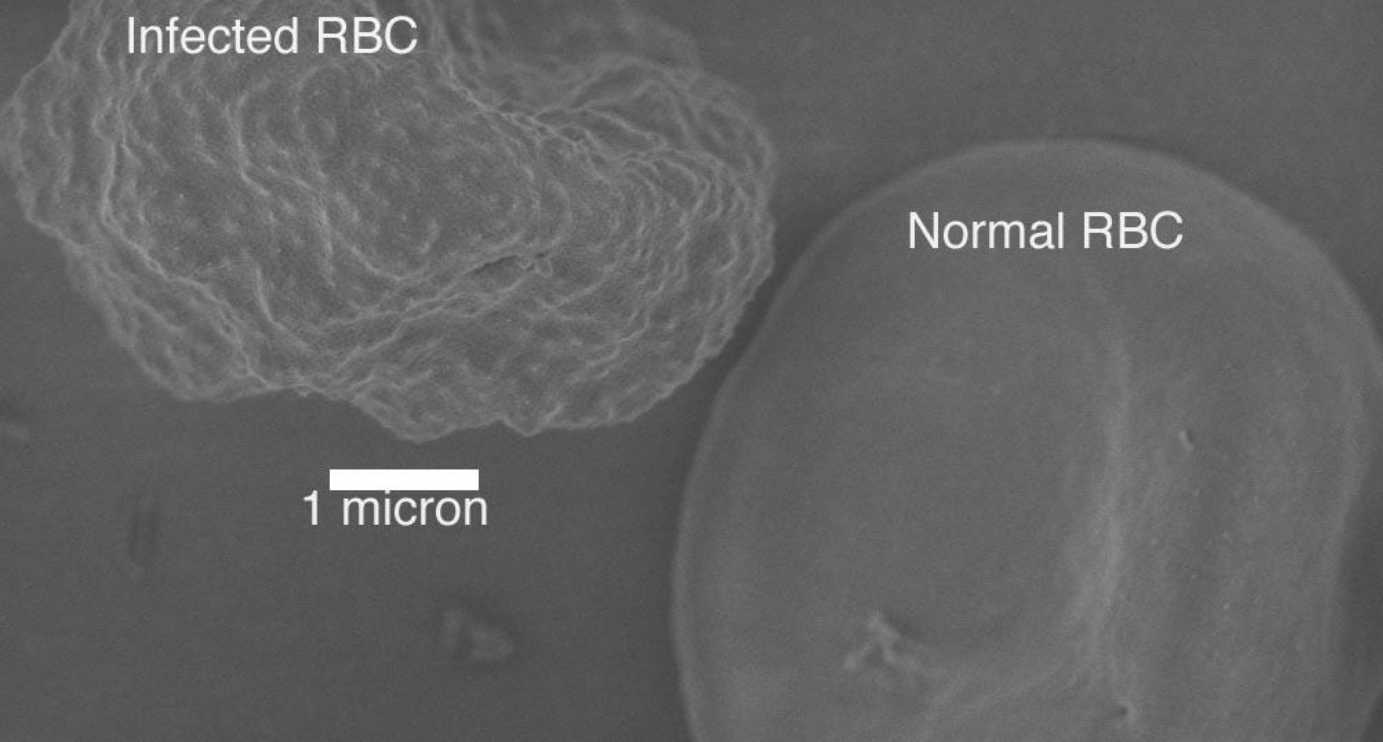
## 2. Cytoadherence, sequestration - Pf

- leads to altered deformability and fragility of parasitized erythrocytes;
- endothelial activation,
- The above have been found to be involved in the development of severe malaria due to Pf

# Pathogenesis of Malaria

## Cytoadherence, sequestration - Pf

- Structural changes in the infected red cells and the resulting increase in their rigidity and adhesiveness are major contributors to the virulence for *P. falciparum* malaria
- Owing to the increased adhesiveness,
  - the red cells infected with late stages of *P. falciparum* adhere to the capillary and postcapillary venular endothelium in the deep microvasculature (**cytoadherence**)



Knobs on surface

Adherent parasites in brain



CDC/Dr. Melvin

# Pathogenesis of Malaria

## Cytoadherence, sequestration - Pf

- Cytoadherence leads to **sequestration** of the parasites in various organs such as
  - the heart, lung, brain, liver, kidney, intestines, adipose tissue, subcutaneous tissues and placenta
- Sequestration of the growing *P. falciparum* parasites in these deeper tissues provides them the microaerophilic venous environment
  - that is better suited for their maturation and the adhesion to endothelium allows them to escape clearance by the spleen and to hide from the immune system

# Pathogenesis of Malaria

## Cytoadherence, sequestration - Pf

- Certain **proteins** expressed on the surface of the infected red cells mediate the adhesion of parasitized RBCs to the endothelium walls of capillaries, organs and to uninfected red cells
  - E.g. *P. falciparum* erythrocyte membrane protein 1 (**PfEMP1**), Histidine rich protein II (**HRP II**) bind to ligands on endothelial cells
    - chondroitin sulfate A (**CSA**) protein (placenta)

# Pathogenesis of Malaria

## Cytoadherence, sequestration - Pf

- **Ligands** include CD36, thrombospondin, vascular cell adhesion molecule 1 (VCAM I), intercellular adhesion molecule II (ICAM II) and E-selectin
- Causing stickiness of iRBCs to endothelial cell lining of small blood vessels (sequestration) , slugging, stasis of blood = “blockage” cause lesions, local anoxia, ischaemia, Increased vascular permeability and unparasitized cells leak in perivascular space

# Pathogenesis of Malaria

## Cytoadherence, sequestration - Pf

- Due to the sequestration
  - only the ring-stage trophozoites of *P. falciparum* are seen circulating in the peripheral blood

# Pathogenesis of Malaria

## Rosetting

- The infected red cells also adhere to the uninfected red cells resulting in the formation of red cell rosettes (rosetting)
- **Rosetting** is mediated by binding of
  - PfEMP1-DBL $\alpha$  on the surface of infected red cells to complement receptor 1
  - CD31, and heparin sulfate-like glycosaminoglycans of uninfected RBCs

# Pathogenesis of Malaria

**Rosetting** - infected and uninfected rbc's in the vital organs can lead to

- ultimately blocking blood flow, limits the local oxygen supply
- This contributes to the development of severe disease

# Pathogenesis of Malaria

## 3. Immunopathology of malaria:

- includes:

1. **Anaemia**= autolysis of unparasitized rbc's, increases splenic clearance, drug induced haemolysis, dyserythropoiesis in BM

2a. **Nephropathies** = Ab/Ag complexes cause lesions in Kidney glomerular walls

- In *P. falciparum*: Acute nephropathy, reversible, oliguria, renal failure due to IgM,
- Malaria antigen and Complement
- Clears after treatment

# Pathogenesis of Malaria

## 2b. Nephropathies = In *P. malariae*:

- Nephropathy is Chronic, progressive, severe
- Deposits of IgG, IgM, complement and Pm antigen in glomerular walls
- Auto immune response to damaged tissue
- Quartan Malaria nephrosis with persistent heavy proteinuria, hypoalbuminaemia, oedema,
- Deterioration of renal functions
- Hypertension.
- Treatment - little effect

# Pathogenesis of Malaria

## 3. Splenomegaly:

- Oedema of the pulp, RES hyperplasia, increased phagocytic fxn
- Tropical Splenomegaly Syndrome (TSS) in young and adults

## 4. Immunodepression:

- . Bone marrow depression (iron sequestration-dyserythropoeisis; dysthrombopoeisis)
- . Auto antibodies
- . Pregnancy
- . Burkitt's lymphoma; endemicity correlating with malaria endemicity

# Incubation period

- The average incubation periods of different species of *Plasmodium* are as follows –
  - *P. vivax*—14 (8–31) days
  - *P. falciparum* —12 (8–14) days
  - *P. ovale* —14 (8–31) days
  - *P. malariae* —28 (18–40) days

# Incubation and Pre-patent period

- The incubation period:
  - is the interval between the entry of sporozoites into the host and the earliest manifestation of clinical illness is the **incubation period**
- The pre-patent period:
  - is the interval between the entry of the parasites into the host and the time when they first become detectable in blood

# Recrudescence

- Commonly seen in *P. falciparum* and *P. malariae* infections, (but can occur in all *P.* species) after the primary attack, sometimes there is a period of latency
  - during which there is no clinical illness
- But some parasites persist in some erythrocytes,
  - although the level of parasitemia is below the fever threshold or sometimes below the microscopic threshold
- Fresh malarial attacks then develop after a period of latency

# Recrudescence

- Usually within 8 weeks after the primary attack and
  - resulting from persistence of the erythrocytic cycle of the parasites are called **recrudescences**
- Recrudescence may be due to
  - waning immunity of the host, or possibly due to antigenic variation, drug resistance or under dosage
- In *P. falciparum* infections, recrudescences are seen for 1–2 years
- In *P. malariae* infection, they may last for long periods, even upto 50 years

# Relapse

- It is seen in *P. vivax* and *P. ovale* infections
- In both these species, 2 kinds of sporozoites are seen
  - some of which multiply inside hepatocytes promptly to form schizonts and others which remain dormant
- These latter forms are called **hypnozoites (from hypnos: sleep)**
  - **Hypnozoites** remain inside the hepatocytes as uninucleated forms for long periods

# Relapse

- Such new attacks of malaria, caused by dormant exoerythrocytic forms
- Reactivated usually from 24 weeks to 5 years after the primary attack to cause **relapse**

# Clinical Features

## Uncomplicated (Benign) Malaria

- The typical picture of malaria consists of
  - **Prodromal** phase (early signs & symptoms)
    - Severe headache, nausea, and vomiting are common & intermittent fever or paroxysms of chills
- **Paroxysms** of chills (intermittent fever)
  - Sudden attack of fever 104- 105 F (40-40.6 C).
  - Release of schizogony products
- **Paroxysm** comprises of 3 successive stages i.e. **cold stage, hot stage and sweating stage**

# Clinical Features

## Uncomplicated (Benign) Malaria

### Cold stage: rigor

- lasts for 15–60 minutes, the patient experiences intense cold and uncontrollable shivering
- **Malarial** pyrogens stimulate secretion of endogenous pyrogens ( monocytes/macrophages to release cytokines like TNF & IL-1 = chills & high-grade fever)
- ☐stimulate thermoregulatory centers in the hypothalamus to conserve heat.
- Shivering, chills, intense cold feeling
- Vasoconstriction = cyanotic lips and fingers
- Muscular pain, malaise, goose flesh

# Clinical Features

## Uncomplicated (Benign) Malaria

### Hot Stage:

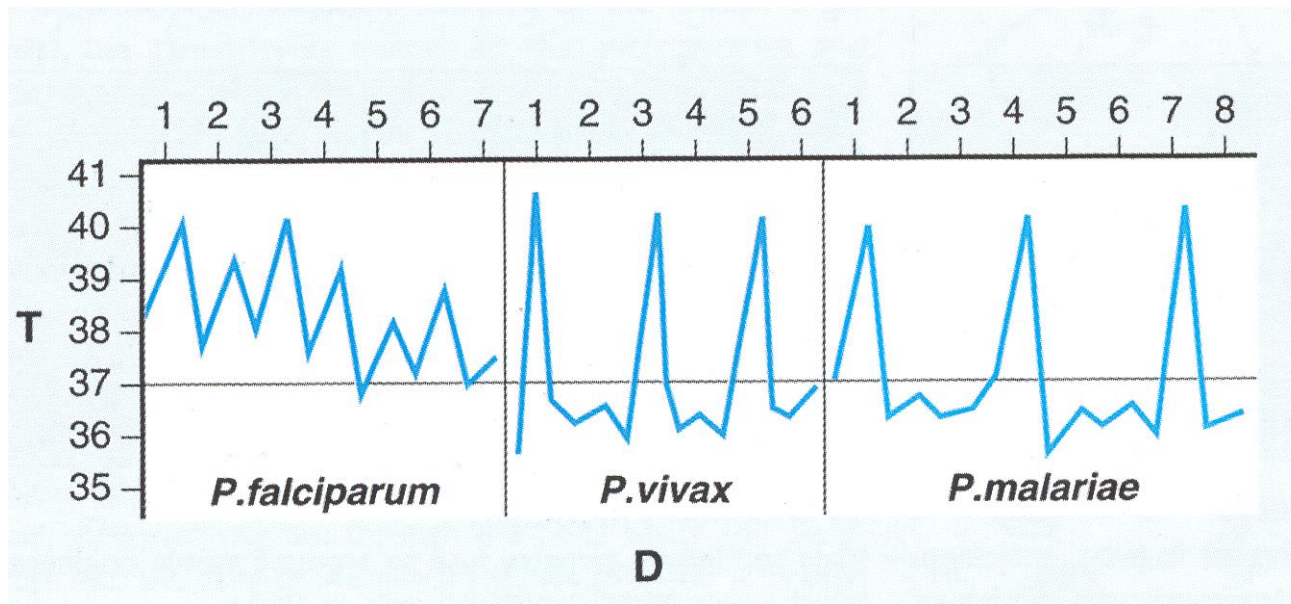
- Body temperature reaches “set Point” 41<sup>0</sup> C (106<sup>0</sup>F) or higher, lasting for 2 – 6 hours
- The patient feels intensely hot
- Dry burning skin, full bounding pulse
- Nausea, vomiting. intense headache

# Clinical Features

## Uncomplicated (Benign) Malaria

### Sweating Stage:

- Return to normal temperature “set point “ by profuse sweating
- Body temperature falls rapidly below normal
- On waking patient feels weak but normal, lasts for 2-4hours

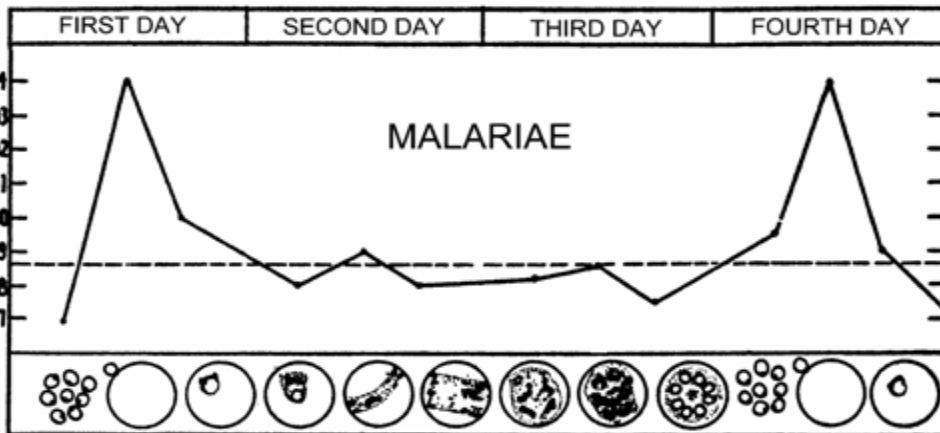
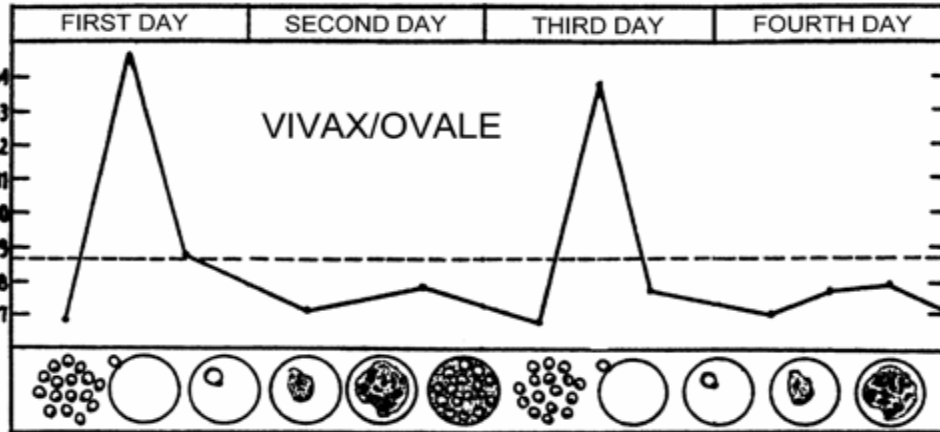
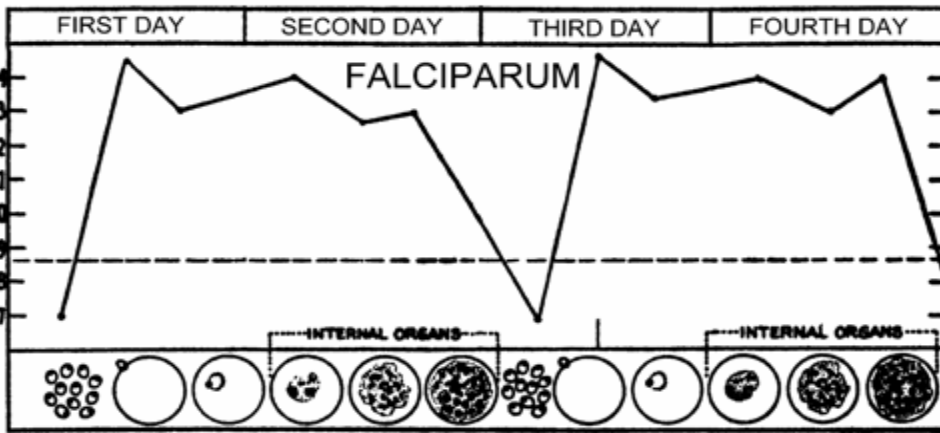


Tertian and quartan fever patterns The asexual blood stages of *Plasmodium falciparum*, *P. vivax* and *P. ovale* require 48 hours to complete their schizogony. Fever is produced when the schizonts mature, i.e. at 48-hour intervals. This gives the classic tertian periodicity, which is, however, uncommon in a primary attack of *P. falciparum* malaria. *P. malariae* requires 72 hours and is associated with quartan fever, i.e. 72 hours between paroxysms.

# Malaria Paroxysm

Tertian malaria

quartan malaria



# Complications

## Severe (Malignant) Malaria

- The most serious and fatal type of malaria is malignant tertian malaria caused by *P. falciparum*
- When not treated promptly and adequately, dangerous complications develop.
  - Which may present in various forms, the most important of which are the cerebral, algid, and septicemic varieties

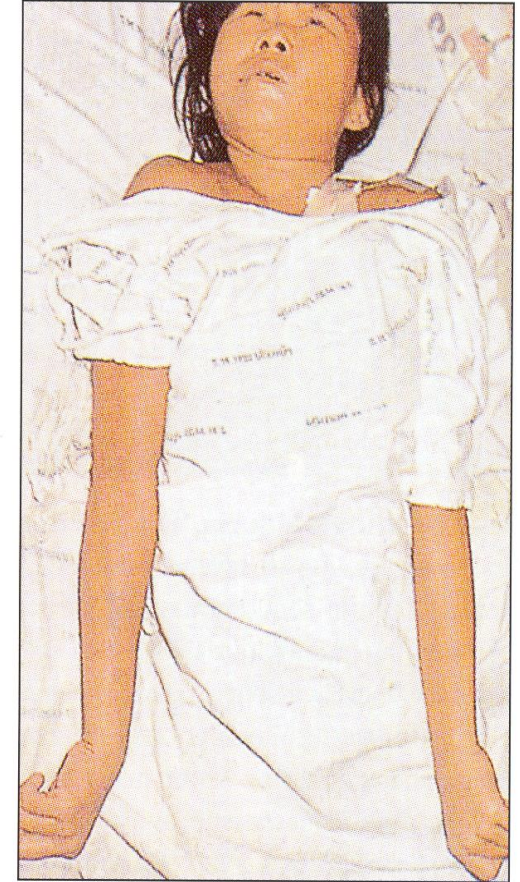
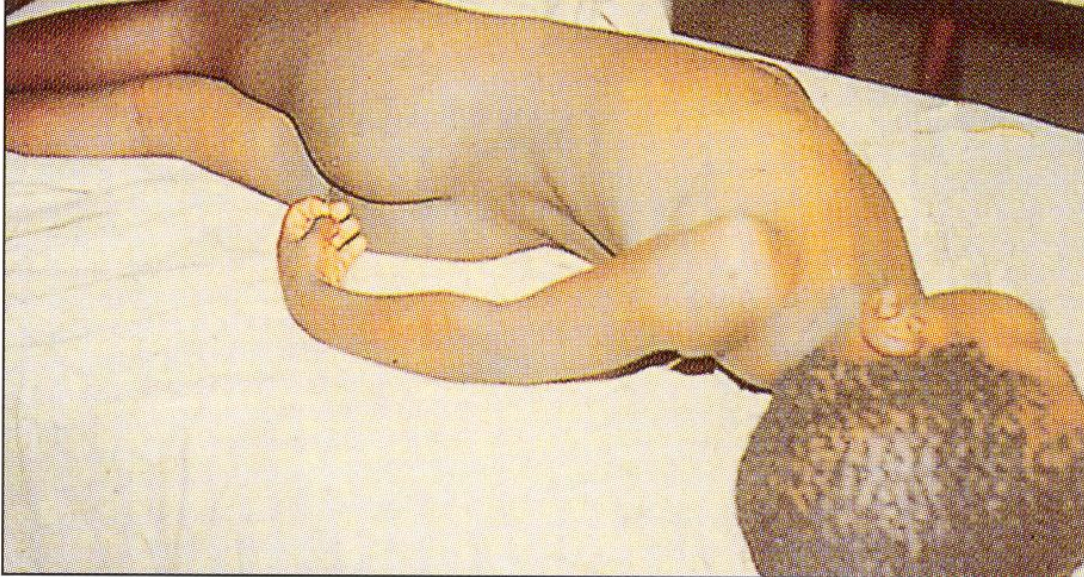
# Clinical features

## Severe (Malignant) Malaria

- **Cerebral Malaria/comatose:** most common cause of death in malignant malaria
- Even with treatment, death occurs in 15% of patients
- Restless, delirious, epileptic, violent, manic.
- Comatose,
- Behavioural changes
- Hyperpyrexia, 40.5oC, 5 % rbc's infected.
- Misdiagnosed as insanity, encephalitis, or meningitis.

# Clinical features

**Cerebral malaria in a comatose Malawian child with opisthotonus In holoendemic areas of Africa, cerebral malaria commonly occurs in children between six months and three years of age--- The opening pressures of cerebrospinal fluid are often raised in children when measured at lumbar puncture.**



**Classic decerebrate rigidity associated with Hypoglycaemia . This Thai woman with cerebral malaria displays classic decerebrate rigidity. which was almost certainly due to a profound quinine-induced hypoglycaemia. The latter is more common during pregnancy. when the warning signs are fits. abnormal behaviour and a change in the level of consciousness.**

# Clinical features

## Severe (Malignant) Malaria

**B. Algid:** cold, pulseless, unconscious, peripheral vascular circulatory collapse, low BP. coma, overwhelming infection – death within hours

# Clinical features

## Severe (Malignant) Malaria

**C. Haemorrhagic:** Bleeding from skin or mucus membrane



**Disseminated intravascular coagulation ( DIC ) in falciparum malaria. Bleeding into the skin with no signs of cerebral malaria.**

# Clinical features

## Severe (Malignant) Malaria

D. **Gastrointestinal:** vomiting, coughing, diarrhoea, or acute dysentery

### E. **Pulmonary oedema:**

- Malaria Shock syndrome
- Fluid overload during treatment
- Disseminated intra-vascular coagulation – DIC  
Induce diuresis and haemodialysis

. Often fatal

F. Respiratory distress (metabolic acidosis bicarbonate less than 15 meq/l)

G. **Hepatorenal syndrome/Haemolytic jaundice** = jaundice and renal failure

# Clinical features

**Severe malarial jaundice** Deep jaundice, which is clearly seen in this Vietnamese man who had severe falciparum malaria, is much more common in adults than in children. Liver failure, however, occurs only in individuals in whom a concurrent viral hepatitis is present.



**Malarial anaemia:** is multifactorial, involving destruction of parasitised cells, haemolysis of uninfected cells, dyserythropoiesis and iron sequestration, malarial anaemia is an important cause of death in children under two years of age.

# Clinical features

H. Jaundice and kidney failure



**Severe malarial jaundice**

# Clinical features

## Severe (Malignant) Malaria

### I. Blackwater fever:

in repeated infections with Pf with inadequate quinine treatment

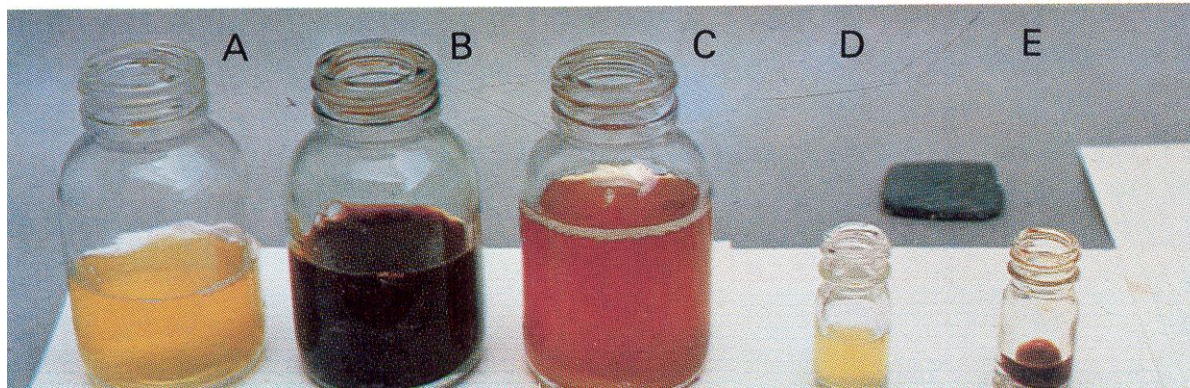
Haemolysins formed against quinized and unparasitised cells – autoimmunity

Haemoglobinuria, bilirubinaemia, haemoglobinaemia

Fever, jaundice, nausea, vomiting, anuria, oliguria,

# Clinical features

Black water fever: Quinine auto antibodies derived from previous infection lyses rbc's coated with new auto antigens.

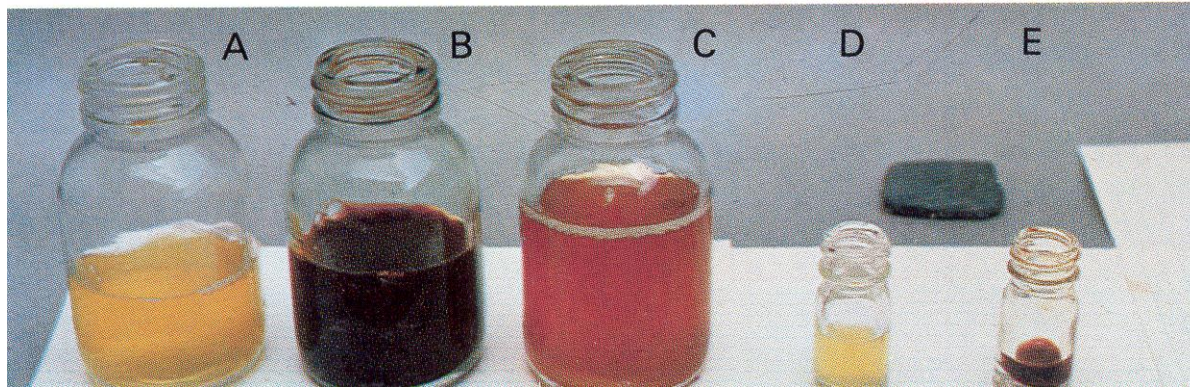


Blackwater urine and serum taken during course of illness An acute haemolytic crisis resulting in malarial haemoglobinuria occasionally occurs in severe attacks (Blackwater fever). Haemoglobinuria can also be drug induced in patients deficient in the enzyme glucose 6-phosphate dehydrogenase (G-6-PD). A = normal urine; B = patient's urine; C = patient's urine, diluted; D = normal serum; E = patient's serum.

# Clinical features

. **Blackwater fever:** Coca –Cola urine

complications of quinine treatment



# Clinical features

J. Severe anaemia (haemoglobin less than 5g/dl or haematocrit less than 15%)

K. Renal failure-presenting as oliguria or anuria

L. Confusion or drowsiness with extreme weakness

M. Pernicious malaria:

Pernicious = Harmful, deadly, or noxious in a way that is not easily notice ' :

**"Protean manifestations: able to appear in various forms, changing, can mimic any disease syndrome"**

# Clinical features

## Malaria in children

1. Pf common
2. Symptoms atypical
3. Drowsiness, vomiting, diarrhoea, unproductive cough, fever without periodicity.
4. Cerebral manifestations- convulsions and coma twitching
5. High body temperature
6. Spleen enlargement, jaundice
7. Severe anaemia fatal in babies



Malarial anaemia: malarial anaemia is an important cause of death in children under 5 years

# Clinical features

## Malaria in children

8. Hyperpyrexia

9. medical shock, renal involvement

10. splenic enlargement, jaundice

11. severe normocytic anemia

12. Pv and Po - milder in children.

13. Pm - Nephrotic syndrome, glomerulonephritis leads  
to gross edema, proteinuria and hypoproteinemia

# Clinical features

## **Malaria in pregnancy**

1. high prevalence: highly susceptible
2. haemolytic anemia- jaundice, ,splenomegaly, death
3. acute renal insufficiency
4. abortions, stillbirths, awaken latent malaria
5. low birth weight
6. Treatment must not be withheld, Intermittent Preventive Treatment (IPTp) or chemophylaxis for at least 3 months

# Immunity

- **Influenced by**
  - Genetics
  - Age
  - Health condition
  - Pregnancy status
  - Intensity of transmission in region
  - Length of exposure
  - Maintenance of exposure

# Immunity

## Innate

- Red cell polymorphism associated with some protection
  - Haemoglobin S sickle cell trait or disease
  - Haemoglobin C and haemoglobin E
  - Thalassaemia a and b
  - Glucose – 6 – phosphate dehydrogenase deficiency (G6PD)
- Rbc membrane changes
  - Absence of certain Duffy coat antigens improves resistance to *P. vivax* (lack fya and fyb-)

# Immunity

## Acquired

1. Transferred from mother to child
  - 3-6 months protection
  - Then children have increased susceptibility
2. Increased susceptibility during childhood
  - Hyper and holoendemic areas
    - By age 5 attacks usually less frequently and severe
    - Can have more parasite densities with fewer symptoms

# Immunity

## **Acquired**

### 3. Meso or hypoendemic areas

- Less transmission and repeated attacks
- May acquire partial immunity and be at higher risk for symptomatic disease as adults

# Immunity

## **Acquired**

- No complete immunity
  - Can be parasitaemic without clinical disease
- Need long period of exposure for induction
- May need continued exposure for maintenance

# Immunity

## Acquired

- Immunity can be unstable
  - Can wane as one spend time outside endemic areas
  - Can change with movement to area with different endemicity
  - Decreases during pregnancy, risk improves with increasing gravidity

# DIAGNOSIS

1. **Clinical diagnosis** – based on Signs and Symptoms being presented by a patient
2. LAB diagnosis of malaria is confirmed by blood tests  
i.e. *microscopic* and *non-microscopic* tests

# DIAGNOSIS

## Microscopic methods

Demonstration of malarial parasites in thick and thin blood smear *Light Microscopy*

- Giemsa-staining of thick and/or thin blood smears → conventional method of diagnosing malaria
  - combination is gold standard
- smears allow species identification
- can calculate the parasite density (prognosis)

# DIAGNOSIS

## Non – microscopic methods

- Immunofluorescence staining and QBC smear

### Fluorescent Microscopy

- Is not as specific and sensitive as light microscopy
- cannot differentiate species and special microscope is required

# DIAGNOSIS

## Non – microscopic methods

- Rapid immunochromatographic test (ICT/RDTs) for detection of malaria antigen (PfHRP2 and PLDH)
- A rapid simple dipstick test → results in 10-15 minutes
- useful in situations where diagnostic expertise or microscopic facilities are limited
- Limitations:
  - cannot determine degree of parasitemia
  - false positives
  - not fully reliable for accurate species diagnosis
- 3 assays currently used for testing: HRP-2, aldolase and pLDH

# DIAGNOSIS

## Non – microscopic methods

- Molecular diagnosis: DNA probe and PCR

### Polymerase Chain Reaction (PCR)

- Has the ability to detect parasitemia at very low levels
- Is helpful in species identification when microscopy is equivocal
- Disadvantages are high cost, labor intensive

# Principles of Treatment

- Treatment of malaria depends on the following factors:
- Type of infection
- Severity of infection
- Status of the host
- Associated conditions/ diseases

# Treatment

- Supportive treatment, anti-malarial drugs
- *P. vivax*, *P. ovale*, and *P. malariae* are mostly treated on an outpatient basis
- *P. falciparum* pts are generally admitted for observation of any complications
  - hospitalized until they are improving clinically and parasite count is declining
  - most can be treated with oral therapy → severe malaria requires IV therapy/ICU

# Treatment of Malaria

Treatment should be prompt to destroy:

- a. All asexual forms in order to prevent clinical attack.

Curative/ therapeutic

=Blood Schizontocide – against schizont stages

Quinine - (Chinchona, Jesuit Powder)

Primaquine - slow, not useful alone

Proguanil - Paludrine (Chloquanide)

Pyrimethamine : sterilizes gametocytes

Pyrimethamine + sulfalene = Metakelfin

Pyrimethamine + sulfadoxine = Fansidar(SP)

Pyrimethamine + Dapsone = Maloprim

Mefloquine, Halofantrine, Amodiaquine

**Quinghousu:** Artemether, Artemisinin,  
Artesunate ,

Coartem<sup>®</sup> (artemether+  
Lumefantrine)

*Artemisia annua*= Chinese herb

Quinghousu

20 years to licence



## **b. Destroy all Hypnozoites + E.E.forms**

- Prevents establishment within the liver  
and Prevents relapses= Tissue schizontocide  
=Sporontocide + tissue Schizontocide eg  
Primaquine, Proquanil in Pf

Toxicity potentiated by Quinacrine in G6 PD  
deficiency

## **c. Destroy gametocytes to prevent mosquito**

Infection. Lowers endemicity

Causal prophylaxis: =Gametocide

e.g Pyrimethamine, Fansidar, Maloprim, Metakelfin  
=Sporontocide

Primaquine =Anti-relapse taken with blood meal.

No drug available against sporozoites  
injected in human blood

**NOTE: antimalarials have selective action on  
different phases of the life-cycle.**

**No single drug can fulfill all 3 objectives**

# NEW DRUG POLICY - 2020

**For simple or uncomplicated malaria in adults**

**First Line Drug:**

- Coartem<sup>R</sup> ( Artemisinin Based Combination Therapy = ABCT, ACT) e.g. Artemether 20mg + Lumefantrine 120mg (AL)

**Second Line Drugs:**

- Oral Quinine 300mg tablet
- Quinine 10mg/kg – IM diluted in saline or water for injection

**For severe or complicated malaria**

- Injectable artesunate 2.4mg/kg body weight IV/IM
- If unavailable artemether (IM) or Quinine 20mg/kg (IV/IM) diluted in 5% or 10% dextrose

# Malaria in Pregnancy

## Uncomplicated malaria

### First line

- Oral Quinine in 1<sup>st</sup>. Trimester (can be used in all trimesters)  
Injectable artesunate 2.4mg/kg BW in 2<sup>nd</sup> and 3<sup>rd</sup> trimesters
- In absence of Quinine, Artemether 20mg+Lumefantrine 120mg can be used in 1<sup>st</sup> trimester

## Severe malaria

Quinine is 1<sup>st</sup>. Line in this case

Injectable artesunate 2.4mg/kg BW in 2<sup>nd</sup> and 3<sup>rd</sup> trimesters

- Intermittent preventive treatment(IPT) – Sulphadoxine + Pyrimethamine given 16 weeks following last monthly period (LMP)**
- 2 consecutive doses given at least 16 weeks apart during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester
  - A total of 3 doses should be given during the entire duration of pregnancy

# Malaria in Children

**For simple or uncomplicated malaria**

**First Line Drug:**

Coartem<sup>R</sup> ( **Artemisinin Based Combination Therapy = ABCT, ACT**) for children above 5kg

- Artemether 20mg +Lumefantrine 120mg (AL)
- Sulphadoxine 500mg + Pyrimethamine 25mg – single treatment of half a tablet

**Second Line Drugs:**

- Quinine 10mg/kg BW diluted in saline (IM)

**For severe or complicated malaria**

- Injectable artesunate 2.4mg/kg BW IV or IM
- Quinine 20mg/kg BW diluted in dextrose (IV)

# Prognosis

- Mortality of untreated falciparum is almost 100% and 10-40% for treated
- Poor prognostic factors:
  - Age < 3
  - Seizures
  - Acidosis
  - Respiratory distress

# Control of Malaria

- Control would therefore involve three living beings:
  - **Man** (*The host*),
  - **Plasmodia** (*The agent*), and
  - **Anopheles mosquito** (*The vector*)
- Control of malaria is possible only by concerted community efforts

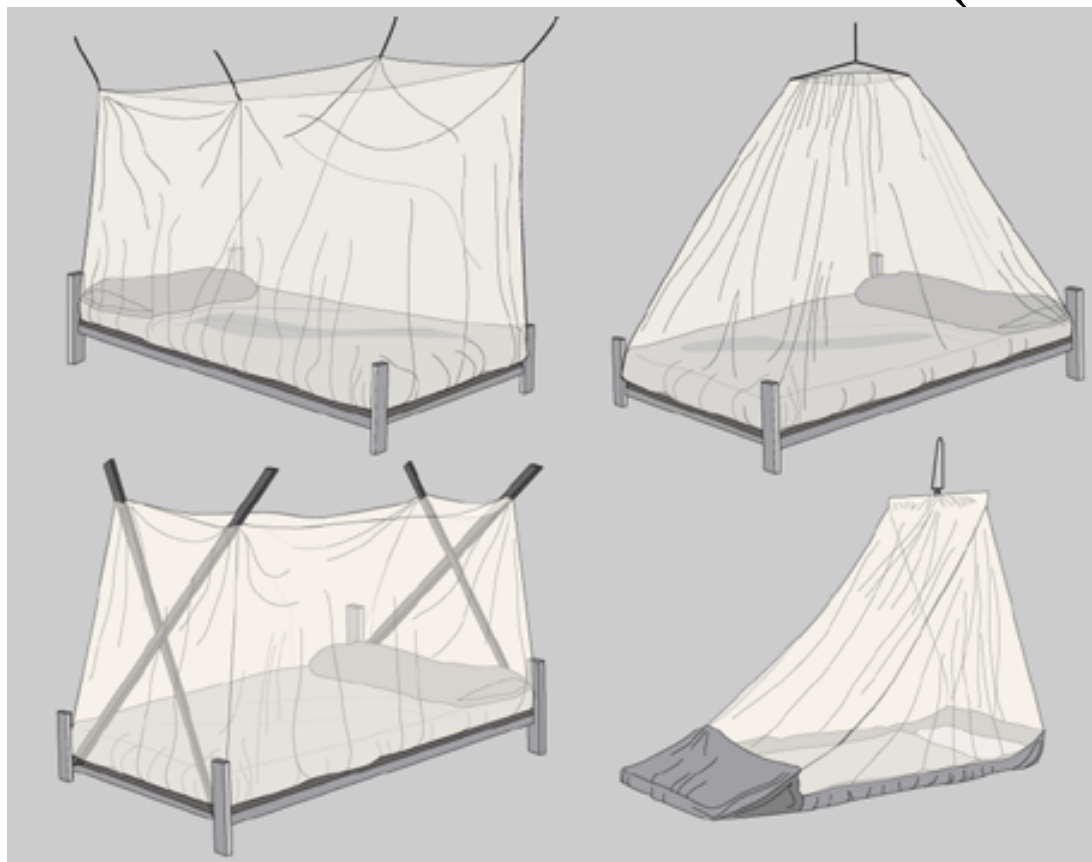
# Control of Malaria

- Early diagnosis and treatment – treat early to reduce parasite load, hence spread; prevent deaths
- Treat completely to prevent spread and relapse
- Ensure compliance with complete treatment
- Personal Protection- prevent malaria by using Insecticide Treated Bednets (ITNs),
- insecticide sprays etc.,
- **Intermittent preventive treatment(IPTp):**  
3 doses SP in 2<sup>nd</sup>. & 3<sup>rd</sup>. trimesters
- and by chemoprophylaxis (for travellers)

# Malaria Control in Zambia

## To Reduce disease burden

### 1. Insecticide Treated Bednets (ITNs)



# Malaria Control in Zambia Cont.

## 2. Indoor Residual Spraying (IRS)

**Missiroli Principle: all houses all walls, regular, adequate –Conc.**

**repelents Citronella, Neem tree**

## 3. Integrated Vector Management

## 4. Care of the sick :

-Prompt and effective Treatment – Coartem is prescription only

-Laboratory Diagnosis

## 5. Prevention of Malaria in Pregnancy(MIP) by Intermittent Prevent Treatment (IPT)

# Assignment

- Mechanism of action and drug resistance of the antimalarials

Thank you