MALARIA

GENERAL

Malaria kills ~1,300,000 worldwide annually.

"Of all the diseases there is no doubt that malaria has caused the greatest harm to the greatest number." C. Landerman

Burdens

- ~41% of world population live in areas with malaria.
- ~300 million persons are carrying the parasite.
- >90% of the parasite carriers are in tropical Africa.
- ~120 million clinical cases of malaria are reported each year.
- ~80% of clinical cases occur in tropical Africa.

Deaths

- ~1 million children die each year from malaria, mostly in Africa.
- P. falciparum most severe
- Common causes of death
  - Cerebral malaria
  - Severe anemia
  - Low birth weight infants with higher neonatal mortality.

Four species of Plasmodium

- *P. falciparum* (worldwide) — rapid death; drug resistance.
- *P. ovale* (western Africa) — can cause prolonged relapses.
- *P. vivax* (worldwide) — can cause prolonged relapses.
- *P. malariae* (worldwide) — the least common species.

Vectors

- Female Anopheles mosquito — need blood for egg maturation.
- 400 species
- 60 species are known vectors; 30 species are major vectors.
- Efficiency vary between species.
- Females live from a few days to months.
- 2 - 4 day cycles of feeding and egg laying.
- Lays 100 - 200 eggs.
- Male mosquito feeds on vegetable juices.

CLINICAL FEATURES

Humoral immunity alters the disease.
Humoral immunity develops slowly over many years.

Incubation period

From first bite to first symptoms.
P. falciparum, P. ovale — about 2 weeks
P. malariae, P. vivax — sometimes longer
If taking anti-malarial drugs — many months

Symptoms

Chills	97%
Fever	97%
Headache	94%
Nausea/Vomiting	62%
Abdominal Pain	56%
Myalgias	50%
Backache	9%
Dark Urine	3%

Malarial paroxysm

Red blood cell rupture and release of merozoites (sporulation).
Irregular patterns during first 2 - 3 weeks.
Regular patterns emerges after 2 - 3 weeks.
Sporulation becomes synchronized.

First paroxysmal is often severe.
Paroxysms may last for weeks if untreated.
Paroxysm severities decrease as humoral immunity develops.

Cold stage
- 20 - 60 minutes
- Rigors and chills

Hot stage
- 3 - 8 hours
- Rising temperatures to 40 - 42C

Wet stage
- Profuse sweating
- Decreasing fever

Anemia
- Increased rate of red blood cell destruction.
- Depressed bone marrow function.
- Disproportionate to parasite burden.
- Enlarged spleen sequesters infected red blood cells.
- "Black water fever" is more common with *P. falciparum*.

Altered blood flow
- Fever causes vasodilatation and hypotension.
- Red blood cells adhere to capillaries.
- Decrease blood flow to organs causes damage.

Cerebral malaria
- Associated mainly with *P. falciparum*.
- Brain is most susceptible organ to hypoxia.
- Symptoms
  - Delirium
  - Convulsions
  - Paralysis
  - Coma and death within 3 days

Other manifestations
- Acute transient glomerulonephritis — *P. falciparum*.
- Progressive renal disease — chronic *P. malariae*.
- Thrombocytopenia — decreased platelets.
- Decreased blood flow to other organs — mesentery.

EPIDEMIOLOGY

Worldwide distribution.
45N - 40S latitude.
Altitudes below 1800 meters.

P. vivax — most widely distributed species.
P. malariae — least common species (subtropical areas).

Intensity of transmission depends on several factors.
- Mosquito density
- Mosquito feeding habits
- Prevalence of infected humans

Hyper-endemic areas
- ≥ 50% of population is parasitemic.
- Transmission is constant or sustained.
- High percentage of population has immunity.
- Immunes have reduced clinical manifestations.
- Mortality seen in
  - Infants and younger children.
  - Non-immune adults who travel into area.

Non-hyper-endemic areas
- Transmission is intermittent or sporadic.
- Low percentage of population has immunity
- Clinical manifestations are not reduced.
- Population suffers repeated epidemics.
- Often seasonal patterns.
- People of all ages susceptible.

Global picture 1990
~59% of world population live in malaria free areas.
~41% of world population live in malaria infested areas.
~32% live in areas where malaria was reduced or eliminated at one time.

75% malaria cases are reported from 9 countries
- Excluding Africa with poor reporting.
- India
- Brazil
- Afghanistan
- Sri Lanka
- Thailand
- Indonesia
- Viet Nam
- Cambodia
- China

United States picture
- ~1000 cases imported annually
- Clinical manifestations develop ≤ 6 months after returning from abroad.
- 40% cases are *P. falciparum*.
- ~99% fatalities are *P. falciparum*.

Barriers to prevention and control
- Inadequate sanitation.
- Precarious living conditions.
- Lack of financial resources.
- Lack of knowledge about biology, ecology and control of vectors.
- Expansion of humans into new geographic areas.
- Weak health infrastructures.

PATHOGEN'S FEATURES

Characteristics
- Sporozoa
- Intracellular protozoa.
- Alternating asexual (blood) and sexual (mosquito) reproduction.

Three kinds of sporozoa are human pathogens.
- Plasmodia — humans and mosquitoes required.
- Toxoplasma — felines pass infection to humans.
- Cryptosporidia — mammals pass infection to humans.

Mosquito life cycle (sporogony)
- Period of 1 - 3 weeks.
- Gut phase
  - Female Anopheles mosquito feeds on malarious human.
  - Mosquito ingests circulating male and female gametocytes.
  - Gametocytes mature and effect fertilization.
  - Zygote invades gut wall and forms an oocyte.
  - Oocyte grows into a cyst.
  - Cyst ruptures and releases sporozoites.
- Salivary gland phase
  - Sporozoites travel to mosquito s salivary gland.
  - Mosquito can now transmit sporozoites to humans.

Human life cycle (schizogony)

Period varies with species.

Liver phase

Infected female Anopheles mosquito feeds on malarious human.
Sporozoites from mosquito's salivary gland are injected.
Sporozoites reach the liver and invade hepatocytes within 1 hour.
Latent infections of liver — *P. vivax*, *P. ovale*
Sporozoites start a round of asexual reproduction.
Merozoites are released into blood circulation.
No clinical manifestations of disease during hepatic phase.
Entire hepatic phase varies from 1 - 2 weeks.

Erythrocyte phase

Merozoites attach to erythrocytes (specific receptor).
Merozoites cause erythrocyte membrane to infold.
Nuclear fission into several parts takes place (extracellular cleft).
6 - 24 daughters form.
Infected erythrocytes rupture releasing merozoites.
Merozoites invade other erythrocytes.
Irregular fevers begin.
Synchronization of sporulation begins.
Paroxysm begins.
Some erythrocytes form gametocytes that do not rupture.
Gametocytes circulate until ingested by a mosquito.
Infection moderated by humoral immune response.
Relapses may occur years later — *P. vivax*, *P. ovale*

Plasmodium vivax

Infects reticulocytes (young erythrocytes).
1 - 2% of circulating erythrocytes.

Plasmodium ovale

Infects reticulocytes (young erythrocytes).
1 - 2% of circulating erythrocytes.

Plasmodium malariae

Infects older erythrocytes.
1 - 2% of circulating erythrocytes.

Plasmodium falciparum

Infects all circulating erythrocytes.
Accounts for severity.

Hemoglobin abnormalities limit parasite burdens.
- Hemoglobin S (sickle cell).
- Hemoglobin C, D, E and Thalassemia.
- Glucose-6-phosphate deficiency.
- Perturbs asexual reproduction of parasite.
- Helps to reduce parasite burden.
- Confers selective advantage.

Laboratory diagnosis
- Thin blood smears.
  - Used for larger parasite burdens.
  - *P. falciparum*
- Thick blood smears
  - Used for smaller parasite burdens.
  - *P. vivax, P. ovale, P. malariae*
- Stains
  - Wright
  - Giemsa
  - Acridine orange
- Serologic tests.
  - Utility?
- DNA probes.
  - Utility?

Humoral immunity
- Develops after several years of infection
- Reduces clinical manifestations of disease.
- Immunity is short lived (goes away after drug therapy)
- Stage specific
  - Sporozoite
  - Merozoite
  - Gametocyte
- Strain specific
  - *P. falciparum*
  - *P. vivax*
  - *P. ovale*
  - *P. malariae*

PREVENTION

Personal protection

Decrease mosquito contact (dusk and early evening).
House screens.
Insecticide bombs within rooms.
Mosquito netting around bed.
Insect repellents.
Long sleeves and pants.

DRUG PROPHYLAXIS

Prevents clinical disease by inhibiting asexual phase.
No drug provide 100% protection.

#1 CHLOROQUINE
Chloroquine-resistant *P. falciparum* is widespread.
500 mg weekly

#2 PYRIMETHAMINE/SULFADOXINE
P/S-resistant *P. falciparum* is increasing.
Alternative drug to chloroquine
12.5/100 mg weekly

#3 DOXYCYCLINE
Often used for short-term prophylaxis.
100 mg daily

#4 MEFLOQUINE
Drug of choice for chloroquine resistant P. falciparum.
More toxic alternative.
250 mg weekly

#1-4 PRIMAQUINE
Take drug upon leaving area to eradicate hepatic schizonts.
79 mg weekly for 8 weeks.

CONTROL PROGRAMS

Reduce human infections and mosquito populations
Critical numbers needed for sustained transmission of disease.
Chemical disruption of mosquito breeding areas.
Residual insecticide sprays.
Physical disruption of mosquito breeding areas.
Reduce wet areas where insects breed.
Declines in malaria were achieved between 1956 - 1968
We are losing the battle at present.

VACCINES

Three advance are facilitated vaccine development
Continuous in vitro culture system — grow large quantities of parasite.
Monoclonal antibodies — identify protective antibodies.
Molecular biology — clone and sequence genes.

Humoral immunity is stage specific.
First goal is to make a one-stage vaccines.
Ultimate goal is to make a three-stage vaccine.

Anti-sporozoite vaccine
(+) Would stop liver infection.
(–) Could fail even if one hepatocyte becomes infected.
Circumsporozoite (CS) protein

Anti-merozoite vaccine
(+) Would reduce clinical disease.
(–) Would not stop gametogenesis.
Vaccine based on SPf66 protein.
Initial trials in South America were promising.
1996 trials in Thailand demonstrated no efficacy.

Anti-gametocyte vaccine
(+) Would stop sexual reproduction in mosquito.
(–) Would not alter clinical disease.

DRUG THERAPIES

Must destroy three parasitic forms
Erythrocyte schizont — stops clinical attacks.
Hepatic schizont — stops relapsing disease.
P. vivax, P. ovale
Erythrocyte gametocyte — stops transmission to mosquito.
No single drug accomplished all these goals.

Drug-sensitive malaria

CHLOROQUINE

Resistant strains have emerged.
P. falciparum (widespread)
P. vivax (New Guinea, Sumatra)

PYRIMETHAMINE/SULFADOXINE

Resistant strains increasing.
Southeast Asia
South America

Drug-resistant malaria

QUININE

First choice for *P. falciparum* resistant strains
More toxic drug than chloroquine.
Less active than chloroquine.

QUININE + DOXYCYCLINE

Combination therapy often used for *P. falciparum*
Intravenous quinine + oral doxycycline for more severe cases

MEFLOQUINE

Resistant strains emerging
More toxic alternative

HALOFANTRINE

ARTESUNATE

ARTEMETHER

Drugs against hepatic schizont.
Terminates latent hepatic infections.
P. vivax, P. ovale

PRIMAQUINE
Resistant strains
P. vivax (New Guinea, Southeast Asia)
Use higher dose primaquine for treatment.
G-6PD defects associated with severe hemolysis.

Drugs against circulating gametocytes.
CHLOROQUINE
Resistant strains
P. falciparum
PRIMAQUINE

MOST COMMON DRUG THERAPIES

Treatment of chloroquine-sensitive malaria
CHLOROQUINE + PRIMAQUINE

Treatment of chloroquine-resistant *P. falciparum*
QUININE + PYRIMETHAMINE/SULFADOXINE or DOXYCYCLINE
Exchange transfusions for severe cases.

BOTTOM LINES

P. falciparum is the most lethal malaria parasite.

We are losing the battle against malaria worldwide.

Resistant strains of malaria are spreading.

Vaccine trials for P. falciparum have failed.

Few drugs are under development by big pharma.

READING

• Waters AP. Guilty Until Proven Otherwise. Science 2003; 301: 1487-1488.

• Schellenberg D et al. Intermittent treatment for malaria and anemia at a time of routine vaccinations in Tanzanian infants: a randomized, placebo-controlled trial. Lancet 2001; 357: 1471-1476.

• Hemingway J, Craig A. New Ways to Control Malaria. Science 2004; 303: 1984-1985.

• Kremsner PG, Krishna S. Antimalarial combinations. Lancet 2004; 364: 285-294.

FIGURE 1

MAP 1. EPIDEMIOLOGICAL ASSESSMENT OF THE STATUS OF MALARIA, 1990

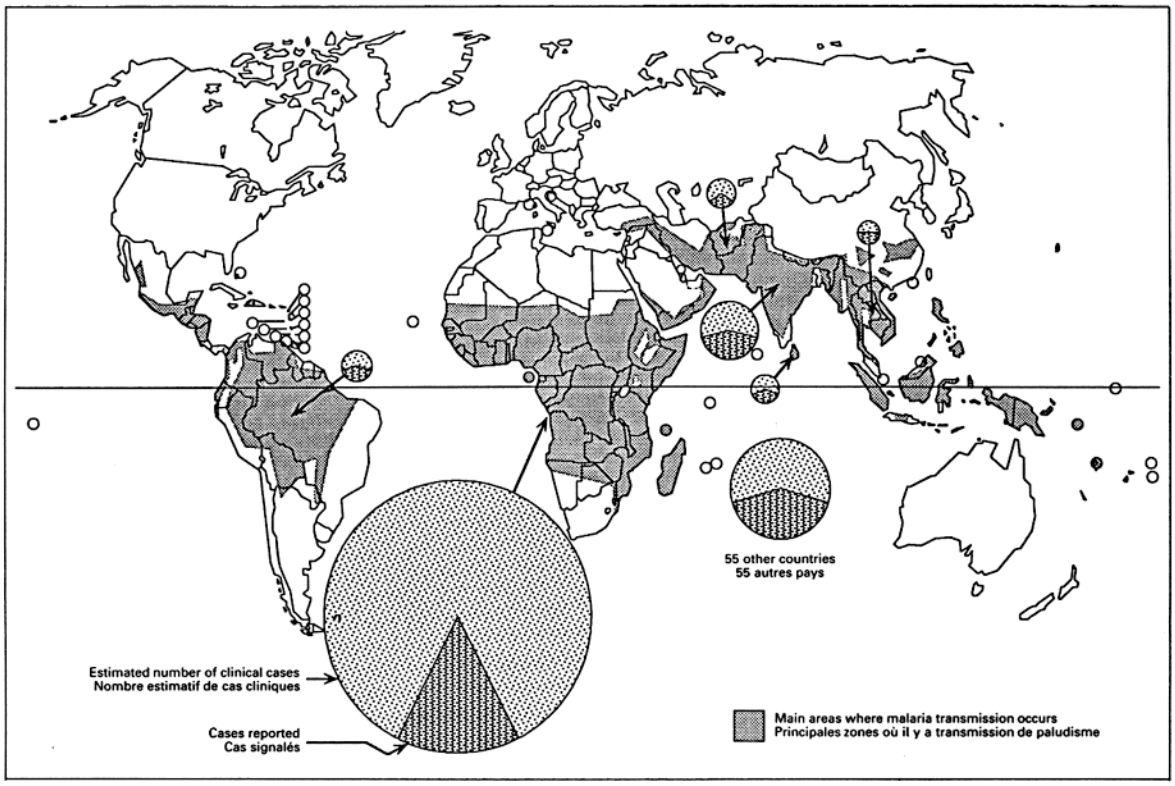


FIGURE 2

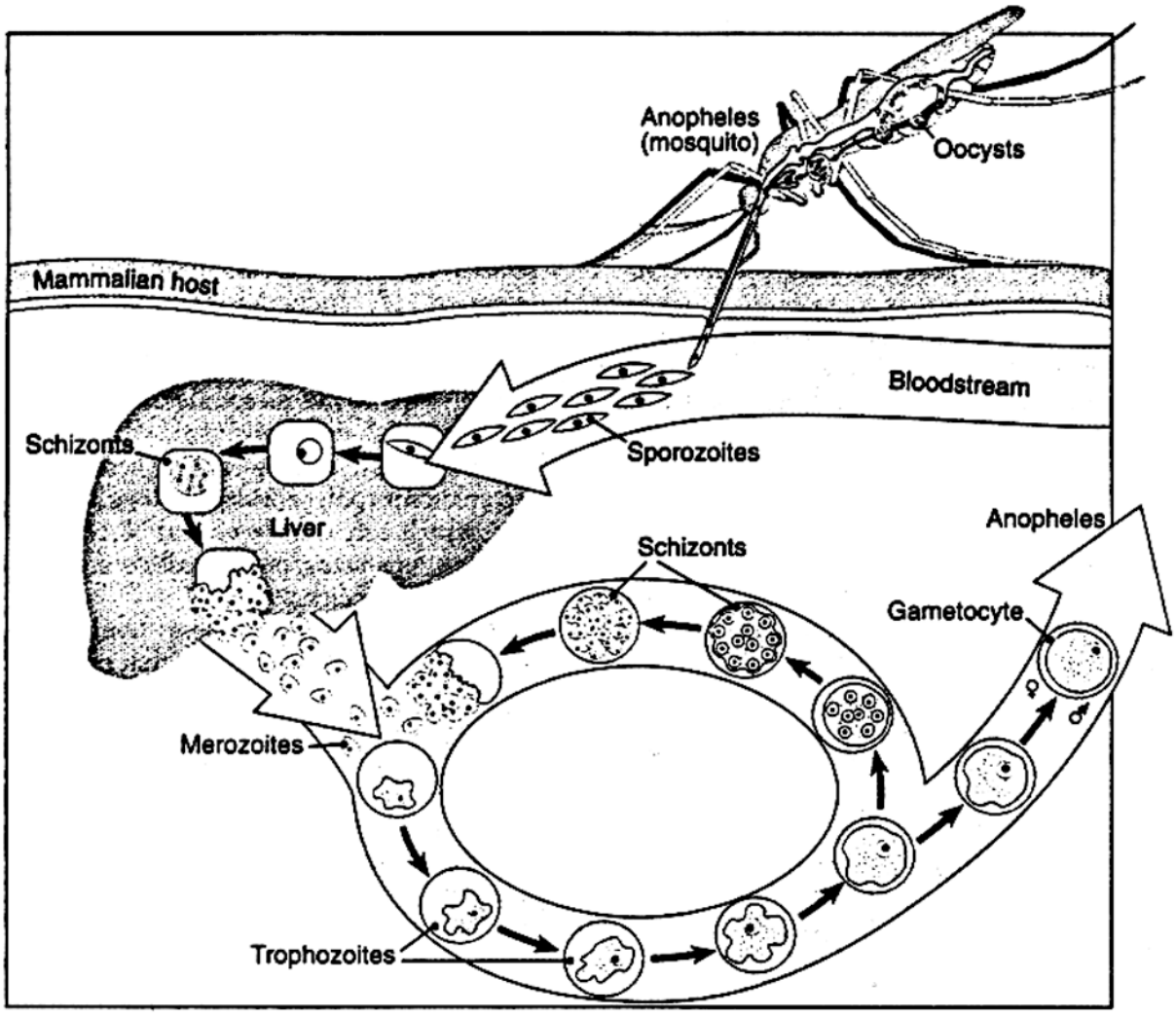
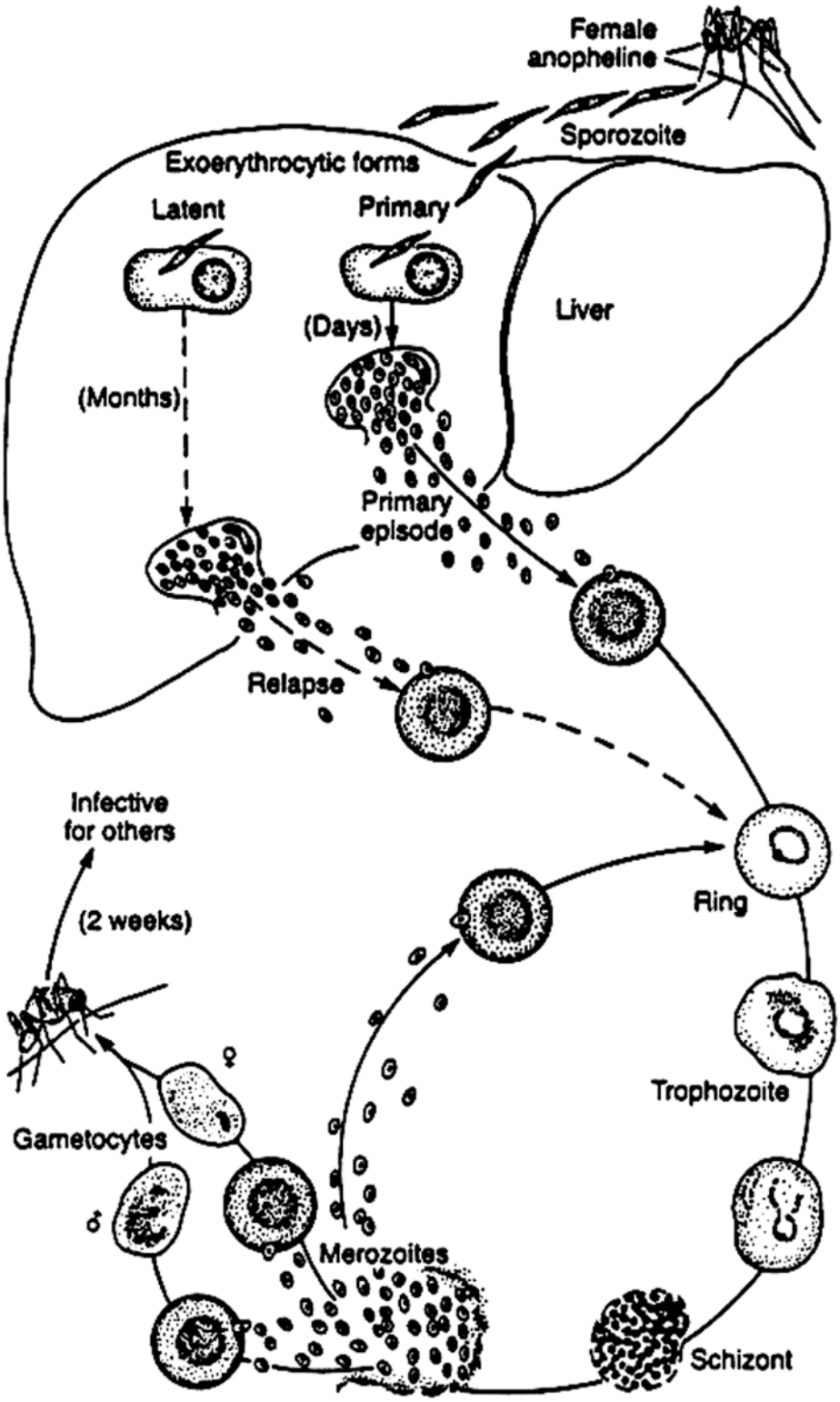

Anopheles
(mosquito)
Oocysts
Mammalian host
Bloodstream
Schizonts
Sporozoites
Liver
Anopheles
Schizonts
Gametocyte
♀
♂
Merozoites
Trophozoites

FIGURE 3


Female anopheline
Sporozoite
Exoerythrocytic forms
Latent
Primary
Liver
(Days)
(Months)
Primary episode
Relapse
Infective for others
(2 weeks)
Ring
Trophozoite
Gametocytes
♀
♂
Merozoites
Schizont