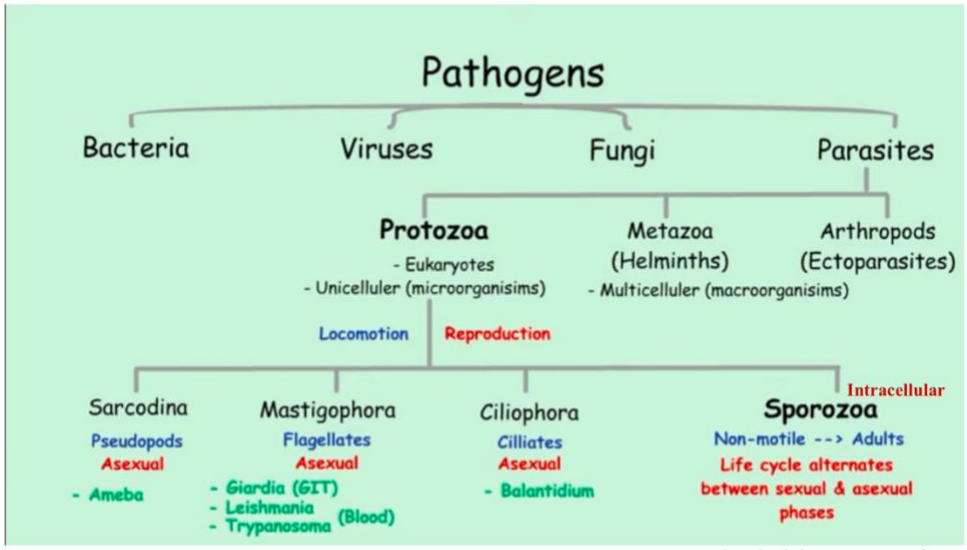
Blood Protozoa



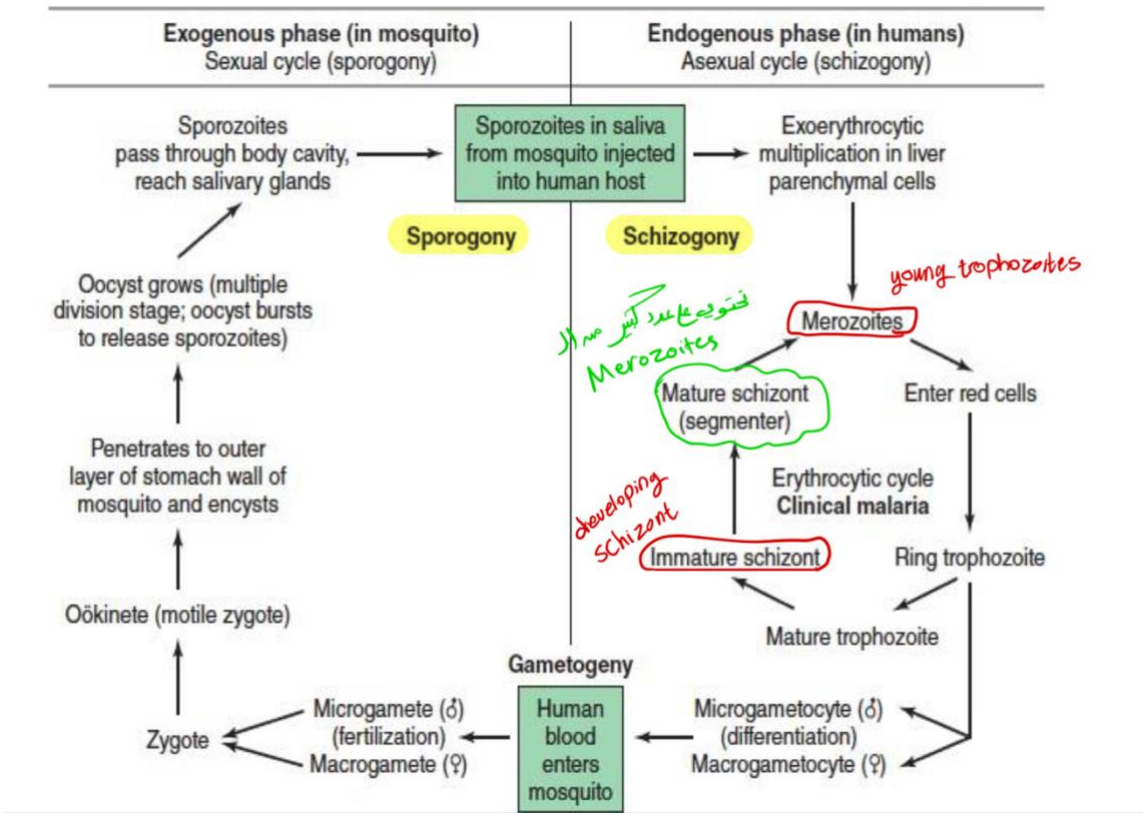
they don't have anorgan of motion butt they are motile and its movement is called Gliding

❖ Plasmodium

- children (from 1-5 years) are the most susceptible group to get infected with malaria, malaria is fatal in this age group.
- Disease Burden increasing due to :
    1) weakening public health
    2) agricultural practices
    3) global warming
    4) lack of vaccine
    5) drug resistance in parasite and vector
    6) population growth in endemic areas
    7) increased travel (migration movements)
- Transmitted by the female of anophelines mosquito.
- The parasite always has two hosts in its life cycle: Dipteran insect host and a vertebrate host.
- They alternate between sexual and asexual reproduction :
    - Sexual happens in the female of Anopheline mosquito
    - Asexual happens in the human

❖Mechanism of Infection

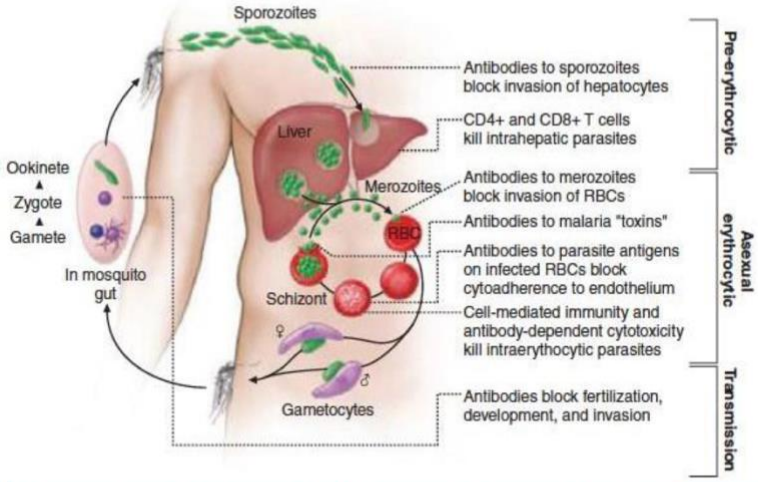
- Exoeryrthrocytic cycle : **Trophozoites** start their asexual reproduction and become **Schizontes** that contains large numbers of **Merozoites** , when this schizont ruptures the merozoites leave the liver and invade the red blood cells (RBCs) , initiating the Erythrocytic cycle.



- Important: The symptoms and signs of the human start once the merozoites are released into the blood (eryhtrocytic cycle).
- Important: Sporogony is sexual reproduction while Schizogony (merogony) is asexual reproduction.
- Important: Merozoites feed on the hemoglobin inside the RBCs consuming it, but they can't degrade it completely, so some metabolites stay in the RBCs producing a pigment called hemozoin or hematin or malarial pigment.
- Always link malaria's fever to periodicity.

- Note that different periodicity for different plasmodium species is due to *the time needed for asexual multiplication inside RBCs*.
- A dormant schizogony may occur in P. vivax and P. ovale organisms, which remain quiescent in the liver. These resting stages (quiescent stage) have been termed hypnozoites and lead to a true relapse, often within 1 year or up to more than 5 years later.
- IMPORTANT: In P.falciparum and P.malariae and P.knowlesi, there is **recrudescence** which is different from the relapse. **Recrudescence**: A repeated attack of malaria due to the survival of malaria parasites in red blood cells, and there are no hypnozoites in the liver, but the plasmodium in the blood are under detectable level (merozoites under threshold) , they cause signs and symptoms when their level is high level in the blood, or when the immune system is weaken.
- Prepatent period : the period between infection and appearance of parasites in the blood.
- Incubation : the time between infection and the appearance of symptoms.
- Some people protected against malaria :
    1) People lack Duffy receptors in their RBCs.
    2) People with Sickle cell traits
    3) People with G6PD
    4) Newborns under 1 years of age because of their HbF as well as the maternal immunity (antibodies from their mother)
- Sickle-cell patients: More vulnerable to serious complications caused by malaria.
- Other modes of transmission to know:
    1) Blood transfusion (note that in this case, there is no exoerythrocytic cycle, the erythrocytic cycle starts immediately)
    2) Organ transplantation
    3) Mother-to-baby transmission
    4) Shared syringes

Malaria transmission cycle

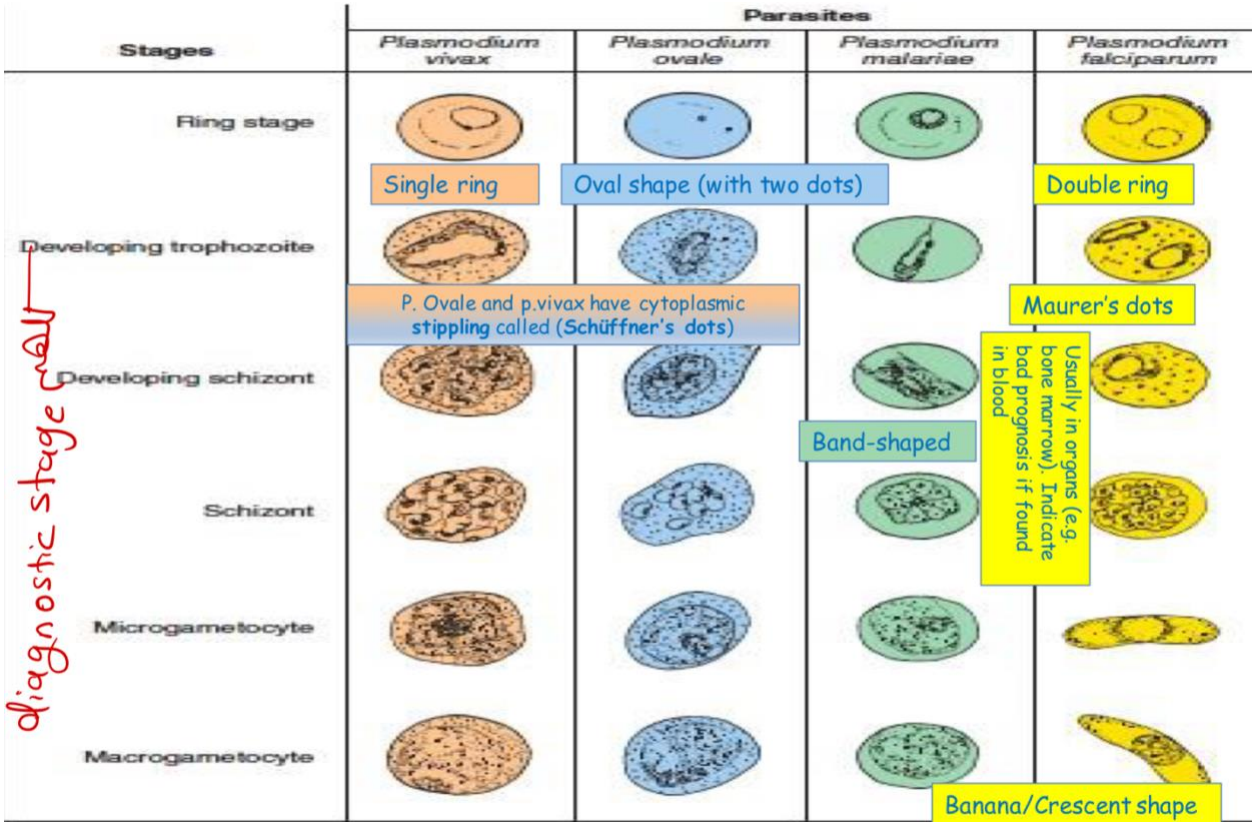


Some features of malaria are:
- Hemolytic anemia
- Fever with paroxysmal periodicity

People who live in endemic areas DON'T gain lifelong immunity to malaria; they rather gain premunition.

Premunition: Immunity against superinfection (NOT reinfection)

Discussion: Who has the highest risk to malaria in Jordan?
- The Jordanian Peacekeeping Forces (قوات حفظ السلام الأردنية) because they stay in high-risk regions for a long time and they are thus exposed to Plasmodium.
- When they return to Jordan, they must be screened for malaria



❖ PLASMODIUM VIVAX

- P. vivax is the most common worldwide.
- It causes disease called BENIGN TERTIAN MALARIA.
- Benign fever (<40℃) and complications (not dangerous)
- Tertian cycle of fever (Fever occurs every third day)
- **Splenomegaly** occurs during the first few weeks of infection.
- After a few days of irregular periodicity, a regular 48-hour cycle is established.
- Pathogenesis and Spectrum of Disease:
  - In patients who have never been exposed to malaria: Symptoms may occur before organisms can be detected in the bloodstream.
  - In other patients with prior exposure to the malaria: The parasites can be found in the bloodstream several days before symptoms appear.

Type of Malaria	Characteristics
Plasmodium vivax (benign tertian malaria)	1. 48-hour cycle 2. Tends to infect young cells → low Parasitemia 3. Enlarged RBCs 4. Schüffner's dots (true stippling) after 8-10 hours — Revise the morphologies we discussed 5. Delicate ring 6. Very ameboid trophozoite 7. Mature schizont contains 12-24 merozoites

❖ PLASMODIUM OVALE

- **LESS**

Plasmodium ovale	1. 48-hour cycle 2. Tends to infect young cells → low Parasitemia 3. Enlarged RBCs with fimbriated edges (oval) 4. Schüffner's dots appear in the beginning (in RBCs with very young ring forms, in contrast to *P. vivax*) Revise the morphologies we discussed 5. Smaller ring than *P. vivax* 6. Trophozoite less ameboid than that of *P. vivax* 7. Mature schizont contains an average of 8 merozoites

❖ PLASMODIUM MALARIAE

- P. malariae is the most common ancestor of Plasmodia (the oldest)
- It causes disease called QUARTAN MALARIA
- Quartan cycle of fever (Fever occurs every fourth day)
- Pathogenesis and Spectrum of Disease:
  - **Proteinuria** is the most common complication in P. malariae infections and may be associated with clinical signs of nephrotic syndrome.
  - With a chronic infection, kidney problems result from deposition within the glomeruli of circulating antigen antibody complexes. Patients may end up having acute kidney failure.
  - A **membrane proliferative type of glomerulonephritis** is the most common lesion seen in quartan malaria.

***Plasmodium malariae* (quartan malaria)**	1. 72-hour cycle (long incubation period) 2. Tends to infect old cells → low Parasitemia 3. Normal size RBCs 4. No stippling 5. Thick ring, large nucleus 6. Trophozoite tends to form "bands" across the cell ^ Pathognomonic 7. Mature schizont contains 6-12 merozoites

❖ PLASMODIUM FALCIPARUM

- ➢ Number one killer (All fatalities that happen because of malaria are due to the P. falciparum)
- ➢ It causes disease called MALIGNANT TERTIAN MALARIA

- It's described as malignant for 2 reasons:

1) Having many complications (most serious complication of P. falciparum is cerebral malaria).
2) Hyperpyrexia (Extreme fevers, 41.7° C (107° F) or higher)
3) childhood febrile convulsions and generalized seizures

- ➢ Schizogony occurs in the spleen, liver, and bone marrow rather than in the circulating blood.
- ➢ Tertian cycle of fever (Fever occurs every third day)
- ➢ **Pathogenesis :**
    1) The infected RBCs produce ECAM protein which forms **projecting knobs** on the surface of RBCs, releasing adhesins from the surface of the RBC → RBC become sticky (to each other and to endothelium; not easy to pass through capillaries).
       This phenomena is called **Cytoadherence** and only occurs in P. falciparum.
    2) RBCs can't enter the brain, so ischemia and hypoxia happens that cause **Cerebral malaria**
    3) **Algid malaria** can be seen as peripheral circulatory shock , fatal malaria with hypovolemic shock
    4) **Black Water Fever** : black coloured urine due to hemoglobinurea
    5) **Tropical splenomegaly syndrome (TSS)**
- ➢ The distribution sites of of the stages of P.falciparum :

- only the ring forms and the gametocytes (occasionally mature schizonts) normally appear in the peripheral blood.

- Other stages of P.falciparum are not found in blood as they enter internal organs like spleen, liver and bone marrow. If it seen in blood this is a grave sign (bad prognosis)

➢ High level of **parasitaemia** due to infection to all shapes and sizes of RBCs

➢ Fever comes in ***three stages***: cold stage > hot stage > sweating stage. The patient initially has chills and feels very cold (his body temperature is very high). Then in the hot stage, the patient suffers from flushing, headaches, nausea/vomiting and his body temperature is still very high. Then in the sweating stage, the patient suffers from profound sweating.

Plasmodium falciparum **(malignant tertian malaria)**	1. 36-48-hour cycle → high parasitemia 2. Tends to infect any cell regardless of age, thus very heavy infection may result 3. All sizes of RBCs 4. No Schüffner's dots (Maurer's dots: may be larger, single dots, bluish) 5. Multiple rings/cell (only young rings, gametocytes, and occasional mature schizonts are seen in peripheral blood) 6. Delicate rings, may have two dots of chromatin/ring, appliqué or accolé forms 7. Crescent-shaped gametocytes

❖ PLASMODIUM KNOWLESI

➢ SIMIAN MALARIA,THE FIFTH HUMAN MALARIA

➢ The **early** blood stages of P. knowlesi resemble those of P. falciparum.

➢ The mature blood stages and gametocytes resemble those of P. malariae.

- Unfortunately, these infections are often misdiagnosed as the relatively benign P.malariae; however, infections with P.knowlesi can be fatal.

Plasmodium knowlesi (simian malaria)*	1. 24-hour cycle 2. Tends to infect any cell regardless of age, thus very heavy infection may result (→ high Parasitemia) 3. All sizes of RBCs, but most tend to be normal size 4. No Schüffner's dots (faint, clumpy dots later in cycle) 5. Multiple rings/cell (may have 2-3) 6. Delicate rings, may have two or three dots of chromatin/ring, appliqué forms 7. Band form trophozoites commonly seen 8. Mature schizont contains 16 merozoites, no rosettes 9. Gametocytes round, tend to fill the cell Early stages mimic *P. falciparum*; later stages mimic *P. malariae*

	P.vivax	P.ovale	P.malariae	P.falciparum	P.knowlesi
Fever cycle	48 hour	48 hour	72 hour	36-48 hour	24 hour
Infected RBCs	Young RBCs	Young RBCs	Old RBCs	All ages of RBCs	All ages of RBCs
Infected RBCs	Enlarged RBCs	Enlarged RBCs	Normal size RBCs	All sizes of RBCs	All sizes of RBCs
Cytoplasmic stippling	Schuffner's dots	Schuffner's dots	_____	Maurer's dots	Faint dots

❖ LABORATORY DIAGNOSIS

1) Routine Methods:

- Gold standard for the diagnosis of malaria is inspecting blood film under the microscope
- Thick and thin blood films.
  - Thick —> presence of plasmodium or not
  - Thin —> which species
- Stains:
  a) Giemsa stain.
  b) Wright's stain.
  c) Fluorescent nucleic acid stains, such as acridine orange.
- Bloodcollectedusing(EDTA)anticoagulant.

2) Serologic Methods:

- Fast, used worldwide but lower sensitivity and specificity.
- Two rapid malaria tests(RMTs):

a) monoclonal antibodies against the histidine-rich protein 2 (HRP2).
b) species-specific parasite lactate dehydrogenase (pLDH).

- Theseproceduresarebasedonanantigencaptureapproachindipstickor cartridge formats.

3) Molecular Diagnostics:

- using a specific DNA probe after PCR amplification of target DNA sequences.

4) Automated Instruments:

- Using automated flow cytometry hematology instruments, there are potential limitations related to the diagnosis of blood parasite infections

❖ THERAPY

- First line of management for non-falciparum malaria: **Quinolines**
- In vivax and ovale, you have to kill hypnozoites: **Primaquine**

- First line of management for falciparum: **Artemisinin-based combination therapies (ACT)**
- Antimalarial drugs are classified according to the stage of malaria against which they are targeted.
- QUINOLINES , ARTEMISININS
- Tetracycline, doxycycline, and clindamycin are used increasingly in combination with other antimalarials to improve their efficacy or prophylactically
- These drugs are referred to as :
  1. Tissue schizonticides (which kill tissue schizonts).
  2. Blood schizonticides (which kill blood schizonts).
  3. Gametocytocides (which kill gametocytes).
  4. Sporonticides (which prevent formation of sporozoites within the mosquito).

❖ CONTROL

Type of control	Measures
Personal protection	Insecticide treated mosquito nets; Mosquito proofing of dwellings; Repellents; Site selection
Environmental management	Drainage & water management; Land reclamation by fillin and drainage
Chemical (Insecticides) control	Residual house spraying; larviciding; space spraying
Other measures	Biological control, Genetic control, Zooprophylaxis

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