A study material for M.Sc. Biochemistry (Semester: IV) Students
on the topic (EC-1; Unit IV)

Malaria

The Deadly Plasmodium Disease

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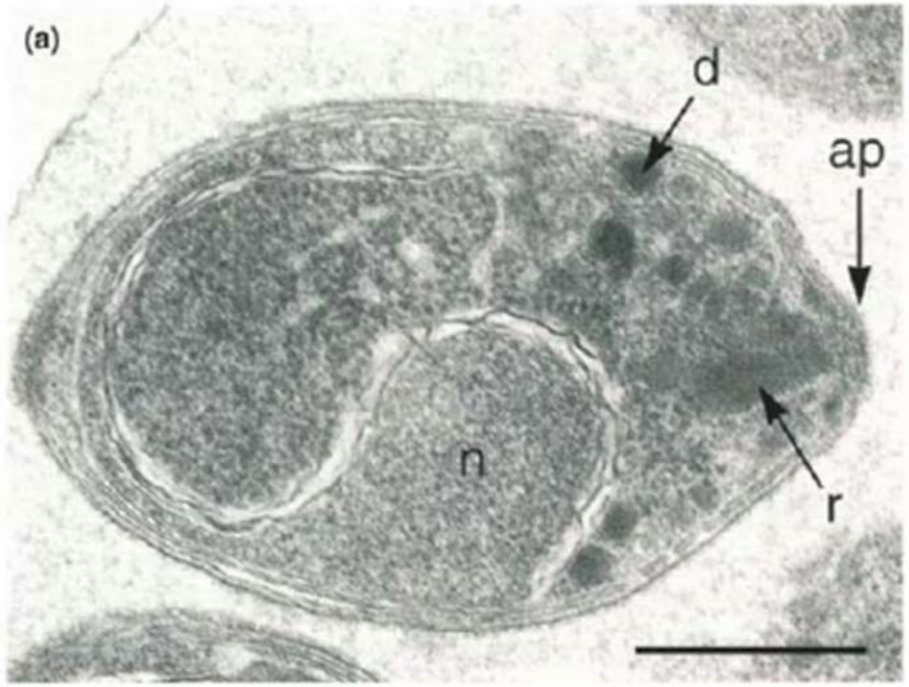
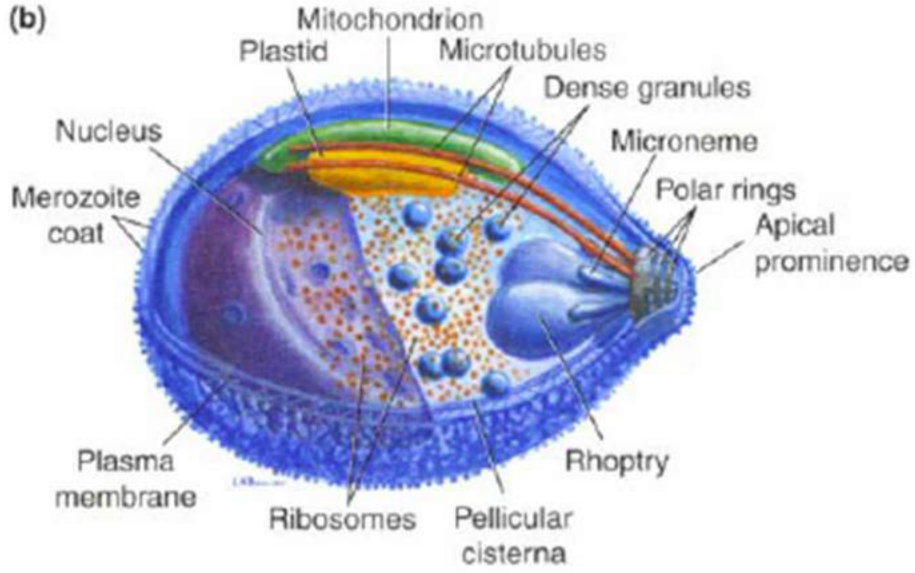
What is Malaria?

- A mosquito-borne infectious disease caused by Protozoan parasites of the genus *Plasmodium.*

- *The disease can be acute or Chronic.*

- French army doctor in Algeria observed parasites inside red blood cells of malaria patients and proposed for the first time that a protozoan caused disease.
- **1907 Nobel Prize for Physiology or Medicine: Charles Louis Alphonse Laveran**





Plasmodium Anatomy

So just who is this Plasmodium?

It's not a bacterium or virus but a eukaryote like us.

However, unlike us it lives a solitary life as a single cell.

Consistent with this, we now know Plasmodium and its relatives have a remnant of the chloroplast called the apicoplast which may help it digest heme and other things it harvests from red blood cells.

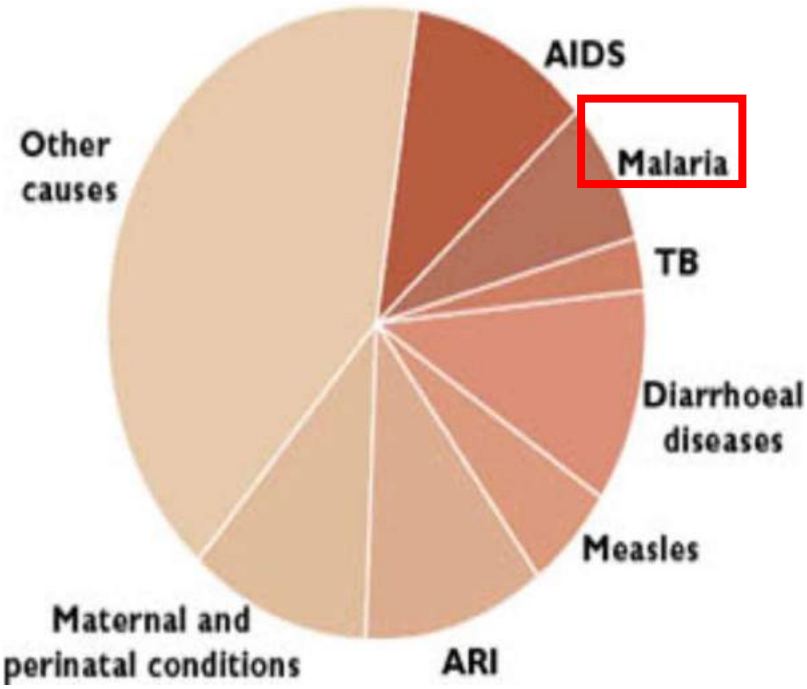
Plasmodium and its relatives also have a specialized Structure at one end of the cell Involved in invading other cells.

We don't have this sort of organelle How might we use that fact??!

Plasmodium's closer relatives Include parasites causing Babesiosis, Toxoplasmosis, and Cryptosporidiosis.

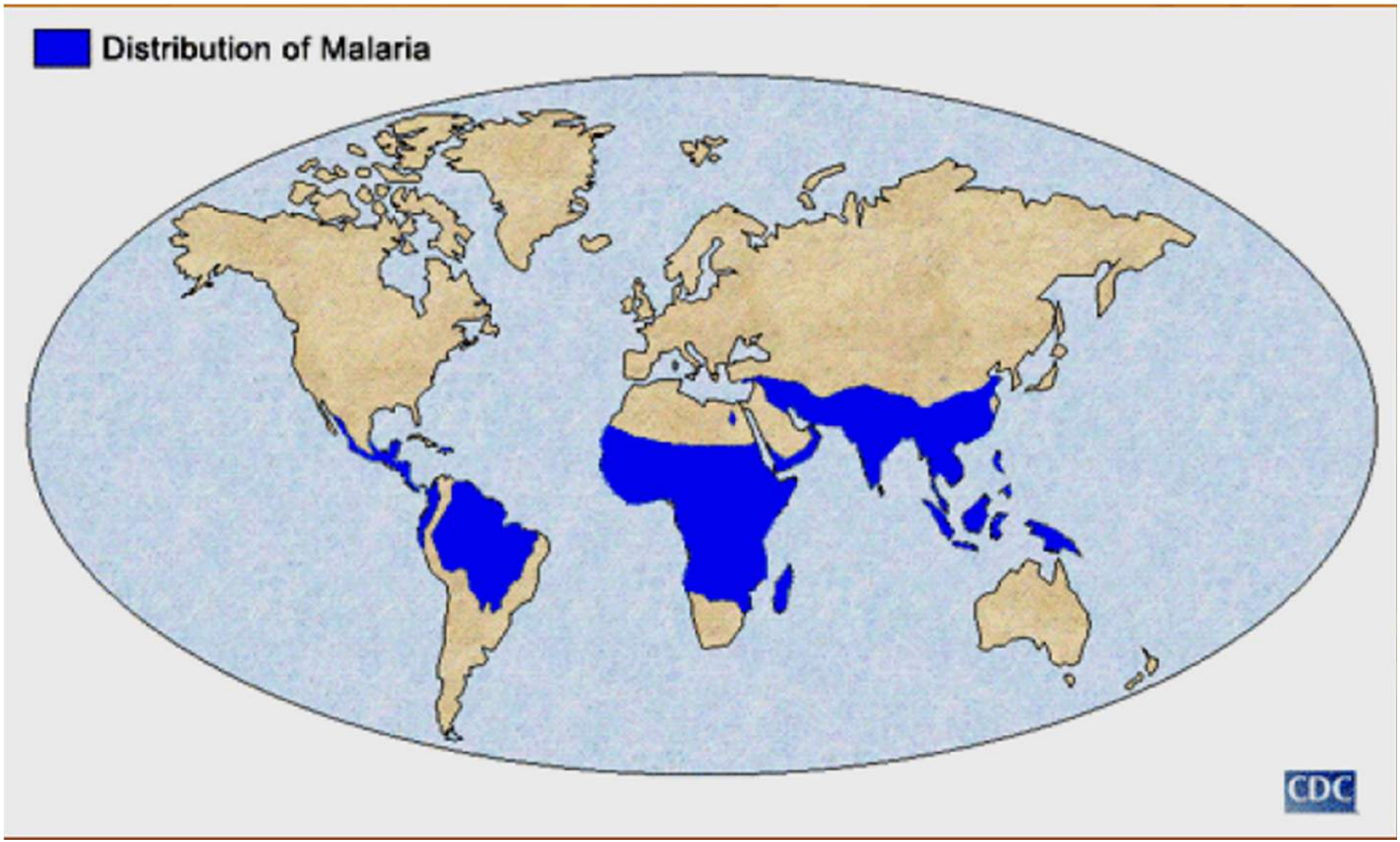
300 million new cases per year making it the most prevalent serious infectious disease!

HIV/AIDS, Tuberculosis and Malaria: The basic facts, 2002 (World Health Organization)			
Disease	Deaths per year	New cases per year	Percentage in developing countries
HIV/AIDS	3 million	5.3 million	92%
Tuberculosis	1.9 million	8.8 million	84%
Malaria	1 million	300 million	99.9%



Leading causes of death in Sub-Saharan Africa, South Asia, and Southeast Asia for persons age 0-44 (World Health Organization)

2.1 billion people live in MALARIOUS areas



The Deadliest Parasite: *Plasmodium Falciparum*

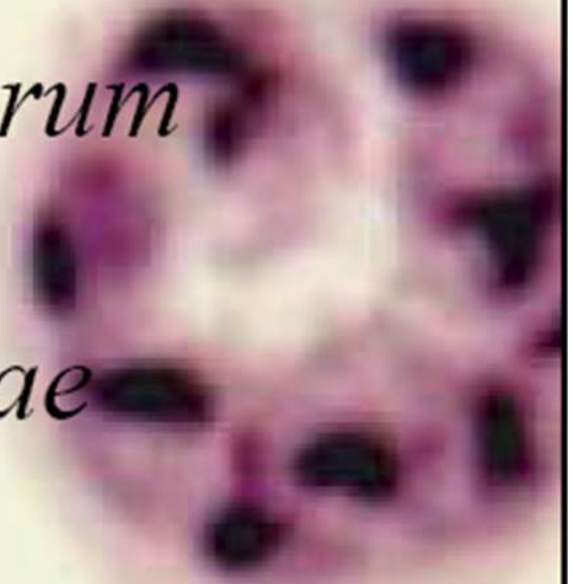
- > 90% of disease burden in sub-Saharan Africa
- Africa's leading cause of mortality (20%) in children age 0 to 5 years
- Main cause of clinical and severe malaria and death

Image: *Plasmodium falciparum* from Medical Structural Genomics of Pathogenic Protozoa

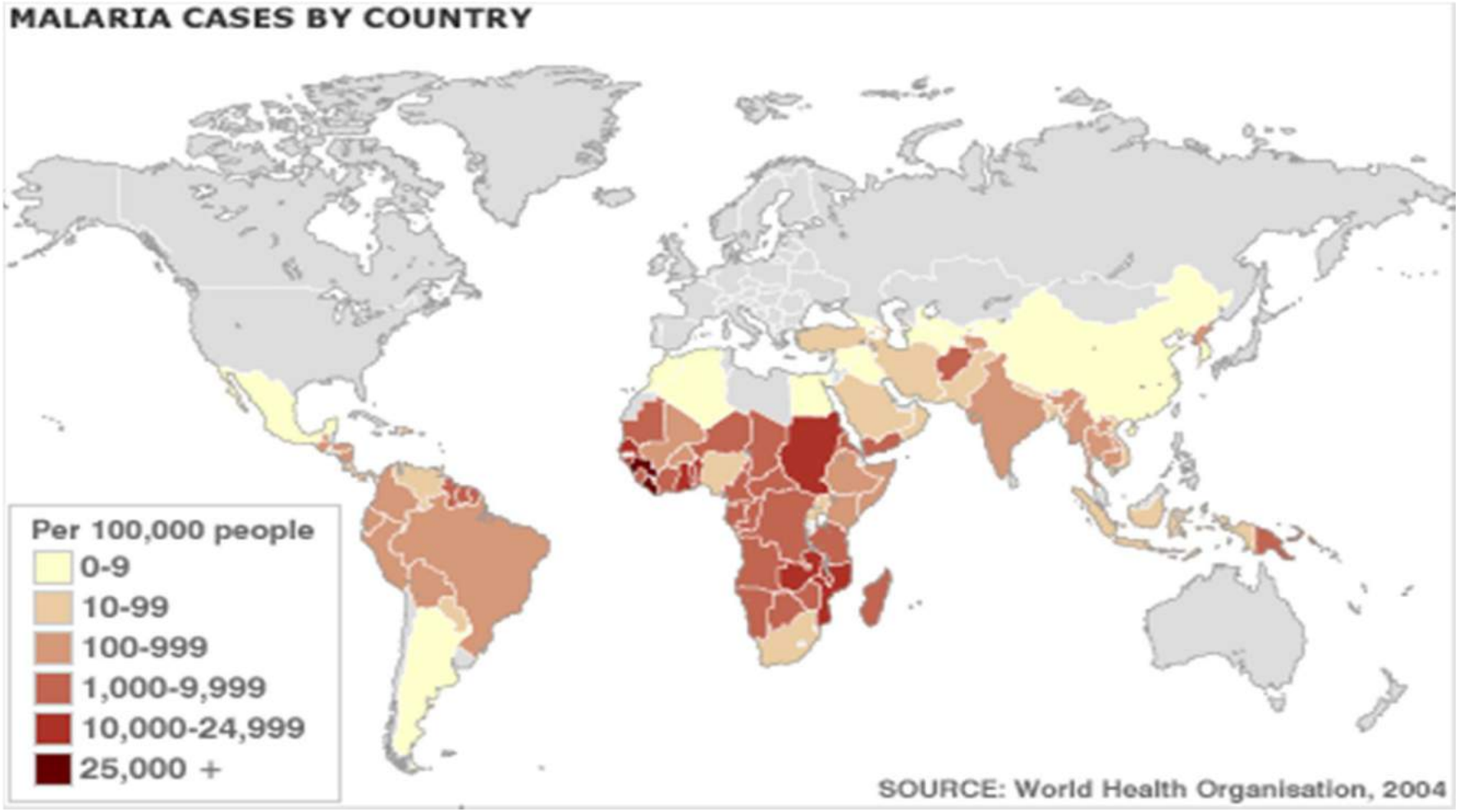
mvi PATH
MALARIA VACCINE INITIATIVE

The Malarias:

Plasmodium falciparum
Plasmodium vivax
Plasmodium malariae
Plasmodium ovale

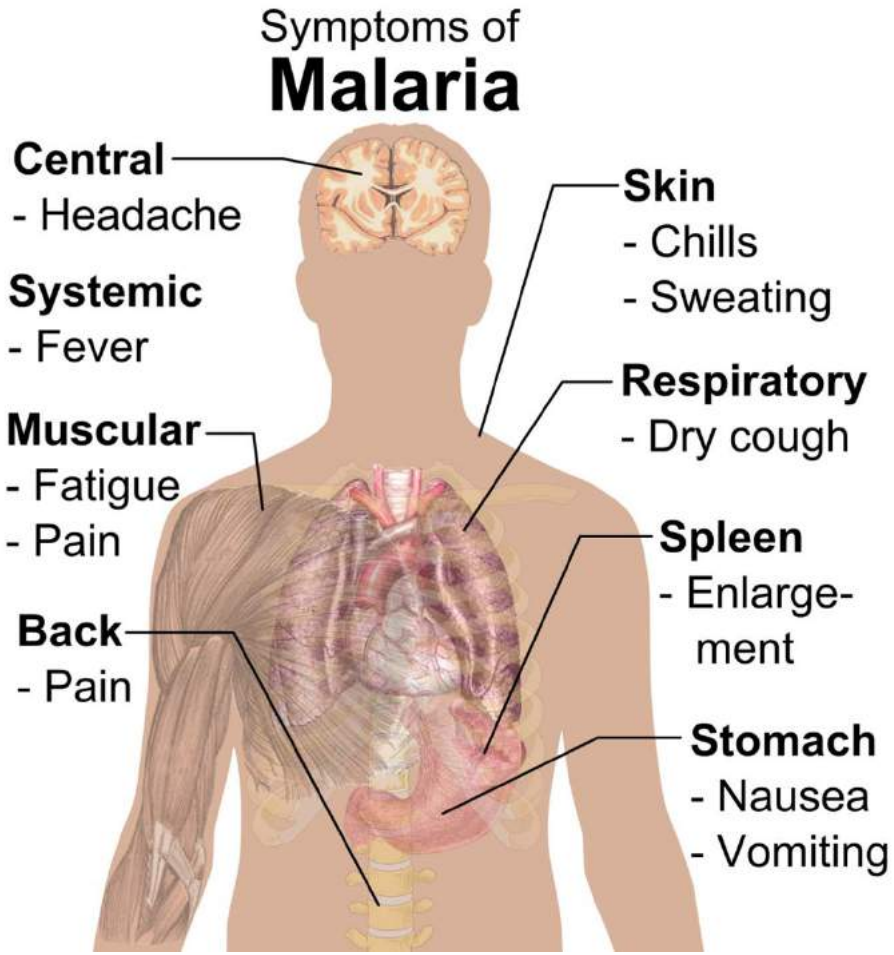


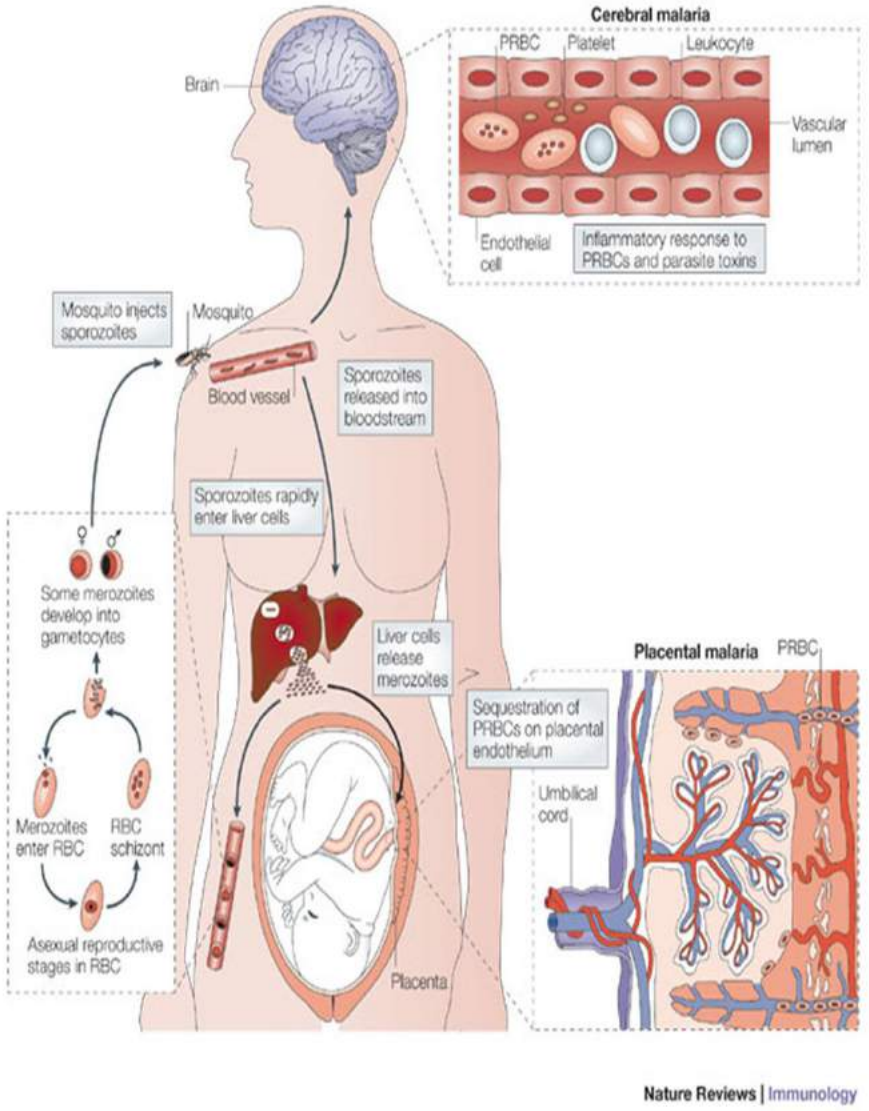
The vast majority of deaths are caused by *P. falciparum* while *P. vivax*, *P. ovale*, and *P. malariae* cause a generally milder form of malaria that is rarely fatal



- Like HIV and TB, malaria is unequally distributed, even in the tropics
- In areas of Africa with high transmission there are 2700 deaths per day = 2 per minute

Symptoms


Symptoms of
Malaria
Central
- Headache
Systemic
- Fever
Muscular
- Fatigue
- Pain
Back
- Pain
Skin
- Chills
- Sweating
Respiratory
- Dry cough
Spleen
- Enlarge-
ment
Stomach
- Nausea
- Vomiting


Cerebral malaria
PRBC
Platelet
Leukocyte
Vascular lumen
Endothelial cell
Inflammatory response to PRBCs and parasite toxins
Brain
Mosquito injects sporozoites
Mosquito
Blood vessel
Sporozoites released into bloodstream
Sporozoites rapidly enter liver cells
Some merozoites develop into gametocytes
Liver cells release merozoites
Merozoites enter RBC
RBC schizont
Asexual reproductive stages in RBC
Placenta
Placental malaria
PRBC
Sequestration of PRBCs on placental endothelium
Umbilical cord
Nature Reviews | Immunology

Acute Symptoms

- Classical features include cyclic symptoms
  - Cold stage: chills and shaking
  - Hot stage: fever, headache, vomiting, seizures in children
  - Sweating stage: weakness
  - Feel well for period of time, then cycle repeats itself.

- Symptoms of falciparium malaria arise 9–30 days after infection.
- Splenomegaly, severe headache, hepatomegaly (enlarged liver), hypoglycemia, and hemoglobinuria with renal failure may occur.
- Renal failure is a feature of black water fever, where hemoglobin from lysed red blood cells leaks into the urine.
- Cerebral malaria is a form of severe malaria that involves encephalopathy specifically related to *P. falciparum* infection.
- It is associated with retinal whitening, which may be a useful clinical sign in distinguishing malaria from other causes of fever.
- Individuals with cerebral malaria frequently exhibit neurological symptoms

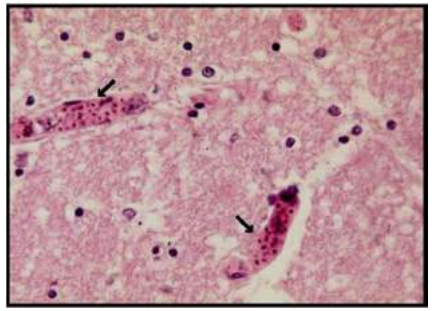
Each disease has a distinct course

- **Tertian Malaria: (*P. falciparum, P. ovale and P. vivax*) fever occurs every third day.**
- **Tertian Malaria:**
- The classic symptom of malaria is paroxysm: a cyclical occurrence of sudden coldness followed by rigor and then fever and sweating, occurring every two days in *P. vivax* and *P. ovale* infections.
- **Quartan Malaria:**
- *P. malariae*. *P. falciparum* infection can cause recurrent fever every 36–48 hours (quartan fever) or a less pronounced and almost continuous fever

- ***P. ovale and P. vivax* can cause chronic malaria, reappearing after months or years due to latent parasites in liver.**
- Severe malaria is usually caused by *P. falciparum* (often referred to as falciparum malaria).

Malarial pathogenesis
Malaria damages the body in a number of ways

- Changes adhesive properties of infected Red blood cells -> blocking blood vessels leading to Tissue hypoxia
- Red blood cell destruction -> anemia



- Waves of parasites bursting red blood cells
  Lead to classic cycles of fever and chills

➢ Malaria is a disease caused by repeated cycles of growth of the parasite *Plasmodium* in the erythrocyte.

➢ Various cellular and molecular strategies allow the parasite to evade the human immune response for many cycles of parasite multiplication.

➢ *P. falciparum is* the most deadly of the human plasmodium caused malaria.

- The pathogenic process occurs only during the erythrocytic cycle.

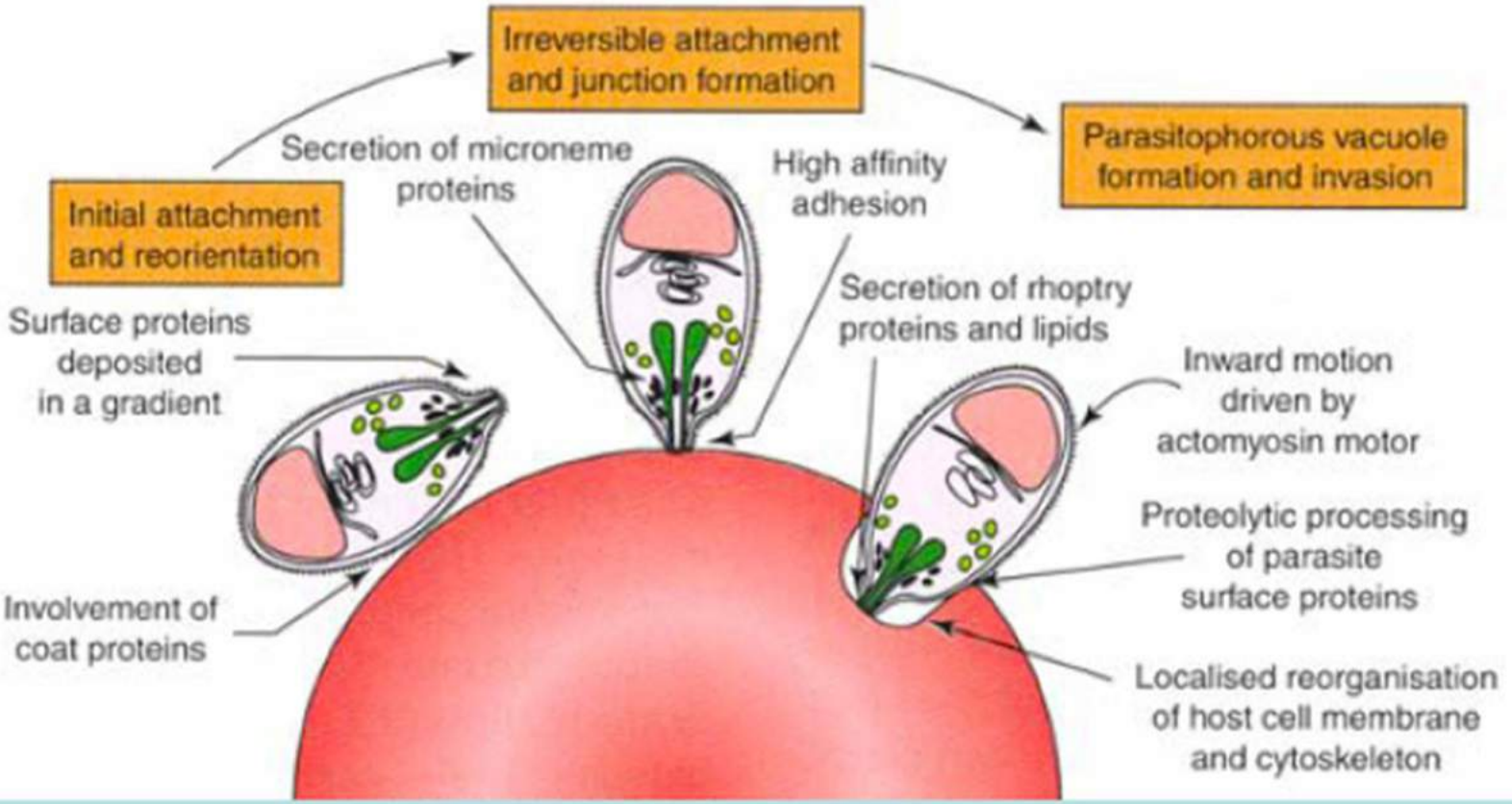
- Parasite transition from the human host to the mosquito vector is mediated by **gametocytes**, sexual stages that are formed in human erythrocytes, which therefore play a crucial part in the spread of the tropical disease.
- The parasitized erythrocytes remain attached until merozoites are formed that are released.

- Predominant form seen in the peripheral circulation is the ring-infected erythrocyte, the young form of the parasite.

- During the erythrocytic cycle, soluble products of *Plasmodium* spp. known as malarial toxins direct systemic release of proinflammatory cytokines.

- Equally important are parasite antigens, which stimulate T cells to directly secrete or induce production of cytokines from other cells.

Mechanisms of Red Cell Invasion By Plasmodium



www.columbia.edu/itc/hs/medical/pathophys/parasitology/2006/PAR-05Color .pdf

Reproduction by multiple asexual fission, characteristic of many sporozoans.

Female Anopheles mosquito (the definitive host) transmits a motile infective form (called the sporozoite) to a vertebrate host such as a human (the secondary host), thus acting as a transmission vector.

A sporozoite travels through the blood vessels to liver cells (hepatocytes), where it reproduces asexually (tissue schizogony), producing thousands of merozoites.

schizogony : Reproduction by multiple asexual fission, characteristic of many sporozoans

These infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 24 new infective merozoites.

Cells burst and the infective cycle begins again.

In a process called *gametocytogenesis*, other merozoites develop into immature gametes, or gametocytes.

When a fertilised mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut.

The male and female gametocytes fuse and form zygotes (ookinetes, which develop into new sporozoites.

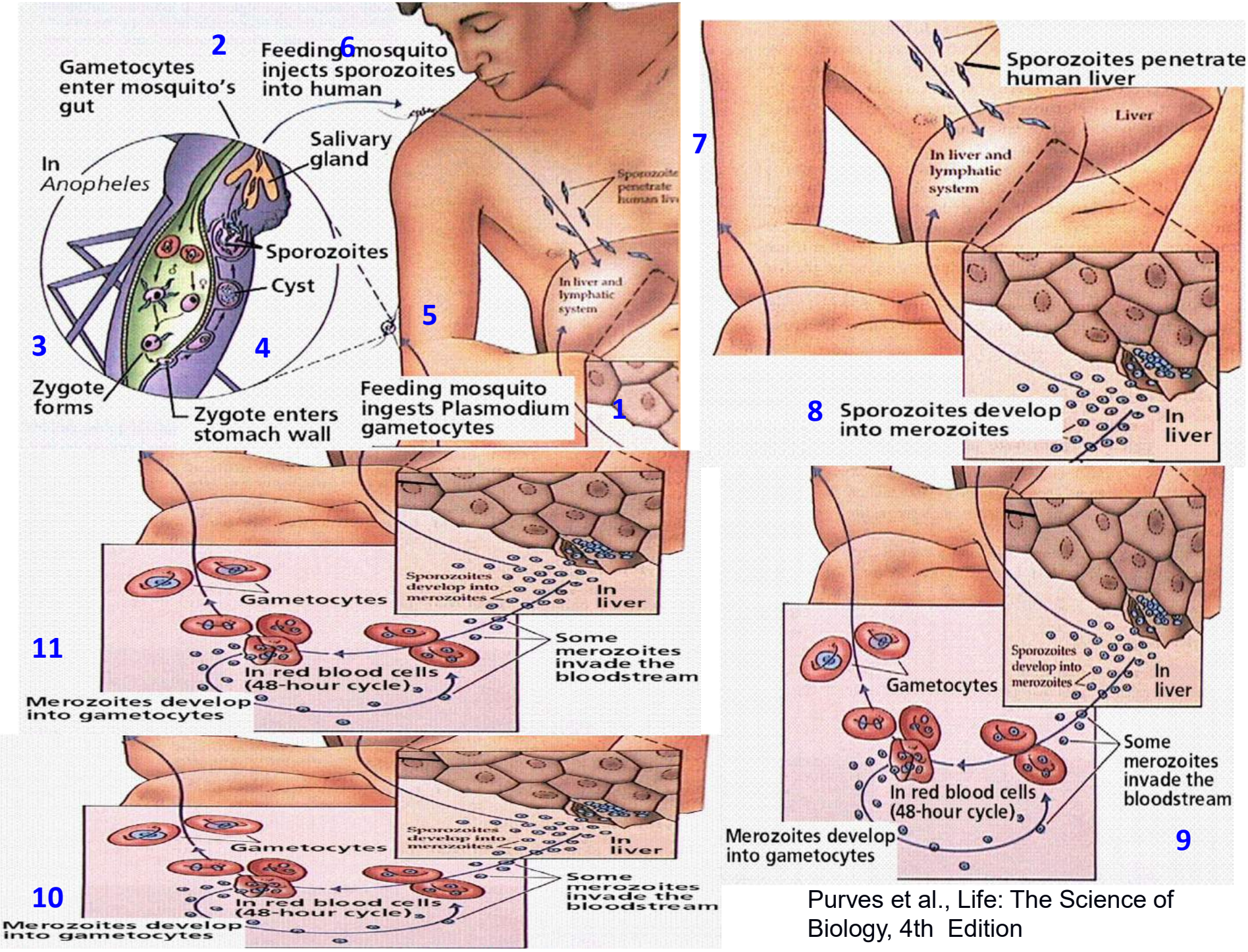
The sporozoites migrate to the insect's salivary glands, ready to infect a new vertebrate host.

The sporozoites are injected into the skin, alongside saliva, when the mosquito takes a subsequent blood meal. This type of transmission is occasionally referred to as anterior station transfer.
Malaria infection develops via two phases: one that involves the liver (exoerythrocytic phase), and one that involves red blood cells, or erythrocytes (erythrocytic phase).

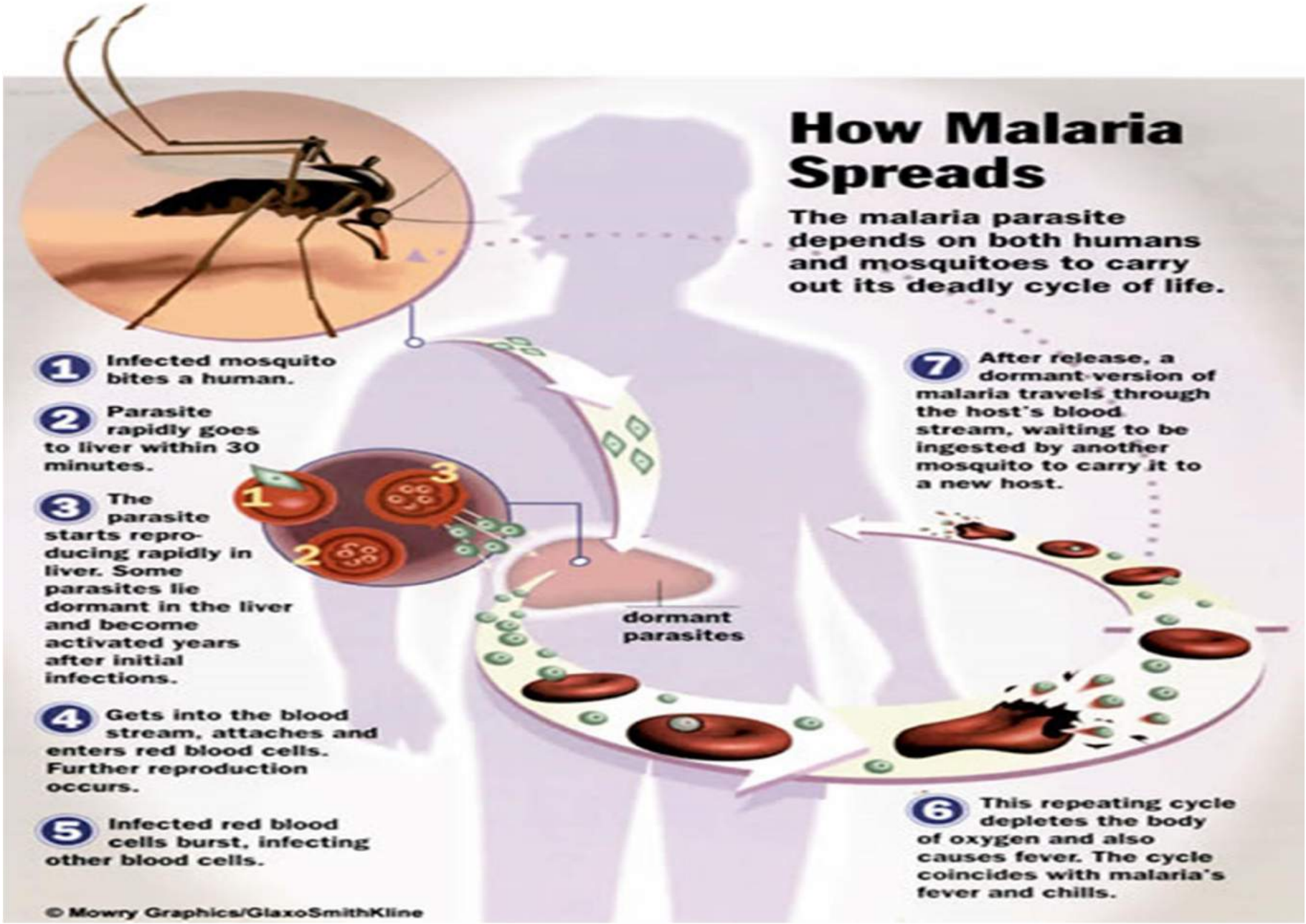
The parasite escapes from the liver undetected by wrapping itself in the cell membrane of the infected host liver cell.

Some *P. vivax* sporozoites do not immediately develop into exoerythrocytic-phase merozoites, but instead produce hypnozoites that remain dormant for periods ranging from several months (7–10 months is typical) to several years.
After a period of dormancy, they reactivate and produce merozoites.

Hypnozoites are responsible for long incubation and late relapses in *P. vivax* infections



Purves et al., Life: The Science of Biology, 4th Edition


How Malaria Spreads
The malaria parasite depends on both humans and mosquitoes to carry out its deadly cycle of life.
1 Infected mosquito bites a human.
2 Parasite rapidly goes to liver within 30 minutes.
3 The parasite starts reproducing rapidly in liver. Some parasites lie dormant in the liver and become activated years after initial infections.
4 Gets into the blood stream, attaches and enters red blood cells. Further reproduction occurs.
5 Infected red blood cells burst, infecting other blood cells.
6 This repeating cycle depletes the body of oxygen and also causes fever. The cycle coincides with malaria's fever and chills.
7 After release, a dormant version of malaria travels through the host's blood stream, waiting to be ingested by another mosquito to carry it to a new host.
dormant parasites
© Mowry Graphics/GlaxoSmithKline

Acknowledgement and Suggested Readings:

1. Medical Microbiology, A guide to Microbial Infections: Pathogenesis, Immunity, Laboratory Investigation and Control; Barber, Irving, Swann and Perera; Elsevier Publication
2. Microbiology, An Introduction; Tortora, Funke and Case; Pearson Publication
3. Microbiology; Prescott, Harley and Klein; The MacGraw-Hill Companies
4. Microbiology: Principles and Explorations; Jacquelyn G Black; John Wiley and Sons Inc.
5. Brock Biology of Microorganisms; Madigan, Martinko, Stahl and Clark; Benjamin Cummings (Pearson Publication)

Thanks