Outline

I. Introduction

WHO reported 263 million estimated malaria cases and 597, 000 deaths globally in 2024 [1]. The causative agent of Malaria is the *Plasmodium* parasite. The parasite is transmitted to humans via the bite of a female *Anopheles* mosquito. Other modes of malaria transmission include blood transfusion, congenital transmission, and laboratory-acquired infections.

There are five *Plasmodium* species that can cause disease in humans – *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. *P. knowlesi* has recently emerged as a notable concern in WHO South-East Asian countries such as Malaysia [1, 2]. *P. falciparum* is considered the most virulent and deadly as it is more commonly associated with severe malaria. *P. falciparum*-infected red blood cells can adhere to the walls of blood vessels (cytoadherence) and become sequestered, which impairs blood flow to vital organs, including the brain (cerebral malaria), potentially leading to fatal outcomes.

II. Life Cycle of Malaria

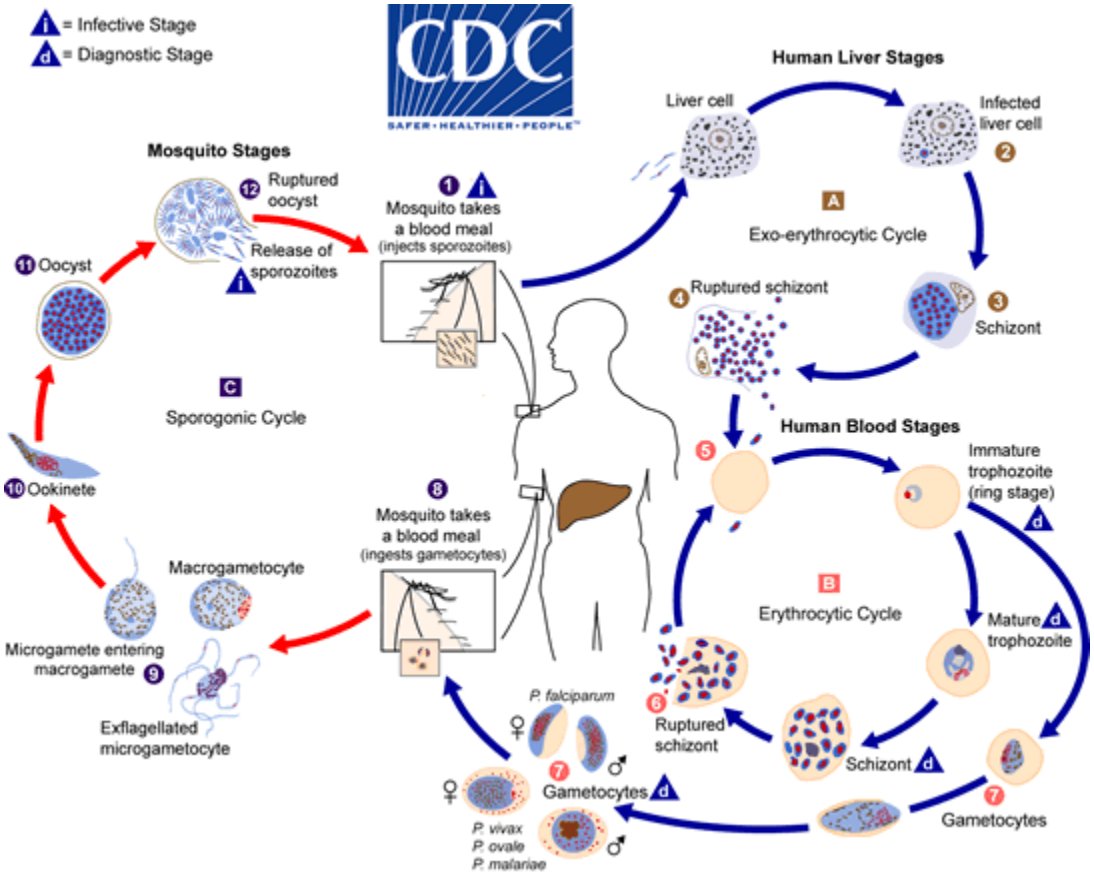

Figure 1: The life cycle of the malaria parasite. This involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host ❶. Sporozoites infect liver cells ❷and mature into schizonts ❸, which rupture and release merozoites ❹. (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony Ⓐ), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony Ⓑ). Merozoites infect red blood cells ❺. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites ❻. Some parasites differentiate into sexual erythrocytic stages (gametocytes) ❼. Blood stage parasites are responsible for the clinical manifestations of the disease.

The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal ❽. The parasites' multiplication in the mosquito is known as the sporogonic cycle Ⓒ. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes ❾. The zygotes in turn become motile and elongated (ookinetes) ❿which invade the midgut wall of the mosquito where they develop into oocysts ⓫. The oocysts grow, rupture, and release sporozoites ⓬, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle.

Description of the life cycle and image from [3].This material is in the public domain and may be freely used or reproduced without obtaining copyright permission.

III. Clinical Features

The clinical symptoms of malaria are non-specific. Malaria infections can be characterized as uncomplicated or severe [4, 5].

	Uncomplicated	**Severe**
Constitutional	Fever, chills, sweats, weakness, general malaise, body aches	Prostration
Hematologic		Severe malarial anemia, bleeding (nose, gums, venepuncture sites, hematemesis, melena)
Cardiovascular		Shock
Respiratory	Increased respiratory rate	Pulmonary edema
Neurological	Headaches	Impaired consciousness, multiple convulsions, Cerebral malaria (Seizures, confusion, coma)
Gastrointestinal	Nausea and vomiting	
Renal		Renal impairment
Liver	Mild jaundice, hepatomegaly	Jaundice with a parasite count > 100 000/ µL (*P. falciparum),* > 20 000/µL (*P. knowlesi)* .
Spleen	Splenomegaly	
Metabolic		Acidosis, severe hypoglycaemia
Others		Hyperparasitemia: *P. falciparum* parasitemia > 10% For *P. knowlesi* > 100 000/µL

**Severe falciparum malaria*: One or more of the following in the "severe" column, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia [4].

IV. Detection and Diagnostic Methods

Recommendation from WHO: Prompt diagnosis and confirmation by microscopy or malaria rapid diagnostic kits in all suspected malaria cases before prescription of antimalarial treatment [6].

- **Giemsa-stained thick and thin blood smears (gold standard)**
  - Thick smear – to detect presence of malaria parasites
  - Thin smear – to determine the Plasmodium species via distinct morphological characteristics of the parasite within blood cells [7]. Also used to access level of parasitemia [(parasitized RBCs/total RBCs) × 100)].
  - Simple and cheap
  - Time consuming, laborious and requires trained personnel
- **Antigen rapid test kits**
  - Detect specific malaria antigens in blood samples (obtained via finger prick)
  - Dependent on the kit: can detect a single species (*P. falciparium* or *P. vivax*), non-*P. falciparum* infections or mixed infections [8].
  - Antigens targeted in RTKs can include
    - Specific for *P. falciparum*-specific protein e.g. histidine-rich protein II (HRP-II) or lactate dehydrogenase (LDH).
    - Pan-specific (all malaria species) antigens e.g. aldolase or pan-malaria pLDH [9]
  - Easy to perform and interpret
  - Expensive

- **PCR**
  - More sensitive and specific but less commonly used due to higher cost and need for specialized equipment.

V. Prevention and Control Strategies

- **Travel recommendations**
  - Use DEET insect repellants
  - Wearing long pants and long-sleeved clothing
  - Use insecticide-treated nets (ITNs – insecticide treated bed nets)
- **Vector control**
  - Reduce mosquito population via indoor residual spray (IRS - regular application of chemical insecticides on inner walls of households) and ITNs [10]
  - Larval source management
- **Chemoprophylaxis (for non-endemic regions)** [11]

Drug	Dosage & Duration	Advantages	Disadvantages
Mefloquine	250 mg weekly, starting 1 week before travel and continuing 4 weeks after leaving	Weekly dosing, affordable	Neuropsychiatric side effects
Doxycycline	100 mg daily, starting 1–2 days before travel and continuing 4 weeks after leaving	Cheap	Daily dosing, photosensitivity, vaginal thrush, oesophagitis
Atovaquone/Proguanil (Malarone)	1 tablet daily, starting 1–2 days before travel and continuing 7 days after leaving	Few side effects, short post-travel duration	Expensive, daily intake

- **Chemoprevention (for endemic regions)** [4]
  - Seasonal malaria chemoprevention (SMC) - intermittent administration of antimalarials during seasonal malaria, regardless of whether the child is infected with malaria
  - Perennial malaria chemoprevention (PMC) - (intermittent preventive treatment in infants, or IPTi) - administration of antimalarials at predefined intervals, regardless of whether the child is infected with malaria, to prevent illness in moderate to high perennial malaria transmission settings
  - Intermittent preventive treatment of malaria in pregnancy (IPTp) - administration of antimalarial medicine at predetermined intervals, regardless of whether the pregnant woman is infected with malaria
- **Vaccines**
  - Two vaccines RTS,S and R21 recommended by WHO for widespread use among children living in sub-Saharan Africa and other regions with moderate to high *P. falciparum* malaria transmission [1, 12, 13].

VI. Treatment Options

Malaria Type	**Treatment** [4, 11]
Uncomplicated malaria	Non-falciparum: Chloroquine, followed by Primaquine (contraindicated in G6PD-deficiency patients due to risk of hemolysis).
	Falciparum (mild): Artemisinin-based combination therapy (ACT) preferred. • artemether-lumefantrine • artesunate-amodiaquine • artesunate-mefloquine • dihydroartemisinin-piperaquine • artesunate + sulfadoxine-pyrimethamine • artesunate-pyronaridine Or oral quinine + Doxycycline.
Severe malaria (*P. falciparum*)	IV Artesunate + Clindamycin or Doxycycline (preferred), or IV Quinene + Doxycycline. Supportive care: Fluid management, blood sugar monitoring, organ support as needed. Hospitalization required until parasitemia clears.

VII. Pathweb Links

Malaria in the spleen
Malaria in the brain

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