# MALARIA

## INTRODUCTION

Malaria is a mosquito-borne infectious disease of humans and other animals caused by protists (a type of microorganism) of the genus *Plasmodium*. It begins with a bite from an infected female mosquito, which introduces the protists via its saliva into the circulatory system, and ultimately to the liver where they mature and reproduce. The disease causes symptoms that typically include fever and headache, which in severe cases can progress to coma or death. Malaria is widespread in tropical and subtropical regions in a broad band around the equator, including much of Sub-Saharan Africa, Asia, and the Americas.

The term malaria originates from Medieval Italian: *mala aria* — "bad air"; the disease was formerly called *ague* or *marsh fever* due to its association with swamps and marshland. Malaria was once common in most of Europe and North America, where it is no longer endemic, though imported cases do occur.

Other *Plasmodium* species cause infections in certain animals. Several mammals, birds and reptiles have their own form of malaria.

## HISTORY

References to the unique periodic fevers of malaria are found throughout recorded history, beginning in 2700 BC in China. Malaria may have contributed to the decline of the Roman Empire, and was so pervasive in Rome that it was known as the "Roman fever".

- **1820** Quinine first purified from tree bark. For many years prior, the ground bark had been used to treat malaria.
- **1880** Charles Louis Alphonse Laveran first identifies the malaria parasite. He is awarded the 1907 Nobel Prize for the discovery.
- **1898** Sir Ronald Ross demonstrates that mosquitoes transmit malaria. He wins the 1902 Nobel Prize for this work.
- **1934** Hans Andersag in Germany discovers the Anti-malarial drug Chloroquine, which is not widely used until after World War II.
- **1939** Paul Hermann Muller in Switzerland tests the insecticide DDT. He wins the Nobel Prize for this work in 1948.
- **1952** Malaria is eliminated in the United States.
- **1955** World Health Organization (WHO) launches Global Malaria Eradication Campaign, which excludes sub-Saharan Africa and is eventually abandoned.
- **1957** First documented case of resistance to Chloroquine is reported.
- **1976** William Trager and JB Jensen grow parasite in culture for the first time, opening the way for drug discovery and vaccine research.
- **1989** The U.S. Food and Drug Administration approves the use of the anti-malaria drugMefloquine hydrochloride, registered as Lariam® by Hoffman-LaRoche.

- **1992** Malaria vaccine candidate RTS,S, developed by GlaxoSmithKline and the Walter Reed Army Institute of Research, enters clinical trials.
- **1996** Insecticide-treated bednets are proven to reduce overall childhood mortality by 20 percent in large, multi-country African study.
- **1998** Roll Back Malaria Partnership (RBM) launched by WHO, UNICEF, UNDP and World Bank with goal of halving malaria incidence and mortality by 2010.
    - WHO adopts home management strategy for malaria whereby trained community volunteers provide antimalarials in remote African communities.
- **2000** The U.N. General Assembly adopts the Millennium Development Goals, setting a target to halt and begin reversing malaria incidence by 2015.
- **2001** WHO prequalifies first fixed-dose Artemisinin combination therapy (ACT), sold by Novartis as Coartem® and recommends ACT as first-line malaria treatment.
- **2002** The Global Fund to Fight AIDS, Tuberculosis and Malaria is established and is led by UCSF's Sir Richard Feachem.
    - Genome sequencing of *Anopheles gambiae* (mosquito) and *Plasmodium falciparum* (parasite) completed.
- **2005** World Health Assembly adopts target of 80 percent worldwide coverage of insecticide nets and ACTs by 2010.
- **2007** UCSF study shows combination malaria therapy effective in treating African children
    - World Malaria Forum convenes in Seattle, hosted by Bill and Melinda Gates Foundation.
- **2008** The Global Health Group at UCSF comes forward with the first high-level strategy for the eventual achievement of malaria eradication. This strategy has since been widely adopted.
    - United Nations adopt April 25 as World Malaria Day.
    - Rectal application of the inexpensive antimalarial drug artesunate proven to save the lives of young children with severe malaria.
    - Representatives of nations around the world meet in New York and endorse the Global Malaria Action Plan (GMAP), which lays out a vision for reducing malaria in the short term and eventually eradicating it when new tools become available.
- **2009** Global health experts at UCSF release new guidance on malaria elimination
- **2010** UCSF study examines progress in meeting international health goals
    - UCSF leads *Lancet* series on malaria elimination
    - UCSF experts outline new strategy to eliminate malaria
- **2011** UCSF taps Sepúlveda to lead global health efforts

## CAUSE OF MALARIA

### Avian malaria

**Avian malaria** is most notably caused by ***Plasmodium relictum***, a protist that infects birds in tropical regions. There are several other species of *Plasmodium* that infect birds, such as-

- *Plasmodium anasum*
- *Plasmodium gallinaceum*

But these are of less importance except, in occasional cases, for the poultry industry. However, in areas where avian malaria is newly introduced, such as the islands of Hawaii, it can be devastating to birds that have lost resistance over evolutionary time.

### In Human

Among the parasites of the genus *Plasmodium* four species have been identified which can cause disease in humans:

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi*.

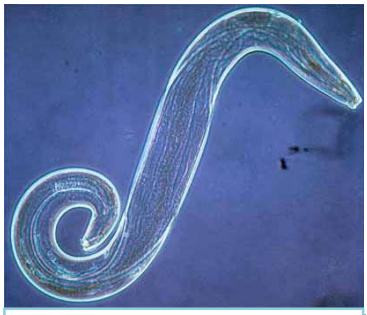


Fig: *Plasmodium falciparum*

### In Monkeys

- *Plasmodium cynomolgi bastianelli*
- *Plasmodium cynomolgi cynomolgi*
- *Plasmodium brasilianum*
- *Plasmodium schwetzi*
- *Plasmodium inui*
- *Plasmodium simium*
- *Plasmodium knowlesi*

### Scientific classification

| | |
|---|---|
| Domain: | Eukaryota |
| Phylum: | **Apicomplexa** |
| Class: | Aconoidasida |
| Order: | Haemosporida |
| Family: | Plasmodiidae |
| Genus: | ***Plasmodium*** |
| Species: | ***P. relictum*** and others of the genus |

## EPIDEMIOLOGY

**Susceptible species:** About 65 Plasmodiun sp. have been isolated from over 1,000 different species of birds. Few of the *Plasmodium* sp. which has been identified appears to be natural parasites of domestic poultry. A number of other species of Plasmodia that occur primarily in passerine birds can infect or have been experimentally transmitted to the domestic fowl.

**Susceptible host:**

- *Plasmodium* can be pathogenic to penguins, domestic poultry, ducks, canaries, falcons, and pigeons, but is most commonly carried asymptomatically by passerine birds.
- Human, reptiles, and other mammals, and non-human primates.

**Susceptible age:** The majority of cases (65%) occur in children under 15 years old.

**Susceptible sex:** Pregnant women are also especially vulnerable: about 125 million pregnant women are at risk of infection each year.

**Malaria statistics:**

- Malaria exists in parts of Africa, Asia, the Middle East, Central/South America, Hispaniola, and Oceania
- 350-500 million people each year are diagnosed with Malaria
- Over 1 million people die from malaria each year
- Most malaria deaths occur in sub-Saharan Africa
- Most people who die of malaria are children
- Malaria was the 4th cause of childhood death in developing countries in 2002
- 10.7% of childhood deaths in developing countries were caused by malaria in 2002

### Distribution:

The geographic distribution of malaria within large regions is complex, and malaria-afflicted and malaria-free areas are often found close to each other. For example, several cities in the Greater Mekong Subregion of Southeast Asia are essentially malaria-free, but the disease is prevalent in many rural regions, including along international borders and forest fringes. In contrast, malaria in Africa is present in both rural and urban areas, though the risk is lower in the larger cities.

*Plasmodium* spp. pathogenic for domestic poultry are found mainly in Africa, Asia and South America. It has been recently identified in American **S**amoa. Malaria is prevalent in tropical and subtropical regions.

**Predisposing factors:**

- Rainfall
- Consistent high temperatures and
- High humidity, along with stagnant waters in which mosquito larvae readily mature, providing them with the environment they need for continuous breeding.

- In drier areas, outbreaks of malaria have been predicted with reasonable accuracy by mapping rainfall. Malaria is more common in rural areas than in cities.

## Hosts and Geographic Distribution of Some Parasites

| Parasite | Host | Geographic Distribution |
|---|---|---|
| *Plasmodium reichenowi* | Chimapanzee | Africa |
| *Plasmodium falciparum* | Human | Africa,Asia,South/Central America |
| *Plasmodium fieldi* | Macaque | Southeast Asia |
| *Plasmodium simiovale* | Macaque | Southeast Asia |
| *Plasmodium hylobati* | Macaque | Southeast Asia |
| *Plasmodium inui* | Macaque | Southeast Asia |
| *Plasmodium knowlesi* | Macaque | Southeast Asia |
| *Plasmodium coatneyi* | Macaque | Southeast Asia |
| *Plasmodium simium* | Spider Monkey | South America |
| *Plasmodium vivax* | Human | Africa,Asia,South/Central America |
| *Plasmodium cynomolgi* | Macaque | Southeast Asia |
| *Plasmodium gonderi* | Madrill | Africa |
| *Plasmodium malariae* | Human | Africa,Asia,South/Central America |
| *Plasmodium brasilianum* | Spider/Howler/Night Monkey | South America |
| *Plasmodium ovale* | Human | Africa |
| *Hepatocystis sp.* | Bat/Primate | Africa, Asia |
| *Plasmodium atheruri* | Rodent | Africa |
| *Plasmodium vinkei* | Rodent | Africa |
| *Plasmodium chabaudi* | Rodent | Africa |
| *Plasmodium berghei* | Rodent | Africa |
| *Plasmodium yoelii* | Rodent | Africa |
| *Plasmodium mexicanum* | Lizard | North America |
| *Plasmodium chiricahuae* | Lizard | North America |
| *Plasmodium elongatum* | Bird | Worldwide |
| *Plasmodium gallinaceum* | Bird | Southeast Asia |
| *Plasmodium relictum* | Bird | Worldwide |
| *Plasmodium floridense* | Lizard | Carribbean/Central America |
| *Plasmodium azurophilum* | Lizard | Carribbean/Central America |
| *Plasmodium faichildi* | Lizard | Central America |
| *Plasmodium agamae* | Lizard | Africa |
| *Plasmodium gigantum* | Lizard | Africa |
| *Plasmodium mackerassae* | Lizard | Australia |

## TRANSMISSION

**Vectors:** *Plasmodium* may exploit several genera of mosquitoes, as vectors and intermediate hosts

- *Culex*
- *Anopheles,*
- *Culiceta*
- *Mansonia* and
- *Aedes*

i. Bites of mosquitoes,
ii. Mechanically by blood transfer as in mass vaccination,
iii. Caponization and injection.

Malaria parasites are transmitted from person to person through Anopheles mosquitoes. When a mosquito bites, blood containing the parasites is taken into the mosquito's gut. Over a period of 10 or more days, the parasites undergo a complex development, the mature parasite eventually coming to reside in the mosquito's salivary glands, ready for transmission to a new person when it bites again. In the next human host, the parasite first infects the liver, undergoes rapid replication in this site for at least five days, and then infects red blood cells. It is in the blood that the parasites causes the most serious symptoms of malaria, including cerebral malaria initiated by parasitised blood cells blocking blood capillaries in the brain.

**Human-to-human transmission of Malaria**
As the parasite exists in human red blood cells, malaria can be passed on from one person to the next through organ transplant, shared use of needles/syringes, and blood transfusion. An infected mother may also pass malaria on to her baby during delivery (birth) - this is called 'congenital malaria'.

## TYPES OF MALARIA

**There are five types of Malaria:**

- ***Plasmodium falciparum (P. faliparum)*** - The most serious form of the disease. It is most common in Africa, especially sub-Saharan Africa. Current data indicates that cases are now being reported in areas of the world where this type was thought to have been eradicated.
- ***Plasmodium vivax (P. vivax)*** - Milder form of the disease, generally not fatal. However, infected animal still need treatment because their untreated progress can also cause a host of health problems. This type has the widest geographic distribution globally. About 60% of infections in India are due to *P. vivax*. This parasite has a liver stage and can remain in the body for years without causing sickness. If the patient is not treated, the liver stage may re-activate and cause relapses - malaria attacks - after months, or even years without symptoms.

- ***Plasmodium malariae (P. malariae)*** - Milder form of the disease, generally not fatal. However, the infected animal still needs treatment because no treatment can also lead to a host of health problems. This type of parasite has been known to stay in the blood of some people for several decades.
- ***Plasmodium ovale (P. ovale)*** - milder form of the disease, generally not fatal. However, the infected human still needs to be treated because it may progress and cause a host of health problems. This parasite has a liver stage and can remain in the body for years without causing sickness. If the patient is not treated, the liver stage may re-activate and cause relapses - malaria attacks - after months, or even years without symptoms.
- ***Plasmodium knowlesi (P. knowlesi)*** - causes malaria in macaques but can also infect humans.

## LIFE CYCLE OF PLASMODIUM SPECIES

### Life Cycle in Man

A female Anopheline mosquito injects the parasite in the form of 'Sporozoites' while taking the blood meal.

**Pre-Erythrocytic Schizogony**

The thread like curved sporozoites with tapering ends, and an elongated nucleus enter the liver cells and develop into 'Merozoites' In P. falciparum pre-erythrocytic Schizogony completes in 6 days, in P. Ovale, 9 days, in P. Vivax 8 days and in P. Malariae 15 days.

**Erythrocytic Schizogony**

- The hepatocytes filled with the parasites rupture liberating merozoites that attack red blood cells. (The blood remains sterile during pre-erythrocytic stage and there are no clinical manifestations or pathological damage).
- During this stage, (The parasites invade the RBC and undergo the following changes in form).

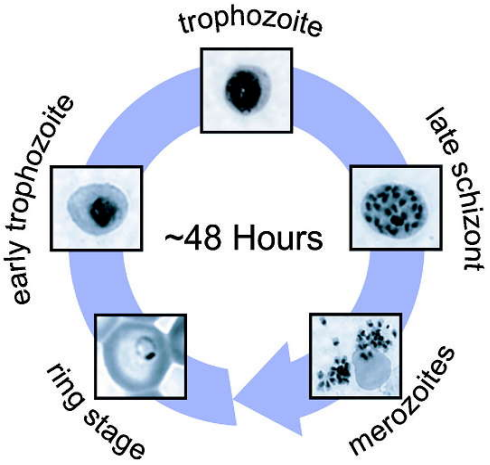



**Fig:** Plasmodium erythrocytic cycle

**Trophozoites**

- Trophozoites: Appear as blue cytoplasmic rings with a red nucleur mass and an unstained area the 'nutrient vacuole' and active amoeboid movements. Pigment granules appear, representing metabolic products.
- Falciparum trophozoite is attached to the periphery of the host red blood cell. The pigment granules are dark brown or black in colour known as 'Maurer's dots'.

**Schuffner's granules'**

- P. vivax, the RBC In becomes distorted and double of its original size. The pigment is yellow dots' (They resemble basophillic stippling).brown in colour and is known as 'Schuffner's granules'.

**Ziemann's granules**

- In P. Malariae, the trophozoite stretches like a band across the infected RBC. Pigment granules are coarse and black known as 'ziemann's granules

**Schizont**

- Schizont is a fully grown trophozoite.
- In *P. falciparum* the nucleus of schizont divides several times and forms round masses called merozoites.
- In *P. Vivax* the merozoites formed from schizont are arranged in a rosette form, with the pigmented mass in the centreExoerythrocytic Schizogony
    - After establishment of blood infection the pre erythrocytic phase disappears completely in P. falciparum, but in P. Vivax, P. Ovale and P. malariae, it persists in the form of local schizogony in the liver.
    - This is responsible for the relapses in these species. The merozoites liberated in this schizogony are called 'Hypnozoites'.

**Gametocytes**

- The sexual cycle starts in the human host with the formation of 'Gametocytes', which further develop inside the female anopheline mosquito
- The human blood must contain at least 12 Gametocytes per mm3 blood and the number of female gametocytes should be in excess.

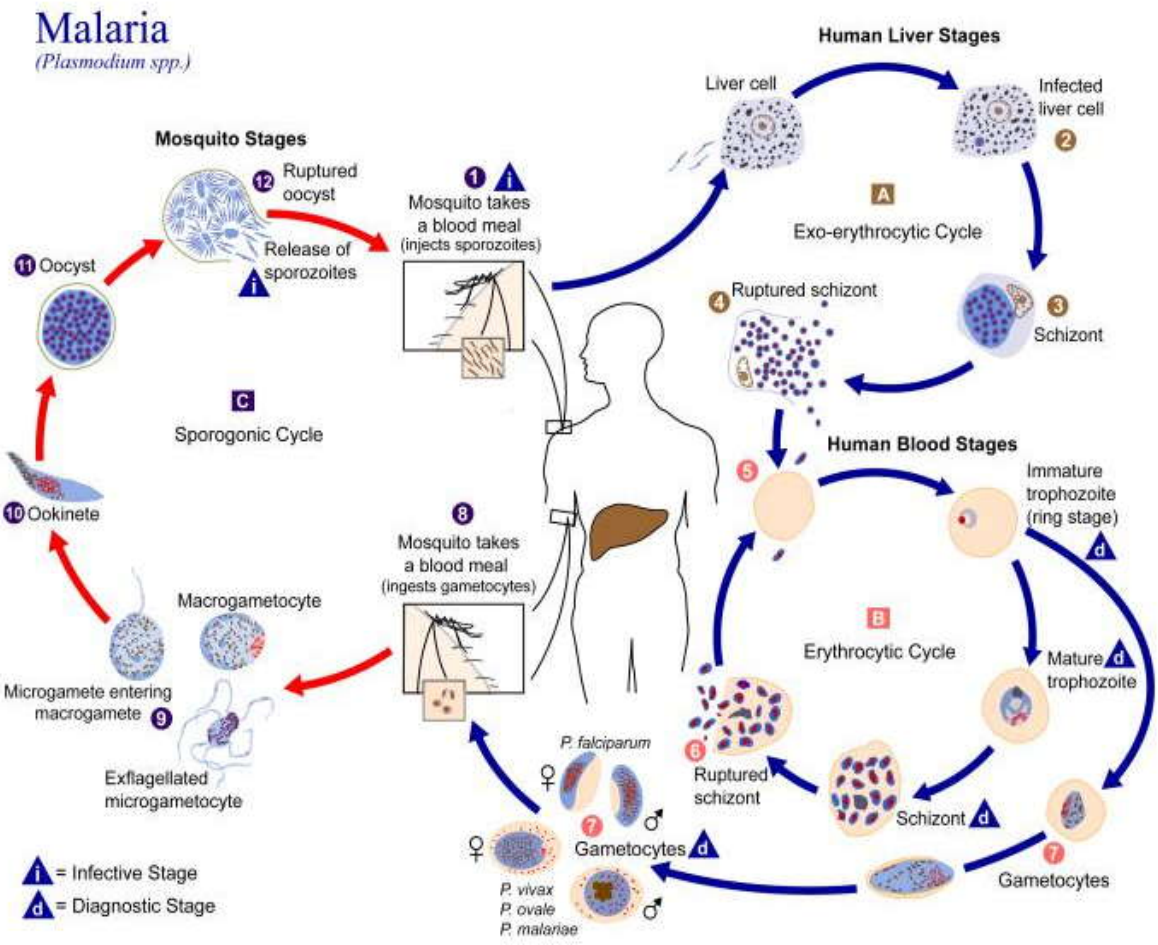



**Fig:** Plasmodium life cycle

## In Mosquito

Only the mature sexual forms develop inside the mosquito. From one micro gametocyte (male gametocyte) 5-8 microgametes are developed in the mid-gut. This is called 'Exflagellation'.

**Sporozoites**

- The macrogametocyte (female) gives rise to only one macrogamete.
- Fusion of male and female gametes results in the formation of a 'Zygote'.
- The Zygote is converted into 'Ookinete' which further develops into 'Oocyst', inside the gut cells of mosquito. The oocyst matures and forms a large number of Sporozoites
- On the 10th day of infection the oocyst ruptures liberating Sporozoites in the body cavity of mosquito. The sporozoites migrate towards the salivary glands where they concentrate in the ducts. At this stage the mosquito is able to transmit the infection to man. A single bite of mosquito is sufficient for this purpose.

## RECURRENT MALARIA

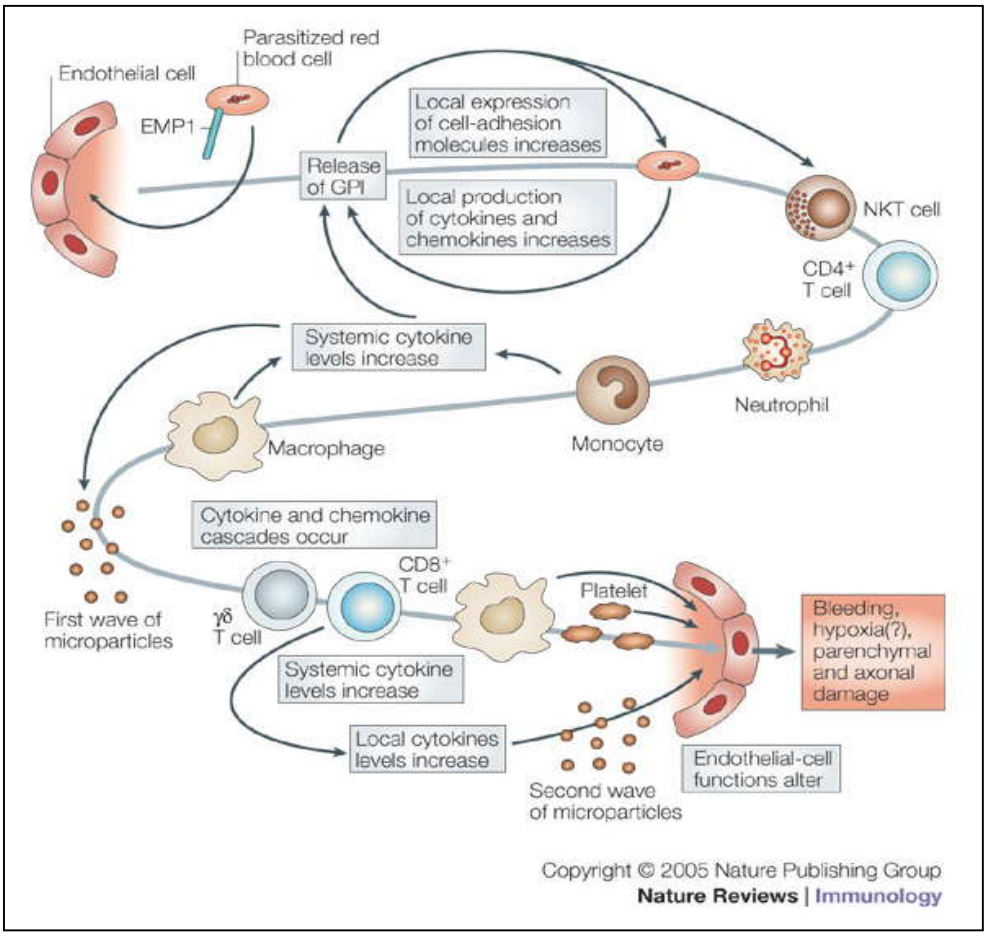
Symptoms of malaria can reappear (recur) after varying symptom-free periods. Depending upon the cause, recurrence can be classified as either recrudescence, relapse, or reinfection. Recrudescence is when symptoms return after a symptom-free period. It is caused by parasites surviving in the blood as a result of inadequate or ineffective treatment. Relapse is when symptoms reappear after the parasites have been eliminated from blood but persist as dormant hypnozoites in liver cells. Relapse commonly occurs between 8–24 weeks and is commonly seen with *P. vivax* and *P. ovale* infections. The longest incubation period reported for a *P. vivax* infection is 30 years. *P. vivax* malaria cases in temperate areas often involve overwintering by hypnozoites, with relapses beginning the year after the mosquito bite. Reinfection means the parasite that caused the past infection was eliminated from the body but a new parasite was introduced. Reinfection cannot readily be distinguished from recrudescence, although recurrence of infection within two weeks of treatment for the initial infection is typically attributed to treatment failure.

## GENETIC RESISTANCE

Due to the high levels of mortality and morbidity caused by malaria-especially the *P. falciparum* species-it has placed the greatest selective pressure on the human genome in recent history. Several genetic factors provide some resistance to it including sickle cell trait, thalassaemia traits, glucose-6-phosphate dehydrogenase deficiency, and the presence of Duffy antigens on red blood cells.

The impact of sickle cell trait on malaria immunity is of particular interest. Sickle cell trait causes a defect in the hemoglobin molecule in the blood. Instead of retaining the biconcave shape of a normal red blood cell, the modified hemoglobin S molecule causes the cell to sickle or distort into a curved shape. Due to the sickle shape, the molecule is not as effective in taking or releasing oxygen, and therefore malaria parasites cannot complete their life cycle in the cell. Individuals who are homozygous (with two copies of the abnormal hemoglobin beta allele) have sickle-cell disease, while those who are heterozygous (with one abnormal allele and one normal allele) experience resistance to malaria. Although the potential risk of death for those with the homozygous condition seems to be unfavorable to population survival, the trait is preserved because of the benefits provided by the heterozygous form.

## PATHOGENESIS




First, parasitized red blood cells (PRBCs) adhere to receptors expressed by brain microvascular endothelial cells, such as intercellular adhesion molecule 1 (ICAM1), through surface expression of Plasmodium falciparum erythrocyte membrane protein 1 (EMP1). When merozoites are released from PRBCs ~4 hours later, parasite glycosylphosphatidylinositol (GPI), which is either released into the blood or present in parasite membranes, functions as a pathogen-associated molecular pattern and toxin, thereby inducing an inflammatory response. A local acute-phase response then occurs, which involves activation of the endothelium and local production of cytokines and chemokines, and this results in upregulation of expression of cell-adhesion molecules by endothelial cells. Within the next ~24 hours, this cycle is perpetuated and exacerbated, owing to increasing parasite numbers and further binding of PRBCs to endothelial cells that have upregulated expression of cell-adhesion molecules. GPI can also function as a ligand for CD1d-restricted natural killer T (NKT) cells, leading to their activation. Activated NKT cells can regulate the differentiation of $CD4^+$ T cells into T helper 1 ($T_H1$) or $T_H2$ cells, depending on which natural-killer-complex loci are expressed, so activation and involvement of $CD4^+$ T cells

occurs. In addition, chemokines recruit monocytes and activate neutrophils (although neutrophils are not known to infiltrate brain microvessels in humans or mice with cerebral malaria). Recruited monocytes can then differentiate into macrophages and become arrested in brain microvessels. Macrophages can also be activated by GPI, a process that is amplified by interferon-γ. Local activated macrophages produce more chemokines, which are released systemically, thereby amplifying infiltration of cells, sequestration of PRBCs and release of microparticles (which are probably of endothelial-cell origin). After several more cycles, γδT cells and $CD8^+$ T cells might become involved, releasing more chemokines and cytokines both systemically and locally and possibly inducing perforin-mediated lesions in the endothelium. Together with locally arrested macrophages, platelets are sequestered and participate in altering endothelial-cell functions. More microparticles of platelet, endothelial-cell and monocyte origin are released, which leads to the dissemination of pro-inflammatory and pro-coagulant effects. Finally, damage to the endothelium, with possible perivascular haemorrhage, axonal injury, and neurotransmitter and metabolic changes, can ensue. The overall disease spectrum in humans might depend on whether all of these processes occur or only some of them.

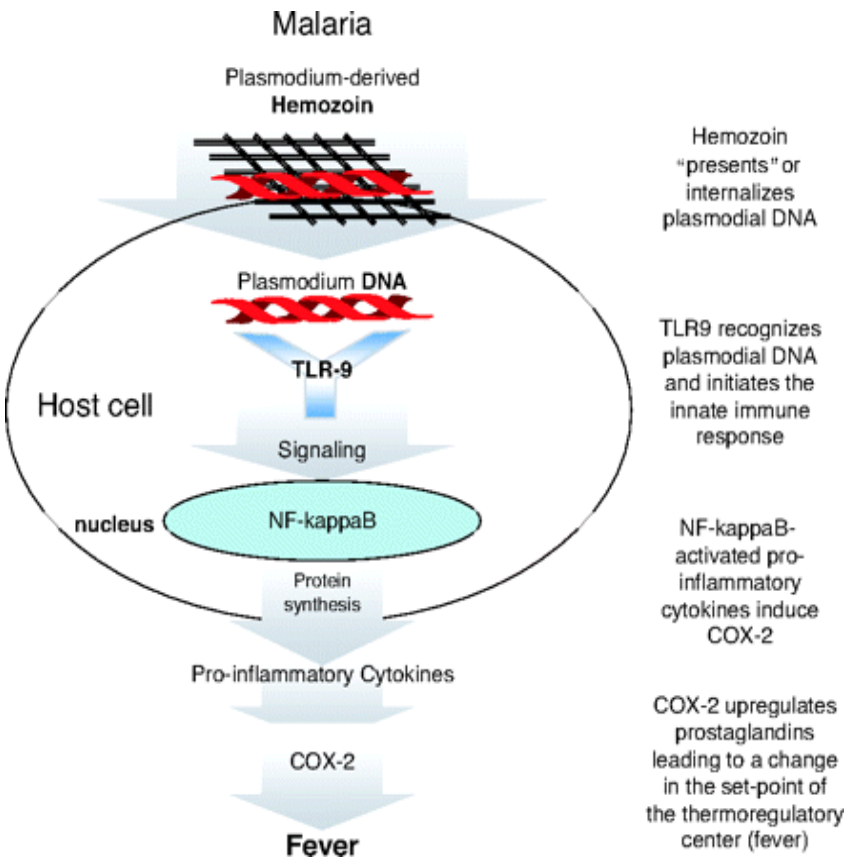



Fig: Induction of fever by malaria parasites

### Malarial Hepatopathy

Liver dysfunction as a result of malaria is rare and is usually a result of a coexisting liver condition such as viral hepatitis or chronic liver disease. The syndrome is sometimes called *malarial hepatitis*, although inflammation of the liver (hepatitis) does not actually occur. While traditionally considered a rare occurrence, malarial hepatopathy has seen an increase, particularly in Southeast Asia and India. Liver compromise in people with malaria correlates with a greater likelihood of complications and death.

## SIGNS AND SYMPTOMS

Incubation period refers to how long it takes from initial infection to the appearance of symptoms. This generally depends on the type of parasite:

- *P. falciparum* - 9 to 14 days
- *P. vivax* - 12 to 18 days
- *P. ovale* - 12 to 18 days
- *P. malariae* - 18 to 40 days

However, incubation periods can vary from as little as 7 days, to several months for *P. vivax* and *P. ovale*. If you are taking medication to prevent infection (chemoprophylaxis) the incubation period is usually longer.

### Symptoms in birds

A bird that has symptoms from *Plasmodium spp*. infection generally has many parasites multiplying in the circulating blood within a week of the mosquito's bite. Birds suffer

- Loss of appetite,
- Shanks and the toes are dry and birds have ruffled feathers
- Extreme leg weakness,
- Nervous signs like twisting of the head
- Greenish-yellow or greenish white diarrhea
- Blood circulation to organs may be impaired, and the liver and spleen may be enlarged, with anemia due to destruction of red blood cells.
- In heavy infections death is common.

### In human:

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, and every three days (tertian fever) for *P. malariae*. *P. falciparum* infection can cause recurrent fever every 36–48 hours (quartan fever) or a less pronounced and almost continuous fever.

The signs and symptoms of malaria typically begin 8–25 days following infection; signs include

- Decreased consciousness
- Significant weakness such that the person is unable to walk
- Inability to feed
- Two or more convulsions
- Low blood pressure (less than 70 mmHg in adults or 50 mmHg in children)
- Breathing problems
- Circulatory shock
- Kidney failure or hemoglobin in the urine
- Bleeding problems, or hemoglobin less than 5 g/dl
- Pulmonary edema
- Low blood glucose (less than 2.2 mmol/l / 40 mg/dl)
- Acidosis or lactate levels of greater than 5 mmol/l
- A parasite level in the blood of greater than 2%
- Retinal damage, and convulsions. splenomegaly (enlarged spleen), fever without localizing signs, thrombocytopenia, and hyperbilirubinemia combined with a normal peripheral blood leukocyte count.

**Gross lesions:**

- Enlargement and blackish discoloration of the liver and spleen
- Presence of pale and watery heart blood.
- Birds that died prior to 21 days PI had some trace deposits of subcutaneous fat and were in relatively good flesh with only minor atrophy of the pectoral muscles.
- Emaciated carcass and prominent keels.
- Impression smears from these tissues often reveals schizonts.
- Schizonts are present in several tissues throughout the body.

## DIAGNOSIS

**Clinical sign and symptom**

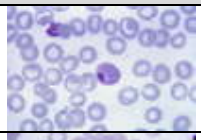
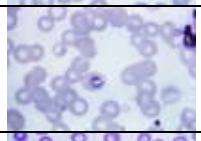
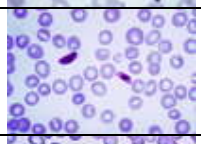
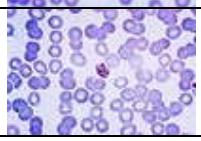
**Laboratory Tests**

Malaria is typically diagnosed by the microscopic examination of blood using blood films or using antigen-based rapid diagnostic tests (RDT).

The most economic, preferred, and reliable diagnosis of malaria is microscopic examination of blood films because each of the four major parasite species has distinguishing characteristics. Two sorts of blood film are traditionally used. Thin films are similar to usual blood films and allow species identification because the parasite's appearance is best preserved in this preparation. Thick films allow the microscopist to screen a larger volume of blood and are about eleven times more sensitive than the thin film.

From the thick film, an experienced microscopist can detect parasite levels (or parasitemia) as few as 5 parasites/μL blood. Diagnosis of species can be difficult because the early trophozoites ("ring form") of all four species look identical and it is never possible to diagnose species on the basis of a single ring form; species identification is always based on several trophozoites.

**Blood films**

| Species | Appearance | Periodicity | Liver persistent |
|---|---|---|---|
| *Plasmodium vivax* |  | Tertian | Yes |
| *Plasmodium ovale* |  | Tertian | Yes |
| *Plasmodium falciparum* |  | Tertian | No |
| *Plasmodium malariae* |  | Quartan | No |

**Antigen tests**

Antigen-based rapid diagnostic tests (RDTs) are often more accurate than blood smears at predicting the presence of malaria parasites.

For areas where microscopy is not available, or where laboratory staff are not experienced at malaria diagnosis, there are RDTs that require only a drop of blood.

Immunochromatographic tests have been developed, distributed and field tested. These tests use finger-stick or venous blood, the completed test takes a total of 15–20 minutes, and the results are read visually as the presence or absence of colored stripes on the dipstick, so they are suitable for use in the field. One disadvantage is that dipstick tests are qualitative but not quantitative – they can determine if parasites are present in the blood, but not how many.

**Molecular methods**

Molecular methods are available in some clinical laboratories and rapid real-time assays (for example, QT-NASBA based on the polymerase chain reaction) are being developed with the hope of being able to deploy them in endemic areas.

PCR (and other molecular methods) is more accurate than microscopy. Levels of parasitemia are not necessarily correlative with the progression of disease, particularly when the parasite is able to adhere to blood vessel walls.

**Tentative Diagnosis**

Areas that cannot afford laboratory diagnostic tests often use only a history of tentative fever as the indication to treat for malaria. Using Giemsa-stained blood smears from patient, one study showed that when clinical predictors (rectal temperature, nailbed pallor, and splenomegaly) were used as treatment indications, rather than using only a history of subjective fevers, a correct diagnosis increased from 2% to 41% of cases, and unnecessary treatment for malaria was significantly decreased.

**Differential diagnosis**

Malaria confused with

- Iron deficiency
- Egg drop syndrome
- Leucocytozoonosis
- Spirochaetosis
- Blood sucking external parasites e.g. fleas, mites, ticks and bugs
- Chicken anaemia agent
- Bbig liver and spleen disease

## TREATMENT OF MALARIA

Treatment of malaria depends on the following factors:

1. Type of infection
2. Severity of infection
3. Status of the host
4. Associated conditions/ diseases

### Type of infection

Treatment obviously depends on the type of infection. Patients with *P. falciparum* malaria should be evaluated thoroughly in view of potential seriousness of the disease and possibility of resistance to anti malarial drugs.

- ***P. vivax:*** Only Chloroquine 25 mg/kg + Primaquine for 14 days.
- ***P. falciparum:*** Treat depending on severity & sensitivity. Primaquine as gametocytocidal is a must to prevent spread.
- **Mixed infections:** Blood schizonticides as for *P. falciparum* and Primaquine as for *P. vivax*.

## Severity of infection

All patients with malaria should be carefully and thoroughly assessed for complications of malaria. Acute, life-threatening complications occur only in *P. falciparum* malaria. Malaria is probably the only disease of its kind that can be easily treated in just 3 days, yet if the diagnosis and proper treatment are delayed, it can kill the patient very quickly and easily.

- All cases of severe malaria should be presumed to have *P. falciparum* malaria.
- If there is any uncertainty about the drug sensitivity of the parasite, it is safer to treat these cases as chloroquine resistant malaria with drugs like quinine or artemisinin.
- All cases of severe malaria should be admitted to the hospital for proper evaluation, treatment and monitoring.
- All cases of severe malaria should be treated with injectable antimalarials (chloroquine, quinine, artemisinin) so as to ensure adequate absorption and plasma drug levels. It is better to use two blood schizonticidal drugs, one fast acting and another slow acting, to ensure complete treatment. Newer drugs available for only oral administration (eg. Mefloquine, Halofantrine) should be avoided.
- All associated conditions should be carefully assessed and treated.

## Status of the host

Treatment of malaria is also dependent on host factors.

- Patient's age and weight
- Functional capacity
- Patients with nausea and vomiting

## Associated conditions/ diseases

Treatment of malaria may have to be modified due to certain associated conditions/ diseases. Therefore, all such should be carefully assessed before starting the patient on anti malarial treatment.

1. **Pregnancy:** Chloroquine can be used safely in all trimesters of pregnancy. Artemisinin is not shown to have any deleterious effects on the fetus. Quinine can be used in pregnancy, but one should be watchful about hypoglycemia. Whereas mefloquine is contraindicated in the first trimester of pregnancy, pyrimethamine/ sulphadoxine is contraindicated in the first and last trimesters. Halofantrine, tetracycline and doxycycline are absolutely contra indicated in pregnancy. Primaquine is also contra indicated in pregnancy, and therefore pregnant women with P. vivax malaria should be started on 500 mg of chloroquine weekly as suppressive chemoprophylaxis against relapse of malaria.

2. **Epilepsy:** Malaria as well as anti malarials can trigger convulsions. Mefloquine is better avoided in these patients. See C.N.S. Disease and malaria

3. **Cardiac disease:** High-grade fever of malaria can exacerbate left ventricular failure and therefore, in all such patients energetic management of malaria is called for. Fever should be controlled with anti-pyretics and tepid sponging. Chloroquine, artemisinin, pyrimethamine/ sulphadoxine, tetracyclines and primaquine can be safely used in these patients. Quinine can also be used carefully. Mefloquine and halofantrine are better avoided in patients with known cardiac illness. See C.V.S. Disease and malaria

4. **Hepatic insufficiency:** None of the antimalarial drugs have any direct hepatotoxic effect. However, chloroquine is not advisable in patients with severe hepatic insufficiency. See liver disease and malaria

5. **Renal failure:** The initial dose of antimalarial drugs need not be reduced in patients with renal failure. However, if the patient requires parenteral antimalarials even after three days and continues to be sick, then the dose can be reduced by one third to half of usual dose. See renal disease and malaria

6. **Dermatitis:** Concomitant use of chloroquine with gold salts and phenyl butazone should be avoided because all the three can cause dermatitis.

## PROGNOSIS OF MALARIA

When properly treated, patient with malaria can usually expect a complete recovery. However, severe malaria can progress extremely rapidly and cause death within hours or days. In the most severe cases of the disease, fatality rates can reach 20%, even with intensive care and treatment. Over the longer term, developmental impairments have been documented in children who have suffered episodes of severe malaria.

Malaria causes widespread anemia during a period of rapid brain development, and also direct brain damage. This neurologic damage results from cerebral malaria to which children are more vulnerable. Some survivors of cerebral malaria have an increased risk of neurological and cognitive deficits, behavioural disorders, and epilepsy. Malaria prophylaxis was shown to improve cognitive function and school performance in clinical trials when compared to placebo groups.

## MALARIA PREVENTION AND CONTROL

Methods used to prevent the spread of disease, or to protect individuals in areas where malaria is endemic, include **prophylactic drugs**, **mosquito eradication**, and the **prevention of mosquito bites**.

**Control Avian Malaria**

Surface modified amorphous nanoporous silica molecules with hydrophobic as well as hydrophilic character can be effectively used as therapeutic drug for combating chicken malaria in poultry industry. The amorphous nanosilica was developed by top-down approach using volcanic soil derived silica as source material. Amorphous silica has long been used as

feed additive for poultry industry and considered to be safe for human consumption by WHO and USDA. The basic mechanism of action of these nanosilica molecules is mediated by the physical absorption of VLDL, serum triglycerides and other serum cholesterol components in the lipophilic nanopores of nanosilica. This reduces the supply of the host derived cholesterol, thus limiting the growth of the malaria parasite *in vivo*.

**Vector control**

Before DDT, malaria was successfully eradicated or controlled also in several tropical areas by removing or poisoning the breeding grounds of the mosquitoes or the aquatic habitats of the larva stages, for example by filling or applying oil to places with standing water. These methods have seen little application in Africa for more than half a century.

**Integrated Vector Management (IVM)**

Integrated Vector Management (IVM) is a process for managing vector population in a way to reduce or interrupt transmission of disease. The aim of IVM is to reduce the number of bites by infected vectors of malaria by control of anophelines mosquitoes; this may include a large number of measures. Anophelines breed in clean water and it may therefore be possible to reduce their densities by proper drainage and other environmental measures or by the use of larvivorous fish Strategy for malaria prevention and control or chemical larvicides. Where such methods have proven effective, they should be systematically promoted.

However, in most high-risk areas, long-term measures targeting adult mosquitoes are more generally effective and applicable. Two such methods are now available: IRS and ITNs. As these methods are costly and based on insecticides, they shall be targeted to high-risk areas, which must be identified according to prevalence of criteria. The choice between IRS and ITNs will be based on operational factors, community acceptance and local experience. The unit of intervention will be the village through microstratification.

**Prophylactic drugs**

Use of prophylactic drugs is seldom practical for full-time residents of malaria-endemic areas, and their use is usually restricted to short-term visitors and travelers to malarial regions.

*Quinine* was used starting in the seventeenth century as a prophylactic against malaria. The development of more effective alternatives such as *quinacrine*, *chloroquine*, and *primaquine* in the twentieth century reduced the reliance on quinine. Today, quinine is still used to treat chloroquine resistant *Plasmodium falciparum*, as well as severe and cerebral stages of malaria, but is not generally used for prophylaxis.

Modern drugs used preventively include *mefloquine* (**Lariam**), *doxycycline* (available generically), and the combination of *atovaquone* and *proguanil hydrochloride* (**Malarone**).

**Indoor residual spraying**

Indoor residual spraying (IRS) is the practice of spraying insecticides on the interior walls of homes in malaria affected areas. The first and historically the most popular insecticide used for IRS is DDT. While it was initially used exclusively to combat malaria, its use quickly

spread to agriculture. In time, pest-control, rather than disease-control, came to dominate DDT use, and this large-scale agricultural use led to the evolution of resistant mosquitoes in many regions. If the use of DDT was limited agriculturally, DDT may be more effective now as a method of disease-control. The DDT resistance shown by Anopheles mosquitoes can be compared to antibiotic resistance shown by bacteria. The overuse of anti-bacterial soaps and antibiotics have led to antibiotic resistance in bacteria, similar to how overspraying of DDT on crops have led to DDT resistance in Anopheles mosquitoes. During the 1960s, awareness of the negative consequences of its indiscriminate use increased ultimately leading to bans on agricultural applications of DDT in many countries in the 1970s.

**Mosquito nets and bedclothes**

Mosquito nets help keep mosquitoes away from people, and thus greatly reduce the infection and transmission of malaria. The nets are not a perfect barrier, so they are often treated with an insecticide designed to kill the mosquito before it has time to search for a way past the net.

Insecticide-treated nets (ITN) are estimated to be twice as effective as untreated nets, and offer greater than 70% protection compared with no net. Although ITN are proven to be very effective against malaria, less than 2% of children in urban areas in Sub-Saharan Africa are protected by ITNs. Since the *Anopheles* mosquitoes feed at night, the preferred method is to hang a large "bed net" above the center of a bed such that it drapes down and covers the bed completely.

**Vaccination**

Vaccines for malaria are under development, with no completely effective vaccine yet available. Presently, there is a huge variety of vaccine candidates on the table.

Pre-erythrocytic vaccines (vaccines that target the parasite before it reaches the blood), in particular vaccines based on circumsporozoite protein (CSP), make up the largest group of research for the malaria vaccine. Other vaccine candidates include: those that seek to induce immunity to the blood stages of the infection; those that seek to avoid more severe pathologies of malaria by preventing adherence of the parasite to blood venules and placenta; and transmission-blocking vaccines that would stop the development of the parasite in the mosquito right after the mosquito has taken a bloodmeal from an infected person. It is hoped that the sequencing of the *P. falciparum genome* will provide targets for new drugs or vaccines.

**Other methods**

**Education** in recognizing the symptoms of malaria has reduced the number of cases in some areas of the East Africa by as much as 20%. Recognizing the disease in the early stages can also stop the disease from becoming a killer. Education can also inform people to cover over areas of stagnant, still water e.g. Water Tanks which are ideal breeding grounds for the parasite and mosquito, thus cutting down the risk of the transmission between people. This is most put in practice in urban areas where there are large centers of population in a confined space and transmission would be most likely in these areas.

## REFERENCES

Malaria site, Web portal: http://www.malariasite.com/malaria/Treatment1.htm

Wikipedia, The free encyclopedia, Web portal: http://en.wikipedia.org/wiki/Malaria

World Health Organization (1958). "Malaria" (PDF). *The First Ten Years of the World Health Organization*. World Health Organization. pp. 172–87.

Sutherland, CJ; Hallett, R (2009). "Detecting malaria parasites outside the blood". *J Infect Dis* 199 (11): 1561–3

Mens, PF; Schoone, GJ; Kager, PA; Schallig, HD (2006). "Detection and identification of human Plasmodium species with real-time quantitative nucleic acid sequence-based amplification". *Malaria Journal* 5 (80): 80.

McCutchan, Thomas F.; Piper, Robert C.; Makler, Michael T. (November 2008). "Use of Malaria Rapid Diagnostic Test to Identify *Plasmodium knowlesi* Infection". *Emerging Infectious Disease* (Centers for Disease Control) 14 (11): 1750–2

Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, et al. Multidrug-Resistant *Plasmodium vivax* Associated with Severe and Fatal Malaria: A Prospective Study in Papua, Indonesia. PLoS Med 2008;5(6):e128.

Sarwo Handayani, Daniel T. Chiu, Emiliana Tjitra et al. High Deformability of *Plasmodium vivax*–Infected Red Blood Cells under Microfluidic Conditions. *J. Infect. Dis*. 2009;199:445–450.

J. Alexandra Rowe, Ian G. Handel, Mahamadou A. Thera et al. Blood group O protects against severe *Plasmodium falciparum* malaria through the mechanism of reduced rosetting. *PNAS* 30 October, 2007;104(44):17471-17476.

Nicholas M. Anstey, Bruce Russell, Tsin W. Yeo, Ric N. Price. The pathophysiology of vivax malaria. *Trends in Parasitology* 2009;25(5):220-227.

Claire L. Mackintosh, James G. Beeson, Kevin Marsh. Clinical features and pathogenesis of severe malaria. *Trends in Parasitology* December 2004;20(12):597-603

Ian A Clark, Alison C Budd, Lisa M Alleva, William B Cowden. Human malarial disease: a consequence of inflammatory cytokine release. *Malaria Journal* 2006;5:85.