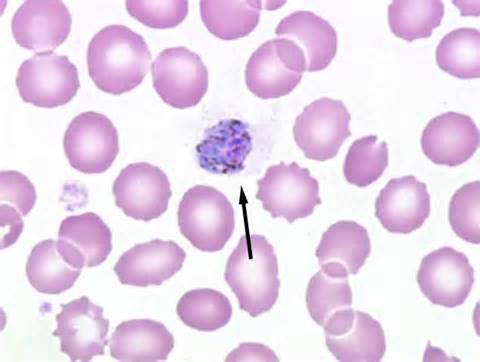
Malaria Parasite and Host cells

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**Introduction**

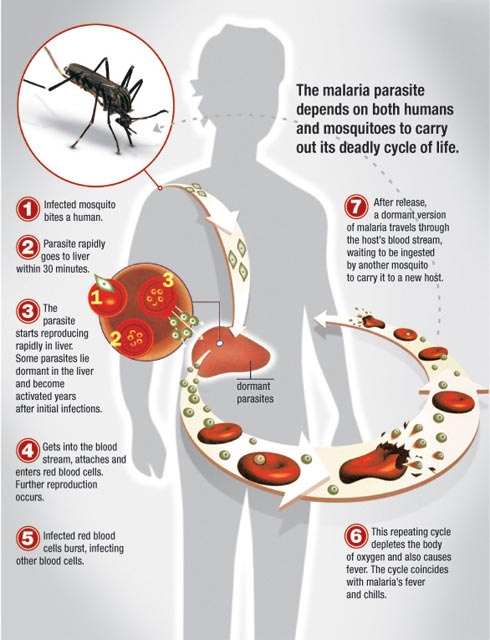
Malaria is a protozoal disease transmitted by the bite of female *Anopheles* mosquito,caused by a parasitic protozoon of the genus *Plasmodium*, which infect human and insect hosts alternatively. The disease is endemic in 90 countries in Africa, Asia, Central and South America. Throughout the world two billion people or 40 % of the world population is at risk. It is estimated that 300-500 million cases occur each year and in Africa alone more than one million children die from malaria each year. In its socio-economic impact malaria is the most important of all transmissible parasitic diseases.

**The parasite**

*Plasmodium* is a protozoan parasite belonging to the order Sporozoa. Four *Plasmodium* species can infect man:

* *P. vivax*
* *P. falciparum*
* *P. ovale*
* *P. malariae*

**Life cycle**

[](http://healthcloseup.com/what-is-the-cerebral-malaria/malaria-life-cycle/)

The interactions between malaria parasite and host cells considered at:

1-invasion strategy

2- intracellular development strategy .

*Plasmodium* is a lower eukaryote with a genetic complexity which combined with the considerable polymorphism of the organism and its ability to adapt to changing situations probably explains why the parasite is so successful.

**Invasion of different host cells**

Plasmodium is intracellular for most of its life-cycle. Specialized invasive stages are required for :

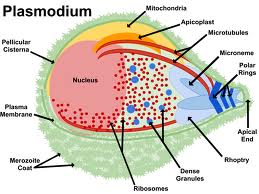
1. The transfer from the mosquito to the vertebrate host (**sporozoite**) .
2. The transfer from the hepatocyte to the erythrocyte or from one erythrocyte to another (**merozoite**).
3. - For the migration out of the mosquito gut (**ookinete**).

These three extra-cellular stages have a specific feature in common:

the presence of a unique set organelles designed for cell invasion, the (**Apical complex )** consists of a cone-shaped projection of the cell membrane designed for boring into tissues and for making contact with the host cell, by means of a number of unique organelles (two rhoptries, a polar ring and a number of micronemes and dense granules).

Rhoptries, micronemes and dense granules (which are all electron-dense on electron micrographs) contain a variety of substances which are discharged into the host cell during the invasion process through a system of ducts which open up at the apica released play a crucial role in destabilizing

(make unstable) the host cell membrane and in formation of an invasion pit, which eventually envelops the merozoite in a membrane-lined cavity - the parasitophorous vacuole. After the merozoite has invaded the red cell, the ‘dense granules’ move to the surface of the parasite and release their contents into the parasitophorous vacuole, further increasing the area of its membrane.

[](http://www.google.com.sa/imgres?lr=&sa=X&hl=ar&biw=1440&bih=720&tbm=isch&tbnid=pSmCWeXwCifJpM:&imgrefurl=http://en.wikipedia.org/wiki/Plasmodium_falciparum_biology&docid=VQOZBj-dc9eBTM&imgurl=http://upload.wikimedia.org/wikipedia/commons/f/fa/Plasmodium.png&w=960&h=720&ei=gplKUtXUBcre4QT9l4EQ&zoom=1&ved=1t:3588,r:99,s:0,i:382&iact=rc&page=4&tbnh=194&tbnw=259&start=72&ndsp=28&tx=156&ty=90)

**Recognition/invasion process**

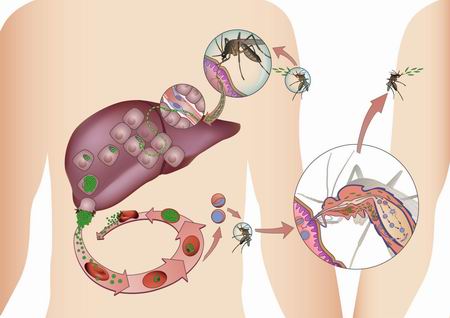
The recognition/invasion process is different at different stages of the life cycle, common to all stages is the initial need for a contact of the apical end of the parasite with the cell membrane. This involves the recognition of a ligand on the host cell membrane by a receptor on the surface of the invasive stage. In all cases, penetration of the parasite into the host cell is an active event, for which the parasite uses its actin-myosin motor for locomotion.

- Merozoite and erythrocyte invasion.

- Ookinete and midgut epithelium invasion .

- Sporozoite and hepatocyte invasion.

**Pthogenesis of Malaria**



**In highly endemic areas:** high mortality among children due to severe anemia, children who survive beyond the first years show decreasing parasitemia and disease (this immunity is not sterile and depends on constant exposure)

**Cytokines & toxins:** -Malaria produces a strong Th-1 type response .

-Elevated serum levels of IFNg and TNFa .

-Cytokines can induce (mimic) many of the symptoms and signs of malaria (shivering, headache, chills, spiking fever, sweating, vasodilation, hypoglycemia)

**Pernicious, Malignant Malaria**

-Is a life threatening complication in acute *falciparum* malaria .It is due to heavy parasitism.

Manifests with:

1- Cerebral malaria – it presents with hyperpyrexia, coma and paralysis. Brain is congested.

2 Algid malaria – presents with clammy (cold) skin due to peripheral circulatory failure

**Cerebral Malaria**

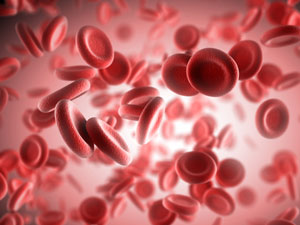
-Malignant malaria can affect the brain and the rest of the central nervous system. It is characterized by Presents with Hyperpyrexia, changes in the level of consciousness, convulsions and paralysis.

**Pathogenesis of Cerebral malaria**

-High cytokine levels could be toxic on their own.

-High levels of cytokine also enhance the second process thought to be responsible for cerebral malaria( sequestration of infected RBCs): Rosetting (adhesion of infected RBCs to other RBCs)

& clumping (adhesion between infected cells)

[](http://www.google.com/url?sa=i&rct=j&q=&esrc=s&frm=1&source=images&cd=&cad=rja&docid=pR6lHkUl9dex8M&tbnid=cu8rZSQ2rpvSJM:&ved=0CAUQjRw&url=http://www.rsc.org/chemistryworld/2013/01/targeting-red-blood-cells-malaria-infected-patients&ei=eY1KUoyRBfOY0AXSooDIDw&bvm=bv.53371865,d.bGE&psig=AFQjCNEdlp-OuEk9j1zQS4BN80dGVMq1fg&ust=1380703921685016) [](http://www.google.com/url?sa=i&rct=j&q=&esrc=s&frm=1&source=images&cd=&cad=rja&docid=bLoaeQ1WkfjrbM&tbnid=zdzbdY-g5zJ_OM:&ved=0CAUQjRw&url=http://quizlet.com/6581085/hl-self-study-malaria-ebv-pnh-and-stem-cells-flash-cards/&ei=1JBKUvCnKYO50QWm6IDwBA&psig=AFQjCNG0BbiYeIFrPZWU789goHskZLkbIw&ust=1380704818973614)

Red blood cells infected with the malaria parasite

can clump together and cause deadly blockages adhesion of infected RBCs to other RBCs

**Black water fever**

It is a manifestation of infection with *P. falciparum* (malignant malaria)*.*

A large number of the red blood corpuscles are destroyed.

Hemoglobin from the RBCs is excreted in the urine, which therefore is dark and almost the color of **cola**.

**Falciparum infections are dangerous why?**

Due to its fatal complications,

1. Cerebral malaria.

2. Malarial hyperpyrexia.

3. Gastrointestinal disorders.

4. **Algid** malaria.

5 **Black water fever** can lead to death.

**Complication of *P. malariae***

Can produce Nephrotic Syndrome . Affects mainly children .

**Alteration of host erythrocytes**

After the malarial parasi infection , the host cell undergoes some structural changes, which may alter its function, appearance or antigenicity.

These alterations increase membrane permeability, increase selective intake of nutrients, or escape from immunity by sequestration.

The alterations (changes) in the membrane of malaria-infected RBCs :

-Change of shape.

- The presence of '**knobs** 'or electron-dense protrusions in *P. falciparum* and *P. malariae*

- The presence of ‘**caveolae**’ or small depressions, at the surface of the red cell

- The cytoadherence to endothelial cells; the adherence to normal erythrocytes "**rosetting**" or to other infected erythrocytes "**auto-agglutination**"=clumbing

- the presence of new metabolic channels new parasite-specific antigens associated with the red cell membrane.

**-**Parasite antigens have been demonstrated on the surface of infected erythrocytes infected with *P. knowlesi, P. falciparum, P. vivax* and others.

- Once the schizont has completed its development, it needs to break through three sets of membranes, in order to release merozoites. At this stage, the parasitophorous vacuole membrane and host cell membrane are already altered and distended and the normally rigid cytoskeleton have been damaged. The breakdown of the host cell is completed through:

The release of parasite proteases and lipases .

The binding of host molecules to the surface of the infected red cell. The binding of host urokinase-type plasminogen activator has been described as essential for meront (schizont) rupture.

**Congenital malaria**

Transplacental infection . In all 4 species Commonly *P.v.* and *P.f.* in endemic areas.

Neonate can be diagnosed with parasitemia within 7 days of birth or longer if no other risk factors for malaria (mosquito exposure, blood transfusion) .

Fever, irritability, feeding problems, anemia, hepatosplenomegal, and jaundice. Acute *falciparum* malaria is a potentially fatal disease causing prolonged, irregular high fever, intense headache and vomiting. Complications include cerebral malaria (characterized by confusion, convulsions and rapidly progressive coma), hypoglycaemia, septicaemia, pneumonia, pulmonary oedema, acute renal failure and massive haemolysis. Chronic or repeated infection often leads to **splenomegaly** and progressive anaemia. Splenic rupture is a dangerous complication of *vivax* malaria.

*falciparum* malaria cause death of Pregnant women, if untreated. In endemic areas they are partially protected by a measure of immunity. This reduces the risk of congenital infection, but it does not protect the placenta that can harbor large numbers of malaria parasites. The fetus is thus inevitably exposed to the effects of placental insufficiency.

Largely as a result of passive transfer of maternal antibodies across the placenta, infants born to immune mothers living in endemic areas are unlikely to acquire malaria for several months after birth. Thereafter, they risk death from severe and recurrent acute attacks during infancy and early childhood. From the age of five until adulthood the severity and frequency of these attacks decrease as immunity develops.

Except among pregnant women, severe malaria is infrequent in adults who have always lived in areas of high transmission.

**Immunity to Malaria**

Influenced by :

– Genetics

– Age

– Health condition

– Pregnancy status

– Intensity of transmission in region

– Length of exposure

– Maintenance of exposure

**Innate immunity**

Red cell polymorphisms associated with some protection

Hemoglobin S sickle cell trait or disease

Hemoglobin C and hemoglobin E

Thalessemia – α and β

Glucose – 6 – phosphate dehydrogenase deficiency (G6PD)

– Red cell membrane changes

Absence of certain Duffy coat antigens improves resistance to *P.vivax*

Acquired

– Transferred from mother to child 3-6 months protection.

– Increased susceptibility during early childhood

– No complete immunity

– Needs long period of exposure for induction

– May need continued exposure for maintenance

Immunity can be unstable:

-Can wane as one spends time outside endemic area

-Can change with movement to area with different endemicity

-Decreases during pregnancy.

Acquired immunity plays an important role in malaria. This is based on the following observations:

 People that become infected get cured, but remain suceptible to new infections

 Young children and foreigners become more ill than indigenous people

 People leaving a malaria area become susceptible to the disease again

Both humural and cellular immunity is involved in the process of acquired immunity

 Humural response:

o gamma globulines from immune Africans protect non-immune individuals.

o antibodies protect against sporozoites before they enter the hepatocytes.

 Cellular response :

o macrophages in liver and spleen are highly activated .

o T-cells have been shown to be important .

These remarks led to the development of vaccines as a protective measure against malaria. A complete protection can not easily, be obtained .However, a vaccine may significantly reduce morbidity caused by the disease amongst young children and travelers.

**Anti-sporozoite vaccines:**

Several experimental malaria vaccines have been developed over the last 10 years. They were based on a single or several *Plasmodium* surface antigens present on either the sporozoite or merozoite stage of the parasite.

1-The first vaccination trials were carried out with the so-called CSP- or circumsporozoite protein-based vaccine. The circumsporozoite protein CSP is highly antigenic.

**Types of vaccine are currently under development:**

1. **Anti-sporozoite vaccines**:

Designed to prevent infection. Since infection with a single sporozoite can lead to the development of a severe blood stage infection an anti sporozoite vaccine must be 100% effective

1. **Transmission-blocking vaccines**:

Designed to arrest the development of the parasite in the mosquito, thereby reducing or eliminating transmission of the disease.

1. **Anti-asexual blood stage vaccines**:

Designed to reduce severe and complicated manifestations of the disease.

Such vaccines could lower morbidity and mortality among children under 5 years of age in Africa, the main risk group, and their development is given priority by WHO. Several such vaccine candidates are currently undergoing clinical and field testing.

TEST PREP

-Alteration in DBCs

-Erythrocytic cycle.