Haemoparasite-Malaria

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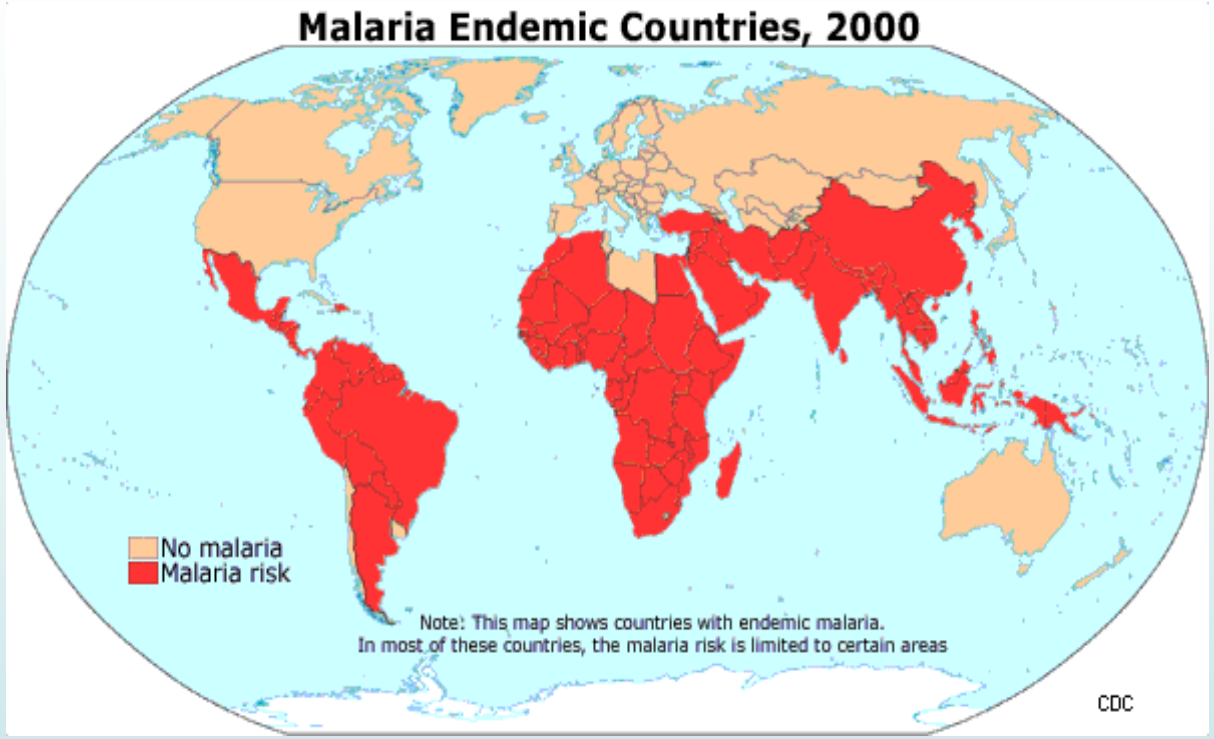
What is malaria ?

Malaria is a disease caused by the protozoan parasites of the genus **Plasmodium.** The 4 species that commonly infect man are:

Species	Major features
P. falciparum	▪ The most important species as it is responsible for 50% of all malaria cases worldwide and nearly all morbidity and mortality from severe malaria ▪ Found in the tropics & sub-tropics
P. vivax	▪ The malaria parasite with the widest geographical distribution ▪ Seen in tropical and sub-tropical areas but rare in Africa ▪ Estimated to cause 43% of all malaria cases in the world
P. ovale	▪ This species is relatively rarely encountered ▪ Primarily seen in tropical Africa, especially, the west coast, but has been reported in South America and Asia
P. malariae	▪ Responsible for only 7% of malaria cases ▪ Occurs mainly in sub-tropical climates

Geographical Distribution of Malaria

Although previously widespread, today malaria is confined mainly to Africa, Asia and Latin America. About 40% of the world's population is at risk of malaria. It is endemic in 91 countries, with small pockets of transmission occurring in a further 8 countries.



Malaria is transmitted by the female anopheles mosquito. Factors which affect mosquito ecology, such as temperature and rainfall, are key determinants of malaria transmission. Mosquitoes breed in hot, humid areas and below altitudes of 2000 meters. Development of the malaria parasite occurs optimally between 25-30^{o}C and stops below 16^{o}C. Indigenous malaria has been recorded as far as 64^{o}N and 32^{o}S.

Malaria has actually increased in sub-Saharan Africa in recent years. The major factor has been the spread of drug-resistant parasites. Other important factors include the persistence of poverty, HIV/AIDS, mosquito resistance to insecticides, weak health services, conflict and population migration.

Endemicity

- ***Endemicity refers to the amount or severity of malaria in an area or community. Malaria is said to be endemic when there is a constant incidence of cases over a period of many successive years.***

Endemic malaria may be present in various degrees. Recognised categories of endemicity include :

A. Hypoendemicity - little transmission and the disease has little effect on the population.

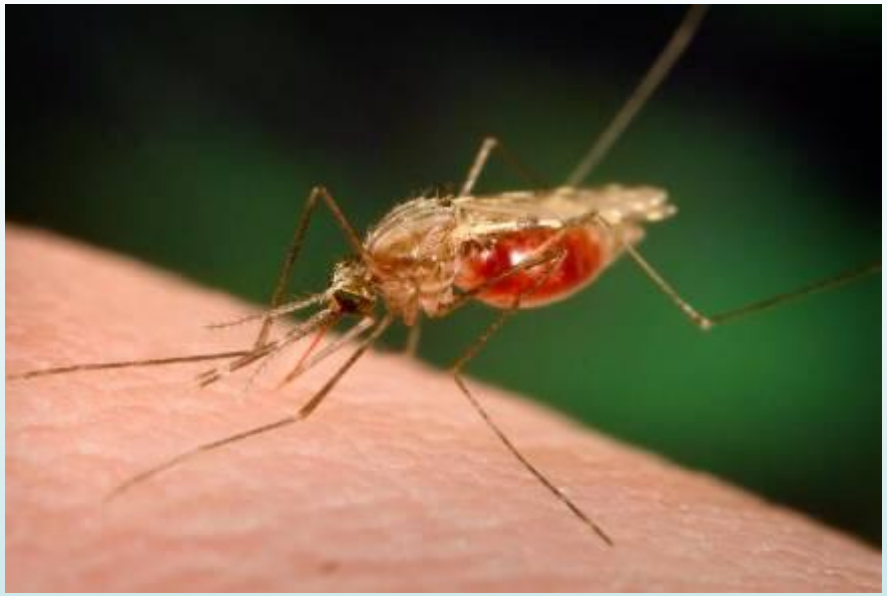
B. Mesoendemicity - varying intensity of transmission; typically found in the small, rural communities of the sub-tropics.

C. Hyperendemicity - intense but seasonal transmission; immunity is insufficient to prevent the effects of malaria on all age groups.

D. Holoendemicity - intense transmission occurs throughout the year. As people are continuously exposed to malaria parasites, they gradually develop immunity to the disease. In these areas, severe malaria is mainly a disease of children from the first few months of life to age 5 years. Pregnant women are also highly susceptible because the natural immune defence mechanisms are impaired during pregnancy.

How is malaria transmitted?

- Malaria parasites are transmitted from one person to another by the bite of a female anopheles mosquito.
- The female mosquito bites during dusk and dawn and needs a blood meal to feed her eggs.
- Male mosquitoes do not transmit malaria as they feed on plant juices and not blood.
- There are about 380 species of anopheles mosquito but only about 60 are able to transmit malaria.
- Like all mosquitoes, anopheles breed in water - hence accumulation of water favours the spread of the disease.



Female *Anopheles* mosquito taking a blood meal

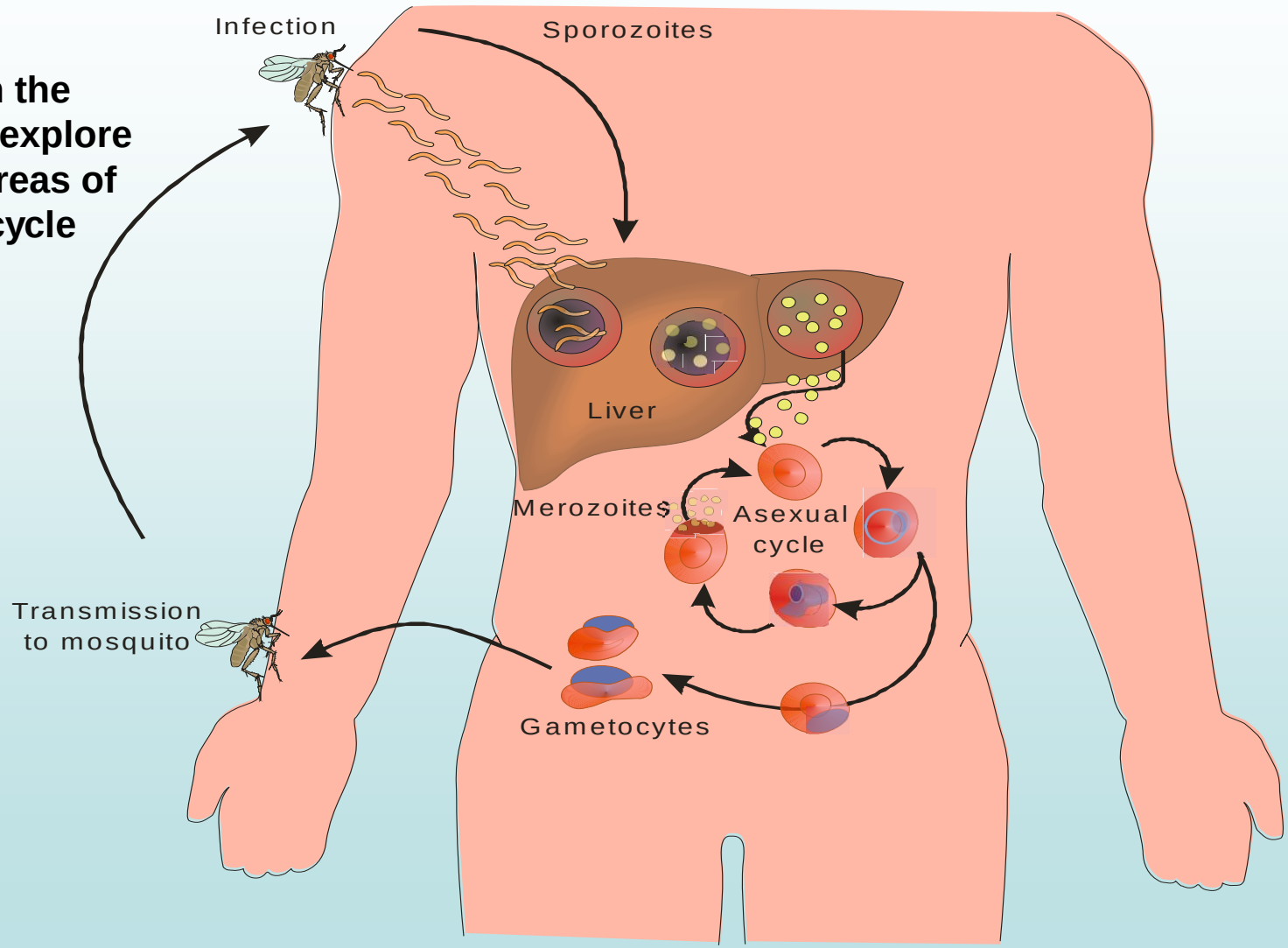
Source:http://phil.cdc.gov/phil/quicksearch.asp

How does infection develop ?

- Plasmodium infects the human and insect host alternatively and several phases of the parasite life cycle are described.
- During feeding, saliva from the mosquito is injected into the human blood stream. If the mosquito is carrying malaria, the saliva contains primitive stages of malaria parasites called sporozoites.
- ***Hepatic, tissue or pre-erythrocytic phase****:* Sporozoites invade and develop in liver cells. The infected hepatocyte ruptures to release merozoites.
- ***Erythrocytic phase****:* Merozoites then invade red blood cells. The red cells lyse and this causes bouts of fever and the other symptoms of the disease. This cycle repeats as merozoites invade other red cells.
- ***Sexual phase****:* Sexual forms of the parasites develop and are ingested when another female anopheles mosquito feeds. These develop into sporozoites in the gut of the insect host and travel to its salivary glands. Then the cycle starts again…
- The life cycle of the malaria parasite is shown on the next slide

The Malaria Parasite Life Cycle

Click on the diagram to explore different areas of the life cycle



Severity of disease and host factors

In addition to parasite factors, several host factors determine the outcome of exposure to malaria:

- **Naturally-acquired immunity.** People who are constantly exposed to malaria gradually acquire immunity, firstly against clinical disease and later against parasite infection. Clinical manifestations of malaria are most severe in the non-immune. In holoendemic areas, these are children aged <5 years and pregnant women. People of any age from areas that are free from malaria, or have limited malaria transmission, are at risk when they are exposed to malaria.

- **Red cell and haemoglobin variants.** Well known examples of inherited factors that protect against malaria are Haemoglobin S carrier state, the thalassaemias and Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Malaria provides the best known example whereby an environmental factor (malaria) has selected human genes because of their survival advantage.

- **Foetal haemoglobin (HbF):** High levels of HbF occur in neonates, and in some people with inherited haemoglobin variants, protect against severe forms of *P. falciparum* malaria.

- **Duffy blood group:** *P. vivax* requires the Duffy blood receptor to enter red blood cells. Therefore, people who do not carry the Duffy blood group are resistant to this malaria species. This explains the rarity of *P. vivax* in Africa, as most Africans are Duffy blood group negative.

The clinical course of *P. falciparum*

Following a bite by an infected mosquito, many people do not develop any signs of infection. If infection does progress, the outcome is one of three depending on the host and parasite factors enumerated in the previous slides:

A. Asymptomatic parasitaemia (“clinical immunity”)
B. Acute, uncomplicated malaria
C. Severe malaria

A. Asymptomatic parasitaemia

This is usually seen in older children and adults who have acquired natural immunity to clinical disease as a consequence of living in areas with high malaria endemicity. There are malaria parasites in the peripheral blood but no symptoms. These individuals may be important reservoirs for disease transmission.

Some individuals may even develop anti-parasite immunity so that they do not develop parasitaemia following infection.

B. Simple, uncomplicated malaria

This can occur at any age but it is more likely to be seen in individuals with some degree of immunity to malaria. The affected person, though ill, does not manifest life-threatening disease.

Fever is the most constant symptom of malaria. It may occur in paroxysms when lysis of red cells releases merozoites resulting in **fever**, **chills** and **rigors** (uncontrollable shivering).

Children with malaria waiting to be seen at a malaria clinic in the south western part of Nigeria. Identifying children with severe malaria, and giving them prompt treatment, is a major challenge when large numbers attend clinics.

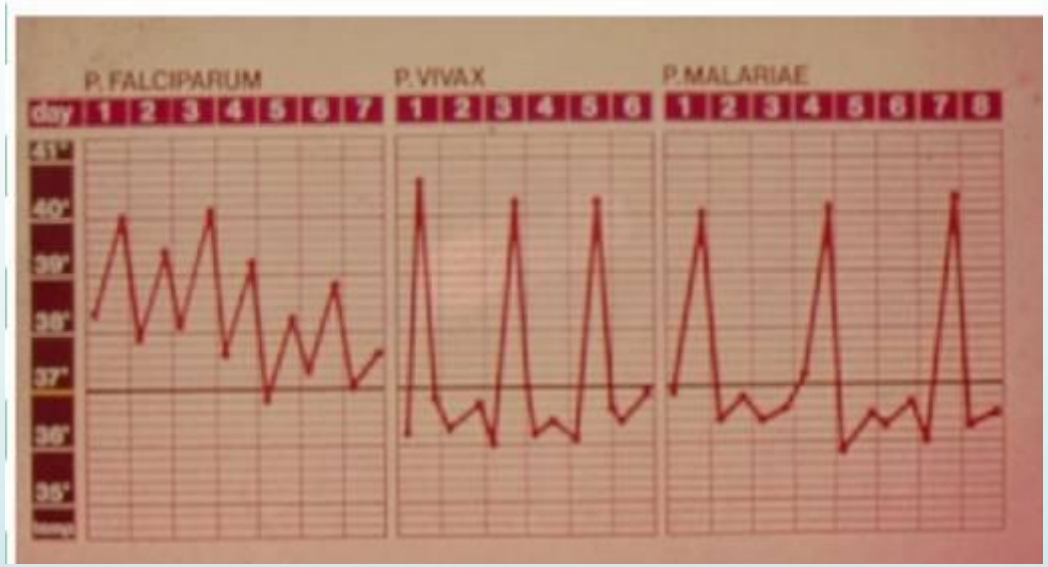
The periodicity of malaria fever

Erythrocytic schizogony is the time taken for trophozoites to mature into merozoites before release when the cell ruptures.

It is shortest in *P. falciparum* (36 hours), intermediate in *P. vivax* and *P. ovale* (48 hours) and longest in *P. malariae* (76 hours).

Typical paroxysms thus occur every

- 2nd day or more frequently in *P. falciparum* (“sub-tertian” malaria)
- 3rd day in *P. vivax* and *P. ovale* (“tertian” malaria)
- 4th day in *P. malariae* infections, (“quartan” malaria)



Note how the frequency of spikes of fever differ according to the Plasmodium species. In practice, spikes of fever in *P. falciparum*, occur irregularly - probably because of the presence of parasites at various stages of development.

Other features of simple, uncomplicated malaria include:

- **Vomiting**
- **Diarrhoea** – more commonly seen in young children and, when vomiting also occurs, may be misdiagnosed as viral gastroenteritis
- **Convulsions** – commonly seen in young children. Malaria is the leading cause of convulsions with fever in African children.
- **Pallor** – resulting mainly from the lysis of red blood cells. Malaria also reduces the synthesis of red blood cells in the bone marrow.
- **Jaundice** – mainly due to haemolysis.

Malaria is a multisystem disease. Other common clinical features are:

- **Anorexia**
- **Cough**
- **Headache**
- **Malaise**
- **Muscle aches**
- **Splenomegaly**
- **Tender hepatomegaly**

These clinical features occur in “mild” malaria. However, the infection requires urgent diagnosis and management to prevent progression to severe disease.

C. Severe and complicated malaria

Nearly all severe disease and the estimated >1 million deaths from malaria are due to *P. falciparum*. Although severe malaria is both preventable and treatable, it is frequently a fatal disease.

The following are 8 important severe manifestations of malaria:
Click on each severe manifestation for details

1. Cerebral malaria
2. Severe malaria anaemia
3. Hypoglycaemia
4. Metabolic acidosis
5. Acute renal failure
6. Pulmonary oedema
7. Circulatory collapse, shock or "algid malaria"
8. Blackwater fever

Note: It is common for an individual patient to have more than one severe manifestation of malaria!

Summary of differences in the clinical features of severe malaria in adults and children

	Frequency of occurrence	
Clinical Manifestation	**Children**	**Adults**
Similar in adults and children		
• Prostration	+++	+++
• Circulatory collapse	+	+
More common in children		
• Cerebral malaria	+++	++
• Severe anaemia	+++	+
• Multiple convulsions	+++	+
• Metabolic acidosis	+++	+
• Hypoglycaemia	++	+ / -
More common in adults		
• Jaundice	+	+++
• Pulmonary oedema	+ / -	++
• Haemoglobinuria	+ / -	+
• Abnormal bleeding	+ / -	+
• Renal failure	+ / -	+

Diagnosis

Malaria is a multisystem disease. It presents with a wide variety of non-specific clinical features: there are no pathognomonic symptoms or signs. Many patients have fever, general aches and pains and malaise and are initially misdiagnosed as having “flu”.

P. falciparum malaria can be rapidly progressive and fatal. **Prompt diagnosis saves lives and relies on astute clinical assessment:**

- **A good history**
  - Residence or a recent visit (in the preceding 3 months) to a malaria endemic area
  - History of fever (may be paroxysmal in nature)
  - Recognise significance of non-specific clinical features such as vomiting, diarrhoea, headache, malaise
- **Physical examination**
  - Identify signs consistent with malaria: fever, pallor, jaundice, splenomegaly
  - Exclude other possible causes of fever (e.g. signs of viral and bacterial infections)

The diagnosis of malaria should be considered in any unwell person who has been in a malarious area recently

Investigations

Blood Film Examination

Thick and thin blood films (or “smears”) have remained the gold standard for the diagnosis of malaria. The films are stained and examined by microscopy.

Thick blood film - Used for detecting malaria: a larger volume of blood is examined allowing detection of even low levels of parasitaemia. Also used for determining parasite density and monitoring the response to treatment.

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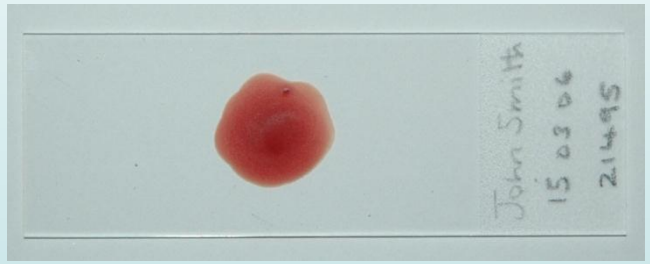

Thin blood film – Gives more information about the parasite morphology and, therefore, is used to identify the particular infecting species of Plasmodium.

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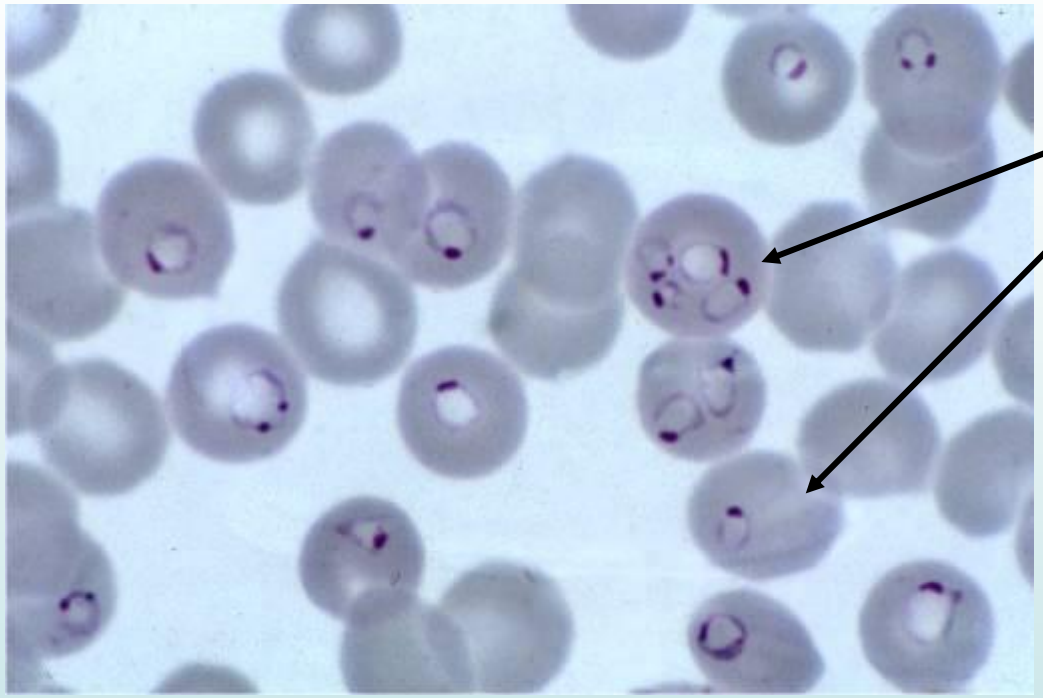
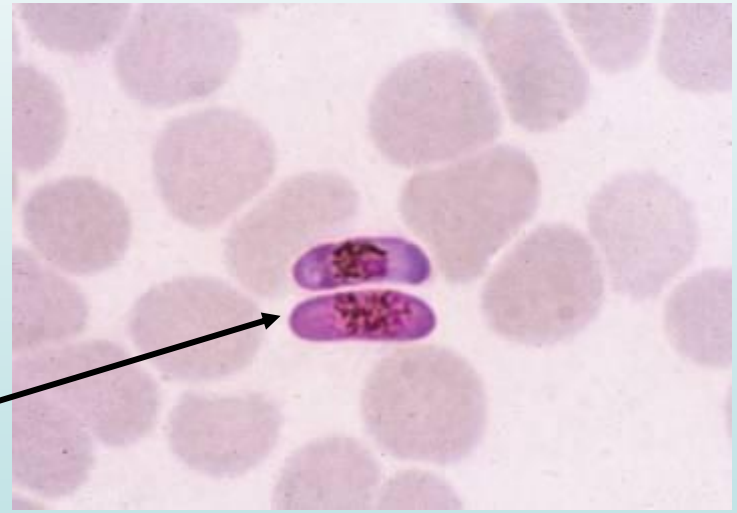
Appearance of *P. falciparum* in thin blood films



Ring forms or trophozoites; many red cells infected – some with more than one parasite



Gametocytes (sexual stages); After a blood meal, these forms will develop in the mosquito gut

http://phil.cdc.gov/phil/quicksearch.asp

Other methods of diagnosis of malaria

These are not routinely used in clinical practice. They include :

a) **Antigen capture kits**. Uses a dipstick and a finger prick blood sample. Rapid test - results are available in 10-15 minutes. Expensive and sensitivity drops with decreasing parasitaemia.

b) **PCR based techniques.** Detects DNA or mRNA sequences specific to Plasmodium. Sensitivity and specificity high but test is expensive, takes several hours and requires technical expertise.

c) **Fluorescent techniques.** Relatively low specificity and sensitivity. Cannot identify the parasite species. Expensive and requires skilled personnel.

d) **Serologic tests.** Based on immunofluorescence detection of antibodies against Plasmodium species. Useful for epidemiologic and not diagnostic purposes.

Malaria in pregnancy

More than 45 million women (30 million in Africa) become pregnant in malaria endemic areas each year.

Common adverse effects of malaria in pregnancy include:

- Maternal anaemia
- Stillbirths
- Premature delivery and intrauterine growth retardation result in the delivery of low birth weight infants

The WHO now recommends **intermittent preventive treatment (IPT):** the administration of anti-malarial drugs (e.g. sulphadoxine-pyrimethamine) during antenatal care whether or not women show symptoms. IPT has been shown to substantially reduce the risk of maternal anaemia in the mother and low birth weight in the newborn.

Previously, chemoprophylaxis (e.g. with chloroquine) was recommended for all women living in malaria endemic areas.

Source: http://phil.cdc.gov/phil/quicksearch.asp

Sources of information

- Malaria. Greenwood BM, Bojang K, Whitty CJ, Targett GA. Review; *Lancet* 2005; **365:**1487-98.
- http://mosquito.who.int/cmc_upload/0/000/015/372/RBMInfosheet_1.htm
  These WHO fact sheets developed by the Roll Back Malaria Partnership cover many different aspects of malaria – including prevention with insecticide-treated bed nets and treatment with atemesinin-based combination therapies
- http://www.cdc.gov/malaria/
  The US Centre for Disease Control and Prevention site for malaria
- http://www.malaria.org/
  Follow the “Learn about malaria” link on the Malaria Foundation’s website. This contains numerous useful and accessible resources.
- http://www.rph.wa.gov.au/labs/haem/malaria/
  An interactive resource from the Royal Perth Hospital, Western Australia. Contains useful self-assessment exercises in malaria diagnosis by microscopy that are set in the context of clinical cases.