

Malaria





Malaria parasites

- Malaria parasites are micro-organisms that belong to the genus *Plasmodium*.
- There are more than 100 species of *Plasmodium*, which can infect many animal species such as reptiles, birds, and various mammals.
- Only four species of *Plasmodium* infect humans in nature. (There are some other species which can, exceptionally or under experimental conditions, infect humans.)

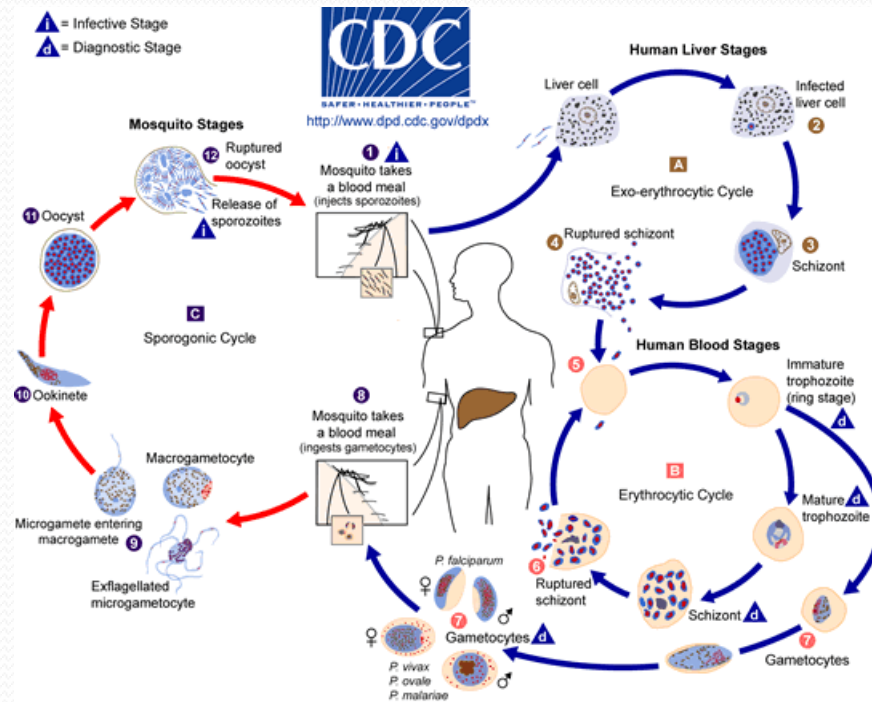
Malaria Parasites

- Four species of malaria parasites can infect humans under natural conditions: *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.
- The first two species cause the most infections worldwide. *Plasmodium falciparum* is the agent of severe, potentially fatal malaria, causing an estimated 700,000 - 2.7 million deaths annually, most of them in young children in Africa.
- *Plasmodium vivax* and *P. ovale* have dormant liver stage parasites ("hypnozoites") which can reactivate ("relapse") and cause malaria several months or years after the infecting mosquito bite.
- *Plasmodium malariae* produces long-lasting infections and if left untreated can persist asymptotically in the human host for years, even a lifetime.

Life Cycle of Malaria

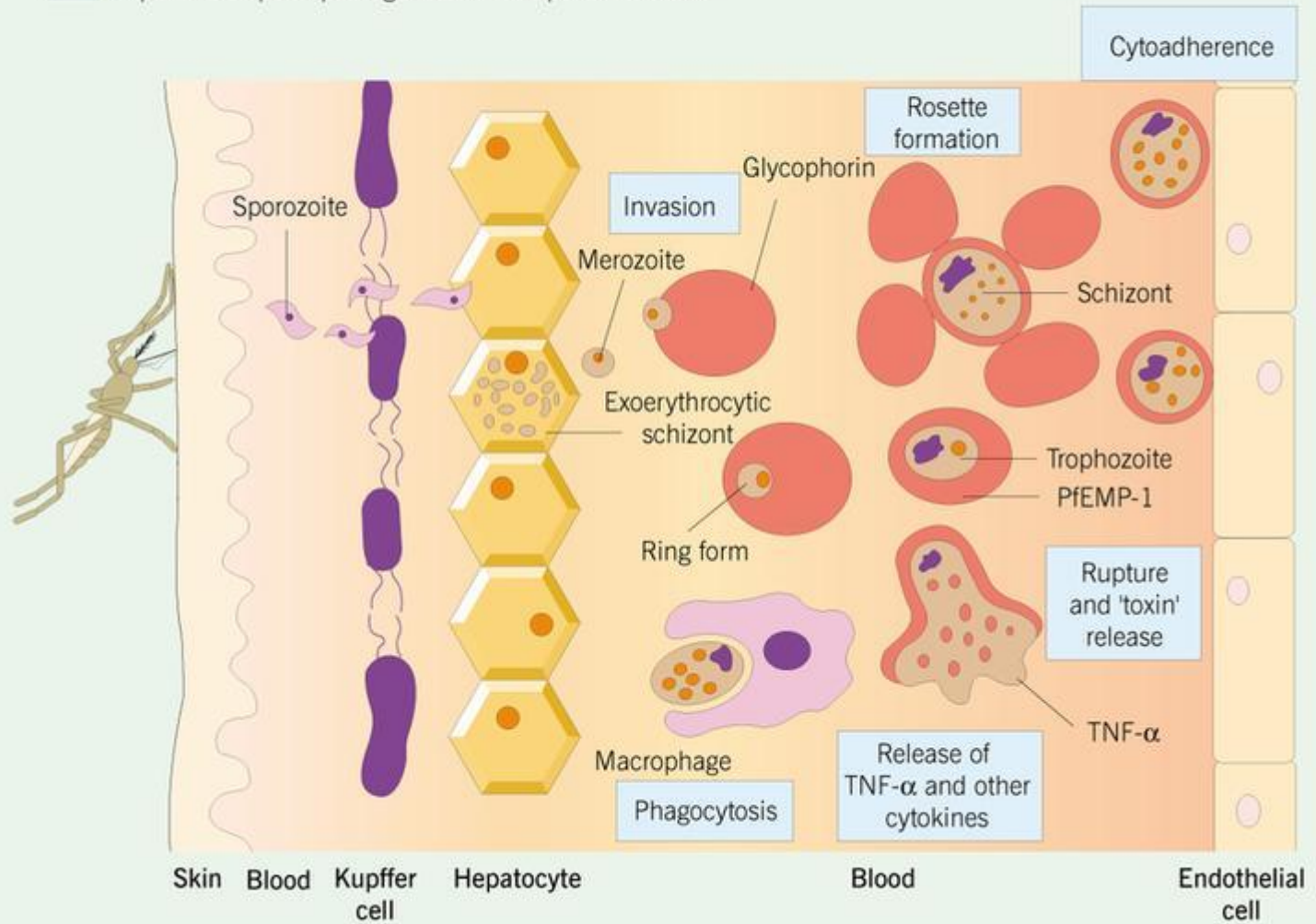
- In nature, malaria parasites spread by infecting successively two types of hosts: humans and female *Anopheles* mosquitoes. In humans, the parasites grow and multiply first in the liver cells and then in the red cells of the blood. In the blood, successive broods of parasites grow inside the red cells and destroy them, releasing daughter parasites ("merozoites") that continue the cycle by invading other red cells.
- The blood stage parasites are those that cause the symptoms of malaria. When certain forms of blood stage parasites ("gametocytes") are picked up by a female *Anopheles* mosquito during a blood meal, they start another, different cycle of growth and multiplication in the mosquito.
- After 10-18 days, the parasites are found (as "sporozoites") in the mosquito's salivary glands. When the *Anopheles* mosquito takes a blood meal on another human, the sporozoites are injected with the mosquito's saliva and start another human infection when they parasitize the liver cells.
- Thus the mosquito carries the disease from one human to another (acting as a "vector"). Differently from the human host, the mosquito vector does not suffer from the presence of the parasites.

Malaria life cycle

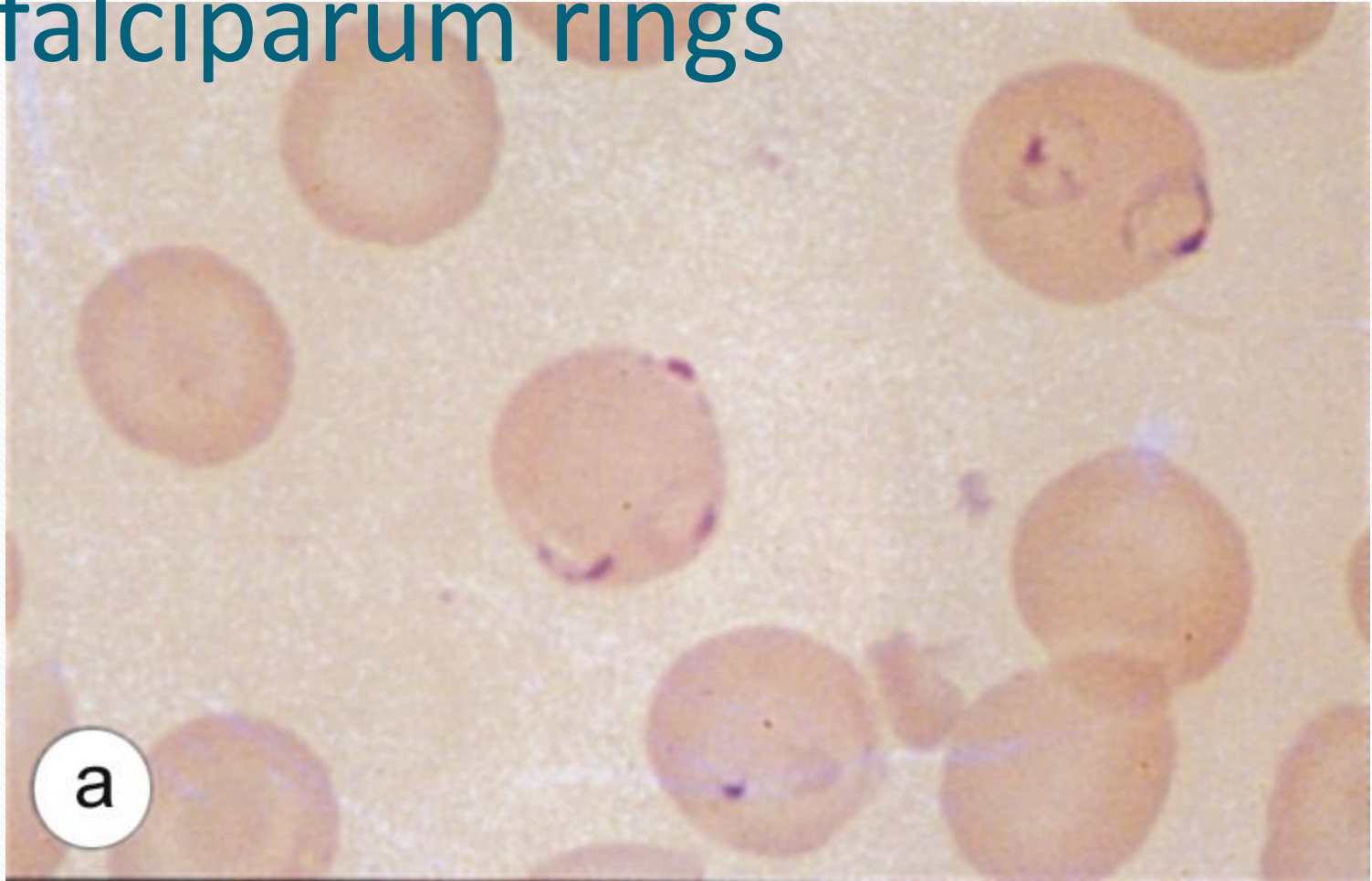


MAJOR CELL INTERACTIONS IN FALCIPARUM MALARIA

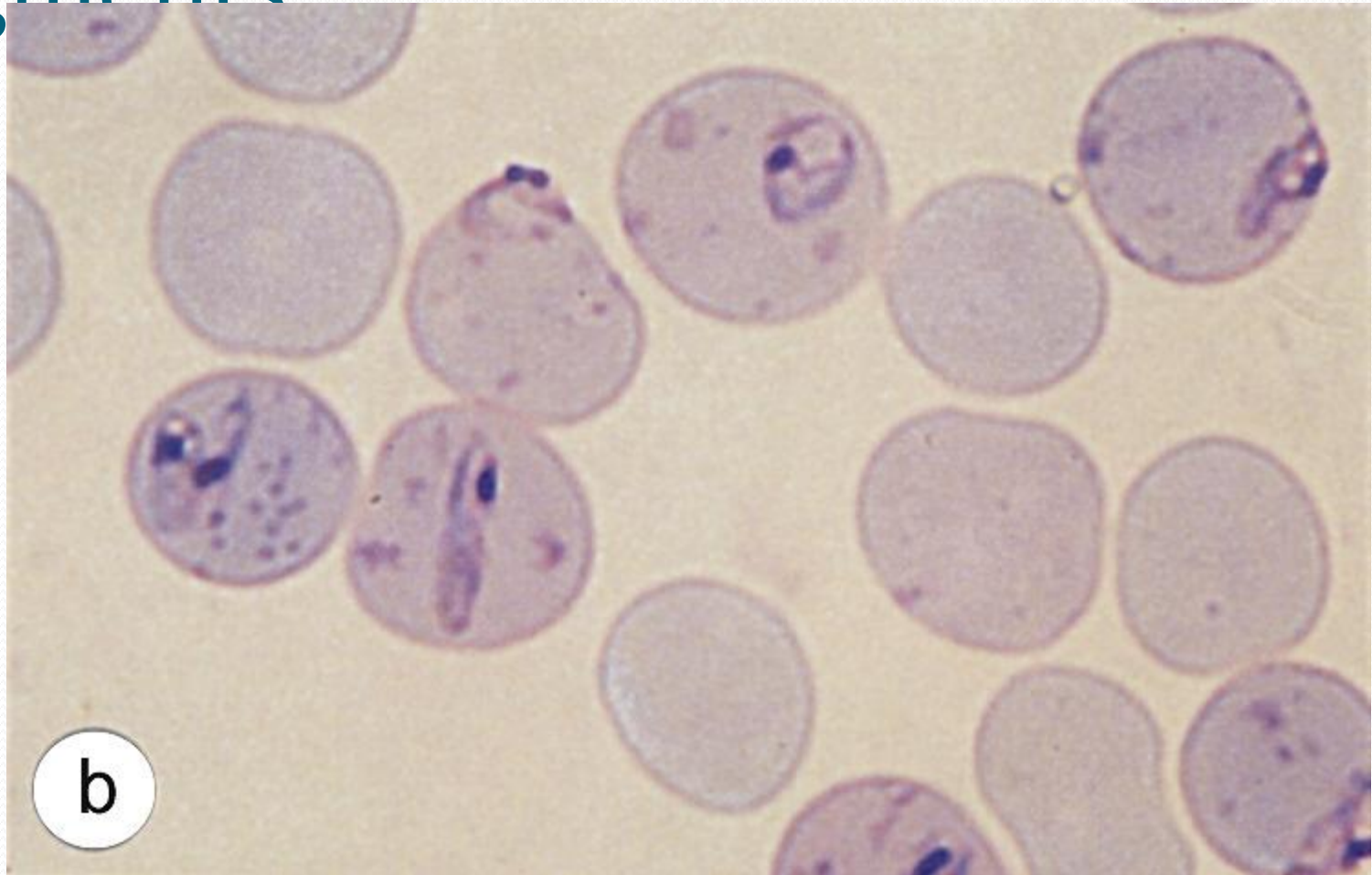
□ Important steps in pathogenesis of falciparum malaria



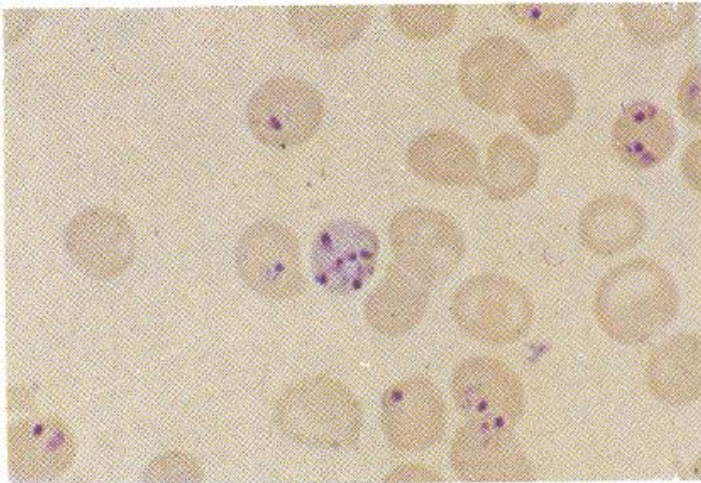
P. falciparum rings



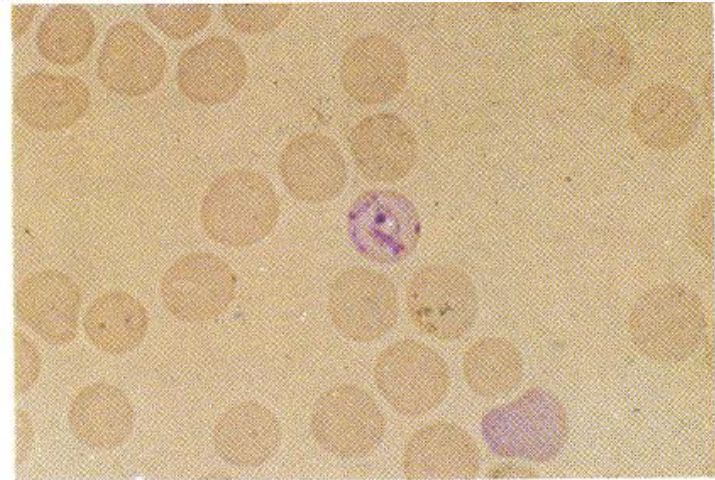
P. falciparum rings and Maurer pigments



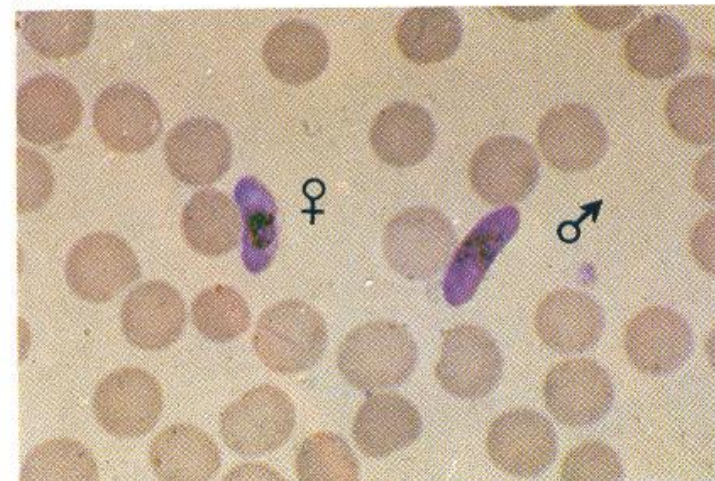
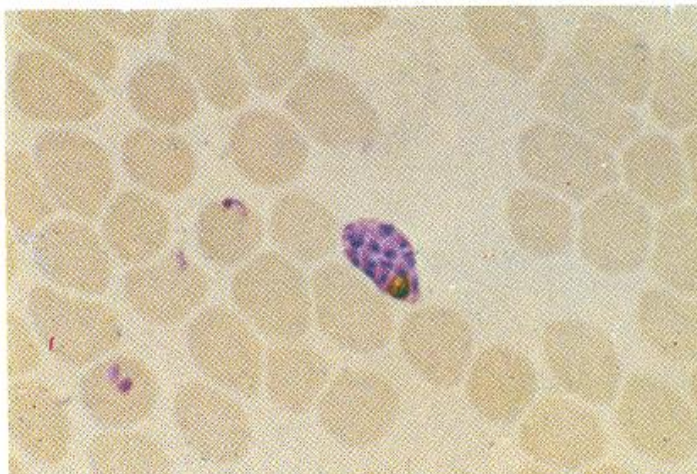
Different stages of malaria parasites, and gametocytes



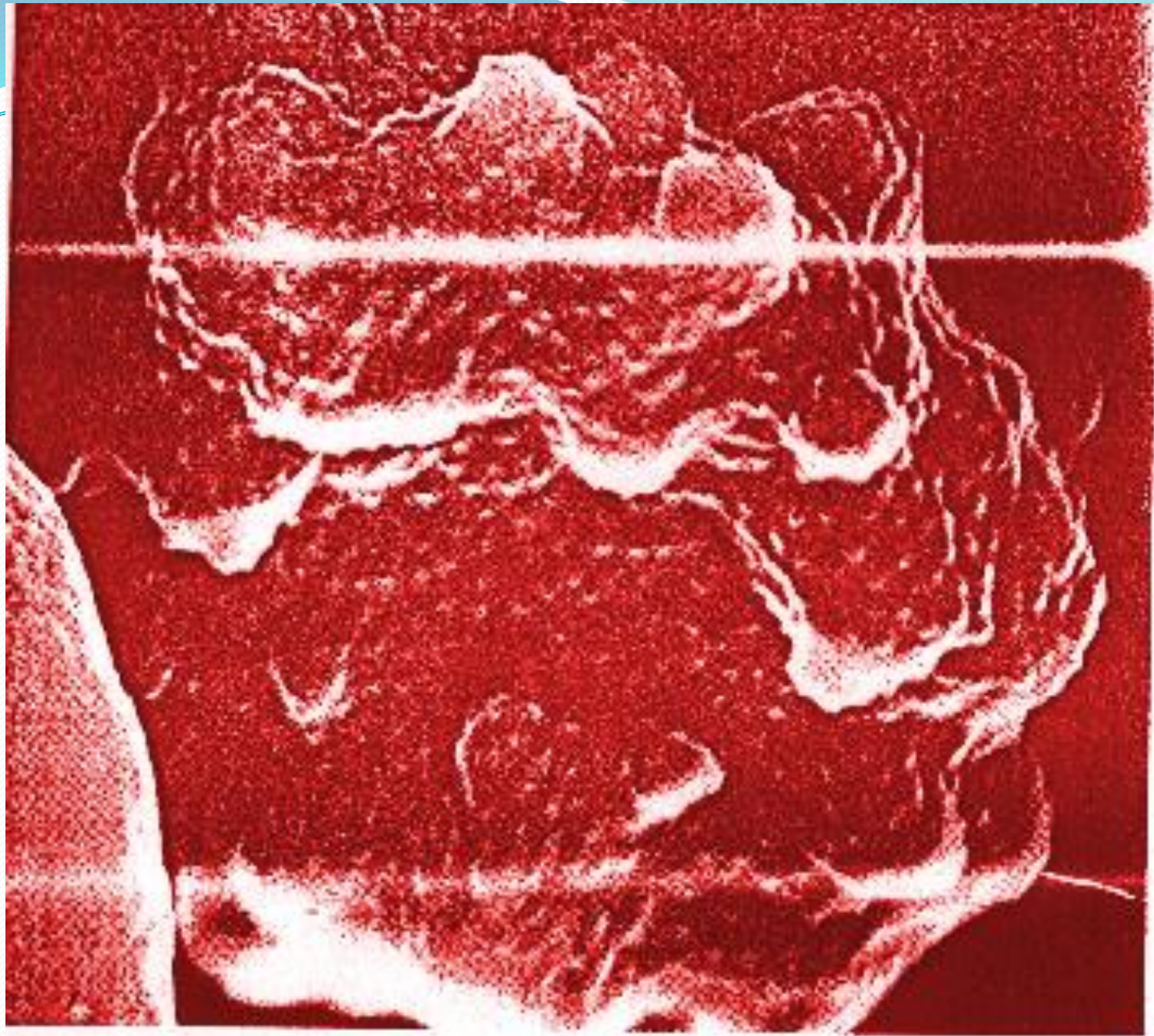
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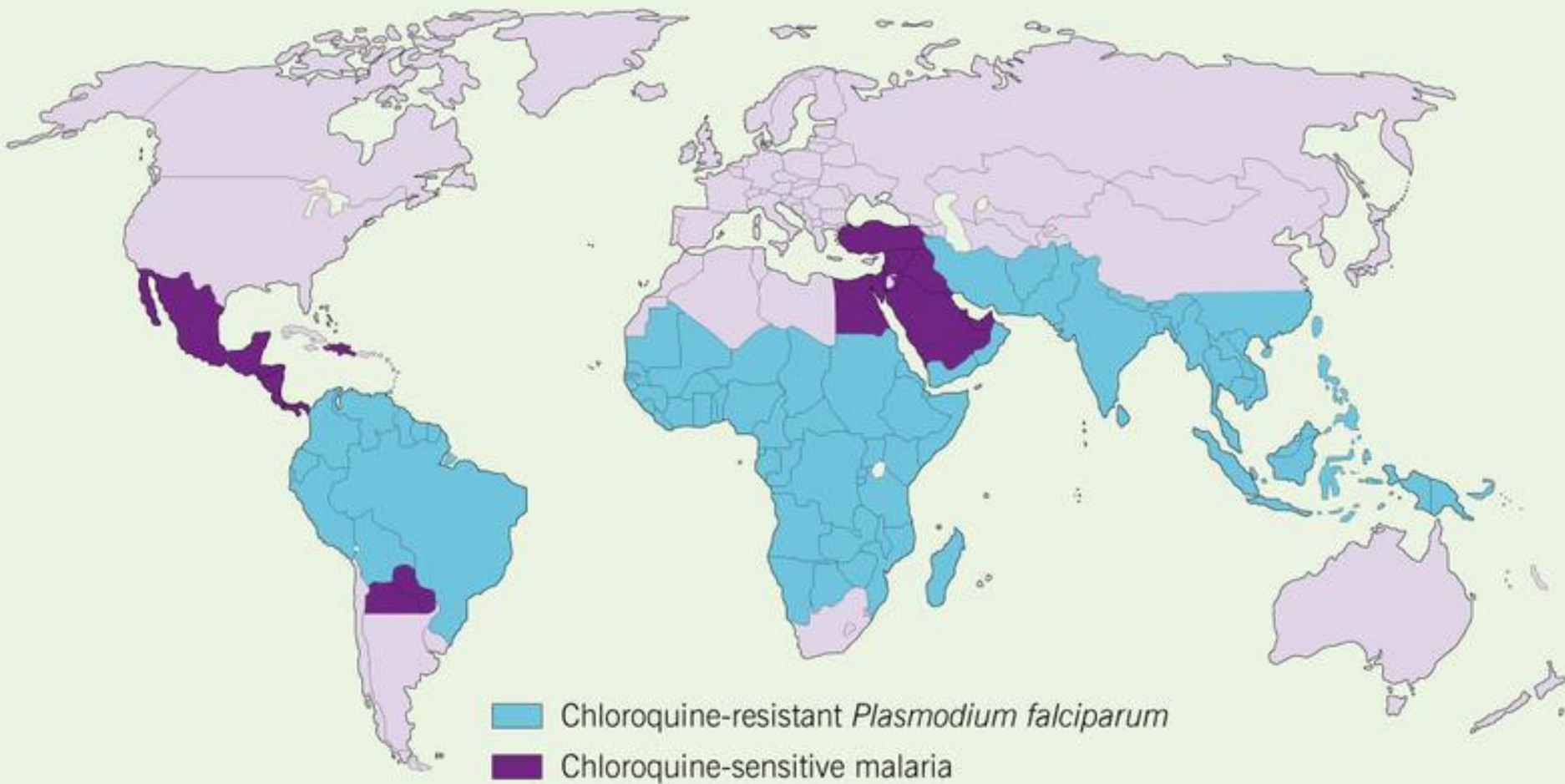
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DISTRIBUTION OF MALARIA AND CHLOROQUINE-RESISTANT *PLASMODIUM FALCIPARUM* (1996)



Incubation Period

- Following the infective bite by the *Anopheles mosquito*, a period of time (the "incubation period") goes by before the first symptoms appear.
- The incubation period in most cases varies from 7 to 30 days.
- The shorter periods are observed most frequently with *P. falciparum* and the longer ones with *P. malariae*.

Uncomplicated Malaria

- The classical (but rarely observed) malaria attack lasts 6-10 hours.
- It consists of:
 - a cold stage (sensation of cold, shivering)
 - a hot stage (fever, headaches, vomiting; seizures in young children)
 - and finally a sweating stage (sweats, return to normal temperature, tiredness)
- Classically (but infrequently observed) the attacks occur every second day with the "tertian" parasites (*P. falciparum*, *P. vivax*, and *P. ovale*) and every third day with the "quartan" parasite (*P. malariae*).

Major symptoms

- More commonly, the patient presents with a combination of the following symptoms:
 - Fever
 - Chills
 - Sweats
 - Headaches
 - Nausea and vomiting
 - Body aches
 - General malaise.
- In countries where cases of malaria are infrequent, these symptoms may be attributed to influenza, a cold, or other common infections, especially if malaria is not suspected.
- Conversely, in countries where malaria is frequent, residents often recognize the symptoms as malaria and treat themselves without seeking diagnostic confirmation ("presumptive treatment").

Physical findings

- Physical findings may include:
 - Elevated temperature
 - Perspiration
 - Weakness
 - Enlarged spleen.
- In *P. falciparum* malaria, additional findings may include:
 - Mild jaundice
 - Enlargement of the liver
 - Increased respiratory rate.

Severe Malaria

- Severe malaria occurs when *P. falciparum* infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. The manifestations of severe malaria include:
 - Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities
 - Severe anemia due to hemolysis (destruction of the red blood cells)
 - Hemoglobinuria (hemoglobin in the urine) due to hemolysis
 - Pulmonary edema (fluid buildup in the lungs) or acute respiratory distress syndrome (ARDS), which may occur even after the parasite counts have decreased in response to treatment
 - Abnormalities in blood coagulation and thrombocytopenia (decrease in blood platelets)
 - Cardiovascular collapse and shock

Other manifestations

- **Other Manifestations of Malaria**
- Neurologic defects may occasionally persist following cerebral malaria, especially in children. Such defects include troubles with movements (ataxia), palsies, speech difficulties, deafness, and blindness.
- Recurrent infections with *P. falciparum* may result in severe anemia. This occurs especially in young children in tropical Africa with frequent infections that are inadequately treated.
- **Malaria during pregnancy** (especially *P. falciparum*) may cause severe disease in the mother, and may lead to premature delivery or delivery of a low-birth-weight baby.
- On rare occasions, *P. vivax* malaria can cause rupture of the spleen or acute respiratory distress syndrome (ARDS).
- Nephrotic syndrome (a chronic, severe kidney disease) can result from chronic or repeated infections with *P. malaridae*.
- Hyperreactive malarial splenomegaly (also called "tropical splenomegaly syndrome") occurs infrequently and is attributed to an abnormal immune response to repeated malarial infections. The disease is marked by a very enlarged spleen and liver, abnormal immunologic findings, anemia, and a susceptibility to other infections (such as skin or respiratory infections).

Blackwater fever



Malaria Relapses

- In *P. vivax* and *P. ovale* infections, patients having recovered from the first episode of illness may suffer several additional attacks ("relapses") after months or even years without symptoms.
- Relapses occur because *P. vivax* and *P. ovale* have dormant liver stage parasites ("hypnozoites") that may reactivate.
- Treatment to reduce the chance of such relapses is available and should follow treatment of the first attack.

Diagnosis

- Diagnosis of malaria can be difficult:
- Where malaria is not endemic any more (such as the United States), health care providers are not familiar with the disease. Clinicians seeing a malaria patient may forget to consider malaria among the potential diagnoses and not order the needed diagnostic tests. Laboratorians may lack experience with malaria and fail to detect parasites when examining blood smears under the microscope.
- In some areas, malaria transmission is so intense that a large proportion of the population is infected but not made ill by the parasites. Such carriers have developed just enough immunity to protect them from malarial illness but not from malarial infection. In that situation, finding malaria parasites in an ill person does not necessarily mean that the illness is caused by the parasites.
- In many malaria-endemic countries, lack of resources is a major barrier to reliable and timely diagnosis. Health personnel are undertrained, underequipped and underpaid. They often face excessive patient loads, and must divide their attention between malaria and other equally severe infectious diseases such as pneumonia, diarrhea, tuberculosis and HIV/AIDS.

Microscopic Diagnosis

- Blood smear stained with Giemsa, showing a white blood cell (on left side) and several red blood cells, two of which are infected with *Plasmodium falciparum* (on right side).
- Malaria parasites can be identified by examining under the microscope a drop of the patient's blood, spread out as a "blood smear" on a microscope slide. Prior to examination, the specimen is stained (most often with the Giemsa stain) to give to the parasites a distinctive appearance.
- This technique remains the gold standard for laboratory confirmation of malaria.
- However, it depends on the quality of the reagents, of the microscope, and on the experience of the laboratorian.



Antigen detection, molecular diagnosis

- **Antigen Detection**

- Various test kits are available to detect antigens derived from malaria parasites. Such immunologic ("immunochromatographic") tests most often use a dipstick or cassette format, and provide results in 2-10 minutes. These "Rapid Diagnostic Tests" (RDTs) offer a useful alternative to microscopy in situations where reliable microscopic diagnosis is not available. Malaria RDTs are currently used in some clinical settings and programs. However, before malaria RDTs can be widely adopted, several issues remain to be addressed, including improving their accuracy; lowering their cost; and ensuring their adequate performance under adverse field conditions. Malaria RDTs are currently not approved by the U. S. Food and Drug Administration (FDA) for use in the United States. The World Health Organization's Regional Office for the Western Pacific (WHO/WPRO) provides technical information, including a list of commercially available malaria RDTs, at <http://www.wpro.who.int/rdt/>.

- **Molecular Diagnosis**

- Parasite nucleic acids are detected using polymerase chain reaction (PCR). This technique is more accurate than microscopy. However, it is expensive, and requires a specialized laboratory (even though technical advances will likely result in field-operated PCR machines).

- **Serology**

- Serology detects antibodies against malaria parasites, using either indirect immunofluorescence (IFA) or enzyme-linked immunosorbent assay (ELISA). Serology does not detect current infection but rather measures past experience.

"Presumptive Treatment"

- In highly endemic areas (particularly in Africa), the great prevalence of asymptomatic infections and lack of resources (such as microscopes and trained microscopists) have led peripheral health facilities to use "presumptive treatment".
- Patients who suffer from a fever that does not have any obvious cause are presumed to have malaria and are treated for that disease, based only on clinical suspicion, and without the benefit of laboratory confirmation.
- This practice is dictated by practical considerations and allows the treatment of a potentially fatal disease.
- But it also leads frequently to incorrect diagnoses and unnecessary use of antimalarial drugs.
- This results in additional expenses and increases the risk of selecting for drug-resistant parasites.

Clinical Diagnosis/ <i>Plasmodium</i> species	Region Infection Acquired	Recommended Drug and Adult Dose ^{1,7}	Recommended Drug and Pediatric Dose ^{1,7} <i>Pediatric dose should NEVER exceed adult dose</i>
Uncomplicated malaria/ <i>P. falciparum</i> or Species not identified	Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	Chloroquine phosphate (Aralen TM and generics) 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours Total dose: 1,500 mg base (=2,500 mg salt)	Chloroquine phosphate (Aralen TM and generics) 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours Total dose: 25 mg base/kg
If “species not identified” is subsequently diagnosed as <i>P. vivax</i> or <i>P. ovale</i> : see <i>P. vivax</i> and <i>P. ovale</i> (below) re. treatment with primaquine	Chloroquine-resistant or unknown resistance ¹ (All malarious regions except those specified as chloroquine-sensitive listed in the box above. Middle Eastern countries with chloroquine-resistant <i>P. falciparum</i> include Iran, Oman, Saudi Arabia, and Yemen. Of note, infections acquired in the Newly Independent States of the former Soviet Union and Korea to date have been uniformly caused by <i>P. vivax</i> and should therefore be treated as chloroquine-sensitive infections.)	A. Quinine sulfate ⁴ plus one of the following: Doxycycline, Tetracycline, or Clindamycin Quinine sulfate: 542 mg base (=650 mg salt) po tid x 3 to 7 days Doxycycline: 100 mg po bid x 7 days Tetracycline: 250 mg po qid x 7 days Clindamycin: 20 mg base/kg/day po divided tid x 7 days	A. Quinine sulfate ⁴ plus one of the following: Doxycycline ⁴ , Tetracycline ³ or Clindamycin Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 to 7 days Doxycycline: 4 mg/kg/day po divided bid x 7 days Tetracycline: 25 mg/kg/day po divided qid x 7 days Clindamycin: 20 mg base/kg/day po divided tid x 7 days
		B. Atovaquone-proguanil (Malarone TM) ⁴ Adult tab = 250 mg atovaquone/ 100 mg proguanil 4 adult tabs po qd x 3 days	B. Atovaquone-proguanil (Malarone TM) ⁴ Adult tab = 250 mg atovaquone/ 100 mg proguanil Peds tab = 62.5 mg atovaquone/ 25 mg proguanil 5 - 8kg: 2 peds tabs po qd x 3 d 9-10kg: 3 peds tabs po qd x 3 d 11-20kg: 1adult tab po qd x 3 d 21-30kg: 2 adult tabs po qd x 3d 31-40kg: 3 adult tabs po qd x 3d > 40 kg: 4 adult tabs po qd x 3d
		C. Mefloquine (Lariam TM and generics) ⁵ 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6-12 hours after initial dose Total dose= 1,250 mg salt	C. Mefloquine (Lariam TM and generics) ⁵ 13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6-12 hours after initial dose Total dose= 25 mg salt/kg
Uncomplicated malaria/ <i>P. malariae</i>	All regions	Chloroquine phosphate: Treatment as above	Chloroquine phosphate: Treatment as above

Antimalarial Drug Information

- Travelers to areas with malaria risk in Africa, South America, the Indian Subcontinent, Tajikistan, Asia, and the South Pacific should take one of the following antimalarial drugs (listed alphabetically):
 - **atovaquone/proguanil**
 - **doxycycline**
 - **mefloquine**
 - **primaquine (in special circumstances).**

Table 2. Drugs Used for The Prophylaxis of Malaria

Drug	Adult dosage	Pediatric dosage
Mefloquine (Lariam)R	228 mg base (250 mg salt) orally, once/week	15-19 kg: 1/4 tab/week 20-30 kg: 1/2 tab week 31-45 kg: 3/4 tab week > 45 kg: 1 tab/week
Doxycycline	100 mg orally, once daily	> 8 years of age: 2 mg/kg orally, once daily up to adult dose of 100 mg/day
Chloroquine phosphate (Aralen)R	300 mg/base (500 mg salt) orally, once/week	5 mg/kg base (6.3 mg/kg salt) orally, once/week up to maximum adult dose of 300 mg base
Hydroxychloroquine sulfate (Plaquenil)R	310 mg/base (400 mg salt) orally, once/week	5 mg/kg base (6.5 mg/kg salt) orally, once/week up to maximum adult dose of 310 mg base
Proguanil (Paludrine)R	200 mg orally, once/day in combination with weekly chloroquine	< 2 years: 50 mg/day 2-6 years: 100 mg/day 7-10 years: 150 mg/day > 10 years: 200 mg/day
Primaquine	15 mg base (26.3 mg salt) orally, once/day for 14 days	0.3 mg/kg base (0.5 g/kg salt) orally, once/day for 14 days