INTERNATIONAL SCHOOL OF MEDICINE

Department of Infectious Diseases

Malaria

(Febris intermittens)

Prepared by Professor Kutmanova A.Z.

Overview

- Introduction
- Etiology, epidemiology
- Pathogenesis
- Clinical features
- Complications
- Diagnosis
- Treatment
- Prevention

World Health Organization

- Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected female *Anopheles* mosquitoes.

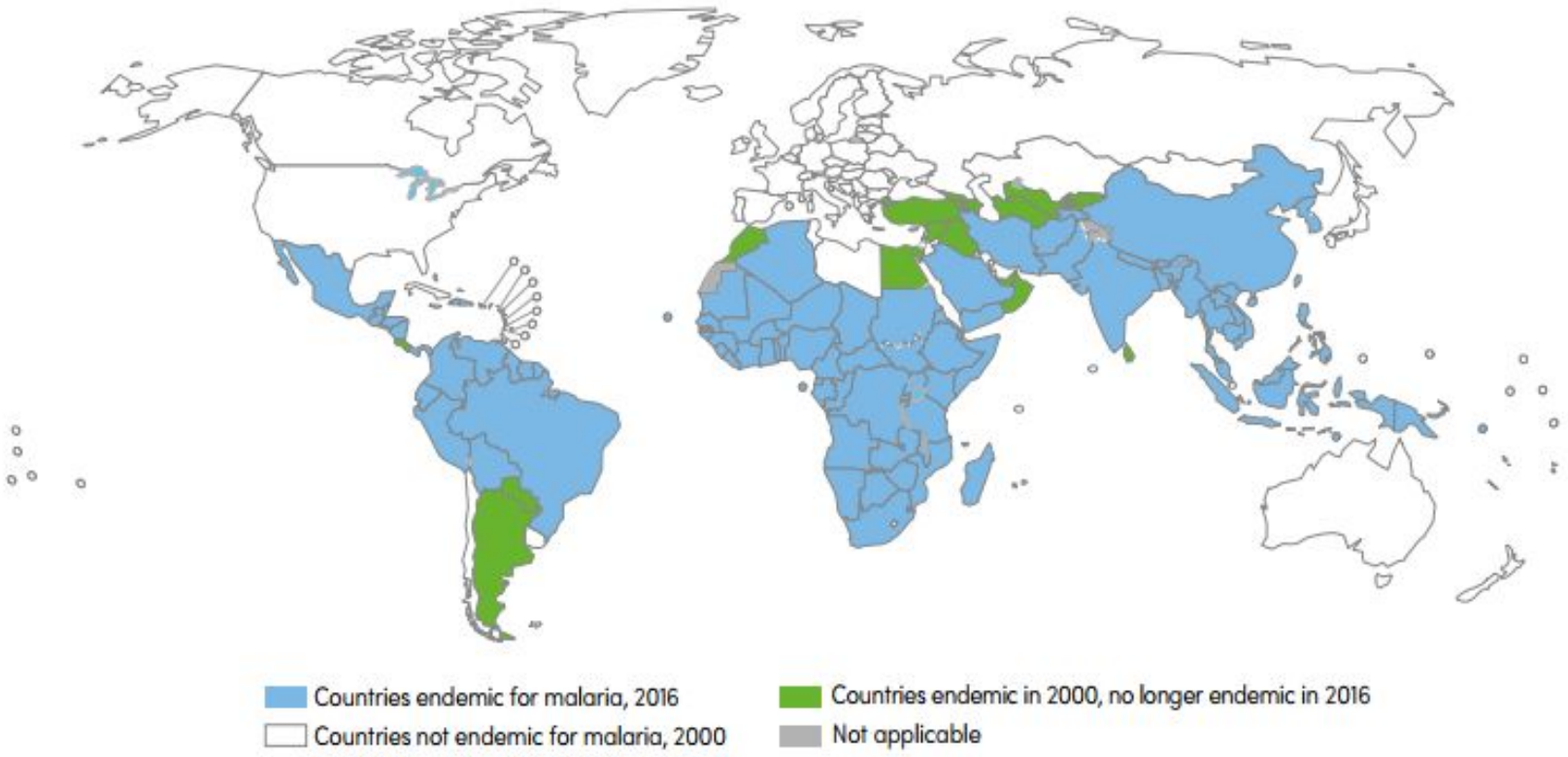
- In 2015, 91 countries and areas had ongoing malaria transmission.

- Malaria is preventable and curable, and increased efforts are dramatically reducing the malaria burden in many places.

- Between 2010 and 2015, malaria incidence among populations at risk (the rate of new cases) fell by 21% globally. In that same period, malaria mortality rates among populations at risk fell by 29% globally among all age groups, and by 35% among children under 5.

- The WHO African Region carries a disproportionately high share of the global malaria burden. In 2015, the region was home to 90% of malaria cases and 92% of malaria deaths.

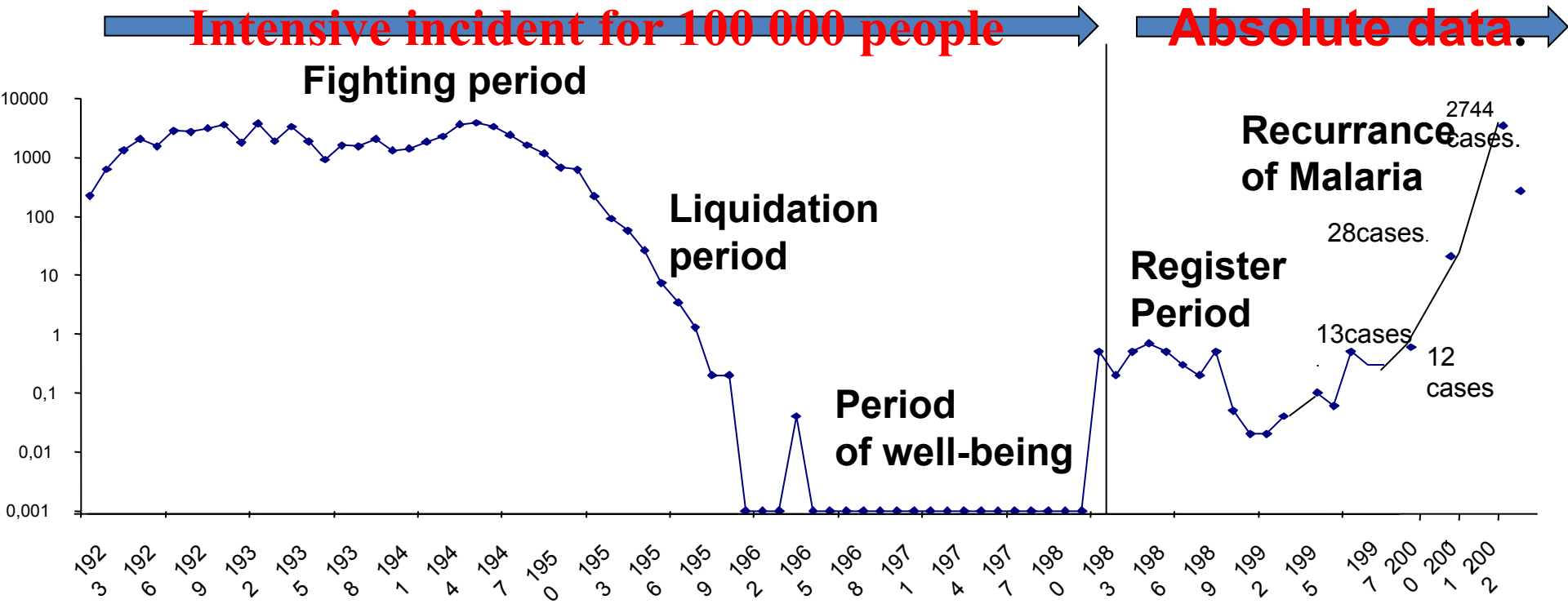
Figure 1.1 Countries endemic for malaria in 2000 and 2016. Countries with 3 consecutive years of zero indigenous cases are considered to have eliminated malaria. No country in the WHO European region reported indigenous cases in 2015 but Tajikistan has not yet had 3 consecutive years of zero indigenous cases, its last case being reported in July 2014. Source: WHO database



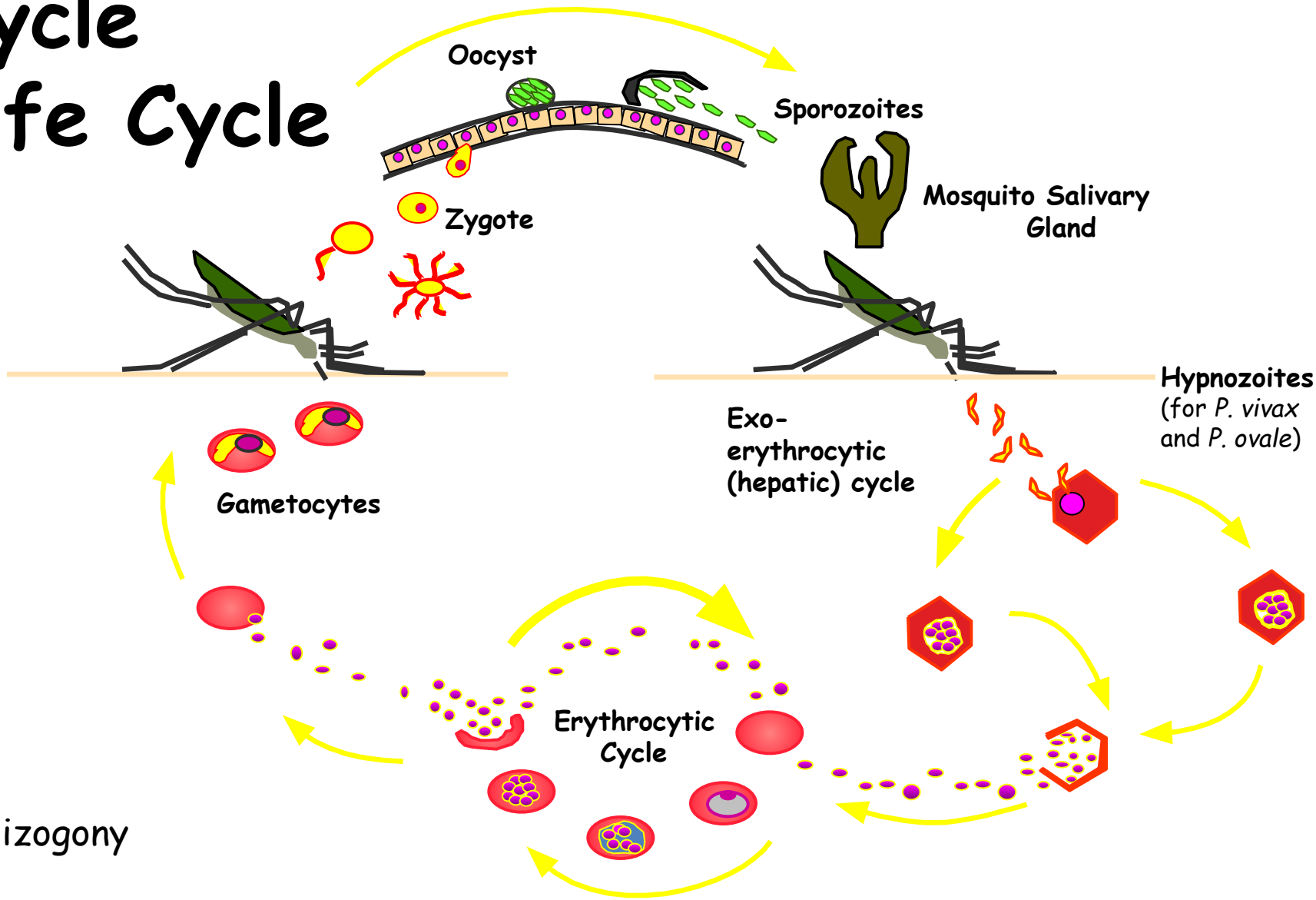
World Health Organization

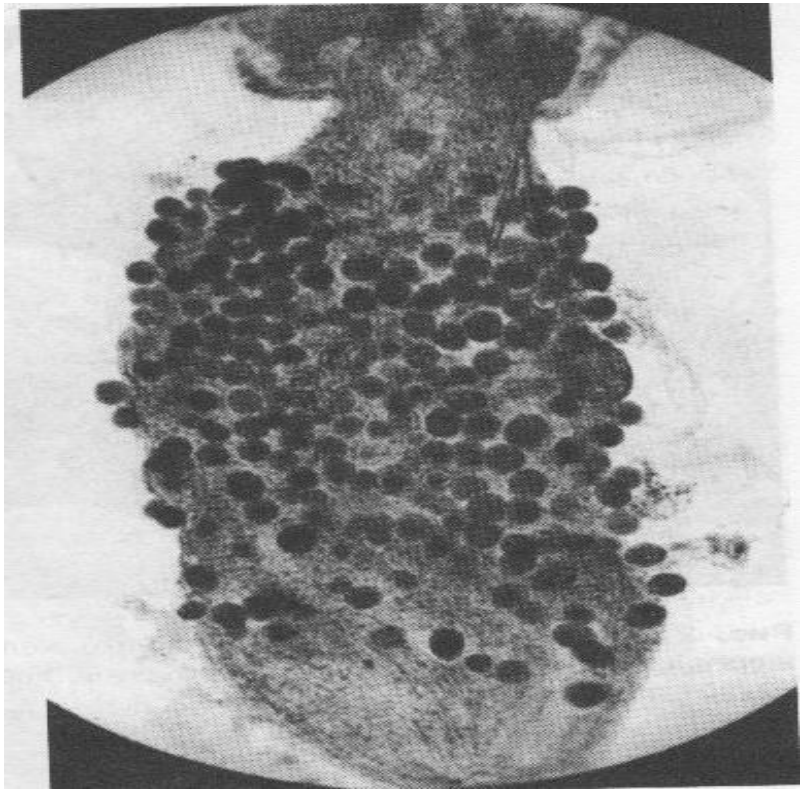
Kyrgyzstan receives WHO certification of malaria elimination

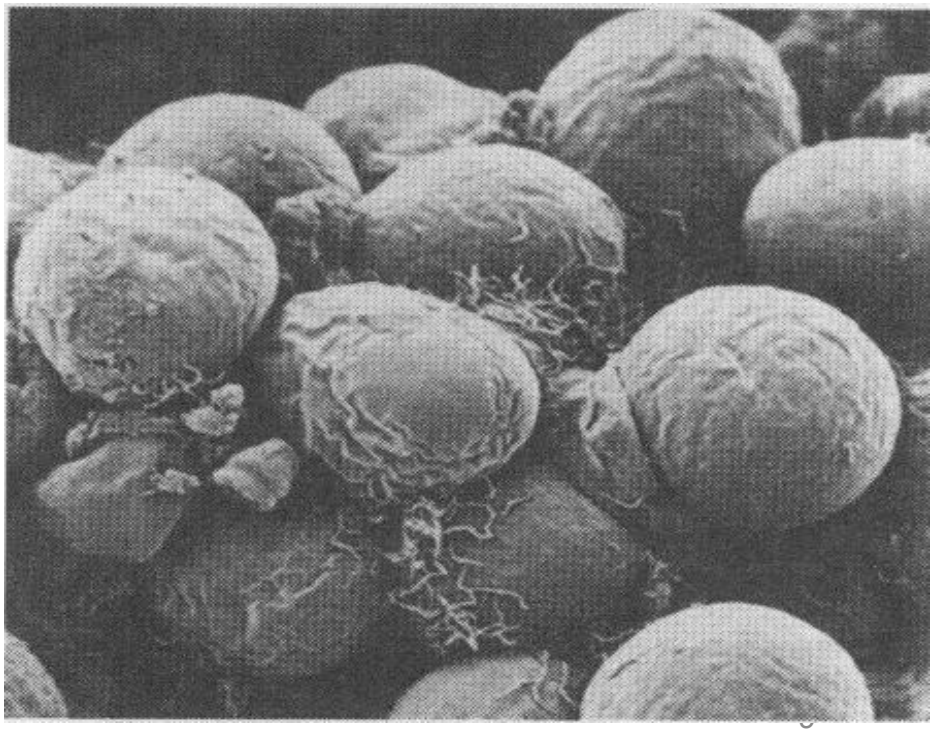
Malaria in Kyrgyzstan in 1923-2002



Malaria Life Cycle
Life Cycle



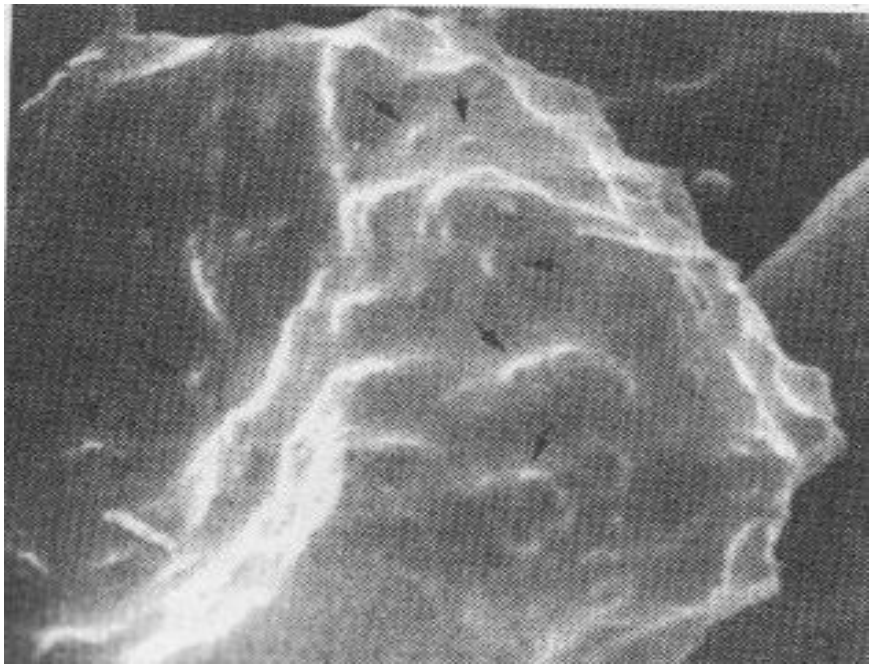


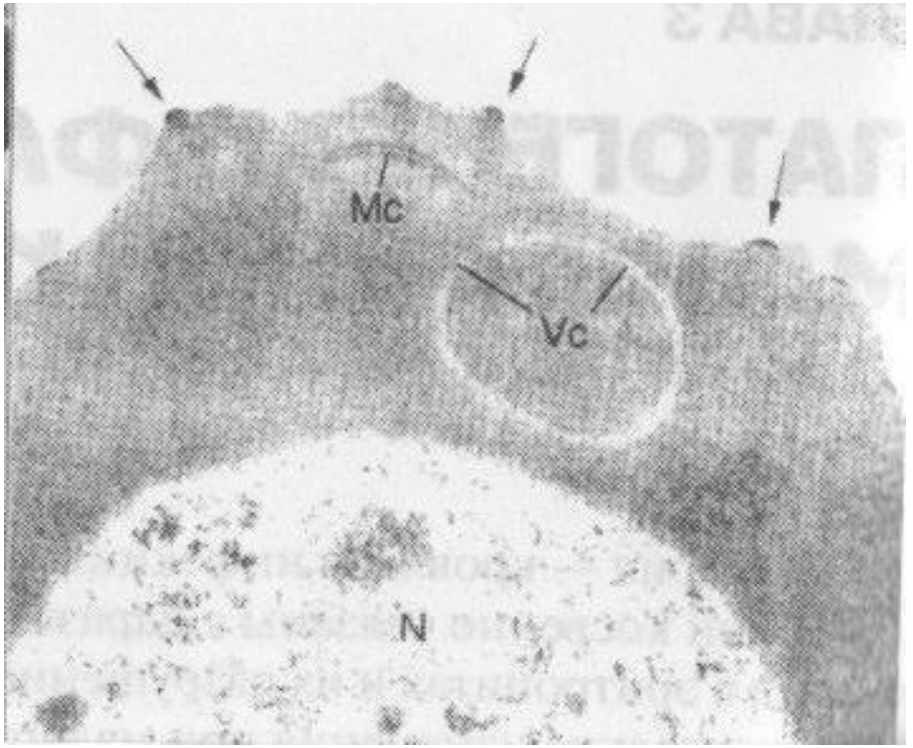


Plasmodium spp. (Malaria)

Pathology and clinical significance:

- When merozoits invade the blood cells, using hemoglobin as a nutrient, eventually, the infected red cells rupture, releasing merozoits that can invade other erythrocytes. If a large numbers of red cells rupture at roughly the same time, a paroxysm (sudden onset) of fever can result from the massive release of toxic substance.
- ***Plasmodium falciparum*** is the most dangerous species.
- ***P. malriae, P. vivax,*** **and** ***P. ovale*** cause milder form of the disease, probably because they invade either young or old red cells, but not both. This is in contrast to *P. falciparum*, which invades cells of all ages.
- *Plasmodium falciparum* is characterized by persistent high fever and orthostatic hypertension. Infection can lead to capillary obstruction and death if treatment is not introduced.




Mc
Vc
N

Clinical presentation

- Early symptoms
  - Headache
  - Malaise
  - Fatigue
  - Nausea
  - Muscular pains
  - Slight diarrhea
  - Slight fever, usually not intermittent
- Could mistake for influenza or gastrointestinal infection

Malarial Paroxysm

- **Prodrome** 2-3 days before
  - Malaise, fever,fatigue, muscle pains, nausea, anorexia
  - Can mistake for influenza or gastrointestinal infection
  - Slight fever may worsen just prior to paroxysm
- **Paroxysm**
  - Cold stage - rigors
  - Hot stage – Max temp can reach 40-41^{o} C, splenomegaly easily palpable
  - Sweating stage
  - Lasts 8-12 hours, start between midnight and midday

Types of Infections

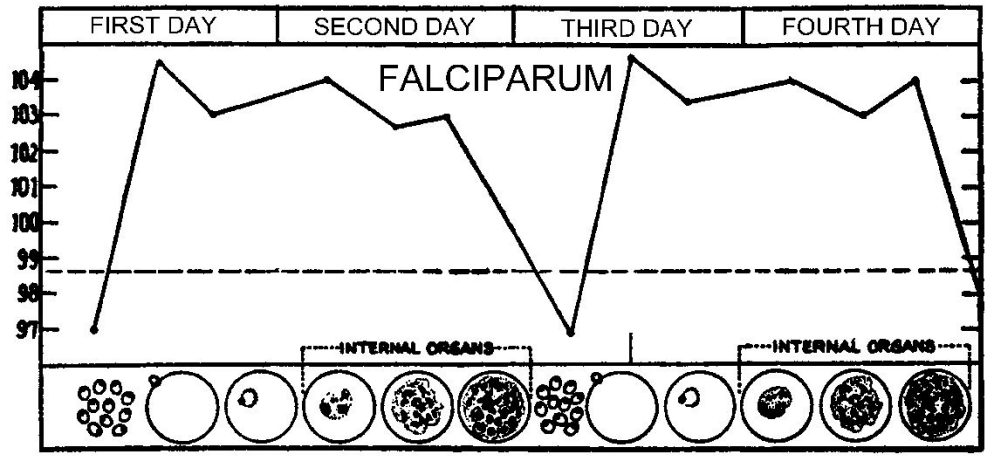
- **Recrudescence**
  - exacerbation of persistent undetectable parasitemia, due to survival of erythrocytic forms, no exo-erythrocytic cycle (*P.f., P.m.*)
- **Relapse**
  - reactivation of hypnozoites forms of parasite in liver, separate from previous infection with same species (*P.v. and P.o.*)
- **Recurrence or reinfection**
  - exo-erythrocytic forms infect erythrocytes, separate from previous infection (all species)
- Can not always differentiate recrudescence from reinfection

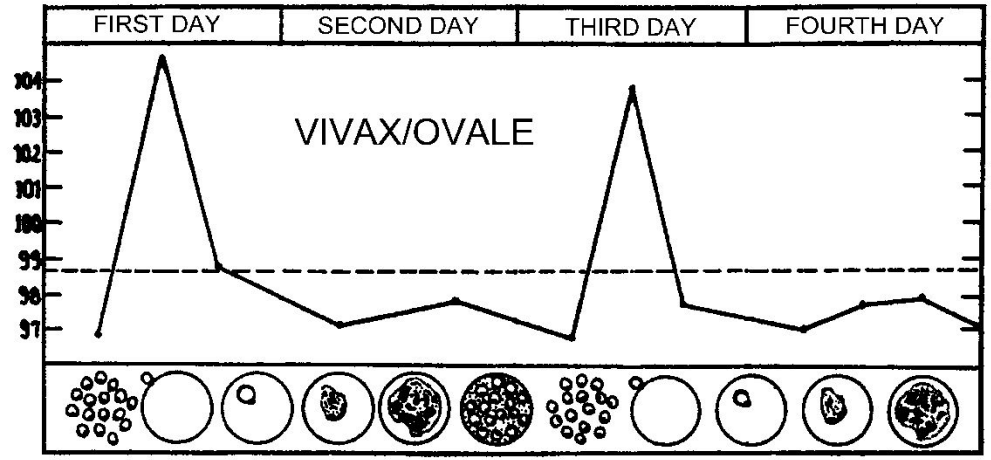
Clinical presentation

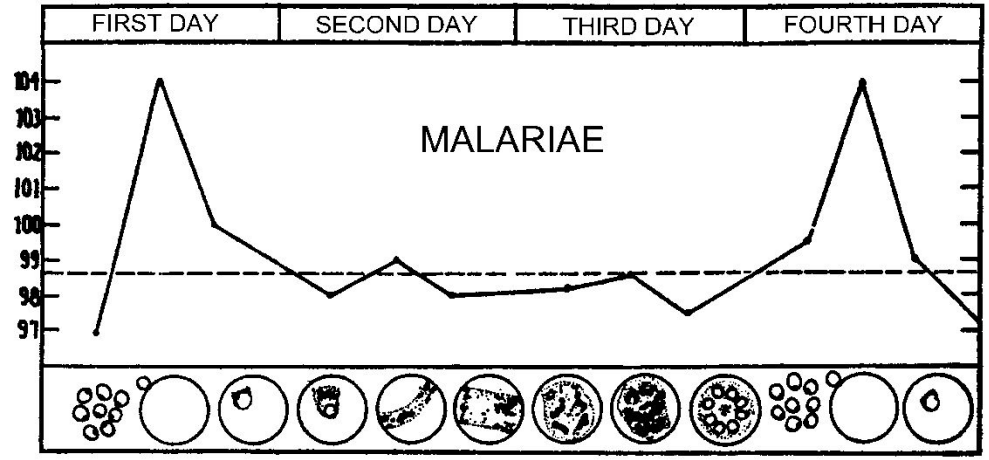
- Varies in severity and course
- Parasite factors
  - Species and strain of parasite
  - Geographic origin of parasite
  - Size of inoculum of parasite
- Host factors
  - Age
  - Immune status
  - General health condition and nutritional status
  - Chemoprophylaxis or chemotherapy use
- Mode of transmission
  - Mosquito
  - Bloodborne, no hepatic phase (transplacental, needlestick, transfusion, organ donation/transplant)

Malarial Paroxysm

- Periodicity
  - Days 1 and 3 for *P.v.*, *P.o.*, (and *P.f.)* - tertian
  - Usually persistent fever or daily paroxyms for *P.f.*
  - Days 1 and 4 for *P.m.* - quartian







Malaria Paroxysm

- **paroxysms associated with synchrony of merozoite release**
- **between paroxysms temper-ature is normal and patient feels well**
- **falciparum may not exhibit classic paroxysms (continuous fever)**

tertian malaria
quartan malaria

Presentation of P.vivax

- Most people of West African descent are resistant to *P.v.*
  - Lack Duffy blood group antigens needed for RBC invasion
- Mild – severe anemia, thrombocytopenia, mild jaundice, tender hepatosplenomegaly
- Splenic rupture carries high mortality
- Headache, dizziness, muscle pain, malaise, anorexia, nausea, vague abdominal pain, vomiting
- Fever constant or remittent

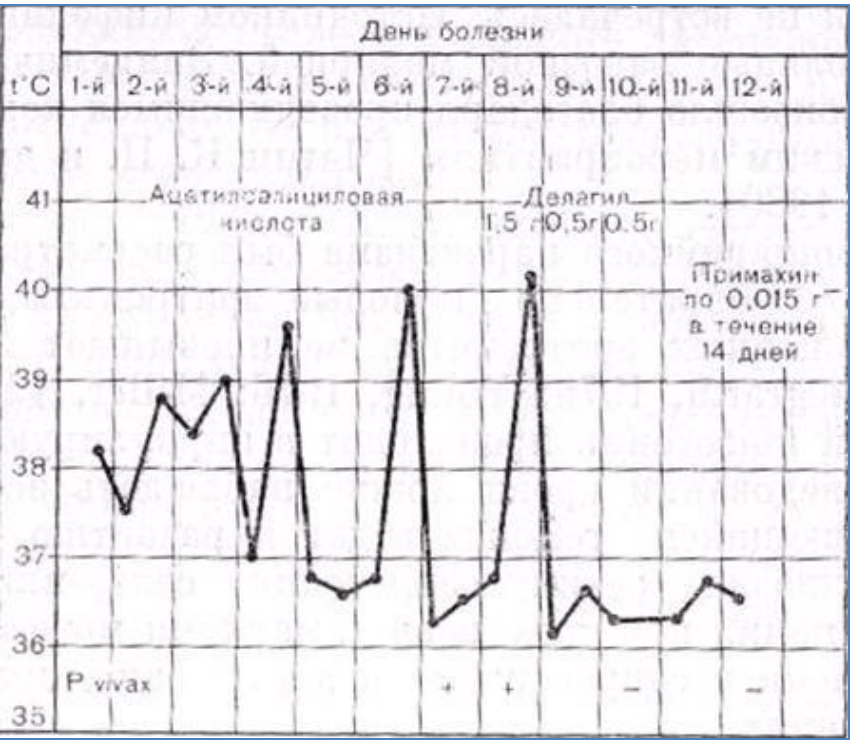
Presentation of P.vivax

- **Incubation period** in non-immunes 12-17 days but can be 8-9 months or longer
- Some strains from temperate zones show longer incubation periods, 250-637 days
- First presentation of imported cases – 1 month – over 1 year post return from endemic area
- **Relapses**
  - 60% untreated or inadequately treated will relapse
  - Time from primary infection to relapse varies by strain
  - Treat blood stages as well as give terminal prophylaxis for hypnozoites

Presentation of P.falciparum

- Lack classical paroxysm followed by asymptomatic period
- Headache, dizziness, muscle pain, malaise, anorexia, nausea, vague abdominal pain, vomiting
- Fever constant or remittent
- Postural hypotension, jaundice, tender hepatosplenomegaly
- Can progress to severe malaria rapidly in non-immune patients
- Cerebral malaria can occur
- Parasites can sequester in tissues, not detected on peripheral smear

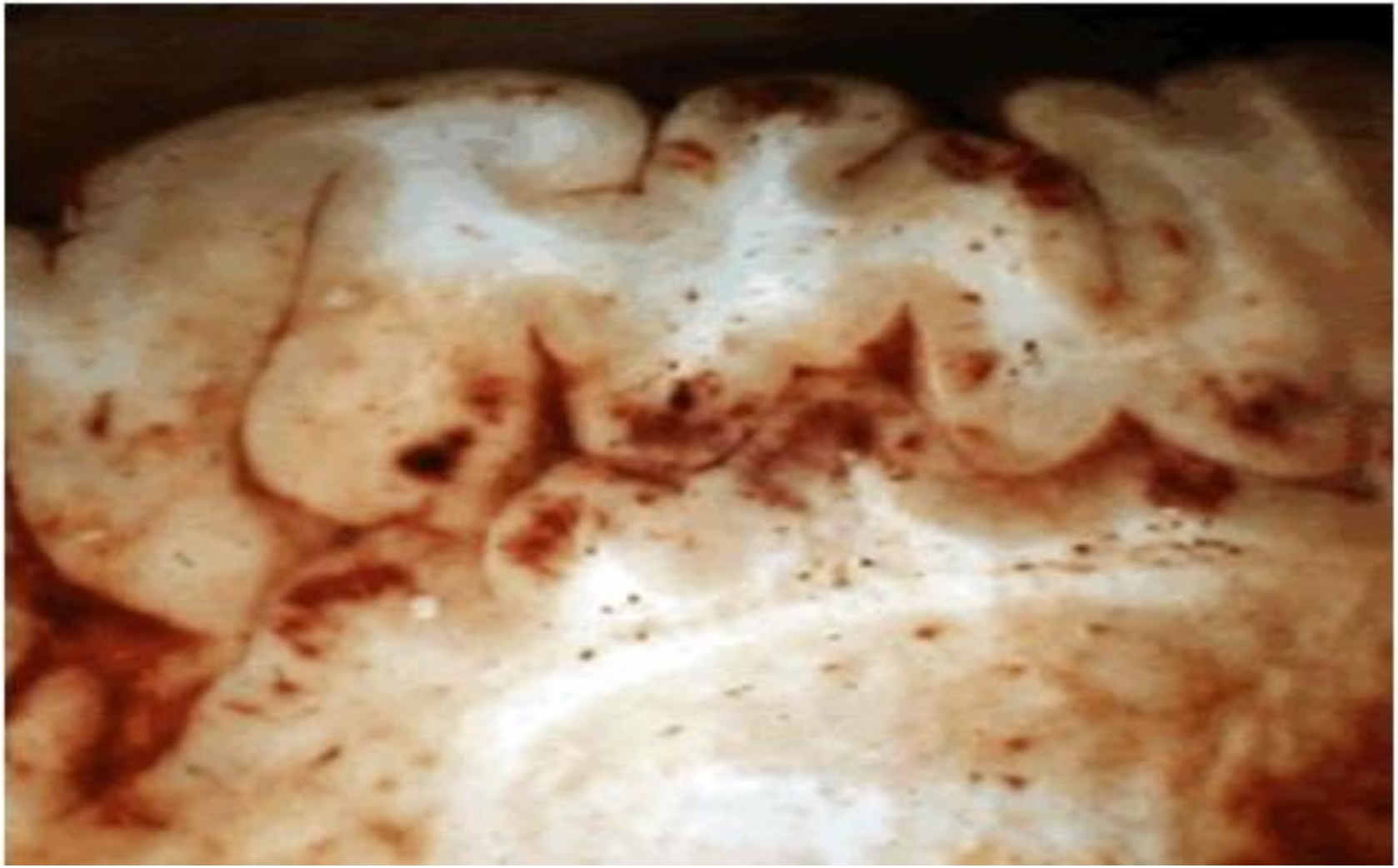
Temperature curves



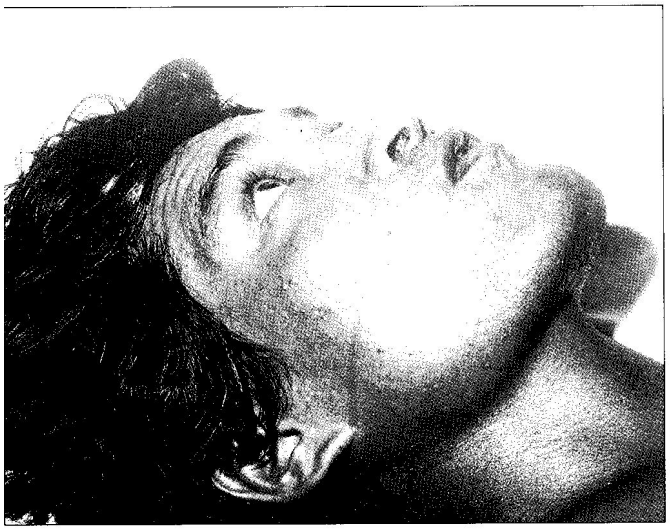
Complication:

- **Coma** - brain edema, disturbance of microcirculation, "sludge" - the aggregates of red blood cells, glued together with fibrin, sealed terminal vessels
- **Acute renal failure** - a violation of the micro-circulation, malarial hemoglobinuria, deficiency of erythrocyte glucose-6-phosphate dehydrogenase
- **Acute pulmonary oedema** - disruption of the microcirculation of cell membranes and capillaries in combination with heart failure
- **Acute adrenal insufficiency** (syndrome Waterhouse – Fridrichsen)

Pathology of the brain in malaria falciparum



Coma



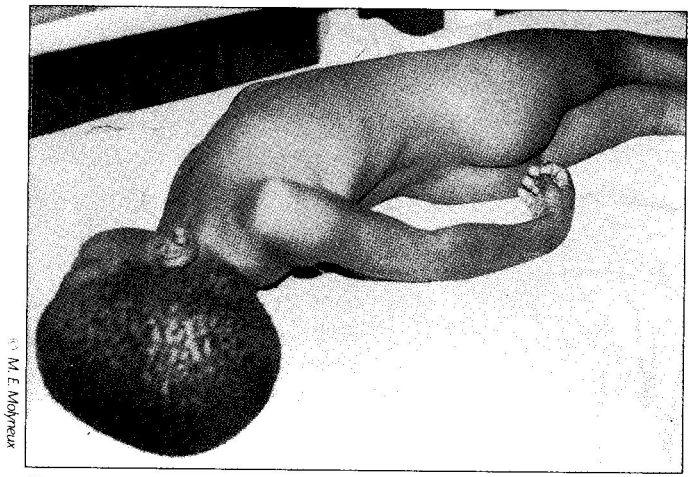
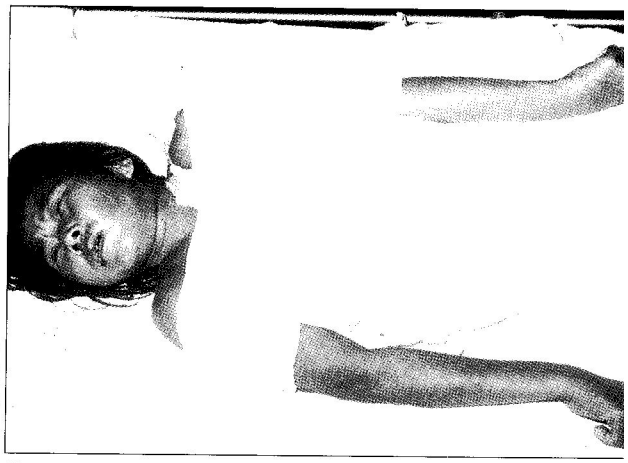
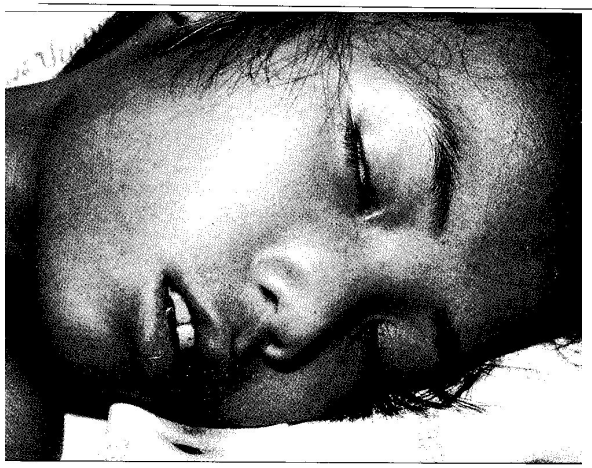


Fig. 7. Opisthotonos in an unrousably comatose child with cerebral malaria. The cerebrospinal fluid cell count was normal

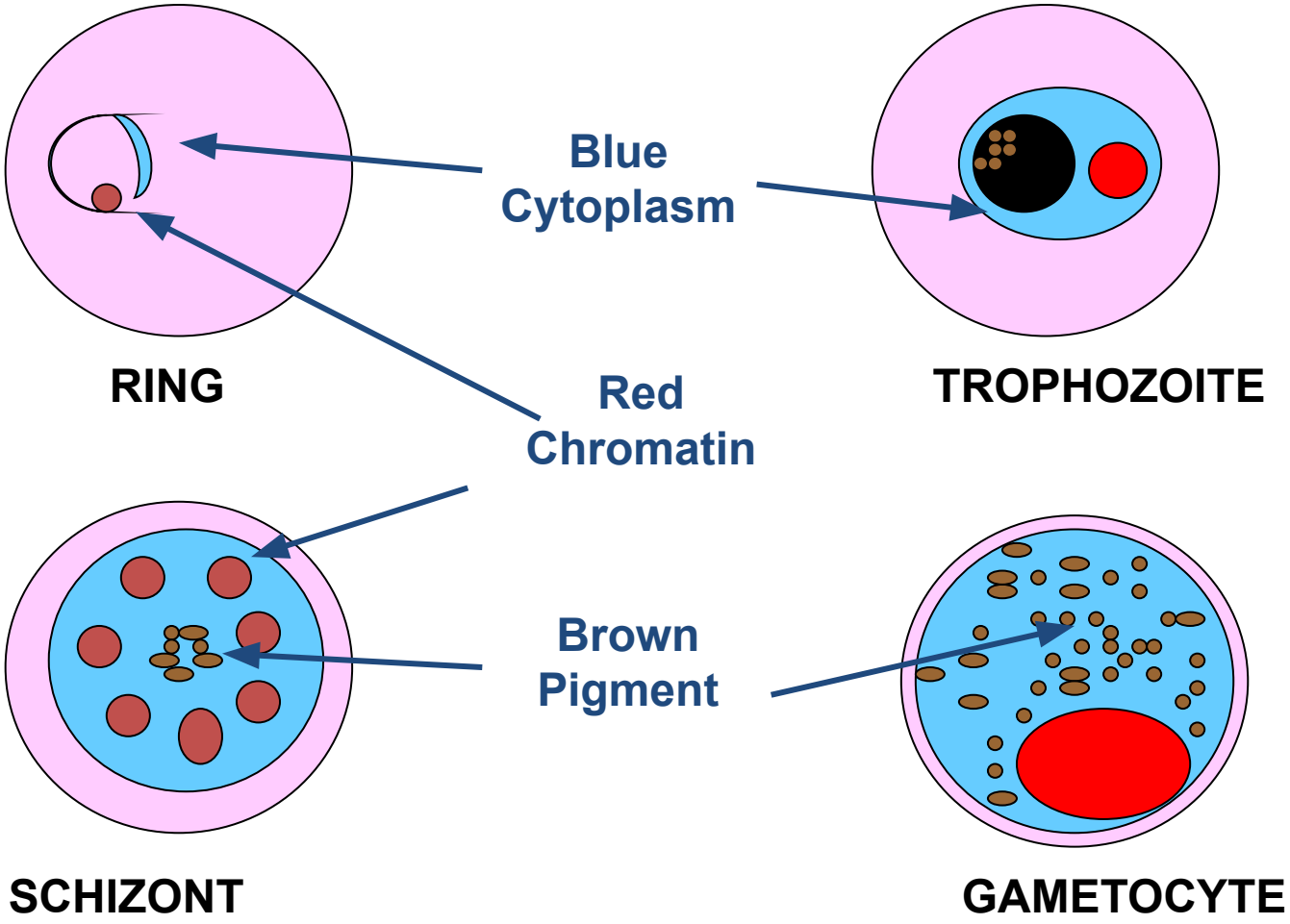




Malaria in pregnant women

- Abortion
- Premature births
- Neonatal complications
- Deaths.
- Often develop severe anemia.
- Often observed the birth of premature infants and cases of stillbirth

Recognizing Erythrocytic Stages:
Schematic Morphology



Parasitemia and clinical correlates

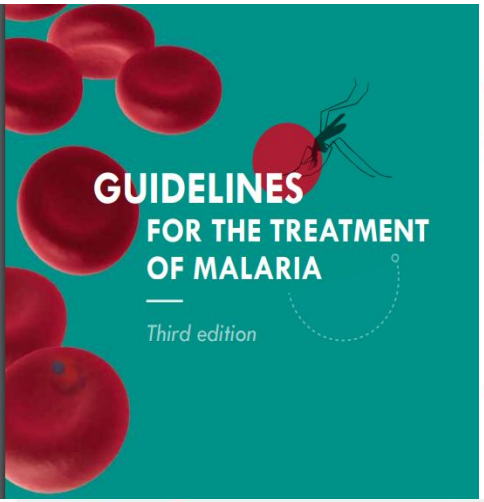
Parasitemia	**Parasites /µl**	**Remarks**
0.0001-0.0004%	5-20	Sensitivity of thick blood film
0.002%	100	Patients may have symptoms below this level, where malaria is seasonal
0.2%	10,000	Level above which immunes show symptoms
2%	100,000	Maximum parasitemia of *P.v.* and *P.o.*

Parasitemia and clinical correlates

Parasitemia	Parasites/µl	Remarks
2-5%	100,000-250,00	Hyperparasitemia/severe malaria*, increased mortality
10%	500,000	Exchange transfusion may be considered/ high mortality

*WHO criteria for severe malaria are parasitemia > 10,000 /µl and severe anemia (haemaglobin < 5 g/l).
Prognosis is poor if > 20% parasites are pigment containing trophozoites and schizonts (more mature forms) and/or if > 5% of neutrophils contain visible pigment.

Hänscheid T. (1999) Diagnosis of malaria: a review of alternatives to conventional microscopy. *Clin Lab. Haem.* 21, 235-245



Recommendations

Diagnosis of malaria

All cases of suspected malaria should have a parasitological test (microscopy or Rapid diagnostic test (RDT)) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.
Good practice statement

Treating uncomplicated *P. falciparum* malaria

Treatment of uncomplicated P. falciparum malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended artemisinin-based combination therapies (ACT):

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)

Strong recommendation, high-quality evidence

Recommendations

Duration of ACT treatment

ACT regimens should provide 3 days' treatment with an artemisinin derivative.
Strong recommendation, high-quality evidence

Revised dose recommendation for dihydroartemisinin + piperaquine in young children

Children < 25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg body weight (bw) per day of dihydroartemisinin and 20 mg/kg bw per day of piperaquine daily for 3 days.
Strong recommendation based on pharmacokinetic modelling

Reducing the transmissibility of treated P. falciparum infections

In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is not required.
Strong recommendation, low-quality evidence

Treating uncomplicated *P. falciparum* malaria in special risk groups

First trimester of pregnancy

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.
Strong recommendation

Infants less than 5kg body weight

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with ACT at the same mg/kg bw target dose as for children weighing 5 kg.
Strong recommendation

Patients co-infected with HIV

In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are being treated with co-trimoxazole, and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.
Good practice statement

Non-immune travellers

Treat travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings with ACT.
Strong recommendation, high-quality evidence

Hyperparasitaemia

People with *P. falciparum* hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving ACT.
Good practice statement

Treating uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

Blood stage infection

If the malaria species is not known with certainty, treat as for uncomplicated *P. falciparum* malaria.
Good practice statement

In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either ACT (except pregnant women in their first trimester) or chloroquine.
Strong recommendation, high-quality evidence

In areas with chloroquine-resistant infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with ACT.
Strong recommendation, high-quality evidence

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.
Strong recommendation, very low-quality evidence

Treating severe malaria

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT (add single dose primaquine in areas of low transmission).
Strong recommendation, high-quality evidence

Revised dose recommendation for parenteral artesunate in young children

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.
Strong recommendation based on pharmacokinetic modelling

Parenteral alternatives where artesunate is not available

If artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.
Conditional recommendation, low-quality evidence

Treating cases of suspected severe malaria pending transfer to a higher-level facility (pre-referral treatment)

Pre-referral treatment options

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.

Strong recommendation, moderate-quality evidence

Where intramuscular injection of artesunate is not available, treat children < 6 years with a single rectal dose (10mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.

Strong recommendation, moderate-quality evidence

Malaria Serology – antibody detection

- Immunologic assays to detect host response
- Antibodies to asexual parasites appear some days after invasion of RBCs and may persist for months
- Positive test indicates past infection
- Not useful for treatment decisions

Malaria Serology – antibody detection

- Valuable epidemiologic tool in some settings
- Useful for
  - Identifying infective donor in transfusion-transmitted malaria
  - Investigating congenital malaria, esp. if mom's smear is negative
  - Diagnosing, or ruling out, tropical splenomegaly syndrome
  - Retrospective confirmation of empirically-treated non-immunes

Polymerase Chain Reaction (PCR)

- Molecular technique to identify parasite genetic material
- Uses whole blood collected in anticoagulated tube (200 µl) or directly onto filter paper (5 µl)
  - 100% DNA is extracted
  - 10% blood volume used in PCR reaction

Artemisinin resistance