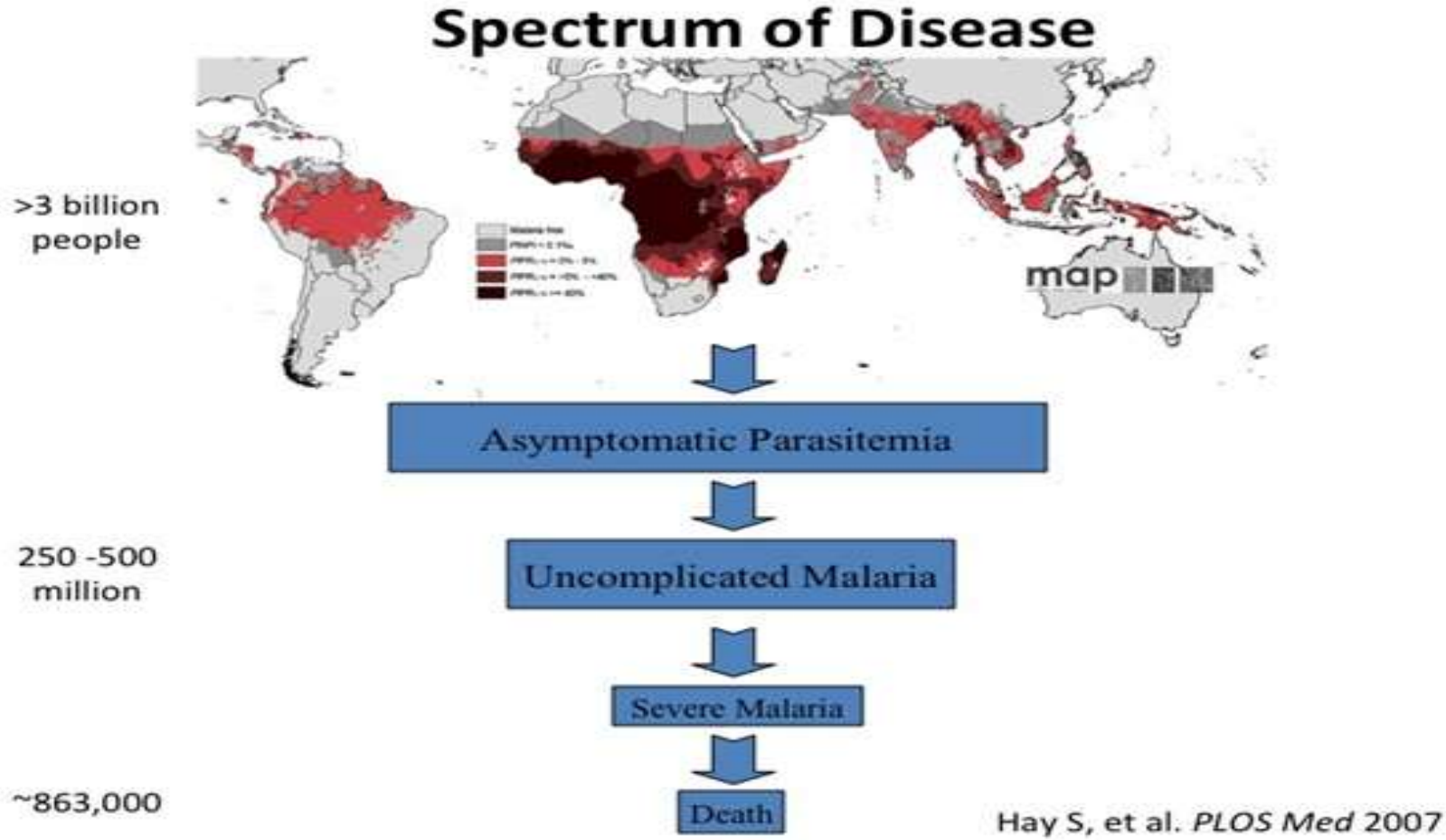
MALARIA

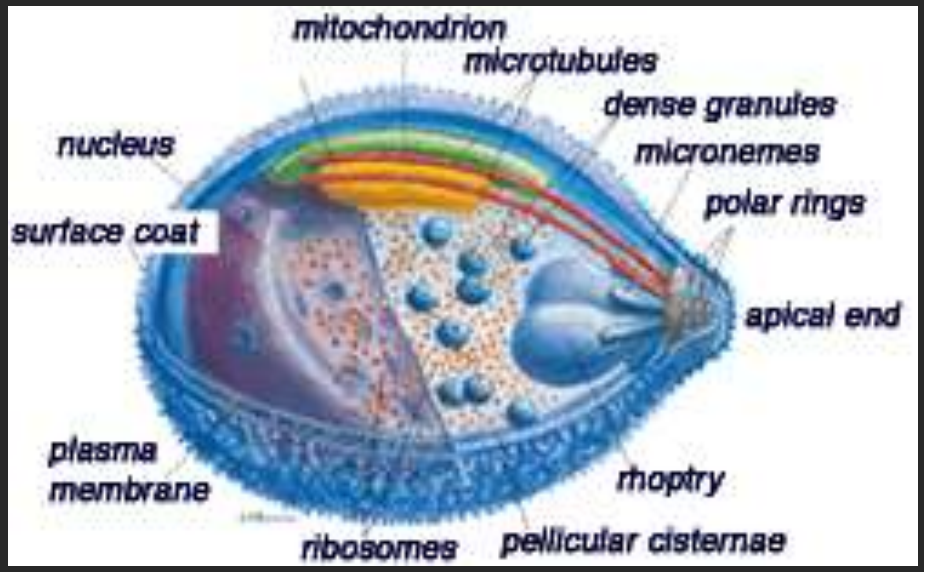
Why malaria?

- **The world`s most devastating human parasitic infection**
  - **affects >40% of the world`s population**
  - **350-500 million cases worldwide**
  - **270-400 million are Falciparum malaria**



TAXONOMIC CLASSIFICATION

Kingdom	**Protista**
Subkingdom	**Protozoa**
Phylum	**Apicomplexa**
Class	**Haematozoea**
Order	**Haemosporida**
Family	**Plasmodiidae**
Genus	***Plasmodium {sub genera- lavarania and plasmodium}***
Species	***falciparum, malariae, ovale, vivax***



There are 165 known species of Plasmodium- may infect reptiles, birds and mammals

Of these, 4 were known to infect humans.

A new species- **Plasmodium knowlesi**- *causes malaria in macaques but can also infect humans.*

Malaria

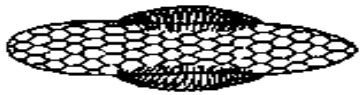
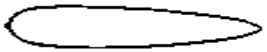
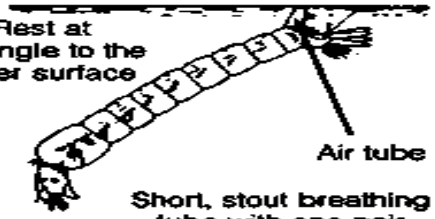
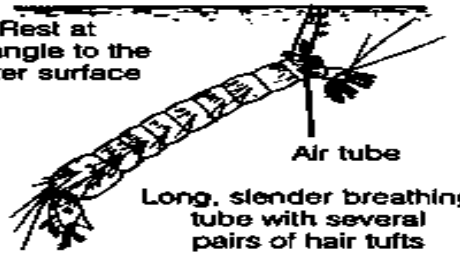
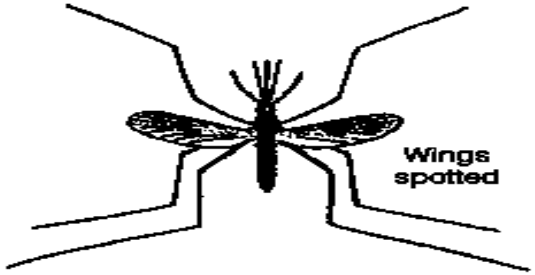
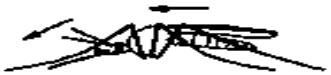
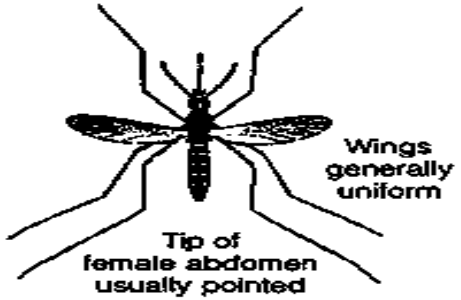
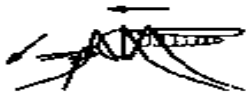
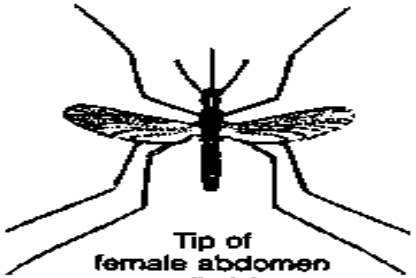
72 species of anopheles mosquito (♀)

90% cases

- *Plasmodium Falciparum*
  - 95% malarial Death
- *Plasmodium vivax*
- *Plasmodium Ovale*
- *Plasmodium Malariae*

Plasmodium knowlesi


© 2002 Dept. Medical Entomology, ICPMR

Anopheles	*Aedes*	*Culex*
Eggs  Laid singly  Has floats	 Laid singly  No floats	 Laid in rafts  No floats
Larvae  Rest parallel to water surface Rudimentary breathing tube	 Rest at an angle to the water surface Air tube Short, stout breathing tube with one pair of hair tufts	 Rest at an angle to the water surface Air tube Long, slender breathing tube with several pairs of hair tufts
Pupae (differ only slightly) 		
Adult Proboscis and body in same straight line   Maxillary palps Maxillary palps as long as proboscis  Wings spotted	Proboscis and body at an angle to one another   Maxillary palps Maxillary palps shorter than proboscis  Wings generally uniform Tip of female abdomen usually pointed	Proboscis and body at an angle to one another   Maxillary palps Maxillary palps shorter than proboscis  Tip of female abdomen usually blunt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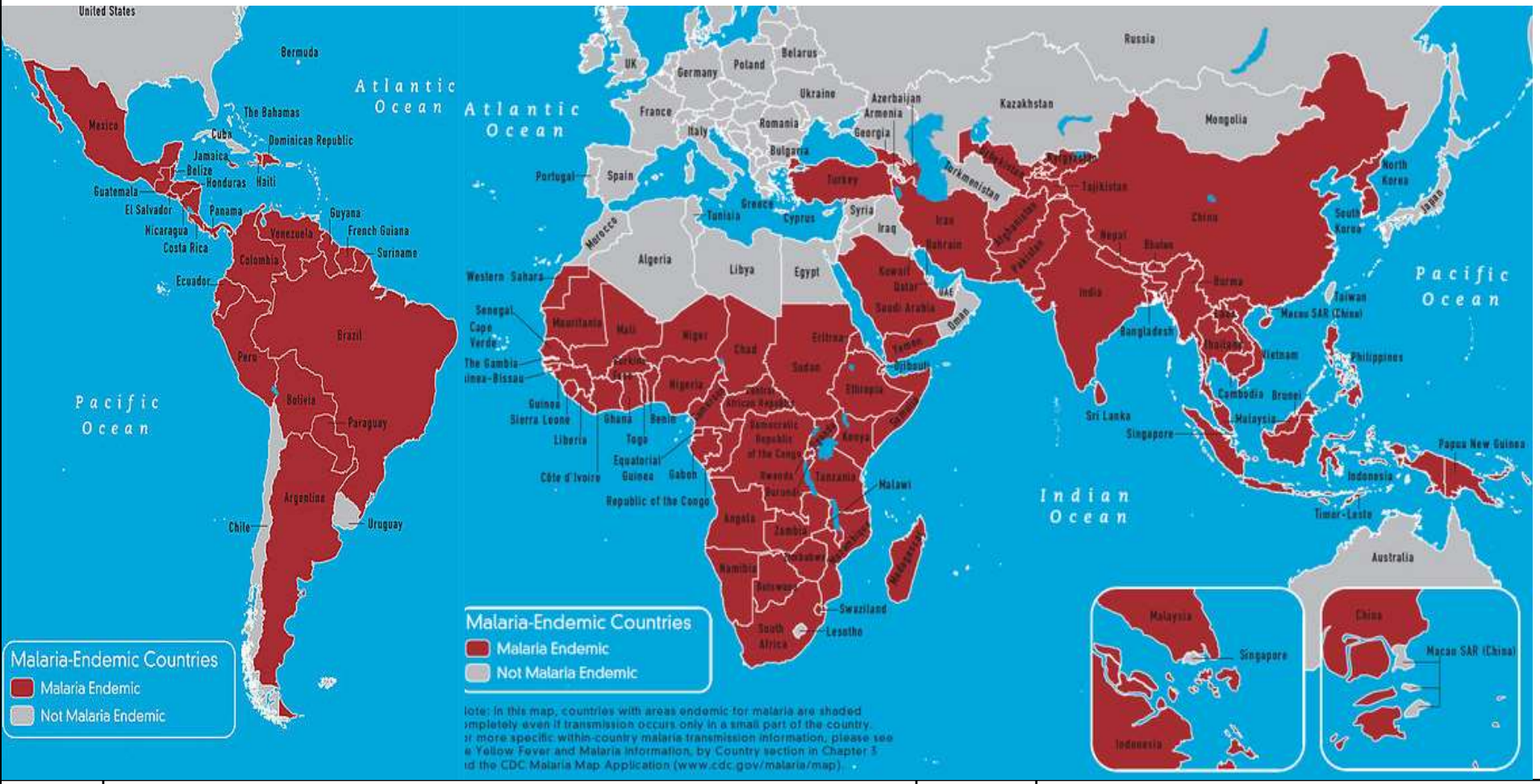
Risk for Travelers

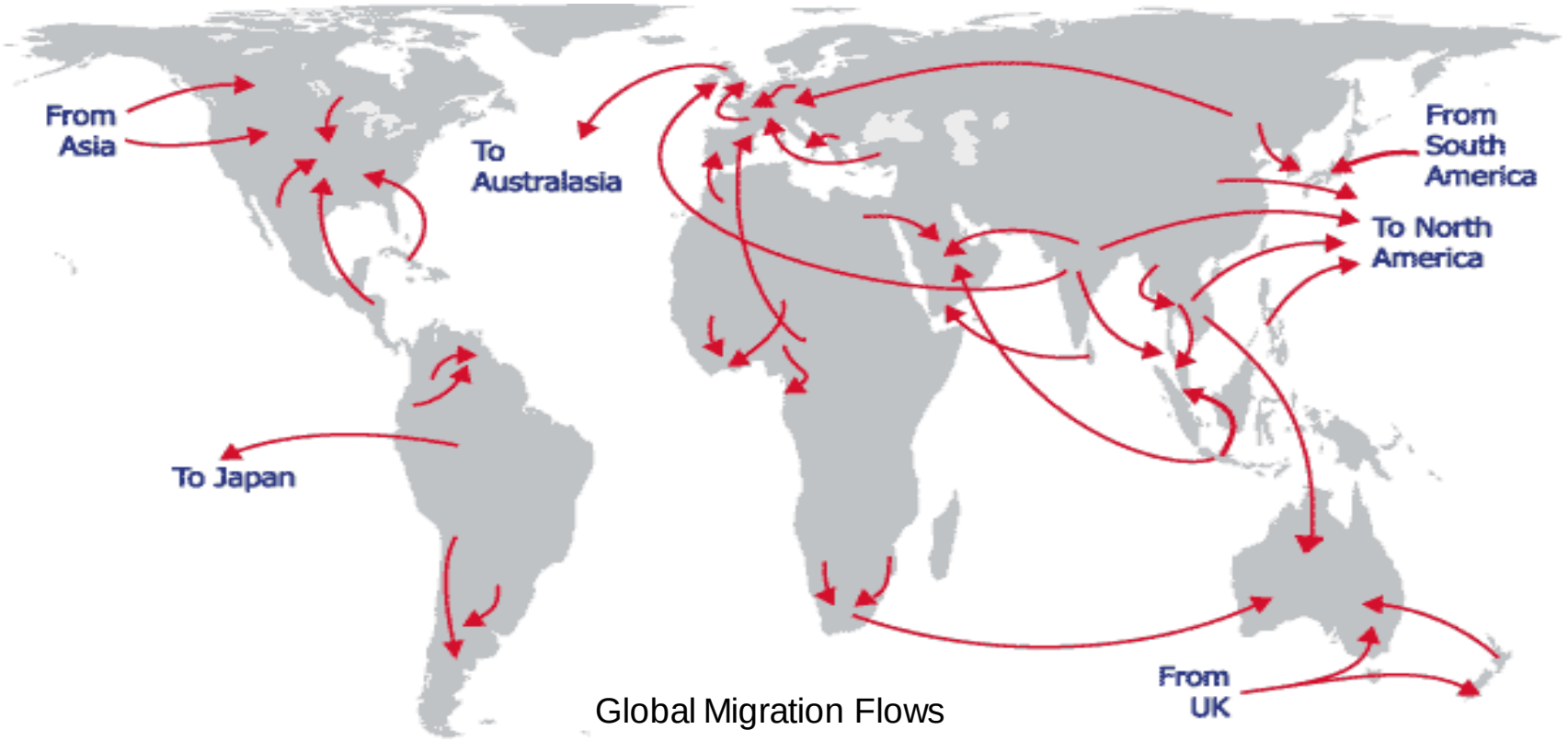
- **Relative risk for infection:**
  - **highest - West Africa, Oceania.**
  - **moderate - other Africa parts, South Asia, South America**
  - **lower - Central America, other parts of Asia.**



India	All areas throughout country **except** none in areas >2,000 m (>6,561 ft) in Himachal Pradesh, Jammu, Kashmir, and Sikkim. Present in cities of Delhi and Bombay (Mumbai)	Chloro quine	*vivax* 40%; *falciparum* 20–40% *malariae, ovale* remainder

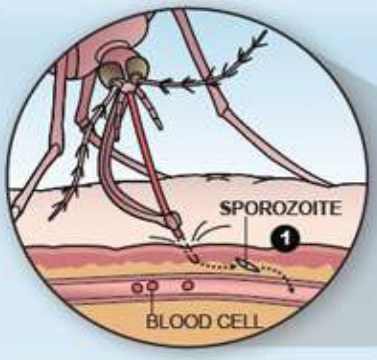
Risk for Travelers

- **High risk associated with I- and II-generation immigrants:**
  - **visit endemic countries of origin**
  - **consider themselves immune**
    - **immunity → slow developed, requires multiple exposures**
    - **older children & adults in endemic. → are protected**
    - **acquired immunity is lost very quickly!!!**



Global Migration Flows

The Life Cycle of Malaria



1 To start the cycle, an infected female *Anopheles* mosquito injects sporozoites into the skin while feeding.

2 Sporozoites enter the blood stream and are carried to the liver, where they infect liver cells.

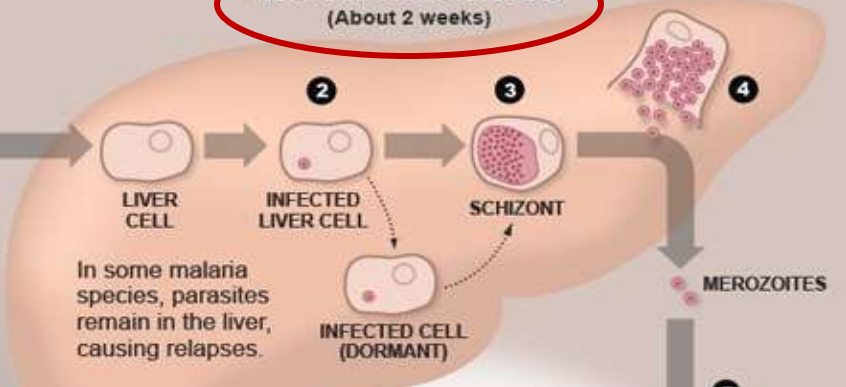
3 Within liver cells, the parasites develop into schizonts.

4 The schizonts rupture, releasing thousands of individual merozoites into the bloodstream.

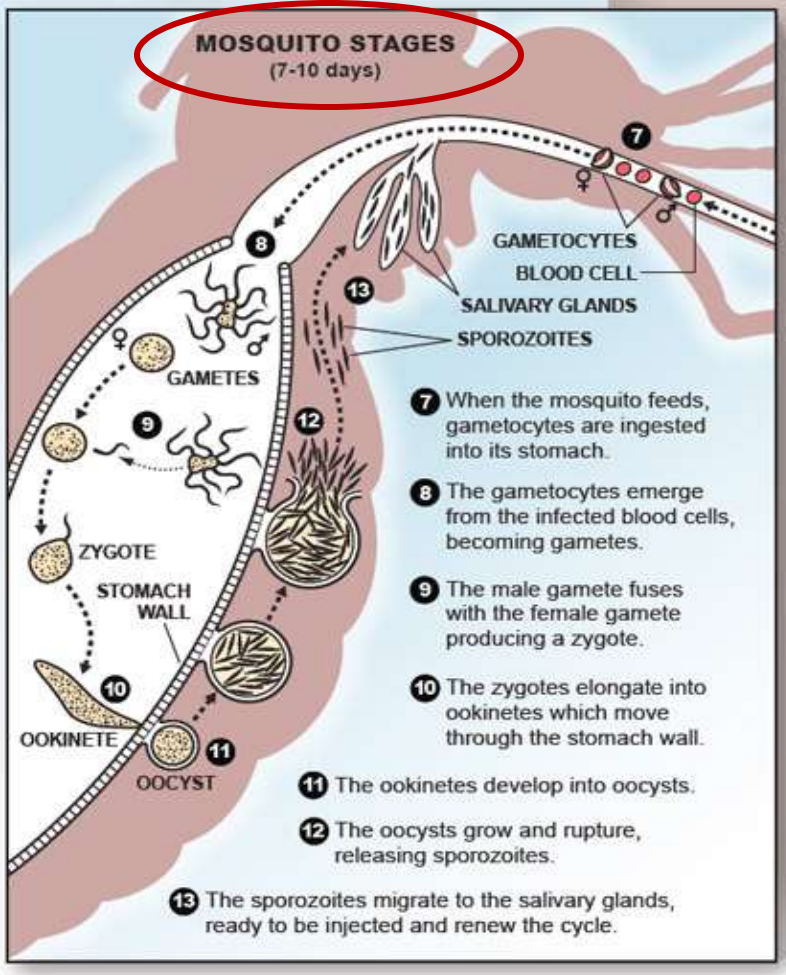
An infected mosquito starts the cycle

SPOROZOITES

HUMAN LIVER STAGES
(About 2 weeks)



MOSQUITO STAGES
(7-10 days)



7 When the mosquito feeds, gametocytes are ingested into its stomach.

8 The gametocytes emerge from the infected blood cells, becoming gametes.

9 The male gamete fuses with the female gamete producing a zygote.

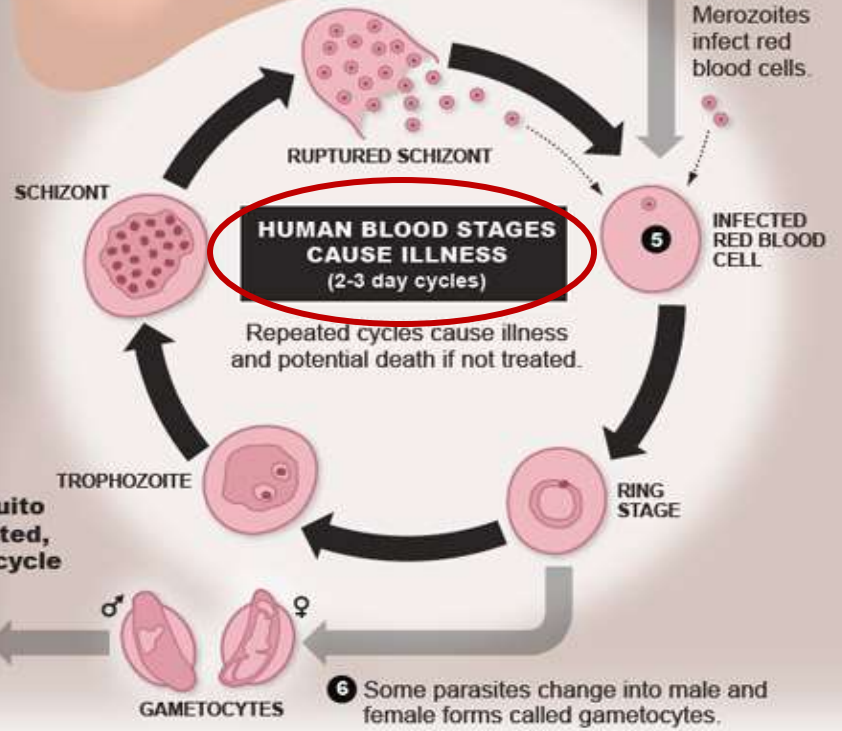
10 The zygotes elongate into ookinetes which move through the stomach wall.

11 The ookinetes develop into oocysts.

12 The oocysts grow and rupture, releasing sporozoites.

13 The sporozoites migrate to the salivary glands, ready to be injected and renew the cycle.

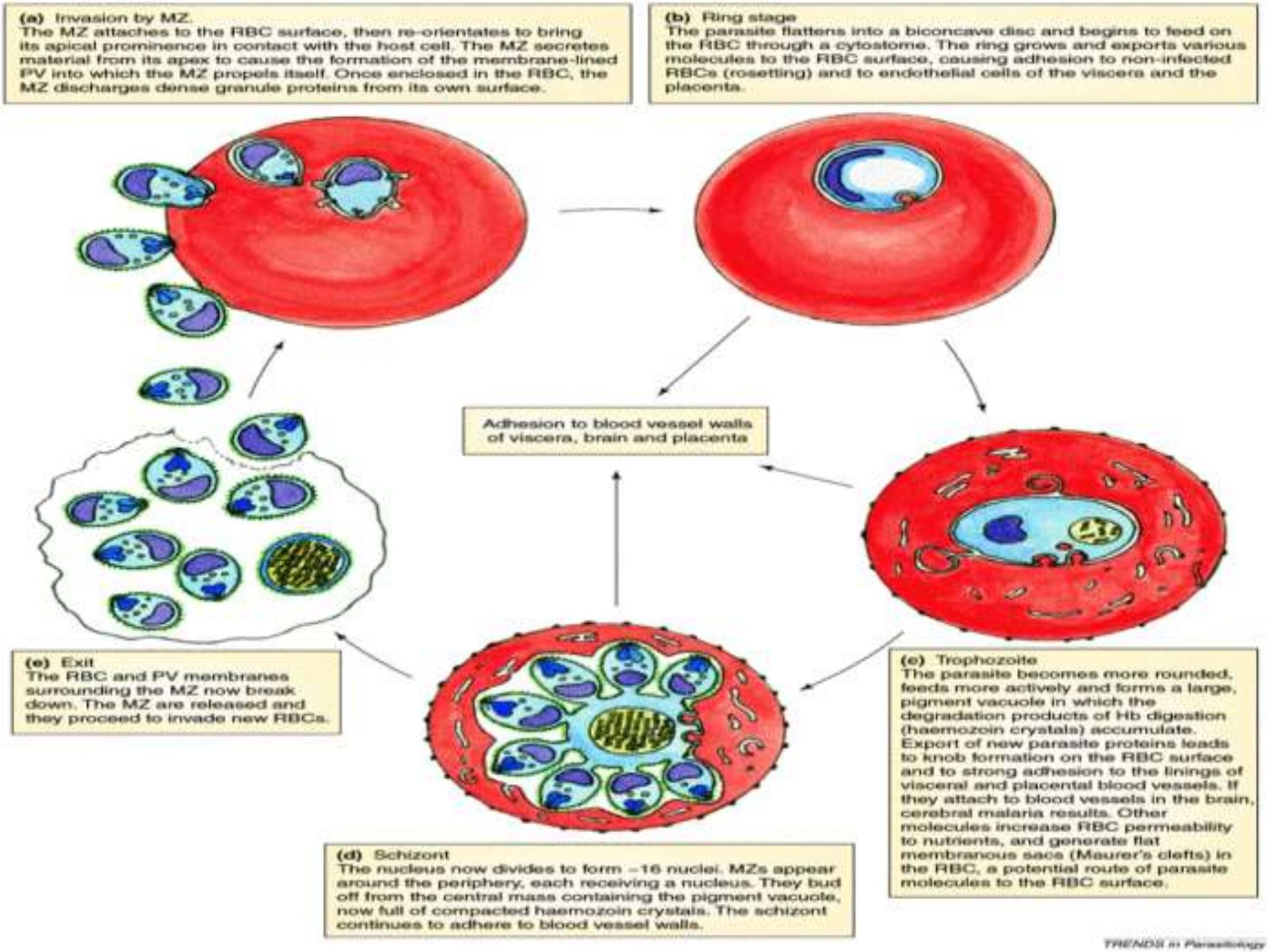
5 Merozoites infect red blood cells.

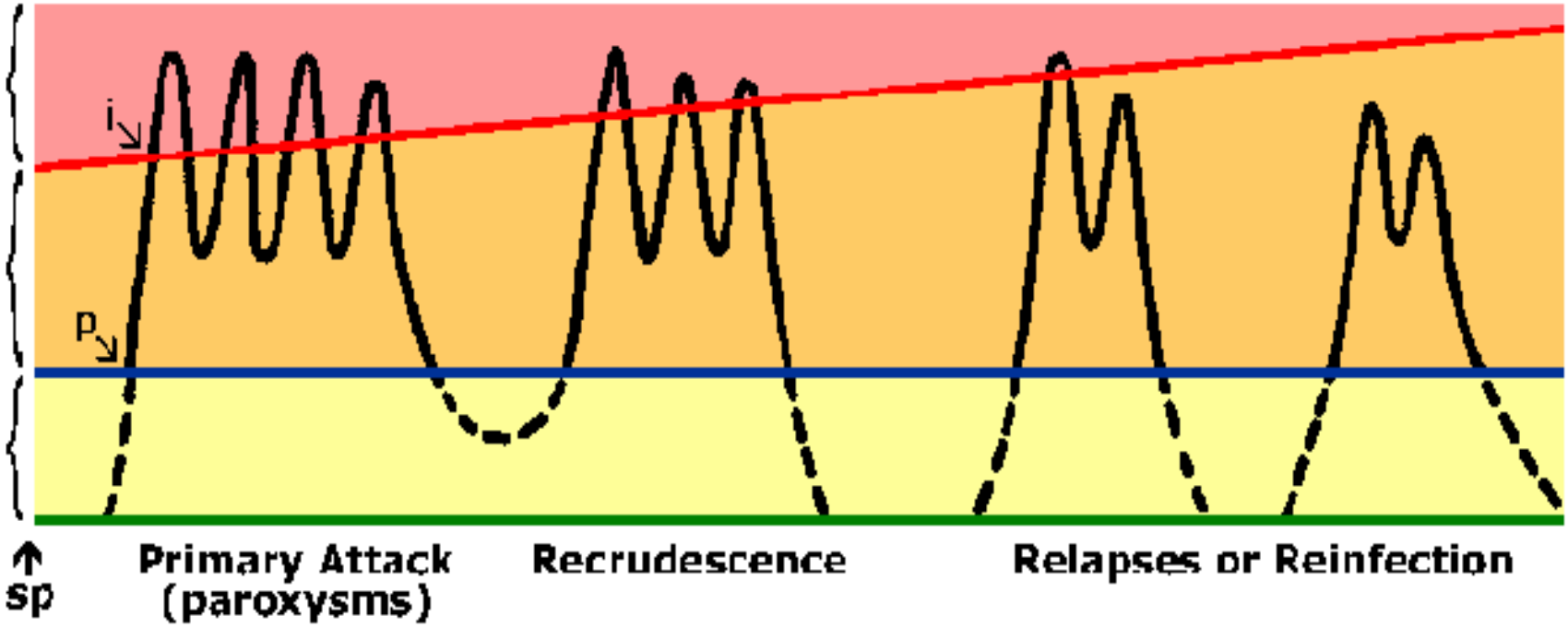


6 Some parasites change into male and female forms called gametocytes.

Another mosquito becomes infected, continuing the cycle

The Carter Center / Graphic by Al Granberg


(a) Invasion by MZ.
The MZ attaches to the RBC surface, then re-orientates to bring its apical prominence in contact with the host cell. The MZ secretes material from its apex to cause the formation of the membrane-lined PV into which the MZ propels itself. Once enclosed in the RBC, the MZ discharges dense granule proteins from its own surface.
(b) Ring stage
The parasite flattens into a biconcave disc and begins to feed on the RBC through a cytostome. The ring grows and exports various molecules to the RBC surface, causing adhesion to non-infected RBCs (rosetting) and to endothelial cells of the viscera and the placenta.
Adhesion to blood vessel walls of viscera, brain and placenta
(c) Trophozoite
The parasite becomes more rounded, feeds more actively and forms a large, pigment vacuole in which the degradation products of Hb digestion (haemozoin crystals) accumulate. Export of new parasite proteins leads to knob formation on the RBC surface and to strong adhesion to the linings of visceral and placental blood vessels. If they attach to blood vessels in the brain, cerebral malaria results. Other molecules increase RBC permeability to nutrients, and generate flat membranous sacs (Maurer's clefts) in the RBC, a potential route of parasite molecules to the RBC surface.
(d) Schizont
The nucleus now divides to form ~16 nuclei. MZs appear around the periphery, each receiving a nucleus. They bud off from the central mass containing the pigment vacuole, now full of compacted haemozoin crystals. The schizont continues to adhere to blood vessel walls.
(e) Exit
The RBC and PV membranes surrounding the MZ now break down. The MZ are released and they proceed to invade new RBCs.
TRENDS in Parasitology

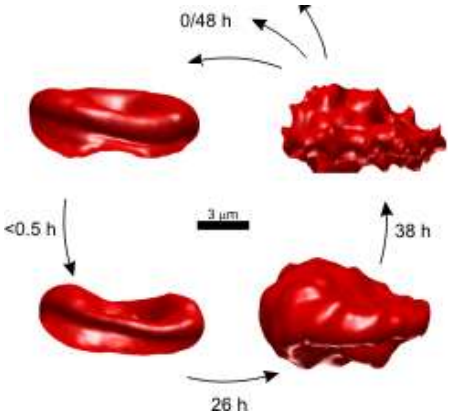


Recrudescence = recurrence of asexual parasitaemia after inadequate or ineffective treatment

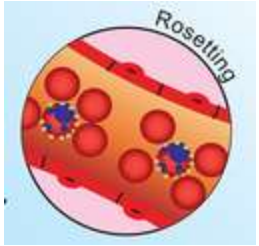
Relapse = recurrence of asexual parasitaemia in vivax / ovale deriving from persisting liver stages

Recurrence = recurrence of asexual parasitaemia following treatment, caused by a recrudescence, a relapse (vivax / ovale) or a new infection

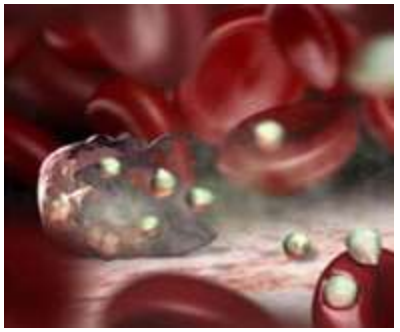
Pathogenesis



- **Plasmodium →** structural, biochemical, mechanical modifications of RBC:
  - ✓ Alter the membrane transport system
  - ✓ Decrease deformability
  - ✓ Increase susceptibility to sludging & destruction
  - ✓ Increase cytoadherance
  - ✓ Shorten of the lifespan

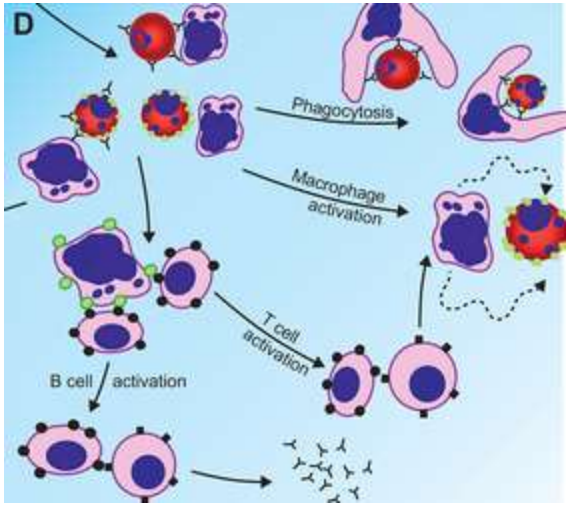


- Rupture of infected RBC →release of:
  - ✓ cellular debris
  - ✓ parasite material and metabolites,
  - ✓ hemozoin pigment = free heme, consists of Fe atom → toxic to cells



Pathogenesis

- Plasmodium
  - → activate macrophages & endothelial cells
  - ↓
  - → secrete cytokines & inflammatory mediators:
    - TNF, IF-γ, IL-1, IL-6, IL-8, macrophage colony-stimulating factor, lymphotoxin, superoxide & NO



Cytokines of the proinflammatory cascade (TNF, IL, IFN-γ, NO) act as double-edged swords in the pathogenesis of malaria

The outcome of malaria is determined by the balance between the pro- and anti-inflammatory cytokines

Cytokines:

1. Inhibit the growth of malarial parasites in lower concentrations

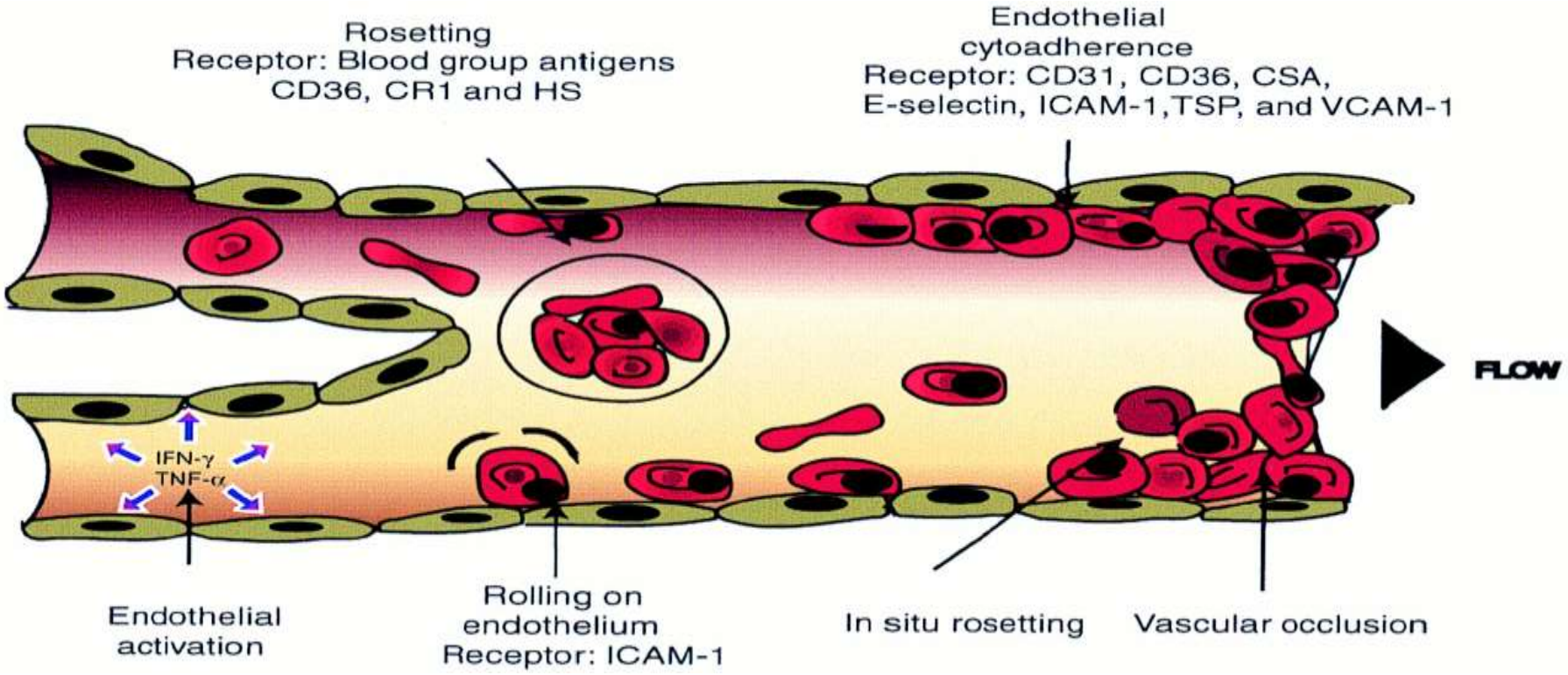
Cytokines:

2. excessive cytokines (failure to down-regulate) lead to:

- decreased mitochondrial oxygen use & **enhanced lactate production**;
- ↑ **cytoadherence** → microvascular obstruction & more hypoxia;
- disturb auto-regulation of local blood flow →lead to **poor circulation** → tissue hypoxia;
- **poor RBC deformability** and multifactorial anemia;
- **reduced gluconeogenesis** and hypoglycemia;
- **myocardial depression** and cardiac insufficiency;
- **loss of endothelial integrity** & vascular damage in the lungs & brain;
- **upregulation of vascular and intercellular adhesion molecules** (ICAMs), particularly in the brain and placenta leading to cerebral malaria and placental dysfunction;
- activation of leukocytes and platelets, promoting **procoagulant activity**.

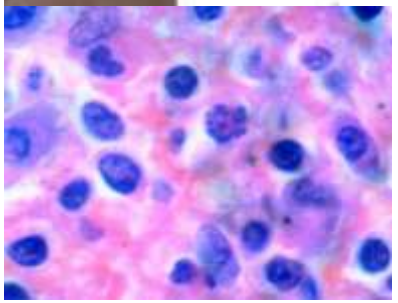
Endothelia changes in malaria

- ↑ adhesiveness for leucocytes & RBC,
- ↑ permeability,
- ↓ electrical resistance,
- ↑ apoptosis



Splenic changes in malaria

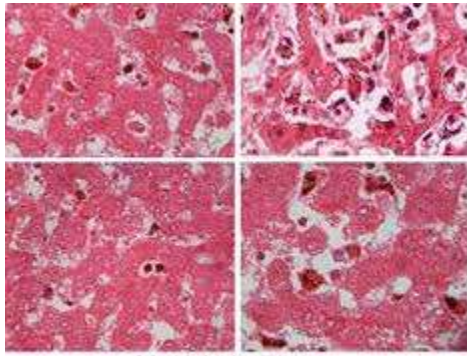
- Spleen enlarged, soft & diffusely pigmented
- Increased phagocytic activity of macrophages → engulf parasite, RBC
- Microscopically: congestion, reticuloendothelial hyperplasia
- Haemorrhages & infarcts are present
- Chronic malaria → fibrotic, foci of mineralization (Gandy-Gamna bodies), brittle, thick capsule



Malarial Spleen showing Schizont (H & E x 1000)

Liver changes in malaria

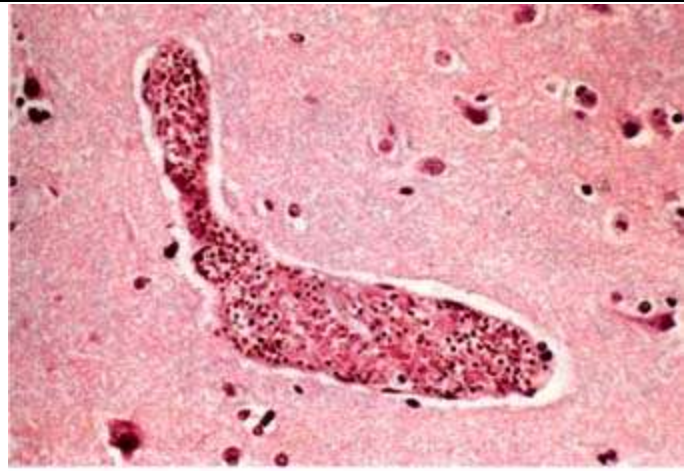
- Enlarged, gray appearance (hemozoin staining)
- Kupffer cells are enlarged & contain malarial pigment
- Pigment paranchymal cells
- Sinusoids & other vessels congestion, focal areas of fatty changes



Malaria in liver
Malarial pigment in macrophages of sinus hepaticus

Brain

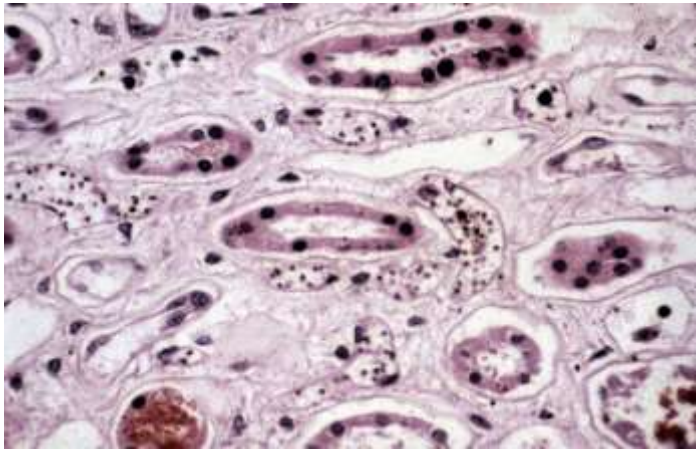
- Cerebral oedema / congestion
- Petechiae in white matter
- Features of raised intracranial pressure
- Capillaries and venular congestion filled with parasitized RBC
- Blockage of blood vessels by parasitized RBC



P. falciparum-infected red cells marginating within a vein in cerebral malaria (from Kumar V, 7th edition, 2005)

Kidney

- Slightly enlarged
- Malarial pigments in the glomeruli
- Cortico-medullary capillaries show parasitized RBC & Hb in tubules
- Acute tubular necrosis & acute renal failure
- Quartan malarial nephropathy can occur in P.malariae infestation
- Blackwater fever



renal tubule shows necrosis with widening of interstitial space (interstitial edema) and the capillaries are dilated and congested with pale -stained red blood cells which contain dark brown pigments

Lungs

- Congested & oedematous
- Fibrin may be deposited in alveoli resulting in shock lung or ARDS

Heart

- May be dilated & flabby
- Pericardial / endocardial petechiae & congested capillaries containing parasitized RBC
- Focal hypoxic lesions
- Focal interstitial infiltrates of the myocardium

GIT

- Oedematous, congested, focal / diffuse haemorrhage
- Small vessels of the intestinal mucosa contain parasitized RBC
- Massive sequestration & parasitisation of the GIT is sometime associated with vasomotor collapse resulting in the clinical syndrome of algid malaria

P.falciparum

⇓

→↑ **adhesiveness** to capillary + postcapillary venular endothelium

→RBC **rosseting**

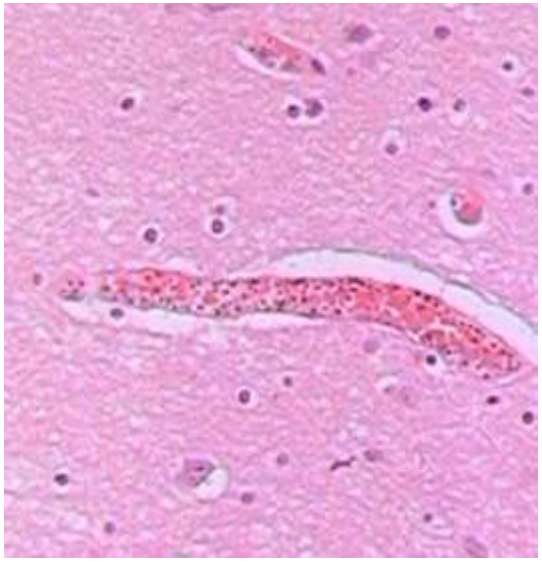
→↑ **sequestration** in heart, lung, brain, liver, kidney, intestines, adipose & subcutaneous tissues, placenta → microaerophilic venous environment

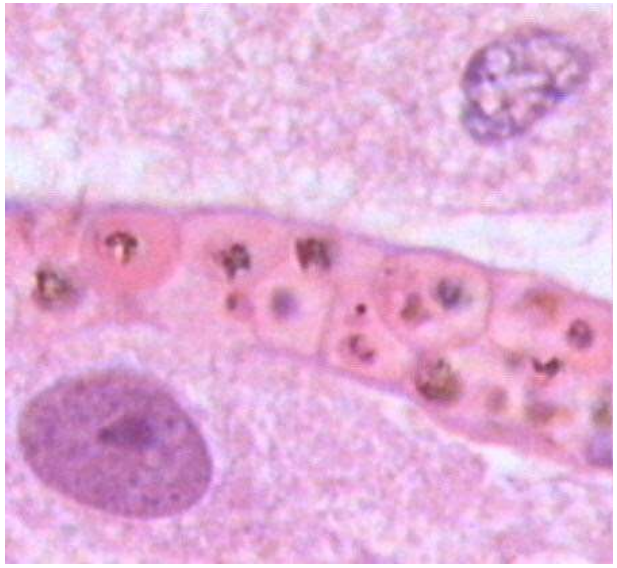
⇓

- ✓ better suited for plasmodium maturation
- ✓ escape clearance of infected RBC by the spleen
- ✓ hide plasmodium from the immune system.

⇓

more efficient RBC invasion





Confer degrees of protection from severe falciparum:

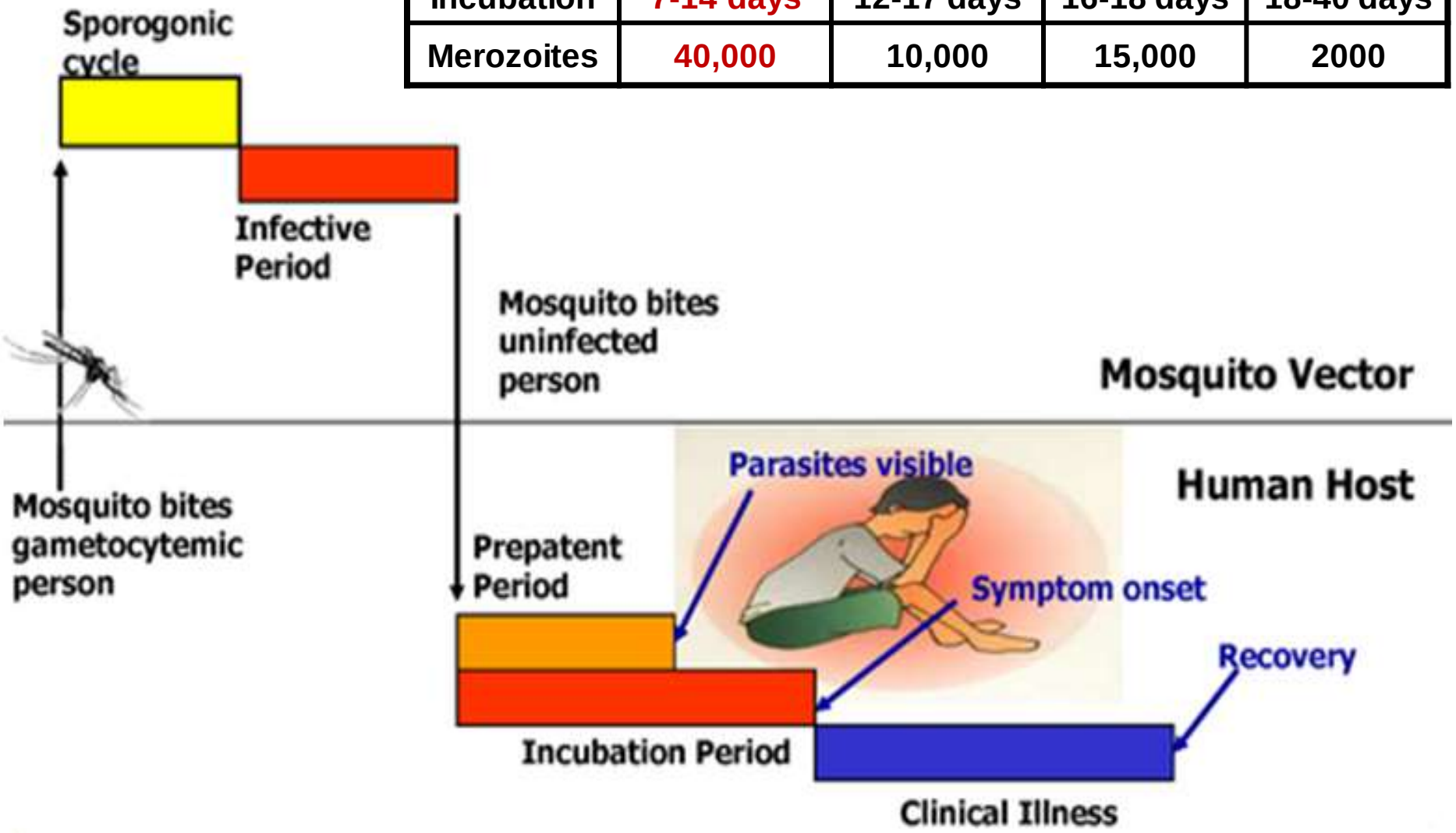
- **α-thalassemia**

→ risk reduced 70% homozygous HbC

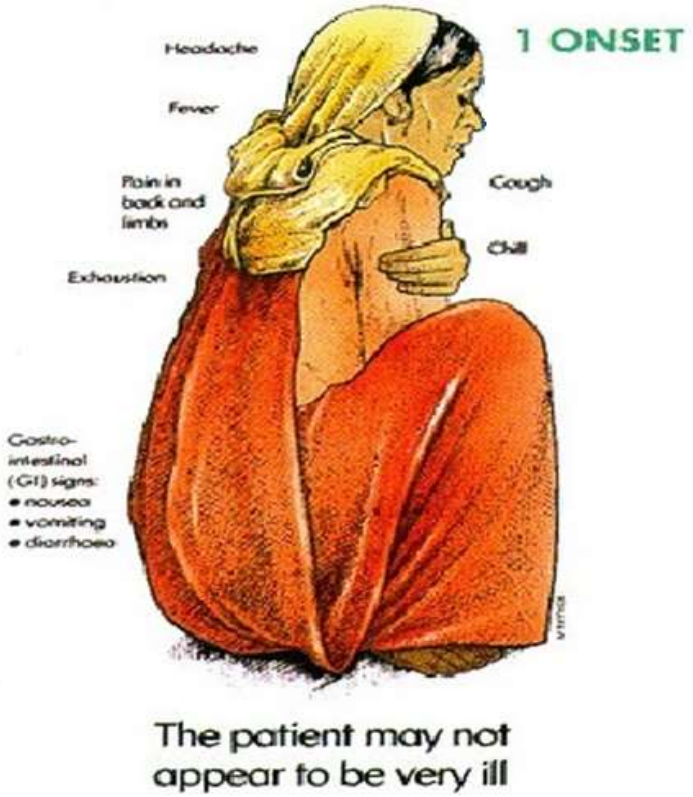
→ risc reduced 90% by heterozygous HbS (sickle-cell trait)

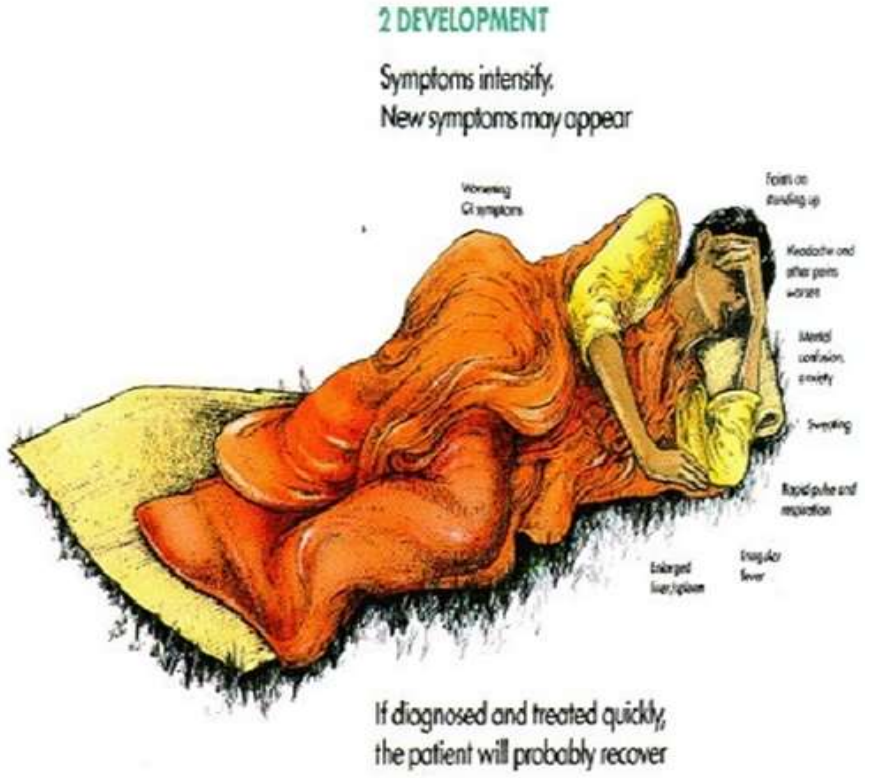
In **Duffy** blood group neg. (No FyFy antigen) → resistance to vivax

	falciparum	*vivax*	*ovale*	*malariae*
Prepatent	6-9 days	8-12 days	10-14 days	15-18 days
Incubation	7-14 days	12-17 days	16-18 days	18-40 days
Merozoites	40,000	10,000	15,000	2000



Prepatent period = time between sporozoite inoculation & appearance of parasites in blood
Sometimes the incubation periods can be prolonged for several months in *vivax, ovale, malariae*





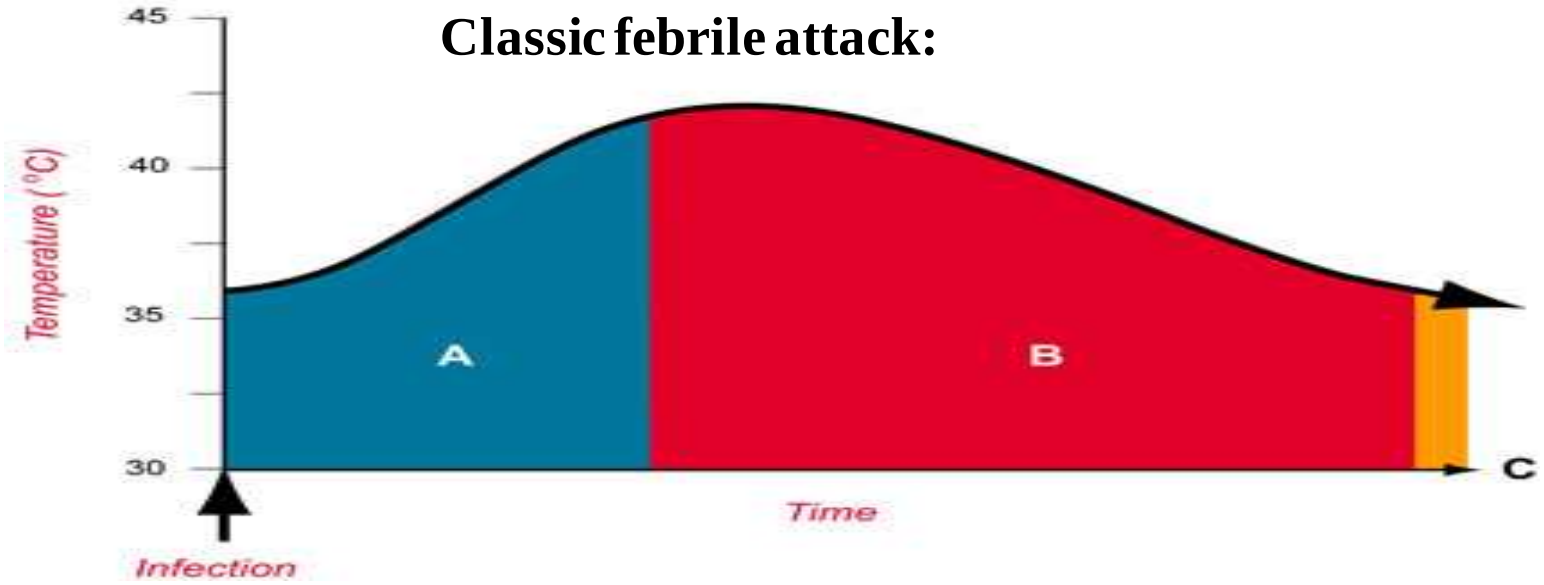
Few days before first classic febrile attack:

- non-specific prodromal 'flu-like' symptoms
- Fever, chills, headache, back & joint pain
- GI (nausea, vomiting, etc)

- Symptoms intensify
- Irregular high fever
- Anxiety, delirium
- Sweating, >Ps, severe exhaustion
- Worsening GI symptoms
- Enlarged spleen & liver

Spleen I week = soft, prone to traumatic rupture
after many bouts = fibrotic, firm

Classic febrile attack:



A. Prodromal or cold stage

Chills for 15 mt to 1 hour

Headache, nausea, vomiting, diarrhea, muscular pains.

Caused due to rupture from the host RBC

B. Hot stage

Lasts for 2-6 hours,

Fever 40C, aching, shivering, dry burning skin, > headache

Starts invading newer RBC

C. Sweating stage

Lasts 2-4 hours,

profuse sweating, declining t^0C

Exhausted & weak ➤ sleep

M. paroxysm usually last 4-8 hours, ~up to 12 hours, except fm → may 36 hours

regular paroxysms separated by asymptomatic intervals = only typical clinical feature of malaria


The cold stage


The hot stage


The sweating stage

- After → pts fall asleep; awakening →feels well
- Patients may also exhibit:
  - splenomegaly (by the end of 1 week of disease)
  - hepatomegaly (slight jaundice)
  - hemolytic anemia

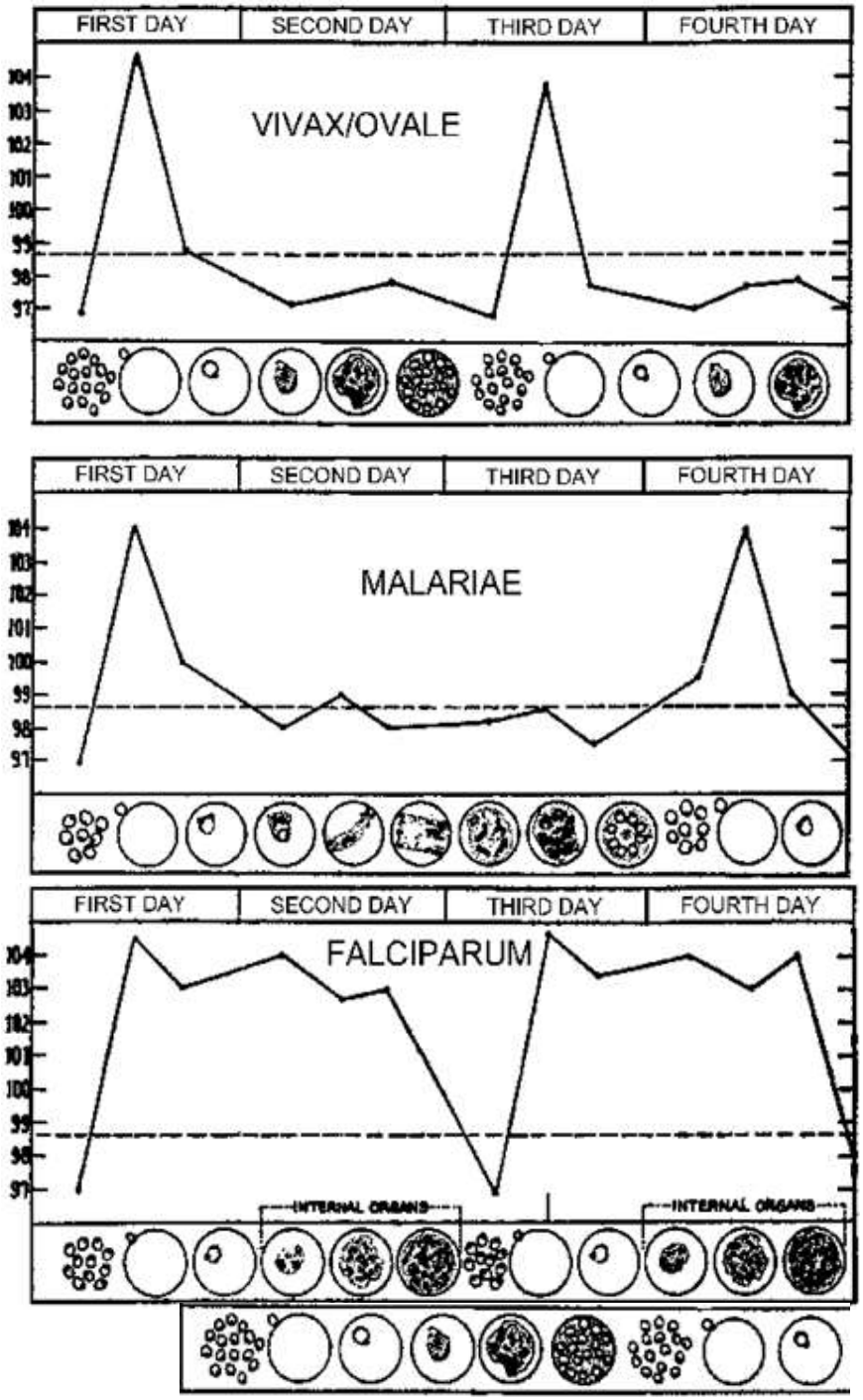
Periodicity = clue in diagnosis

Parasites usually undergo a synchronous schizogony →

Simultaneous rupture RBC →intermittent fever paroxysmus

***P. falciparum* may not exhibit distinct paroxysms !**

In non-*falciparum* infections, fever disappears after a few paroxysms, even in the absence of treatment; relapses or recrudescence may occur a few weeks or months later.



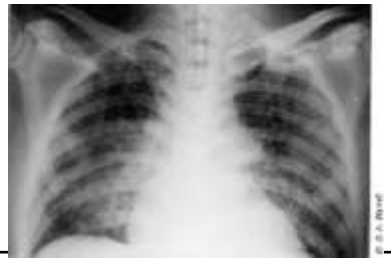
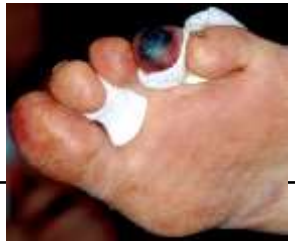
Disease Severity and Duration

	vivax	ovale	malariae	falciparum
Initial Paraoxysm Severity	moderate to severe	mild	moderate to severe	severe
Average Parasitemia (mm^3)	20,000	9,000	6,000	50,000-500,000
Maximum Parasitemia (mm^3)	50,000	30,000	20,000	2,500,000
Symptom Duration (untreated)	3-8+ weeks	2-3 weeks	3-24 weeks	2-3 weeks
Maximum Infection Duration (untreated)	5-8 years	12-20 months	20-50+ years	6-17 months
Anemia	++	+	++	++++
Complications			renal	cerebral

Indicators of severe malaria and poor prognosis

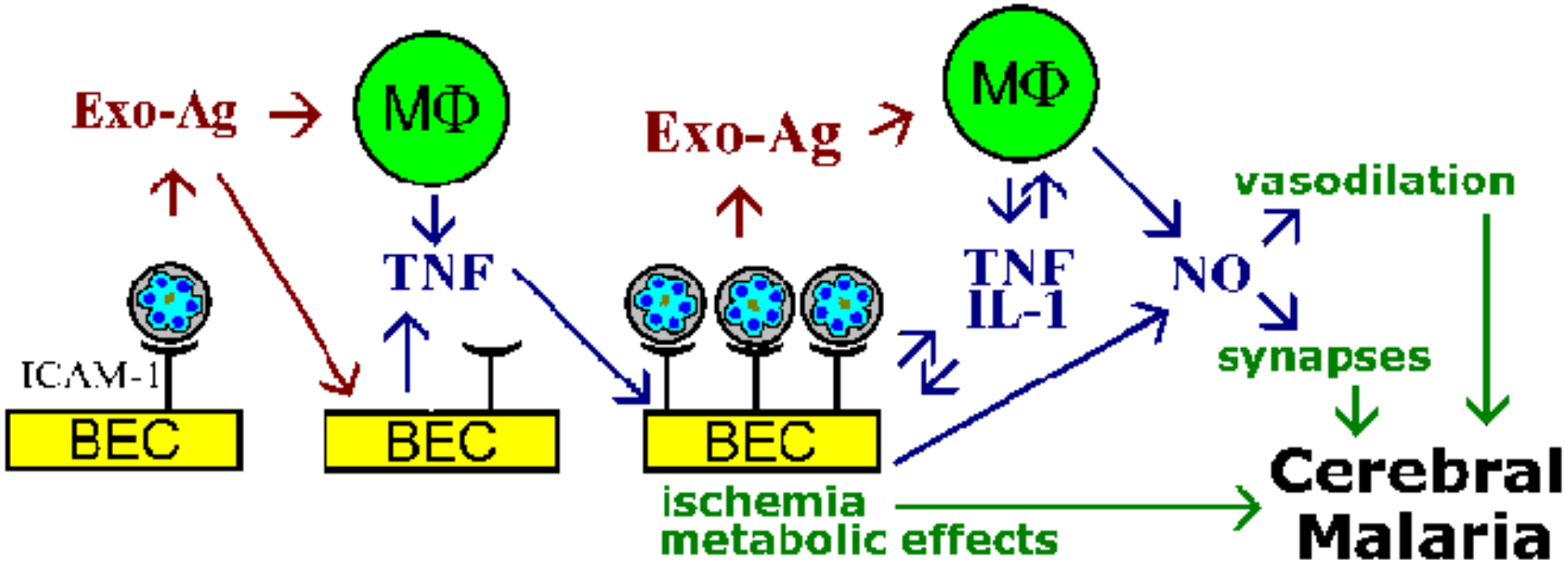
Manifestation	Features
1. Cerebral malaria:	Glasgow <11; Coma persist for >30 min after generalized convulsion 
2. Severe anemia	Ht <15% or Hb < 50 g/l & parasite count >10000/µl 
3. Renal failure	Urine output <400 ml/24 hours in adults (<12 ml/kg/24 hours in children) & serum creatinine >265 µmol/l (> 3.0 mg/dl)
4. Metabolic / Lactic acidosis	Metabolic acidosis → arterial blood pH <7.35, plasma bicarbonate <22 mmol/L. Hyperlactatemia → plasma lactate 2-5 mmol/L. Lactic acidosis → pH <7.25 & plasma lactate >5 mmol/L.

Indicators of severe malaria and poor prognosis

Manifestation	Features
5. Pulmonary edema or ARDS	Breathlessness, bilateral crackles, etc. pulmonary oedema. Basis: Rx, hypoxemia, positive end-expiratory pressure 
6. Hypoglycemia	Blood glucose <2.2 mmol/l (<40 mg/dl).
7. Hypotension and shock (algid malaria)	Systolic blood pressure <50 mmHg in children 1-5 y.o.; <70mm Hg pts ≥5 yo; core-skin temperature difference >10^0C
8. Abnormal bleeding and/or DIC	Spontaneous bleeding from the gums, nose, GI tract, retinal haemorrhages and/or lab. evidence of DIC 
9. Repeated generalised convulsions	≥3 generalized seizures within 24 hours
10. Haemoglobinuria 	Macroscopic black, brown or red urine; not associated with effects of oxidant drugs or enzyme defects (like G6PD)

Indicators of severe malaria and poor prognosis

11. Impaired consciousness	not falling into the definition of cerebral malaria. These patients are generally arousable
12. Prostration	Extreme weakness, needs support
13. Hyperparasitemia	5% parasitized RBC or >250 000 parasites/µl (in nonimmune)
14. Hyperpyrexia	Core body temperature above 40^0C
15. Jaundice	Serum bilirubin >43 mmol/l (>2.5 mg/dl).
16. Fluid / electrolyte disturbances	Dehydration, postural hypotension, clinical hypovolemia
17. Vomiting of drugs	Pts with persistent vomiting → parenteral therapy.
18. Complicating or associated infections	Aspiration bronchopneumonia, septicemia, urinary tract infection etc.
19. Other indicators of poor prognosis	WBC >12,000/cumm; high CSF lactate (>6 mmol/l); low CSF glucose; AlAt >3xN; low antithrombin III levels; peripheral schizontemia; papilloedema/retinal oedema
20. Malarial Retinopathy	Frequent in children, less adults



- Cytoadherence inf. RBC to brain endothelial cells (BEC) ⇨
- release of exo-antigens ⇨ stimulate the BEC and macrophages (MF) ⇨
- secrete cytokines, TNF ⇨ an increased expression endothelial cell receptors ⇨
- increase cytoadherence ⇨ vascular blockage, hypoxia, localized metabolic effects (eg., hypoglycemia, lactic acidosis).
- TNF-a stimulate nitric oxide (NO).
- Nitric oxide ⇨ interfere with neurotransmission ⇨ affect neuronal function ⇨ vasodilation ⇨ intracranial hypertension.

Signs of cerebral malaria	Adults	Children
Oncet	Part of multi-organ disease	**Suddenly**
Cough	Uncommon	**In early stage**
Seizures	Less common	**Frequent**
Brain swelling, intracranial hypertension	Less common	**Frequent**
Brainstem signs (abnormalities in posture, pupil size and reaction, ocular movements or abnormal respiratory patterns	Less common	**Frequent**
Retinal changes (hemorrhages, peripheral & macular whitening, vessel discoloration)	Less common	**Frequent**
Anemia	Less common	**Frequent**
Hypoglycemia	Pregnant, quinine	**Common**
Jaundice	**Frequent**	Less common
Acute renal failure, hemoglobinuria	**Frequent**	Less common
Pulmonary edema, ARDS	**Frequent**	Less common
Development of unconsciousness	Insidious	**Rapid**
Metabolic acidosis	+	+
Coma recovery time	Slow, 2-4 days	Rapid, 1-2 d
Persistent neurological deficits	<3%	10%

Neurological signs in cerebral malaria coma:

- Cerebral malaria often starts with:
  - generalized convulsions followed by
  - persistent unconsciousness (for at least 30 minutes)
- Mild neck stiffness may be seen
- Absent → signs of meningeal irritation & signs of raised intracranial tension but the patient may be opisthotonic (decorticate rigidity). Pupils are normal.
- Papilloedema is rare and should suggest other possibilities.
- Transient abnormalities of eye movements, especially dysconjugate gaze
- Fixed jaw closure and tooth grinding (bruxism) are common.
- Pout reflex may be ellicitable, but other primitive reflexes → usually absent.
- Corneal reflexes are preserved except in case of deep coma.
- Deep jerks and plantar reflexes are variable.
- Abdominal and cremasteric reflexes are not ellicitable.

Pts also have anemia, jaundice, hepatosplenomegaly.

- CSF: pressure N - ↑, clear, WBC <10/µl; protein ↑, lactic acid ↑

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

Acute renal failure in severe malaria

- Occur in <1%, but mortality 45%
- Diagnosed when sr.crea.>3mg/dl in adults (>1.5 mg/dl in children); urine output <400ml/24 hrs
- Is common in adults, rare in children
- Vulnerable group of pts:
  - Pregnant
  - High parasitemia
  - Very high jaundice
  - Prolonged dehydration
  - NSAID therapy
- 2 subsets of presentations:
  a. ARF as a component of multiorgan failure →poor prognosis, associated with anemia, jaundice, hypoglycemia, acidosis or coma
  b. Present as a sole complication – appears as a later stage when other complications subsided/treated → prognosis good

ARF treatment

Fluid challenge:

20ml/kg of NaCl over one hr. Monitor for fluid overload after each 200ml by chest auscultation. Urine output should be 20 ml/hour

If no urine after fluid therapy → Diuretic challenge:

IV loop diuretic – Furosemide in incremental dose 40-100-200-400mg at ½ hour interval

If no improvement → Dopamine challenge:

Inj dopamine slow IV infusion at 2.5 – 5mcg/kg/min

75% of oliguric & 5% of anuric responds with increased urine output

If ineffective → futher fluid is restricted

Caution: complication of dopamine – gangrene, ototoxicity

http://www.docstoc.com/docs/70069428/ACUTE-RENAL-FAILURE-IN-SEVERE-MALARIA-gangrene

Factors that make pregnant women more vulnerable to malaria:

- ✓ Relapses, recrudescence & severe malaria is more common
- ✓ Premature labour, low birth weight, > mortality, congenital malaria
- ✓ Severe anaemia, hypoglycemia, acute pulmonary edema

WHY?

1. Parasites are preferentially sequestrated in the placenta
2. Acquired immunity against malaria decline during pregnancy.
3. During the II half of pregnancy, there is a transient immuno-suppression due to:
    - high levels of adrenal steroids
        - chorionic gonadotrophin
        - alpha-fetoprotein
    - depression of the role of lymphocytes.

First 6 months in infants is usually free of inf. due to:

- ➢ Transplacentally acquired immunity
- ➢ High conc of foetal Hb
- ➢ PABA in breast milk

Complications

- *Vivax, ovale & malariae* malaria → Relatively benign.
- Chronic malariae malaria → Nephrotic syndrome.

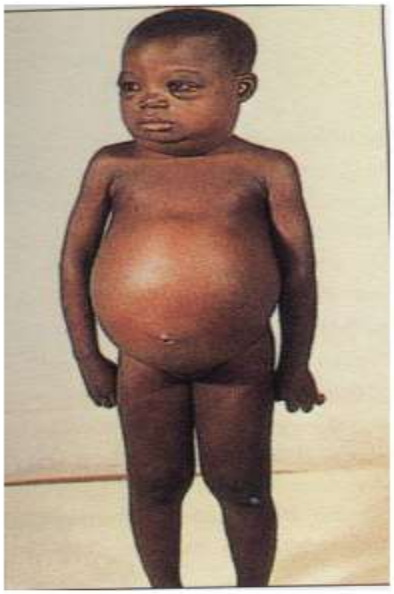
Parasite produces increased amount of antigens.

Immune system produces increased amount of antibodies.

Antigens attach to antibodies producing immune-complex in blood.

Immune-complexes are deposited on the glomerular walls activating the complement → Tissue damage.

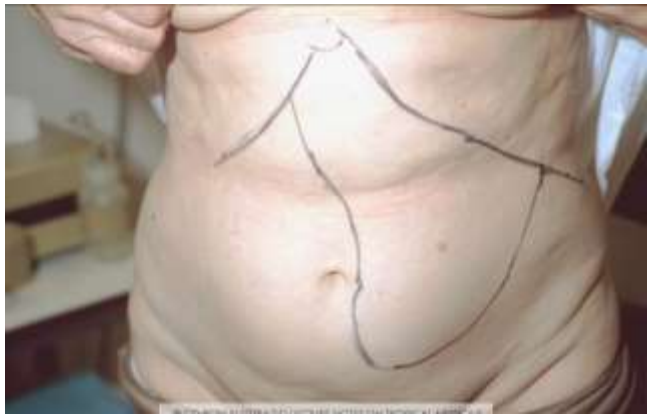
C1, 4, 2, 3, 5, 6, 7, 8, 9 → MAC

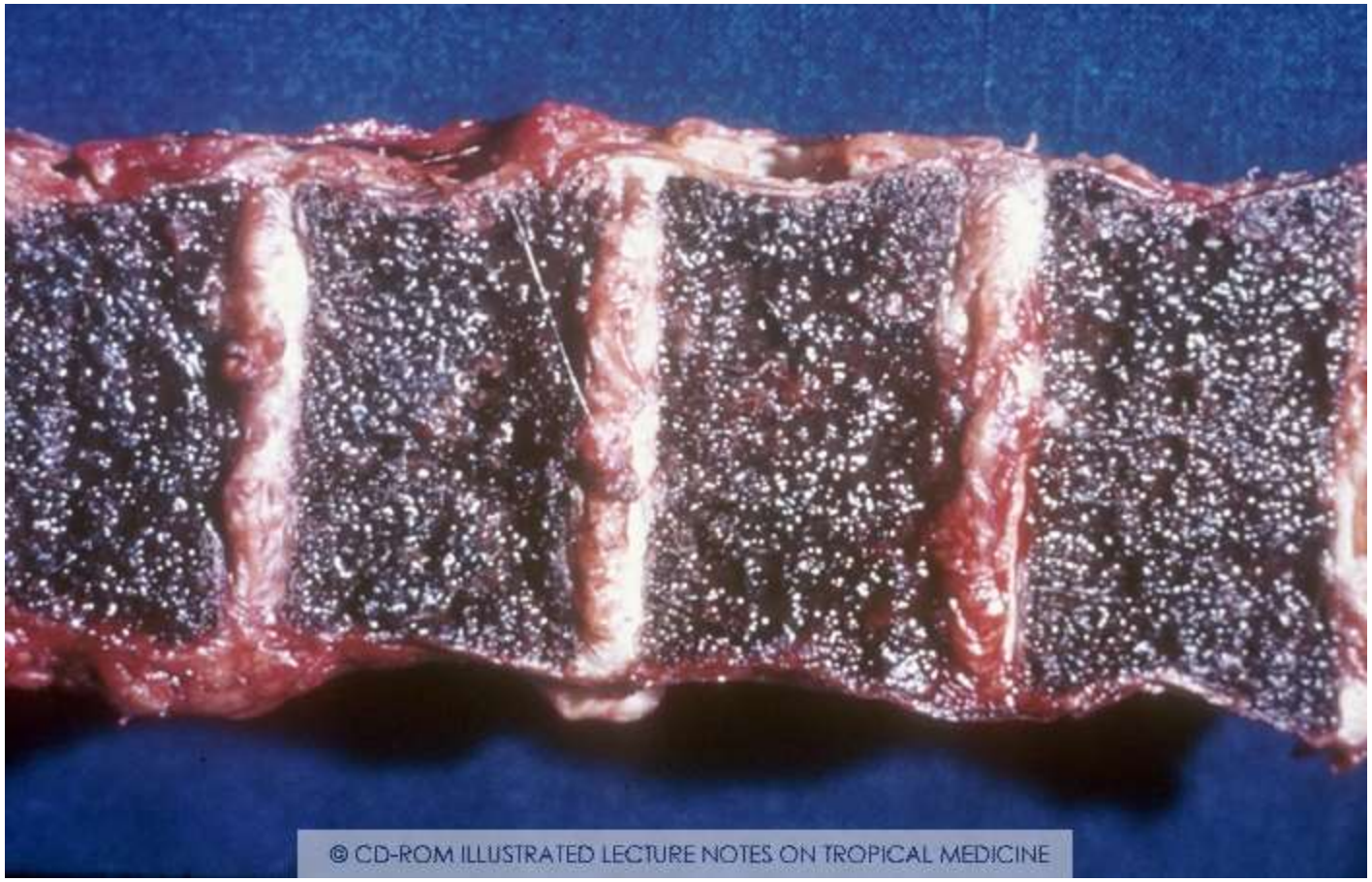


Child has nephrotic syndrome

Tropical splenomegaly syndrome (HIMSS)

- **Large spleen>1000g**
- **Moderate anaemia**
- **High IgM level**
- **Liver sinusoidal lymphocytosis**
- **Chronic low-grade malarial infection**





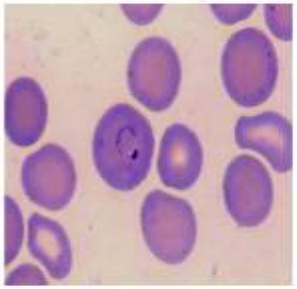
Black pigmentation of the bone marrow in the spine,
due to accumulation of malaria pigment (repeated malaria).

WHO is recommend:

- parasitological confirmation → before treatment is started
- treatment on the basis of clinical suspicion → when parasitological diagnosis is not accessible.

Diagnosis

1- Thin and thick blood films to demonstrate the parasite.



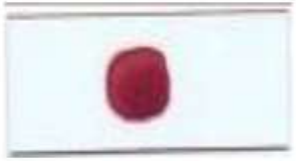
Giemsa stained blood films

Thin blood film

One drop of blood spread on a slide

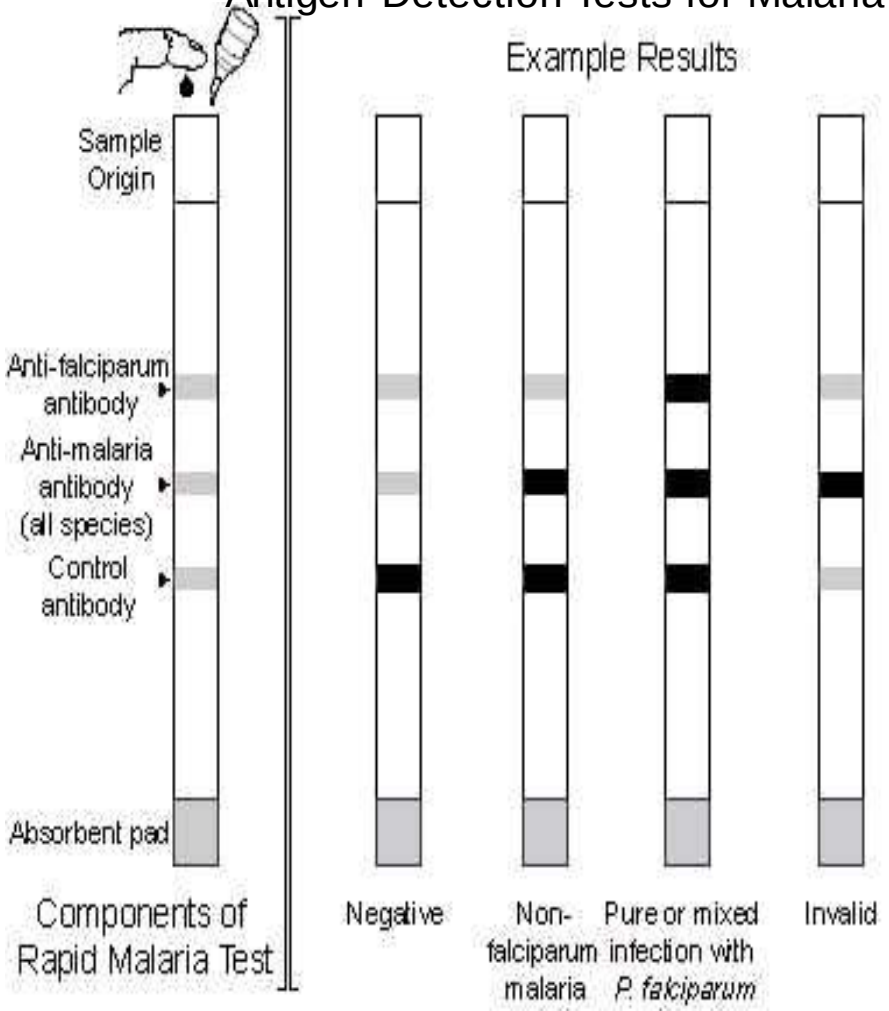
Finger prick

Thick blood film



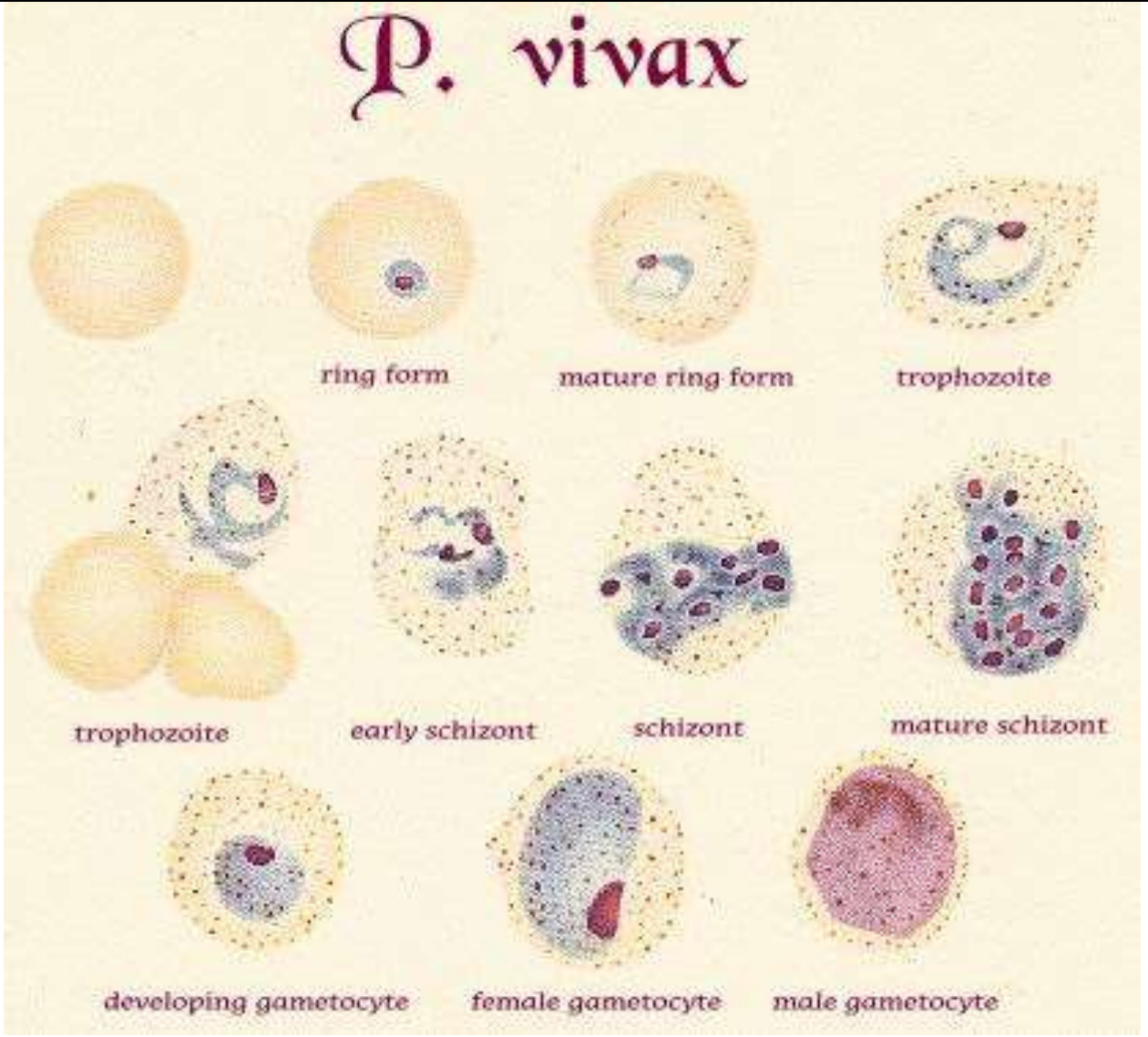
4 drops of blood spread in a small circle on a slide

Antigen Detection Tests for Malaria



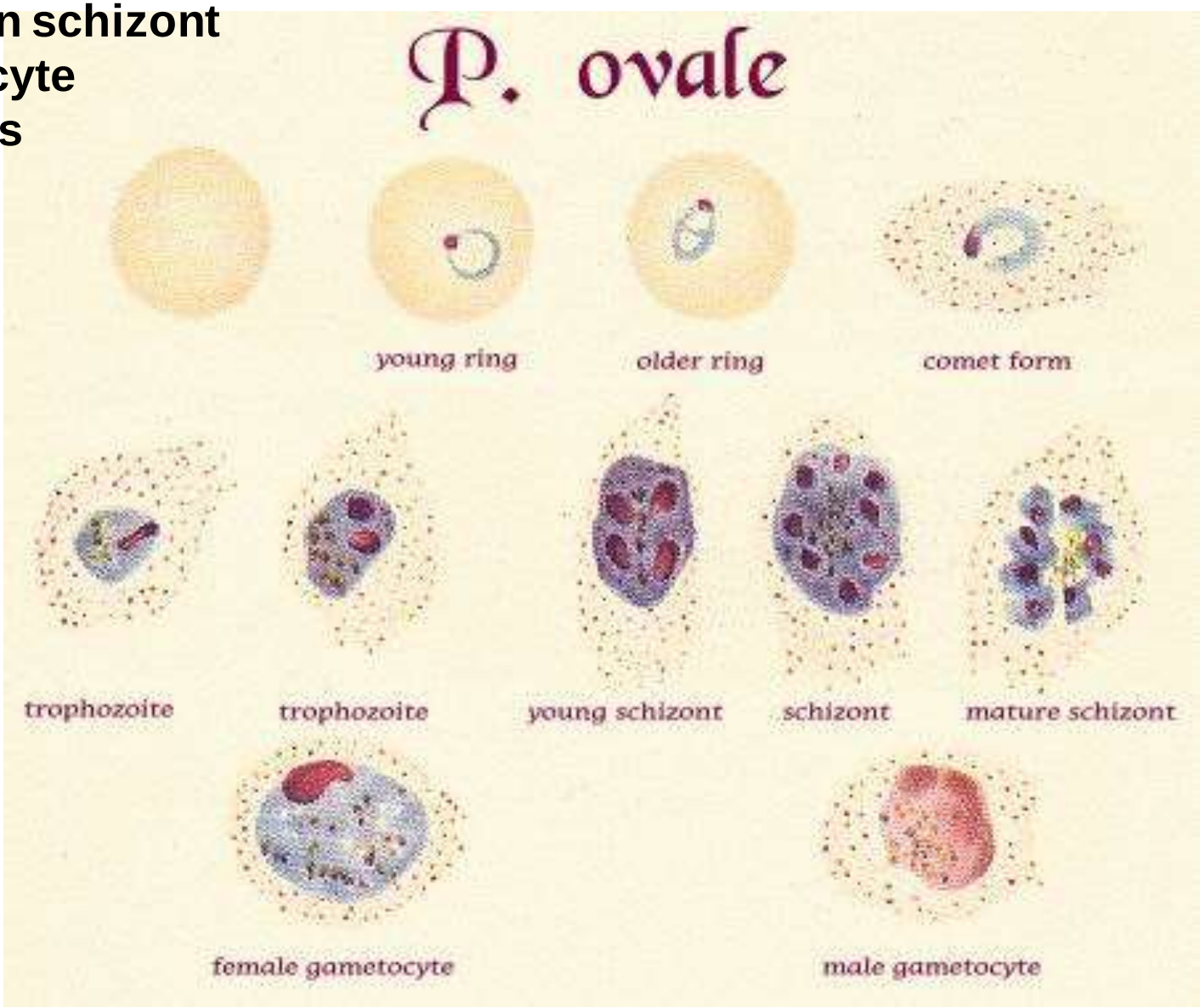
Vivax

enlarged erythrocyte
Schüffner's dots
'ameboid' trophozoite
prefer reticulocytes



Ovale

- similar to *P. vivax*
- compact trophozoite
- fewer merozoites in schizont
- elongated erythrocyte
- prefer reticulocytes



Malariae

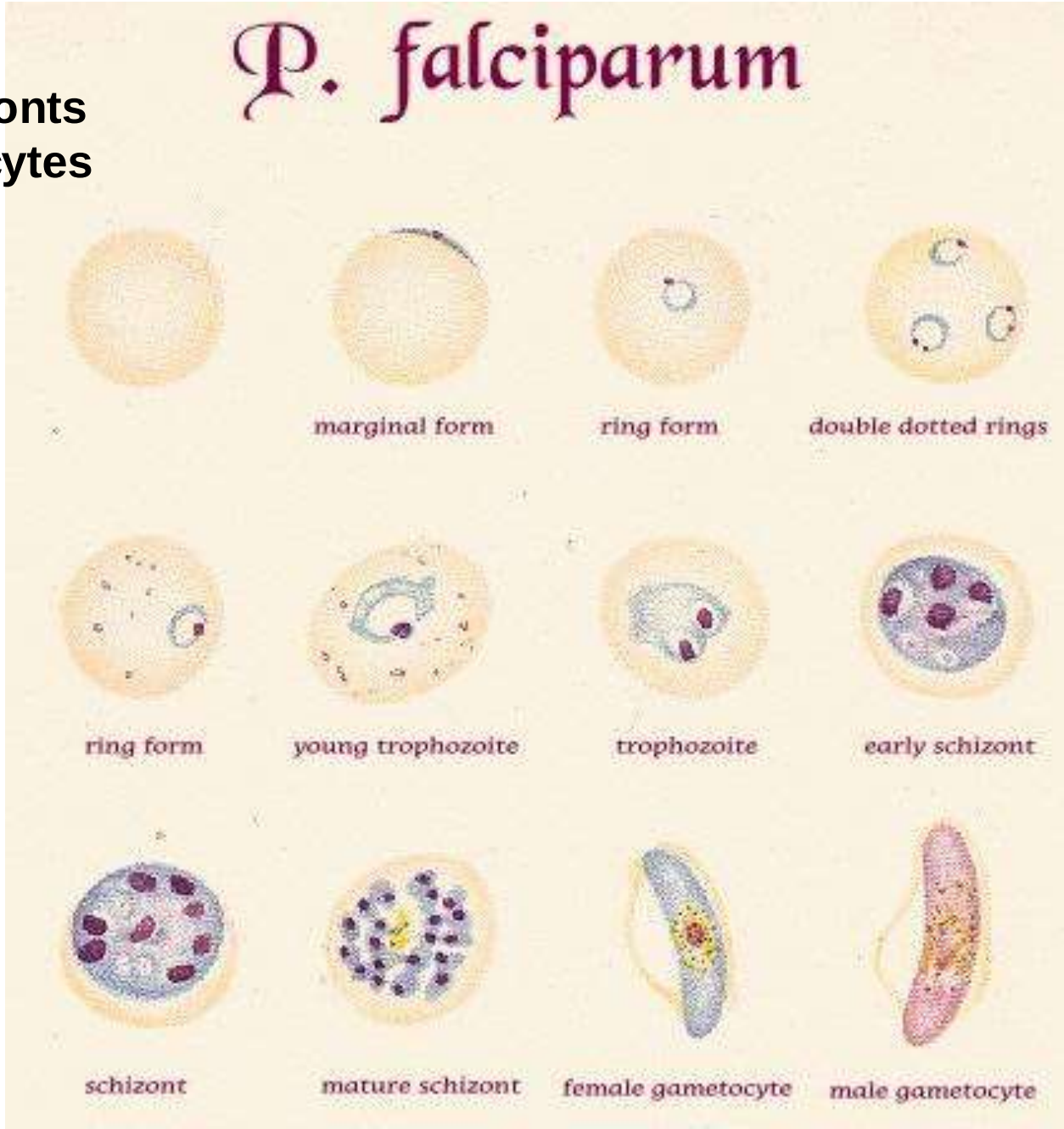
compact parasite

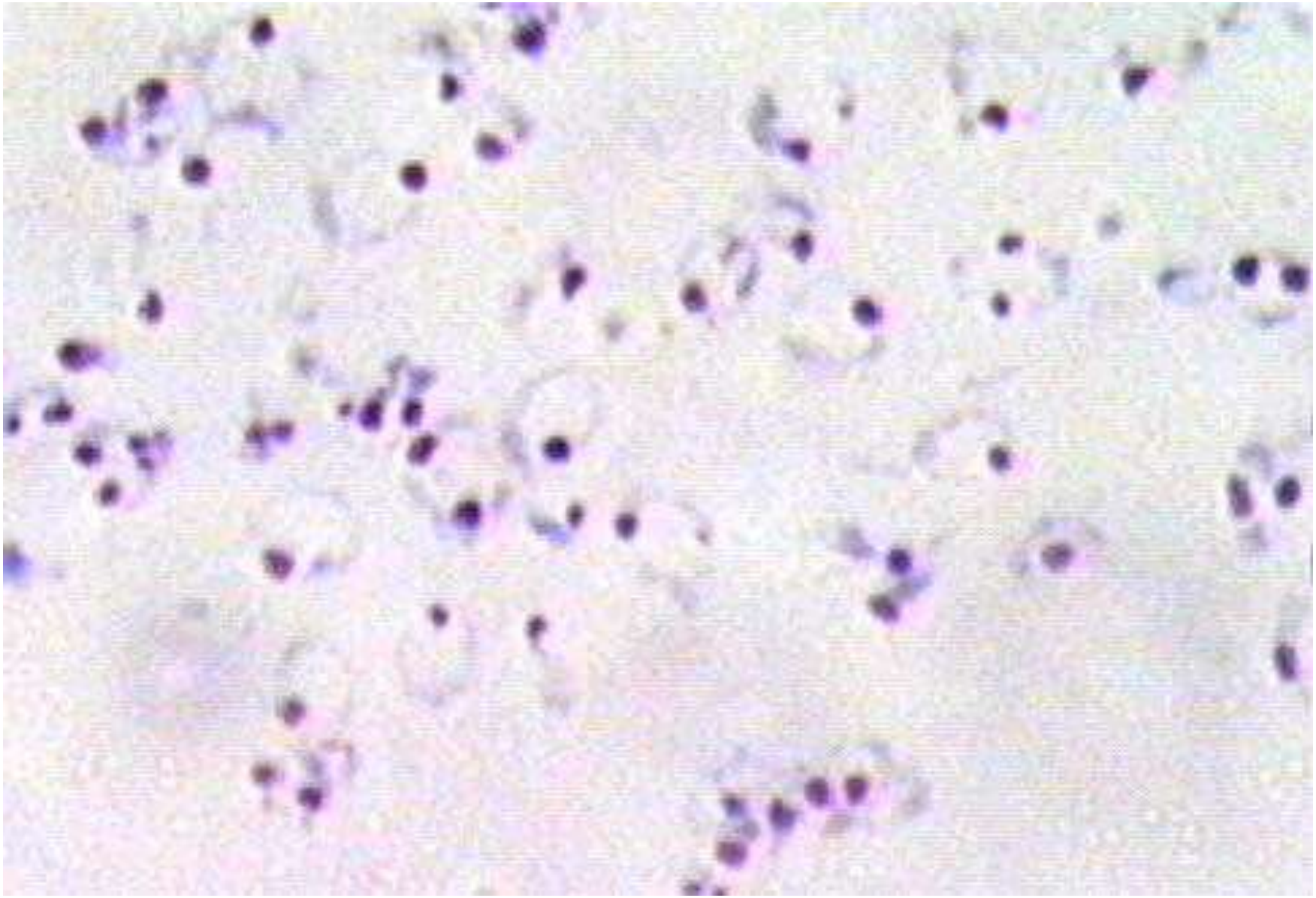
merozoites in rosette

prefers senescent erythrocytes

Falciparum

numerous rings
smaller rings
no trophozoites or schizonts
cresent-shaped gametocytes
all erythrocytes





Plasmodium knowlesi

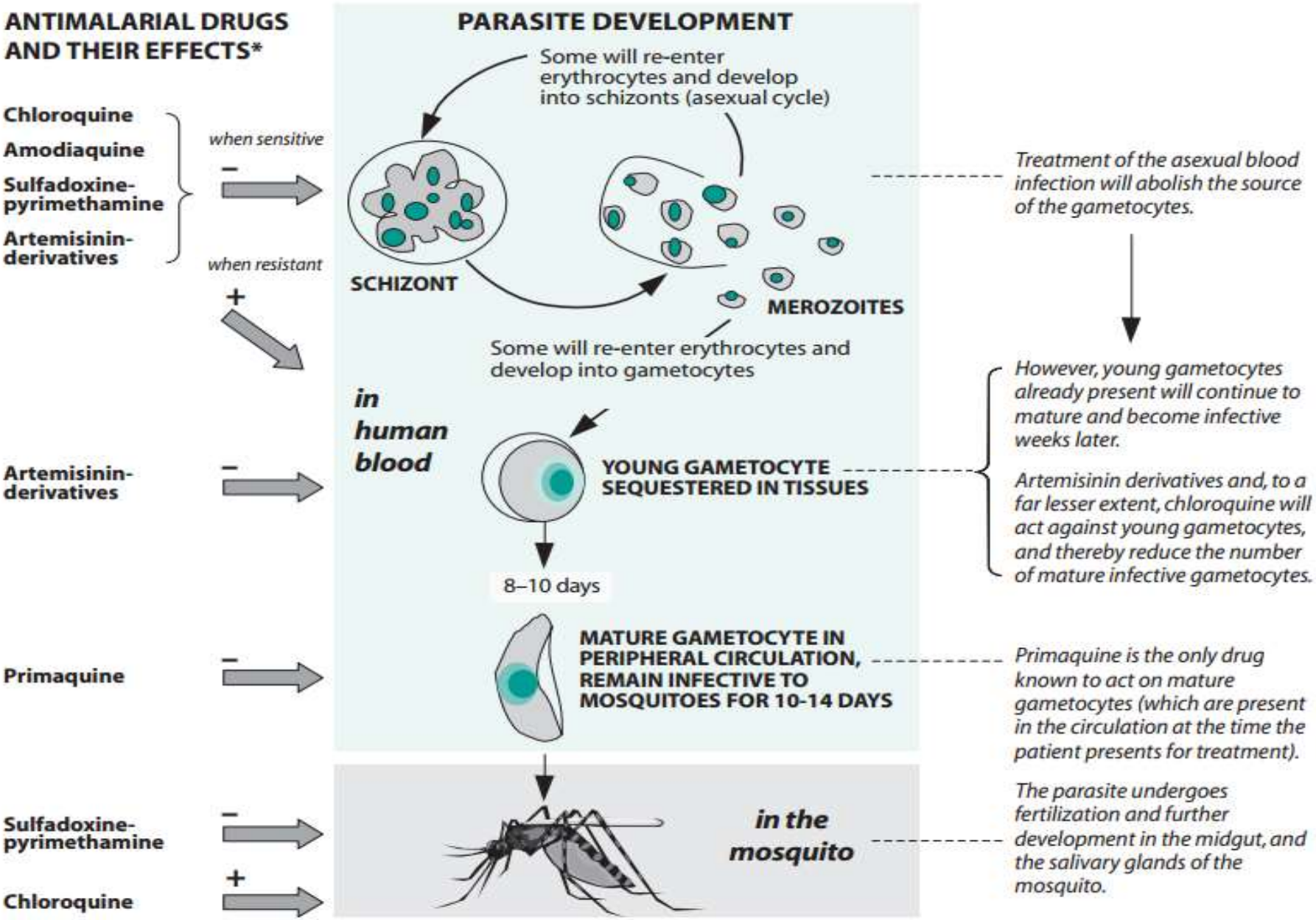
- a primate malaria parasite
- commonly found in South East Asian countries particularly in Borneo, Cambodia,Malaysia, Myanmar, Philippines, Singapore, Thailand
- absent in Africa
- malaria in long-tailed macaques, also infect humans
- asexual erythrocytic cycle of about 24 hours
- fever is quotidian
- a potentially very severe disease if it remains untreated
- microscopically indistinguishable from *Plasmodium malariae, but* early trophozoites are identical to those of *Plasmodium falciparum*
- Incubation 10-12 days
- responds treatment with chloroquine and primaquine
- severe cases treatment - as for severe falcipaum malaria.

Drug Class	**Examples**
Fast-acting blood schizontocide	**choloroquine (+ other 4-aminoquinolines), quinine, quinidine, mefloquine, halofantrine, antifolates (pyrimethamine, proquanil, sulfadoxine, dapsone), artemisinin derivatives (quinhaosu)**
Slow-acting blood schizontocide	**doxycycline (+ other tetracycline antibiotics)**
Blood + mild tissue schizontocide	**proquanil, pyrimethamine, tetracyclines**
Tissue schizontocide	**primaquine**
Gametocidal	**primaquine, artemisinin derivatives, 4-aminoquinolines**
Combinations	**Fansidar (pyrimethamine + sulfadoxine), Maloprim (pyrimethamine + dapsone), Malarone (atovaquone + proquanil)**

Factors Contributing to Development and Spread of Drug Resistance

Factor	Comments
self-treatment	Individuals may only take the drug until symptoms clear or will take lower doses to save money.
poor compliance	Individuals may not complete the full course of treatment because of drug side effects.
mass administration	The widespread use of a drug in an area of intense transmission increases drug pressure by exposing a larger parasite population to the drug.
long drug half-life	Drugs that are slowly eliminated will lead to a longer exposure of the parasite to subtherapeutic drug concentrations.
transmission intensity	High levels of transmission may allow re-infection while drugs are at sub-therapeutic levels.

Transmission of *Plasmodium falciparum* and the effects of antimalarials



Aims of antimalaria treatment			
Aims	**Causation**	**Drugs class**	**Drugs**
Alleviate sympt.	**Blood forms**	**Fast-acting blood schizontocide**	**choloroquine (+other 4-aminoquinolines) quinine, quinidine, mefloquine, halofantrine, antifolates (pyrimethamine, proquanil, sulfadoxine, dapsone), artemisinin & its derivatives (artesunate, artemether, dihydroartemisinin)**
		Slow-acting blood schizontocide	**doxycycline (+ other tetracycline antibiotics)**
	Blood + tissue	**Blood + mild tissue schizontocide**	**proquanil, pyrimethamine, tetracyclines**
Prevent relapses	**Hypnozoites**	**Tissue schizontocide**	**primaquine**
Prevent spread	**Gametocytes**	**Gametocidal**	**primaquine, artemisinin derivatives, 4-aminoquinolines (limited?)**

Never use mefloquine after quinine (may increase myocardial toxicity

WHO 2010: treatment for uncomplicated P.Falciparum

- combination of ≥2 or more antimalarials with different mechanisms of action
- artemisinin-based combination therapy (ACT) are recommendet
- ACT must be given ≥ 3 days
- Recommended ACT:
  - artemether + lumefantrine,
  - artesunate + amodiaquine,
  - artesunate + mefloquine,
  - artesunate + sulfadoxine-pyrimethamine,
  - dihydrortemisinin + piperaquine.
- Second-line antimalarial treatment:
  - artesunate + tetracycline, doxycycline or clindamycin 7 days;
  - quinine + tetracycline or doxycycline or clindamycin
- 7 days.

WHO 2010: Treatment of falciparum in pregnancy

I trimester:

- quinine + clindamycin // artesunate + clindamycin 7 days;
- ACT is indicated only if the other are not available

II & III trimesters:

- ACT or artesunate + clindamycin // quinine + clindamycin 7 days

WHO 2010: Treatment of severe Falciparum malaria

- Artesunate 2.4 mg/kg IV / IM: time = 0 → 12 h → 24 h → 1/day.

Alternative:

- artemether 3.2 mg/kg IM on admission → 1.6 mg/kg/day or or
- quinine 20 mg salt/kg IV infusion / IM on admission → 10 mg/kg x 8 h;

Give parenteral antimalarials for ≥ 24 h , and, thereafter:

– artemether plus lumefantrine,
– artesunate plus amodiaquine,
– dihydroartemisinin plus piperaquine,
– artesunate plus sulfadoxine-pyrimethamine,
– artesunate plus clindamycin or doxycycline,
– quinine plus clindamycin or doxycycline

WHO 2010: Treatment of uncomplicated vivax malaria

- chloroquine 25 mg base/kg divided over 3 days +
  + primaquine 0.25 mg base/kg with food /day for 14 days (oceania, south-east asia → primaquine 0.5 mg/kg)
- ACT + primaquine ← chloroquine-resistant vivax malaria.

Mild-moderate G6pd → primaquine 0.75mg base/kg/week: 8weeks.
severe G6pd deficiency = primaquine contraindicated

Artesunate plus sulfadoxine-pyrimethamine is not effective against P. vivax in many places.

Chemoprophylaxis

- **Primary chemoprophylaxis regimens involve:**
  - **a) taking a medicine before travel ➤**
  - **b) during travel ➤**
  - **c) a period of time after leaving the malaria endemic area**
- **Presumptive antirelapse therapy (terminal prophylaxis).**

– **Atovaquone/Proguanil (Malarone): ≠*P*;**

a) 1-2d b) 1/day c) 7d + Primaquine last 1we + 1we

– **Chloroquine (Aralen) & Hydroxychloroquine (Plaquenil):**

1-2we➤1/we➤4we + Primaquine last 2we

– **Doxycycline: ≠*P*; 1-2d➤1/day➤4we + Primaquine last 2we**

– **Mefloquine: ≠*depression*; 2we➤1/we➤4we + Primaq. 2we**

– **Primaquine: ≠*G6PD-deficiency*; 1-2d➤1/day➤7d; obviates the need for presumptive antirelapse therapy.**

Treatment of malaria in pregnancy

Chloroquine → can be used safely in all trimesters of pregnancy.

Artemisinin → can be considered if the situation demands.

Quinine → can be used in pregnancy, but watchful about hypoglycemia.

Mefloquine → contraindicated in the first trimester of pregnancy

Pyrimethamine/ sulphadoxine → contraindicated in the first and last trimesters.

Halofantrine, tetracycline, doxycycline → absolutely contraindicated

Primaquine → contraindicated in pregnancy

Therefore pregnant with P. vivax → chloroquine 500 mg weekly as suppressive chemoprophylaxis against relapse of malaria.

In the I with uncomplicated falciparum → quinine + clindamycin for 7 days and quinine monotherapy if clindamycin is not available.

Artesunate + clindamycin for 7 days → if this treatment fails.

Treatment of malaria

- **Atovaquone/proguanil** 2 adult tablets bid for 3 days
- **Quinine sulfate** 650 mg q 8 h for 3 or 7 days + *one of the following:*
  - Doxycycline 100 mg bid for 7 days,
  - Tetracycline 250 mg qid for 7 days,
  - Clindamycin 7 mg/kg tid for 7 days
- **Mefloquine** 750 mg, then 500 mg 12 h later
- **Artemether/lumefantrine** 6 doses (1 dose = 4 tablets) over 3 days (at 0, 8, 24, 36, 48, and 60 h)
- **Artesunate** 4 mg/kg once/day for 3 days

Parenteral drugs (all plasmodium)

- **Quinidine gluconate**

  10 mg/kg loading dose (up to 600 mg) in normal saline over 1 h, then continuous infusion of 0.02 mg/kg/min until oral drugs can be started

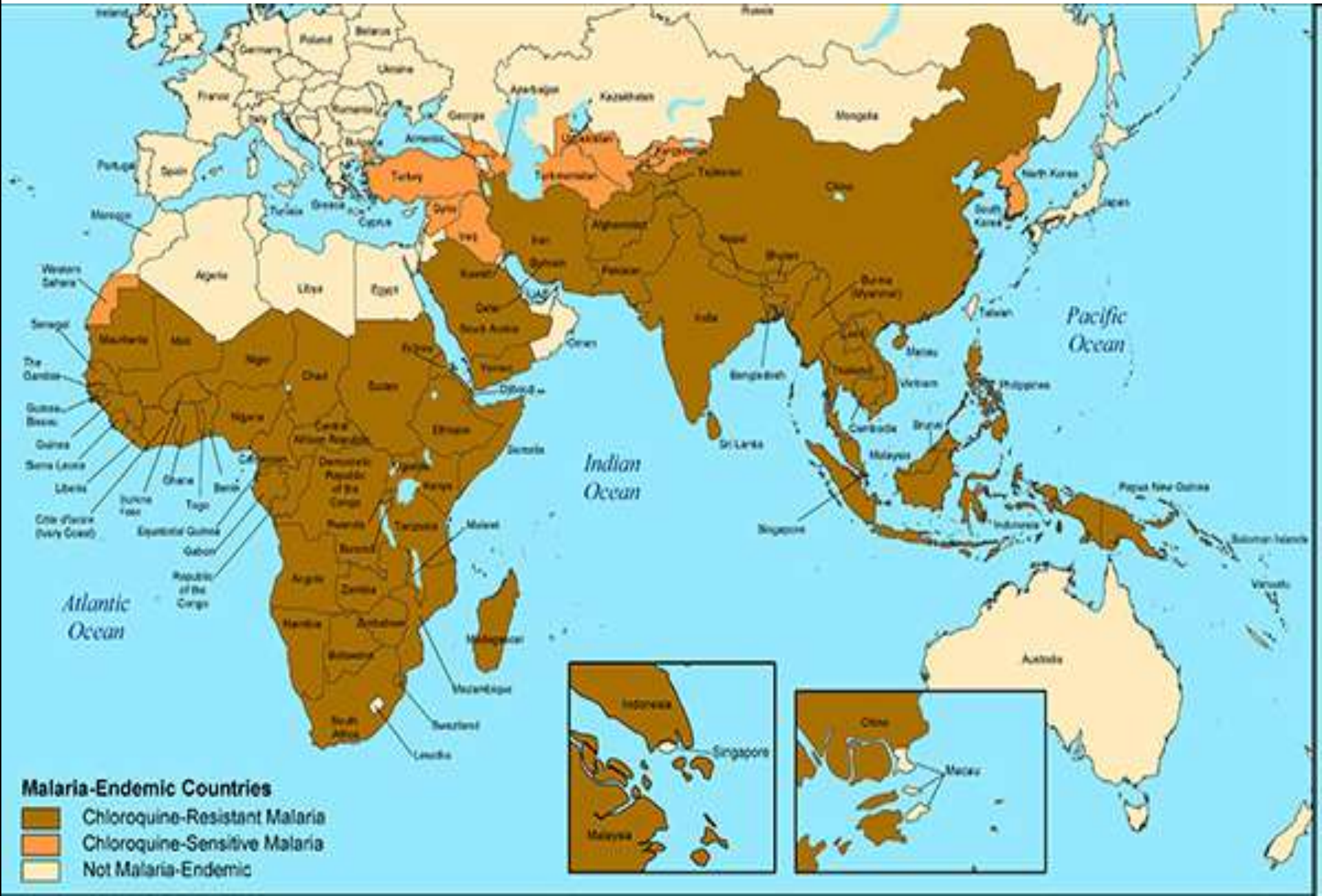
- **Quinine dihydrochloride**

  20 mg/kg loading dose in 5% dextrose over 4 h, then 10 mg/kg over 2–4 h q 8 h (up to 1800 mg/day) until oral drugs can be started

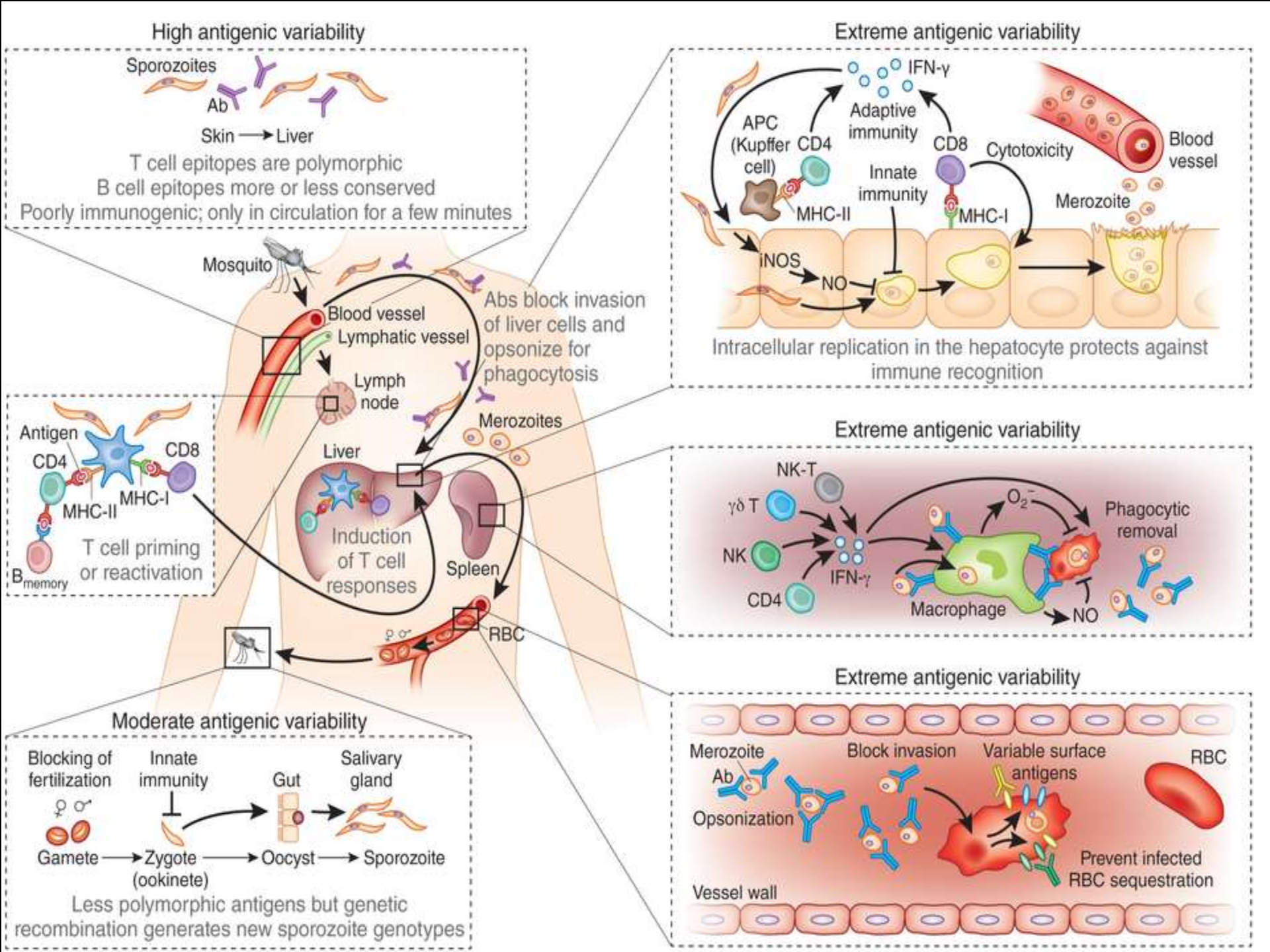
- **Artesunate** *plus* another drug

  2.4 mg/kg IV at 0, 12, 24, and 48 h

CDC. Malaria Risk Information and Prophylaxis, by Country



CDC. Malaria Risk Information and Prophylaxis, by Country


High antigenic variability
Sporozoites
Ab
Skin → Liver
T cell epitopes are polymorphic
B cell epitopes more or less conserved
Poorly immunogenic; only in circulation for a few minutes
Extreme antigenic variability
IFN-γ
Adaptive immunity
APC (Kupffer cell)
CD4
MHC-II
CD8
MHC-I
Cytotoxicity
Innate immunity
Blood vessel
Merozoite
iNOS
NO
Intracellular replication in the hepatocyte protects against immune recognition
Mosquito
Blood vessel
Lymphatic vessel
Lymph node
Abs block invasion of liver cells and opsonize for phagocytosis
Merozoites
Liver
Antigen
CD4
CD8
MHC-II
MHC-I
B memory
T cell priming or reactivation
Induction of T cell responses
Spleen
RBC
Extreme antigenic variability
NK-T
γδ T
NK
CD4
IFN-γ
O2−
Phagocytic removal
Macrophage
NO
Moderate antigenic variability
Blocking of fertilization
Innate immunity
Gut
Salivary gland
♀ ♂
Gamete → Zygote (ookinete) → Oocyst → Sporozoite
Less polymorphic antigens but genetic recombination generates new sporozoite genotypes
Extreme antigenic variability
Merozoite
Ab
Opsonization
Block invasion
Variable surface antigens
RBC
Prevent infected RBC sequestration
Vessel wall

Sporozoites, injected into the skin by the biting mosquito, drain to the lymph nodes, where they prime T and B cells, or the liver, where they invade hepatocytes. Antibodies (Ab) trap sporozoites in the skin or prevent their invasion of liver cells. IFN-γ–producing $CD4^+$ and $CD8^+$ T cells inhibit parasite development into merozoites inside the hepatocyte. However, this immune response is frequently insufficient, and merozoites emerging from the liver invade red blood cells, replicate, burst out of the infected erythrocyte and invade new erythrocytes. Merozoite-specific antibodies agglutinate and opsonize the parasite and can inhibit the invasion of red blood cells through receptor blockade. Antibodies to variant surface proteins also opsonize and agglutinate infected red blood cells (RBCs) and prevent their sequestration (cytoadherence) in small blood vessels. IFN-γ–producing lymphocytes activate macrophages and enhance the phagocytosis of opsonized merozoites and iRBCs. Complement-fixing antibodies to gametocyte and gamete antigens lyse parasites inside the mosquito gut or prevent the fertilization and development of the zygote. Sporozoite, liver-stage and gametocyte and gamete antigens are somewhat polymorphic, whereas merozoite antigens and variant surface antigens are highly polymorphic. APC, antigen-presenting cell.

Clinical case

- A 30 year-old woman, HIV-positive, delivers by planned cesarean section an apparently normal female baby.
- The mother is a native of the Congo who came to France 2 years ago and has not traveled outside France since then.
- The only abnormality found in the baby at delivery is an anemia (12.3 g/dL hemoglobin).
- At 6 weeks post-delivery, the infant is brought in for a fever of one-day duration.
- She is found to have a temperature of 38.5°C and both hepatomegaly (3 cm) and splenomegaly (3 cm).
- Serologic tests for HBs and HCV are negative, and PCR, DNA and RNA for HIV are negative.
- More routine laboratory exams show: hemoglobin 6.4 g/dL, platelets 122,000/µL, LDH 1080 IU/Ml.
- What is your diagnosis?
  - No malaria
  - *Plasmodium falciparum*
  - *Plasmodium vivax*
  - *Plasmodium ovale*
  - *Plasmodium malariae*

Clinical case

- An 18-year-old Australian soldier, had been previously well and was taking daily 100 mg doxycycline prophylaxis.
- He had a three-day history of fever, rigors, nausea and diarrhoea before presenting to a field hospital.
- In hospital he was intubated. He was febrile to 39.6°C, hypotensive, BP 80/50 mmHg, oliguric, low oxygen saturation .
- Thick and thin films demonstrated young rings trophozoites whith two small chromatin dots, also trophozoites in dysmorphic, granulated, enlarged erythrocytes.
- Hyperparasitaemia was evident with a measured parasite load of 60% RBCs infected.
- IV quinine and artesunate was started.
- On the 4-day of his illness a petechial rash was noted. Chest X-ray = consistent with pulm. oedema.
- He was acidotic, hyponatraemic, anaemic, profoundly thrombocytopaenic, mildly coagulopathic and jaundiced.
- His urea was 25mmol/l and creatinine was 403 µmol/l.
- A thick film showed that 1% of RBCs are infected.
- Intravenous quinine 600 mg tds was continued for another 48 hours.
- On the 5-day of his illness the parasite count had fallen to 400/µl.
- The thick film was negative after four days of quinine and three doses of artesunate.

Clinical case

- **An 18-year-old Australian soldier, previously well, daily 100 mg doxycycline prophylaxis.**
- **He had a 3-day history of fever, rigors, nausea, diarrhoea**
- **In hospital: 39.6°C, BP 80/50 mmHg, oliguric, low oxygen saturation .**
- **Thick and thin films → young rings trophozoites whith two small chromatin dots, also trophozoites in dysmorphic, granulated, enlarged erythrocytes.**
- **Hyperparasitaemia 60% RBCs infected.**
- **IV quinine + artesunate was started.**
- **On the 4-day of his illness:**
  - **a petechial rash**
  - **chest X-ray = pulm. oedema.**
  - **acidotic, hyponatraemic,**
  - **anaemic, profoundly thrombocytopaenic, mildly coagulopathic**
  - **Jaundiced, urea 25mmol/l, creatinine 403 µmol/l.**
- **A thick film showed that 1% of RBCs are infected.**
- **IV quinine 600 mg tds was continued for another 48 hours.**
- **The thick film was neg after 4 days of quinine & 3 doses of artesunate.**
- **Inotropes were ceased by day 3 of hospitalization.**
- **The acute lung injury was slow to resolve.**
- **IV ATB and quinine were ceased on day 6.**
- **Intermittent haemodialysis was commenced on day 7, extubated on day 10,**
- **Six weeks later he no longer required haemodialysis.**

Drugs used in the prophylaxis of malaria

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Atovaquone/ proguanil (Malarone)	Prophylaxis in all areas	Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride. 1 adult tablet orally, daily	Pediatric tab contain 62.5 mg atovaquone and 25 mg proguanil: 5–8 kg: 1/2 pediatric tablet daily; >8–10 kg: 3/4 daily; >10–20 kg: 1 daily; >20–30 kg: 2 daily; >30–40 kg: 3 daily; >40 kg: 1 adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time while in the malarious area and for 7 days after leaving such areas. Contraindicated in severe renal impairment (creatinine clearance <30 mL/min). Take with food or a milky drink. Not recommended for prophylaxis for children <5 kg, pregnant women, and women breastfeeding infants weighing <5 kg.
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive malaria	300 mg base (500 mg salt) orally, once/week	5 mg/kg base (8.3 mg/ kg salt) orally, once/week, up to maximum adult dose of 300 mg base	Begin 1–2 weeks before travel to malarious areas. Take weekly while in area and for 4 weeks after leaving such areas. May exacerbate psoriasis.

Drugs used in the prophylaxis of malaria

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Doxycycline (many brand names and generic)	Prophylaxis in all areas	100 mg orally, daily	≥8 years of age: 2 mg/ kg up to adult dose of 100 mg/day	Begin 1–2 days before travel to malarious areas. Daily while in area and for 4 weeks after leaving such areas. Contraindicated in children <8 years of age and pregnant women.
Hydroxychloroquine sulfate (Plaquenil)	only in areas with chloroquine-sensitive malaria	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	Begin 1–2 weeks before travel to malarious areas. Take weekly while in area and for 4 weeks after leaving such areas.
Mefloquine	Prophylaxis in areas with mefloquine-sensitive malaria	228 mg base (250 mg salt) orally, once/week	≤9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once/week; >9–19 kg: 1/4 tablet once/week; >19–30 kg: 1/2 tablet once/week; >31–45 kg: 3/4 tablet once/week; ≥45 kg: 1 tablet once/ week	Begin at least 2 weeks before travel to malarious areas. Take weekly while in area and for 4 weeks after leaving such areas. Contraindicated in allergic to related compounds (e.g., quinine, quinidine) and in persons with active depression, anxiety, psychosis, schizophrenia. Not recommended for persons with cardiac conduction abnormalities.

Drugs used in the prophylaxis of malaria

Primaquine	**Prophylaxis for short-duration travel to areas with principally *P.vivax***	**30 mg base (52.6 mg salt) orally, daily**	**0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily**	**Begin 1–2 days before travel to malarious areas. Take daily while in area and for 7 days after leaving such areas.** **Contraindicated in G6PD deficiency. Contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level.**
Primaquine	**Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale***	**30 mg base (52.6 mg salt) orally, once/day for 14 days after departure from the malarious area.**	**0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, once/day for 14 days after departure from the malarious area**	**Indicated for persons who have had prolonged exposure to *P. vivax* and *P. ovale* or both. Contraindicated in persons with G6PD[1] deficiency. Contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level.**

- http://www.malariasite.com/malaria/Evolution.htm
- http://www.slideshare.net/doctorrao/malaria-1478424
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3031473/
- http://www.sudanjp.org/uploads/9/2/7/0/9270568/cerebral_malaria_in_children.pdf
- http://apps.who.int/iris/bitstream/10665/79317/1/9789241548526_eng.pdf
- http://www.nature.com/nm/journal/v19/n2/fig_tab/nm.3083_F1.html
- VIDEO: http://www.youtube.com/watch?v=OEDhe4MPEMc
- **Cerebral Malaria; Mechanisms Of Brain Injury And Strategies For Improved Neuro-Cognitive Outcome:** http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056312/
- http://en.impact-malaria.com/web/e-learning_malaria
- http://bmb.oxfordjournals.org/content/75-76/1/29.full
- http://www.malariasite.com/malaria/Complications3.htm
- Malaria site: all about malaria: http://www.malariasite.com/index.htm
- WHO Malaria treatment guidelines: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf

- **Recumbent [rɪ'kʌmbənt]** лежачий; лежащий; откинувшийся (*на что-л.*) **semirecumbent =** полулежащий, находящийся на полупостельном режиме
- **Lassitude ['læsɪt(j)uːd]** *усталость, утомление; апатия* **Синонимы:** weariness, tiredness