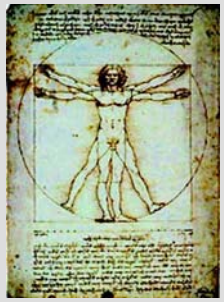

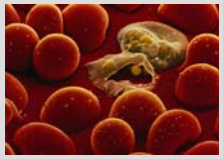

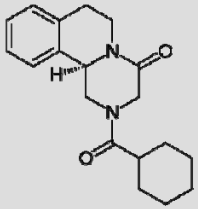

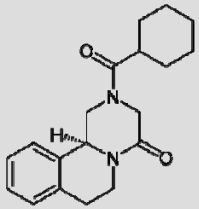

University of São Paulo
Institute of Biomedical Sciences
Department of Parasitology
Unit for Drug Discovery
Carsten Wrenger

Plasmodium and Malaria

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1) History
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Malaria – History from the early beginning

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- Malaria probably played a part in dissuading Genghis Khan (1162-1227) from invading Western Europe

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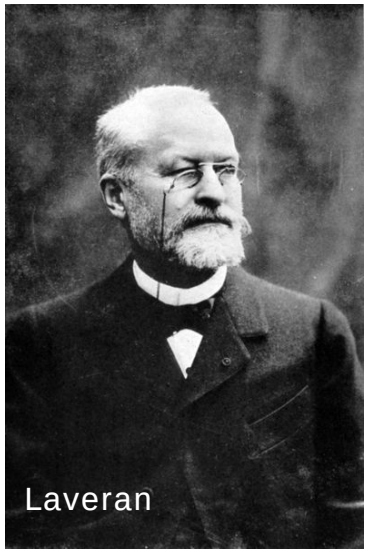
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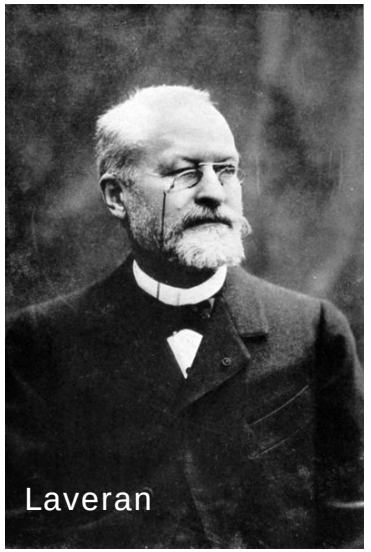
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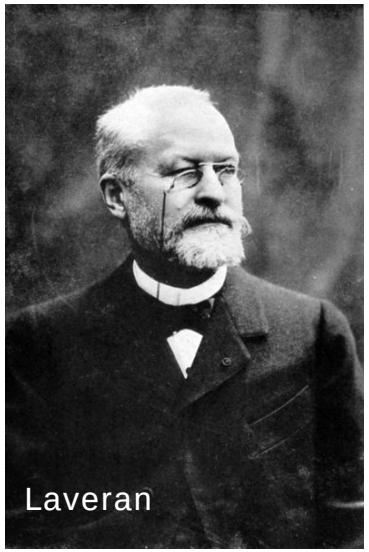
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- Discovery of Dichlordiphenyltrichlorethan (DDT) as toxin against athropodes by Paul Hermann Müller (Nobel Prize 1948)

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- Artemisinin, discovered by Tu Youyou, last line of malaria defence? (Nobel Prize 2015)

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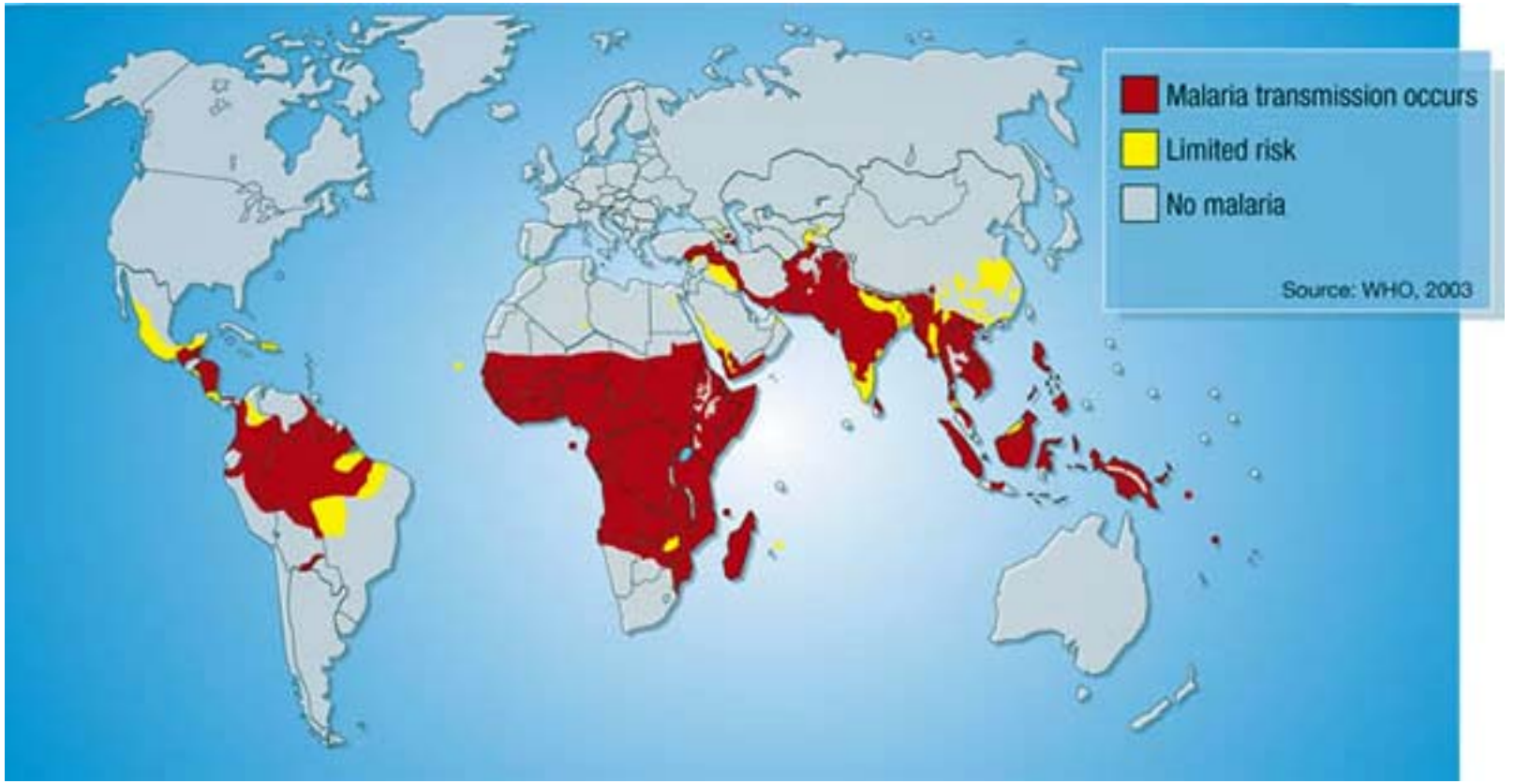
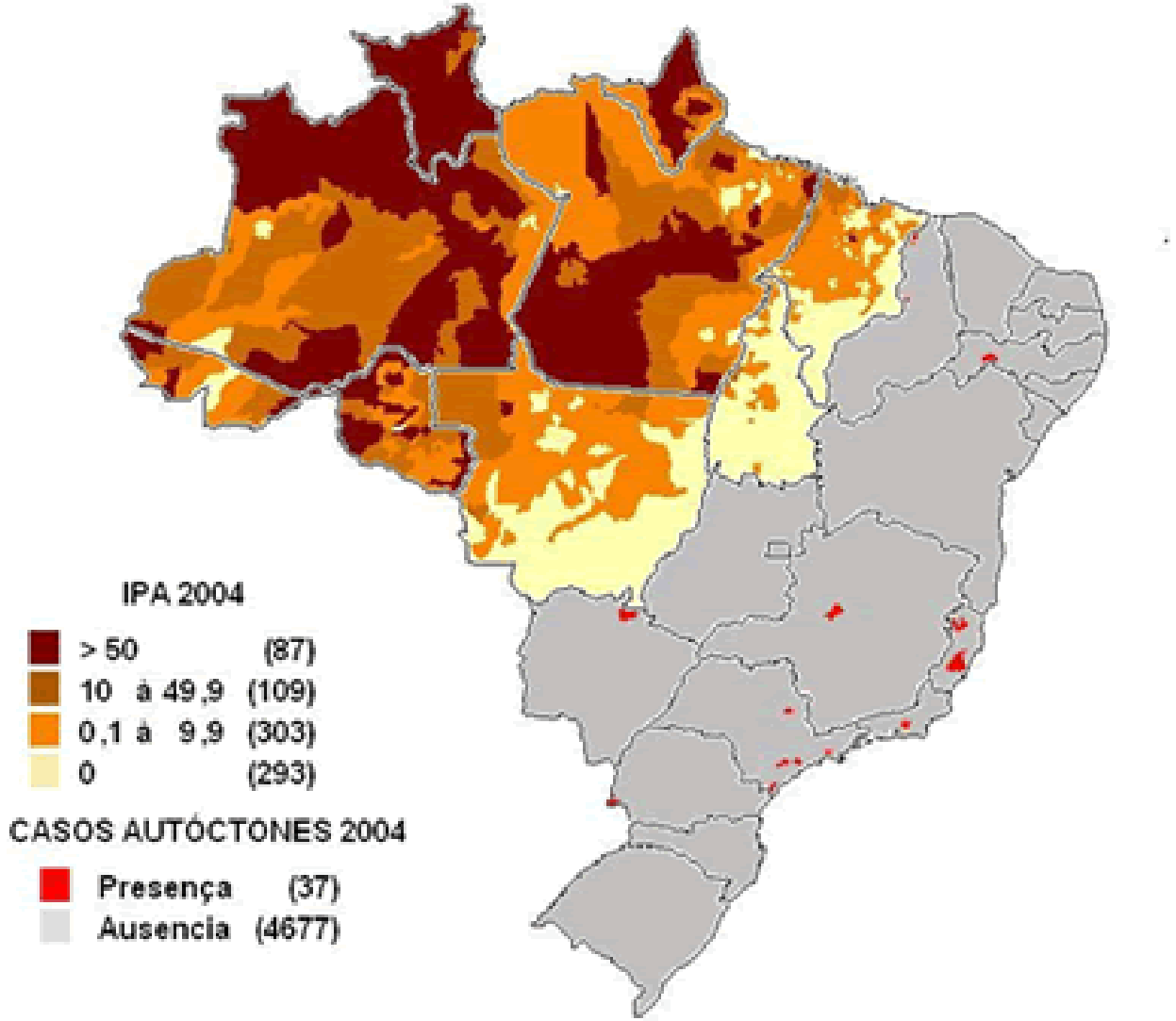
Malaria World Wide



- 300 – 500 million cases every year
- 450.000 deaths every year
- Pregnant women and children under the age of 5 years are at risk
- 90% of malaria cases are in Africa

Malaria in Brazil

Mapa transmissão da malária. BRASIL, 2004.



Fonte: SVS/MS. Atualizados em 06.10.2005. Dados sujeitos a alteração

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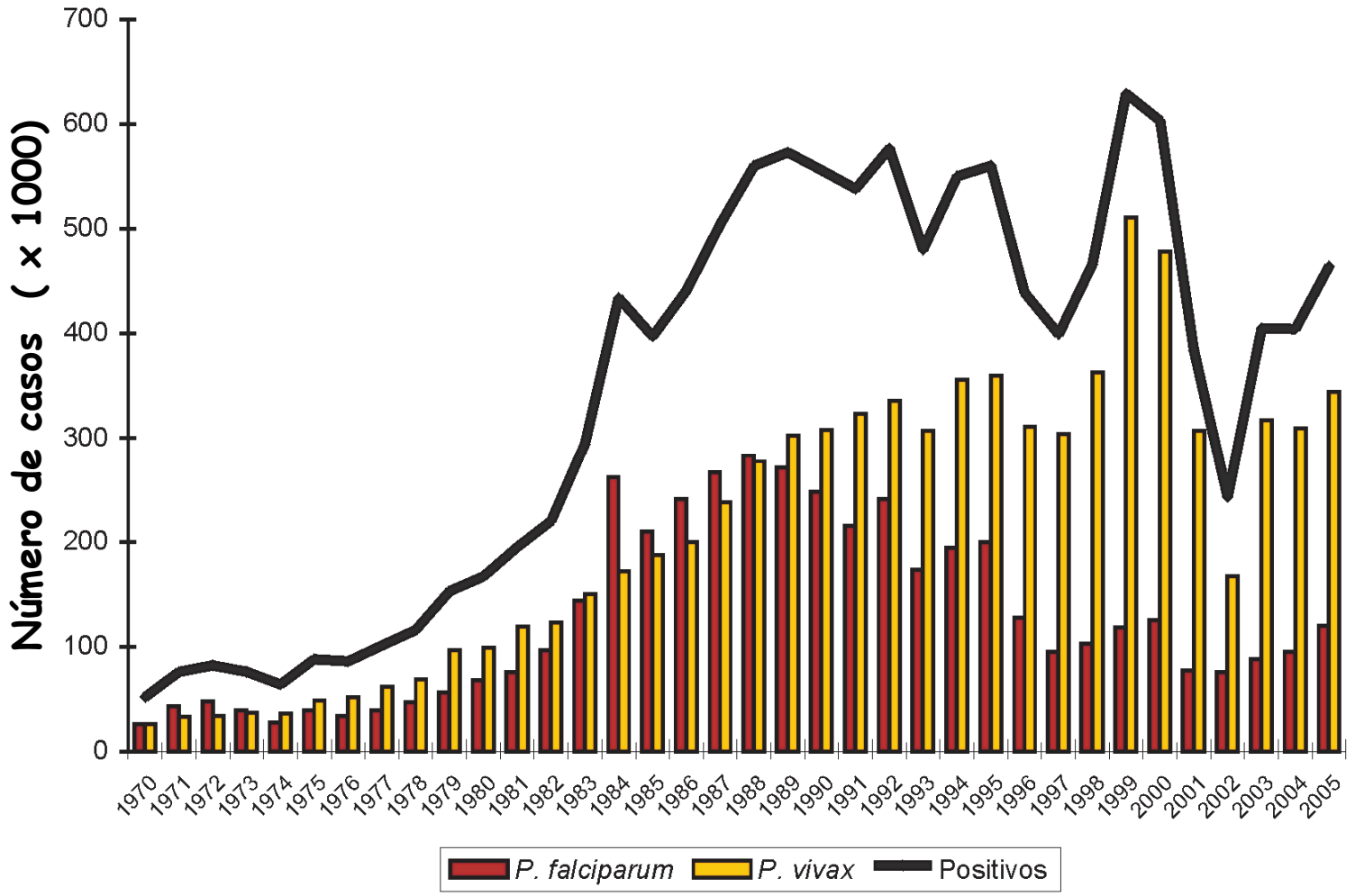

✓ About 75% of the malaria cases are caused by P.vivax

Fonte: Ministério da Saúde

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Anopheles

- development in different types of water – brackish, sweet etc

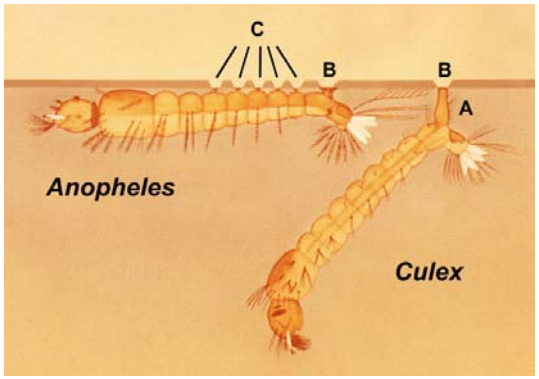
- complete sporogony of Plasmodium in the mosquito

- 30 – 50 species are transmitted by a bloodmeal

- most important vectors are *A. gambiae* in Africa and *A. Darlingi in Brazil*

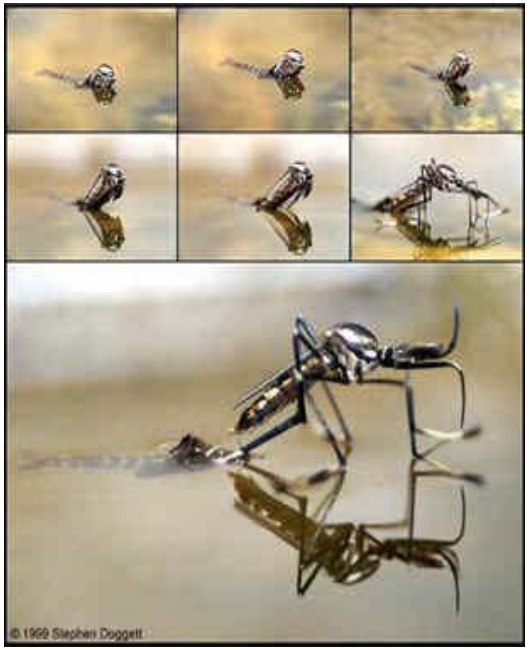
Holometabolism – Development of the mosquito

Eggs – 1-3 days



Pupas – 24 hs

Adults
- Male ~ 15 days
- Female ~ 40 - 50



2-3 day after a bloodmeal of a female - 70 -90 eggs

Malaria vectors

Anopheles darlingi

Anopheles gambiae

Taxonomy of *Plasmodium*

Protozoa

Apicomplexa

Conoidasida

Haemosporida

Plasmodium

P. vivax
P. falciparum
P. ovale
P. malariae
P. knowlesi

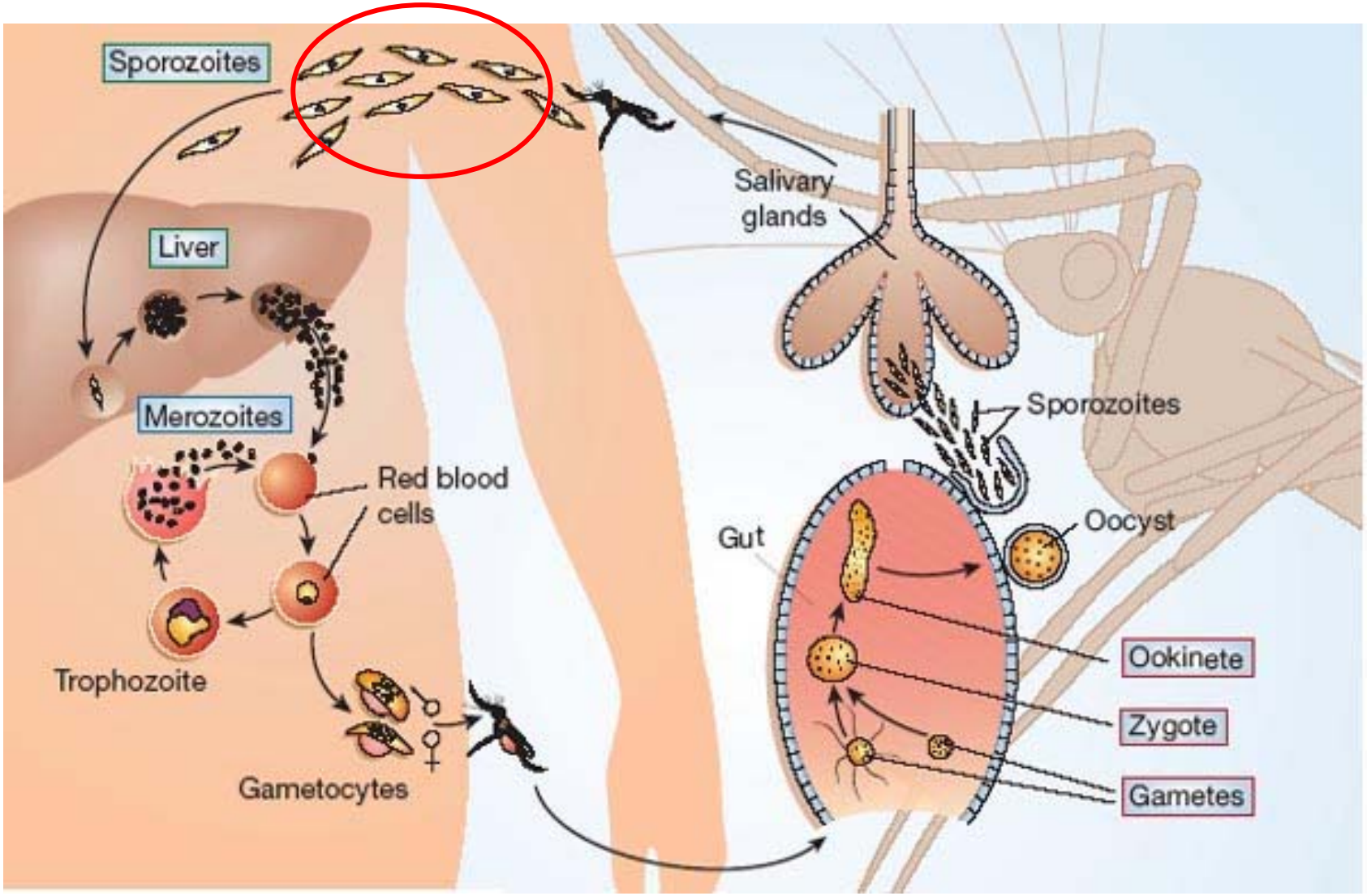
Intermediate host: HUMAN

Definite host: MOSQUITO

Species of *Plasmodium* and their hosts

Species	Naturai host	Geographical location
P. falciparum	Human	Tropics
P. vivax	Human	Tropics and Subtropics
P. malariae	Human/Chimpanzee	Tropics and Subtropics
P. ovale	Human	Tropics in Africa and Asia
P. reichenowi	Chimpanzee	Central Africa
P. cynomolgi	Monkeys	Asia
P. fieldi	Monkeys	Malaysia
P. inui	Monkeys	India and Asia
P. knowlesi	Monkeys and Human	Malaysia
P. simiovale	Monkeys	Sri Lanka
P. gonderi	Monkeys	Central Africa
P. yoelii	Rodents	Central Africa
P. berghei	Rodents	Central Africa
P. gallinaceum	Chicken	Asia

Lifes cycle of *Plasmodium*

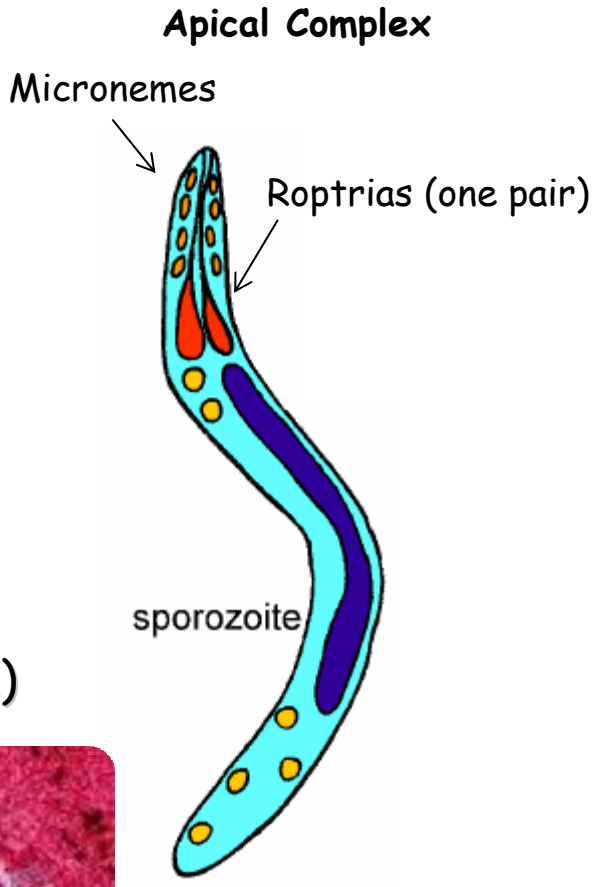


Sporozoite

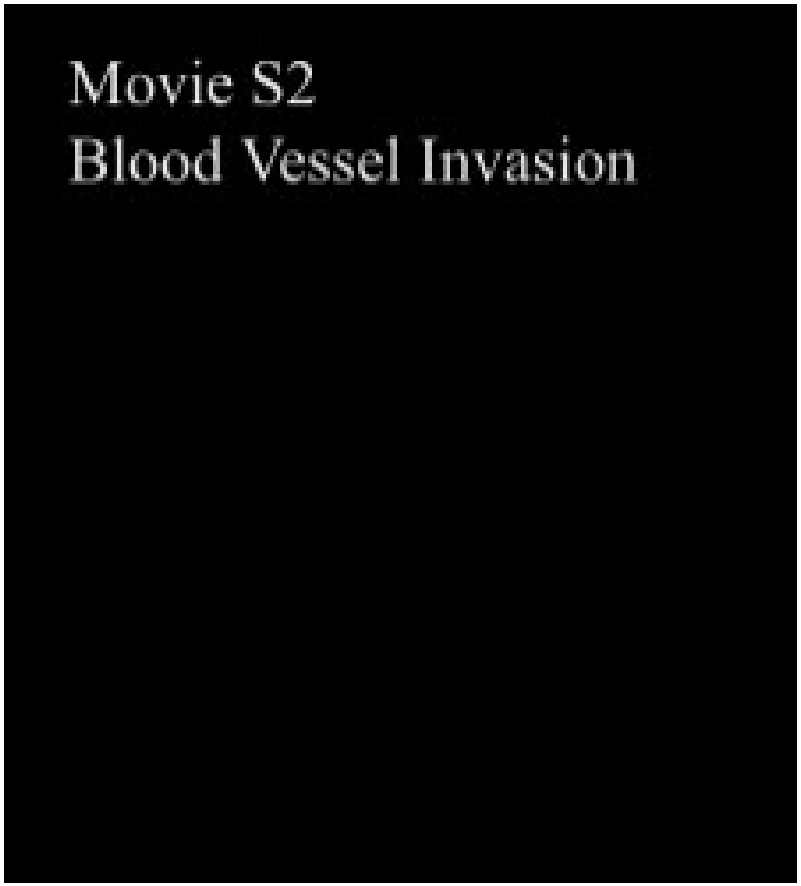
- ✓ 10-15 µm long by 1 µm in diameter
- ✓ 2 membranes (external and internal)
- ✓ Roptrien and micronemes: proteins required for penetration
- ✓ 2 surface proteins have adhesive properties to the hepatocyte:

  CSP (circumsporozoite protein)

  TRAP (anonymous protein related to thrombospondin)

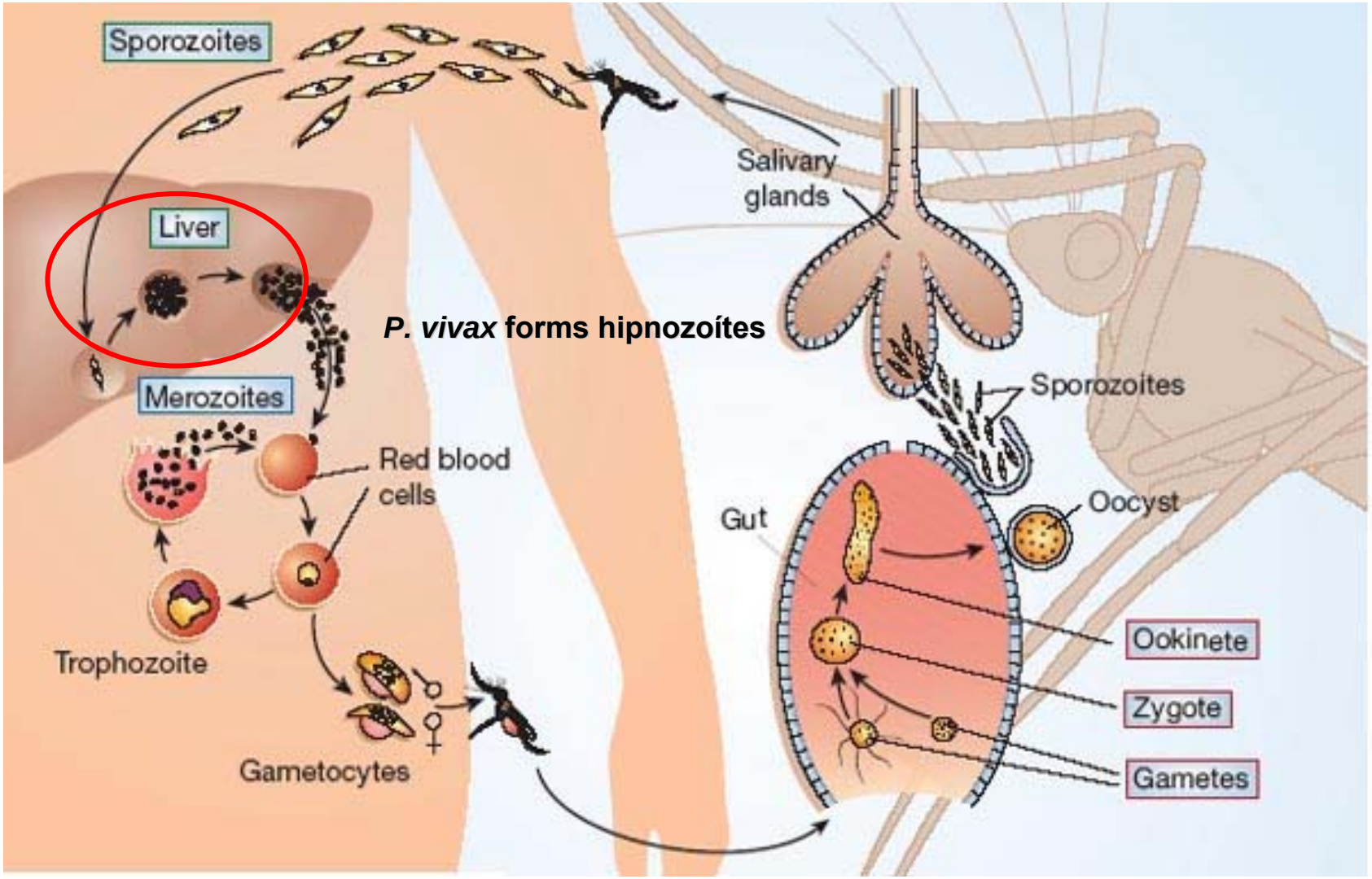


Movement of the sporozoites

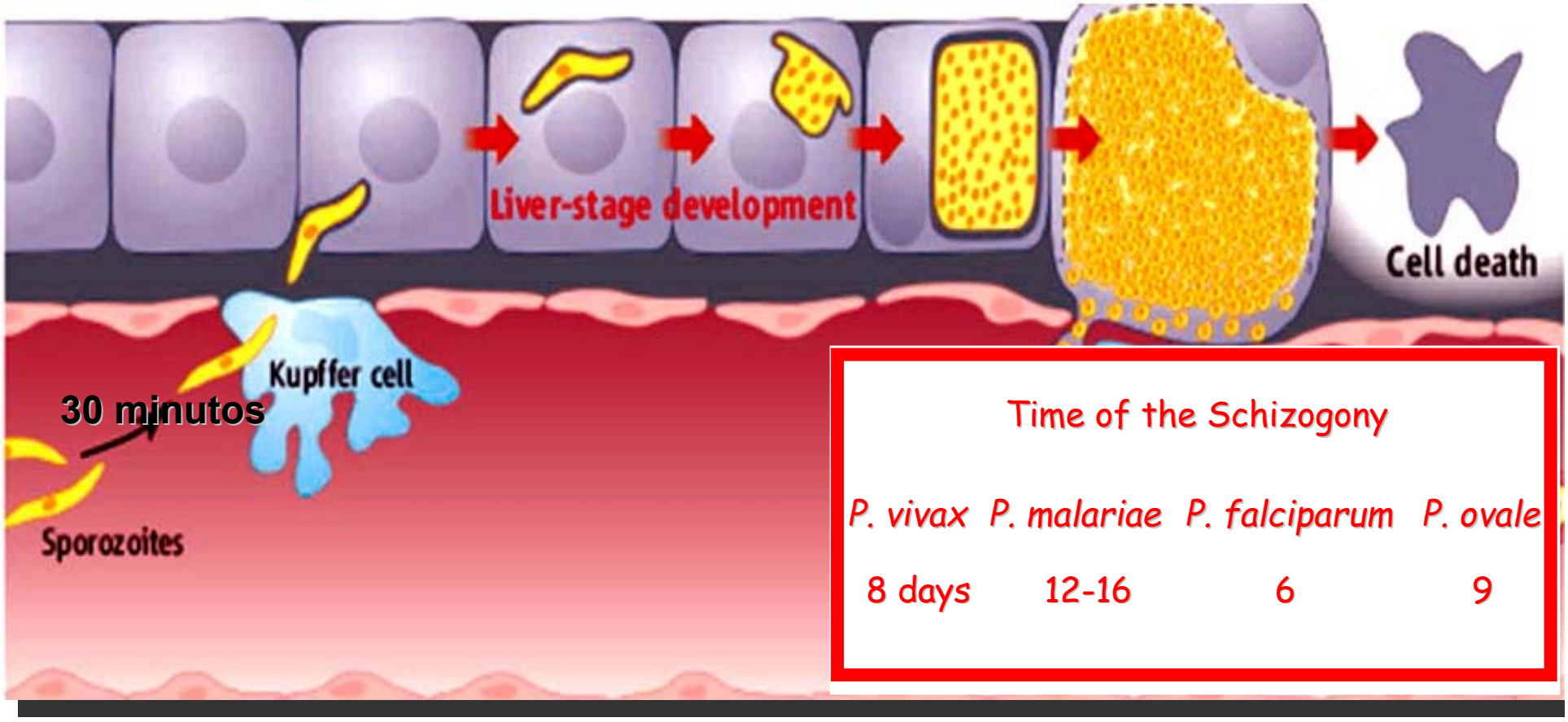


Source: Amino, R

Lifes cycle of *Plasmodium*



Liver phase development

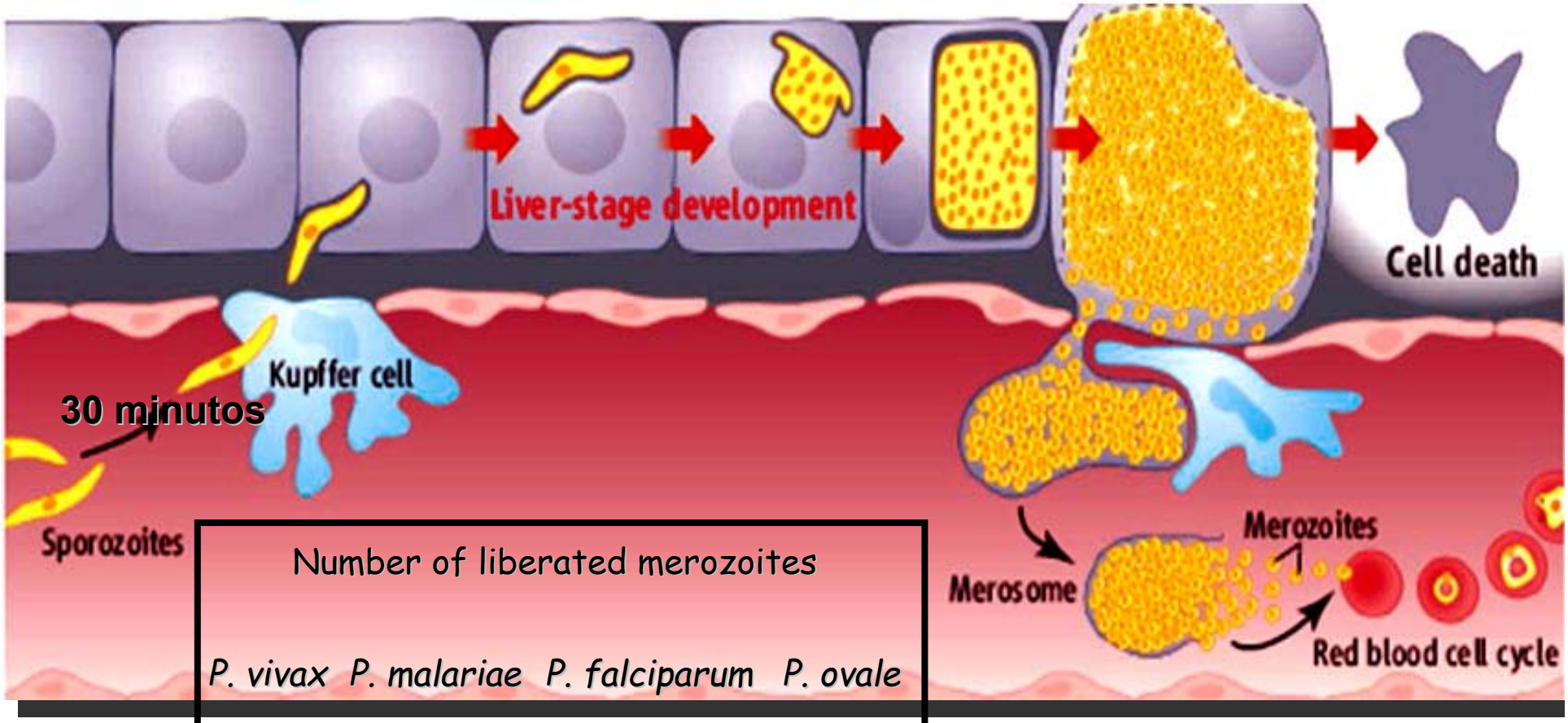


Time of the Schizogony

P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
8 days	12-16	6	9

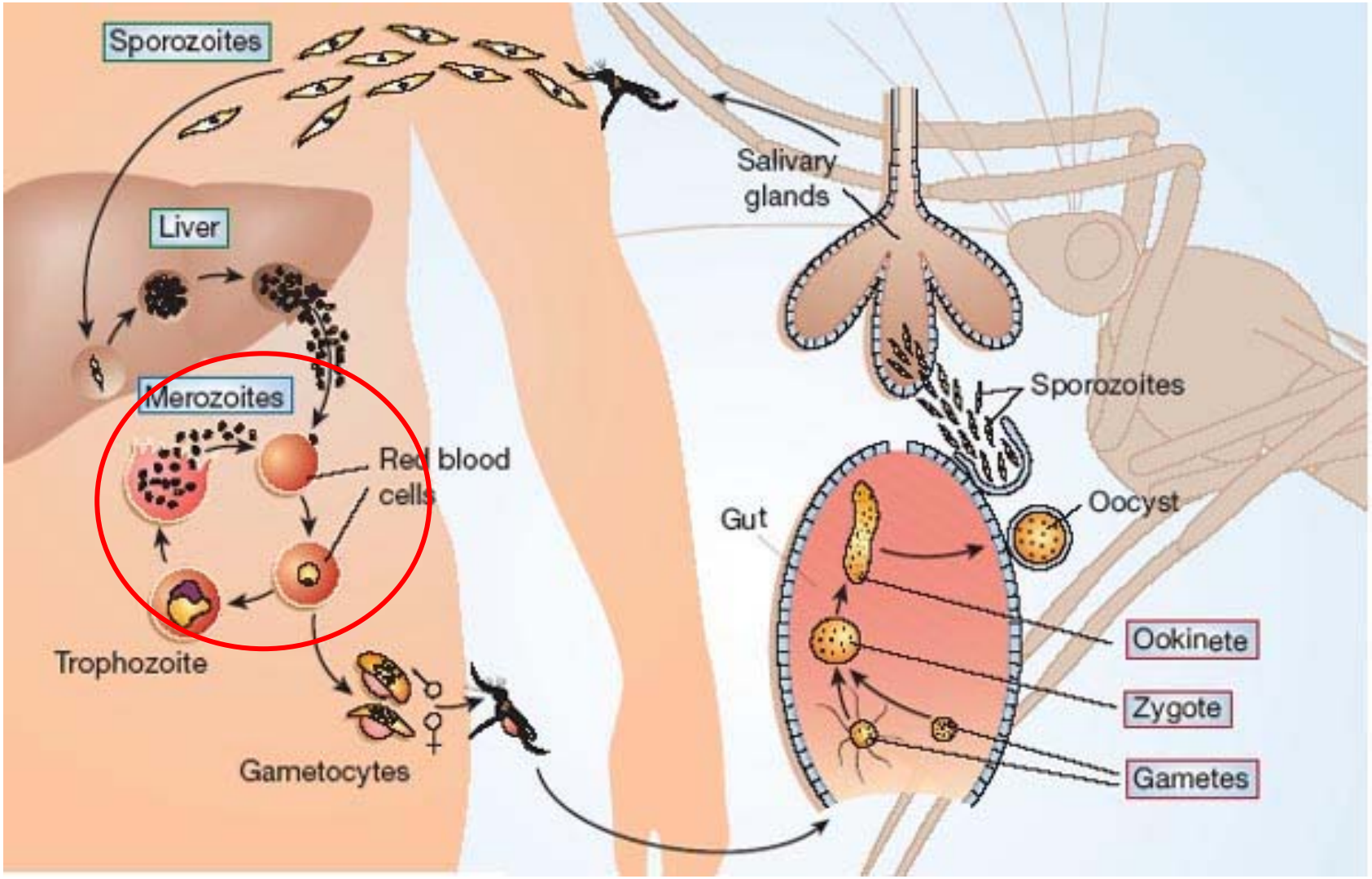
"The parasite then undergoes a process known as schizogony (the nucleus divides without dividing the membrane), giving rise to a structure known as schizont."

Liver phase development



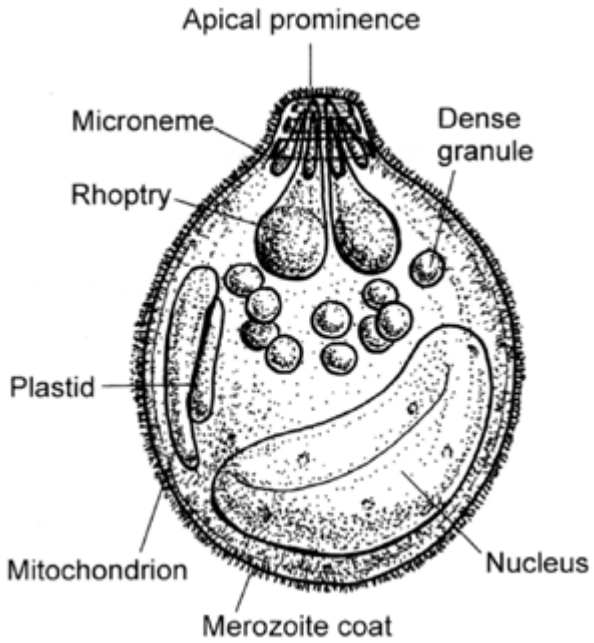
Number of liberated merozoites			
P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
10.000	2.000	40.000	15.000

Lifes cycle of *Plasmodium*



Merozoite

- ✓ invade red blood cells
- ✓ has an ovale shape
- ✓ 1 x 1,5 μm
- ✓ 2 membranes (external and internal)
- ✓ roptria and micronemes: Proeteins required for penetration



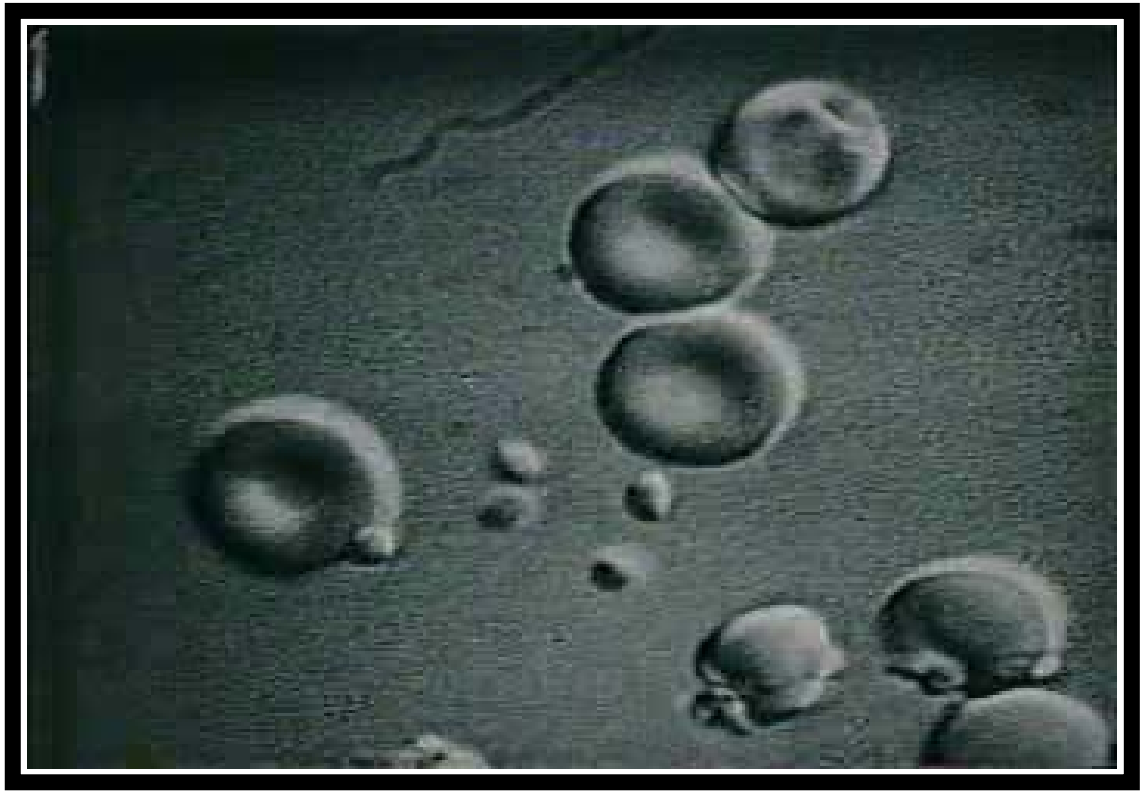
Types of red blood cells which are infected

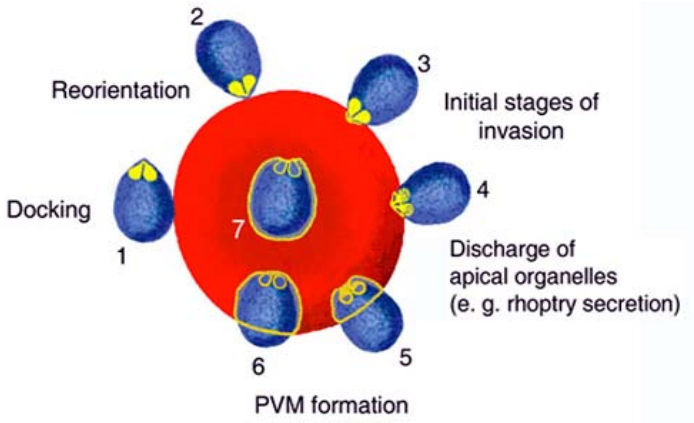
P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
Reticulocytes	Erythrocytes	All types	Reticulocytes

Invasion by the merozoite

- Invasion of the red cell is facilitated by the secretion of enzymes in the roptria
- The firm interaction / invasion depends on proteins from the surface of the merozoite and the red blood cell:

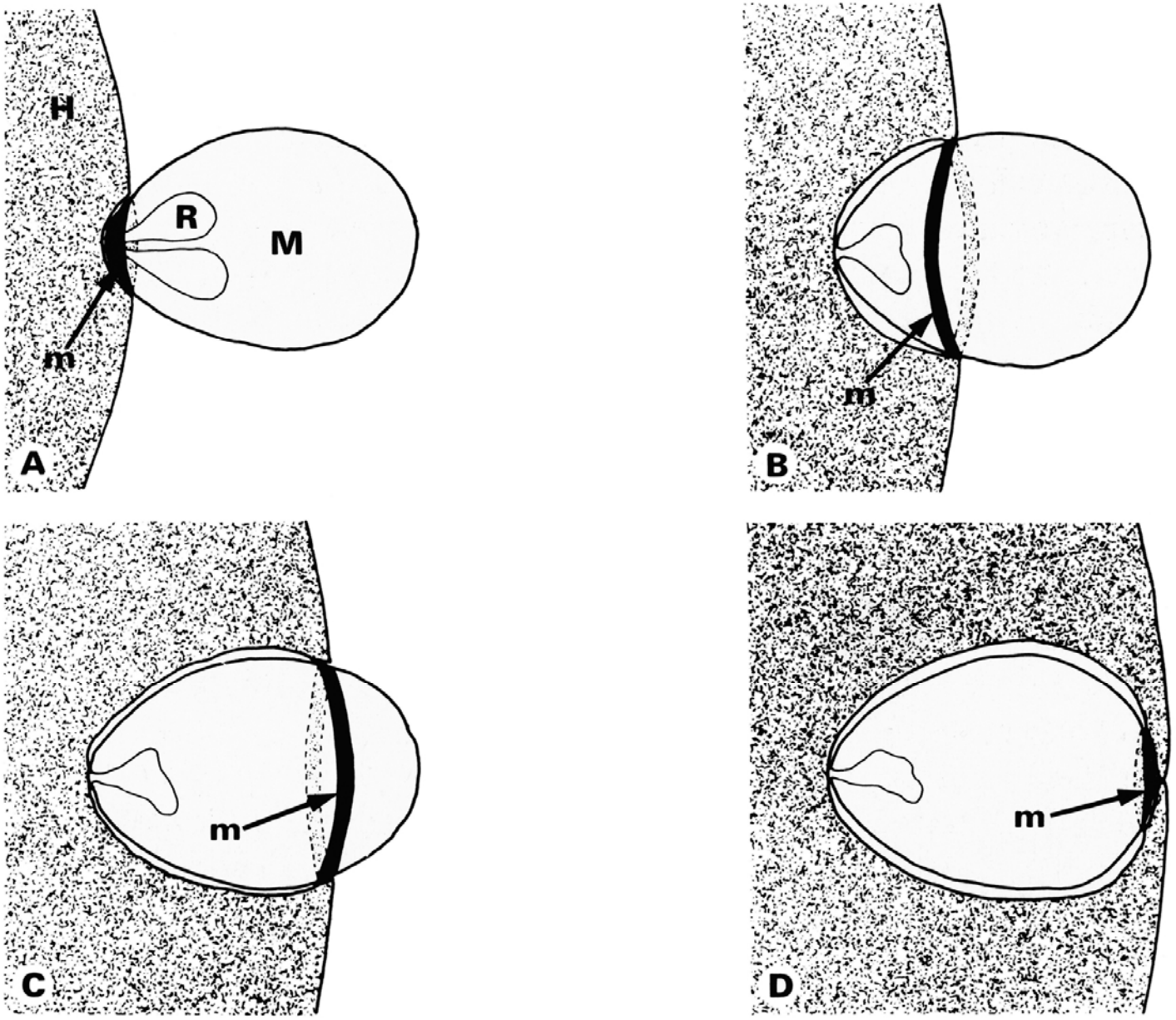
- *P. vivax*: Duffy binding protein 1 and 2 (parasite) and Duffy factor (RBC)
- *P. falciparum*: EBA-175 (parasite) and glycophorins (RBC)



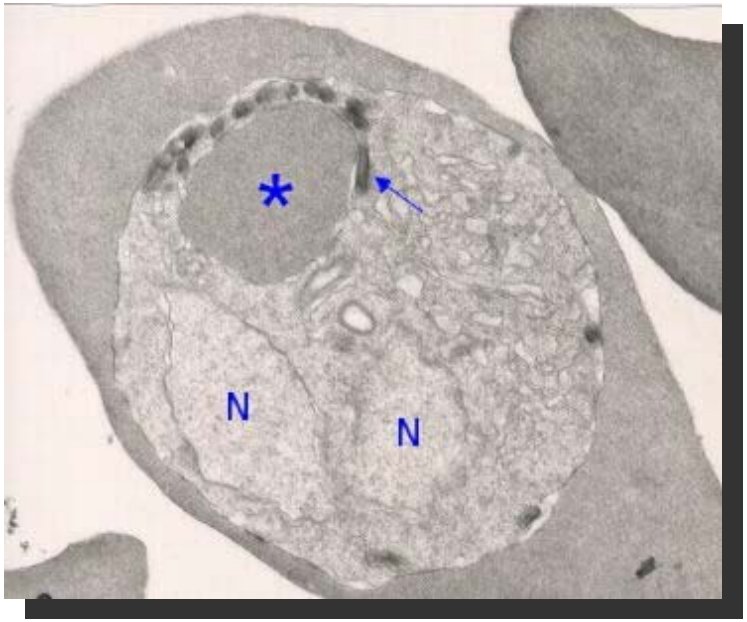


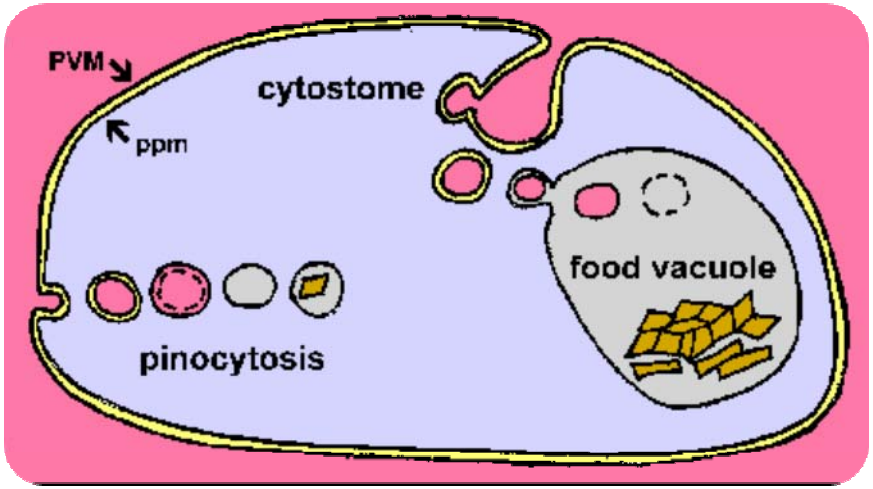
Source: NIH

Invasion by the merozoite



Trophozoite





✓ It is the form found inside the erythrocyte after 10-18 hours of infection.

✓ Digest hemoglobin from the red blood cell into the alimentary vacuole.

✓ Mature trophozoite: initiates the expression of proteins capable of localizing on the surface of the erythrocyte.

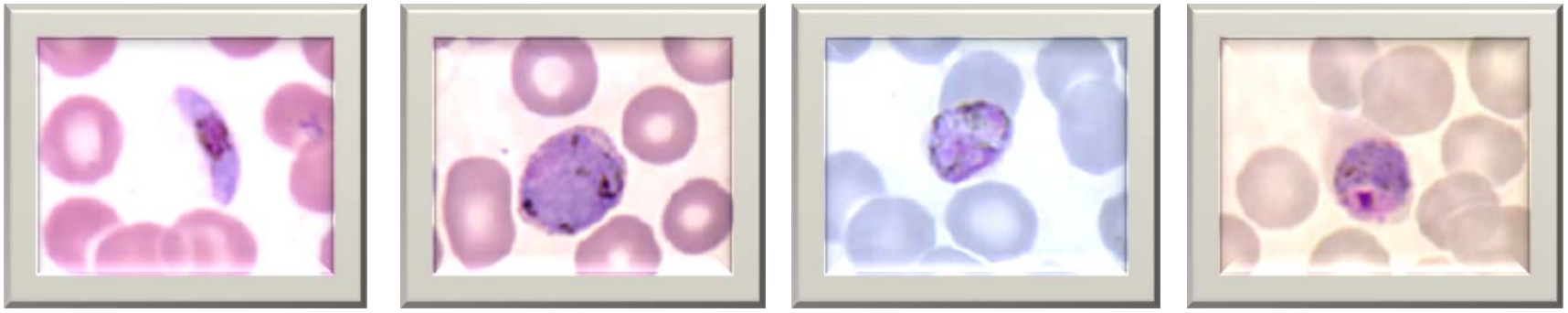
Schizont

- Schizogony: form of asexual reproduction in which multiple mitoses occur, giving rise to a multinucleated cells.
- Once the nucleus and organelles have replicated, cytokinesis occurs, giving rise to merozoites.
- They express proteins that will be embedded in the surface of the infected red blood cell.

Number of created merozoites			
P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
12-24	6-12	8-24 (or +)	4-16

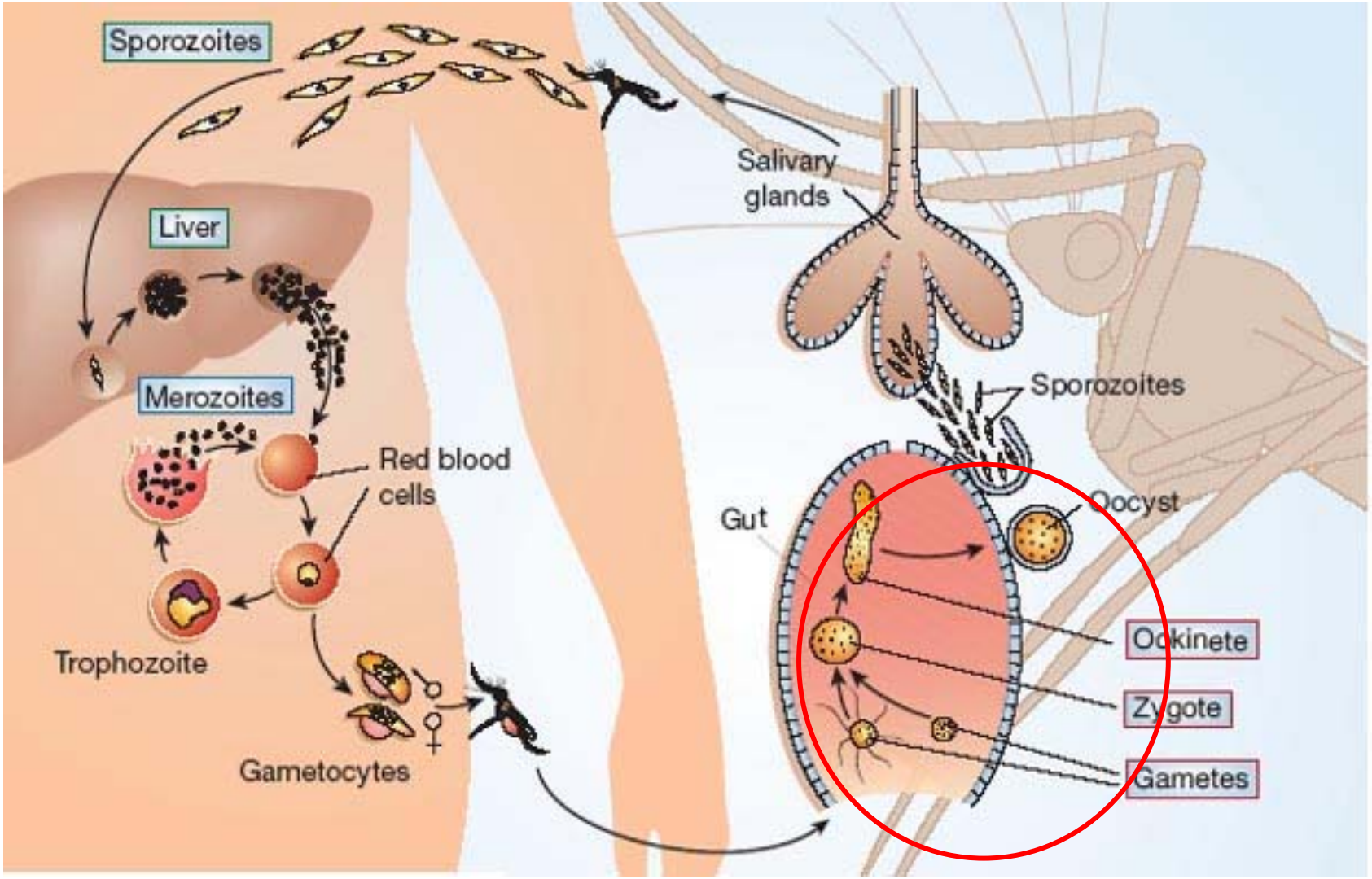
Gametogenesis

- ✓ Formation of gametes (male and female gametocyte).
- ✓ Stimulus or mechanism that triggers differentiation is unknown.
- ✓ *P. falciparum*: 12-15 days for development.
- ✓ *P. vivax*: 36 hours

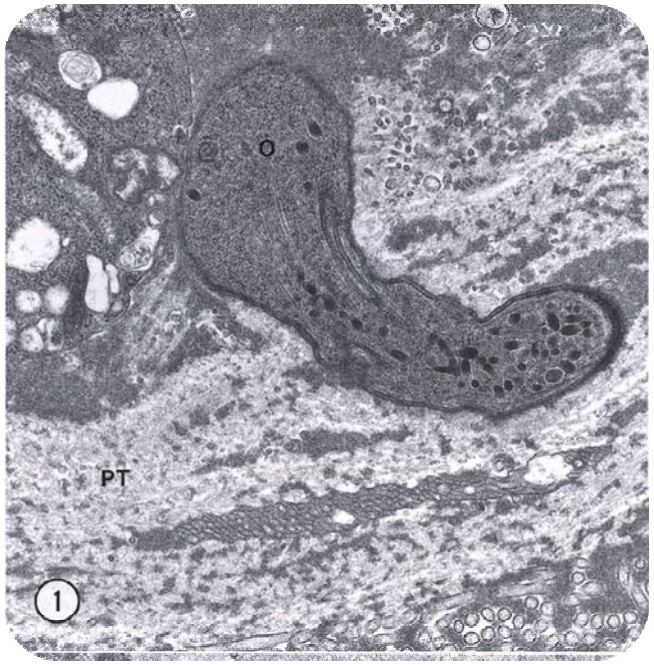


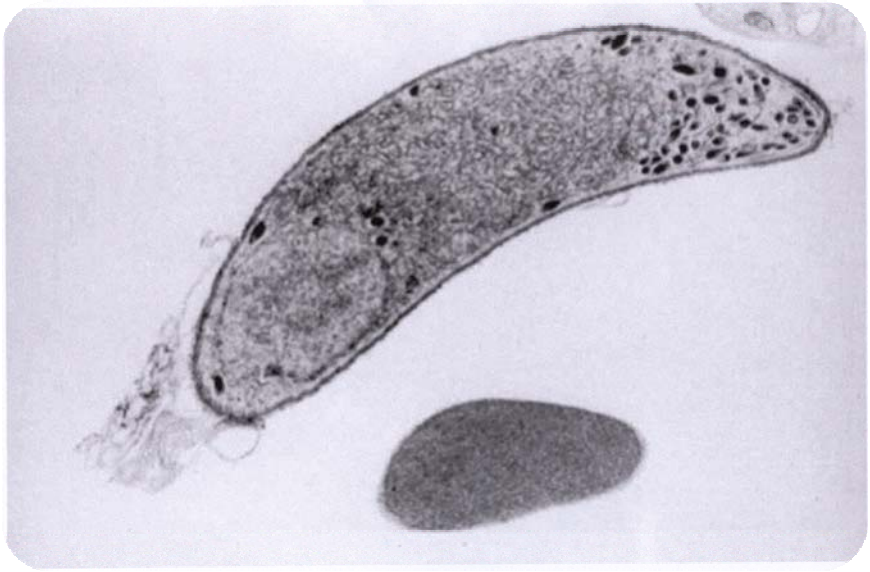
P. falciparum *P. vivax* *P. malariae* *P. ovale*

Lifes cycle of *Plasmodium*



Zygote and Ookinate

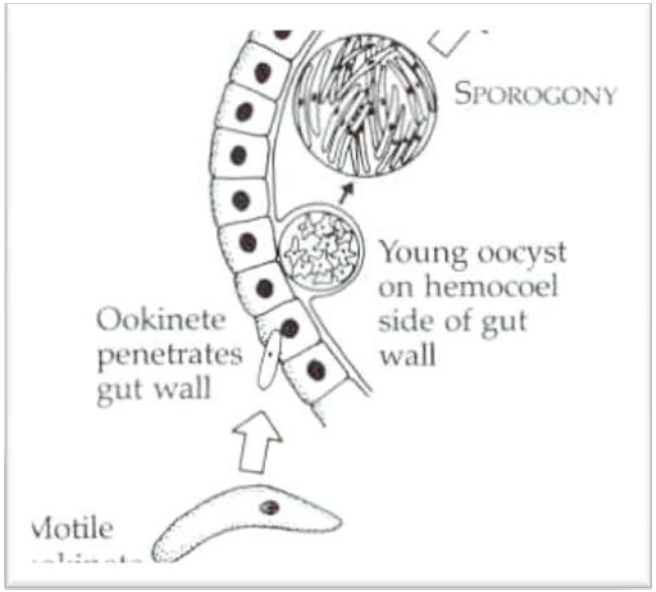




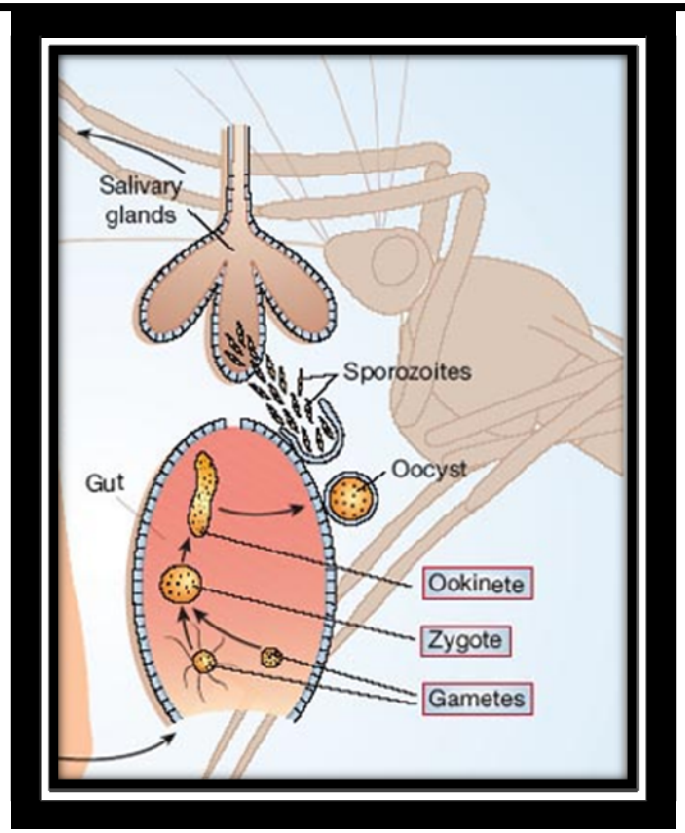
- Fertilization forms a diploid zygote.
- Matura for 18-24 hours. .
- It stretches, acquires mobility (oocineto) and moves to cross the wall of the stomach of the mosquito
- Size varies from 10-20 mm (depending on the species)

Ookinate to Oocyst

- ✓ **The oocineto becomes oocyst when it is surrounded by a thick capsule with 0.1-0.2 mm of thickness.**
- ✓ **10-12 days of development for *P. falciparum* and 8-10 days for *P. vivax.***
- ✓ **Reduced, haploid nuclear division again.**
- ✓ **multiplication to form thousands of sporozoites.**



Ookinate to Oocyst



Important factors for transmission

- competent vectors
- appropriate ecological conditions for the vectors
- average temperature above 16-20 ° C
- infected individuals (-> gametocyte source!)

Plasmodium and Malaria

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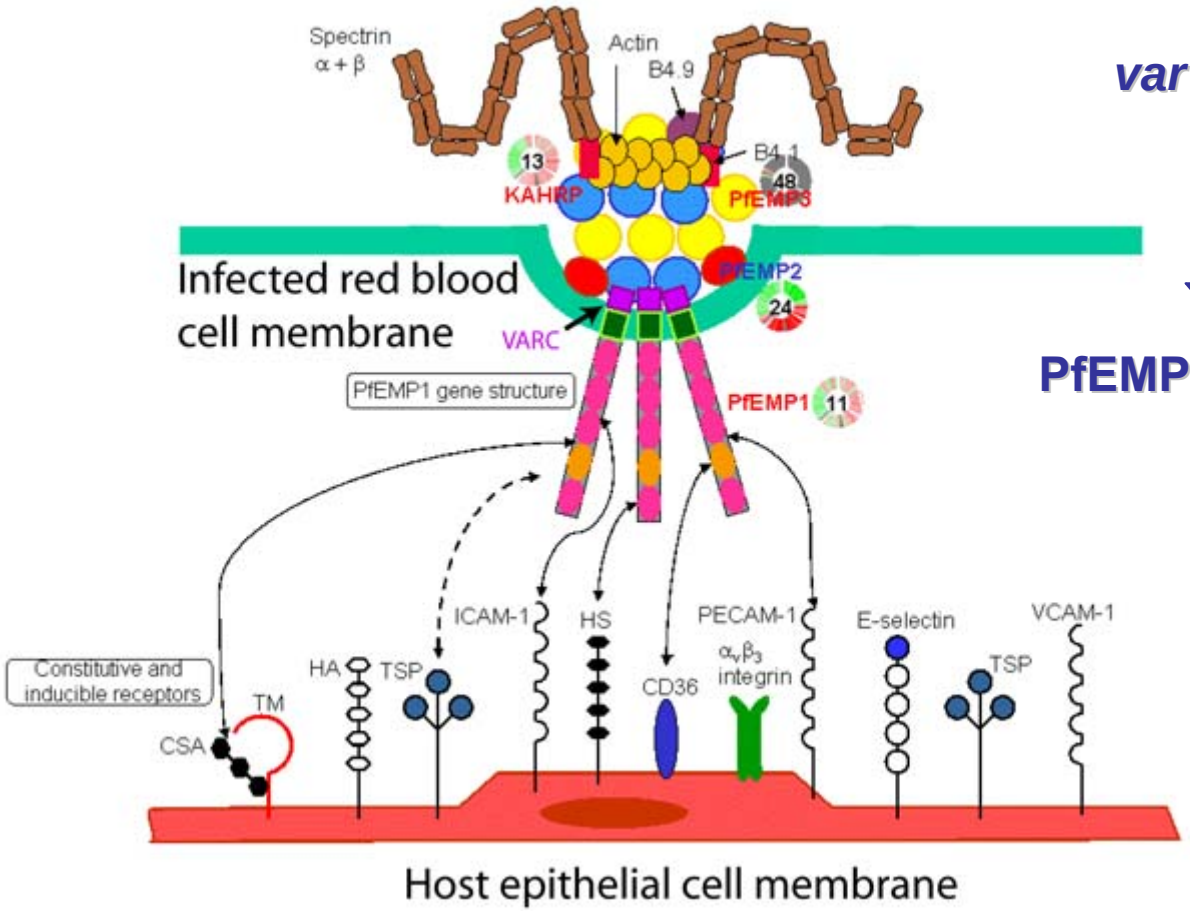
Modulating the Host's Immune Response

- Intracellular growth in cells with little or no MHC class 1 presentation

- Do not let infected erythrocytes pass through the spleen: cytoadherence (*P. falciparum* only) and antigenic variatio

Host cell modification

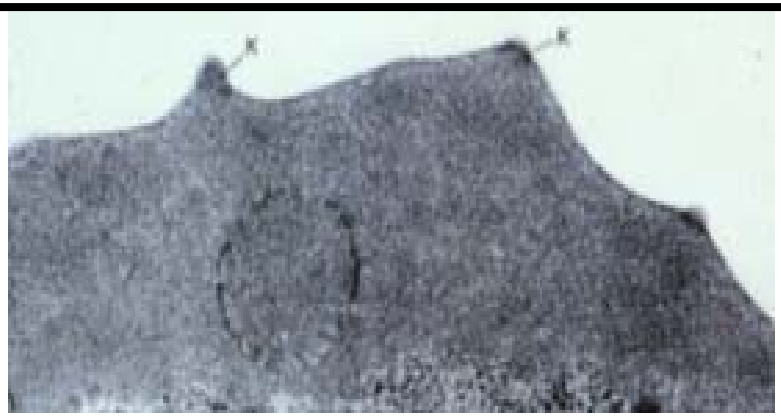


***var gene family* (±60 copies)**

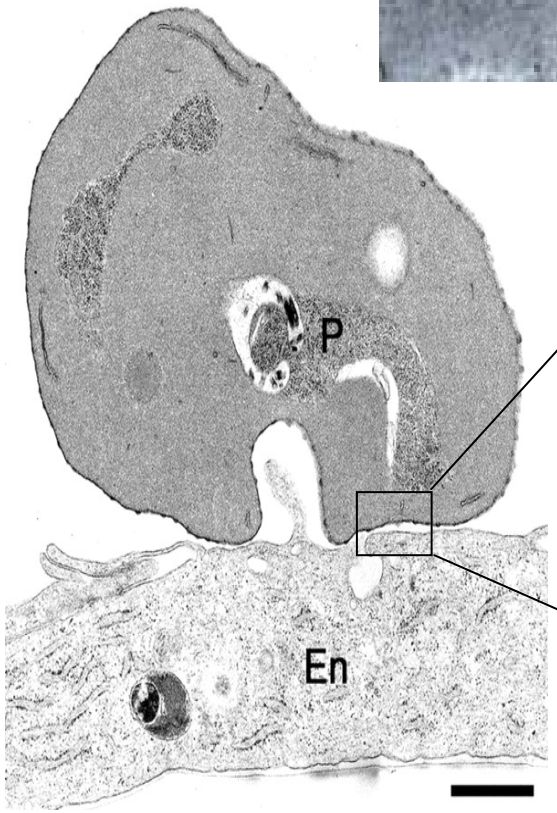
PfEMP-1 protein

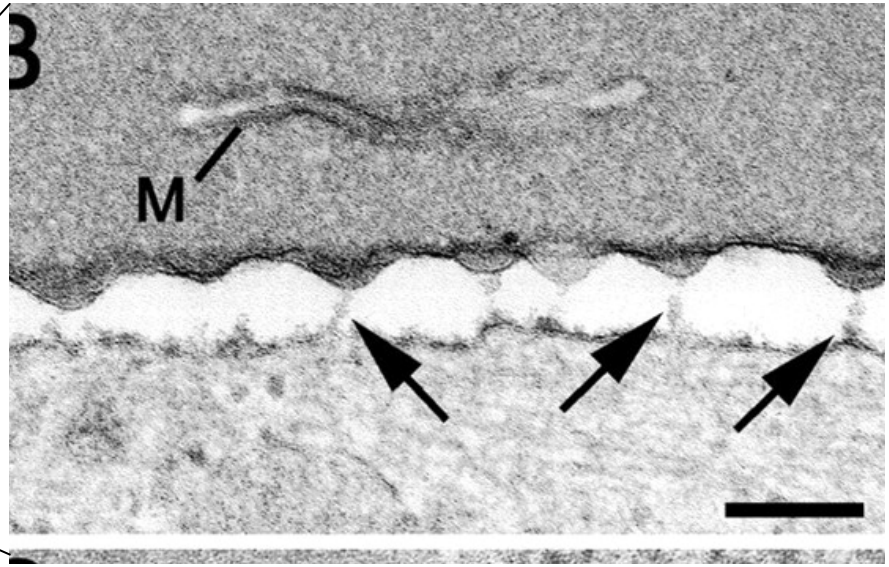
Mackintosh *et al.*, TRENDS in Parasitology, 2004.

Host cell modification - knobs



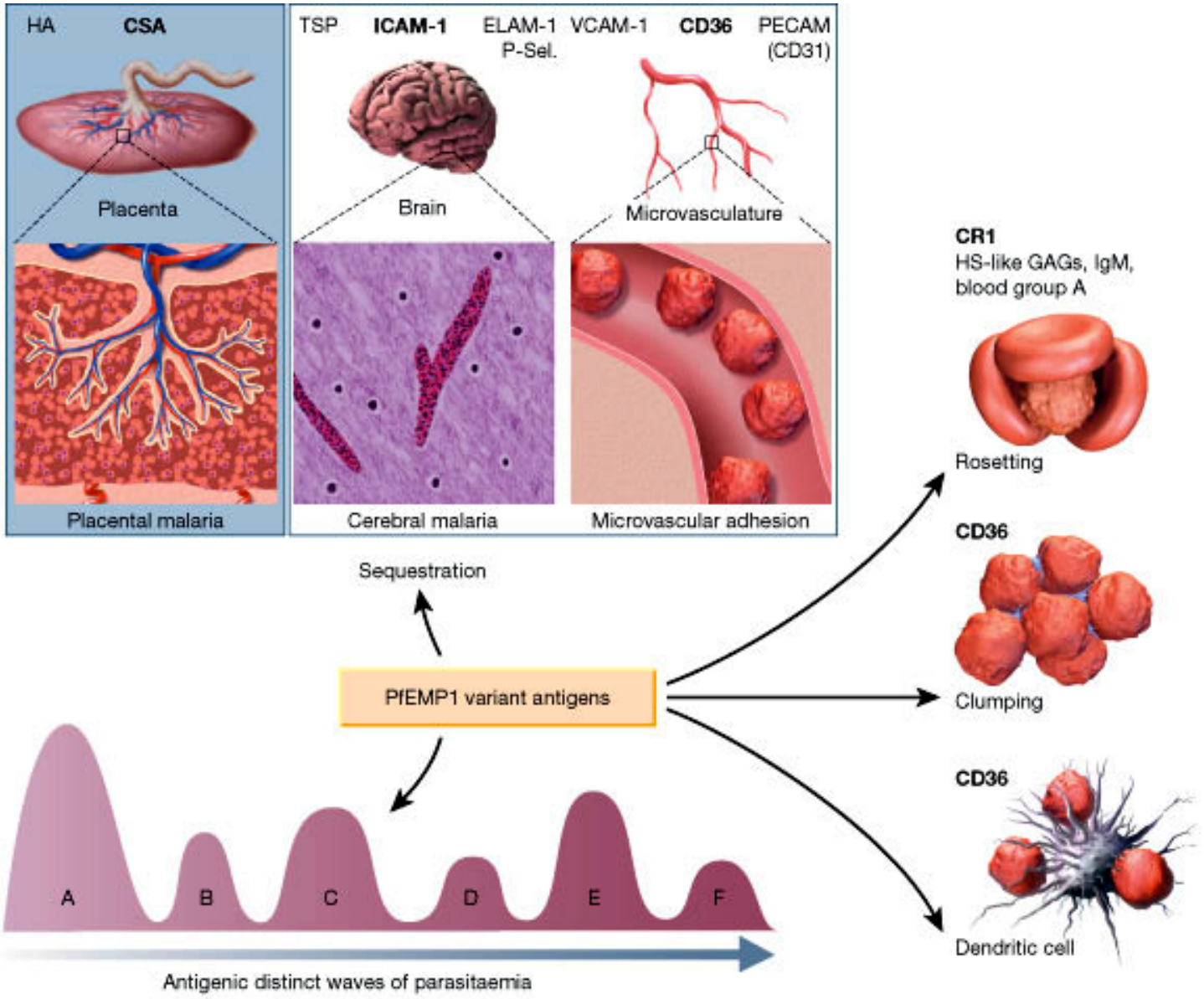
iRBC





(Horrocks et al. 2005)

Host cell modification - knobs



Miller *et al*., 2000

Pathogenesis

	P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
Incubation period	8-27 days	15-30 days	8-25 days	9-17 days
Formation of Hipnozoites	YES	NO	NO	YES
Number of merozoite per mature schizont	10.000	2.000	40.000	15.000
Average Parasitemia (mm^3)	50.000	20.000	50.000-500.000	9.000
Infection of RBC (type)	Reticulocytes	Erythrocytes	All types	Reticulocytes

Clinical aspects

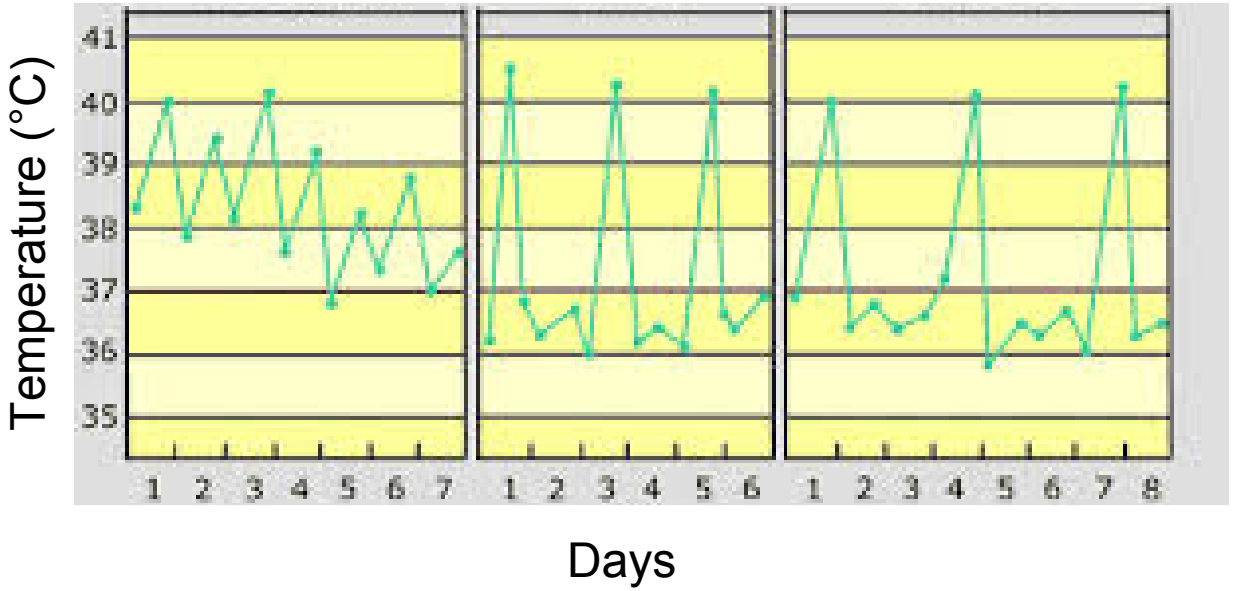
Symptoms of infection with Plasmodium sp. in non-immune people

- **fever**
- **headache**
- **sweating**
- **arthralgia**
- **myalgia**
- **chills**

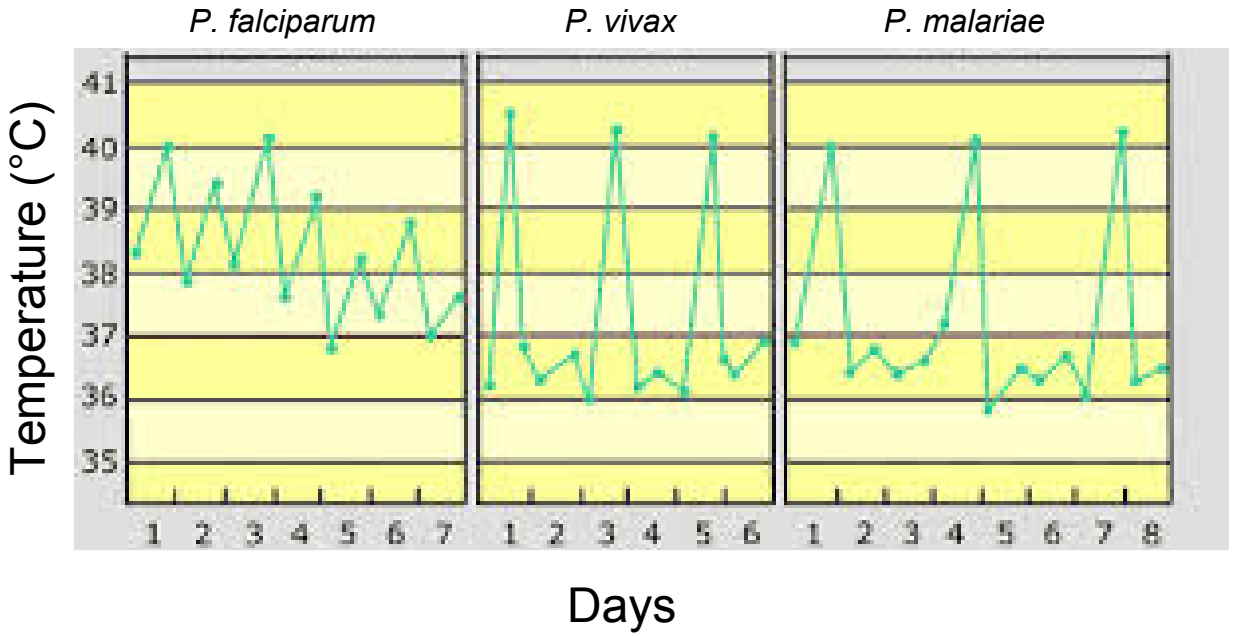
Common: intermittent fever

sometimes: splenomegaly,diarrhea, vomiting and anemia

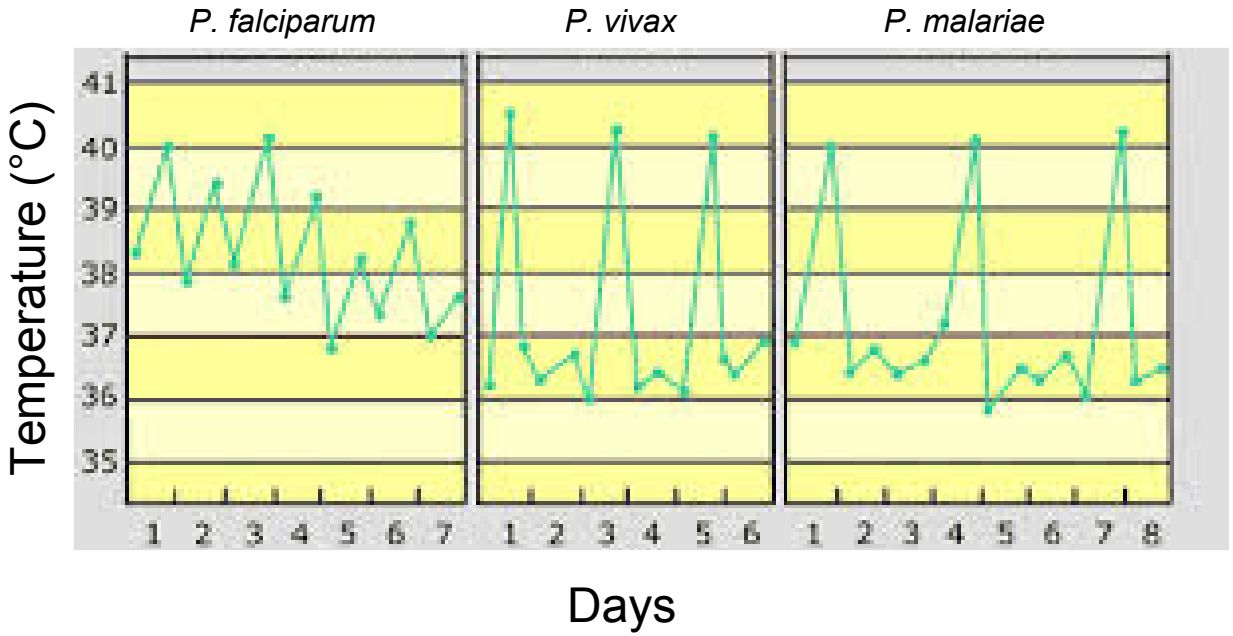
Fever and malaria



Fever and malaria



Fever and malaria



P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
48 horas	72 horas	36-48 horas	48 horas
Terçã benigna	Quartã	Terçã maligna	Terçã leve

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Diagnostics

-> Detection and discrimination of blood forms

- Thin Blood Film stained with Giemsa stain
  (when there are many parasites:> 0.1% parasitemia)

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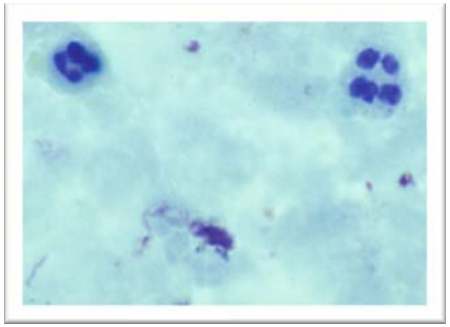
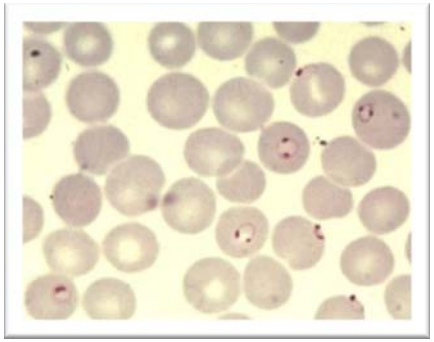
Diagnostics

Thick Blood Film



✓High sensitivity

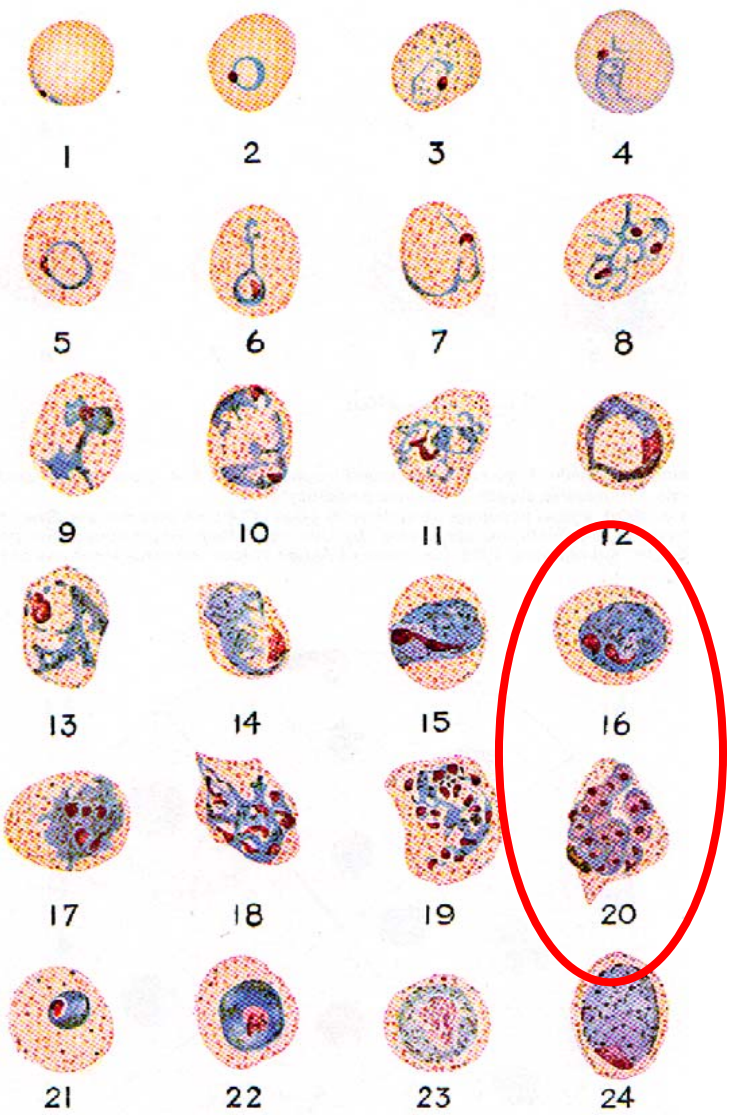
Thin Blood Film



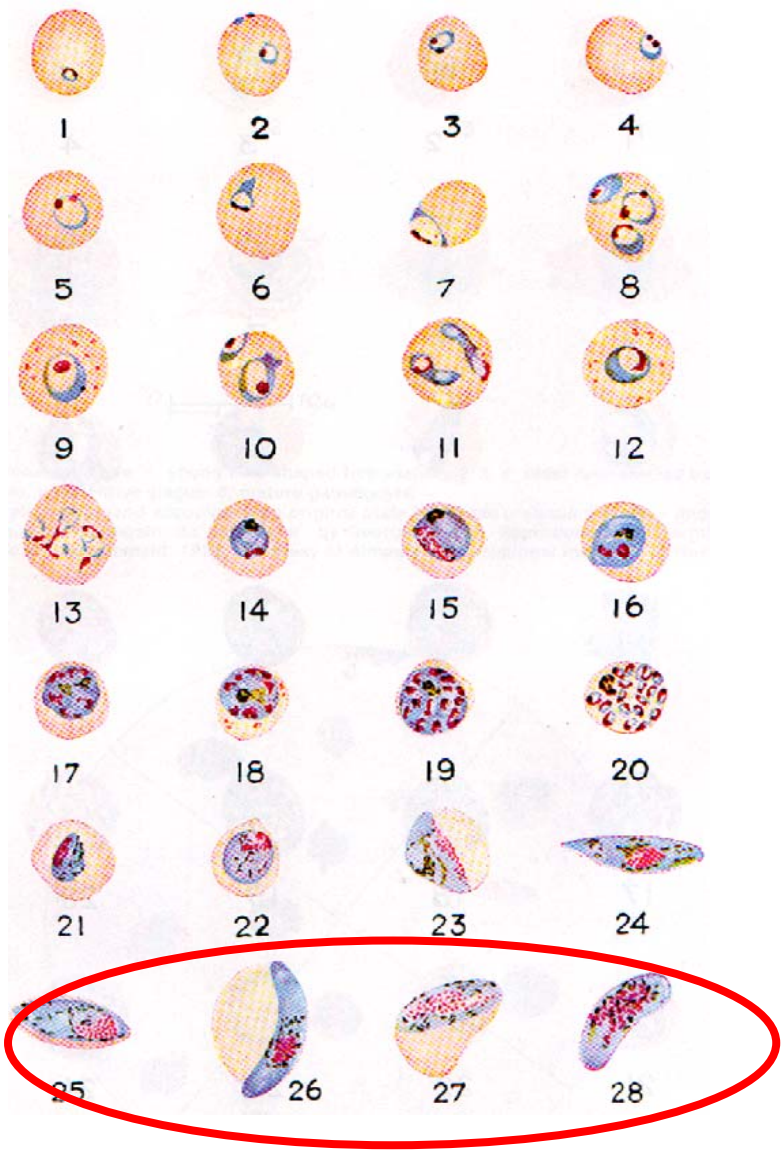
✓High specificity

Diagnostics

P. vivax



P. falciparum



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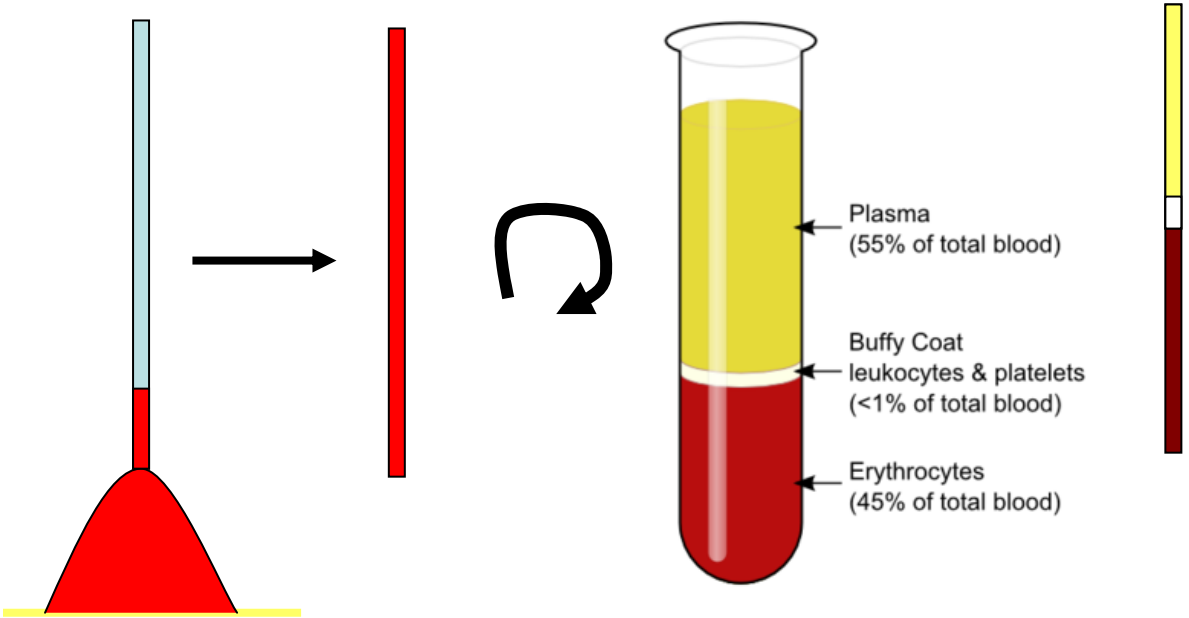
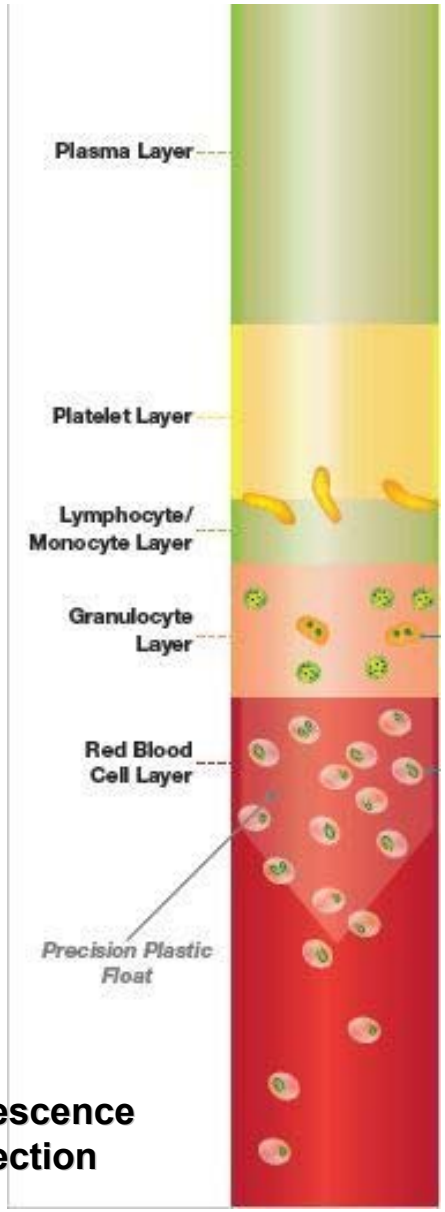
- QBC (quantitative buffy coat)

Diagnostics – QBC test



UV



Microtubules impregnated with Acridine Orange (Staining of DNA & RNA)

Fluorescence detection

Diagnostics

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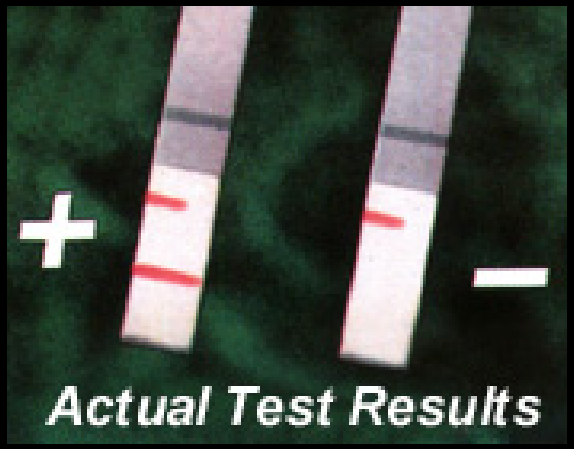
- QBC (quantitative buffy coat)
- "Dip stick" tests, detect malarial antigens
  circulating (in the field): Histidin rich protein

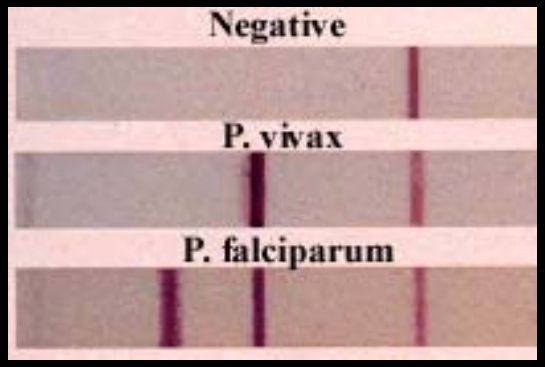
Examples of RDTs:

„Rapid Diagnostic Tests“

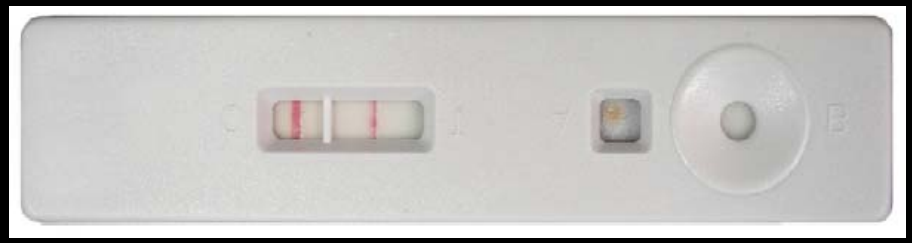


Para Sight F test

OptiMal Assay Kit



OptiMal assay Result



- Require minimal training
- 2 to 6 steps, take 5 to 30 minutes
- US $1.20 to $13.50 per test.
- None approved by FDA for diagnosis of malaria in US

Diagnostics

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- Serology

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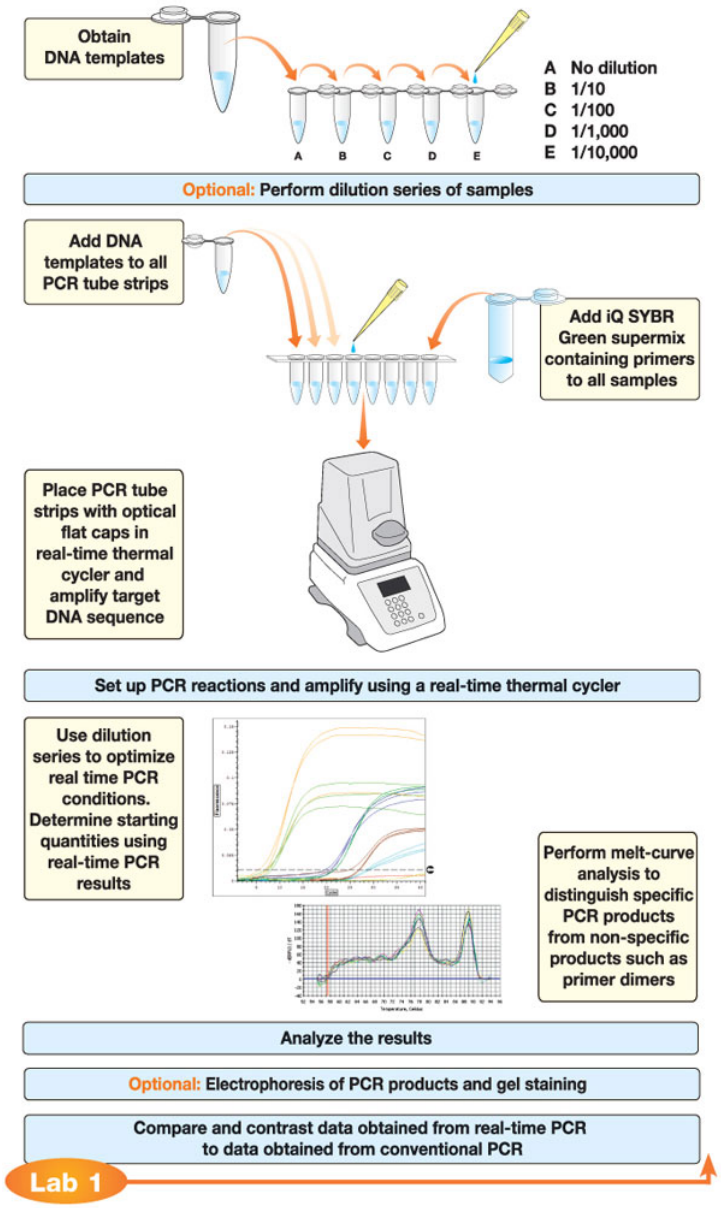
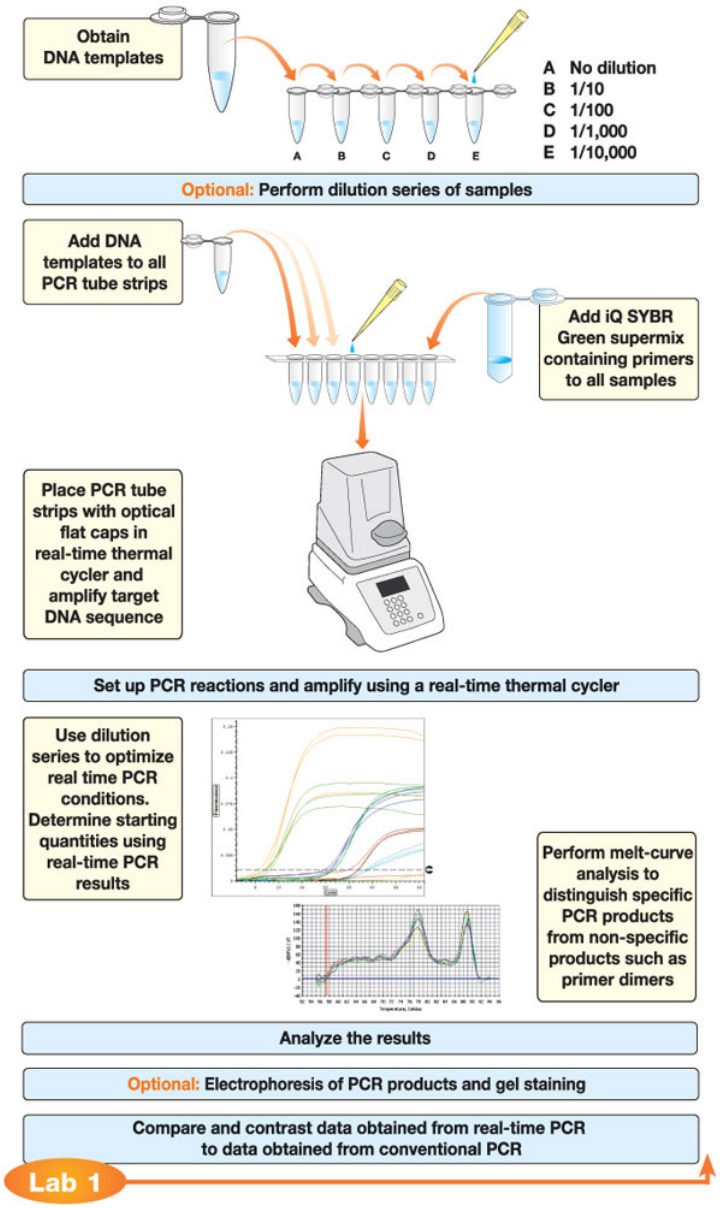
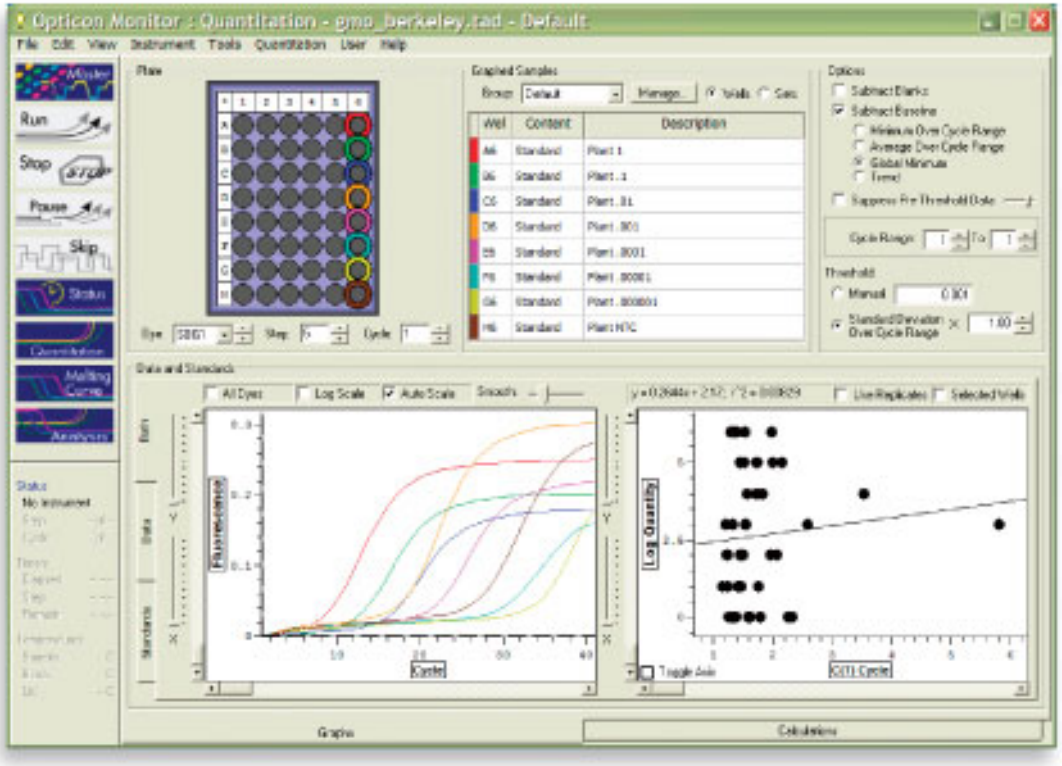
- "Dip stick" tests, detect malarial antigens circulating (in the field): Histidin rich protein
- Serology
- Polymerase chain reaction (PCR)

Real-Time PCR according to BioRad



Real-Time PCR according to BioRad





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Malaria therapy

- The diagnosis of the infecting species is essential!
- Treatment should always be supervised by a physician
- It is necessary to consider which stages to combat (Hypnozoites, gametocytes, trophozoites)

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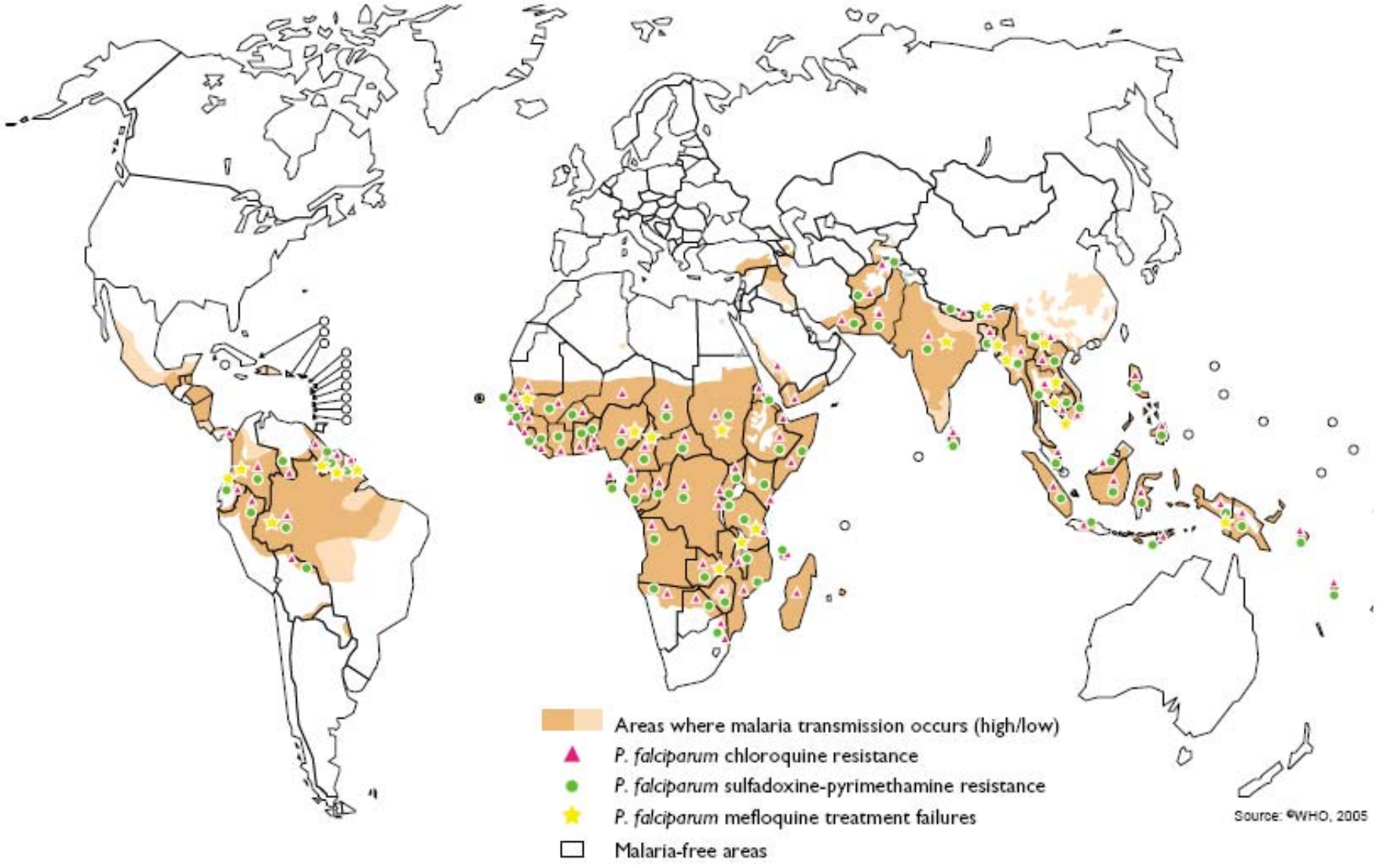
Trofozoites: Quinine, Chloroquine, Mefloquine, Halofantrin, Pyrimethamine, Tetracycline, Doxycycline, Artemisinin and derivatives

Hepatic stages: Primaquine, Proguanil, Tetracyclines

Gametocytes: Primaquine, Chloroquine, Amodiaquine

***P. vivax* therapy:** Chloroquine + Primaquine
***P. falciparum* therapy:** Artemisinin + Amodiaquine or Artememysin + Mefloquine

Drug resistance



Drug resistance - COSTS

Drugs	US $
• Chloroquina (Resochina)	0,08
• Sulfadoxin/Pirimethamina (Fansidar)	0,13
• Amodiaquin	0,30
• Artesunat	1,20
• Quinino	1,50
• Mefloquin	2,00
• Artemether/Lumefantrin (Riamat)	2,40
• Halofantrin	5,00
• Atovaquona/Proguanil (Malarone)	30,00

Manson‘s 2003

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Prevention in Brazil

- Chemoprophylaxis is possible but should be limited to emergency cases (splenectomized persons)
- Use repellent when possible, use of mosquito nets impregnated with pyrethroids
- Use of gloves in the surgical treatment of malaria
- Contamination test in blood banks
- Propaganda

1

Omaze okufuna akatimba k'ensiri akateekebwamu eddagala erirwamu okusobola okwekuuma gwe n'abaanabo obutakwatibwa omusujja gwa nsiri.

2

Nga tonnakozesa katimba ko akapya, kaleke kayitemu empewo eddagala eritta ensiri lisobole okukabuna obulungi okumala olunaku lumu.

5

Omusujja gw'ensiri gusinga kuba gwabulabe eri abakyala abali embuto, abaana abali wansi w'emyaka etaano (5) n'abantu abalina akawuka ka silimu. Era bano beetaaga okusula mu butimba bw 'ensiri obwateekebwamu eddagala erirwamu buli kiro.

6

Emisana, akatimba kazingeko waggulu kaleme okwonooneka.

3

Saba omwagalwawo akuyambe okuwanika akatimba nga akozesa obuguwa obuli ku nsonda z'akatimba.

4

Ekiro, akatimba kafundikire mu mufaliso oba omukeeka ensiri zibe nga tezirina weziyita.

7

Akatimba ko kooze bwekaba kaddugadde nga okozesa amazzi ne sabuuni (emirundi etaano (5) omwaka okumala emyaka ena (4).

8

Akatimba tokaanika mu musana wabula kaanike mu kisikirize naddala mu busubi wansi w'omuti.

Omaze okufuna akatimba k'ensiri akateekebwamu eddagala erirwamu okusobola okwekuuma gwe n'abaanabo obutakwatibwa omusujja gwa nsiri.

Nga tonnakozesa katimba ko akapya, kaleke kayitemu empewo eddagala eritta ensiri lisobole okukabuna o olunaku lumu

Omusujja gw'ensiri gusinga kuba gwabulabe eri abakyala abali embuto, abaana abali wansi

Emisana, akatimba kazingeko waggulu kaleme okwonooneka.

Saba omwagalwawo akuyambe okuwanika akatimba nga akozesa obuguwa obuli ku nsonda z'akatimba.

Ekiro, akatim mufaliso oba nga tezirina

Omaze okufuna akatimba k'ensiri akateekebwamu eddagala erirwamu okusobola okwekuuma gwe n'abaanabo obutakwatibwa omusujja gwa nsiri.

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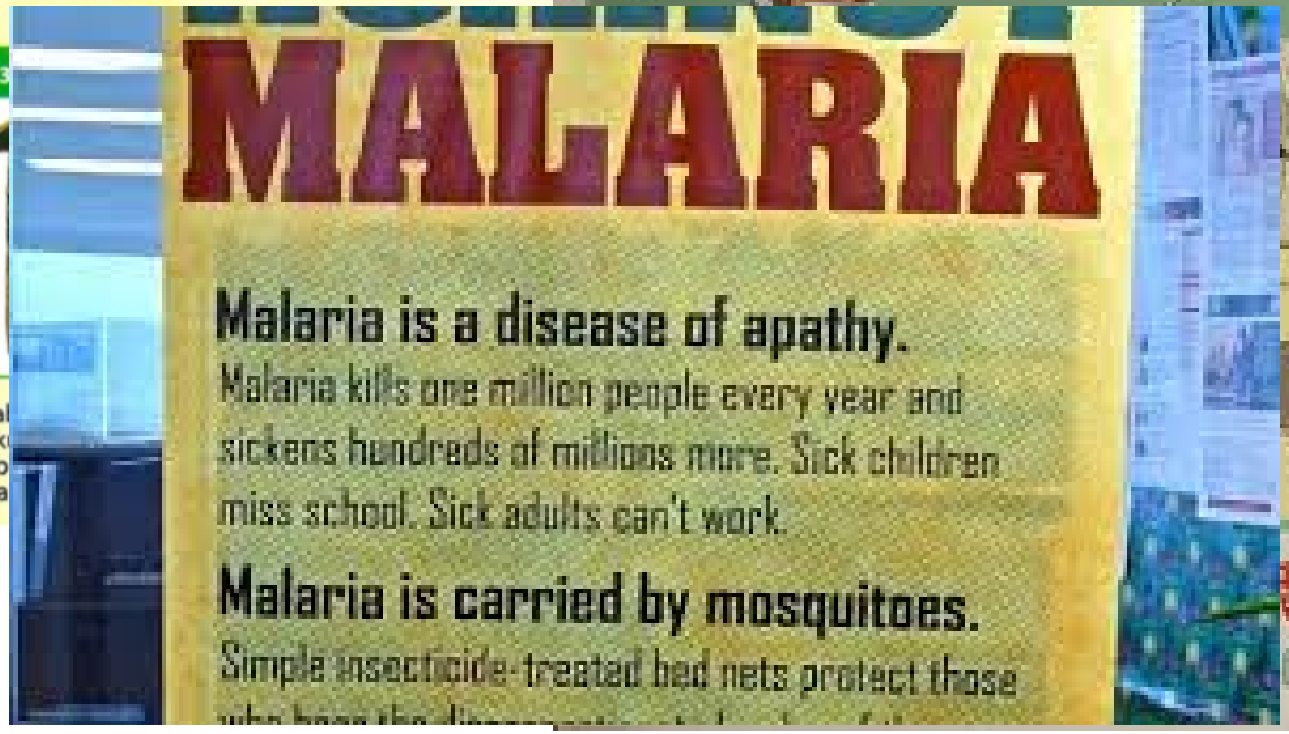
Emisana, akatimba kazingeko waggulu kaleme okwonooneka.



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●. http://www.cdc.gov/malaria