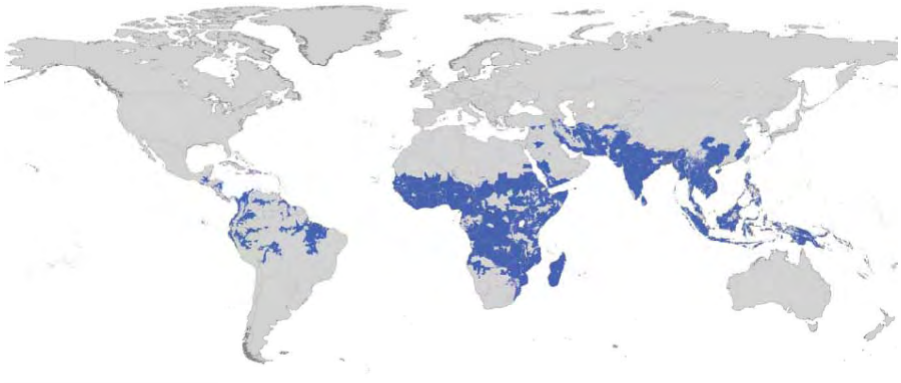
The Malarias:

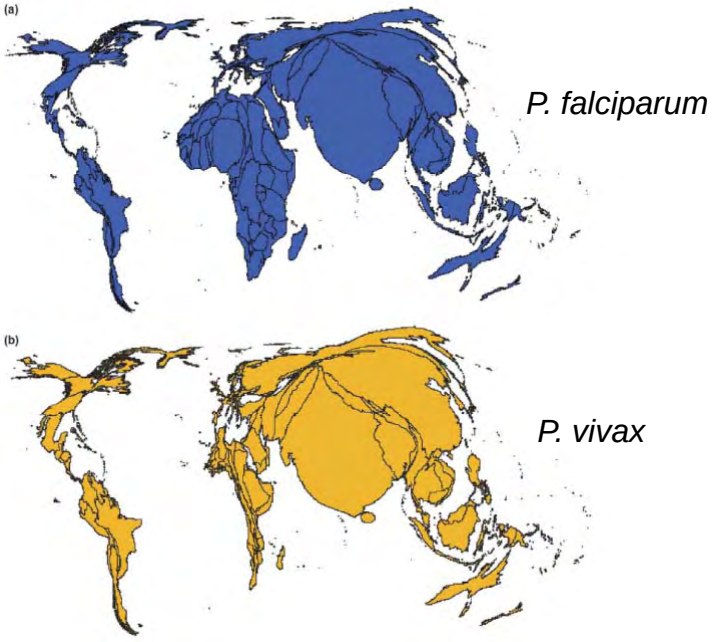
Plasmodium falciparum
Plasmodium vivax
Plasmodium malariae
Plasmodium ovale

Distribution of Plasmodium falciparum



Distribution Of Plasmodium vivax

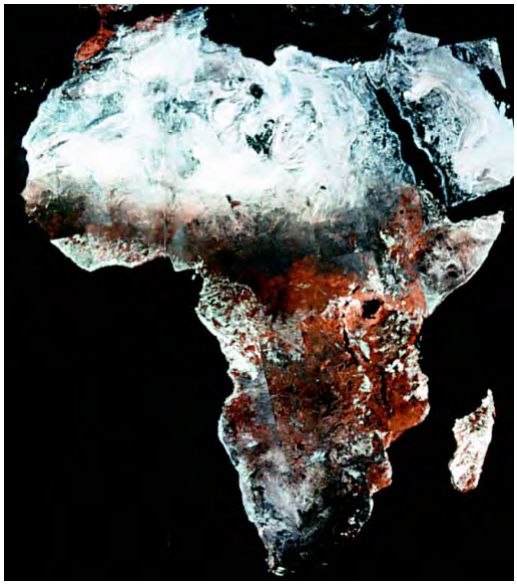
Global Risk By Country-Proportionality Plot



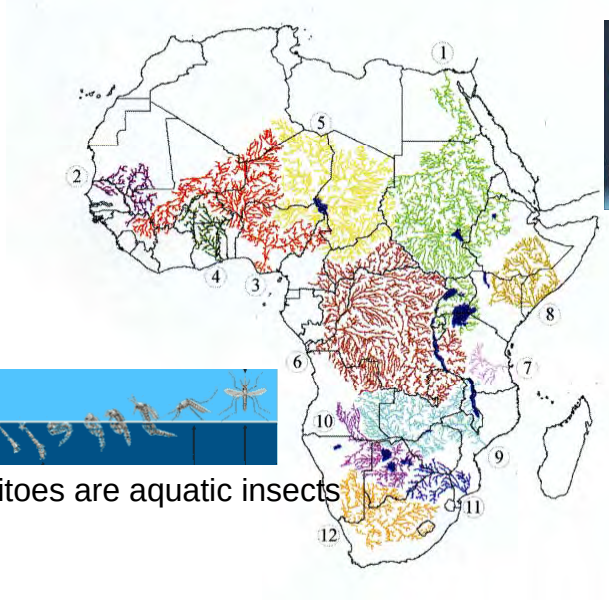
P. falciparum

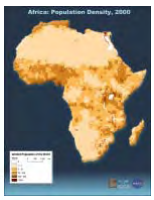
P. vivax

3 million deaths/yr. 1 million in Africa, mostly children below the age of 5



Watersheds of the African Continent





Population density

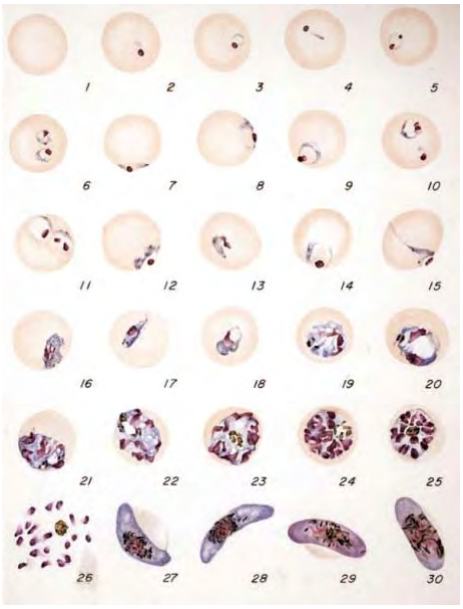
Mosquitoes are aquatic insects

World Situation

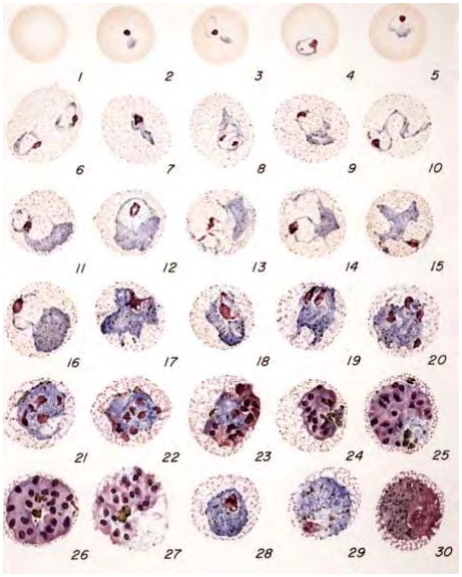
- Approx. 2 billion infections/yr
- Economic and social development reduced
- 27% of the world lies within the malaria transmission zone
- New unstable transmission area: Bangladesh
- Impact of malaria on population change ?

Adult *Anopheles dirus* taking a blood meal from one of the authors (RWG)

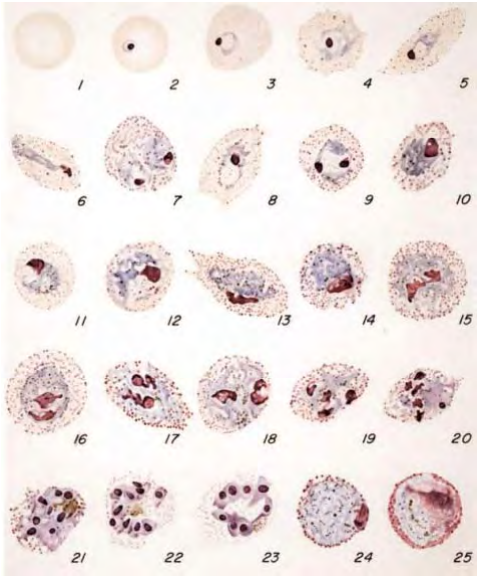
Plasmodium falciparum



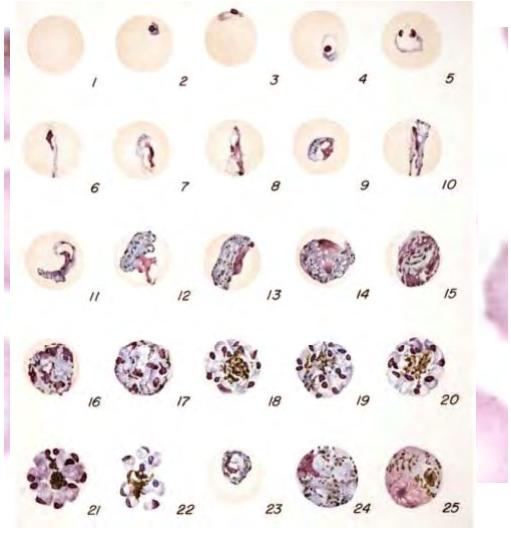
Plasmodium vivax



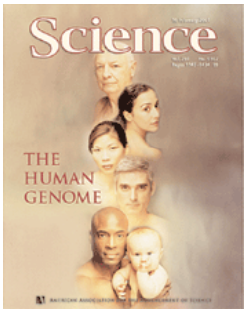
Plasmodium ovale



Plasmodium malariae



The biology of plasmodium is complex, both in the ***definitive host*** the mosquito, and the ***intermediate host***, the human.

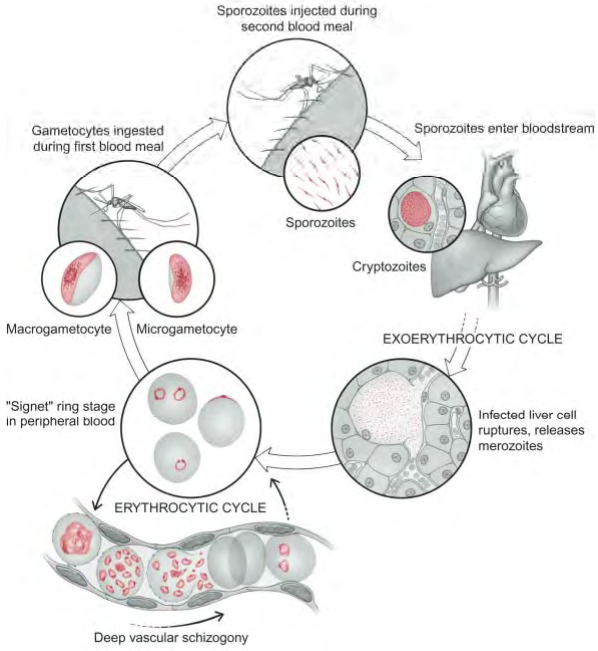


People

Parasites

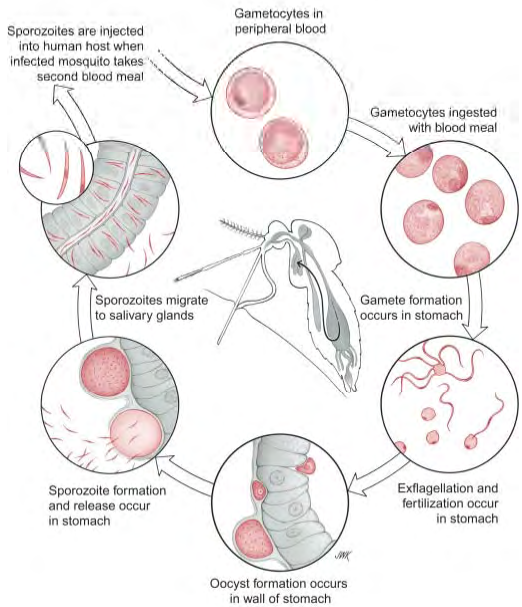
Pests

Plasmodium falciparum

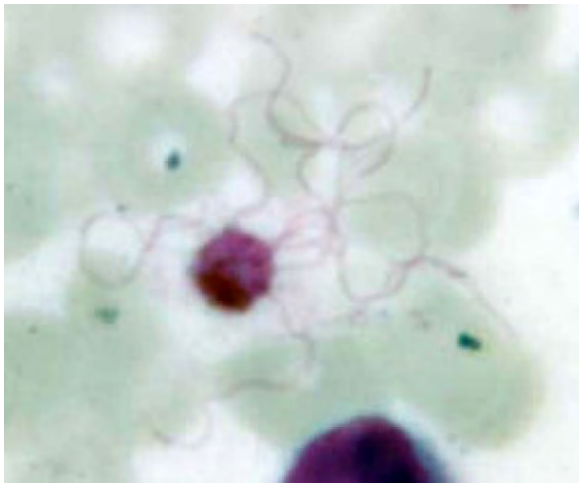


Adult *Anopheles dirus* still taking a blood meal from one of the authors (RWG)

Mosquito Cycle (Sporogany)

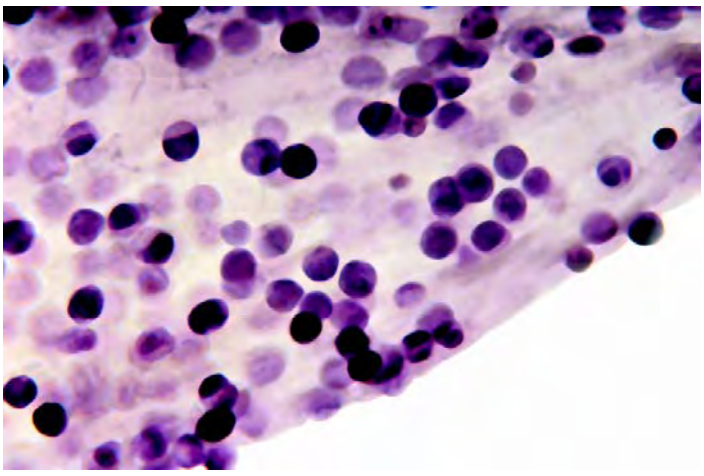


Ex-flagellation of the microgametocyte
of a malaria parasite in mosquito stomach

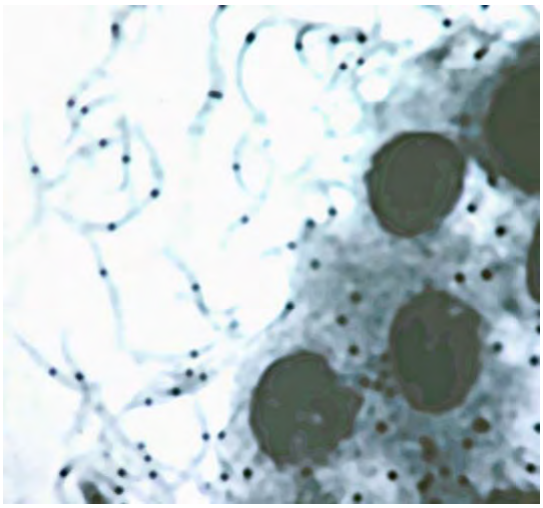


Portion of an infected mosquito stomach.

Note numerous oocysts on outer wall.



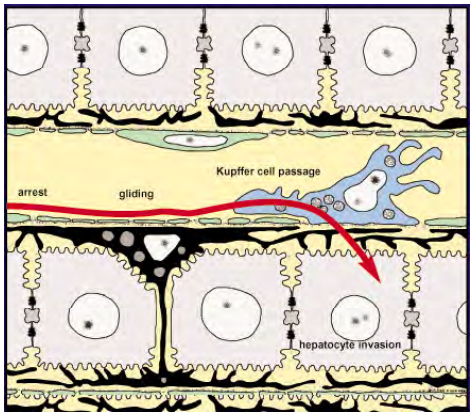
Sporozoites of malaria in infected mosquito stomach preparation



Light micrograph

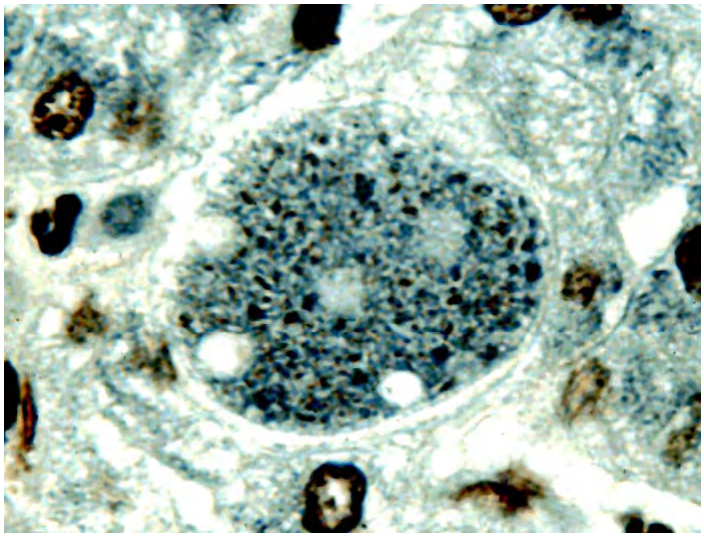
SEM Photo: Photini Sinnis

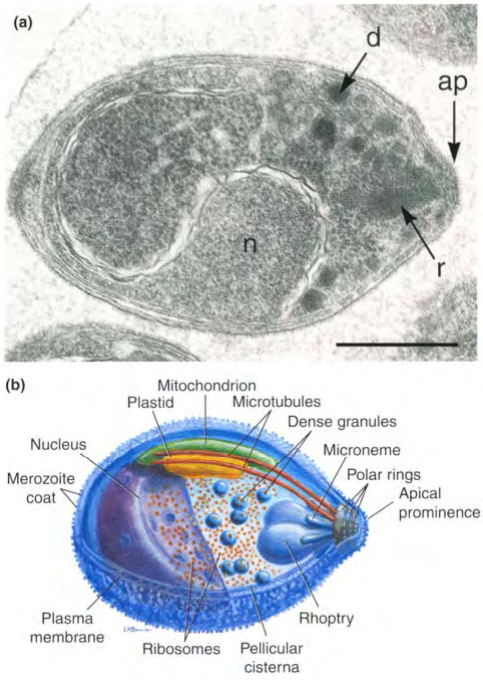
Entry Of Sporozoites Into Parenchymal Cells Of The Liv



From: Ute Frevert
NYU School of Medicine

Exo-erythrocytic stages of malaria in liver parenchymal cell



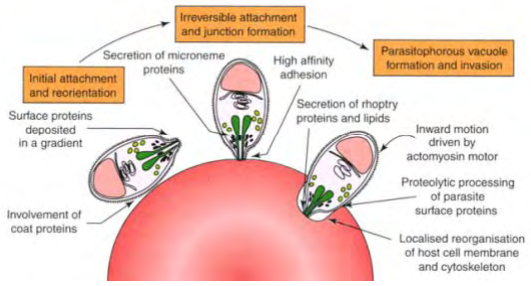


Plasmodium Anatomy

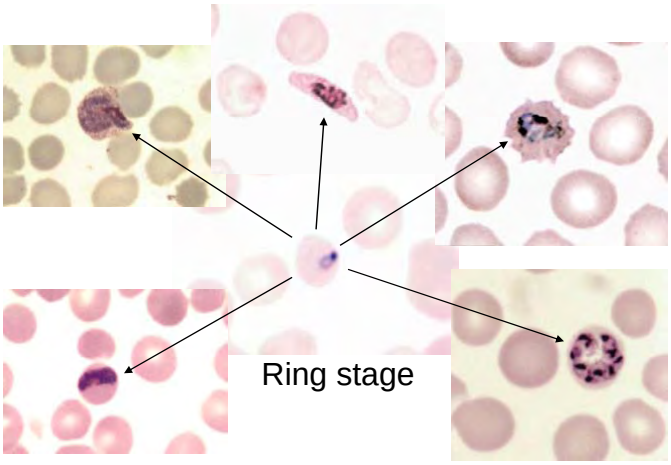
Transmission EM of merozoite entering a red cell.

Note points of attachment

Mechanisms of Red Cell Invasion By Plasmodium



Erythrocytic stages of malaria:
All infections begin with the ring stage
regardless of the the species



Pathogenesis

- Destruction of erythrocytes; anemia
- Liberation of parasite and erythrocyte material into circulation
- Host reaction to these events (multiple organ system disease,
- *P. falciparum* has unique sequestration in micro-circulation of vital organs interfering with flow and tissue metabolism (metabolic acidosis in acute disease)
- Long-term effects of repeated infections - learning deficit, reduced growth rate, spontaneous abortion; all may be due to prolonged metabolic acidosis

Clinical Signs & Symptoms

- Fever, paroxysms of shaking chills
- Tertian vs quartan fever pattern
- Symptoms when other organs involved
- Hemolysis: icterus, jaundice, enlarged spleen

Retinopathy and Severe Malaria

FIGURE 1. Severe macular whitening (**solid arrow**) completely surrounding the foveola of a Malawian child with cerebral malaria. Papilledema is present as well as a white-centered hemorrhage temporal to the macula and cotton wool spots above superior temporal arcade. The **open arrow** indicates glare (photographs provided by Nicholas A. V. Beare).

FIGURE 2. Macular whitening around inferior fovea and temporal macula (**solid black arrow**). White-centered hemorrhages are temporal to the disc and on the superior macula. Peripheral whitening is outside the vascular arcades (**solid white arrow**). **Open arrow** indicates glare.

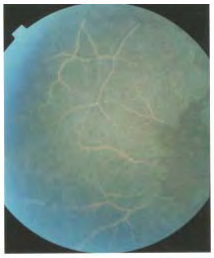


FIGURE 3. White retinal vessels in an area of confluent peripheral retinal whitening.

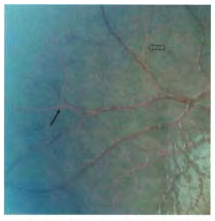


FIGURE 4. Vessel changes in same child as in Figure 1, including examples of tramlining (**solid arrow**) and orange vessel (**open arrow**).

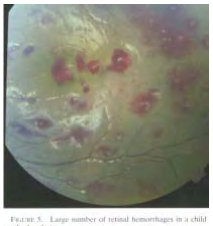
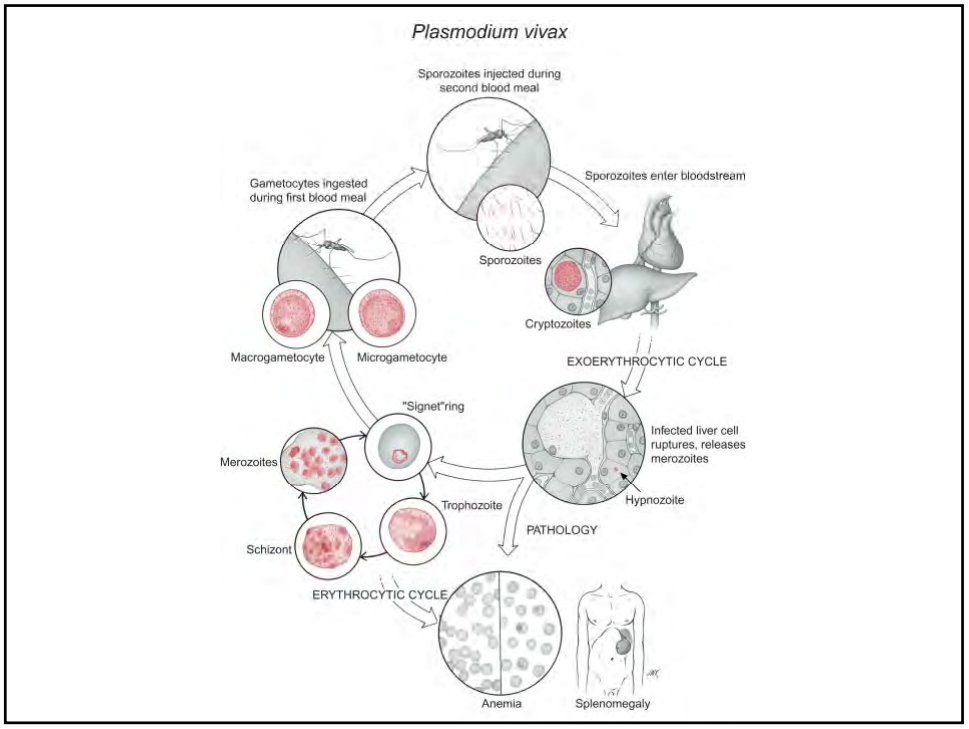
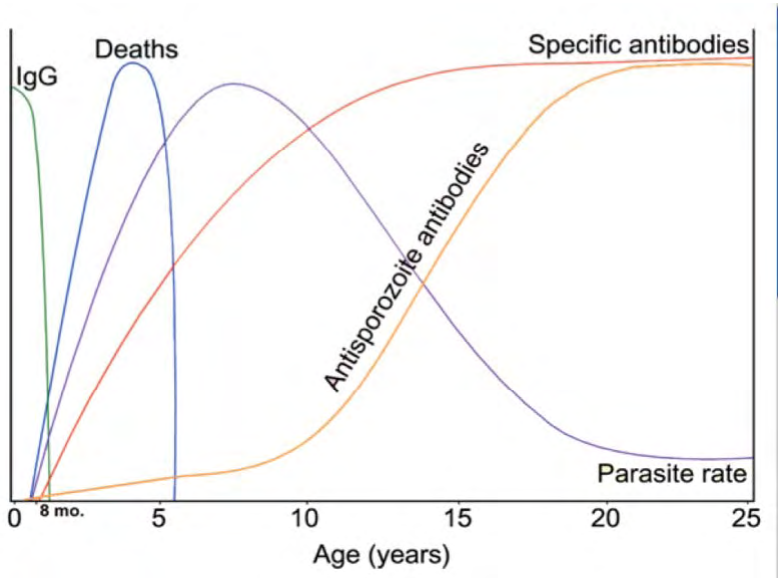


FIGURE 5. Large number of retinal hemorrhages in a child cerebral malaria.

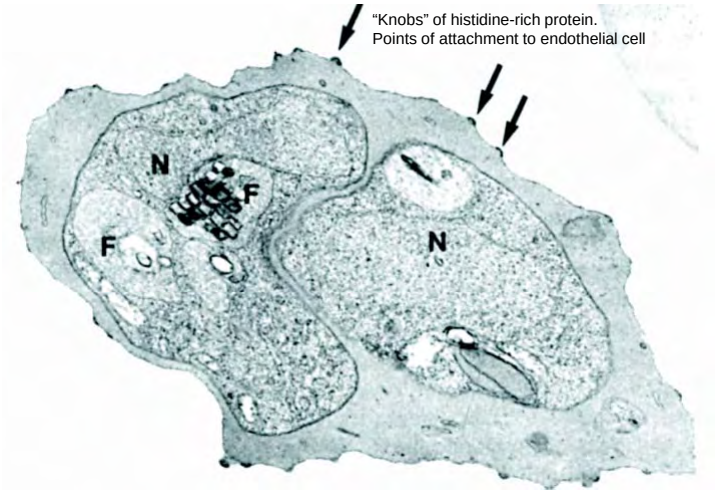
Am J Trop Med Hyg. 2006. Beare, N, et al. Vol. 75: 790-797



Susceptibility to malaria, antibody production, and lethality.

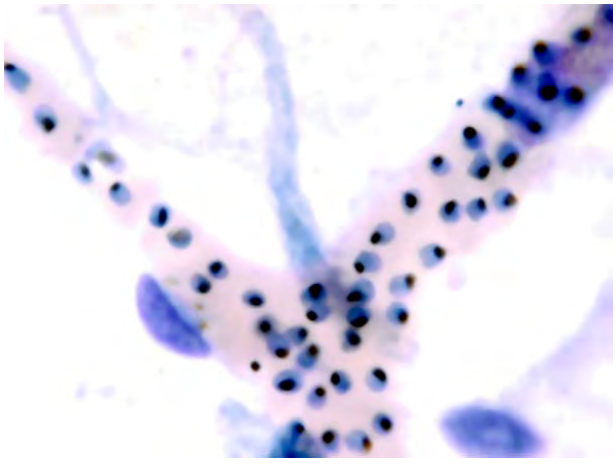


Transmission EM: RBC infected with *P. falciparum*

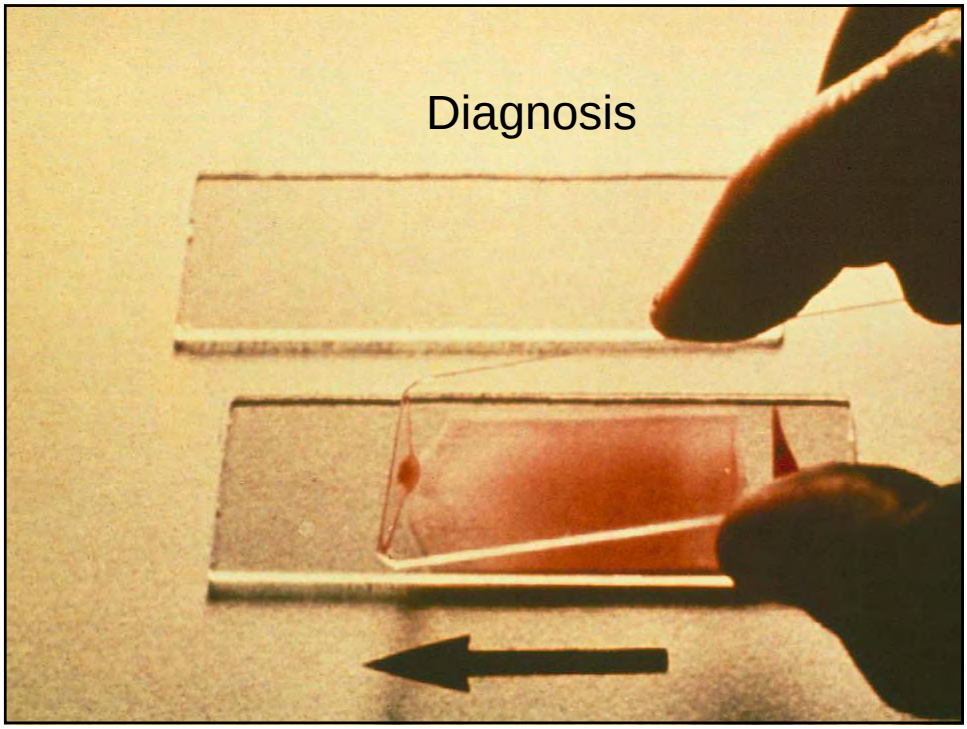


N = Nucleus; F = food vacuole

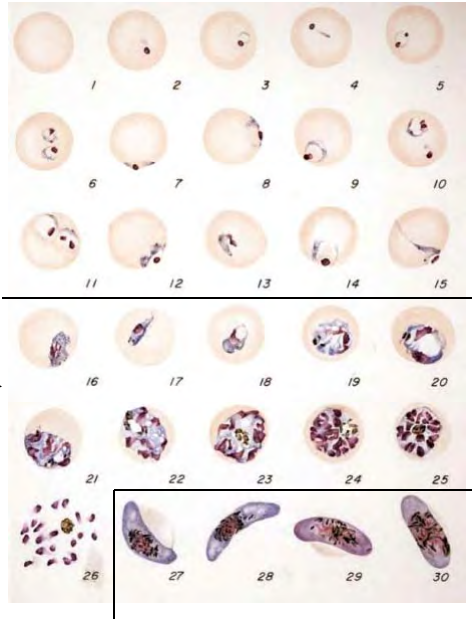
Cerebral malaria: experimental infection in monkey



stain: tissue Giemsa



Plasmodium falciparum



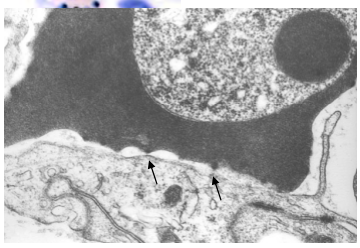
Not in peripheral blood: 16-26

In peripheral blood: 1-15; 27-30

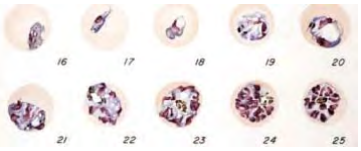
Normal RBC

Atomic force microscopy of knobs

In situ RBCs
with *P. falciparum*

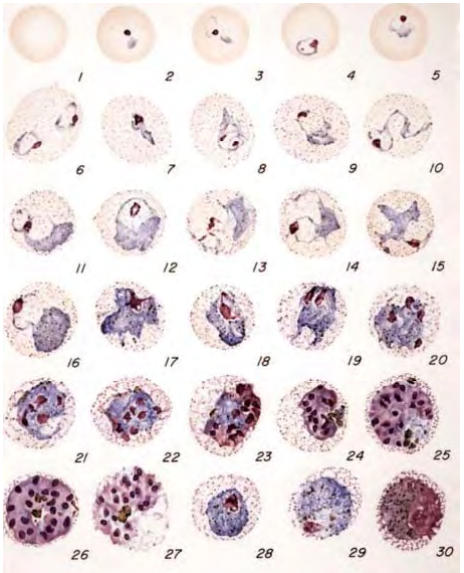


Electron micrograph of knobs



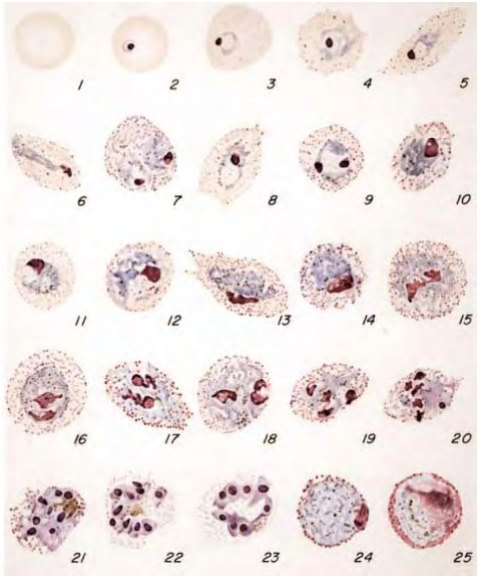
Stages of *P. falciparum* with knobs

Plasmodium vivax



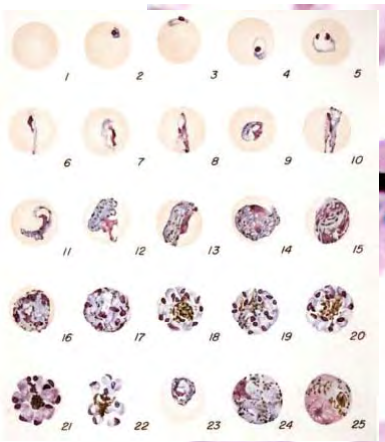
Infected RBCs larger than non-infected RBCs, Schüffner's dots

Plasmodium ovale



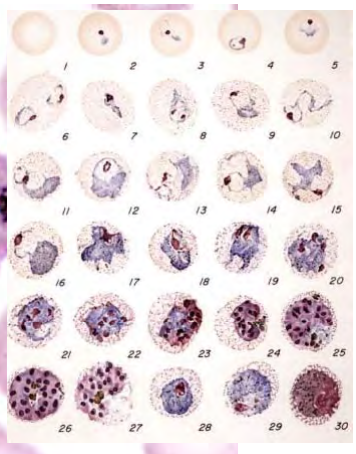
Same as *P. vivax*

Plasmodium malariae



Infected RBCs same size as non-infected RBCs,
No Schüffner's dots

Plasmodium vivax

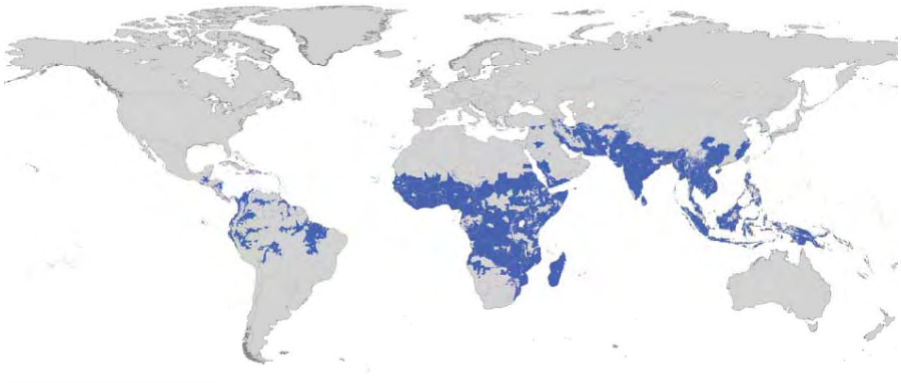


Infected RBCs enlarged

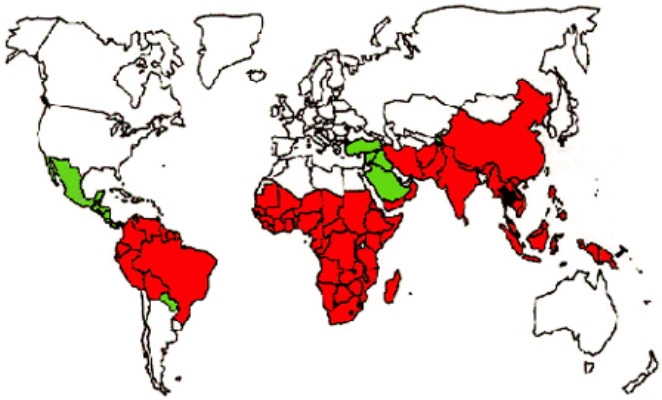
Treatment

- Type of malaria
- Knowledge of regional resistance
- Severity of illness (oral vs intravenous)
- Age of patient

Distribution of Plasmodium falciparum

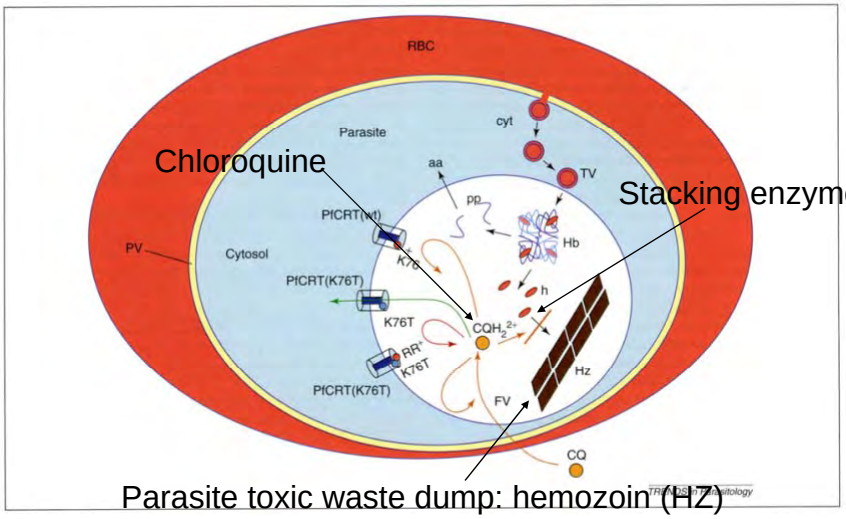


Drug-resistant Malaria



Red - chloroquine resistant
Green - chloroquine sensitive
Black - chloroquine and mefloquine resistant

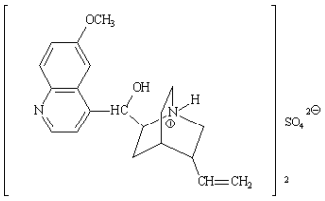
Mode of Action of Chloroquine
And Mechanisms of Drug Resistance



The parasite uses the protein portion of hemoglobin
and discards the heme moiety as hemozoin.

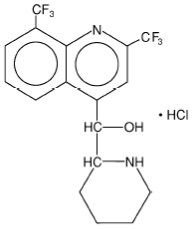
Drugs Of Choice:

A. Parent Compound



Quinine

C. Newer Derivative

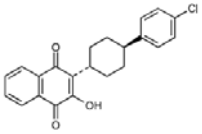


Mefloquine

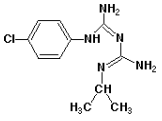
B. Older Derivative: extensive resistance

Chloroquine

D. Drugs of choice



Atovaquon



Proguanil

Treatment: Anti-Folates

Pteridine **+** PABA (Para-aminobenzoic Acid)

Dihydropteroate Synthetase ← **Sulfonamides / Dapsone**

Folic acid

Dihydrofolic acid

Dihydrofolate reductase ← **Pyrimethamine, Proguanil**

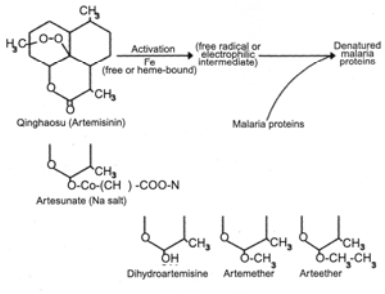
Tetrahydrofolic acid

Artemesinin

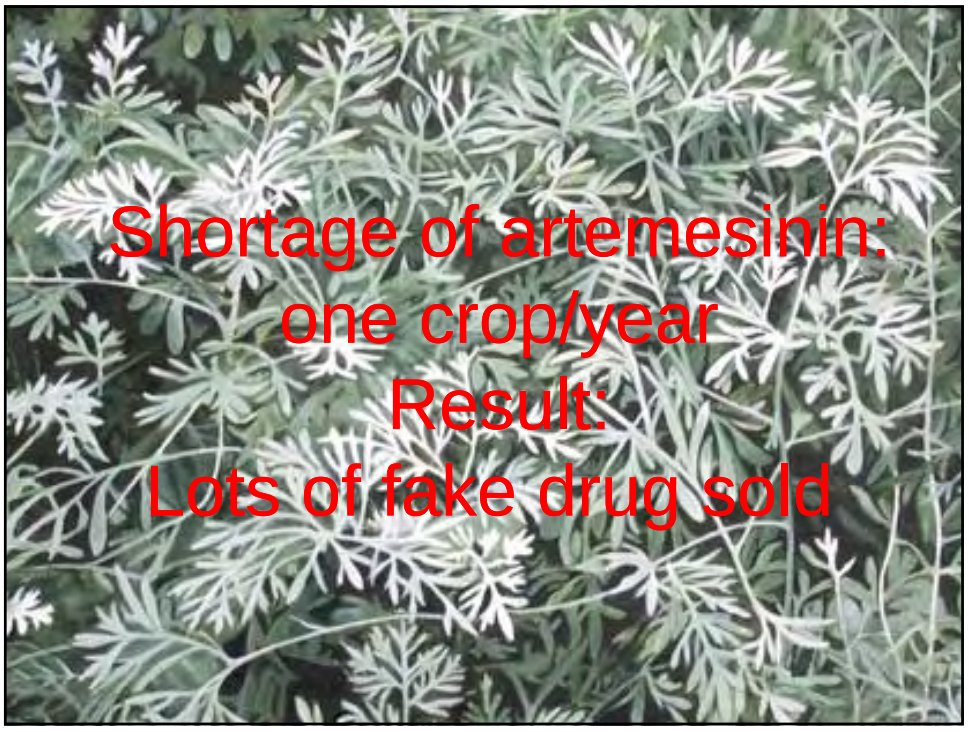
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2002, p. 1510–1515 Vol. 46, No. 5
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.5.1510–1515.2002

In Vitro Interactions of Artemisinin with Atovaquone, Quinine, and Mefloquine against *Plasmodium falciparum*

S. Gupta,[1] M. M. Thapar,[1] W. H. Wernsdorfer,[2] and A. Björkman[1]*



Artemisia sp.



Antimalarial Prophylaxis

- North American travelers lack immunity to malaria
- Risk of acquiring malaria depends on rural travel, altitude, season of travel.
- Highest risk in low lying areas during rainy season
- Personal protection measures against mosquitoes as important as drugs.
- Insect repellants, mosquito nets, clothing covering body
- Antimalarial drugs do not prevent infection and initial liver stage

nature Vol 438|24 November 2005|doi:10.1038/nature04024

LETTERS

The entomological inoculation rate and *Plasmodium falciparum* infection in African children

D. L. Smith[1], J. Dushoff[1,2], R. W. Snow[3,4] & S. I. Hay[3,5]

Conclusion of article: 20% of the children harbor 80% of the infections because they are bitten more often.

Q: Since mosquitoes home in on us via CO_2, body temperatur and perhaps other odors, is there a genetics to our propensity for some of us being bitten more often than others?

Types of Preventive Measures: Drugs

- Prophylaxis with medications based on knowledge of geographic resistance patterns
- Mefloquine, Doxycycline, Atovaquone-Proguanil
- Self treatment: Fansidar, Quinine
- Combination of both: Chloroquine chemoprophylaxis with standby Rx (Not Recommended!)
- MDR resistance a problem in Thailand, Cambodia and Increasingly E. Africa

Future Research

Vaccine; none yet but many being tested

Rapid detection methods for field use

New and Better drugs

- Safety in Children
- Safety in Pregnant Women
- 1 dose cure
- Cheap to make and distribute