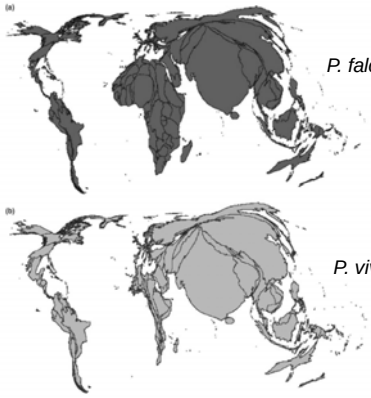
The Malarias:

Plasmodium falciparum
Plasmodium vivax
Plasmodium malariae
Plasmodium ovale

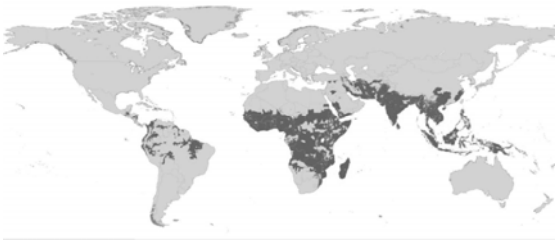
Global Risk By Country-Proportionality Plot



P. falciparum

P. vivax

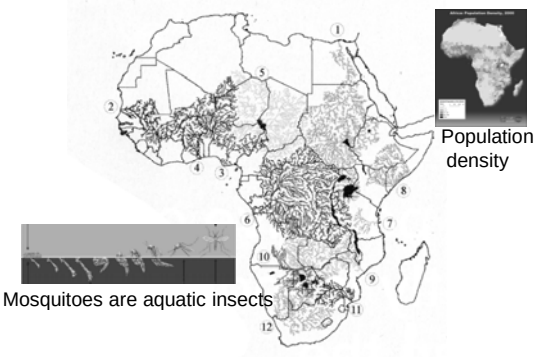
Distribution of Plasmodium falciparum



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

Distribution Of Plasmodium vivax

Watersheds of the African Continent



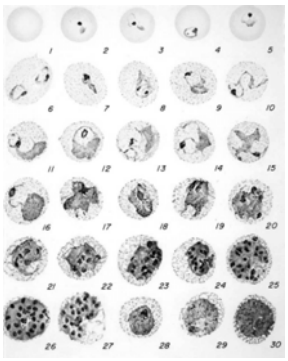
Population density

Mosquitoes are aquatic insects

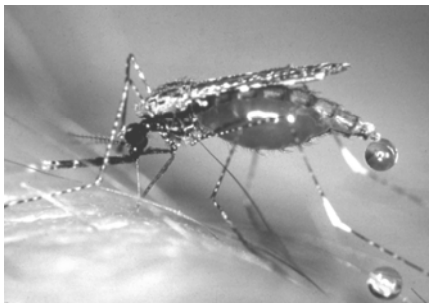
World Situation

- 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 ?

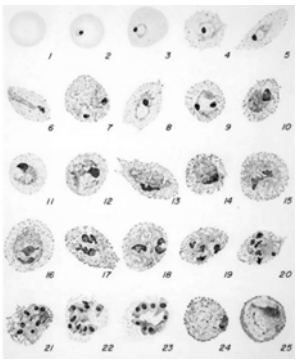
Plasmodium vivax



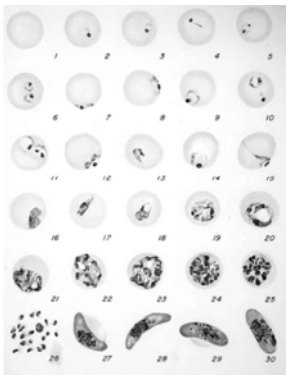
Adult *Anopheles dirus* taking a blood meal from one of the authors (RWG)



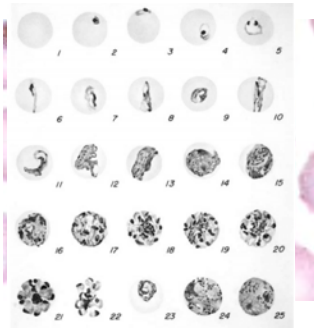
Plasmodium ovale



Plasmodium falciparum



Plasmodium malariae

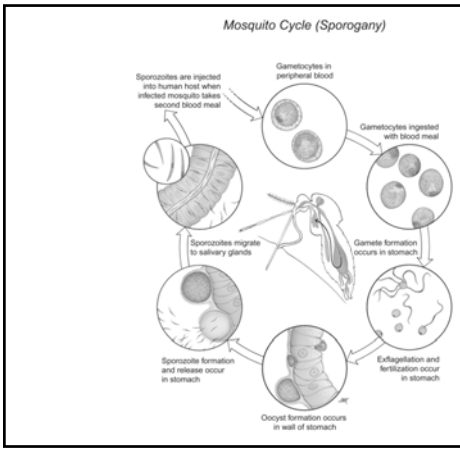


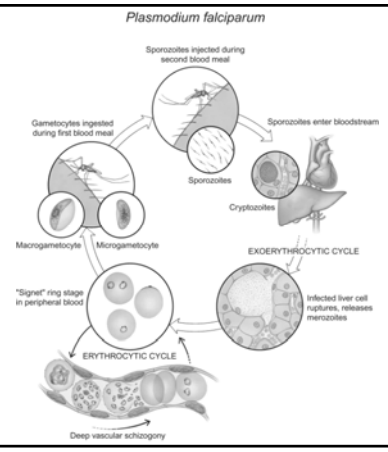
The biology of plasmodium is complex, both in the ***definitive host*** the mosquito, and the ***intermediate host***, the human.

People

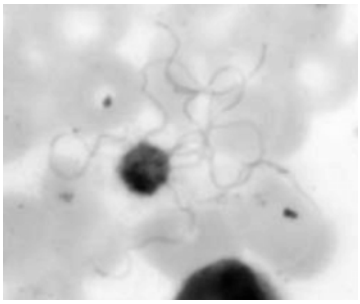
Parasites

Pests





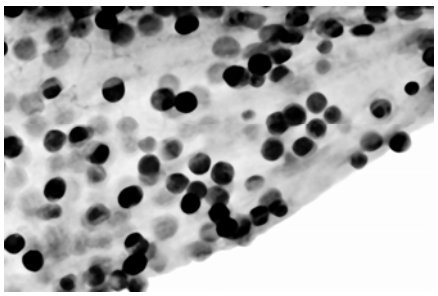
Ex-flagellation of the microgametocyte of a malaria parasite in mosquito stomach



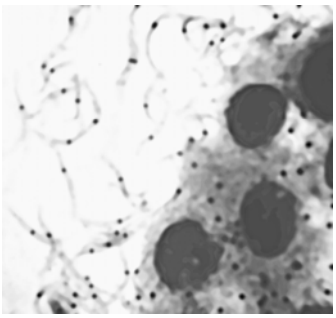
Adult *Anopheles dirus* still taking a blood meal from one of the authors (RWG)

Portion of an infected mosquito stomach.

Note numerous oocysts on outer wall.

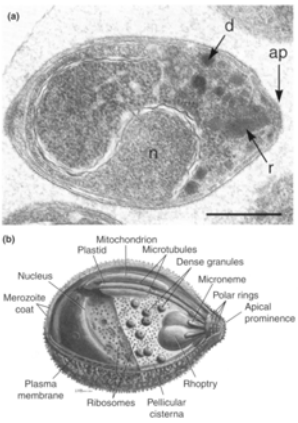


Sporozoites of malaria in infected mosquito stomach preparation



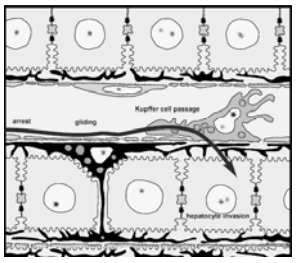
Light micrograph

SEM Photo: Photini Sinnis



Plasmodium Anatomy

Entry Of Sporozoites Into Parenchymal Cells Of The Liv

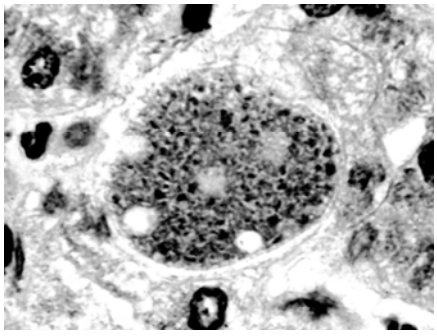


From: Ute Frevert
NYU School of Medicine

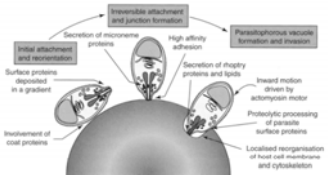
Transmission EM of merozoite entering a red cell.

Note points of attachment

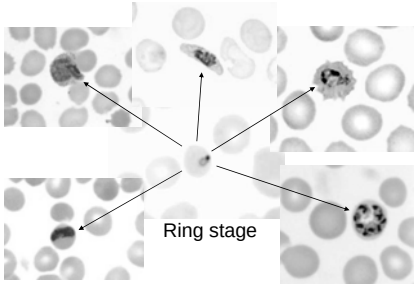
Exo-erythrocytic stages of malaria in liver parenchymal cell



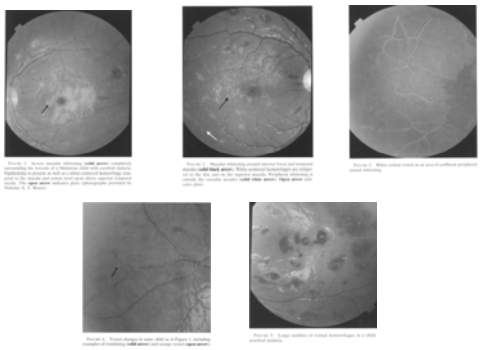
Mechanisms of Red Cell Invasion By Plasmodium



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



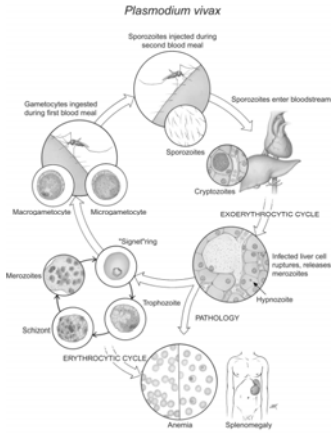
Retinopathy and Severe Malaria



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

Pathogenesis

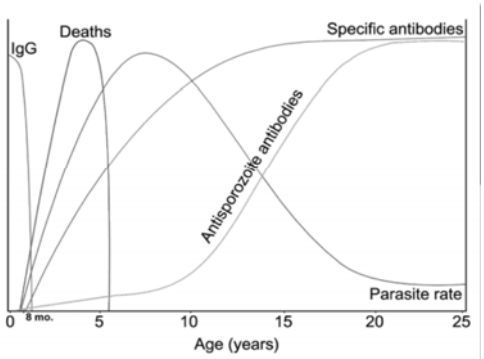
- Destruction of erythrocytes; anemia
- Liberation of parasite and erythrocyte material into circulation
- Host reaction to these events (multiple organ system disease,
- *P. falciparum* has unique sequestration in micro-circulation of vital organs interfering with flow and tissue metabolism (metabolic 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

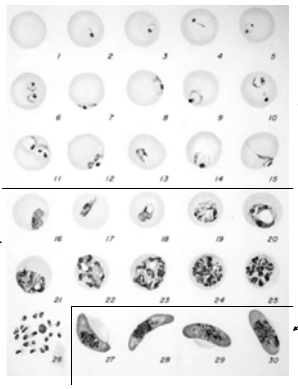
Susceptibility to malaria, antibody production, and lethality.



Transmission EM: RBC infected with *P. falciparum*

N = Nucleus; F = food vacuole

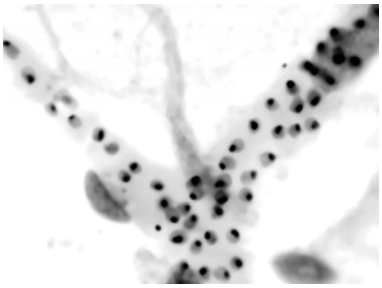
Plasmodium falciparum



Not in peripheral blood: 16-26

In peripheral blood: 1-15; 27-30

Cerebral malaria: experimental infection in monkey

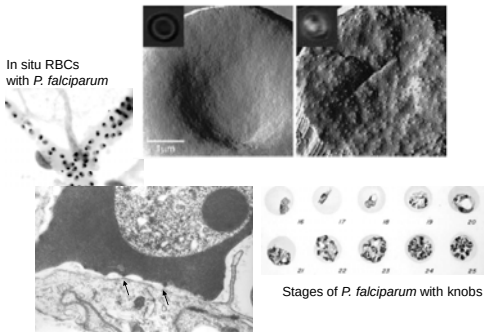


stain: tissue Giemsa

Normal RBC

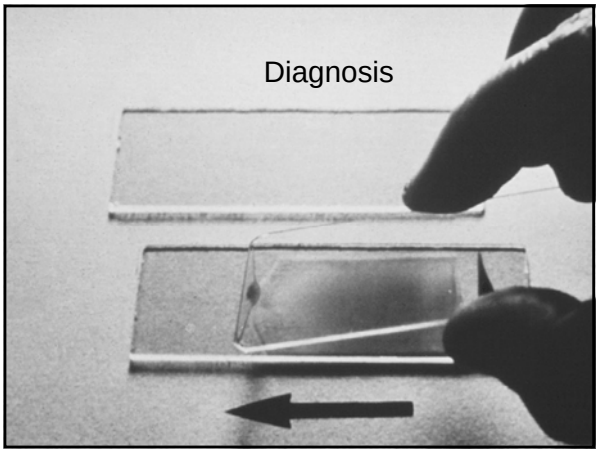
Atomic force microscopy of knobs

In situ RBCs with *P. falciparum*

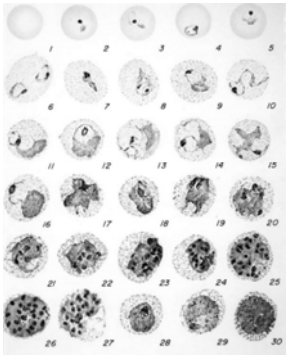


Electron micrograph of knobs

Stages of *P. falciparum* with knobs

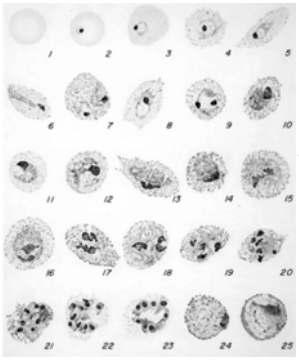


Plasmodium vivax



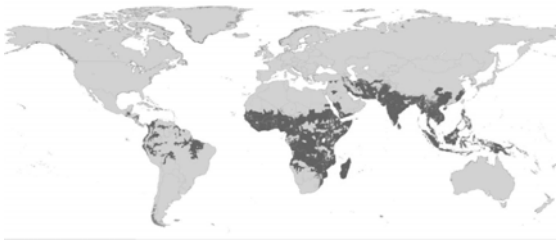
Infected RBCs larger than non-infected RBCs, Schüffner's dots

Plasmodium ovale

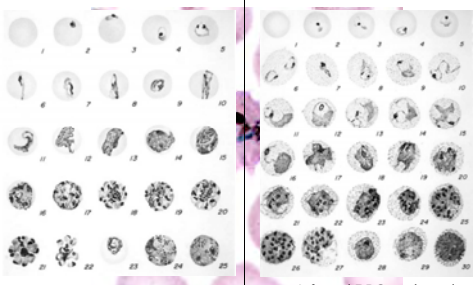


Same as *P. vivax*

Distribution of Plasmodium falciparum



Plasmodium malariae | *Plasmodium vivax*



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

Infected RBCs enlarged

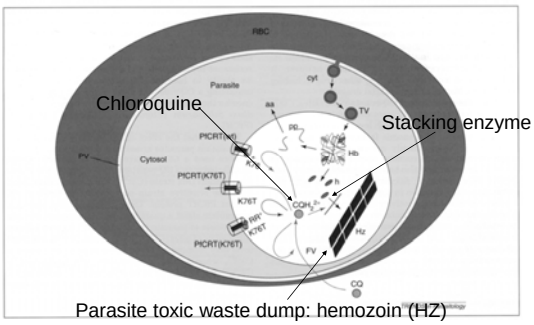
Drug-resistant Malaria

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

Treatment

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

Mode of Action of Chloroquine
And Mechanisms of Drug Resistance

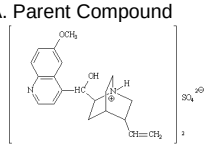


Parasite toxic waste dump: hemozoin (HZ)

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

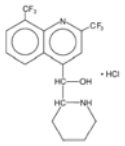
Drugs Of Choice:

A. Parent Compound



Quinine

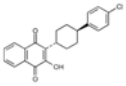
C. Newer Derivative



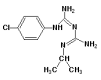
Mefloquine

B. Older Derivative: extensive resistance

D. Drugs of choice



Chloroquine



Atovaquon Proguanil

Treatment: Anti-Folates

Pteridine + PABA (Para-aminobenzoic Acid)

Dihydropteroate Synthetase ← **Sulfonamides / Dapsone**

↓

Folic acid

↓

Dihydrofolic acid

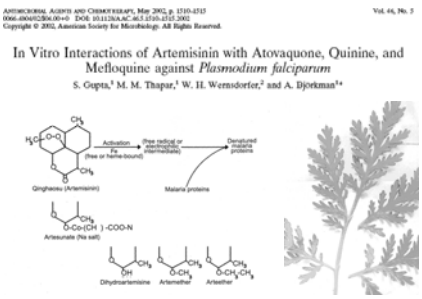
↓

Dihydrofolate reductase ← **Pyrimethamine, Proguanil**

↓

Tetrahydrofolic acid

Artemesinin



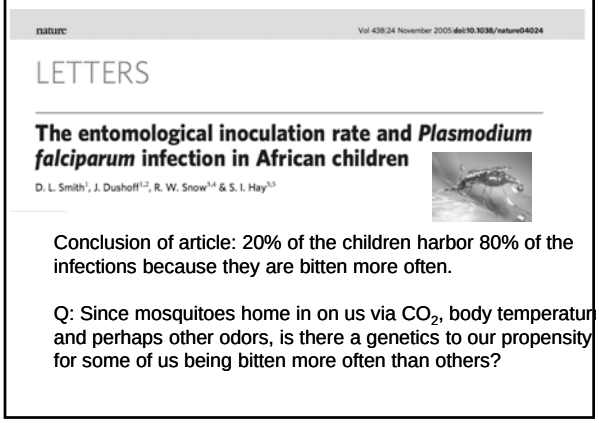
In Vitro Interactions of Artemisinin with Atovaquone, Quinine, and Mefloquine against *Plasmodium falciparum*

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



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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?

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

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