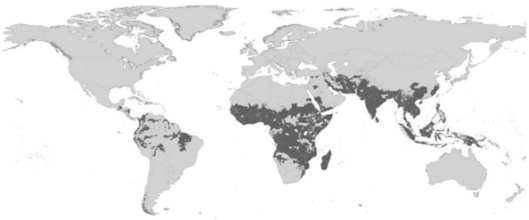
The Malarias:

Plasmodium falciparum
Plasmodium vivax
Plasmodium malariae
Plasmodium ovale

Distribution of Plasmodium falciparum



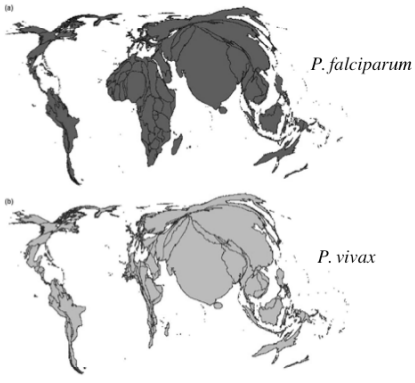
Distribution Of Plasmodium vivax

Table 2. PAR of malaria derived from extractions using the global spatial limits for *P. falciparum* and *P. vivax* in 2005

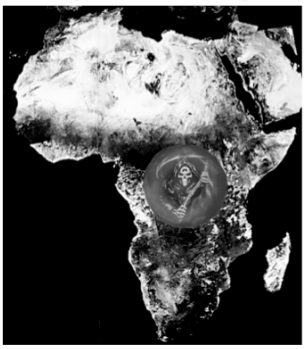
WHO region	*P. falciparum* risk[a]	*P. vivax* risk[a]
SEARO	1.252	1.347
AFRO	0.525	0.050
WPRO	0.438	0.890
EMRO	0.245	0.211
AMRO	0.050	0.078
EURO	0.000	0.020
Total	2.510	2.596

[a]The risk is given in billion (1,000,000,000) persons. Abbreviations: WHO, World Health Organization; SEARO, South East Asian Regional Office; AFRO, African Regional Office; WPRO, Western Pacific Regional Office; EMRO, Eastern Mediterranean Regional Office; AMRO, American Regional Office; EURO, European Regional Office.

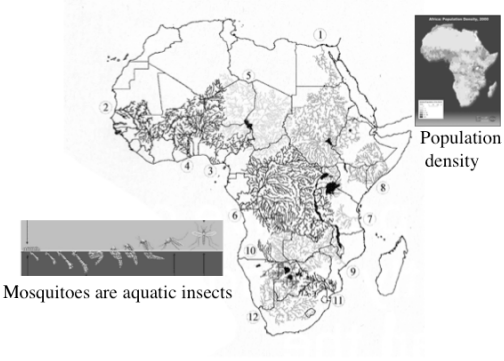
Global Risk By Country-Proportionality Plot



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



Watersheds of the African Continent



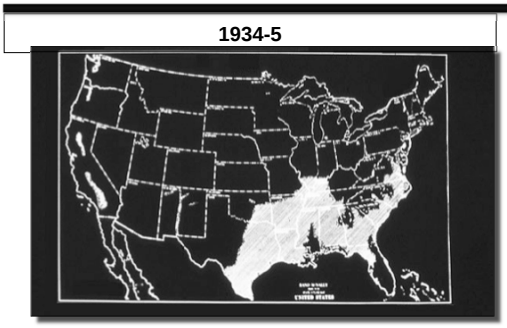
Population density

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 ?

Malarious Area of the United States

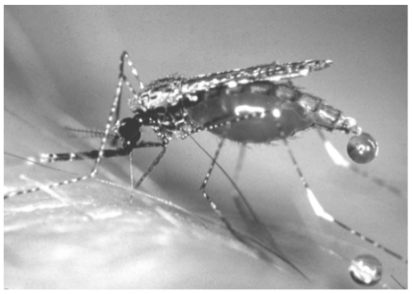


Malaria put bite on Jersey man

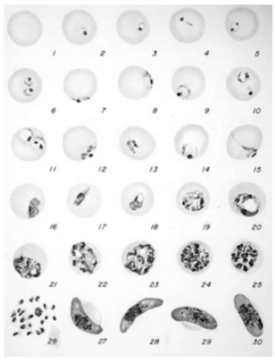
By JANET A. HINES
Staff Writer

The life cycle of the malaria parasite

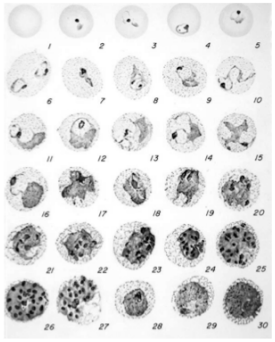
Adult *Anopheles dirus* taking a blood meal from one of the authors (RWG)



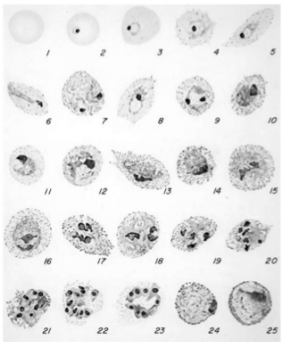
Plasmodium falciparum



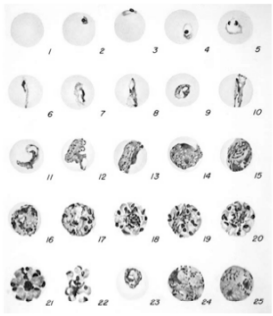
Plasmodium vivax



Plasmodium ovale



Plasmodium malariae



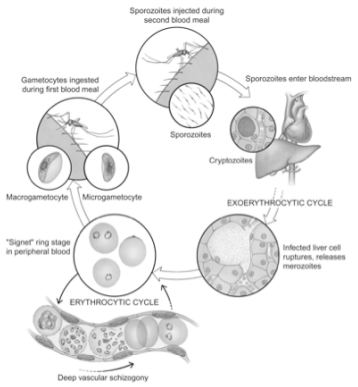
The biology of plasmodium is complex, both in the ***definitive host*** the mosquito, and the ***intermediate host***, the human.

People

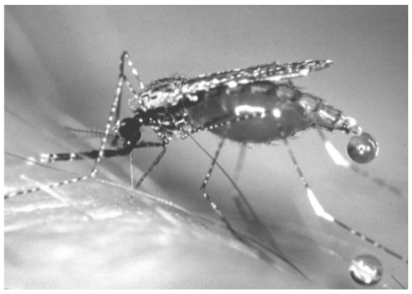
Parasites

Pests

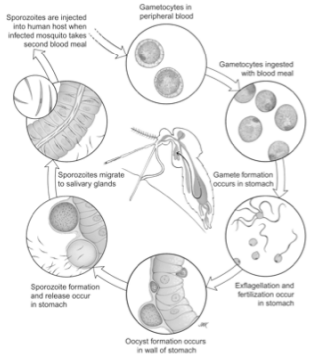
Plasmodium falciparum



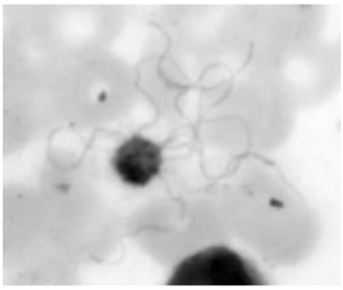
Adult *Anopheles dirus* still taking a blood meal from one of the authors (RWG)



Mosquito Cycle (Sporogany)

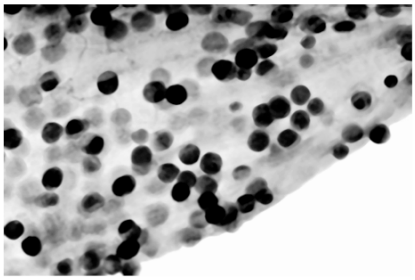


Ex-flagellation of the microgametocyte
of a malaria parasite in mosquito stomach

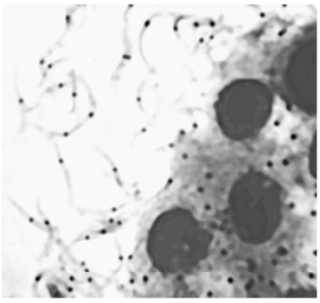


Portion of an infected mosquito stomach.

Note numerous oocysts on outer wall.



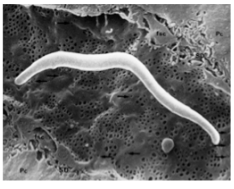
Sporozoites of malaria in infected
mosquito stomach preparation

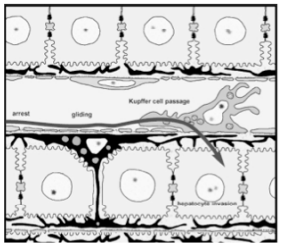


Light micrograph

SEM Photo: Photini Sinnis

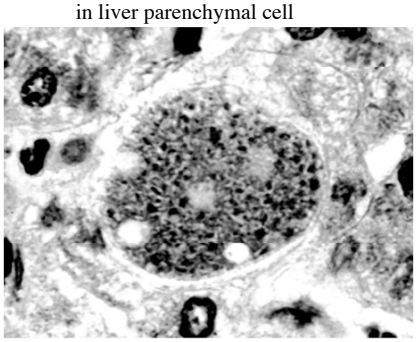
Entry Of Sporozoites Into Parenchymal Cells Of The Liver

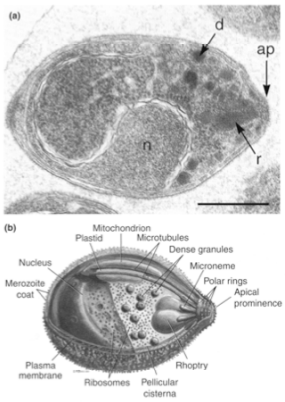




From: Ute Frevert
NYU School of Medicine

Exo-erythrocytic stages of malaria
in liver parenchymal cell



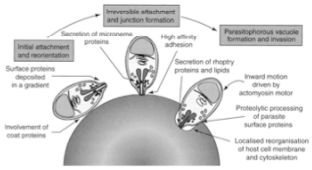


Plasmodium Anatomy

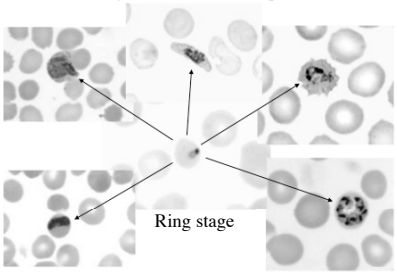
Transmission EM of merozoite entering a red cell.

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



Ring stage

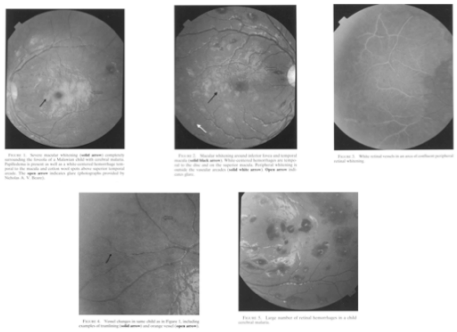
Pathogenesis

- 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

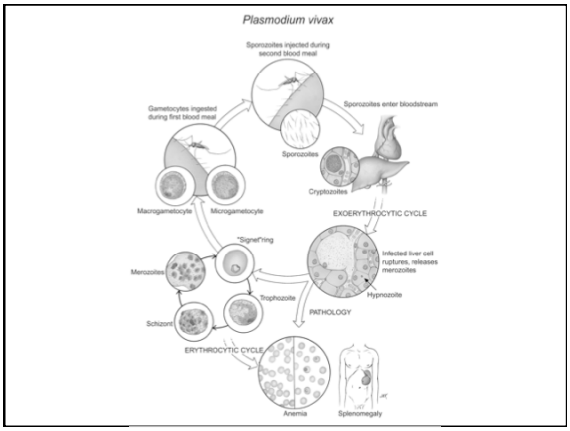
Clinical Signs & Symptoms

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

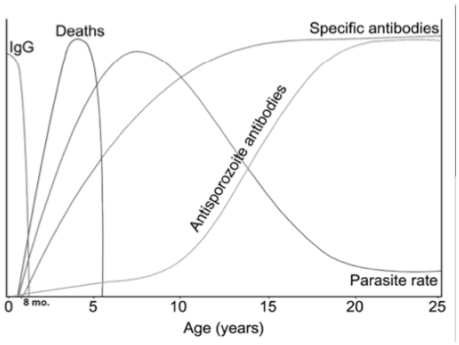
Retinopathy and Severe Malaria



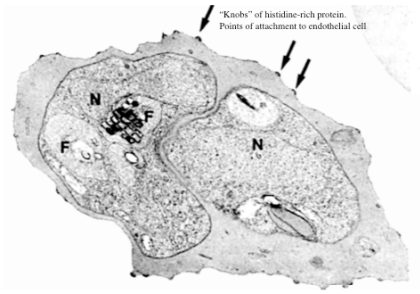
Am J Trop Med Hyg. 2006. Beare, N, et al. Vol. 75: 790-797



Susceptibility to malaria, antibody production, and lethality.

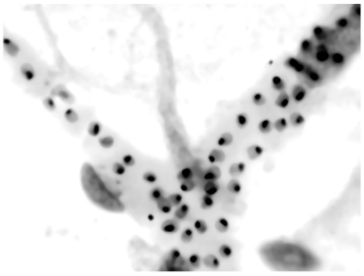


Transmission EM: RBC infected with *P. falciparum*



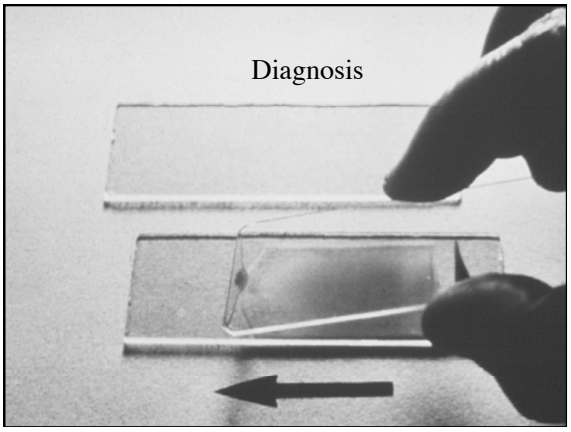
N = Nucleus; F = food vacuole

Cerebral malaria: experimental infection in monkey

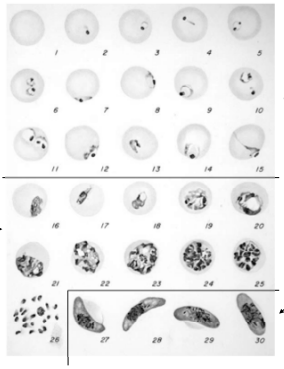


stain: tissue Giemsa

Diagnosis



Plasmodium falciparum



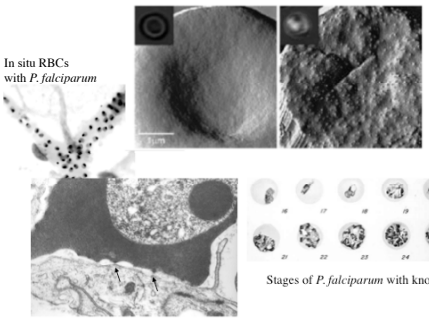
Not in peripheral blood: 16-26

In peripheral blood: 1-15; 27-30

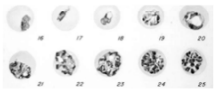
Normal RBC

Atomic force microscopy of knobs

In situ RBCs with *P. falciparum*

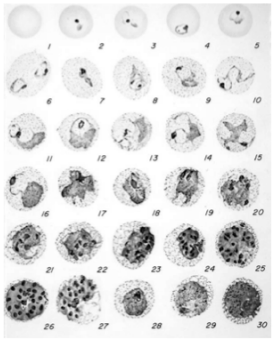


Electron micrograph of knobs



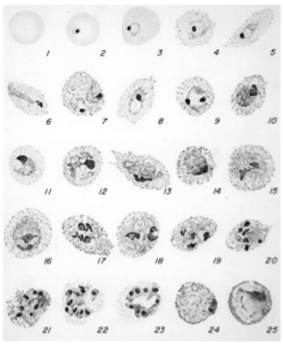
Stages of *P. falciparum* with knobs

Plasmodium vivax



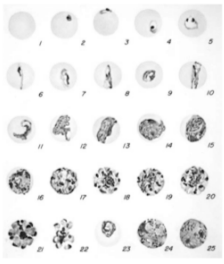
Infected RBCs larger than non-infected RBCs, Schüffner's dots

Plasmodium ovale



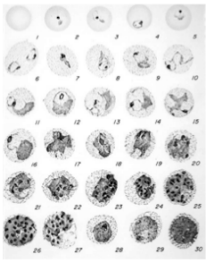
Same as *P. vivax*

Plasmodium malariae



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

Plasmodium vivax

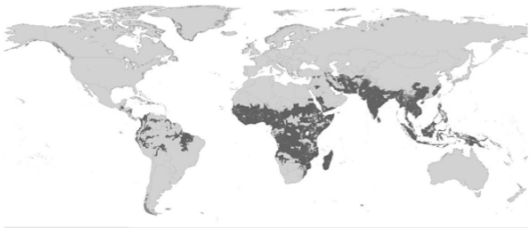


Infected RBCs enlarged

Treatment

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

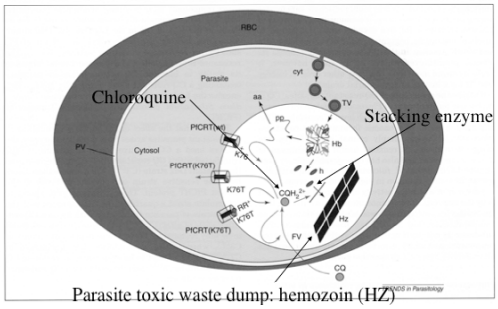
Distribution of Plasmodium falciparum



Drug-resistant Malaria

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

Mode of Action of Chloroquine
And Mechanisms of Drug Resistance

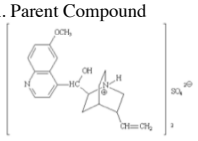


Parasite toxic waste dump: hemozoin (HZ)

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

Drugs Of Choice:

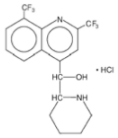
A. Parent Compound



Quinine

B. Older Derivative: extensive resistance

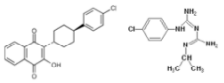
C. Newer Derivative



Mefloquine

D. Drugs of choice

Chloroquine



Atovaquon Proguanil

Treatment: Anti-Folates

Pteridine + PABA (Para-aminobenzoic Acid)

Dihydropteroate Synthetase ← **Sulfonamides / Dapsone**

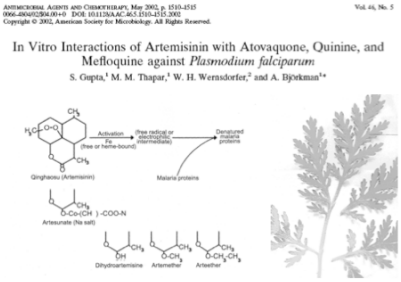
Folic acid

Dihydrofolic acid

Dihydrofolate reductase ← **Pyrimethamine, Proguanil**

Tetrahydrofolic acid

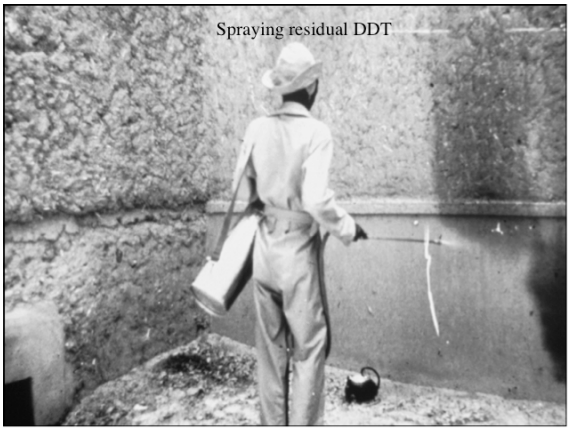
Artemesinin



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.


Spraying residual DDT

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 temperature and perhaps other odors, is there a genetics controlling our susceptibility to being bitten?

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
- New and Better drugs
  - Safety in Children
  - Safety in Pregnant Women
  - ? 1 dose