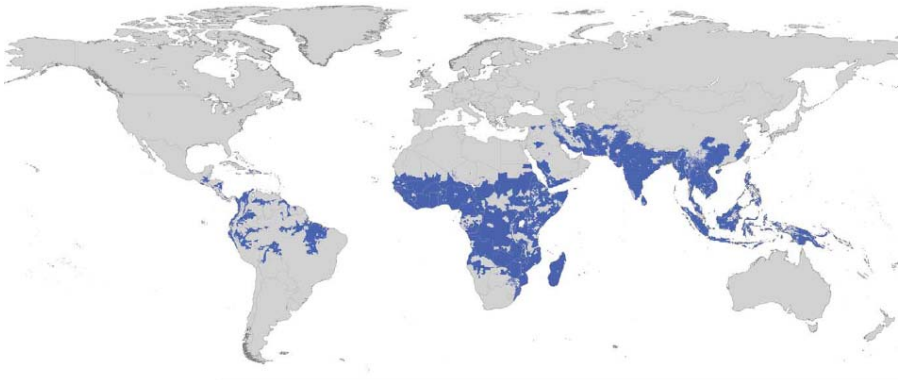
The Malarias:

Plasmodium falciparum
Plasmodium vivax
Plasmodium malariae
Plasmodium ovale

Distribution of Plasmodium falciparum



Distribution Of Plasmodium vivax

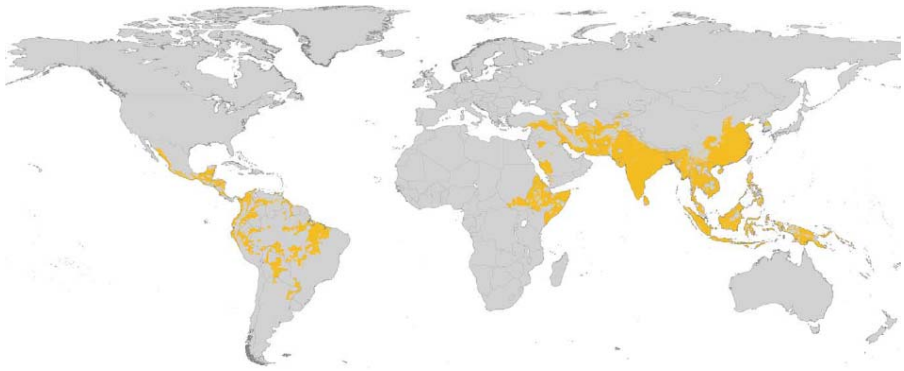
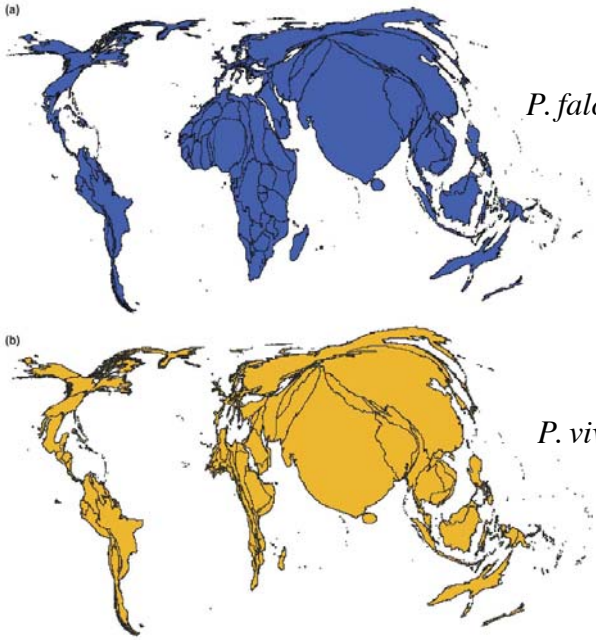


Table 2. PAR of malaria derived from extractions using the global spatial limits for *P. falciparum* and *P. vivax* in 2005

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.

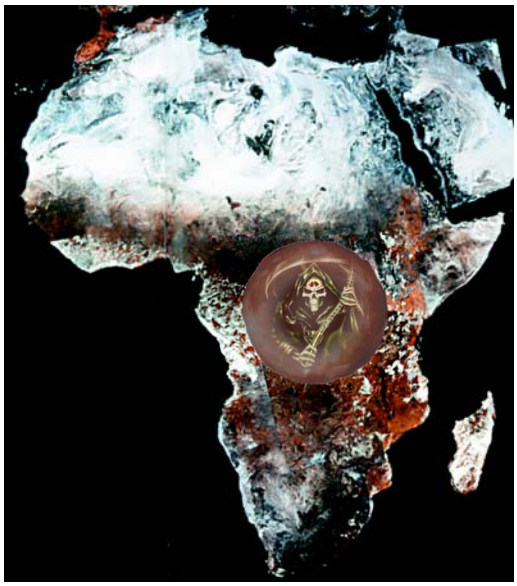
Global Risk By Country-Proportionality Plot



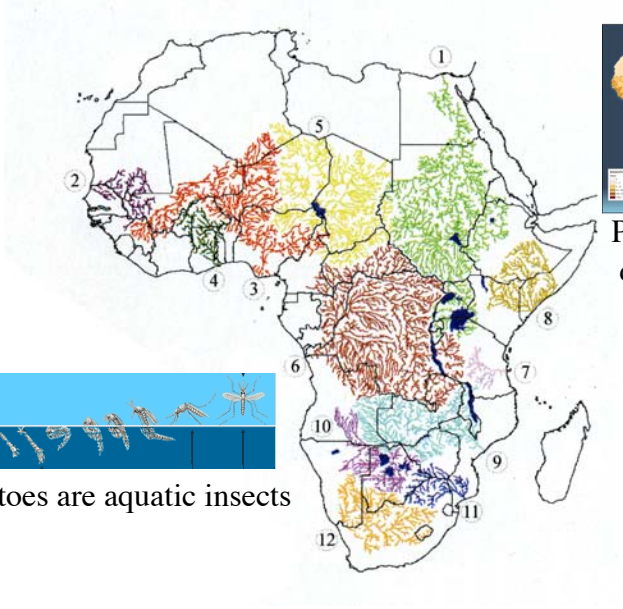
P. falciparum

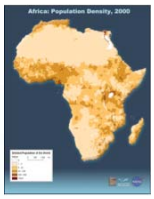
P. vivax

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

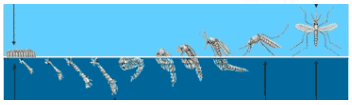


Watersheds of the African Continent





Population density



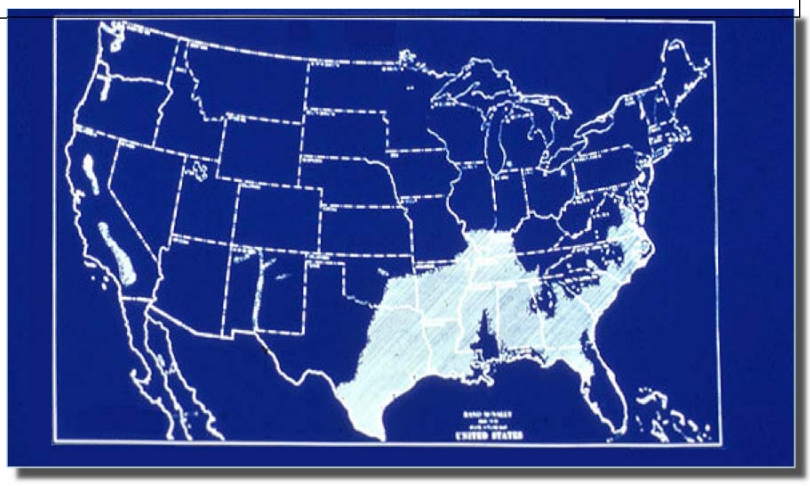
Mosquitoes are aquatic insects

World Situation

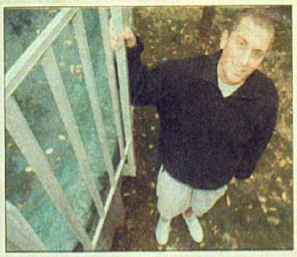
- Approx. 2 billion infections/yr
- Economic and social development reduced
- 27% of the world lies within the malaria transmission zone
- New unstable transmission area: Bangladesh
- Impact of malaria on population change ?

Malarious Area of the United States

1934-5



Malaria put bite on Jersey man



By JANET A. HINES
Staff Writer

A mosquito bite put 19-year-old college student Vincent Battista in the hospital, where doctors diagnosed him with an illness that hasn't been contracted in New Jersey since 1991.

Battista had malaria.

"He had a better chance of winning the lottery than contracting malaria," said infectious disease specialist Dr. Patricia Ruggeri-Weigle of Westfield. "There's a one-in-8-million chance of someone in this state contracting malaria without leaving the country."

Centers for Disease Control and Prevention experts said they are aware of Battista's case but are not worried about a widespread outbreak as the mosquito population diminishes at the onset of cooler weather.

"The cold climate is not conducive to ongoing transmission — mosquitoes can't thrive in it," said Dr. Lawrence Barat of the centers. "By the time health departments identify these cases, transmission has stopped."

The state Department of Health and Senior Services is in the process of confirming the doctors' diagnosis, spokesman Dennis McGowen said.

"Once we confirm that it is malaria, we will try to identify where the mosquito contracted the parasite," McGowen said. "Malaria is not common in New Jersey. The mosquito would have had to pick it up from someone who is infected and doesn't realize it."

The disease attacks red blood cells and is more common in tropical climates. The source is a specific breed of mosquito, called anopheles quadrimaculatus, which is prevalent in New Jersey, McGowen said.

However, cases of the mosquito transmitting the disease are extremely rare in this country, he said.

The disease is usually contracted when people travel to countries where there are malaria epidemics and return home with the illness, Barat said. Most people receive inoculations before they visit those countries.

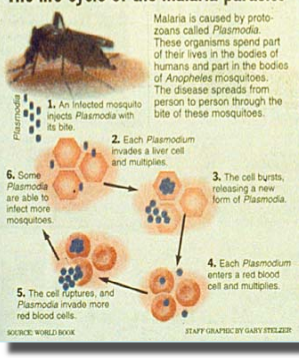
Each year, the centers receive about 1,200 malaria reports. Ten or fewer are transmitted to people who receive the disease while living in the United States. The last reported cases in New Jersey occurred in Monmouth and Camden counties in 1991, Barat said.

There are four types of malaria, and some forms are deadly, Ruggeri-Weigle said. In Battista's case, doctors are treating him with a two-week program of drugs to stave off future recurrences. But there is a chance that the malaria will reappear years from now.

Battista of North Plain-

See MALARIA, A-4

The life cycle of the malaria parasite



Malaria is caused by protozoans called *Plasmodia*. These organisms spend part of their lives in the bodies of humans and part in the bodies of *Anopheles* mosquitoes. The disease spreads from person to person through the bite of these mosquitoes.

SOURCE: WORLD BOOK

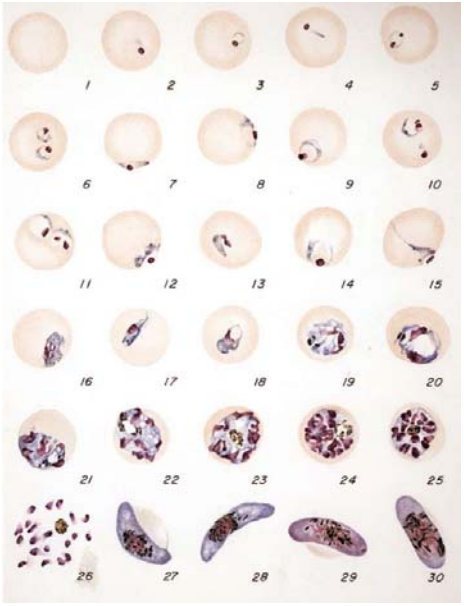
STAFF GRAPHIC BY GARY STELZER

STAFF PHOTO BY MARY EUGENE

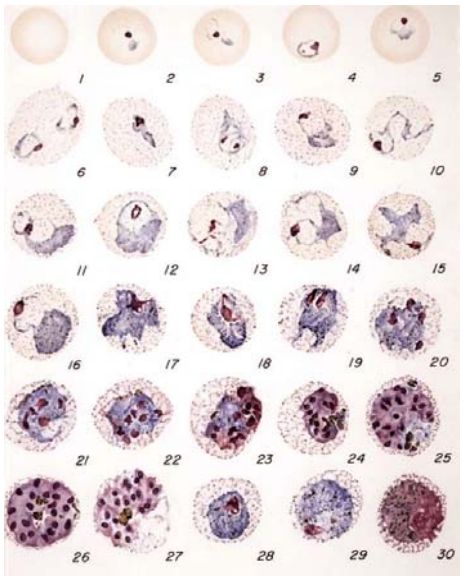
Top, Vincent Battista of North Plainfield, who was afflicted with malaria, is fully recovered. Left, a graphic describes the life cycle of the malaria parasite.

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

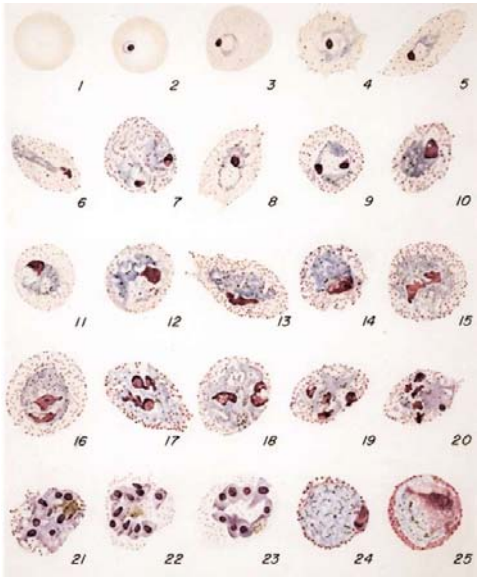
Plasmodium falciparum



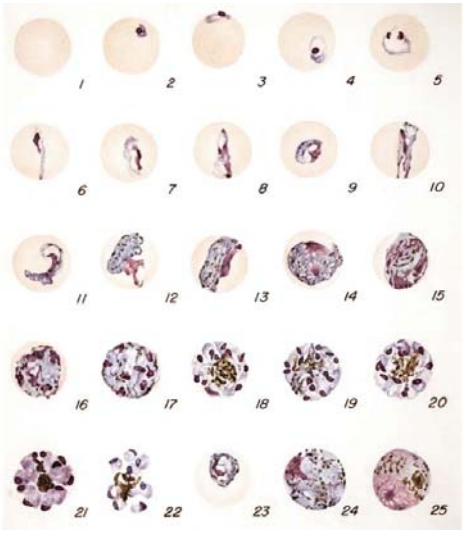
Plasmodium vivax



Plasmodium ovale



Plasmodium malariae

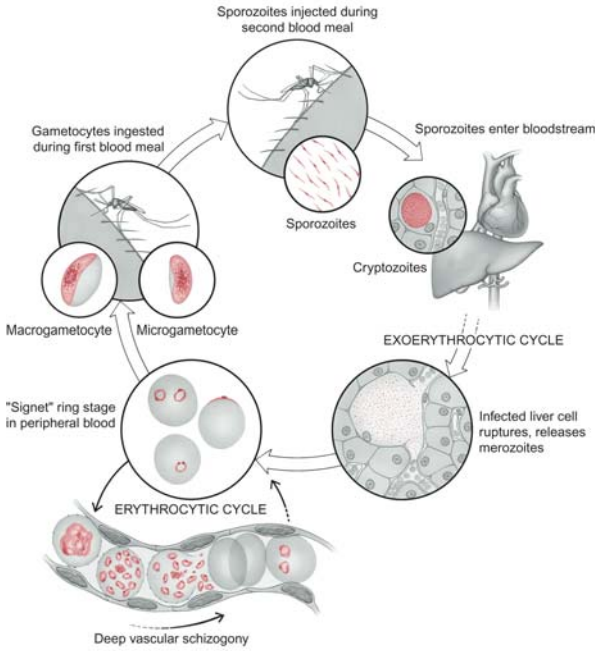


The biology of plasmodium is complex, both in the ***definitive host*** the mosquito, and the ***intermediate host***, the human.

People

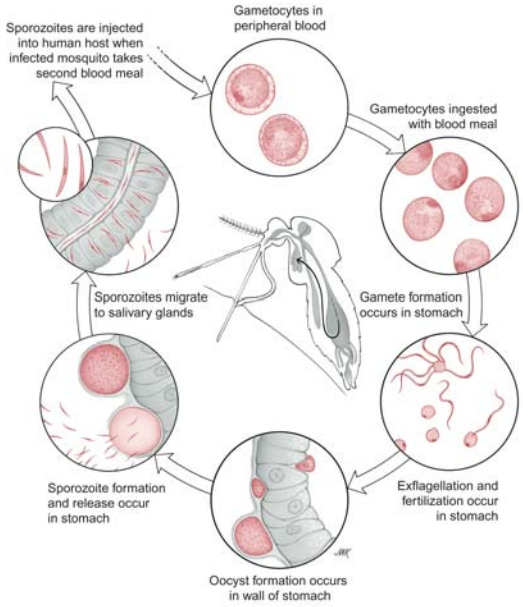
Parasites

Pests

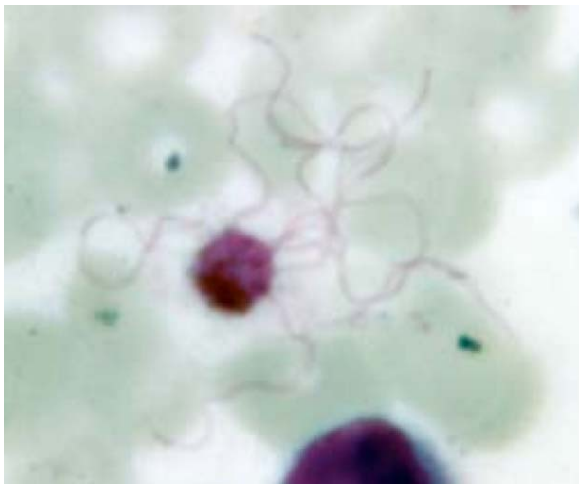


Adult *Anopheles dirus* still taking a blood meal from one of the authors (RWG)

Mosquito Cycle (Sporogany)

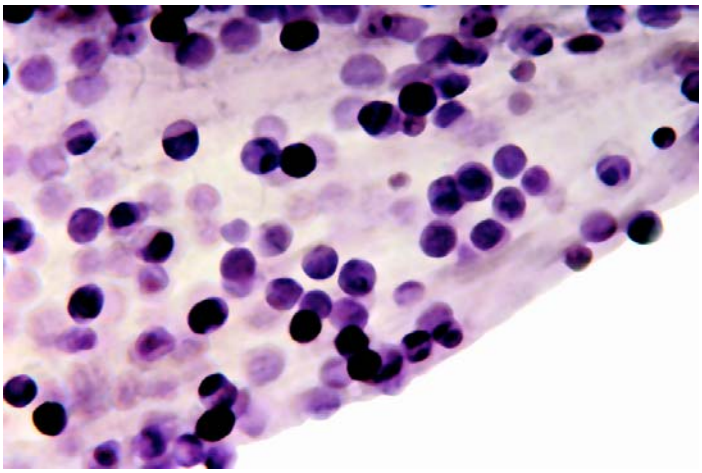


Ex-flagellation of the microgametocyte of a malaria parasite in mosquito stomach

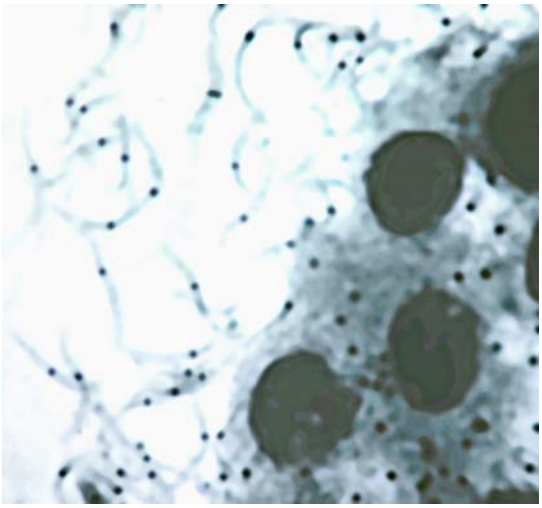


Portion of an infected mosquito stomach.

Note numerous oocysts on outer wall.



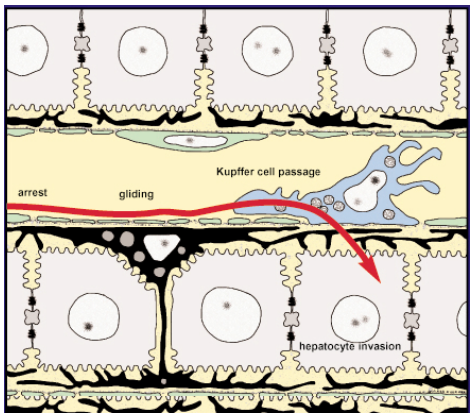
Sporozoites of malaria in infected mosquito stomach preparation



Light micrograph

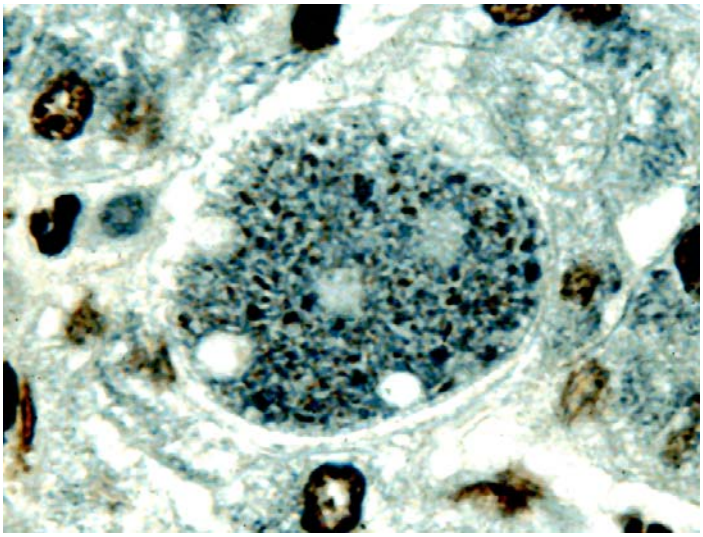
SEM Photo: Photini Sinnis

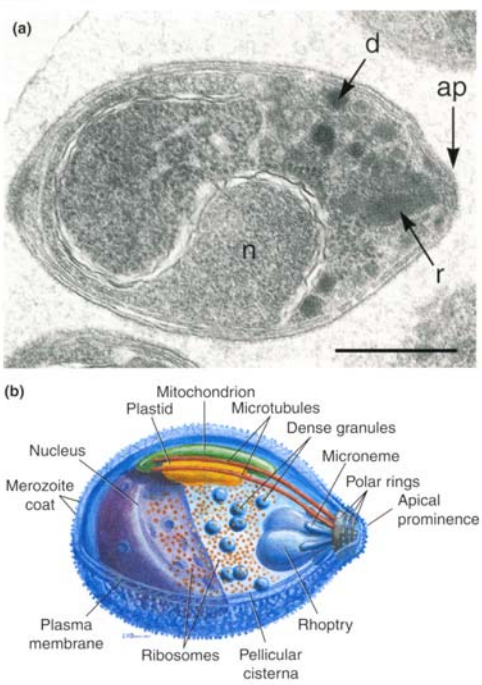
Entry Of Sporozoites Into Parenchymal Cells Of The Liver



From: Ute Frevert
NYU School of Medicine

Exo-erythrocytic stages of malaria
in liver parenchymal cell

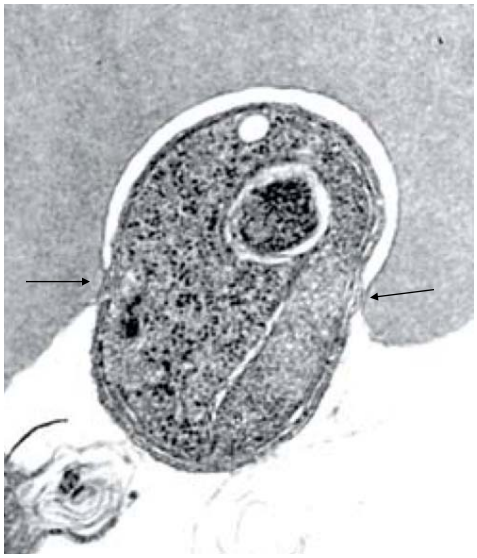




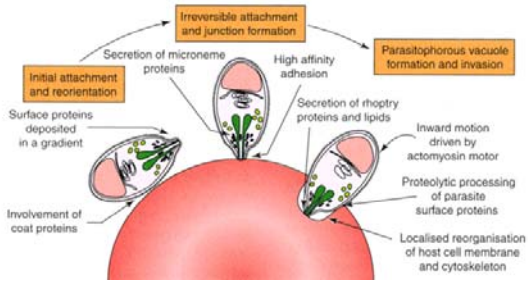
Plasmodium Anatomy

Transmission EM of merozoite entering a red cell.

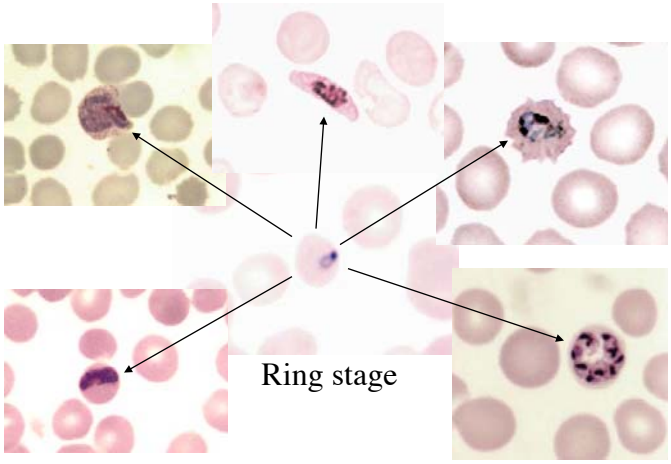
Note points of attachment



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

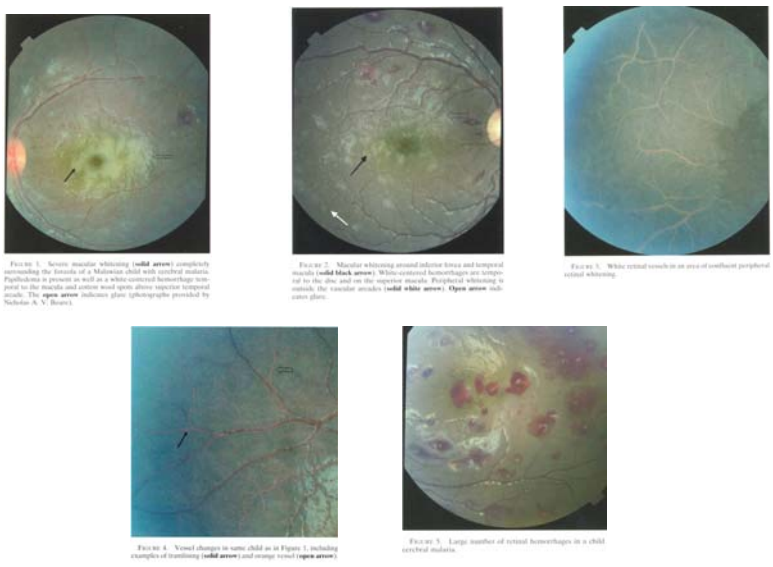
Pathogenesis

- 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

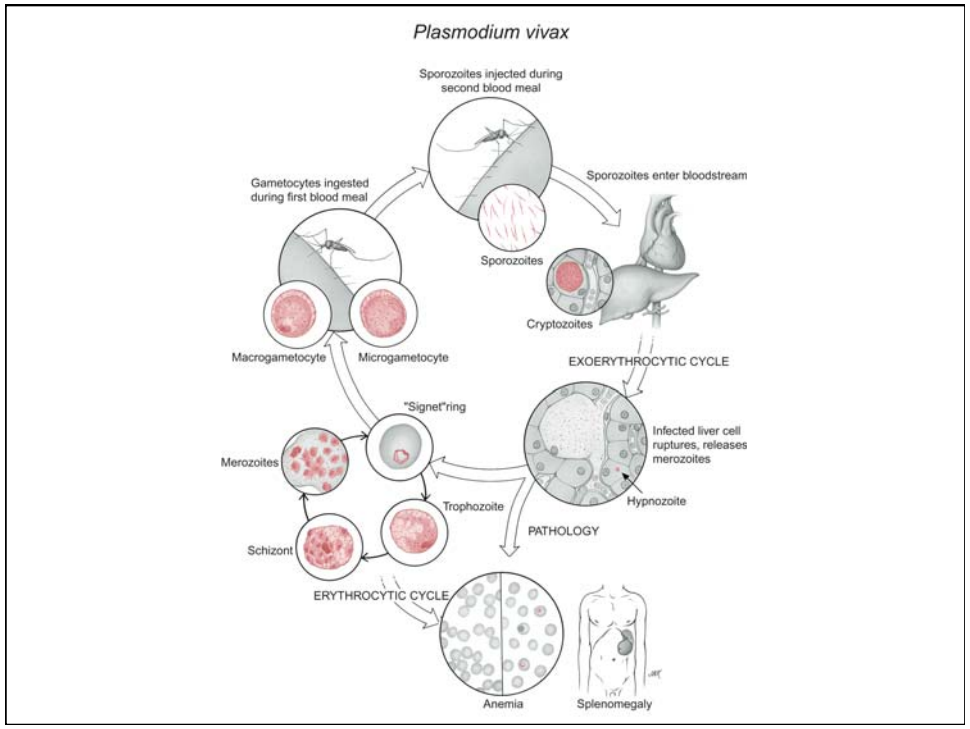
Clinical Signs & Symptoms

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

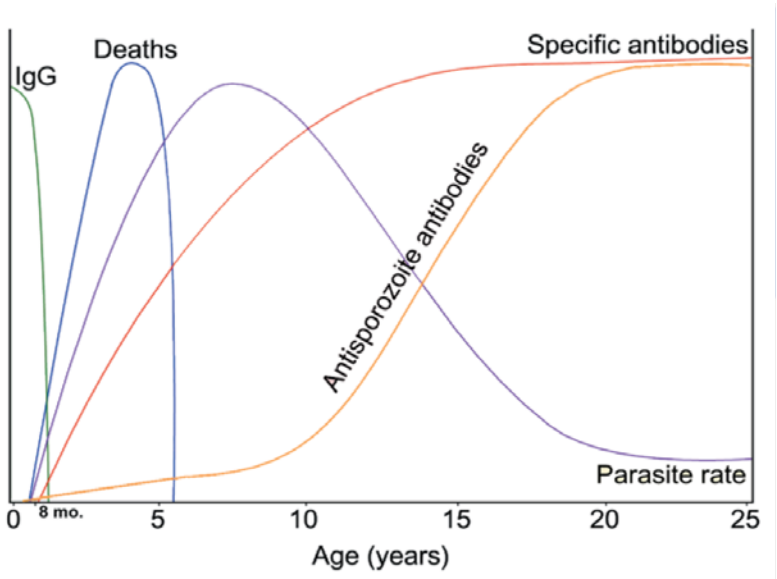
Retinopathy and Severe Malaria



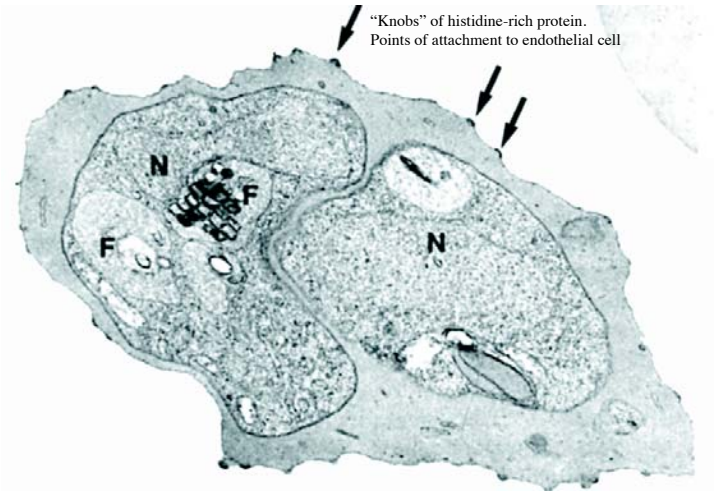
Am J Trop Med Hyg. 2006. Beare, N, et al. Vol. 75: 790-797



Susceptibility to malaria, antibody production, and lethality.

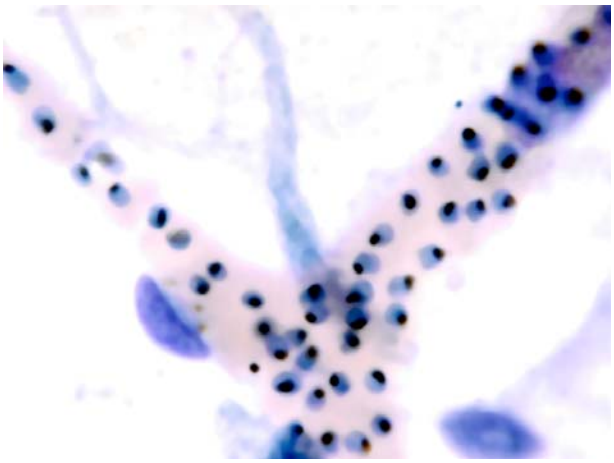


Transmission EM: RBC infected with *P. falciparum*

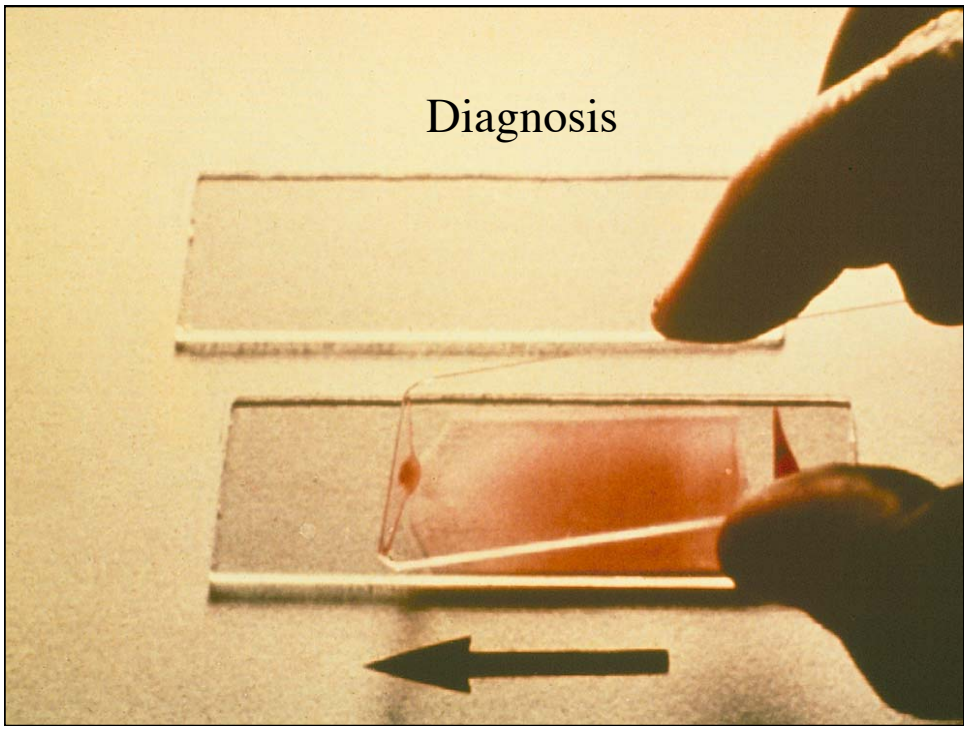


N = Nucleus; F = food vacuole

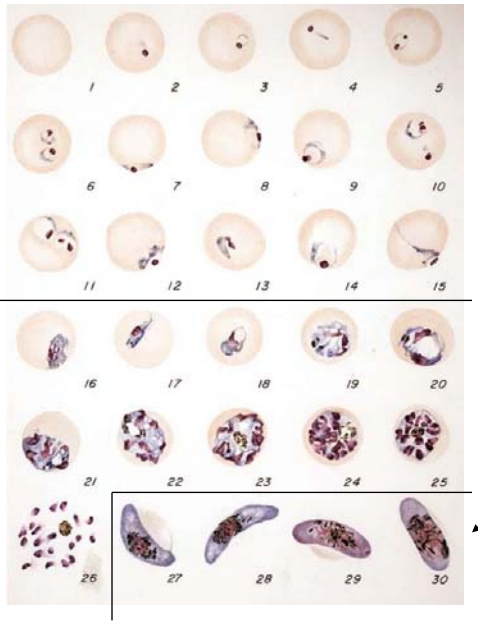
Cerebral malaria: experimental infection in monkey



stain: tissue Giemsa



Plasmodium falciparum

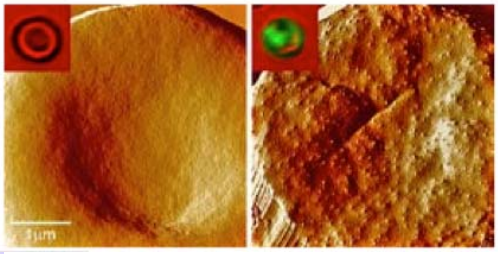


Not in peripheral blood: 16-26 →

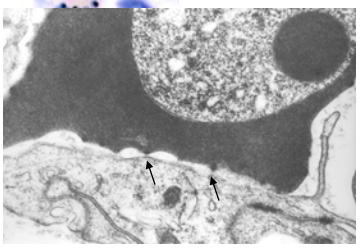
In peripheral blood: 1-15; 27-30

Normal RBC

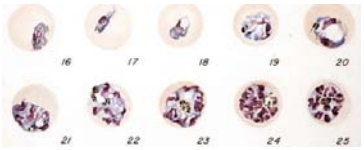
Atomic force microscopy of knobs



In situ RBCs with *P. falciparum*

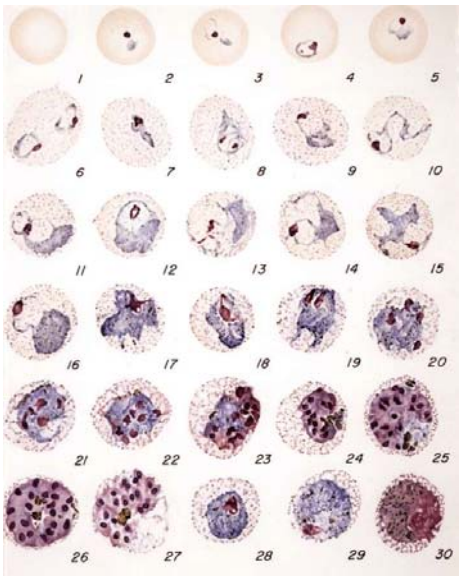


Electron micrograph of knobs



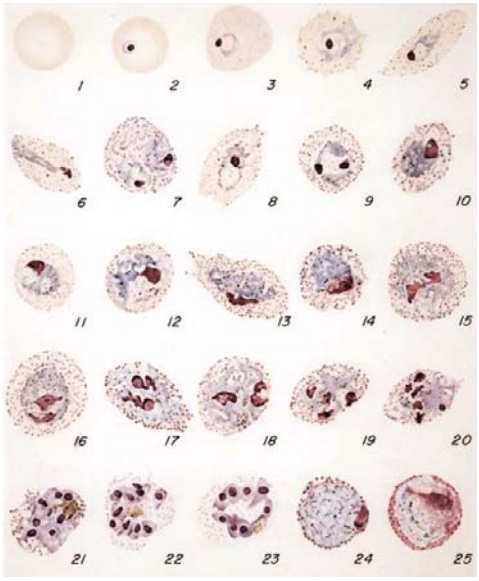
Stages of *P. falciparum* with knobs

Plasmodium vivax



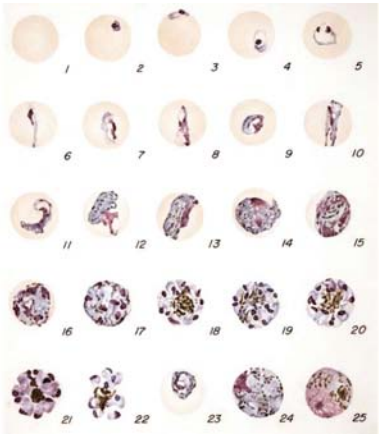
Infected RBCs larger than non-infected RBCs, Schüffner's dots

Plasmodium ovale



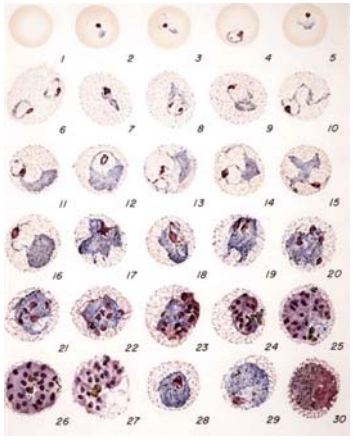
Same as *P. vivax*

Plasmodium malariae



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

Plasmodium vivax

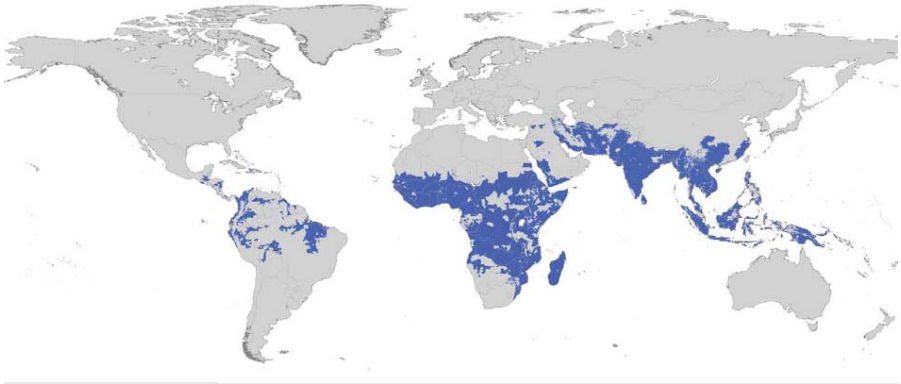


Infected RBCs enlarged

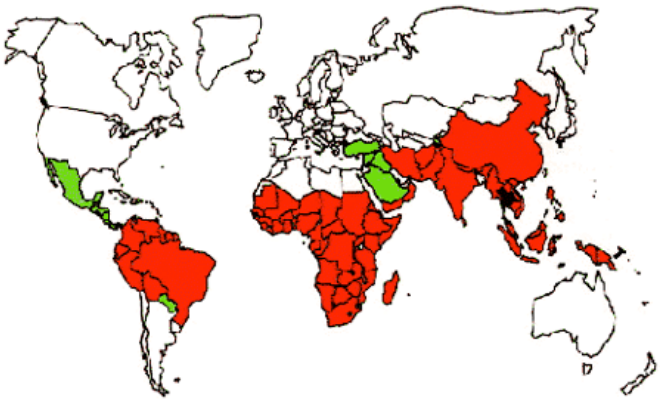
Treatment

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

Distribution of Plasmodium falciparum

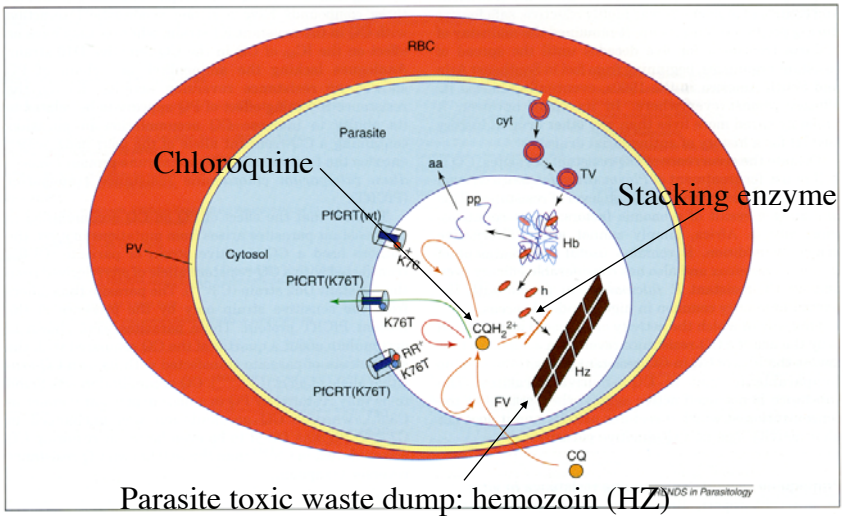


Drug-resistant Malaria



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

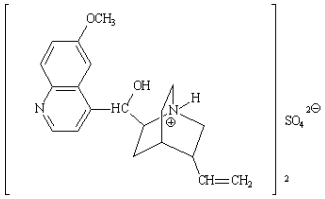
Mode of Action of Chloroquine
And Mechanisms of Drug Resistance



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

Drugs Of Choice:

A. Parent Compound

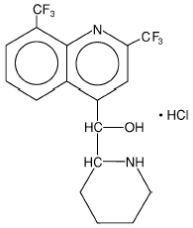


Quinine

B. Older Derivative: extensive resistance

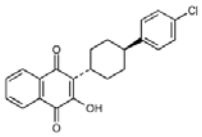
Chloroquine

C. Newer Derivative

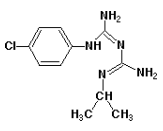


Mefloquine

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**

↓

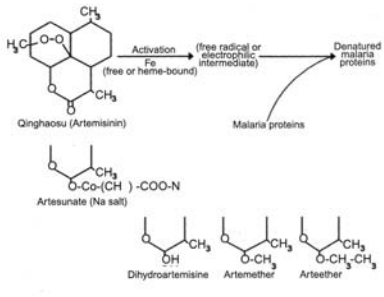
Tetrahydrofolic acid

Artemesinin

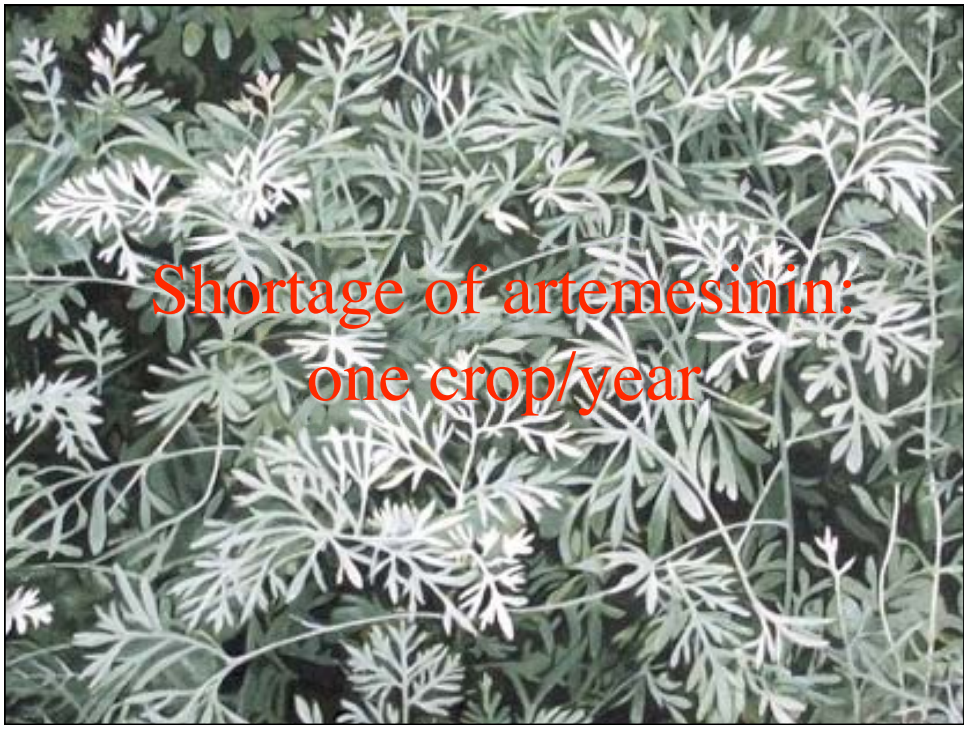
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2002, p. 1510–1515 Vol. 46, No. 5
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.5.1510–1515.2002

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.


Shortage of artemesinin:
one crop/year


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