The Malarias:

*Plasmodium falciparum*
*Plasmodium vivax*
*Plasmodium malariae*
*Plasmodium ovale*

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

Watersheds of the African Continent

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

**Mosquito Cycle (Sporogony)**

1. Sporozoites are injected into human host when infected mosquito takes a blood meal.
2. Sporozoites migrate to salivary glands.
3. Gametocytes in peripheral blood.
4. Gametocytes ingested with blood meal.
5. Gamete formation occurs in stomach.
6. Gametogenesis and fertilization occur in stomach.
7. Oocyst formation occurs in wall of stomach.
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

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

(a)

(b)
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 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

Susceptibility to malaria, antibody production, and lethality.
Transmission EM: RBC infected with *P. falciparum*

"Knobs" of histidine-rich protein. Points of attachment to endothelial cell

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
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

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**Mode of Action of Chloroquine And Mechanisms of Drug Resistance**

- **Chloroquine**
- **Stacking enzyme**
- **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

[Chemical structure of 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

Dihydrofolate acid

Dihydrofolate reductase

Pyrimethamine, Proguanil

Tetrahydrofolate acid
Artemesinin

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

Artemesinin

Shortage of artemesinin:
one crop/year
Result:
Lots of fake drug sold
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
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 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