Malaria

COL Christian F. Ockenhouse M.D. Ph.D.
Director, Division of Malaria Vaccine Development
U.S. Military Malaria Vaccine Program
Walter Reed Army Institute of Research
Silver Spring, MD 20910

A-B-C-D

A. Situational **A**wareness

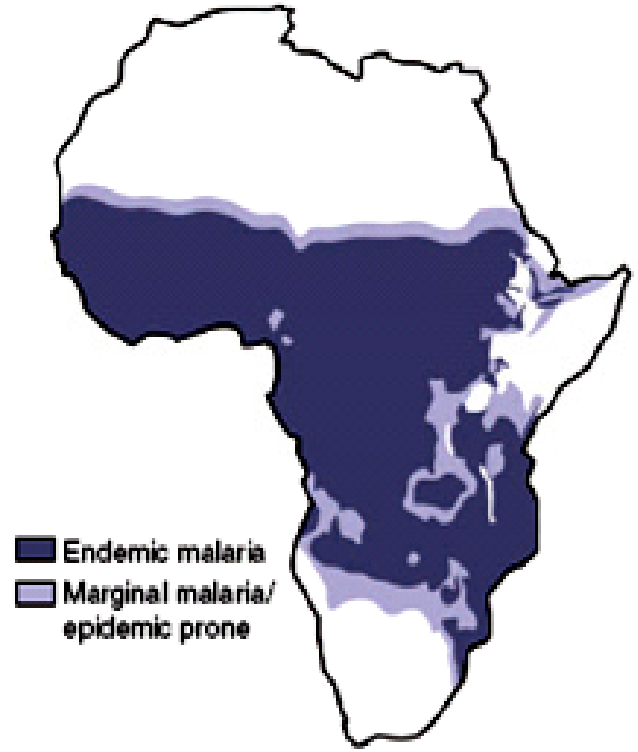
B. Avoid Mosquito **B**ites

C. Compliance with **C**hemoprophylaxis

D. Seek early **D**iagnosis and Treatment

Distribution of Malaria & Abnormal Hemoglobin Genes in Africa

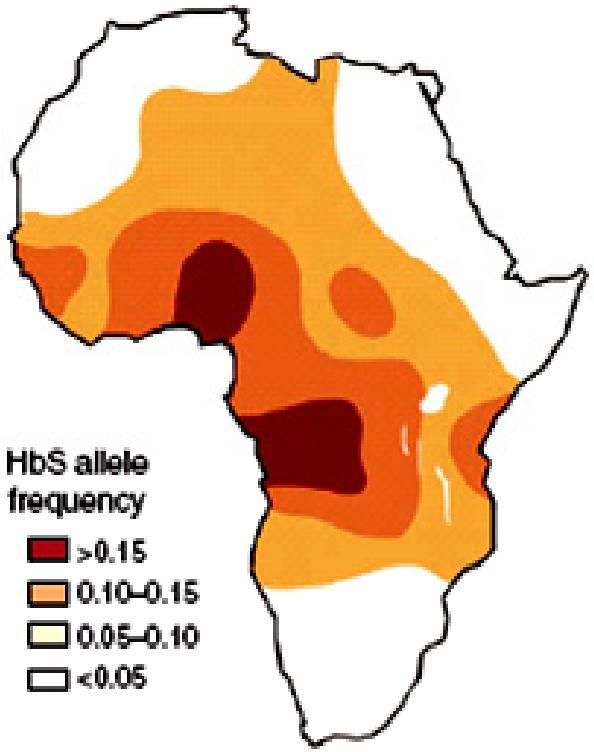
Malaria



re.com/naturegenetics

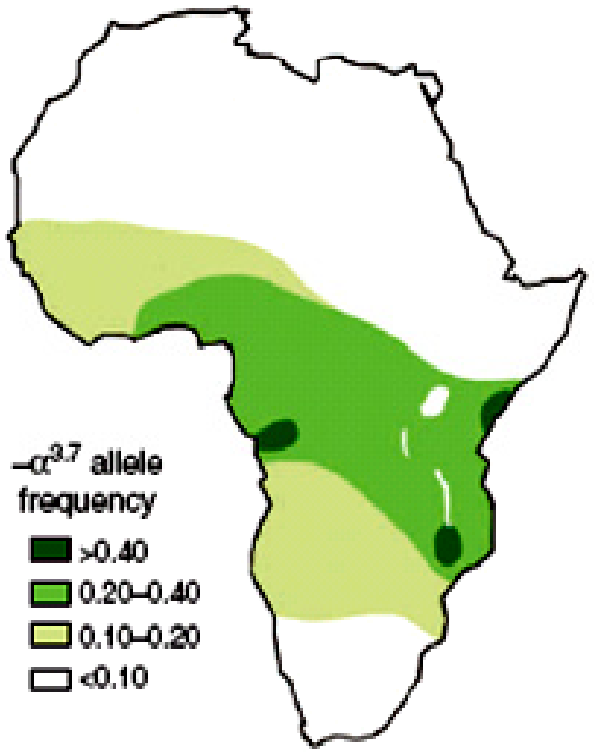
Historic distribution of malaria in Africa

Sickle-cell



Protection against severe and lethal malaria

Alpha-thalassaemia



Protection against severe malaria anemia

- Haldane's hypothesis explains human abnormal red cell enzymes (G6PD), hemoglobins (Hb C, Hb E, Hb S) and red cell surface proteins (loss of Duffy antigen) as balanced polymorphisms in the context of malaria

Nobel Prizes in Malaria

On November 6, 1880, a French army surgeon stationed in Constantine, Algeria, was the first to notice parasites in the blood of a patient suffering from malaria.

In 1907, Alphonse Laveran was awarded the prize, "in recognition of his work on the role played by protozoa in causing diseases"

On August 20, 1897, a British army surgeon in Secunderabad, India first discovered the mosquito transmission of malaria.

In 1902, Ronald Ross was awarded the prize "for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it"

Malaria in World War II and in Vietnam

"Doctor," he said, "this will be a long war if for every division I have facing the enemy I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease!"

GEN Douglas MacArthur 1943

In November 1942, U.S. hospital admissions for malaria reached 178 per 100 men per month at Guadalcanal.

In Vietnam, malaria was the leading cause of disease non battle injuries for U.S. military for missed duty days.

Malaria in Ia Drang Valley, Vietnam 1965

In 1965, Army Vietnam rate = 98/1000 per year

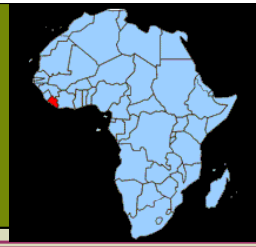
Ia Drang Valley rates reached 600/1000 per year

Ia Drang Valley - **2 Maneuver battalions inoperative due to malaria**

By 1969, *P. vivax* patients were being returned to duty in 5 to 8 days, and *P. falciparum* patients in 17 to 19 days.

1LT Rick Rescorla, Platoon Leader, B Co 2/7 Cav in Bayonet Attack on the morning of 16 Nov 1965 at LZ X-Ray, Ia Drang Valley

Joint Task Force Liberia 2003



- 225 Marines in Monrovia, Liberia < 2 weeks
  - Attack rate = 36% (80/225)
  - Evacuated to USA = 19% (43/225)
  - Severe = 2% (5/225)
    - 5 in intensive care unit
    - 4 on ventilators

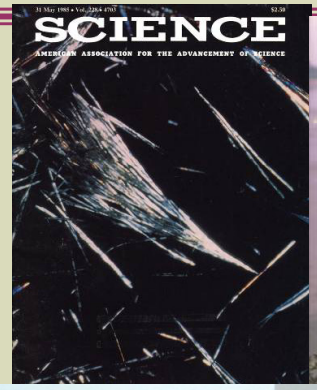
- Prevention for military
  - Difficult in operational areas
  - Requires consistent, reliable use of:
    - Mosquito repellants
    - Bed nets
    - Treated uniforms
    - Antimalarial drugs (drug-resistance, side-effect & compliance)

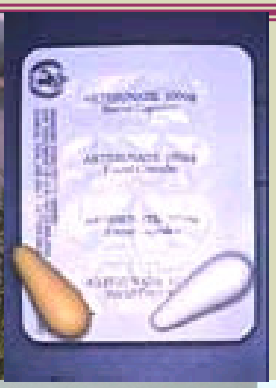
- Diagnostic / treatment delay = high risk severe disease

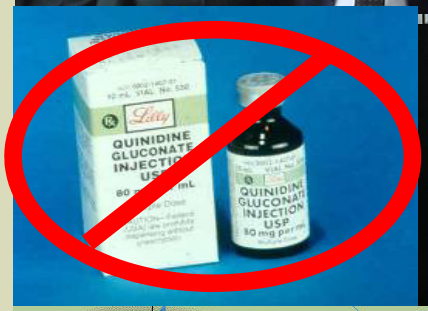
http://www-nehc.med.navy.mil/downloads/prevmed/JTFMalaria.pdf Malaria and the Military Fact Sheet
http://www.malariavaccine.org/files/FS_Malaria-Military_9-15-04.pdf

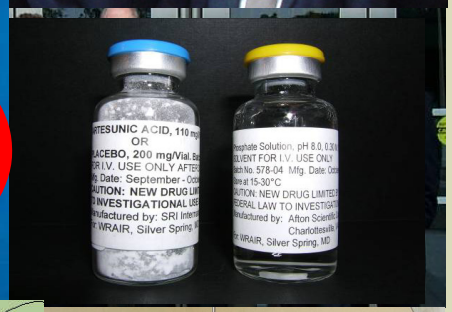
WRAIR's Development of the Artemisinins
Science, Clinical Trials & Registration

- 1st laboratory outside of China to purify and characterize drug from plants
- Co-developed combinations for MDR falciparum (ACTs)
- Supported registration of artemisinin suppositories for severe malaria by WHO
- Conducted 1st FDA-approved Phase 1 & 2 studies with intravenous artesunate
  - **Safety Trials in U.S.**
  - **Treatment trials in Kisumu, Kenya**
  - **Needed replacement for IV quinidine**
  - **Anticipate licensure soon**
  - **Available for compassionate use**









Klayman DL. Qinghaosu (artemisinin): an antimalarial drug from China. Science. 1985 May 31;228(4703):1049-55. Review.

Falciparum Malaria Becomes Resistant to Antimalarial Drugs
Continuous Drug Development and Licensure is Required

Drug	Introduced	First Reported Resistance	Difference (Years)
Quinine	1632	1910	278
**Chloroquine	1945	1957	12
**Proguanil	1948	1949	1
**Sulfadoxine-pyrimethamine	1967	1967	0
**Mefloquine	1977	1982	5
**Malarone	1997	2002	5
Artemisinin/ Proguanil (Coartem)	~2000	?	

Quinine | Chloroquine | Proguanil | Fansidar | Mefloquine | Malarone

What is Malaria? think host-vector-parasite

- Potentially lethal parasitic disease (Plasmodium falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi)
- Transmitted between humans (reservoir) by mosquitoes (the vector, *Anopheles*)
- **Initial malaria**: fever, chills, muscle aches, headaches, fatigue, rigors

  ACUTE ILLNESS
- **Untreated**: severe anemia, kidney failure, coma, convulsions, respiratory distress

  DEATH 
- **Treated: Watch out for relapses!**
  - *P. falciparum* – inadequate treatment ~ within 1 month
  - *P. vivax* - hypnozoites –weeks to months later

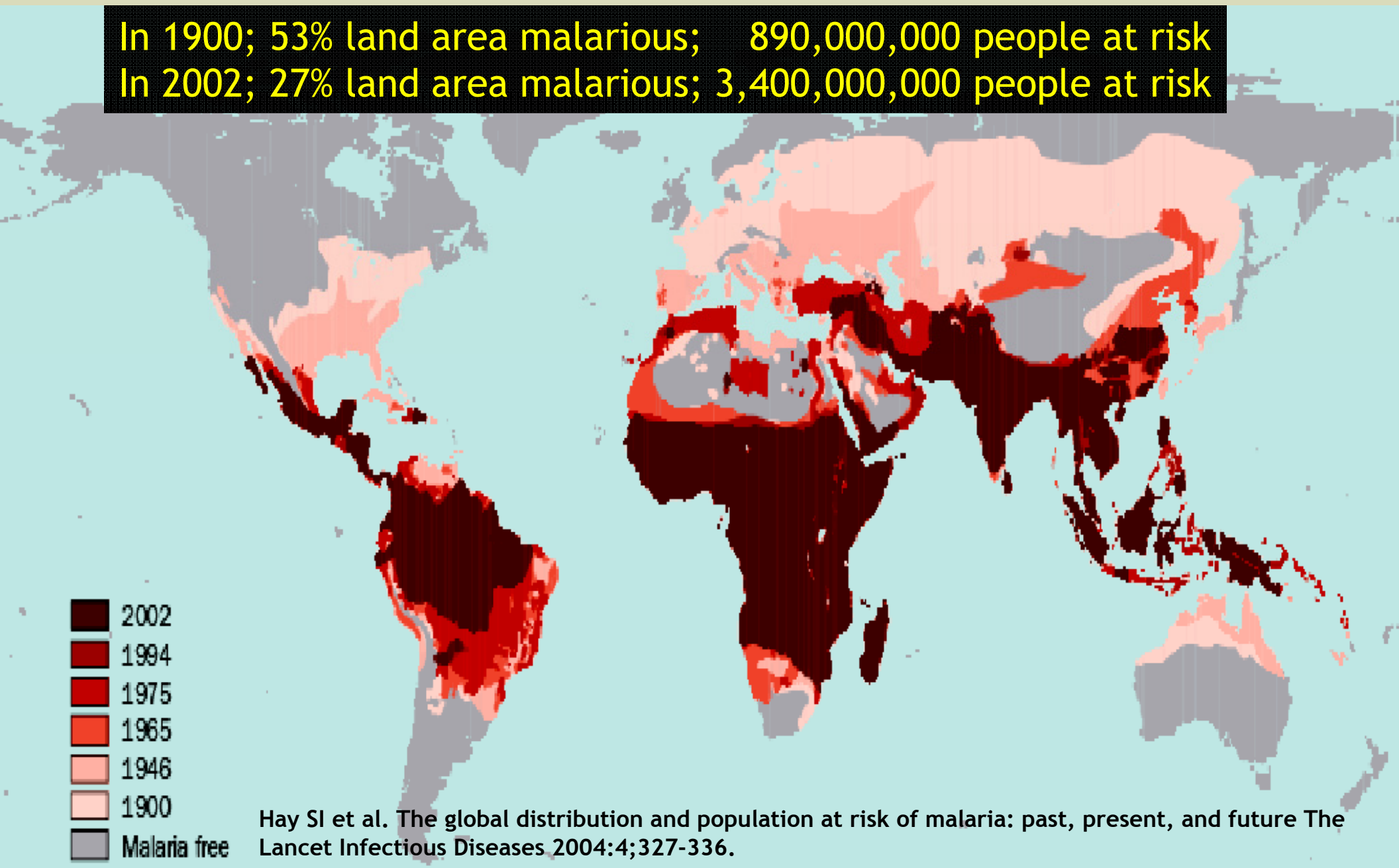
Malaria is still a big deal

- Every day, 3000 children die of malaria
- Malaria is the #1 cause of death of young African children
- Malaria is resurgent: more cases now than ever in history
- Inadequate prevention:
  - Bed nets save lives - but not widely used
  - DDT/insecticides save lives – but not adequately used
- Inadequate treatment
  - Poor diagnosis -
  - Drug resistance:
    - affordable drugs not effective
    - effective drugs not affordable
- No malaria vaccine yet licensed

Child with severe malaria

Global Distribution of Malaria Since Pre-Intervention 1900-2002

In 1900; 53% land area malarious; 890,000,000 people at risk
In 2002; 27% land area malarious; 3,400,000,000 people at risk

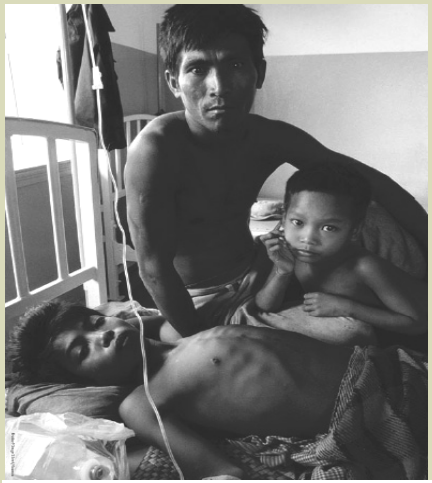


Hay SI et al. The global distribution and population at risk of malaria: past, present, and future The Lancet Infectious Diseases 2004:4;327-336.

The Host (Reservoir) of Malaria

New Guinean 10 month old with severe malaria and older brother

African children with large spleens due to malaria



Asian boy with malaria and family

Indian malaria patients

U.S. military

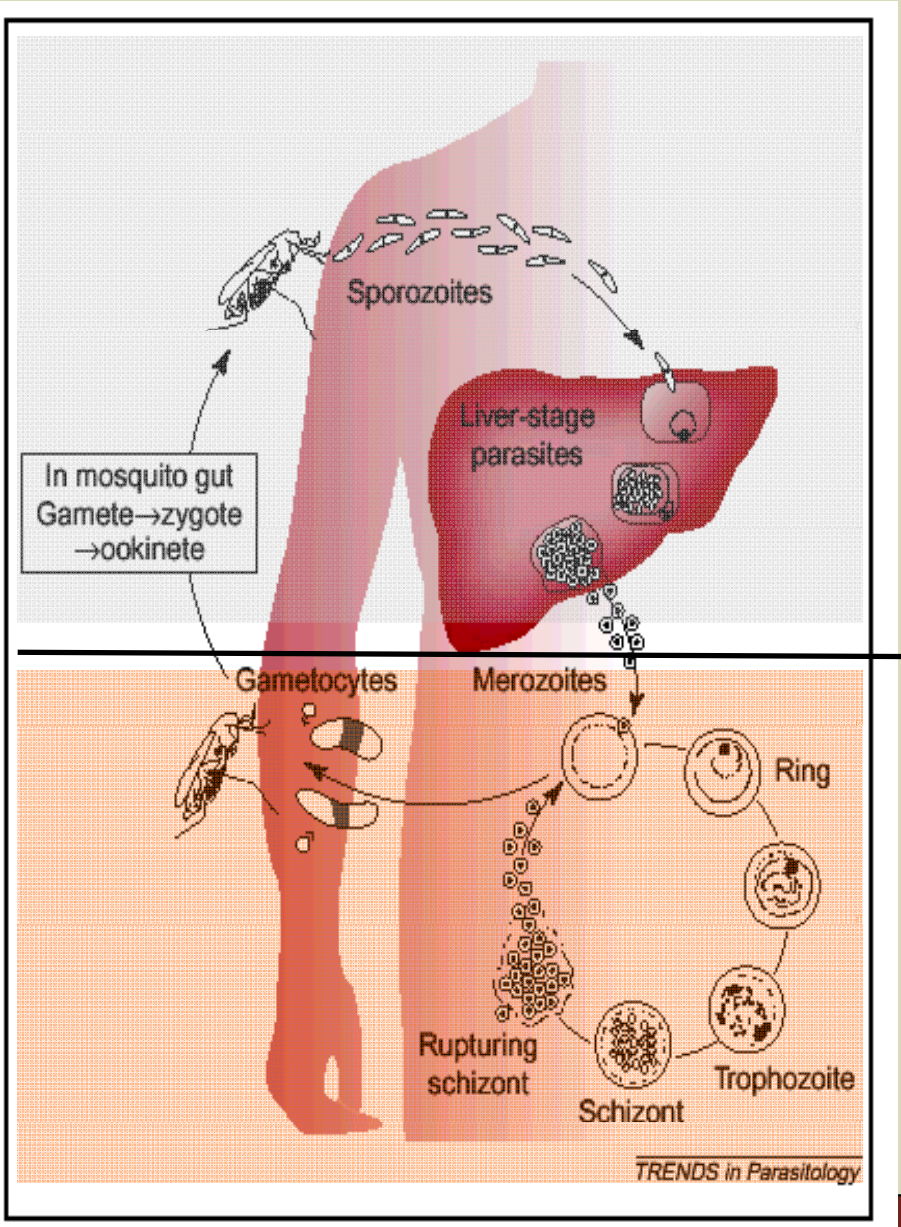
The Vector of Malaria

Anopheles gambiae, the most common species of mosquito transmitting malaria

The face of the female Anopheles

Without the female Anophelene mosquito, there would be no malaria

Plasmodium falciparum Life Cycle and Disease



NO SYMPTOMS

Sporozoite Stage (minutes)

- From Mosquito - To Liver:
- 1-10 sporozoites

Liver Stage (6 days)

- Enter Liver - Leave Liver
- 30-300,000 merozoites

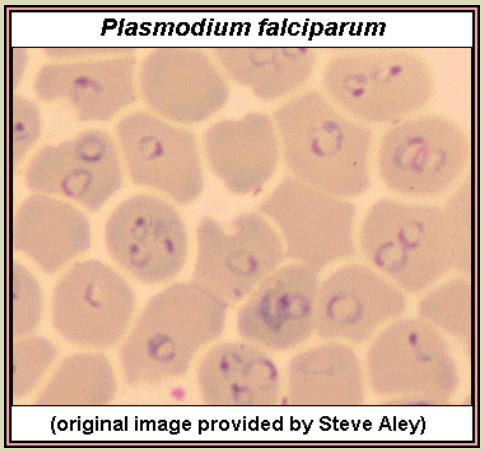
DISEASE & DEATH

Blood Stage (days - weeks)

- Enter RBCs - Leave RBCs
- 100,000,000 iRBCs = mild
- 1,000,000,000,000 iRBCs = moderate
- 100,000,000,000,000 iRBCs = severe
- $>10^{14}$ iRBCs = death

Malaria Anemia

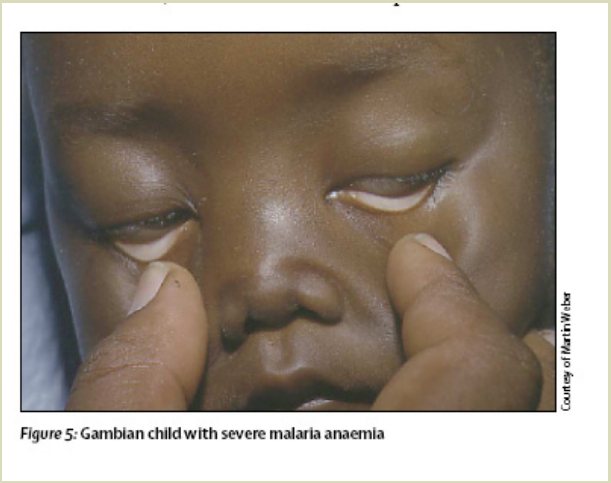
Severe Red Cell Destruction // Suppressed Red Cell Production



Plasmodium falciparum can infect > 25% of red cells, & destroy them

Pale palm of Kenyan child with severe malaria anemia held in the palm of his mother

Mother with malaria in 1st pregnancy at high risk for severe anemia, death, low birth weight and infant death



Pale eyelids in Gambian child with severe malaria anemia

Clinical findings

Uncomplicated

- fever
- non-specific flu-like symptoms
- GI (nausea, diarrhea, vomiting)
- not rash, not upper respiratory sytmpoms

Severe

- prostration
- mental status changes leading to unconsciousness (cerebral malaria
- acute respiratory distress syndrome

Cerebral Malaria – Long Term Burden

- 10% death rate for cerebral malaria
- Brain damage in survivors
- Acute and long term disability
  - Deficits in
    - Attention
    - Memory
    - Visual-spatial skills
    - Language
  - Educational impairment

Prevention
A – B – C - D

A. Situational **A**wareness

B. Avoid Mosquito **B**ites

C. Compliance with **C**hemoprophylaxis

D. Seek early **D**iagnosis and Treatment

- pre-travel preparation
- assess malaria risk in geographic location
- length of stay
- urban vs rural

Prevention
A – B – C - D

A. Situational **A**wareness

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C. Compliance with **C**hemoprophylaxis

D. Seek early **D**iagnosis and Treatment

- personal protection
  - shirt sleeves rolled down
  - DEET (concentrations 30-50%

Prevention
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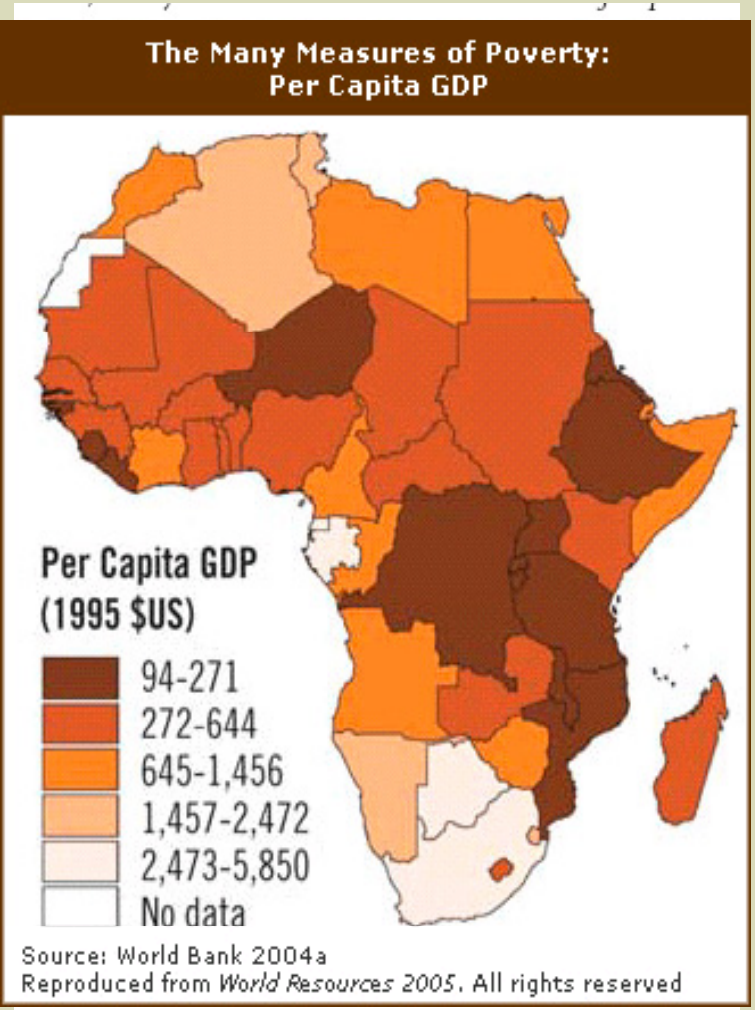
D. Seek early **D**iagnosis and Treatment

- insecticide-treated bed nets (ITNs)
- military use depends upon pre-treatment with permethrin and deployability

ITNs – Insecticide Treated Nets



- ITNs versus no nets // protective effect
  - 50% reduction in malaria attacks
  - 45% reduction in severe malaria attack
  - 17% reduction in death
- Additional benefits
  - Improved maternal health & hematocrits
- Cost: about $1
- Cost effective: Yes
- Usage: Less than 10% of children at risk
- Issues:
  - Too expensive for poor users to purchase
  - Requires retreatment with insecticide
  - Requires repair
  - Requires education to promote use

Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004;(2):CD000363.

Indoor Residual Spraying (IRS)
DDT Use and Cumulative Malaria Cases in South America

Cumulative numbers of cases (x 1000)

140
120
100
80
60
40
20
-20

70
60
50
40
30
20
10
0

Sprayed houses per 1000 population

Prevention
A – B – C - D

A. Situational **A**wareness

B. Avoid Mosquito **B**ites

C. Compliance with **C**hemoprophylaxis

Anti-malarial Drug	Dosage	Frequency
Doxycycline	One tablet (100 mg)	Daily
Atovaquone-proguanil (Malarone®)	One tablet (250 mg atovaquone plus 100 mg proguanil)	Daily
Mefloquine (Lariam®)	One tablet (250 mg)	Weekly
Chloroquine (Aralen®)	One tablet contains 500 mg of chloroquine phosphate USP, equivalent to 300 mg chloroquine base	Weekly

Chemoprophylaxis: Adverse Reactions

1. Doxycycline
   - Take with food (GI distress)
   - Skin rash (hypersensitivity to sun; wear hat, long sleeves)
2. Malarone
   - take with food/whole milk
   - abdominal pain, rash
3. Mefloquine (Larium)
   - neuropsychiatric reactions
   - No longer first line in U.S. Army (TSG-drective)
4. Chloroquine
   - Retinal changes on long-term prophylaxis

Diagnosis

A. Situational **A**wareness
B. Avoid Mosquito **B**ites
C. Compliance with **C**hemoprophylaxis
D. Seek early **D**iagnosis and Treatment

A. Malaria Blood Film – thick and thin blood smears
   - What do you need?
     - Clean glass slides
     - Giemsa stain
     - Microscope with high power objective (100x)
     - Training

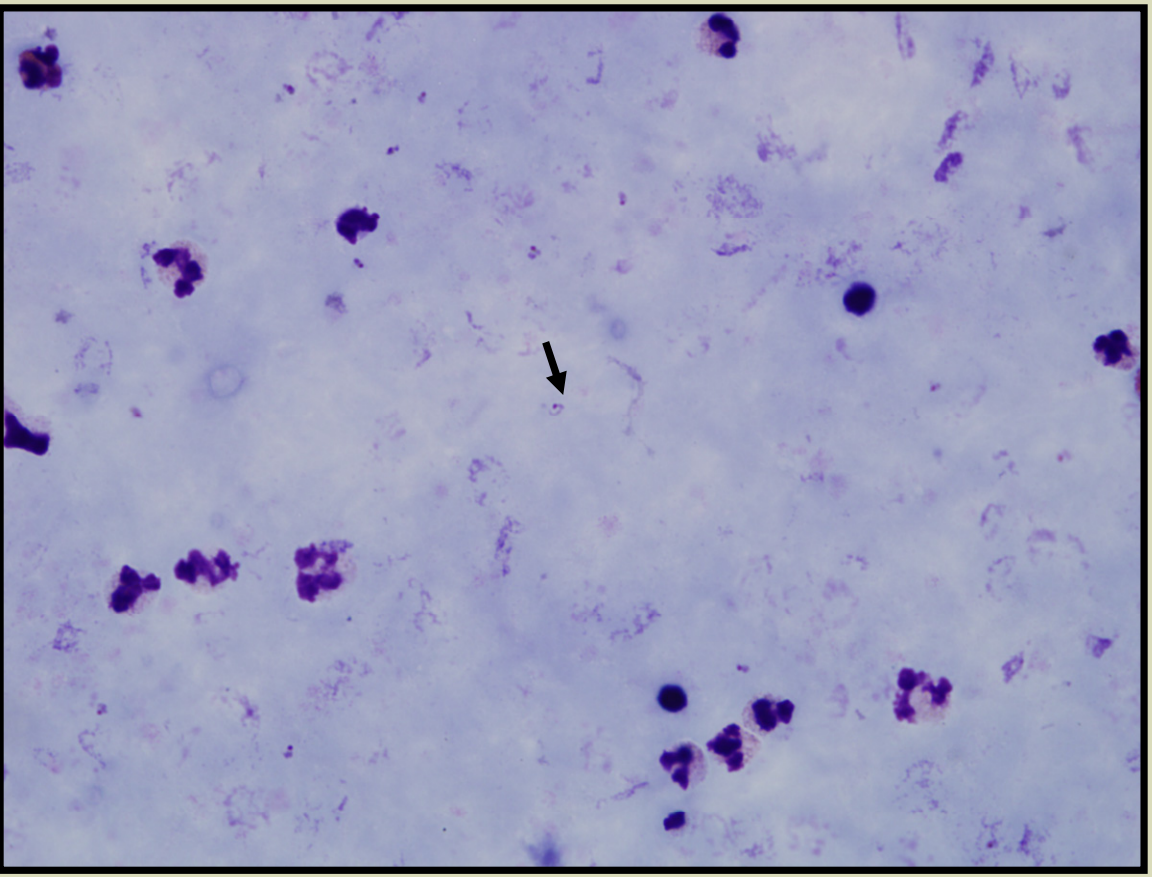
B. Rapid Diagnostic Tests (RDTs)
   - What do you need?
     - RDT card
     - Developing reagents (check expiration, cold storage)
     - Training

C. What to do if first test is negative and you still suspect malaria?

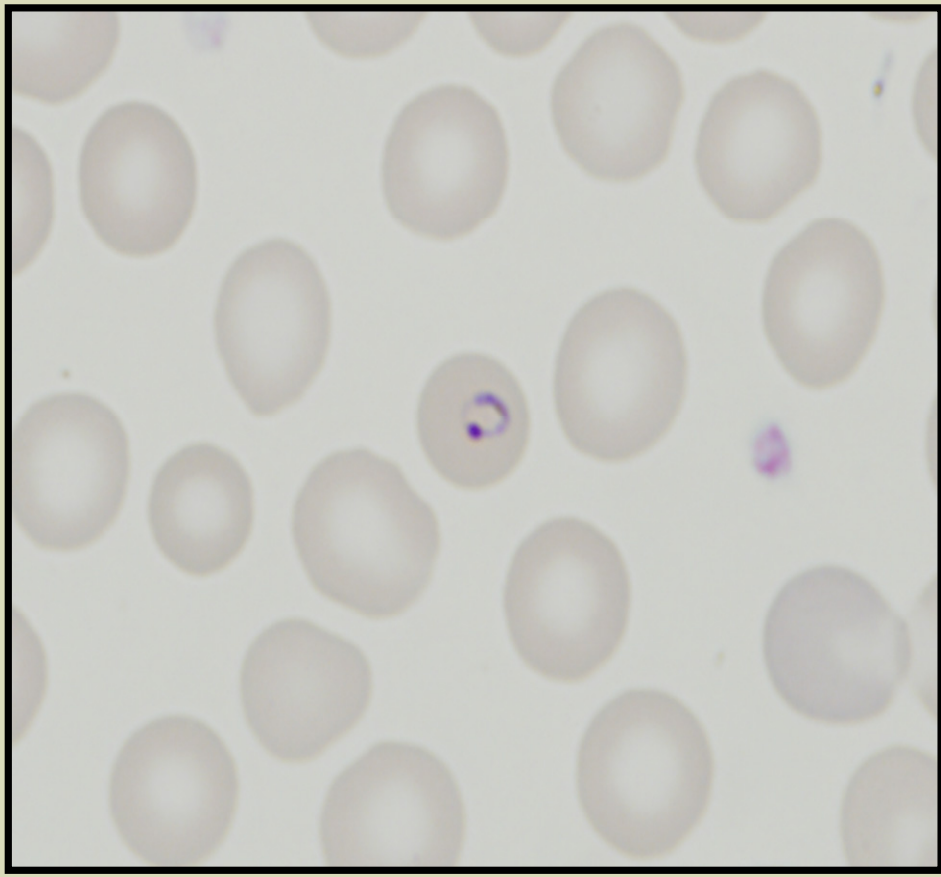
Prevention
A – B – C - D

Seek early **D**iagnosis and Treatment

Thick blood smear



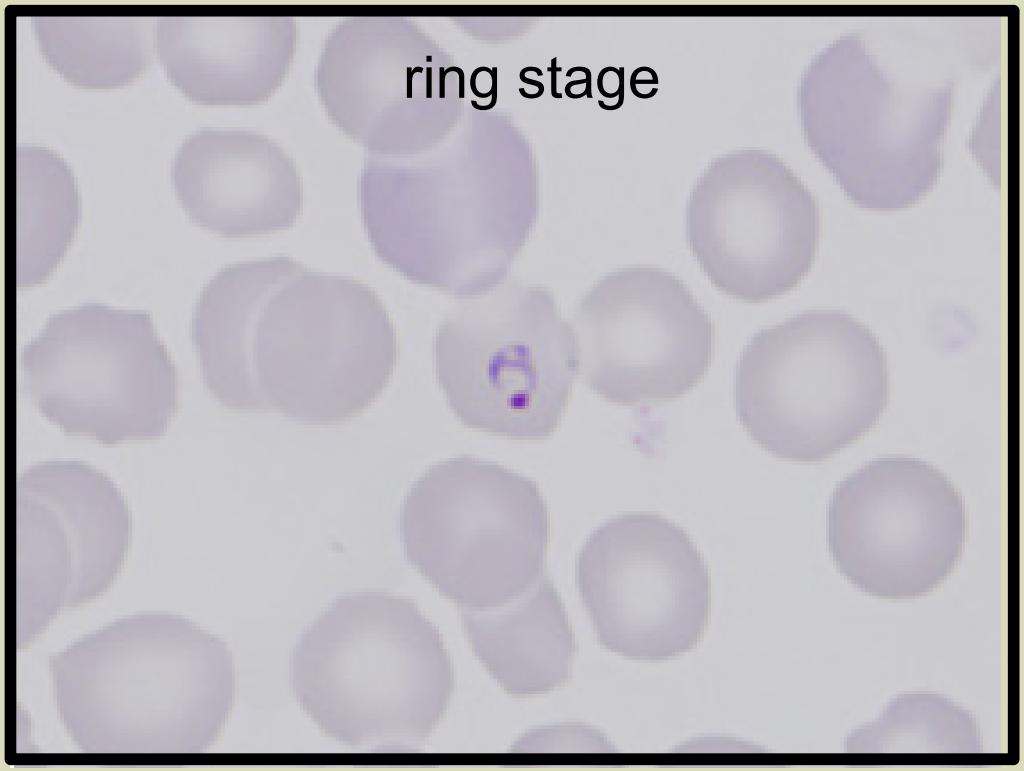
Thin blood smear



Species of Malaria

Plasmodium falciparum

Peripheral blood



Sequestered parasite stage

Species of Malaria

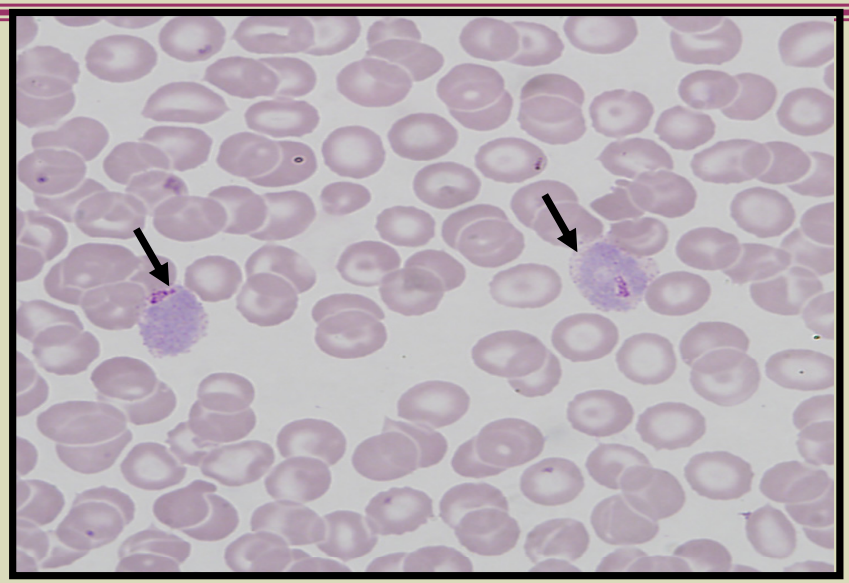
Plasmodium vivax

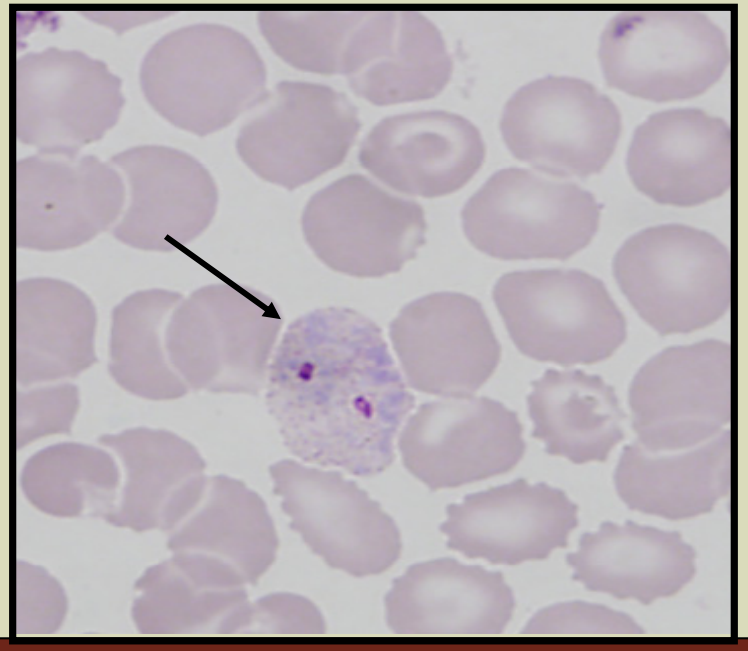
1991 Somalia

1997-present, Republic of Korea

2003-present, Afghanistan

2005 Horn of Africa





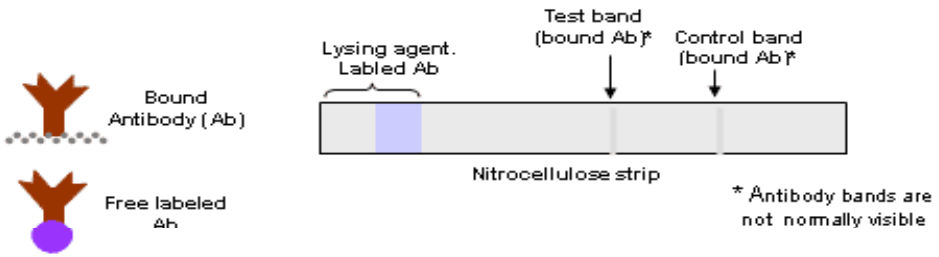
Factors influencing rapid test performance

- quality of manufacture
- species of parasite
- number, viability, and the strain of parasites present
- condition of the RDT (including storage conditions)
- technique and care used in performing the test
- correct interpretation by the reader.

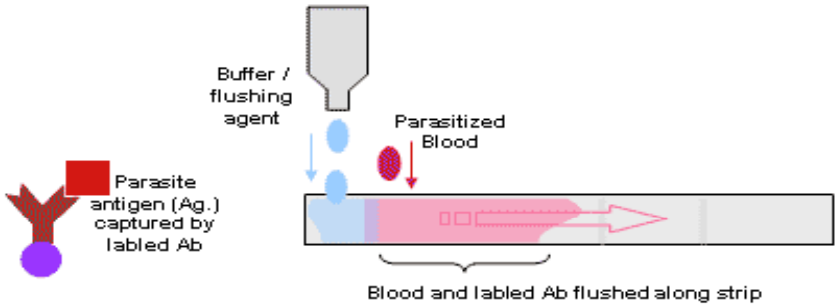
Rapid Diagnostic Testing

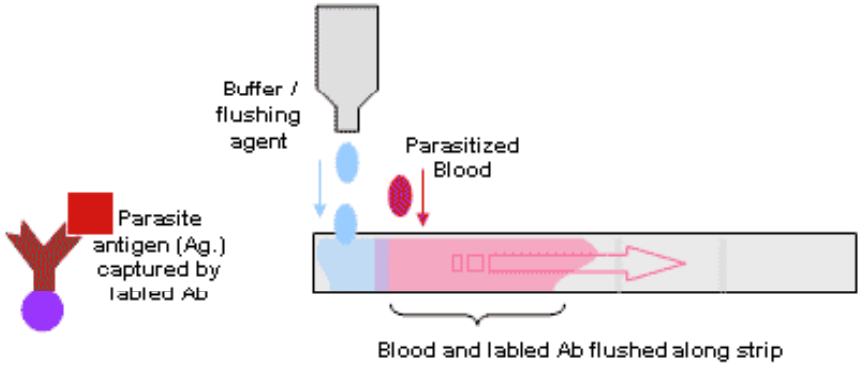
Mode of action of common malaria RDT format

1. Dye-labeled antibody, specific for target antigen, is present on the lower end of nitrocellulose strip or in a plastic well provided with the strip. Antibody, also specific for the target antigen, is bound to the strip in a thin (test) line, and either antibody specific for the labeled antibody, or antigen, is bound at the control line.

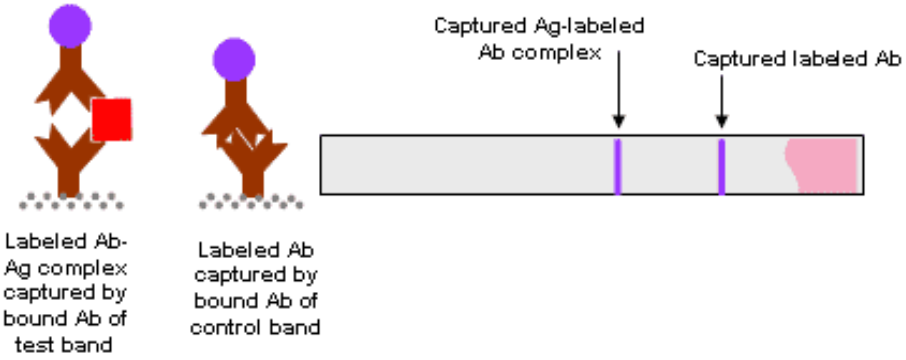


2. Blood and buffer, which have been placed on strip or in the well, are mixed with labeled antibody and are drawn up strip across the lines of bound antibody.

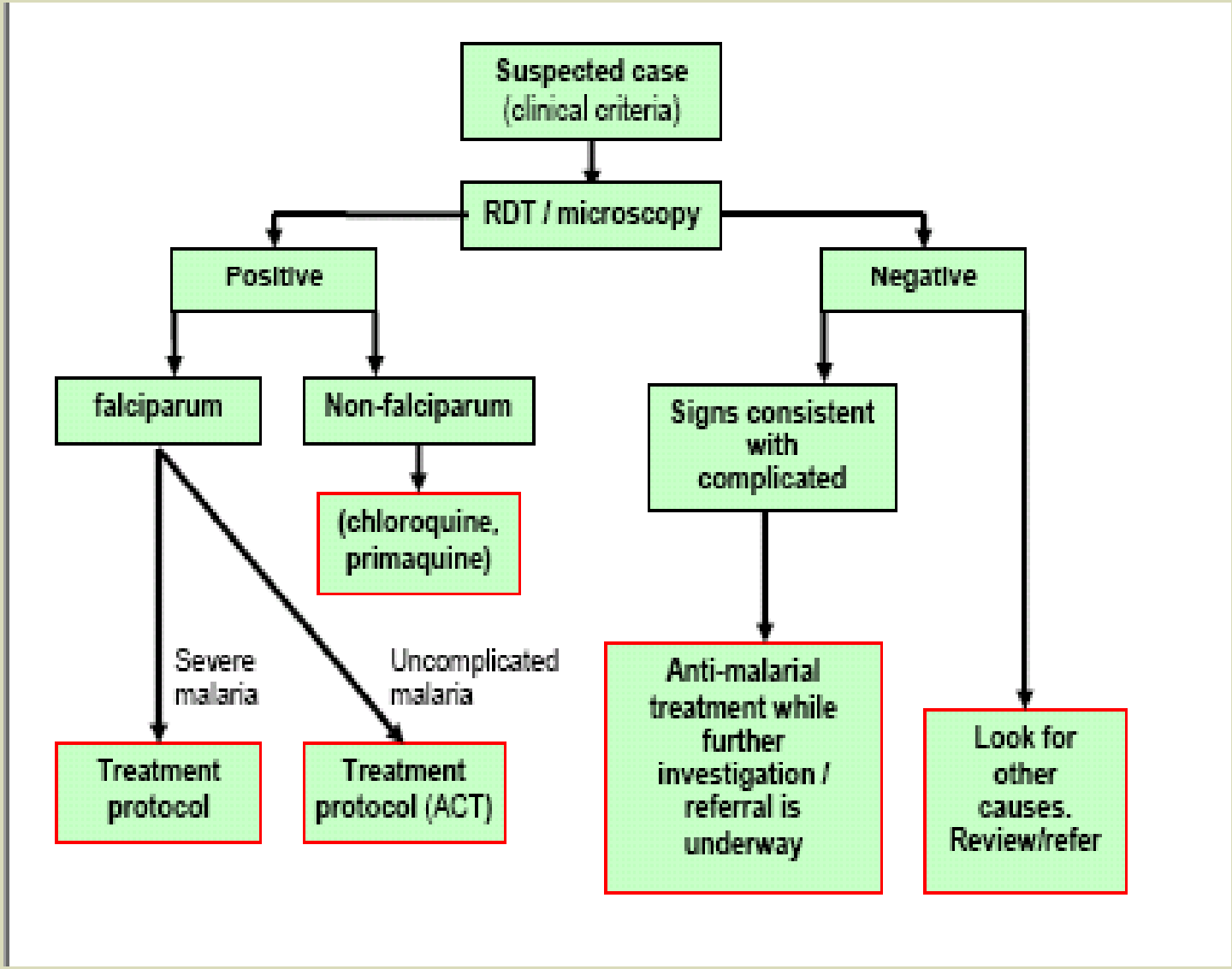




3. If antigen is present, some labeled antibody will be trapped on the test line. Excess-labeled antibody is trapped on the control line.



Diagnostic and Treatment Strategy



Treatment regimens

CDC Malaria Hotline: (770) 488-7788 Monday-Friday 8 am to 4:30 pm EST (770) 488-7100 after hours, weekends and holidays

Antimalarial Drug	Dosage	Regimen	Possible Side Effects/contraindications
Artemether/ lumefantrine (Coartem®, Riamet®)	1 tablet (20 mg artemether plus 120 mg lumefantrine) (take with food/milk)	A 3-day treatment schedule with a total of 6 oral doses Initial dose at Dx followed by the 2nd dose 8 hours later, then 1 dose po bid for the following 2 days. adult: 4 tablets per dose	Hypersensitivity to artemether or lumefantrine
Atovaquone/ proguanil (Malarone®)	1 adult tablet (250 mg atovaquone plus 100 mg proguanil (take with food/milk)	A 3-day treatment scheudle: 4 tablets per dose daily for three consecutive days	Hypersensitivity, abd pain, nausea, skin rash, vomiting, headache, avoid use with creatinine clearance < 30 ml/min

Treatment regimens

CDC Malaria Hotline: (770) 488-7788 Monday-Friday 8 am to 4:30 pm EST (770) 488-7100 after hours, weekends and holidays

Antimalarial Drug	Dosage	Regimen	Possible Side Effects/contraindications
Quinine sulfate/doxycycline	Quinine:8 mg base/kg (650 mg tablets (salt) doxycycline: 100 mg tablets	Quinine: 542 mg base = 650 mg salt 3 times daily for 7 days; US manufactured quinine sulfate capsule is in a 324mg dosage; therefore 2 capsules should be sufficient for adult dosing Doxycycline: 1 tablet q12 hrs for 7 days	Stomach cramps, diarrhea, blurred vision, lightheadedness, dizziness, unusual bleeding, arrhythmias, tinnitus
Mefloquine (Lariam®)	One tablet (250 mg salt)	3 tablets at Dx and 2 tablets in 6-12 hours (total 1250 mg salt treatment dose)	Neuropsychiatric event, sleep disturbances, vivid dreams, insomnia, dizziness, dysphoria, contraindicated in persons with depression or history of seizures

Severe malaria treatment options

Antimalarial Drug	Dosage	Possible Side Effects/contraindications
Quinidine gluconate plus doxycycline	Quinidine gluconate: 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hours. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America. Doxycycline: Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hours and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.	Stomach cramps, diarrhea, blurred vision, lightheadedness, dizziness, unusual bleeding, arrhythmias, tinnitus
IV artesunate (CDC Hotline, M-F 770-488-7788; after hours,weekends,holidays, 770-488-7100)	Must be done under IND with instructions for preparation and administration by CDC only for hospitalizxed patients within the U.S.	

P. vivax malaria treatment options

Think of *P. vivax* infections as having both an acute phase and latent asymptomatic phase

Treat acute *P. vivax infection*

Chloroquine : 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours
Total dose: 1,500 mg base (=2,500 mg salt) OR
Hydroxychloroquine (PlaquenilTM and generics)
620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours
Total dose: 1,550 mg base (=2,000 mg salt)

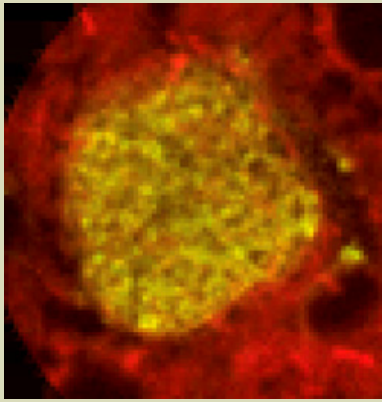
AND

Primaquine (radical cure) **must test for** G6PD deficiency !

Before starting primaquine

if G6PD negative or low levels (< 6%) primaquine causes hemolysis

- prescribe 30 mg base (NOT 15 mg) = 2 tablets qd x 14 days



The Situation is Dire

- Malaria is a personal tragedy
  - Death in infants and in 1st pregnancies
  - Sickness, long term disability, chronic illness in survivors
- Malaria is a global health tragedy
  - Malaria kills 3,000 children a day
  - Malaria hastens spread of HIV infection**
- Malaria is an economic-political tragedy
  - Major cause of disability adjusted life years (DALYS)
  - Prevents development in Africa
  - A cause and a consequence of poverty