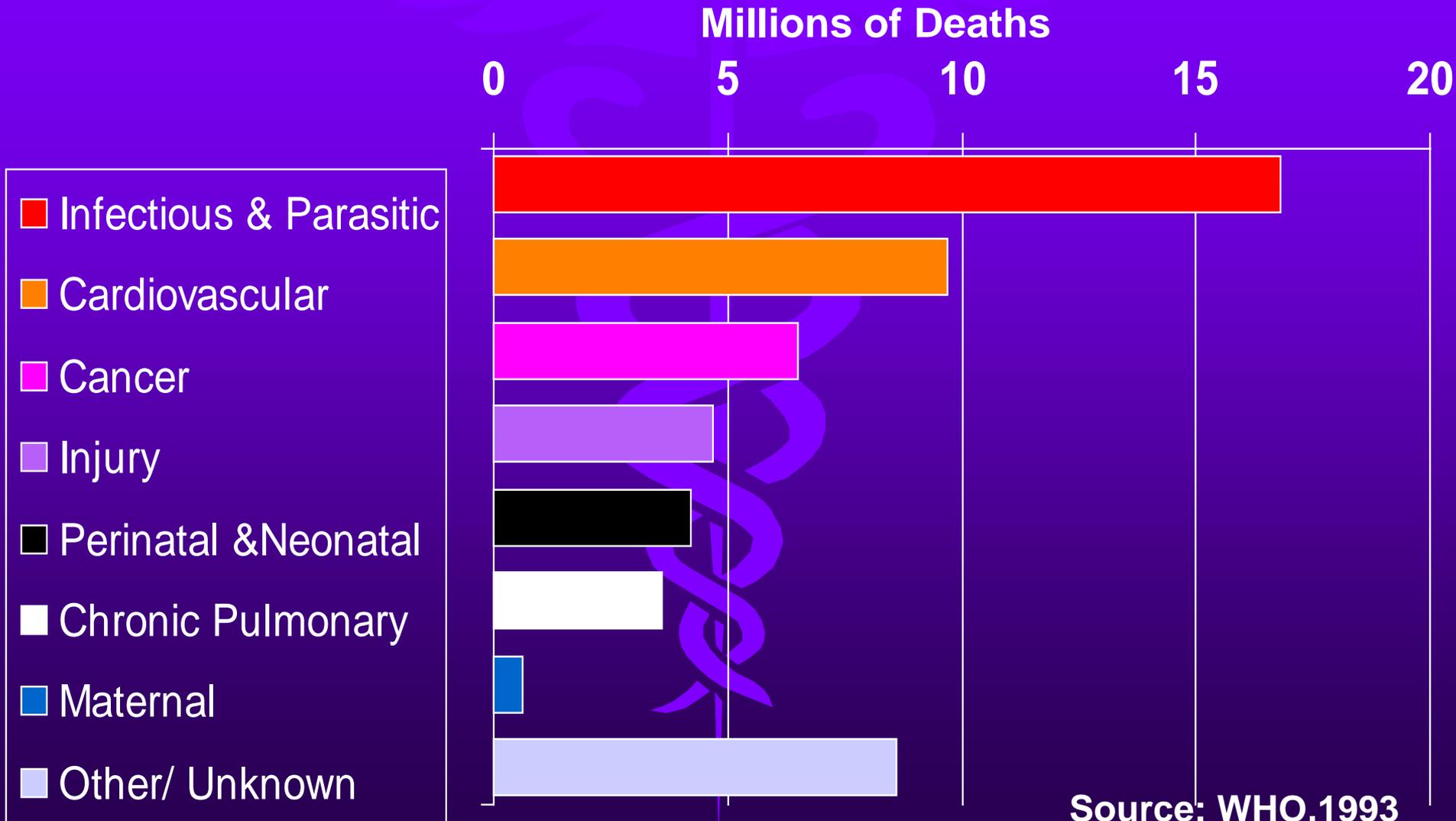




Malaria

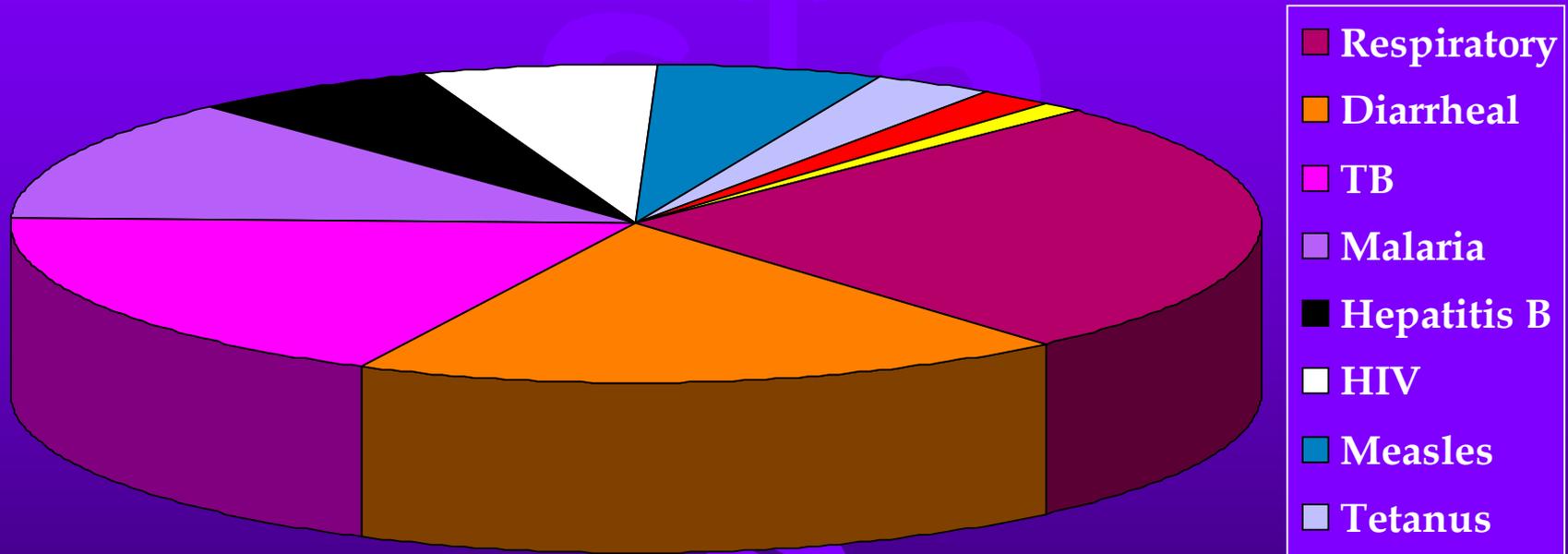
COL Ted Cieslak MD FAAP FIDSA

Worldwide Human Deaths By Cause



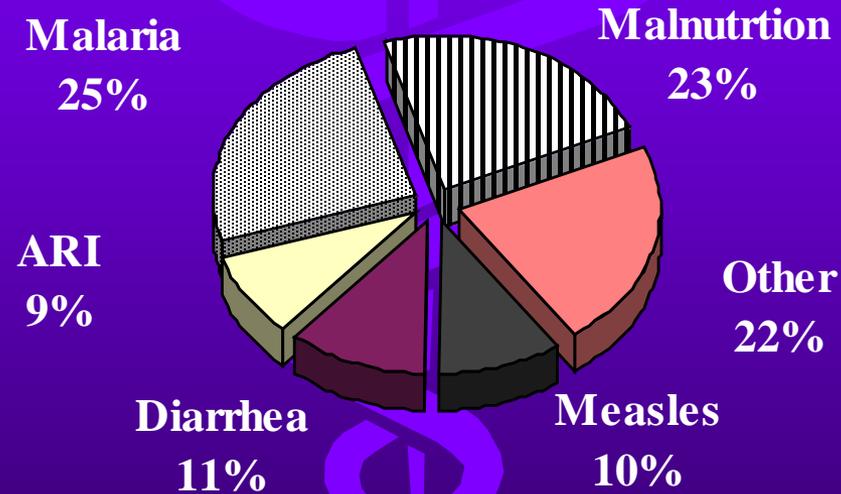
Infectious Diseases

The 10 Biggest Killers



LRI 3.7 million
TB 2.9 million
Diarrhea 2.5 million
Malaria ~2.0 million

FOUR Infectious Sources of Mortality in the Developing World



Children less than 5 years old, Malawi, 1990



Overview

- Malaria is a huge global problem
- Current strategies are inadequate
- DoD is making progress towards malaria solutions
- Multi-pronged efforts are ongoing

What is Malaria?



- Potentially lethal parasitic disease (*Plasmodium* species)
- Transmitted between humans (reservoir) by mosquitoes (the vector)
- **Initial malaria:** fever, chills, muscle aches, headaches, fatigue, rigors
  **ACUTE ILLNESS**
- **Untreated:** severe anemia, kidney failure, coma, convulsions
  **DEATH** 
- **Survivors:** Often become chronic carriers
  **ILL HEALTH, LEARNING DISABLED**
  **RESERVOIRS OF INFECTION**



- Chinese writings (2700 BC)
- The Eber's papyrus (1550 BC)
- Hippocrates (described malaria fevers)
- Greek civilizations affected by “bad air”, the rich summered in the highlands
- Malaria in the United States
 - First military expenditure in 1775 (\$300) for quinine to protect G. Washington's troops
 - In Civil War (1861-65) 50% white and 80% of black troops w/ malaria annually



The Situation is Dire

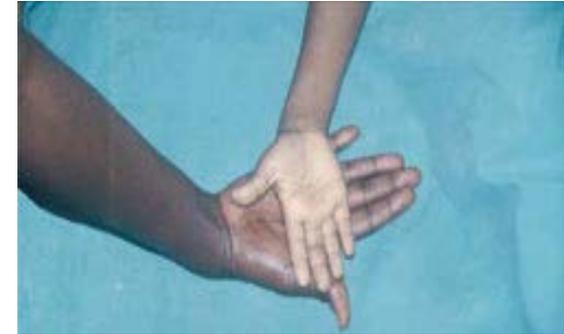
- Malaria is a personal tragedy
 - Death in infants and in 1st pregnancies
 - Sickness, long term disability, chronic illness in survivors
- Malaria is a global health tragedy
 - Malaria kills 3,000 children a day
 - Malaria hastens spread of HIV infection**
- Malaria is an economic-political tragedy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

**Abu-Raddad LJ et al. Links Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006;314:1603-6

The Global Malaria Problem



- **#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**



Hand of child with severe malaria anemia in the palm of his mother



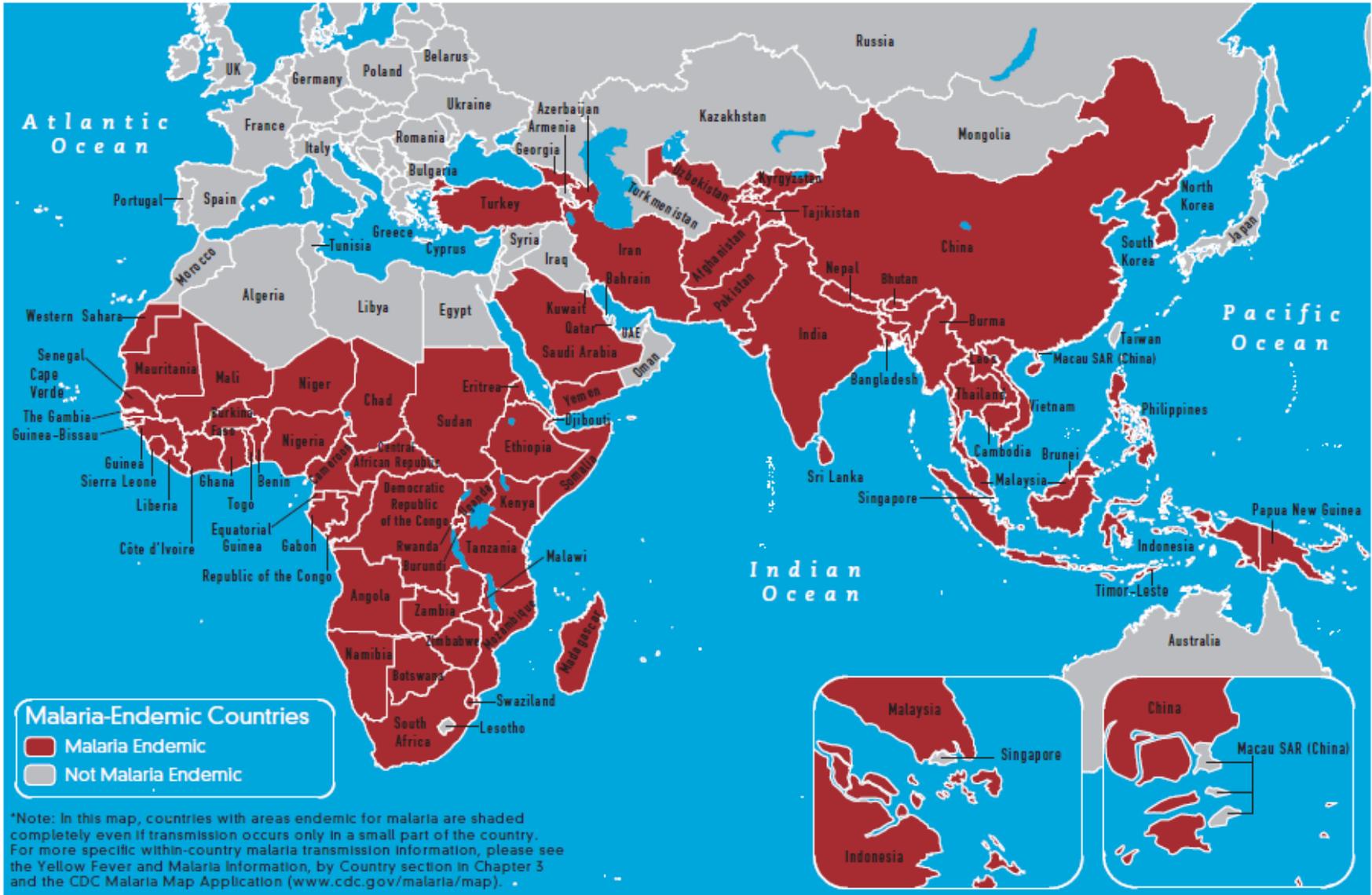
Child with severe malaria



Malaria's World

- The Tropics
 - South of 20 degrees North latitude
 - North of 20 degrees South latitude
 - Below 5000 feet
- The Chloroquine-sensitive world
 - Caribbean, Latin America north of the canal, Middle East
- The Chloroquine-resistant world
 - Subsaharan Africa, South Asia, Latin America south of canal
- The Mefloquine-resistant world
 - The Thai-Burmese & Thai-Cambodian borders

The Malarious World



The Malarious New World

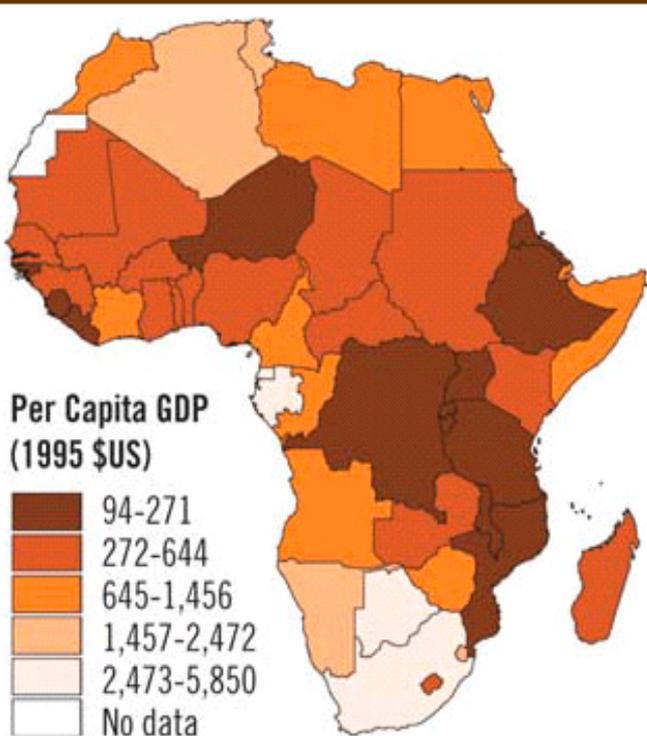


Mefloquine Resistant Malaria



Insecticide-Treated Nets

The Many Measures of Poverty:
Per Capita GDP



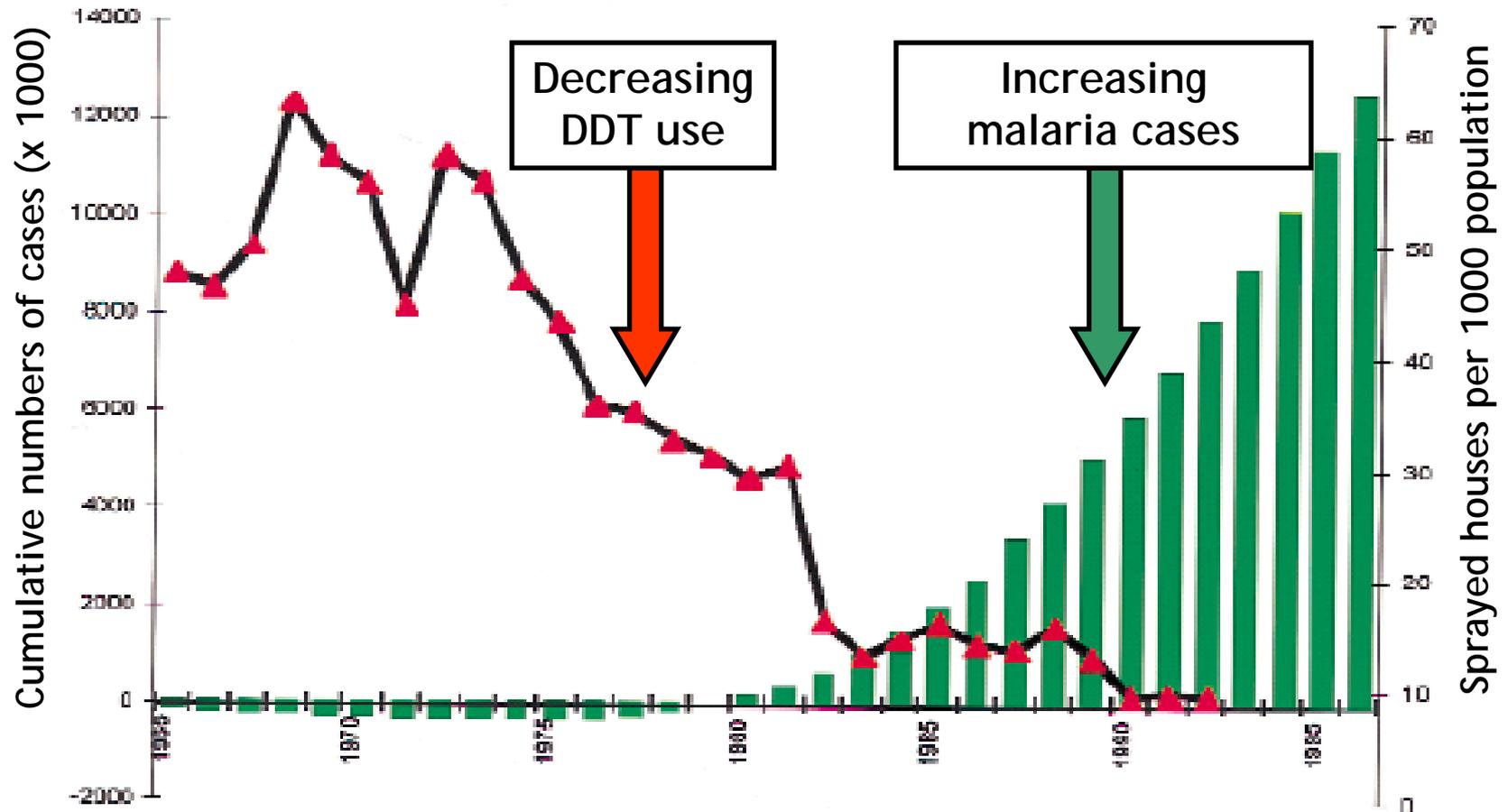
Source: World Bank 2004a
Reproduced from *World Resources 2005*. All rights reserved

- 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
 - Improved infant health & birth weights
- Cost: about \$6
- 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



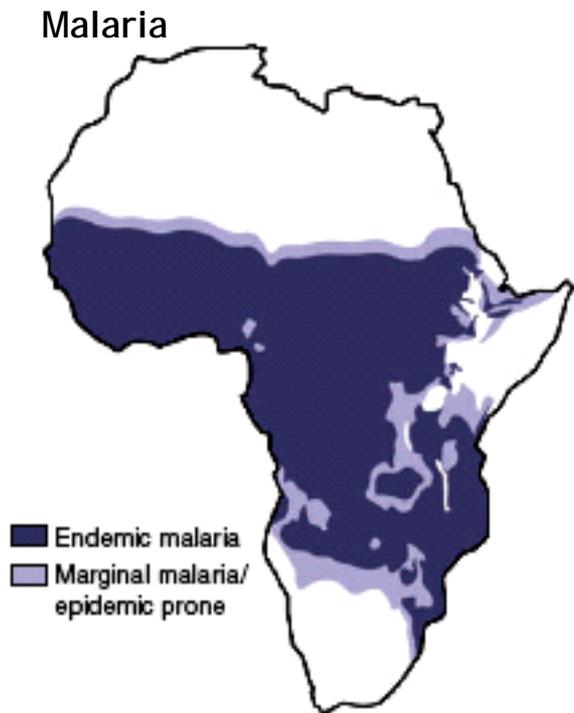
DDT Use and Malaria in South America

House Spray Rates, 1965-92, and Cumulative Malaria Cases, pre- vs. post-1979 (Brazil, Colombia, Ecuador, Peru, Venezuela)

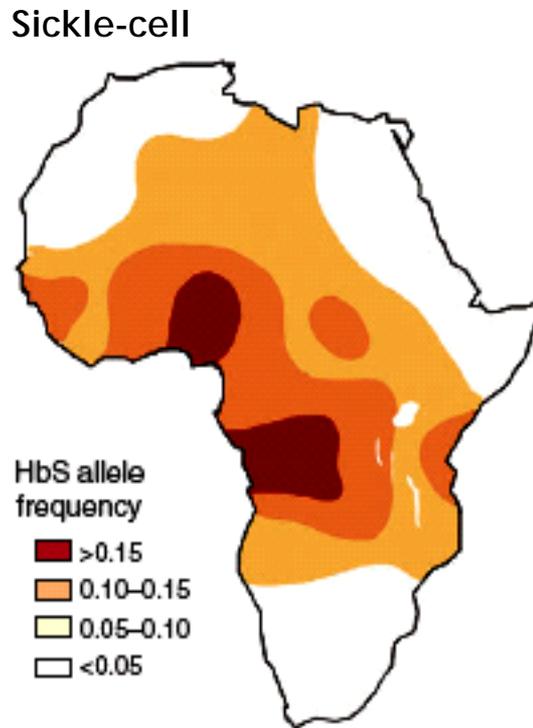




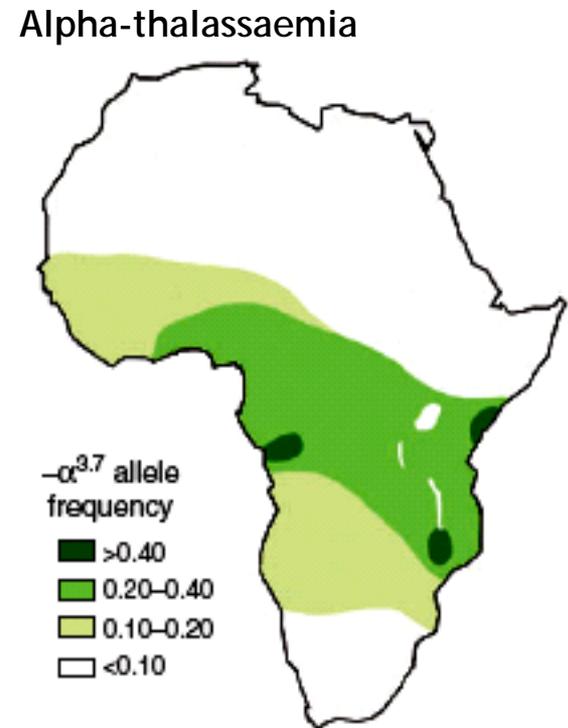
Distribution of Malaria & Abnormal Hemoglobin Genes in Africa



Historic distribution of malaria
in Africa



Protection against severe and
lethal malaria



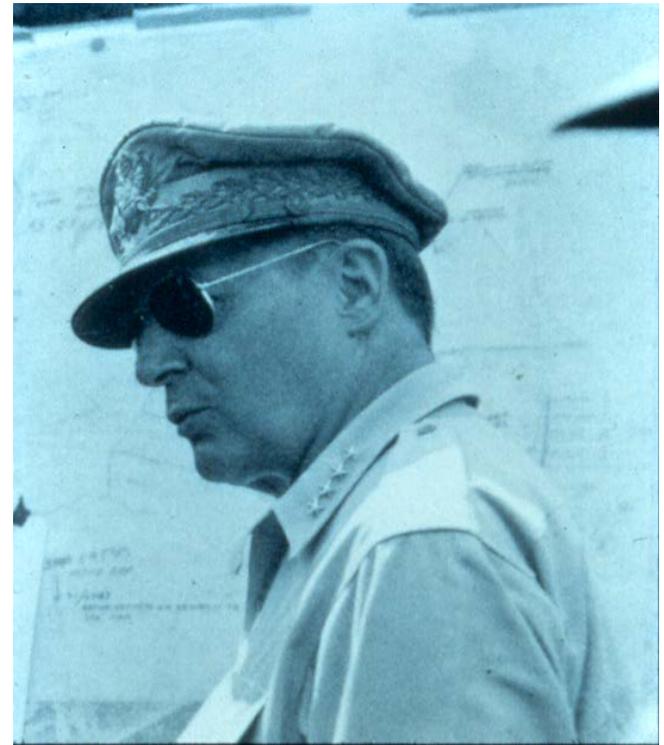
Protection against severe
malaria anemia

- 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

General Douglas MacArthur

"Doctor, 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".

General Douglas MacArthur, May 1943 to Colonel Paul F. Russell, MC, the American army malaria consultant.



General William Slim

- Field Marshall The Right Honorable Viscount Slim
- 13th Governor General of Australia
- Commander, British 14th Army in Burma
 - 1 wounded/120 ill
 - 84% annual malaria rate
- Sacked COs with <95% prophylactic compliance
- “I only had to sack three”





The Destabilizing Effect of Malaria

- There are huge impacts of HIV/AIDS, malaria, and MTb on the critical infrastructures that sustain the security, stability, and viability of modern nation-states
- In the developing world (esp Africa) these diseases undermine education and health systems, economic growth, micro enterprises, policing and military capabilities, political legitimacy, family structures, and overall social cohesion
- Undermine the stability of already weakened states, adds to their vulnerability to extremists/terrorists who will seek to corrupt or coerce them into providing converts, cover, or cooperation
- The real global war can be thought of being against these diseases - needs to be comprehensive, fought at many levels and on many fronts

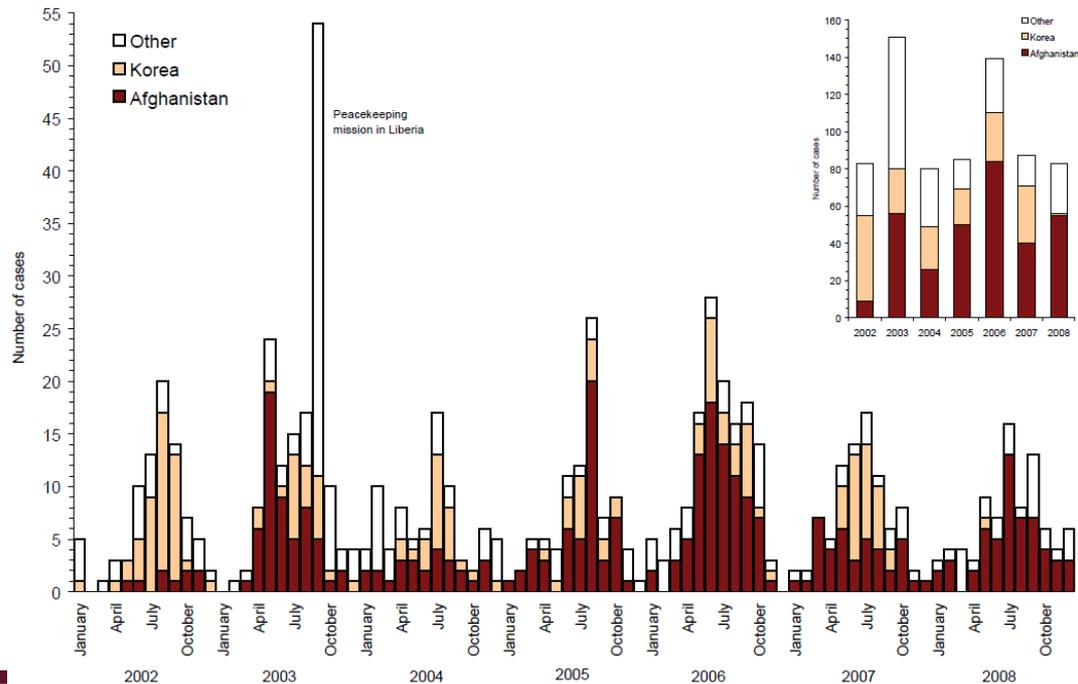


Recent Military History

- Somalia 1992-3 (233 cases; 77% *P. vivax*)
- US Army-wide 1995-2002
 - (30-75 cases/yr; ~ 75% *P. vivax*)
- Afghanistan 2002
 - (38 cases)
- Liberia 2003
 - (80 cases)
- Afghanistan today
 - (>100 cases/yr)
- Haiti 2010
 - (10 cases)
- Liberia 2009
 - (multiple cases, 1 death)
- Liberia 2010
 - (7 cases)



Figure 2. Malaria cases among U.S. service members, by estimated location of infection acquisition and month and year (inset) of clinical diagnosis/report, U.S. Armed Forces, January 2002-December 2008





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 (travelers)
 - 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





The Dawn of the Antibiotic Era

A N A S T A S I S
CORTICIS PERUVIÆ,
SEU
CHINÆ CHINÆ

DESECTIO,
SEBASTIANI BADI GENVENSIS
Præcipue utilis in Malaria, et

Publicæ Sanitatis in Civitate Genævæ.
Cura

V E N T I L A T I O N E S
IOANNIS IACOBI CHEFLETII,
MEDICINÆ

TOPICI FORTYMATI PLEMPHÆ,
Belgicæ Medicinæ.

*Opera in tres libros digesta, et in hanc Dissertationem
Medicæ, et Philoſophiæ.*

ILLUSTRATIONE D.
IOANNI LYCÆ DVRATIO



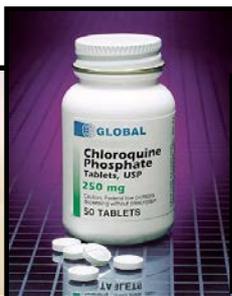
GERF. M., Type-set in Genævæ. In BCL. MDCC.

- 1630: Countess Chinchon, the wife of Spanish Viceroy, was saved from terminal malaria by bark powders recommended by the Jesuits of Saint Paul's College in Lima, Peru
- 1632: Jesuit Barnabe' de Cobo, in his capacity of procurator of the Peruvian province of his order, he brought the bark from Lima to Spain, and afterwards to Rome and other parts of Italy



Plasmodium falciparum Resistance

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





Anopheline mosquitoes

50-80 species capable of transmission

<40 medically important

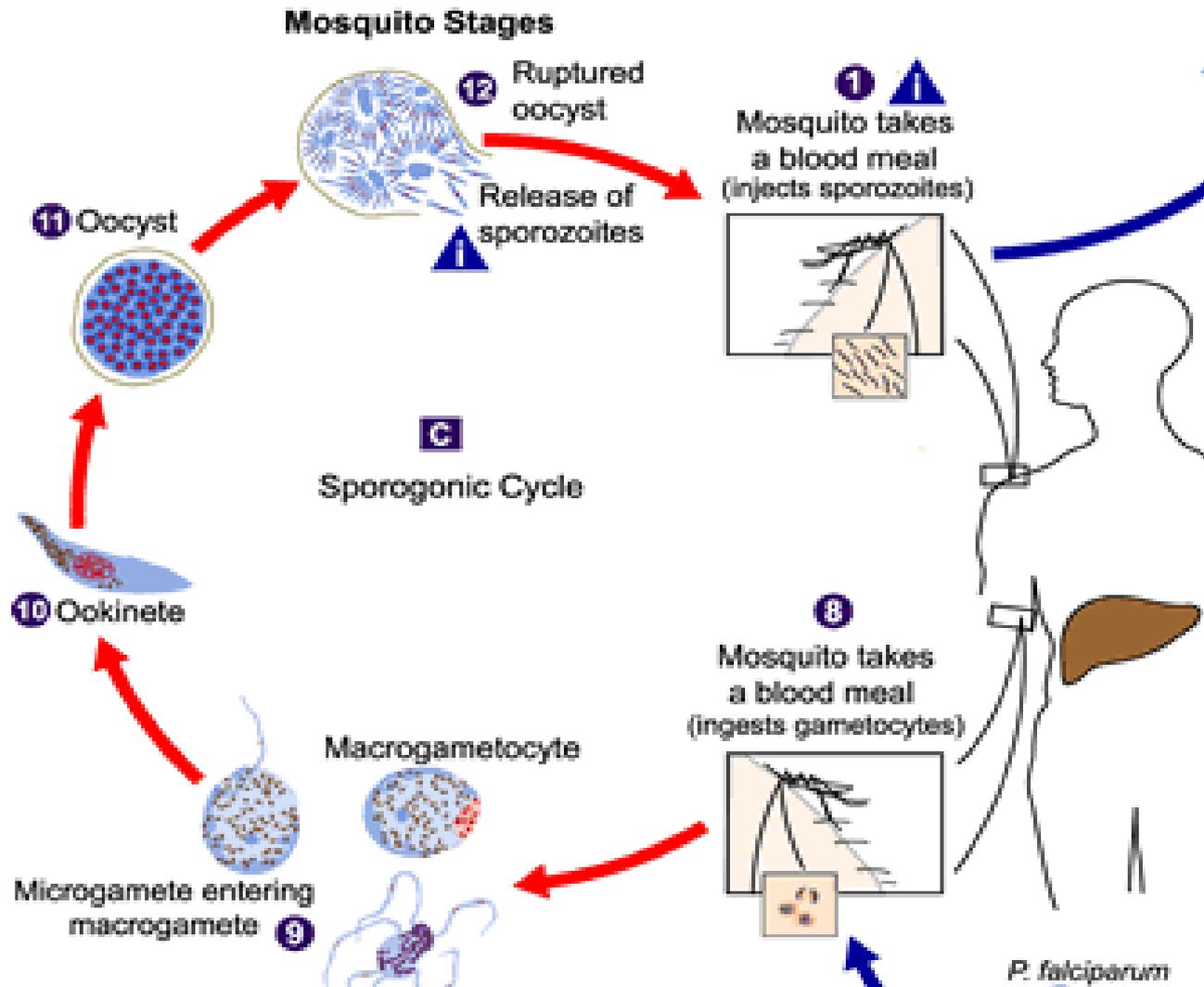
Female requires blood meals for egg broods

Anopheline Mosquitos

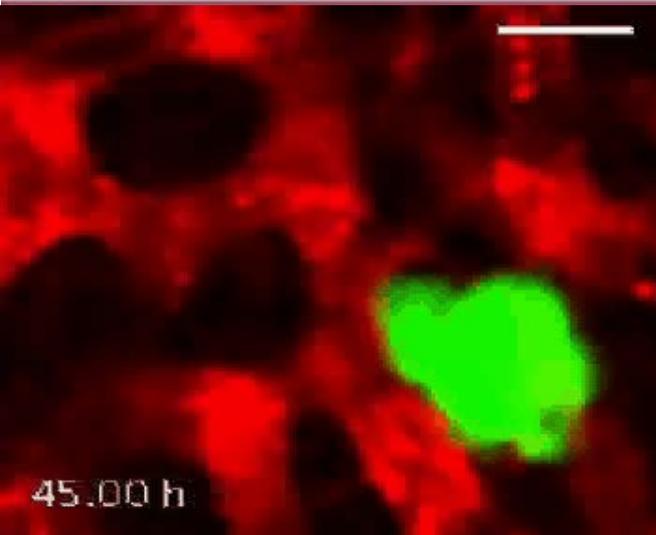
- Life cycle – 7 to 20 days (egg to adult)
 - egg -> larva -> pupa -> adult
 - Females mate once and lay 200-1000 eggs in 3-12 batches over a lifetime
 - Find their host by chemical and physical stimuli



Malaria Development in Mosquitoes



From Red Cell to Red Cell



RED = LIVER CELLS
GREEN = MALARIA PARASITES

ACTION

- LIVER CELL BURSTS
- PARASITES ESCAPE



RED = NORMAL RBC
BLUE = MALARIA PARASITE
BLACK = INFECTED RBC

ACTION

- INVADES RBC
- RBC SWELLS
- RBC RIGID
- RBC STICKY KNOBS



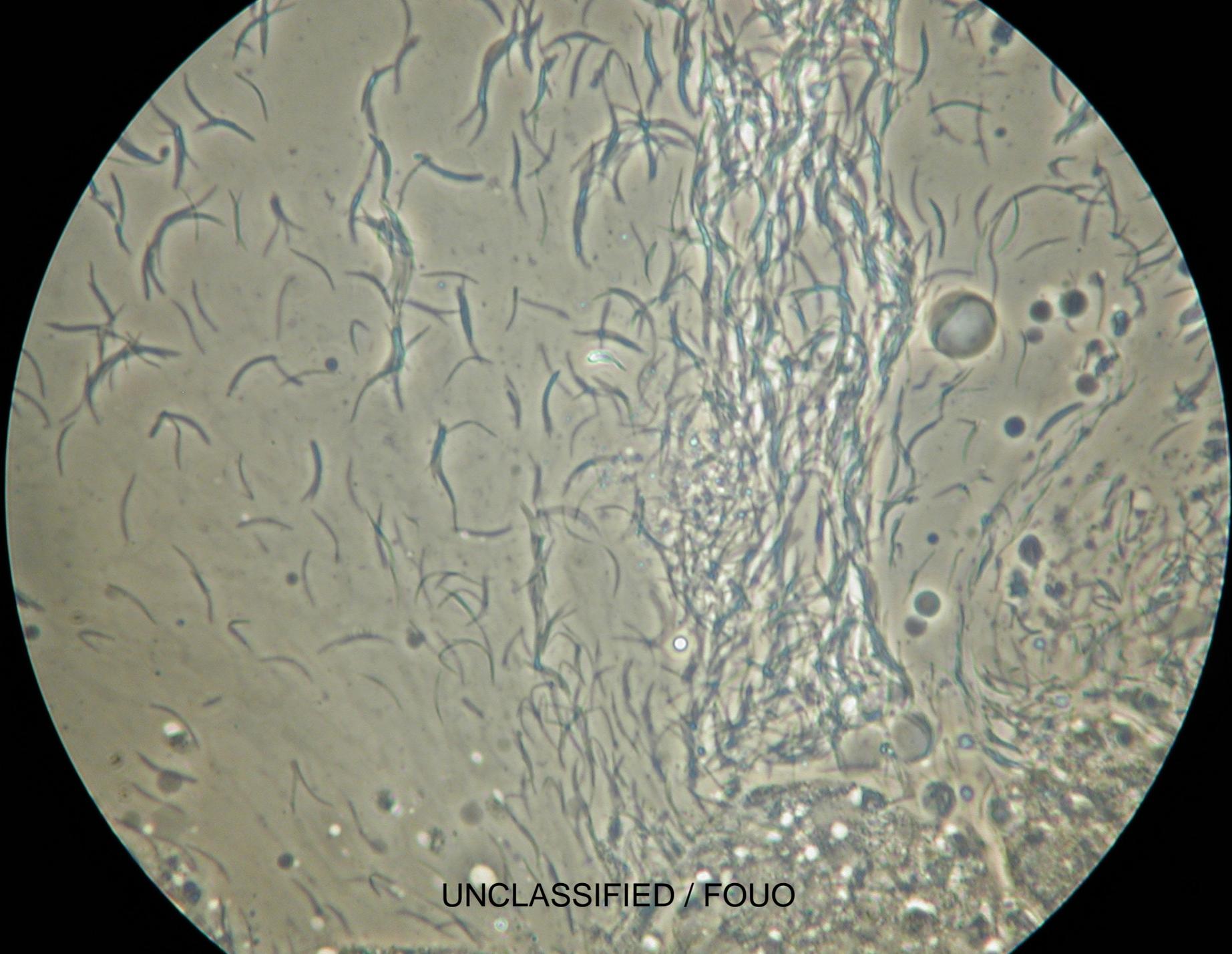
RED = NORMAL RBC
BLUE = MALARIA PARASITE
BLACK = INFECTED RBC

ACTION

- INFECTED RBC STICKS TO BLOOD VESSEL WALL
- RELEASE OF NEW PARASITES



UNCLASSIFIED / FOUO



UNCLASSIFIED / FOUO



Malaria Parasites and Their Life Cycles

- Four human forms of malaria
 - *Plasmodium vivax*
 - 48h cycle, young RBCs, worldwide
 - *Plasmodium malariae*
 - 72h cycle, older RBCs, worldwide
 - *Plasmodium ovale*
 - 48h cycle, young RBCs, Africa
 - *Plasmodium falciparum*
 - 48h cycle, all RBCs, Tropical regions



Pre-Patent & Incubation Periods

SPECIES	PREPATEMENT PERIOD	INCUBATION PERIOD
<i>P. falciparum</i>	11 - 14 days	8 - 15 days
<i>P. vivax</i>	11 - 15 days	12 - 20 days
<i>P. ovale</i>	14 - 26 days	11 - 16 days
<i>P. malariae</i>	21 - 28 days	18 - 40 days



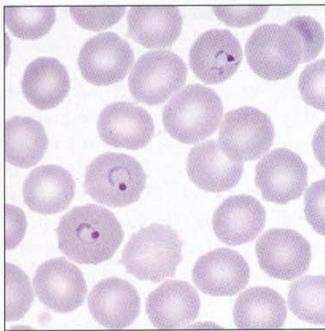
Plasmodium knowlesi

- Simian species of malaria naturally infecting macaques in Southeast Asia
- Resembles human species by microscopy
 - *P. malariae* (affects any age cell like *P. falciparum*)
- 24 hour replication cycle
 - Can cause severe and fatal infections
- Large numbers of human cases reported initially from Malaysian Borneo
- Subsequent reports of human cases in Peninsular Malaysia, Singapore, and the Philippines

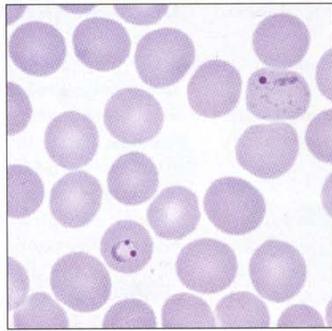


Diagnosis

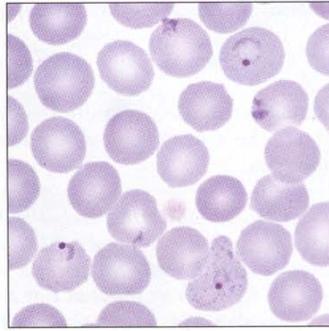
- Gold standard – Giemsa thick & thin smears
 - Species and parasite density determined
 - Labor intensive, modest cost
 - False negative circumstances
 - Parasites not present in circulation
 - False positive circumstances
 - Parasites seen may not be the cause of fever in endemic areas (Kisumu example of misdiagnosis...)
 - In highly endemic areas, clinical diagnoses made



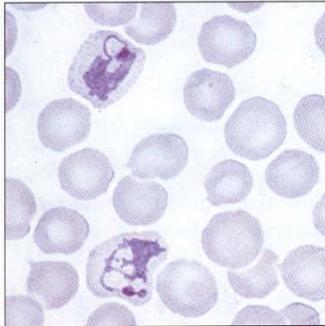
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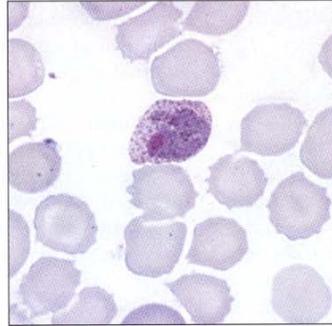
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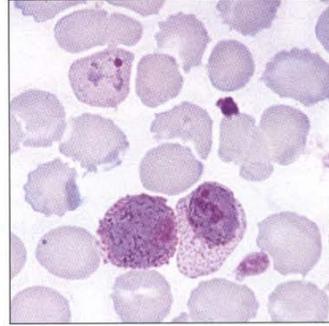
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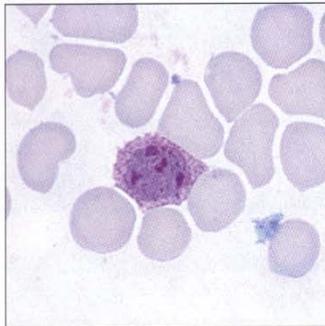
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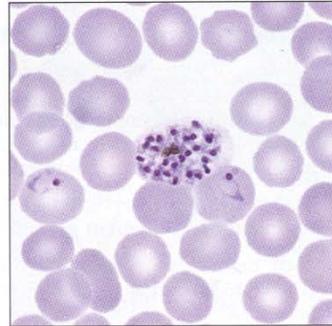
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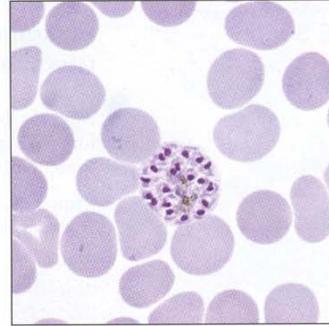
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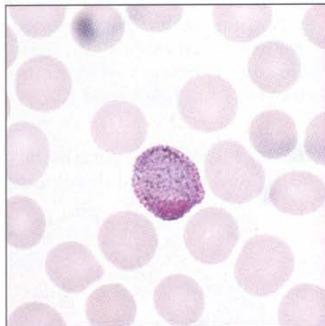
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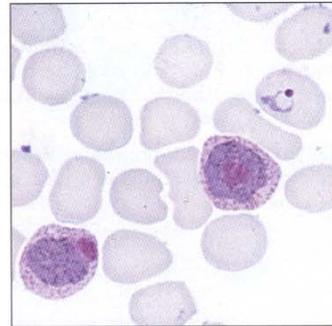
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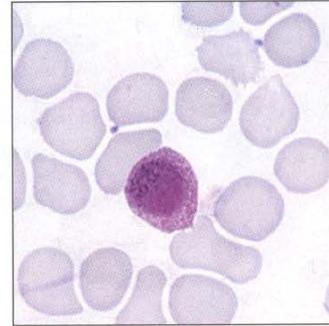
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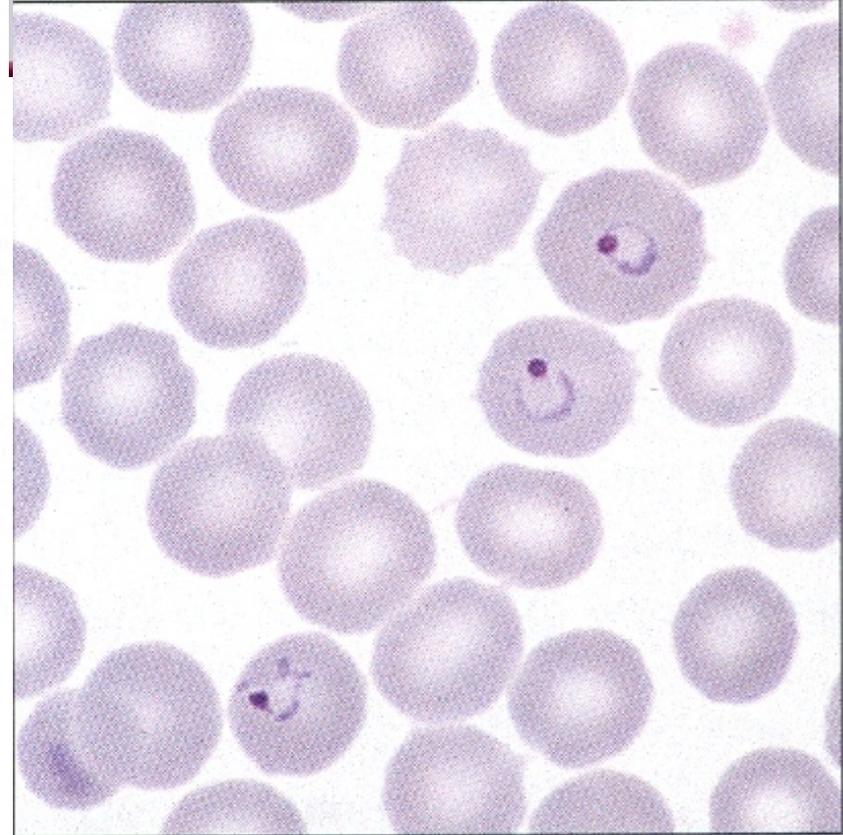
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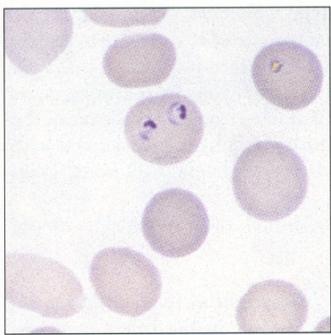
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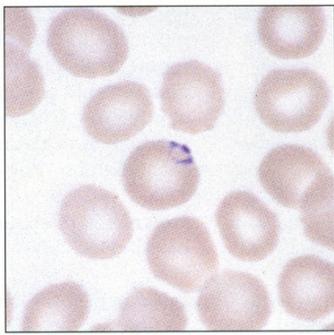
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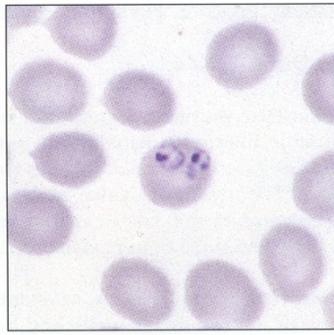
Plasmodium vivax



1



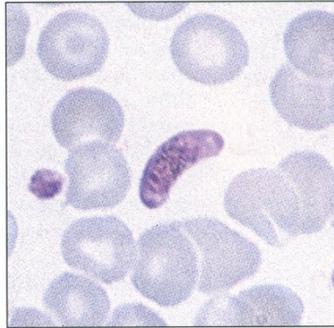
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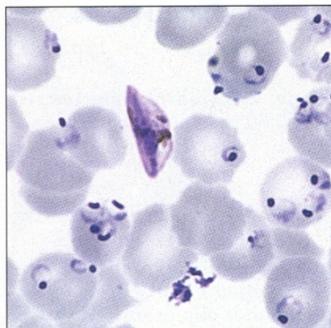
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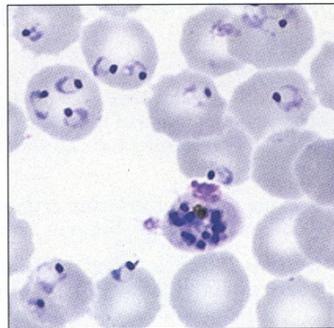
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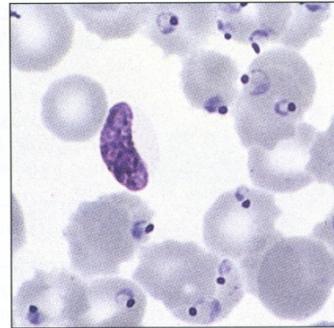
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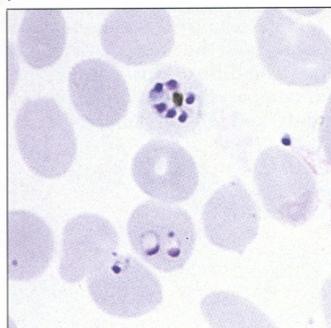
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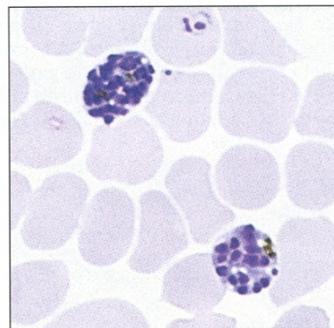
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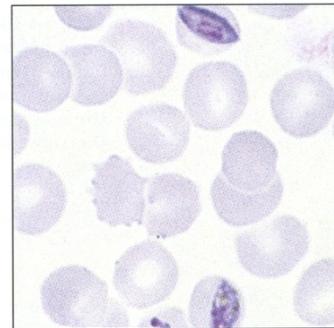
9



10



11



12



Plasmodium falciparum



UNCLASSIFIED / FOUO



NOW[®] ICT Malaria (Binax, Inc., Portland ME)



- Less than 15 minutes
- Non-microscopic
- Single reagent
- Minimally-trained operator
- Environmentally robust
- RDTs will NOT replace malaria microscopy
 - Confirmatory test for species, parasite density
 - Back-up to rule out inaccurate results

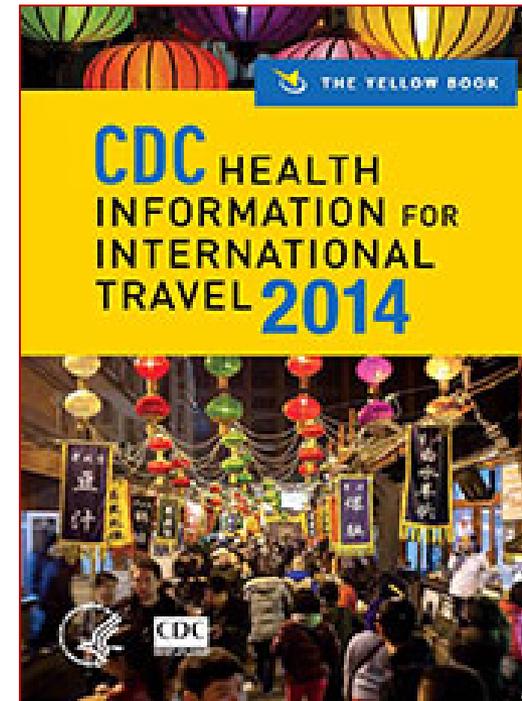


Parasite Growth in the Blood

Log+ increase in parasites per 48-hour cycle (for *P. falciparum*)

Threshold	Parasitemia	Parasites/ml	Parasite burden
Expert Microscopy	0.0005%	20-50/ml	10^8 parasites
Symptoms in non-immunes	0.002%	100/ml	10^9 parasites
Malaria RDT	0.005%	100-1000/ml	10^{9-10} parasites
Severe malaria	2%	100,000/ml	10^{12} parasites
Death	10%	500,000/ml	10^{13} parasites

- **Intravenous treatment of severe malaria**
 - Quinidine gluconate
 - Treatment IND with IV Artesunate
- **Oral treatment of uncomplicated *P. falciparum* malaria**
 - Proguanil / atovaquone (Malarone®)
 - Artemether-lumefantrine (Coartem®)
 - Quinine sulfate + doxy or PS
 - Mefloquine (Lariam®)
 - Chloroquine (Aralen®)
- **Available and can be used (Rx adjuncts)**
 - Doxycycline, clindamycin, azithromycin
- **Radical cure of relapsing malaria**
 - Chloroquine + primaquine







Antimalarial Issues

DRUG

Artemisinin

Atovaquone

Azithromycin

Chloroquine

Doxycycline

Fansidar

Halofantrine

Mefloquine

Primaquine

Proguanil

Quinidine gluconate

Quinine

PROBLEMS

Recrudescence, Neurotoxicity

Resistance

Limited efficacy

Resistance

Phototoxicity, GI intolerance

Resistance, Allergic Rxns

Cardiotoxicity

Resistance, Psychiatric effects

Narrow Therapeutic Index

Resistance, Mouth ulcers

Going off the market?

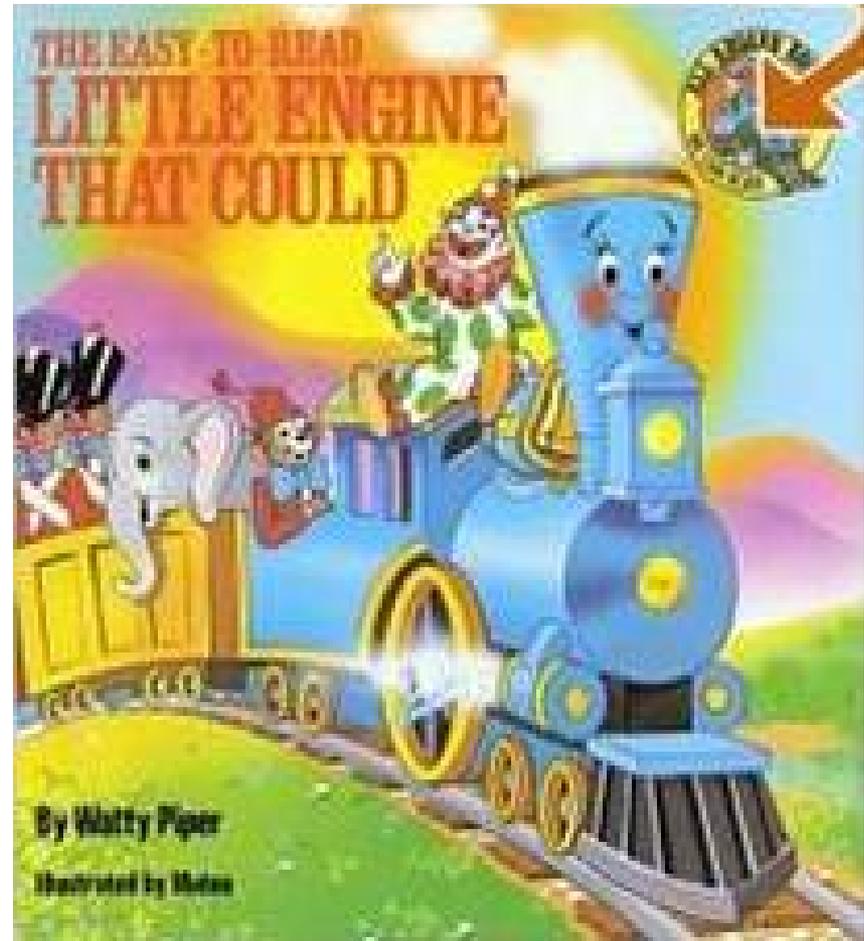
Resistance, Tinnitus



DoD Antimalarial Drug Program

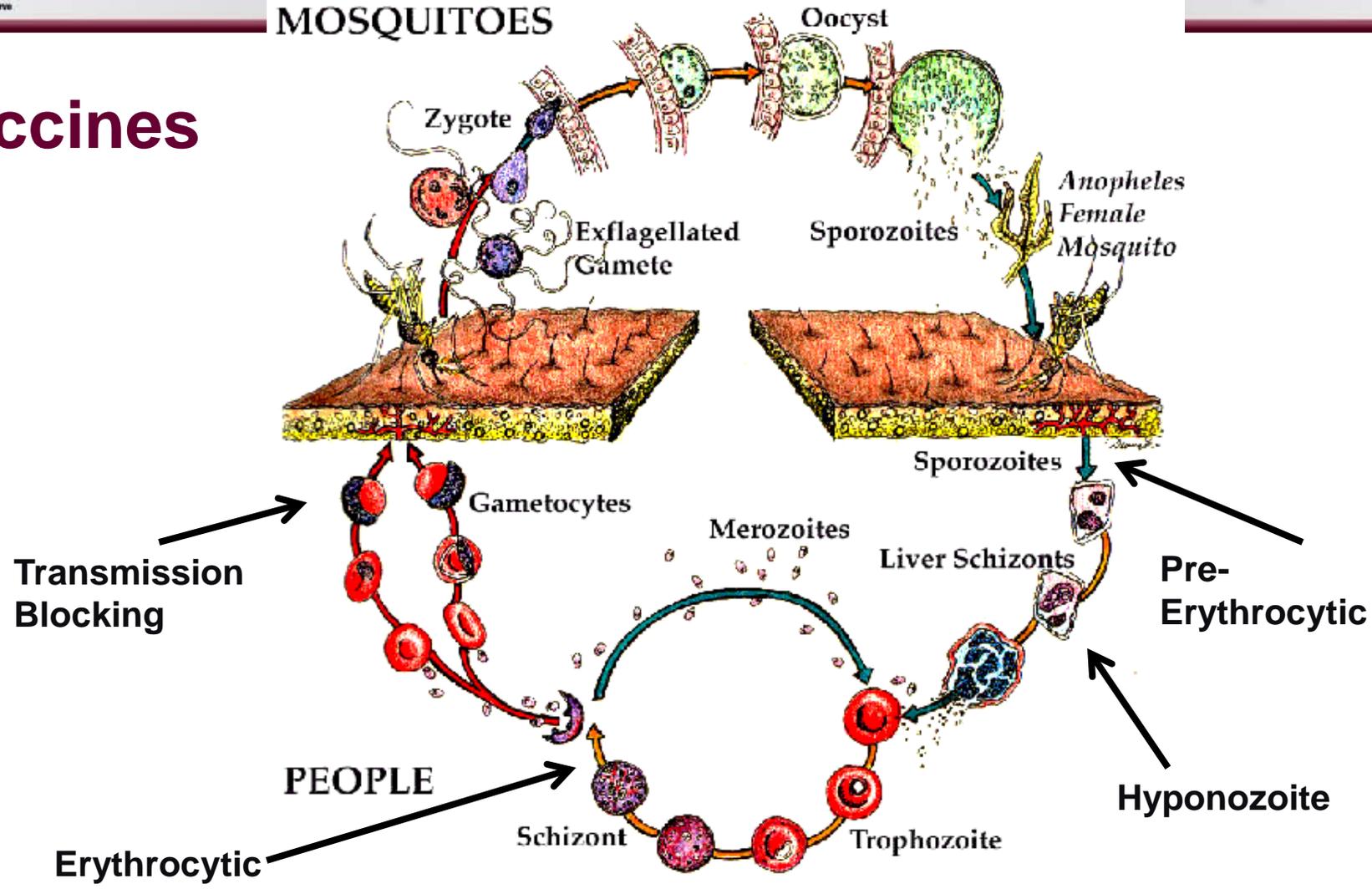
The Biggest Little Drug Company in the World

- 63 IND's filed with FDA
 - Chloroquine
 - Primaquine
 - C-P Tablets
 - Mefloquine
 - Doxycycline
 - Halofantrine
 - Fansidar
 - Malarone
 - IV Artesunate



MOSQUITOES

Vaccines





Approaches to Control

- Vector Control Methods
 - Breeding site control
 - Larvacide
 - Adulticide
 - Bed nets & personal protection
- Treatment Strategies
 - Passive case finding and self-referral
 - Home treatment early in course of disease
 - Prophylaxis in selected groups



Controversies in Malaria Management

- **Prophylaxis... drug to use?**
 - Mefloquine vs. Malarone vs. Doxycycline
- **Prophylaxis... to do or not?**
 - Short-term vs. Long-term Deployments
- **Prophylaxis... duration?**
 - Continuous vs. Interrupted
- **RDTs...**



Take Home Points

- Malaria continues to evolve, not just in resistance, but in new species
- Malaria is as important a consideration for force health protection today as ever
- Malaria is not just a force health protection issue, but a strategic stability operations consideration in the global war on terrorism
- We have more tools today than ever, but we can lose them at any time and we must understand and respect their limitations



Combatting Malaria

- **Requires expensive, sustained efforts**
- **Medical facilities are not equipped to quickly and accurately diagnose and effectively treat malaria**
- **Effective control efforts if subsidized and applied**
 - **Indoor Residual Spraying (IRS) with DDT - saves lives**
 - **Insecticide-treated Bed Nets (ITNs) - save lives**
 - **Artemisinin combination treatment – saves lives**
 - **Improved diagnosis – save expensive drugs for greatest need**
 - **World is waiting for a malaria vaccine**
- **Eradication requires multiples efforts and multiple solutions**



“Science is not an accessory occupation for man but an essential activity...”

Teilhard de Chardin
“The Phenomenon of Man”

Questions?

