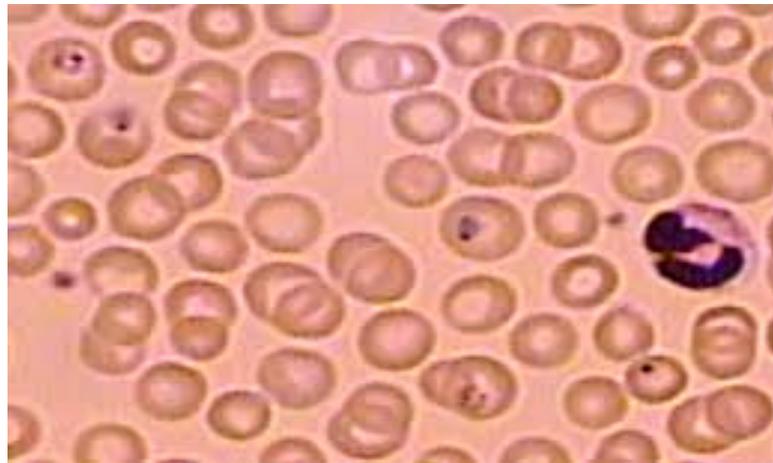


Malaria



**Arthur Lyons, COL, MC, FS
DASG-FP, OTSG
23 SEP 2014**

Disclosures

- **Conflict of interest:**
 - I have no patents or financial interest in the antigens and vaccines discussed today
- **Pre-clinical:**
 - All pre-clinical work was conducted under IACUC approved protocols in AAALAC-accredited facilities
- **Clinical & Field Trials:**
 - Informed consent was obtained prior to screening and enrolment
 - Trials were conducted according to ICH and FDA guidelines
- **Non-official:**
 - All opinions expressed are personal and are not official

Overview



- Malaria is a large 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**

Ancient Roman bones reveal malaria

ROMAN from Page 2A skeletal remains."

Dr. David Soren, a classical archaeologist at the University of Arizona in Tucson, praised the DNA results as "new and really exciting" because "the idea that this deadly type of malaria really existed in Imperial Rome had never been documented."

An international team led by Soren excavated the children's cemetery in the early 1980s and discovered more than 50 small

skeletons. Most of them, found in earthen jars, were the remains of stillbirths and early infant deaths. The falciparum parasite is known to cause aborted fetuses and infant mortality. A few of the older skeletons had porous and pitted cranial surfaces, which can be the result of an infectious disease like malaria.

This and considerable circumstantial evidence led Soren to the hypothesis that malaria epidemics might have had grave consequences on Rome. Scientists at the University of Rome have

found evidence showing that falciparum malaria came from Africa, underwent mutations in Sardinia and was introduced in the marshy, mosquito-infested Tiber River basin by the fifth century.

Dr. Frank Homer, a Roman historian at Arizona, noted accounts of pestilence spreading through the countryside at this time and causing "sweats and chills," symptoms typical of malaria. It was in 492, a year or two after the infant burials, that Attila, marching toward Rome, suddenly decided against entering

the city.

If the DNA tests have indeed linked the infant deaths to malaria and not some other cause, Soren said he hopes other archaeologists would take notice and begin to incorporate biomolecular research in their investigations.

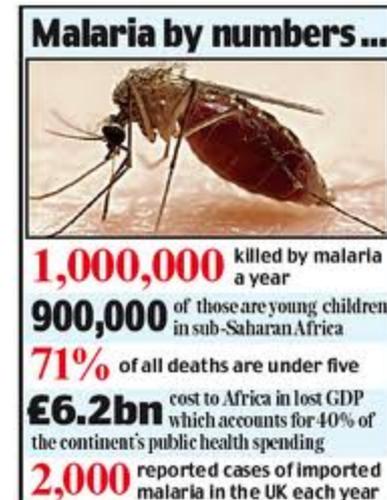
"I think in 10 or 15 years, this will come to be standard practice in archaeology," he said. "We need not just excavate bones and throw them into a closet. We need to take those bones and make samples for DNA testing."

History

- 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**



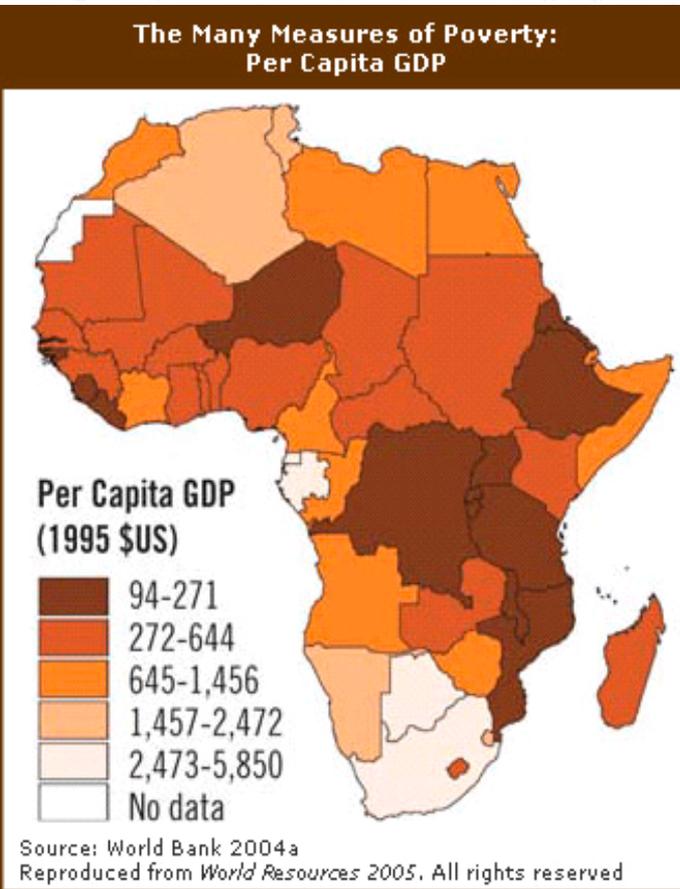
Hand of child with severe malaria anemia in the palm of his mother



Child with severe malaria

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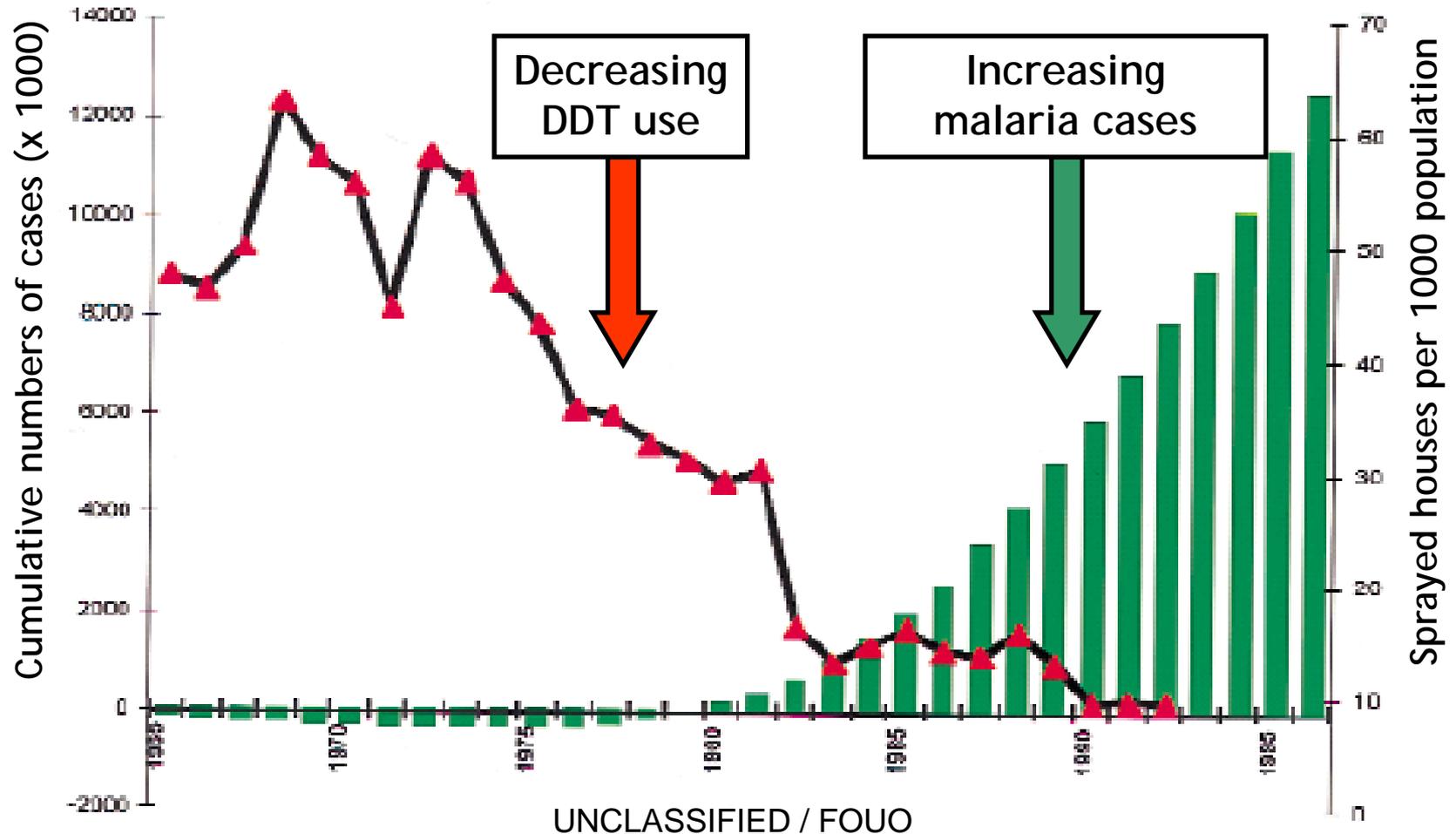
ITNs – Insecticide Treated Nets



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

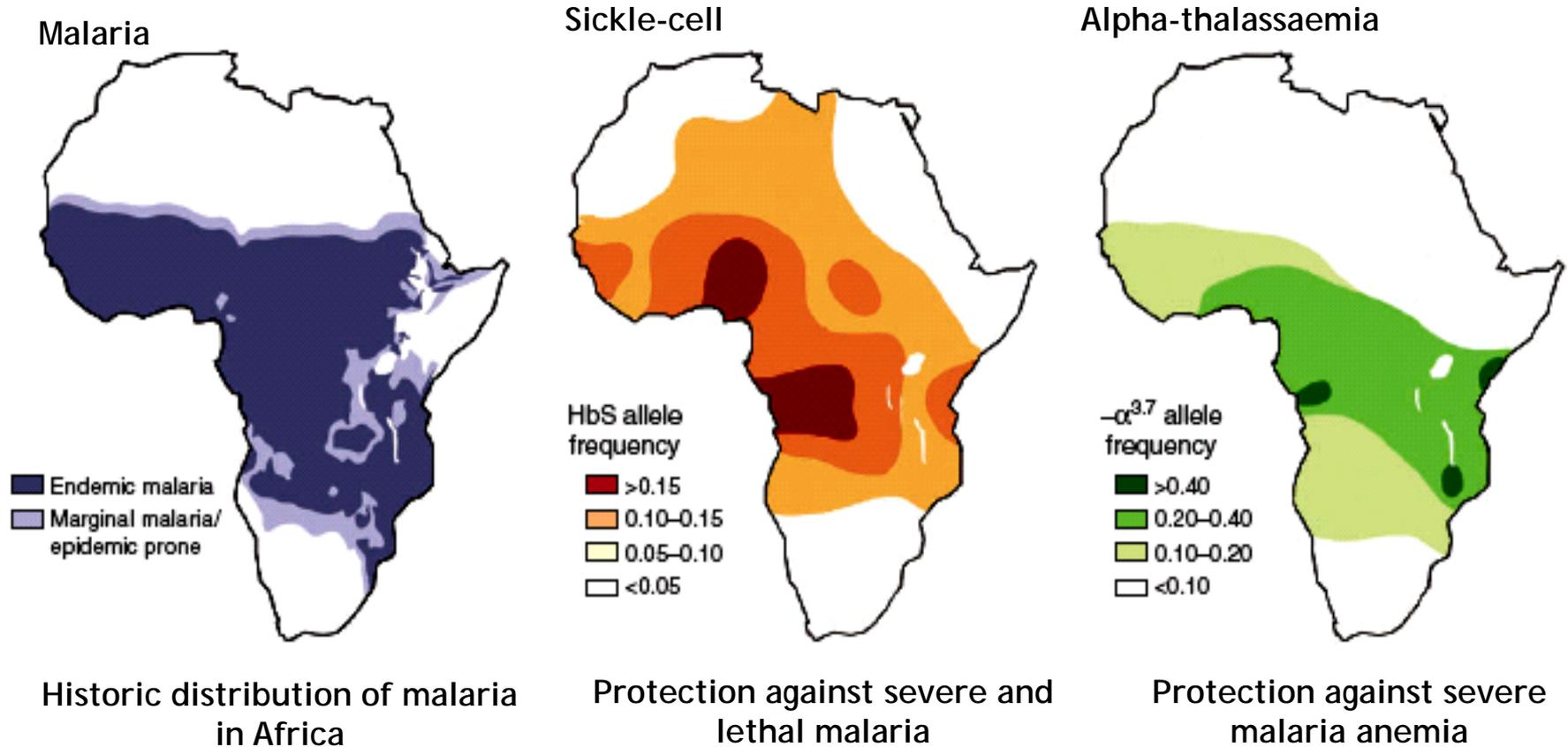
Indoor Residual Spraying (IRS) DDT Use and Cumulative Malaria Cases in South America

House Spray Rates, 1955-82, and Cumulative Malaria Cases, pre- vs. post-1979
(Brazil, Colombia, Ecuador, Peru, Venezuela)



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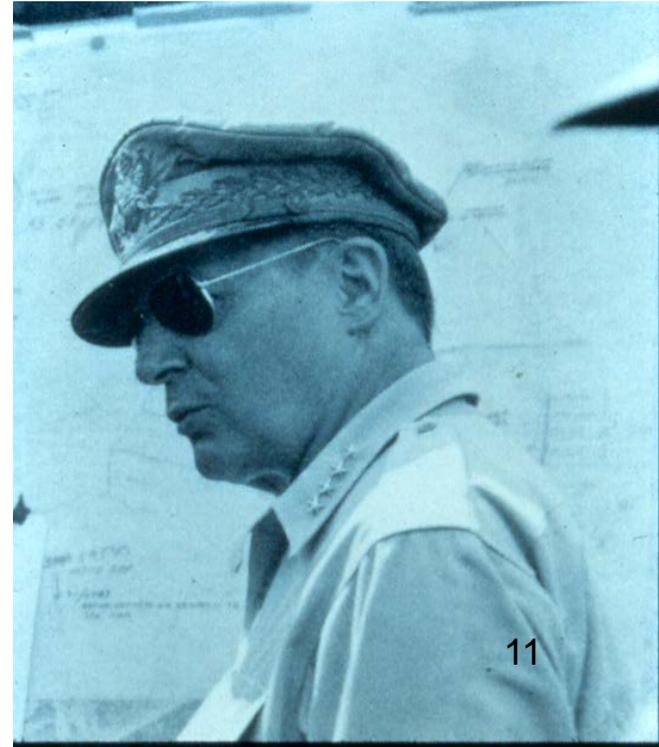
Distribution of Malaria & Abnormal Hemoglobin Genes in Africa



- 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

- *"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.



Destabilization Effect

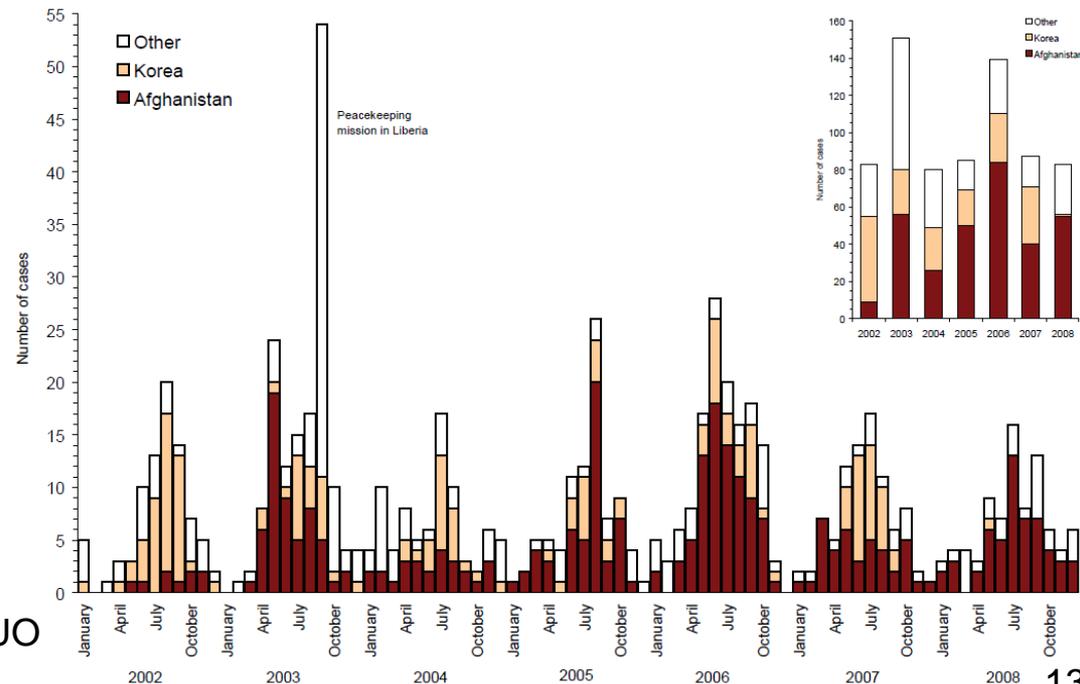
- There are huge impacts of HIV/AIDS, malaria, and MTb on the critical infrastructures that sustain the security, stability, and viability of modern nation-states
- In the developing world (esp Africa) these diseases undermine education and health systems, economic growth, micro enterprises, policing 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

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

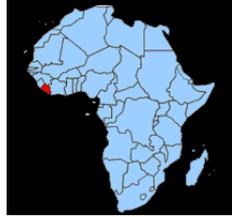


Figure 2. Malaria cases among U.S. service members, by estimated location of infection acquisition and month and year (inset) of clinical diagnosis/report, U.S. Armed Forces, January 2002-December 2008



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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
- Vaccine would be of great benefit



A N A S T A S I S
CORTICIS PERUVIÆ,

BY
CHINA CHINA

PERUVIÆ,

SEBASTIANI BADI GENVENSIS

Præcipuus Medicus in Mædica,

Et

Publicæ Sanitatis in Chancery Consistoris.

Comit

V E N T I L A T I O N E S

IOANNIS IACOBI CHEFLETII,

Medici Regii

VOPICI FORTYNNATI FLEMPELII,

Medici Medicorum.

*Operis in uno libro abſoluti, quod in Bibliotheca
Medicæ, & Philoſophiæ.*

ILLUSTRISSIMO D.

IOANNI LYCÆ DVRATIO



GENOVA, Typis Societatis Illustrissimæ. M. DC. LXXII.

- **Jesuit's Bark**, due to alkaloids, is the most celebrated specific remedy for all forms of malaria. It is obtained from several species of the genus cinchona, of the order Rubiaceae
- **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** (1582-1657) rendered important services in the exploration of Mexico and Peru. 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 Becomes Resistant to Antimalarial Drugs Continuous New Drug Development and Licensure is Required

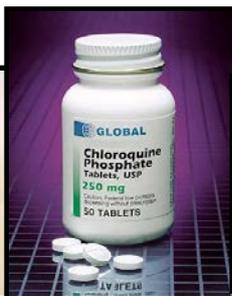
Drug	Introduced	First Reported Resistance	Difference (Years)
Quinine	1632	1910	278
**Chloroquine	1945	1957	12
**Proguanil	1948	1949	1
**Sulfadoxine-pyrimethamine	1967	1967	0
**Mefloquine	1977	1982	5
**Malarone	1997	2002	5

** WRAIR support for US FDA approval

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Quinine



Chloroquine



Proguanil



Fansidar

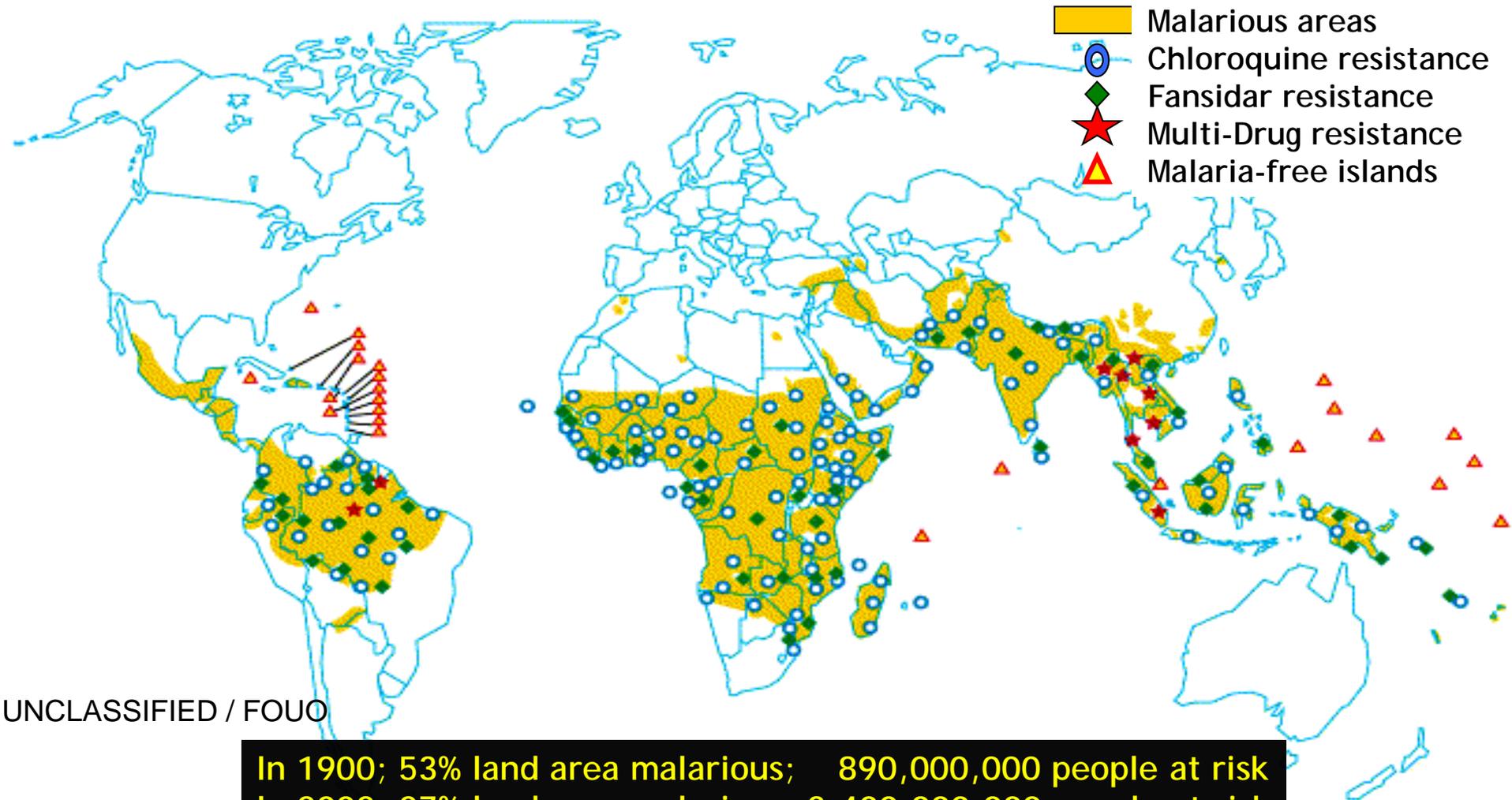


Mefloquine



Malarone

Multi-Drug Resistant *Falciparum* Malaria Means that Effective Drugs (ACTs) are not Affordable

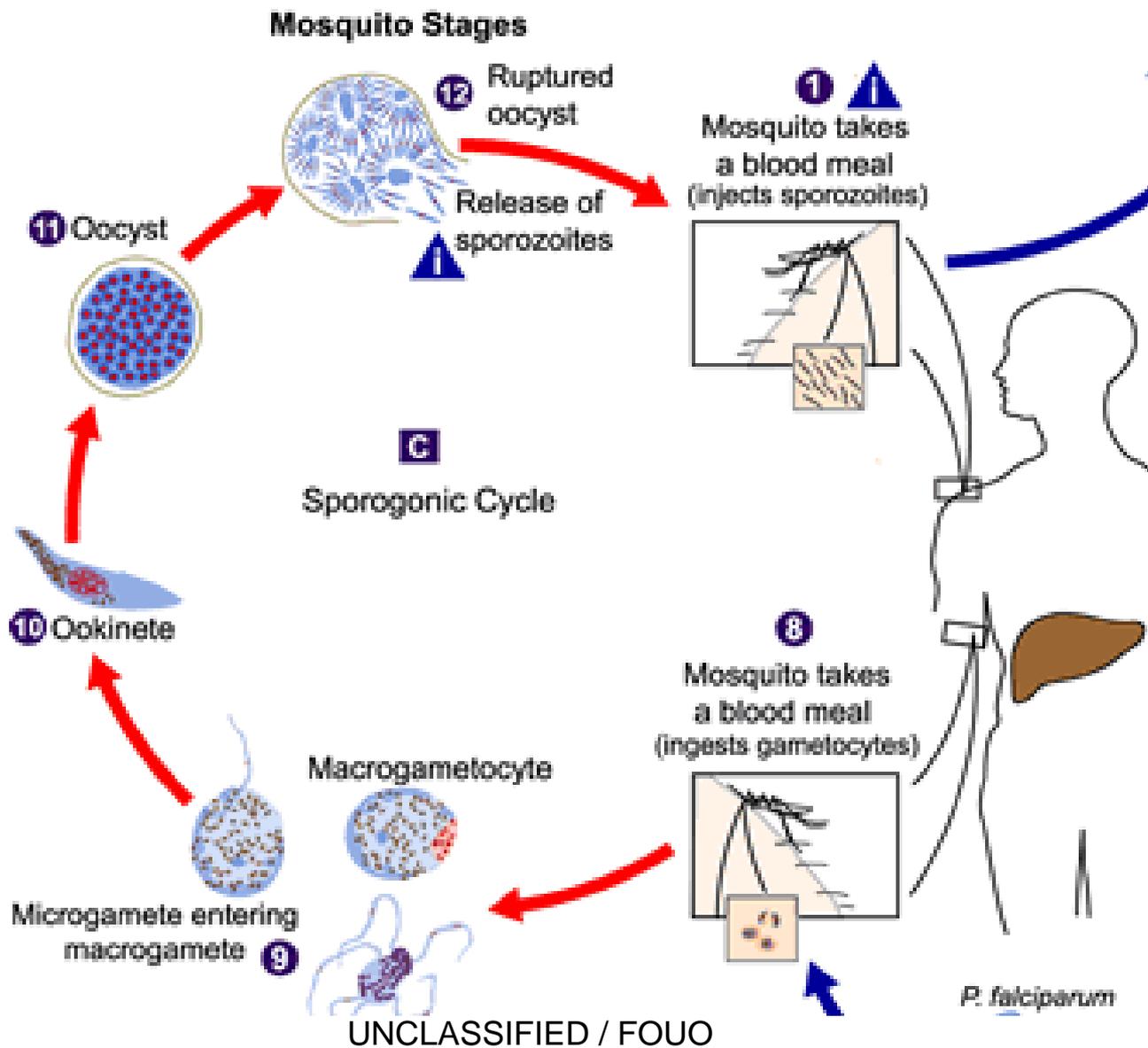


P. vivax: chloroquine prophylactic or treatment failure



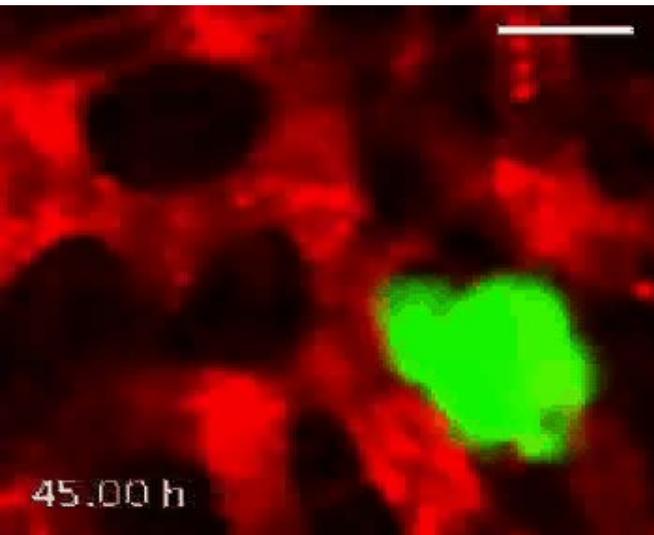
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Malaria Development in Mosquitoes



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From Red Cell to Red Cell and Again



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
- UNCLASSIFIED / FOUO



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

ACTION

- INFECTED RBC STICKS TO BLOOD VESSEL WALL ²⁰
- RELEASE OF NEW PARASITES

Malaria-infected RBC



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Anopheline Mosquitos



- 50->80 species capable of transmission
- <40 really important
- Female requires blood meals for egg broods

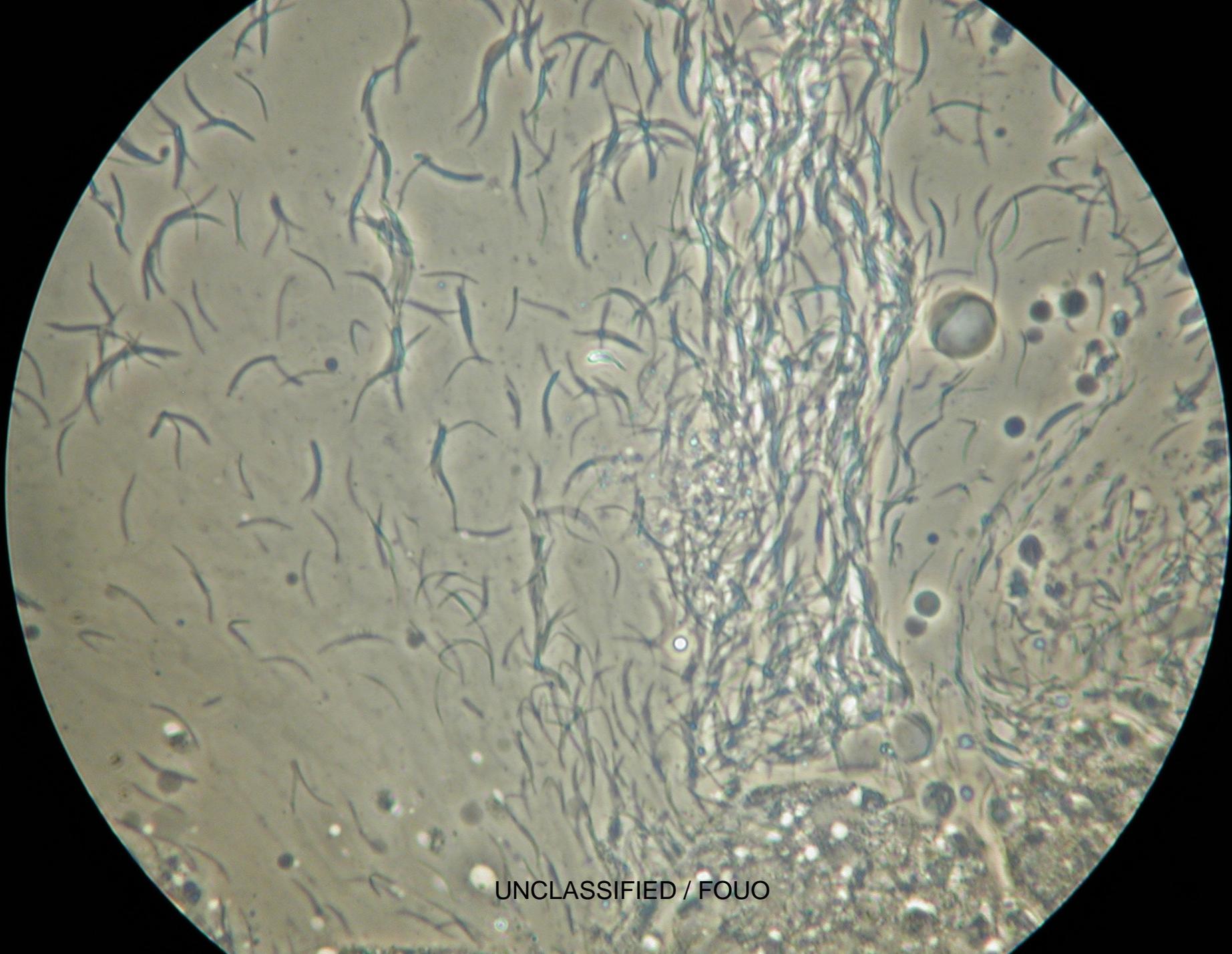


Anopheline Mosquitos

- 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
 - Average life span of mosquito < 3 weeks
- Malaria development – 7 to 12 days
 - Each male & female gametocyte produce >10,000 sporozoites

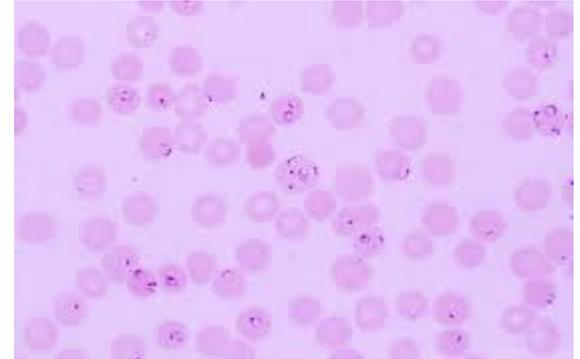


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Malaria Parasites and Their Life Cycles



- 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

Prepatent & Incubation Periods (parasites in blood vs. illness)

SPECIES	PREPATENT 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

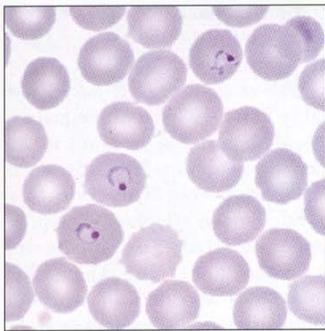
Plasmodium knowlesi

- 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

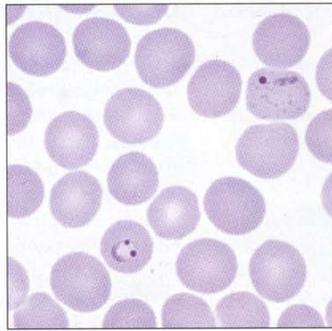
Diagnosis



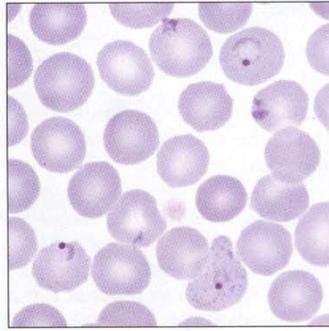
- Gold standard – Giemsa thick & thin smears
 - Species and parasite density determined
 - Labor intensive, modest cost
 - False negative circumstances
 - Parasites not present in circulation
 - False positive circumstances
 - Parasites seen may not be the cause of fever in endemic areas (Kisumu example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



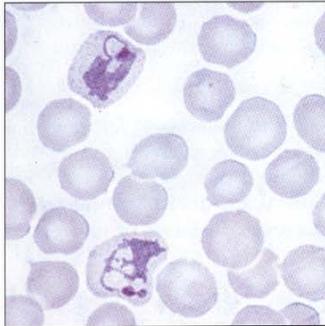
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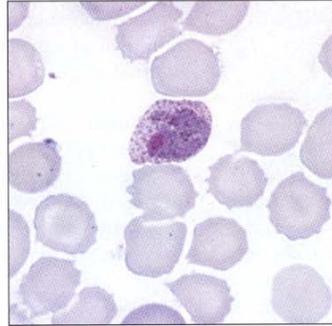
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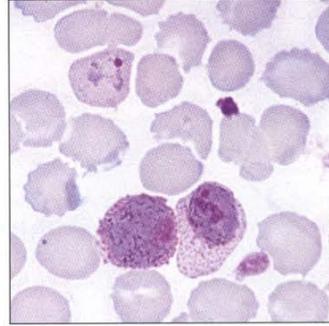
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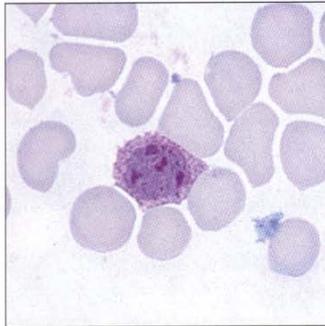
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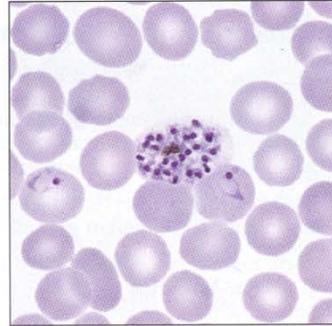
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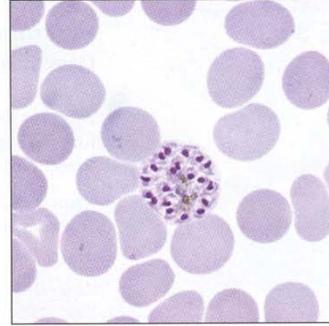
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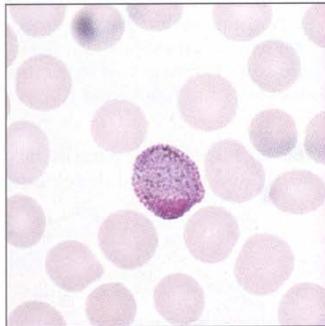
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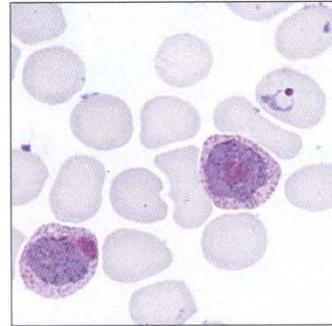
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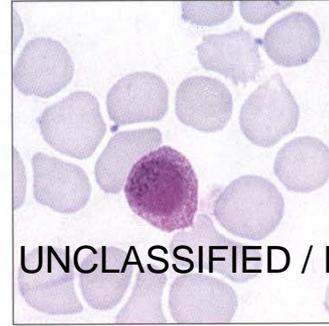
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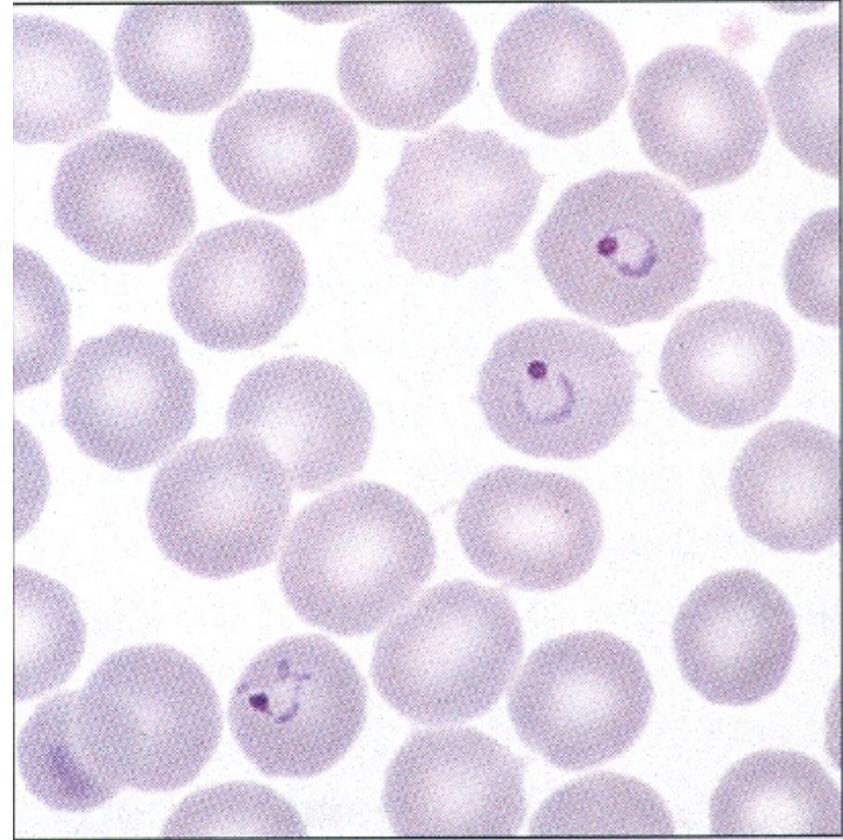
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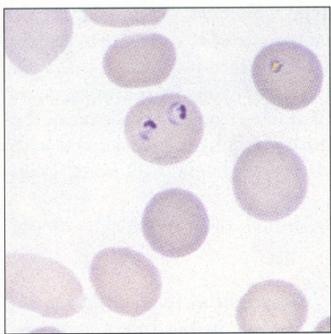


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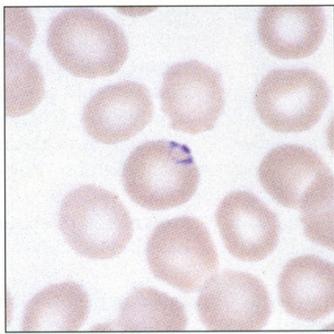


Plasmodium vivax

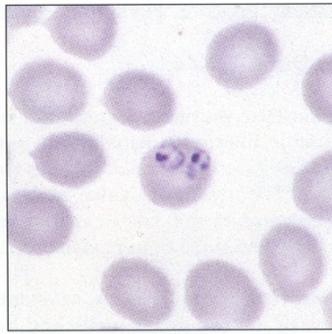
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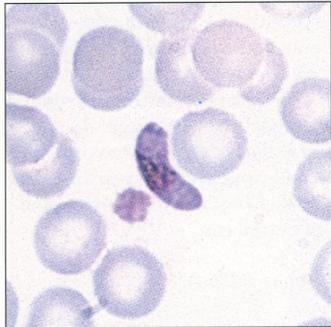
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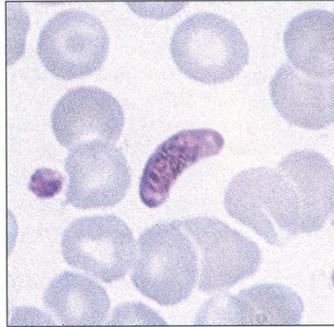
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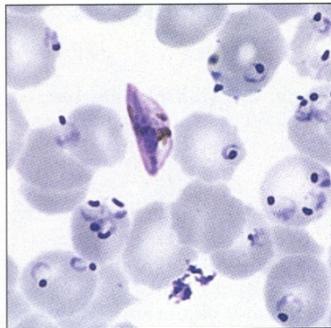
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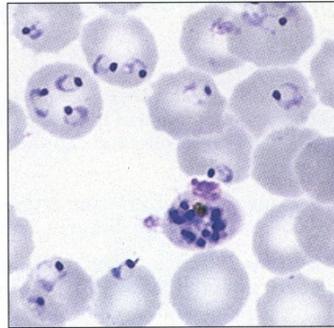
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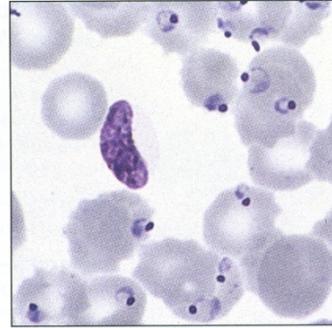
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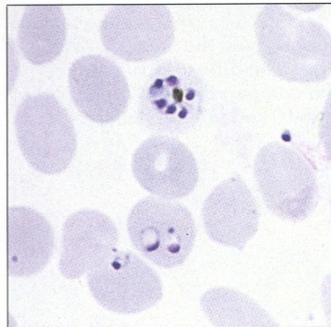
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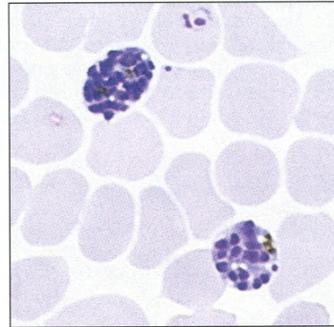
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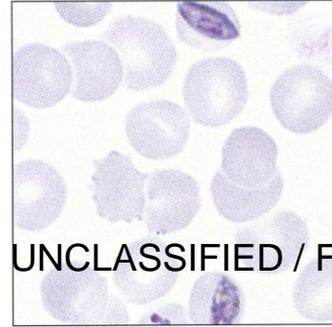
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12



Plasmodium falciparum

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Rapid Diagnostic Tests

- Currently acceptable test(s)
 - *Binax Now*, Inverness Medical Innovations, Inc.
- Reliability
 - False negatives – Prozone Effect
 - Hyperparasitemia – too much antigen
 - HRP-2 assays (16/17) most affected; pLDH and aldolase not affected
- Follow-up
 - FDA ‘clearance’ Labeling – what does it actually say?

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

- *“Good doctors are useless without good discipline. More than half the battle against disease is fought not by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine is taken, that shorts are never worn, that shirts are put on and sleeves turned down before sunset. . . I therefore had surprise checks of whole units, every man being examined. If the overall result was less than 95% positive, I sacked the commanding officer. I only had to sack three; by then the rest had got my meaning.”*

General Slim, Burma Campaign, WW II
(Under General Slim, the malaria rate in troops decreased from 12 per 1,000/day to 1 per 1,000/day)

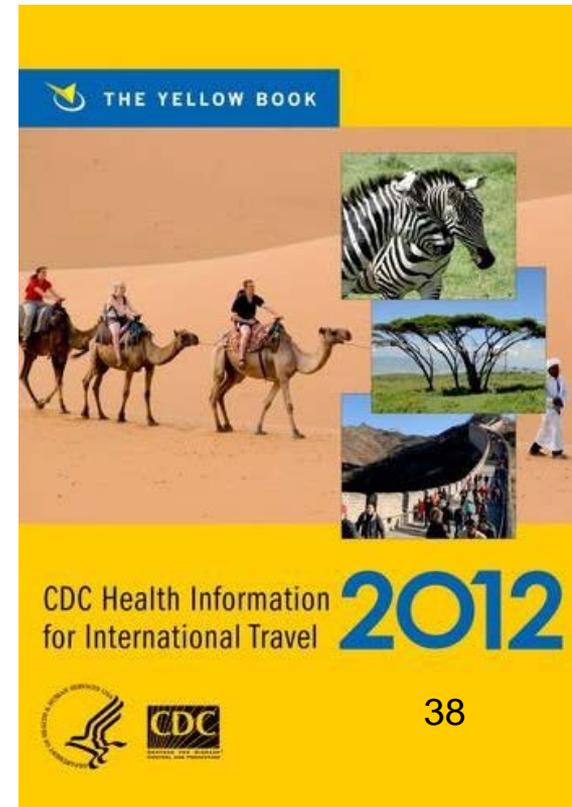
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Malaria Treatment US '2012'

- **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

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CDC's Compassionate Use IND

- WRAIR produced 1,000 vials of the “clinical lot” for compassionate use (another 10,000 vials being produced now – available in May 2010)
- CDC has a Compassionate Use IND for IV AS
 - Compassionate Use IND went into effect on 21 June, 2007
 - Complete cross-reference to U.S. Army IND for IV AS
 - Administered by Domestic Response Unit & Malaria Branch
 - Announcement Made on 03 August, 2007 in MMWR
- Now released to Canadians, and will be made available in Australia, EU, and elsewhere

Evidence of Artemisinin-Resistant Malaria in Western Cambodia

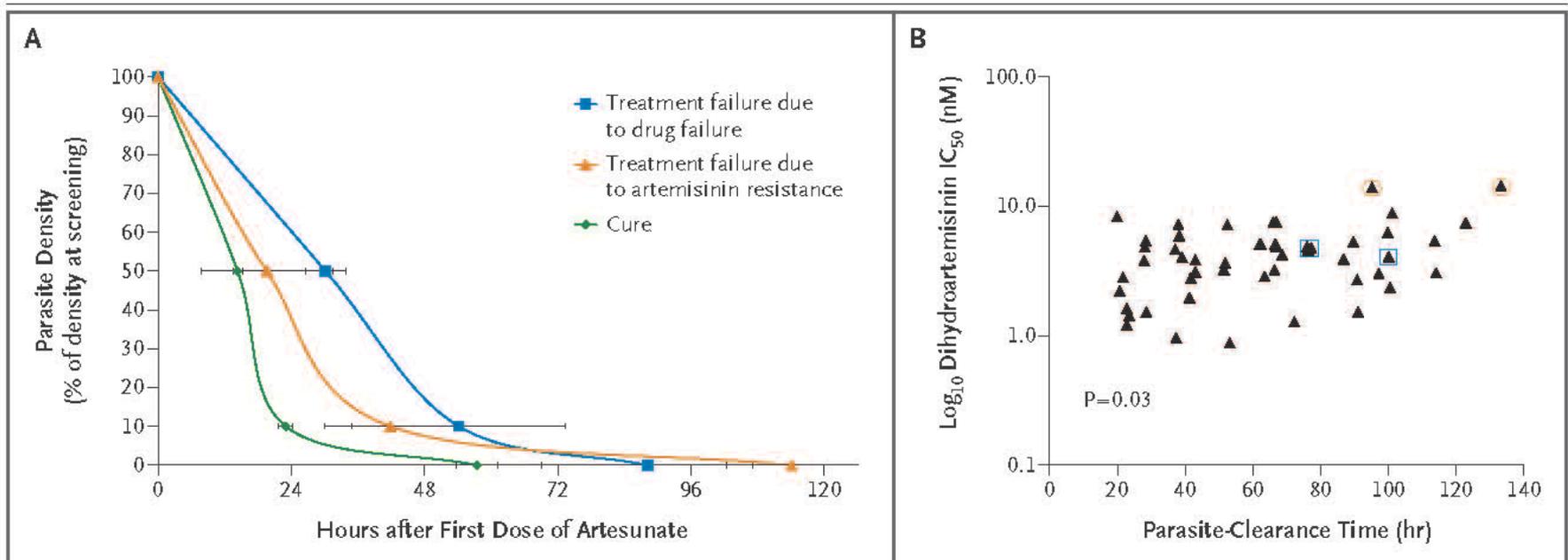


Figure 1. Parasite Density, Parasite-Clearance Time, and 50% Inhibitory Concentration (IC₅₀) among Patients Receiving Artesunate, According to Clinical Outcome.

Panel A shows the parasite-reduction curves for the 56 patients who were cured, the 2 patients classified as having artemisinin-resistant infections, and the 2 with drug failures (i.e., patients who had recrudescence but who were not classified as having artemisinin-resistant infection, since the drug level was inadequate). The data points and horizontal I bars denote the means and standard errors. Panel B shows the parasite-clearance times in the artesunate group, as compared with the IC₅₀ for dihydroartemisinin (R=0.31, P=0.03). Orange circles indicate patients whose infection was classified as artemisinin-resistant, and blue squares patients in whom treatment failed but whose infection was not classified as resistant.

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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

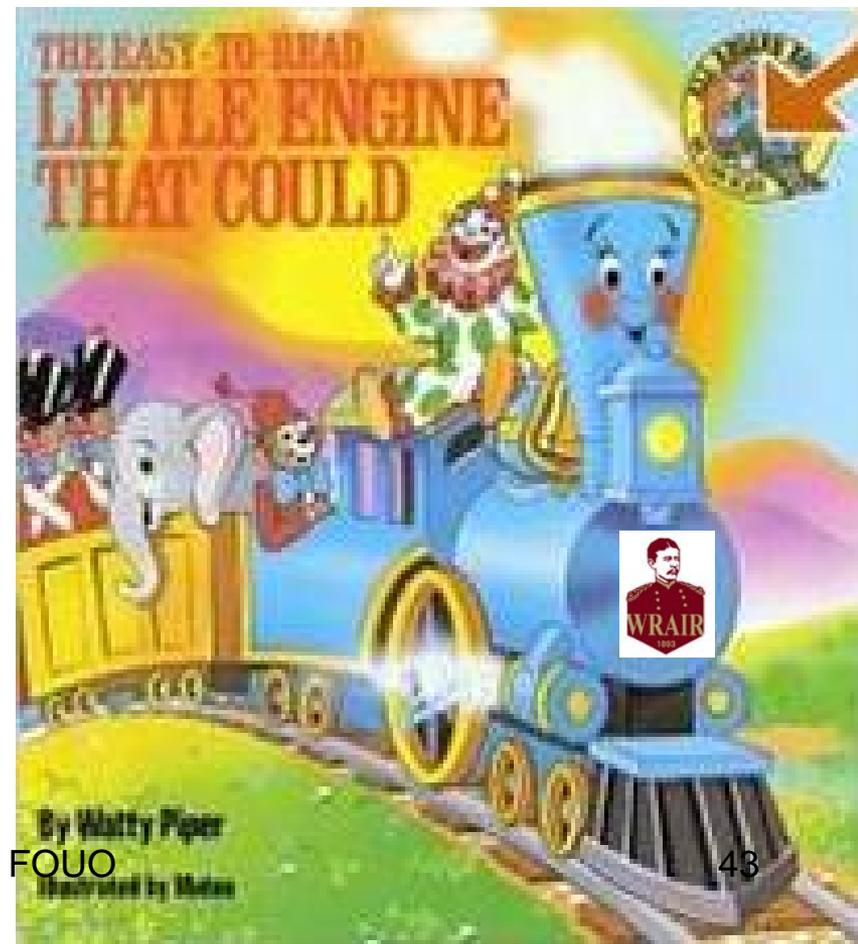
Going off the market?

Resistance, Tinnitus

DoD Antimalarial Drug Program

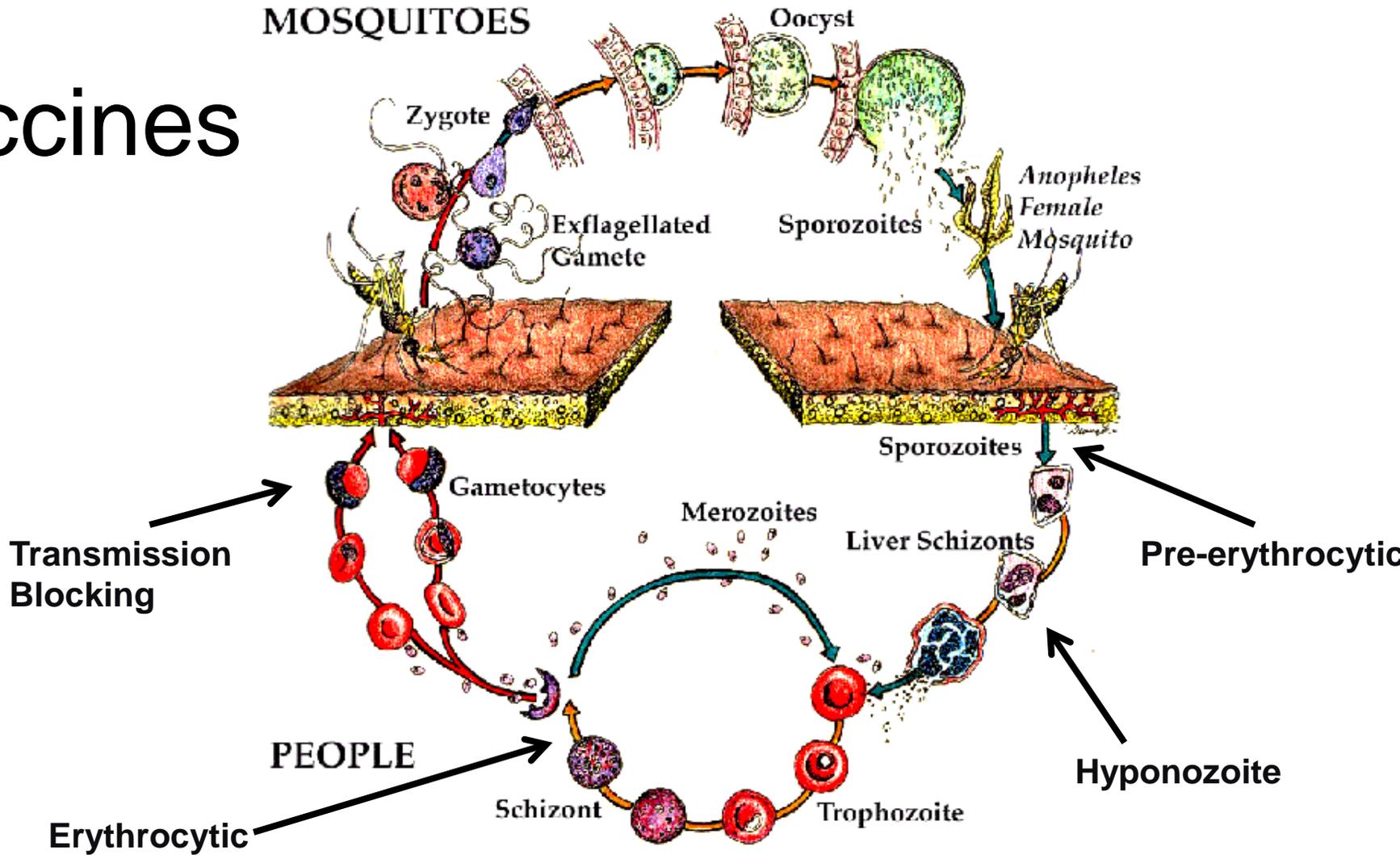
The Biggest Little Drug Company in the World

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



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Vaccines



Approaches to Control

- Vector Control Methods
 - Breeding site control, larvacide, adulticide, bed nets and personal protection
- Treatment Strategies
 - Passive case finding and self-referral
 - Home treatment early in course of disease
 - Prophylaxis in selected groups



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Controversies in Malaria

- **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...**

Malaria

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

Reality – Case study

- 45 y/o Male from Ivory Coast. Lived there 20 yrs ago and now owns property and visits every few years
- Last visit 2008 and took prophylaxis. Went this year from Feb to mid-Mar and had an uneventful stay but did not take prophylaxis
- Returned 15Mar and on the 24th or so got fevers/chills and rigors
- Used OTCs 1 day, had syncope while at work
- Civ ER via EMS on the 26th. Labs sig only for platelets 60s and dx falciparum malaria by giemsa with 0.7% parasitemia
- Give him a script of oral quinine and doxy. He took doxy but was unable to fill oral quinine due to pharmacy availability (cost)
- On the 28th felt worse. Parasitemia now 0.5% and labs the same with platelet 46 main abnormal other than mild prerenal azotemia
- Response to malarone po first 24hr in ICU and d/c after 3rd day
- 14d of primaquine given due to overabundance of caution. Seen Monday and he was doing well



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Fighting 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 combinations treatment – saves lives**
 - **Improved diagnosis – use expensive drugs for those that need it**
 - **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” 51

QUESTIONS?

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