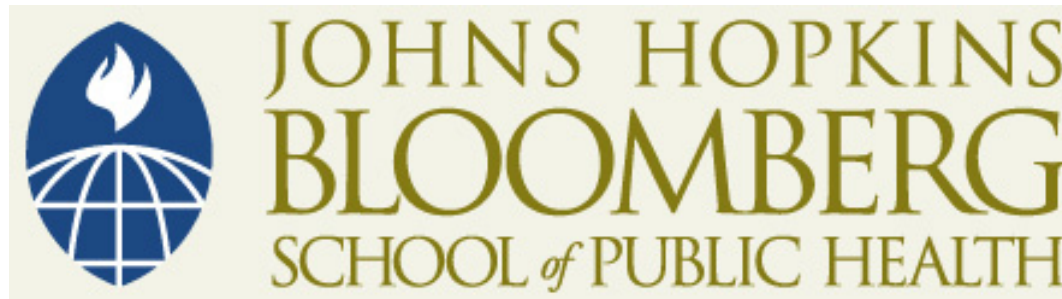


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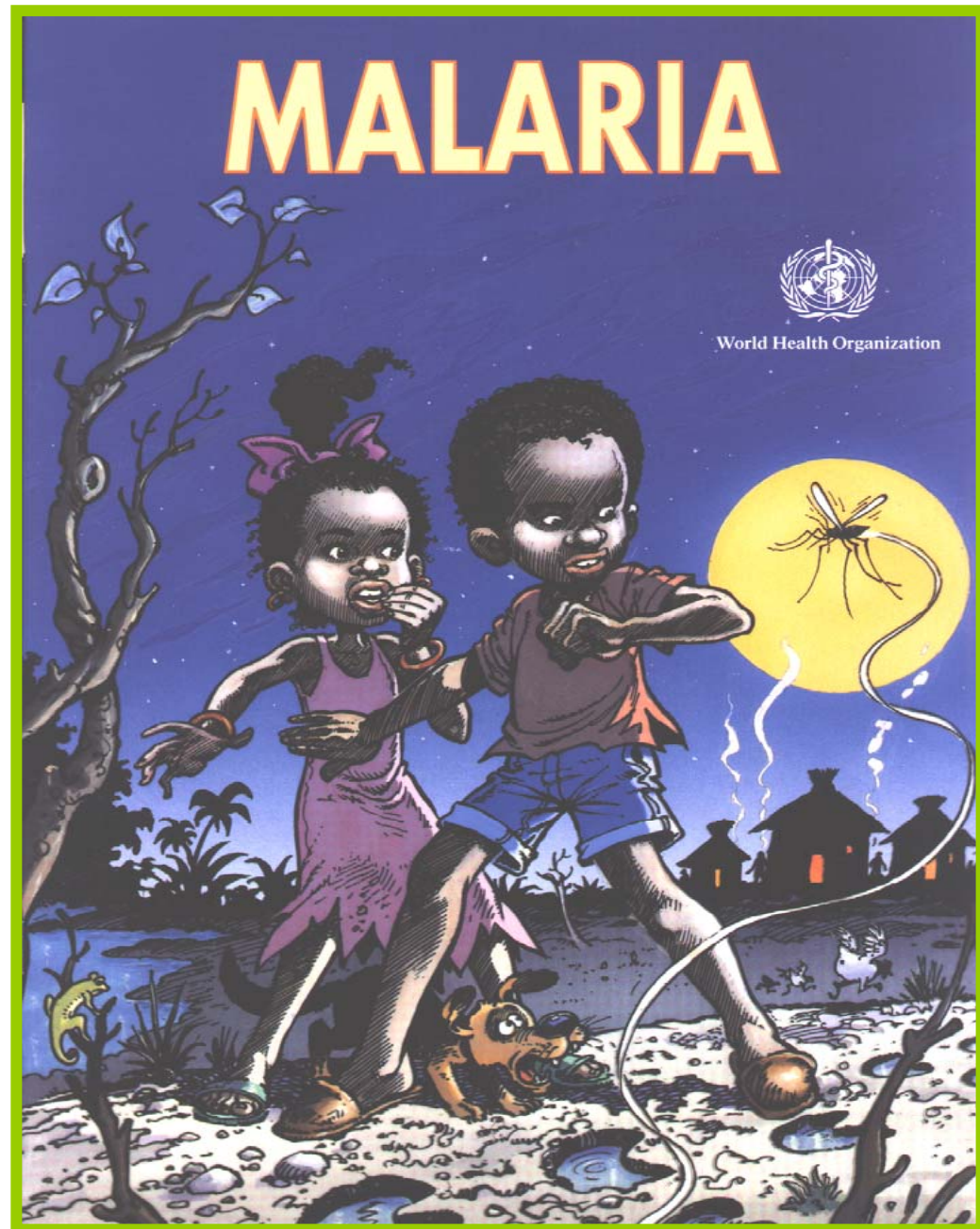


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# Malariology Overview

History, Lifecycle,  
Epidemiology, Pathology,  
and Control

David Sullivan, MD



# Malaria History

- 2700 BCE: The Nei Ching (Chinese Canon of Medicine) discussed malaria symptoms and the relationship between fevers and enlarged spleens.
- 1550 BCE: The Ebers Papyrus mentions fevers, rigors, splenomegaly, and oil from Balantines tree as mosquito repellent.
- 6th century BCE: Cuneiform tablets mention deadly malaria-like fevers affecting Mesopotamia.
- Hippocrates from studies in Egypt was first to make connection between nearness of stagnant bodies of water and occurrence of fevers in local population.
- Romans also associated marshes with fever and pioneered efforts to drain swamps.
- Italian: “aria cattiva” = bad air; “mal aria” = bad air.
- French: “paludisme” = rooted in swamp.

# Cure Before Etiology: Mid 17<sup>th</sup> Century - Three Theories

- PC Garnham relates that following: An earthquake caused destruction in Loxa in which many cinchona trees collapsed and fell into small lake or pond and water became very bitter as to be almost undrinkable. Yet an Indian so thirsty with a violent fever quenched his thirst with this cinchona bark contaminated water and was better in a day or two.
- Alternatively, Indians working in mountain mines drank cinchona tea to stop shivering.
- Subsequent story is administration of bark to Countess of Cinchon by Jesuits

# Malaria and Military

- Revolutionary War: US Congress bought cinchona bark from South America to treat soldiers with malaria.
- Civil War: 1,200,000 cases 8,000 deaths.
- WWI: Almost 5,000 cases with 7 deaths in US Navy and Marines; more than 100,000 cases in British and French soldiers.
- WWII: 500,000 cases in US Army; more than 110,000 cases with 90 deaths in US Navy and Marines.

"This will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease." - General Douglas MacArthur

# Malaria: The Trail of Pigment

- 1847: Meckel identified pigment in blood of insane person.
- 1848: Virchow pictured and described pigmented bodies in blood of malarial patient
- 1850: Hirsch connected presence of pigment and intermittent fever
- 1880: Laveran identified pigment in body of living parasite in 26 patients. He is credited with describing the etiologic agent of malaria.

- In the 1890's British scientist Patrick Manson theorized that mosquitoes may be involved in malaria transmission. Manson had recently found that mosquitoes could vector filarial worms that caused elephantiasis.
- Two Johns Hopkins medical students Opie and MacCallum who were the first to describe sexual reproduction of *Plasmodium* in birds and man.
- Manson to Ross, 3/22/1898: "Don't forget MacCallum's discovery of the flagellum impregnation of halteridium spheres ... I think I mentioned to you what I thought was the explanation, if MacCallum is right, of the mosquito pigmented cell."

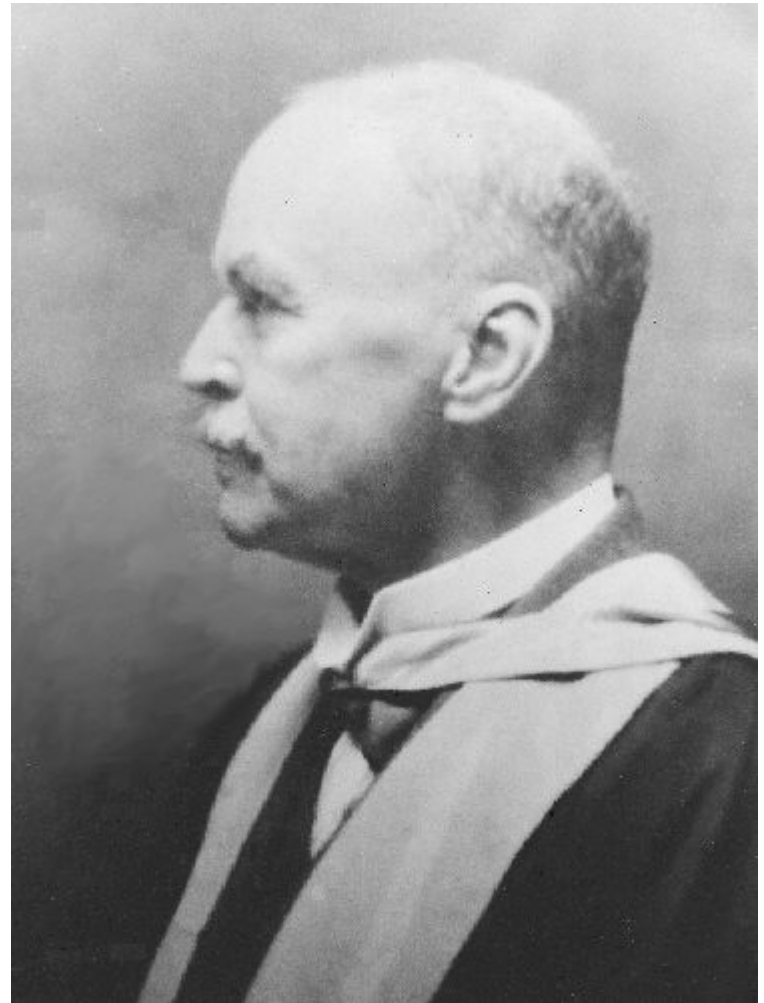
Ronald Ross comments on cells outside the stomach of the *Anopheles* mosquito:

"but what now arrested attention was the fact that each of these bodies contained a few granules of black pigment absolutely identical in appearance with the well-known and characteristic pigment of the parasite of malaria (large quartans and crescent-derived spheres)."

Ross, Ronald *British Medical Journal* 1:1786-1788 (1897)

Manson to Ross, 4/29/1898

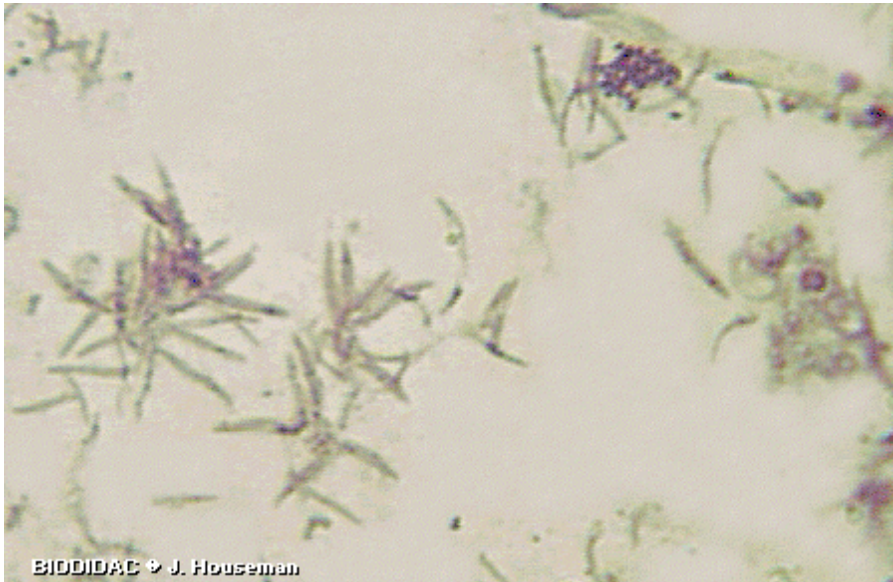
"It is a delight to watch how the thing is panning out. What a frightful shock it would have been to us had the Yanks done this."



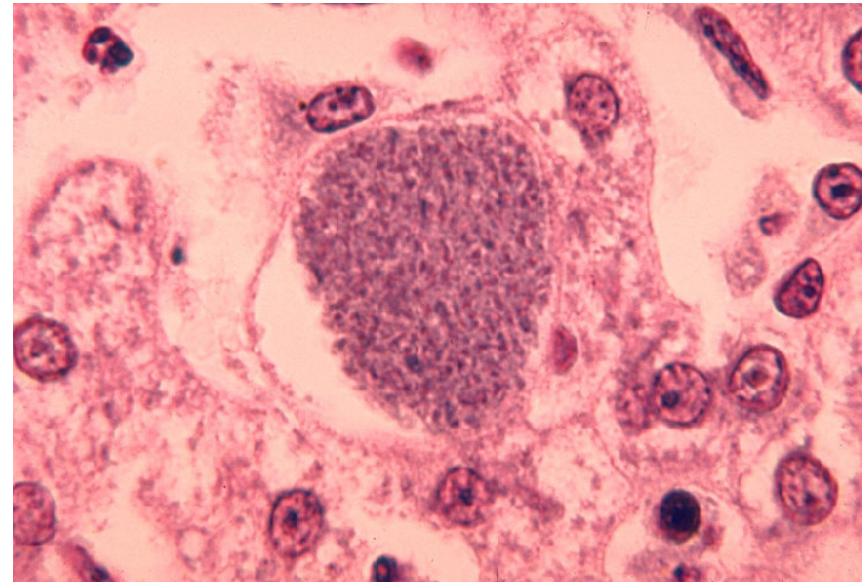
Source: CDC



# 1948: Shortt and Garnham Describe Exoerythrocytic Stages of Human Malaria Parasites

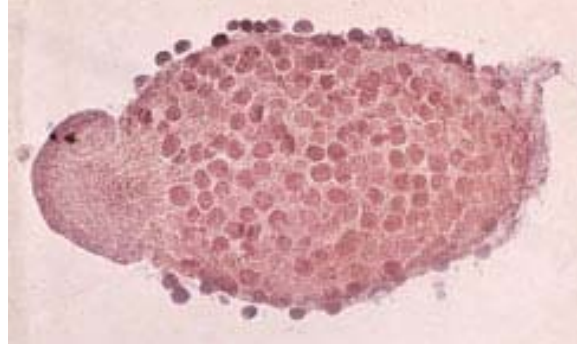


Malarial sporozoites in mosquito salivary gland smear.  
Source: BIODIDAC/J. Houseman



Histopathology of malaria exoerythrocytic forms in liver.  
Source: CDC

Definitive host  
mosquito

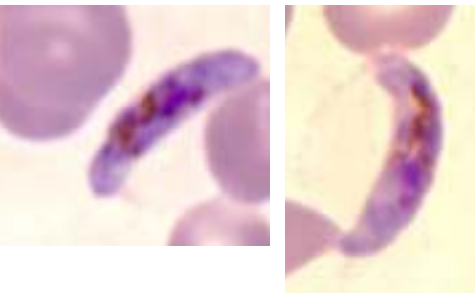


Oocysts on gut wal



28 days  
In mosquito

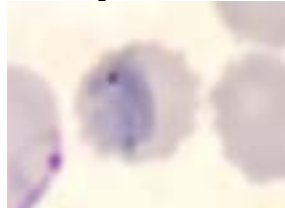
Ingests 3 ul of blood  
With **100-300** gametes



Gametocytes  
Viable for 28 days

# Plasmodium Life Cycle

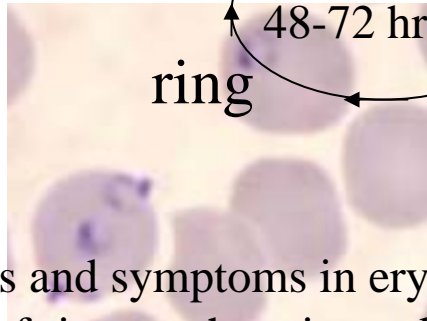
trophozoite



schizont

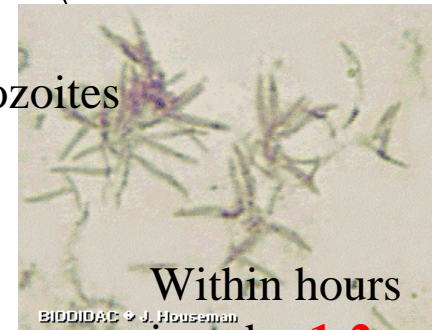


ring



48-72 hrs

**100's**  
Sporozoites



Within hours  
invades **1-2**

liver cells



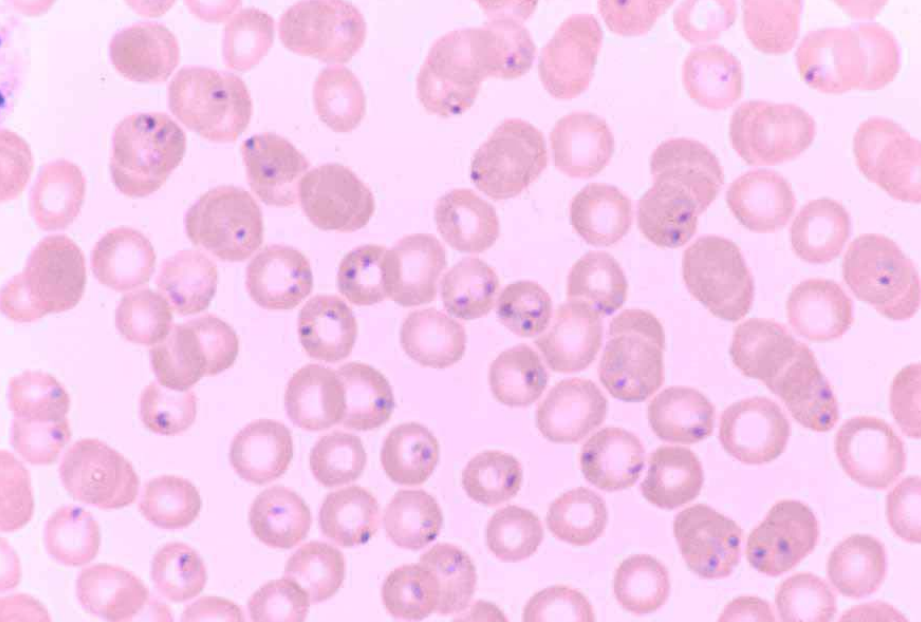
**1,000's**  
released

Merozoites in liver for seven to 10 days. *P. vivax* & ovale hypnozoite for Months.

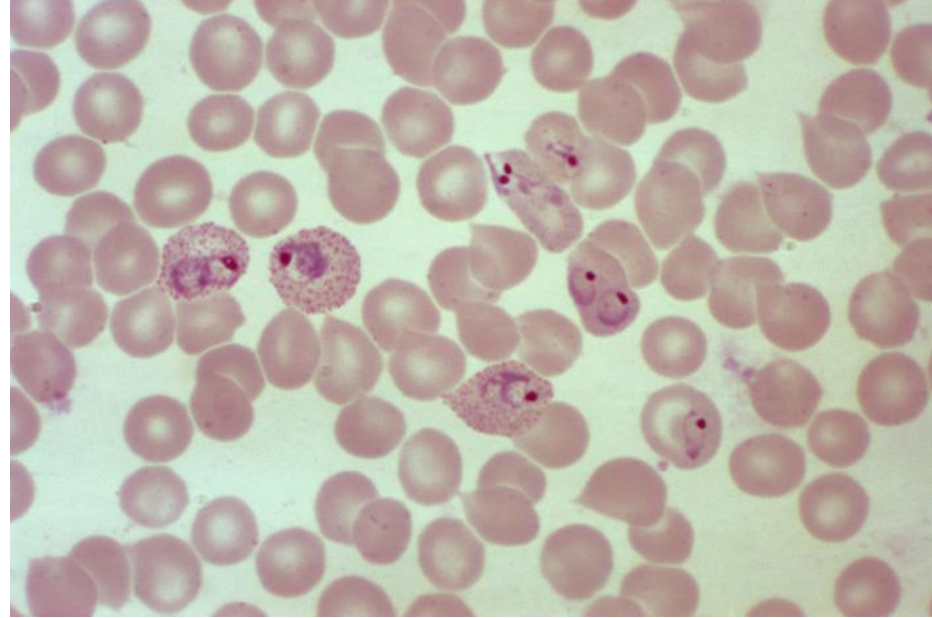
Clinical signs and symptoms in erythrocytic stages of ring, trophozoite and schizont

# Malaria Species

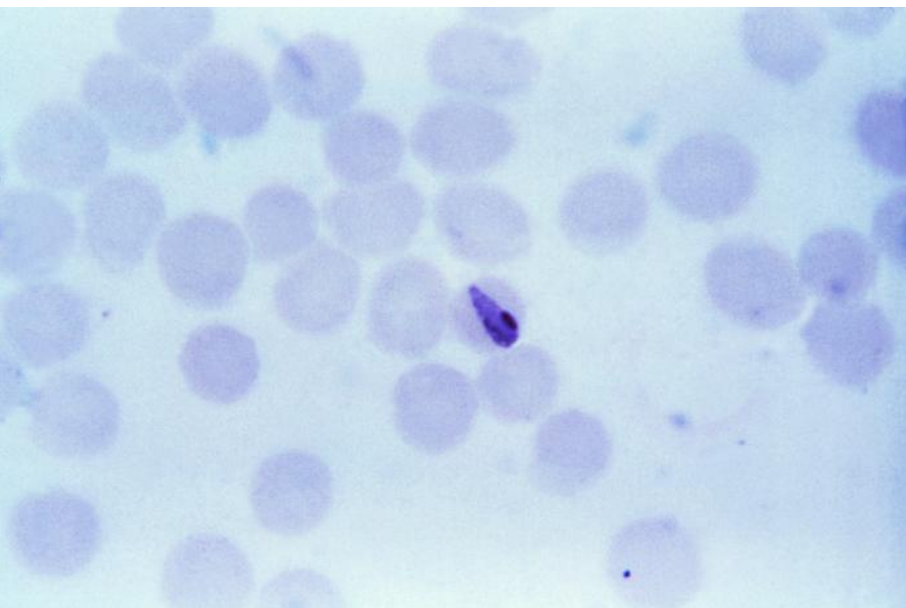
	<b>P. falciparum</b>	<b>P. vivax</b>	<b>P. ovale</b>	<b>P. malariae</b>
Hepatic Development Phase	5-6	8	9	15
Erythrocytic Cycle (days)	2	2	2	3
Hypnozoites (relapses)	No	Yes	Yes	No
Merozoites per schizont	30,000	10,000	15,000	2,000
RBC preference	All; prefers younger cells	Retics	Retics	Older RBCs



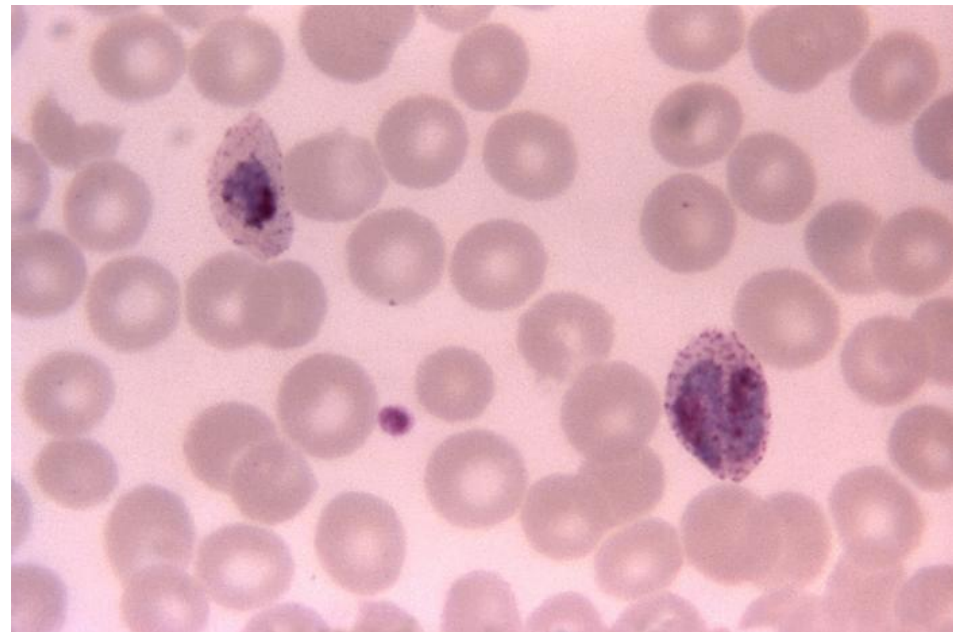
*Plasmodium falciparum*: High percent rings  
Source: Thomas Spahr and David Sullivan JHMRI



*Plasmodium vivax*: Enlarged erythrocytes  
Source: CDC/Dr. Mae Melvin



*Plasmodium malariae*: Band forms  
Source: CDC/ Steven Glenn, Lab & Consultation Division

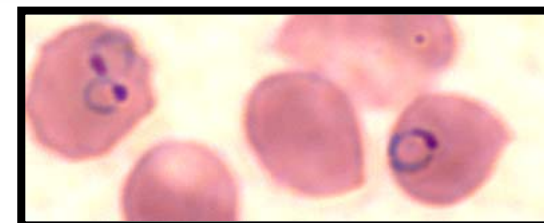
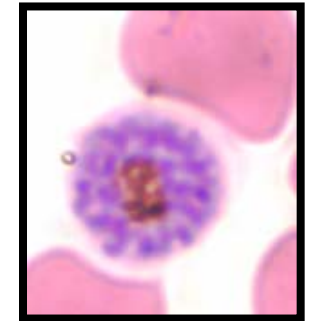
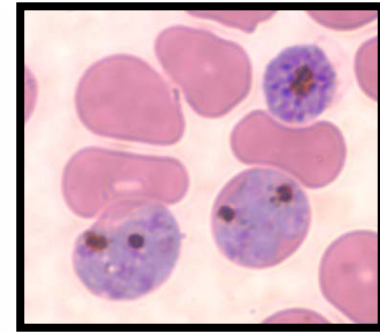
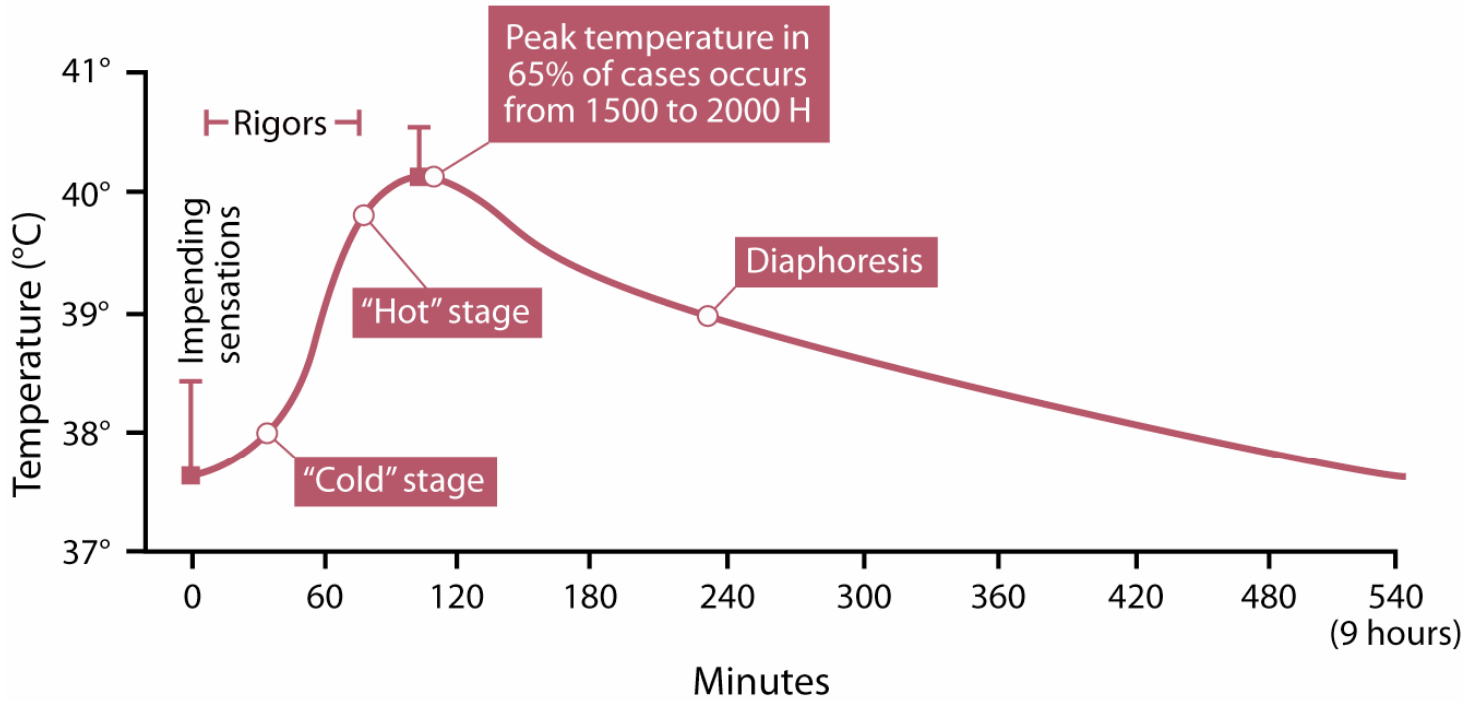


*Plasmodium ovale*: Oval or comet shape  
Source: CDC/Dr. Mae Melvin

# Classical Malaria: Hippocrates 5th Century BCE

- Fever
- Splenomegaly
- Anemia

# The Malaria Rigor



CTLT

Pyrogenic density is parasite density at time of fever.

*P. vivax* pyrogenic density is 100 parasites / $\mu$ l

*P. falciparum* pyrogenic density ranges from 0 to 10,000/ $\mu$ l in nonimmunes

Semi-immune can have up to 100,000 par/ $\mu$ l without fever

# Clinical Complications of Malaria

## ***P. falciparum***

1. Cerebral coma
2. Anemia
3. Pulmonary edema
4. Renal Failure
5. Shock
6. Lactic acidosis
7. Hypoglycemia
8. Tropical splenomegaly
9. Pregnancy
  - a. Maternal death
  - b. Stillbirth
  - c. Low birth weight
  - d. Anemia

## ***P. vivax (P. ovale)***

1. Splenic rupture
2. Anemia (mild)
3. Debilitating fevers
4. Higher TNF- $\alpha$  per parasite

## ***P. malariae***

1. Immune complex
2. Glomerulonephritis, leading to nephrotic syndrome

**Edema  
brought on  
by nephrosis  
associated  
with malaria.**



Source: CDC/Dr. Myron Schultz

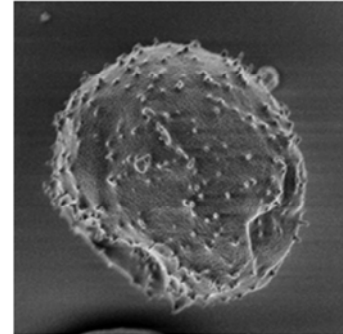


Why do we see predominately rings only in peripheral circulation with *P. falciparum*?

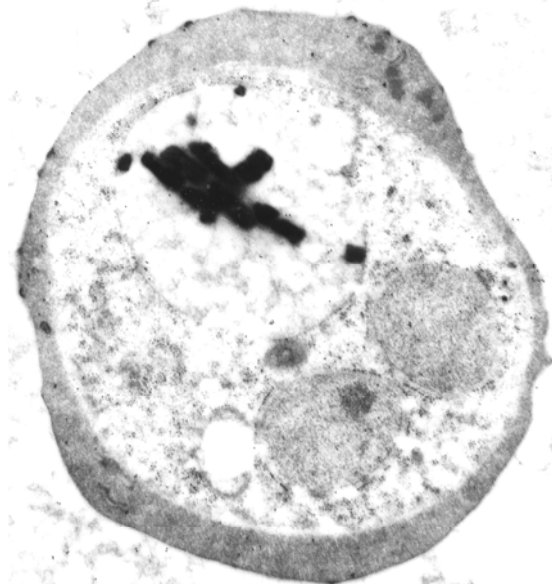
## *P. falciparum* Remodels Both Outside and Inside of Erythrocyte



Normal erythrocyte

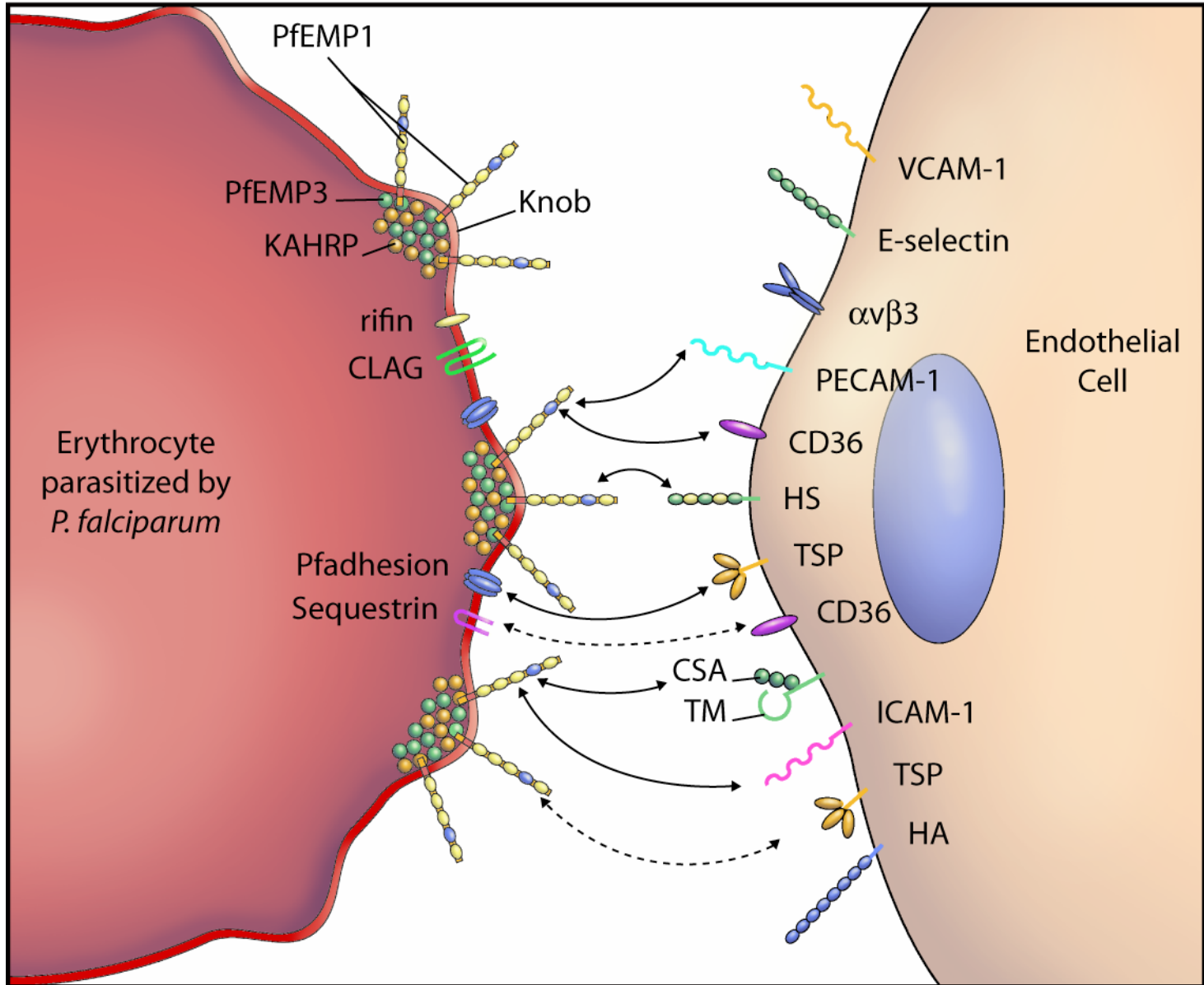


Infected erythrocyte



Infected erythrocyte

# *P. falciparum* Cytoadherence



# Placental Malaria

## Unstable epidemiology

Maternal death, abortion, stillbirth, premature delivery, low birthweight

## Stable (Holoendemic) epidemiology

Clinical symptoms and parasitemia is higher in primigravida  
Low birthweight

## Non-immunes

Higher mortality

Progressive anemia

Quinine induced hypoglycemia

# The Numbers

- 70 kg person X @70 ml / kg = 4.9 liters of blood @ 5 liters =  $5 \times 10^3$  ml =  $5 \times 10^6$   $\mu$ l
- $5 \times 10^6$  RBCs per  $\mu$ l of blood
- $2.5 \times 10^{13}$  RBCs
- 1% parasitemia (50,000 ul)= 1 in 100 iRBCs =  $2.5 \times 10^{11}$  parasites per person
- A million people each day have this symptomatic burden =  $2.5 \times 10^{17 \pm 1}$  total parasites in world

# Recrudescence & Relapse

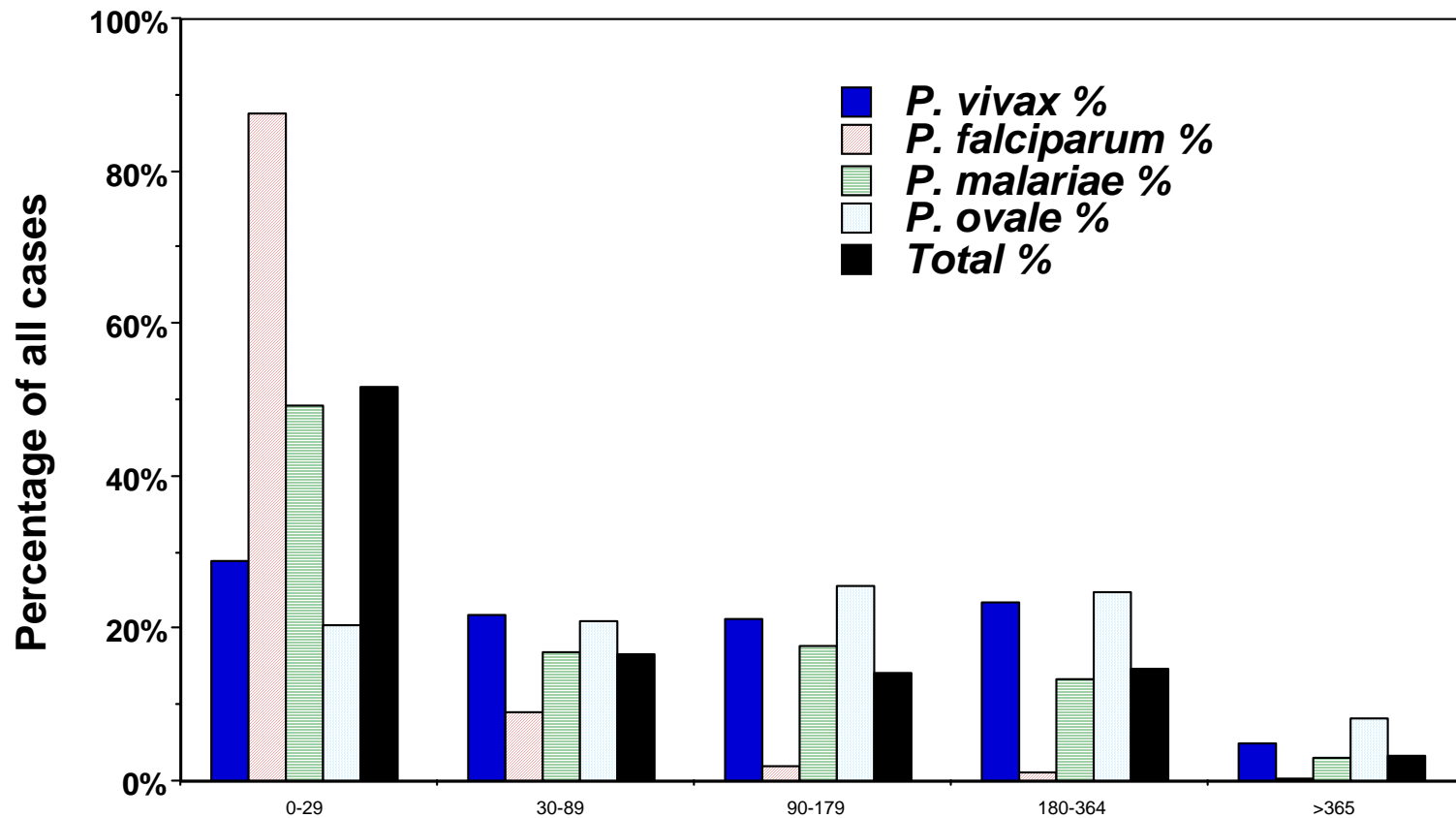
## Recrudescence

Renewed manifestation of infection due to survival of erythrocytic forms

## Relapse

Renewed manifestation of infection arising from survival of exoerythrocytic forms (hypnozoites)

*P. vivax* or *P. ovale* only

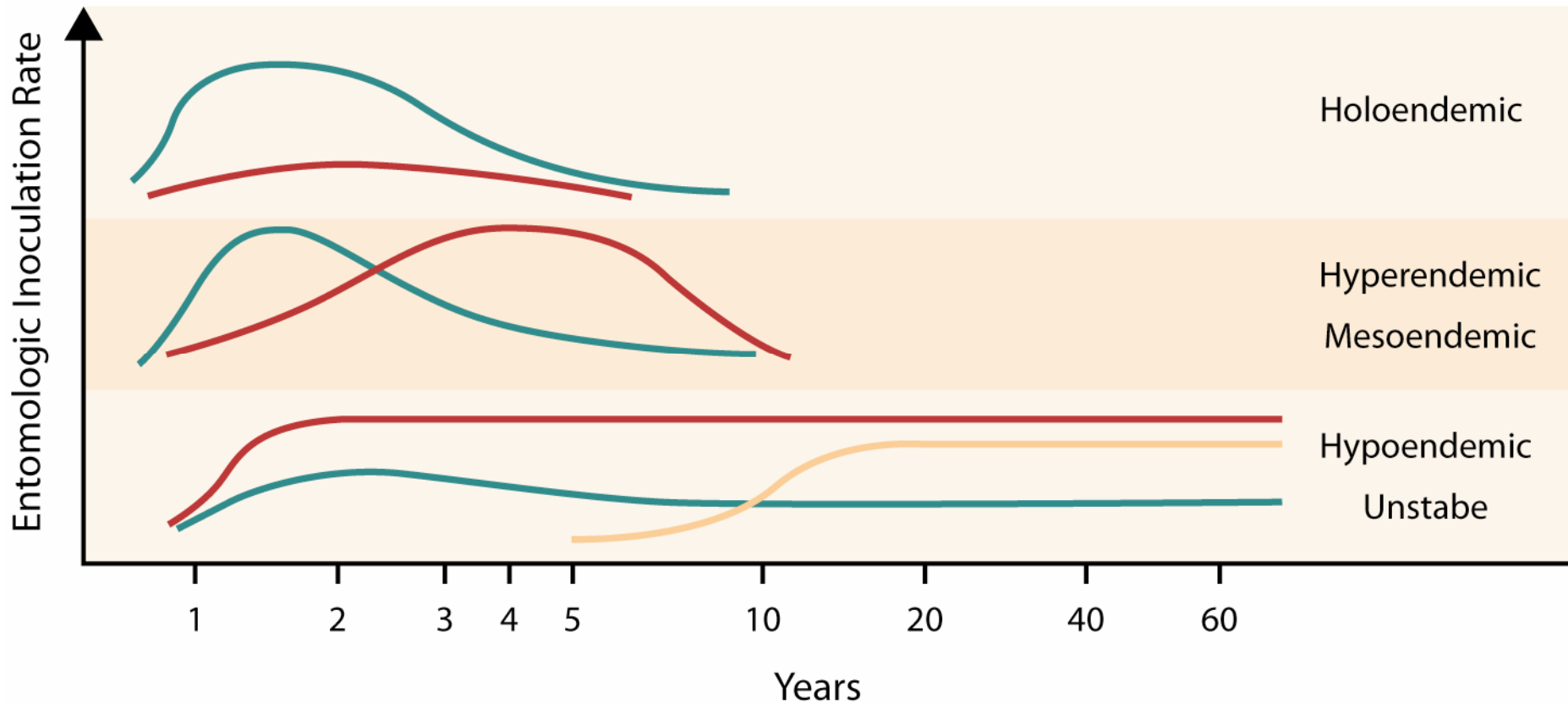


**Days to Onset of Illness for all US cases in 4 yrs**

Interval (days)	<i>P. vivax</i>	<i>P. falciparum</i>	<i>P. malariae</i>	<i>P. ovale</i>	Total
0-29	750	<b><u>1,542</u></b>	103	27	<b><u>2422</u></b>
30-89	562	157	35	28	782
90-179	554	35	37	34	660
180-364	605	21	28	33	687
>365	<b><u>127</u></b>	7	6	11	151
Total	2598	1762	209	133	4702

- 100 countries in malaria endemic areas.
- half in sub-Saharan Africa.
- 2.4 billion at risk.
- 300 to 500 million cases each year.
- 1.0 to 2.7 million deaths in children.
- Malaria constitutes 25% of child mortality in Africa.
- 90% of all malaria mortality is in under children under 5.
- Low birth weight, preterm delivery, cerebral malaria, and severe malarial anemia are major causes of mortality.
- Sequelae from severe clinical complications include cognitive impairment, behavioral disturbances, spasticity, and epilepsy as well as vision, hearing, and speech impairments.

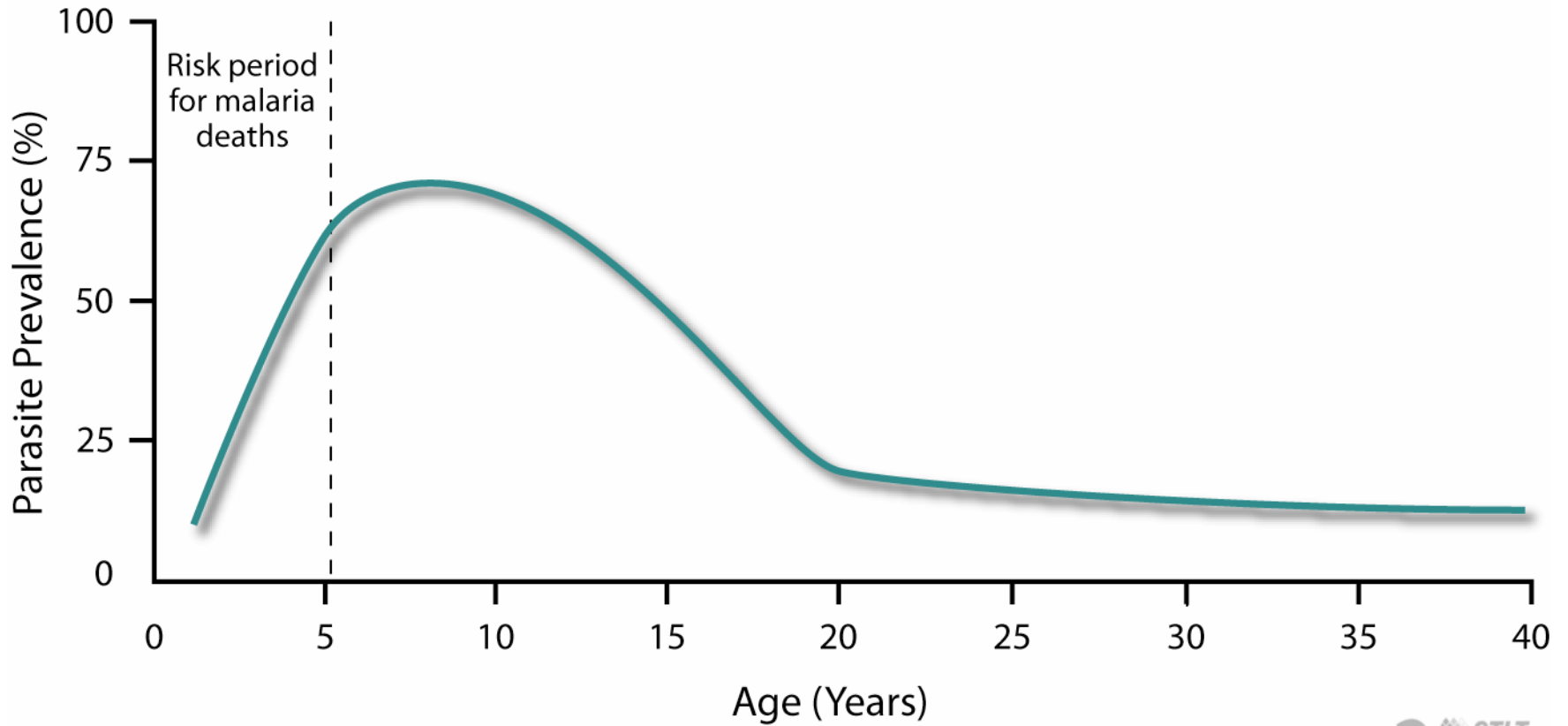
# Relationship Between Age and Clinical Presentations of Severe Falciparum Malaria at Different Levels of Malaria Transmission



- Severe anemia
- Cerebral malaria
- Renal failure



## Age and Death Rates in Hyperendemic or Holoendemic Area



# Parasite Control

1. Vector control & Sanitation

2. Vaccines?

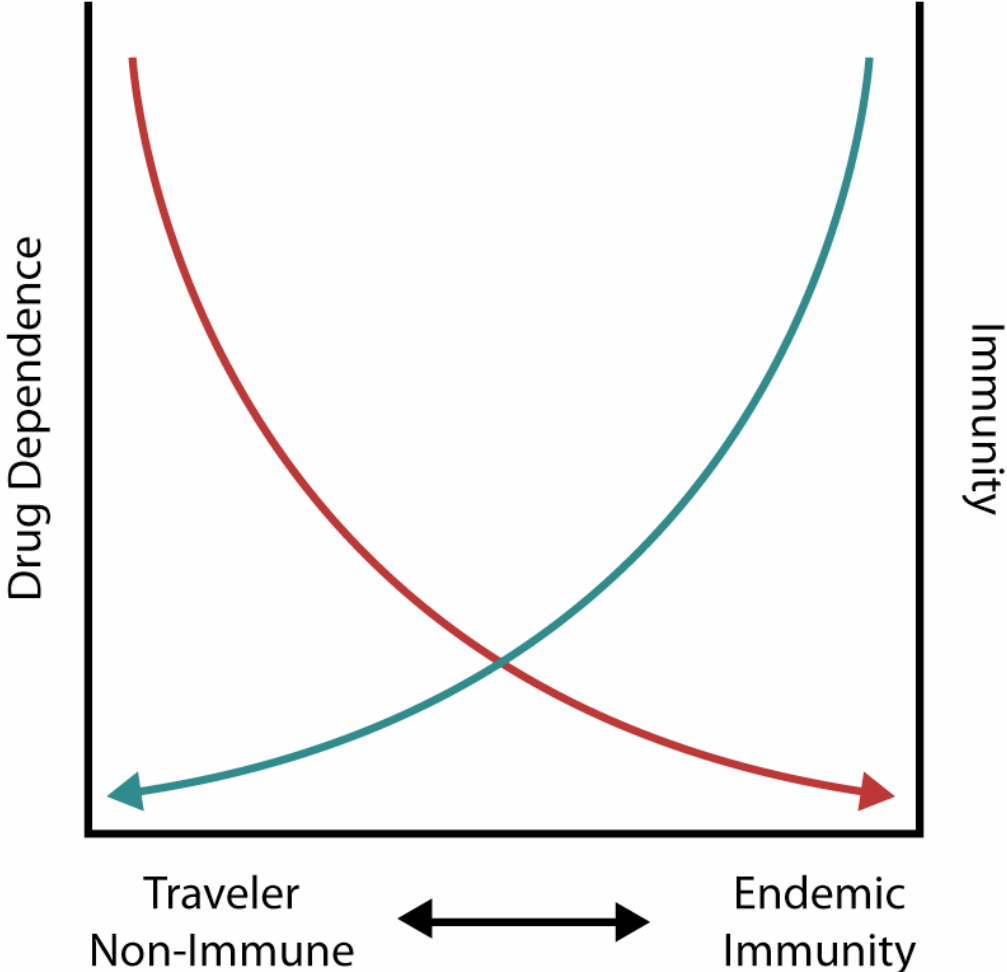
3. Chemotherapy

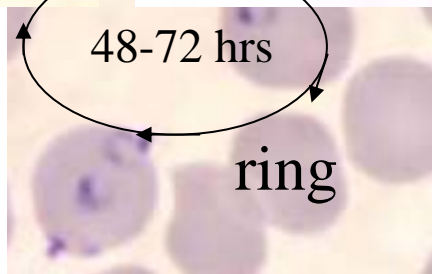
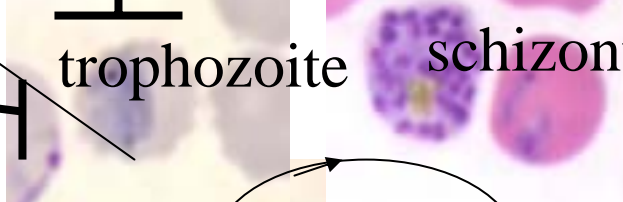
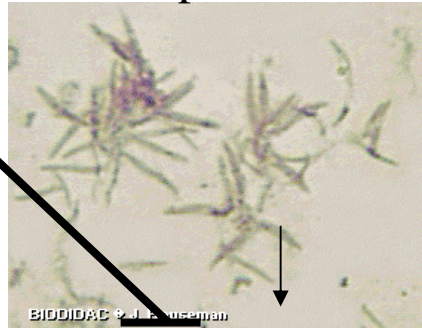
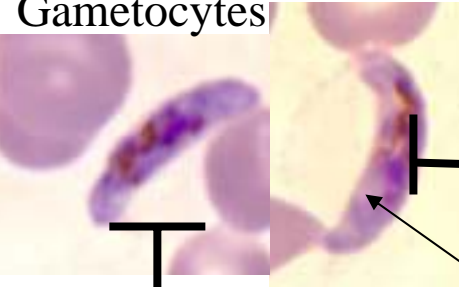
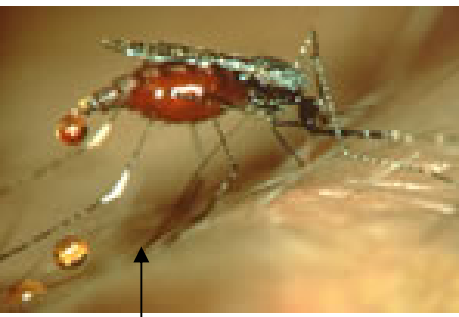
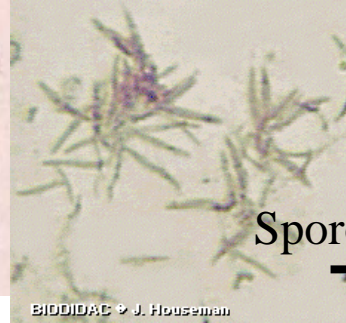
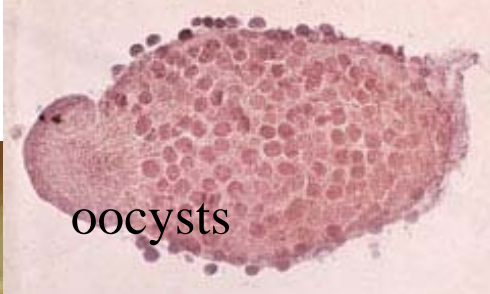
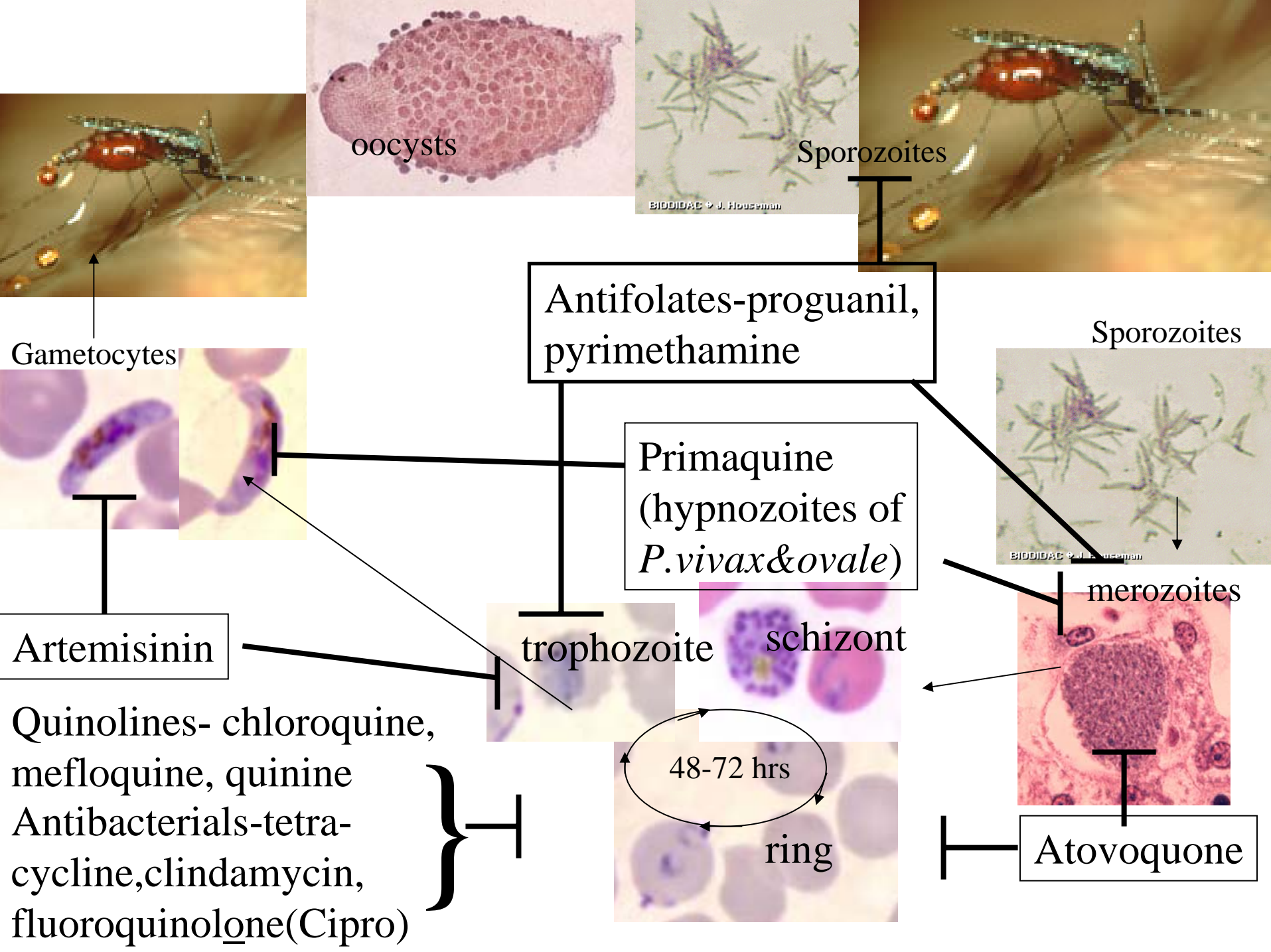
Protective (prophylaxis)

Curative

Prevention of transmission

# Drug Dependence is Related to Immune Status





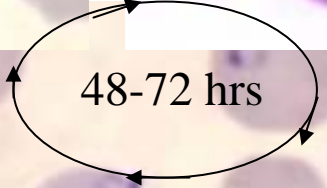
**Artemisinin**

**Antifolates-proguanil, pyrimethamine**

**Primaquine (hypnozoites of *P. vivax* & *ovale*)**

**Quinolines- chloroquine, mefloquine, quinine**  
**Antibacterials- tetracycline, clindamycin, fluoroquinolone (Cipro)**

**Atovoquone**



# INNATE RESISTANCE TO MALARIA

Red Cell Polymorphism and Malaria: Polymorphic alternative versions of the same gene coexist in a population at frequencies well above that explained by repeated occurrence of the mutation that produces the variant.

## The Malaria Hypothesis

Geographical distribution of red cell polymorphisms due to selective effect of malaria on heterozygote.

Conditions with reasonable evidence to support the malaria hypothesis are: Sickle cell trait and disease, thalassemia's, glucose-6-phosphate dehydrogenase deficiency and, Duffy blood group and hereditary ovalocytosis.

# Hemoglobin Variants

Hemoglobin S: valine for glutamic acid at AA 6 in beta chain

Hemoglobin C: lysine for glutamic acid at AA 6 in beta chain

Hemoglobin E: lysine for glutamic acid at AA 26 in beta chain

**"Stimulate the Phagocytes. Drugs are a Delusion."**

GB Shaw, *The Doctor's Dilemma* 1906

**"I myself have been infected with malaria only once in spite of nineteen years' of service in India and thirteen subsequent 'malaria expeditions' to warm climates; and I attribute this to my scrupulous use of the bed net."**

Ronald Ross *Studies on Malaria* 1928.

**"We must learn to shoot microbes with magic bullets."**

Paul Ehrlich in *Microbe Hunters* Paul de Kruif 1926

# Summary

- How often the mosquito bites influences disease severity.
- Fever corresponds with rupture from erythrocyte.
- In lethal *P. falciparum* rings predominate in circulation because older forms are adhering to tissue capillary beds to cause hypoxia and end organ damage.
- *P. falciparum* malaria is a medical emergency in the nonimmune patient.
- Human genetic polymorphisms such as sickle cell disease, thalassemia's, glucose 6 phosphate deficiency, and lack of Duffy factor protect from severe disease but not infection.
- *P. vivax* and *ovale* can relapse from liver after effective erythrocyte treatment. Primaquine specifically treats this liver stage.
- *P. falciparum* resistance refers to recrudescence where red blood cell parasites decrease in number before rising again.
- Most current antimalarials do not effect gametocytes, which translates to infectivity to the mosquito



# Johns Hopkins University Malaria Firsts

- Under Osler's direction, Johns Hopkins Hospital was the first in the world to perform routine malaria blood film analysis on all febrile patients in 1889.
- Two medical students, Opie and MacCallum, were the first to describe sexual reproduction of *Plasmodium* in birds and humans.
- In 1897, Welch actually coined the species name of *falciparum* in contrast to the proposed "falciforme" for the lethal Aestivo-Autumnal fever.
- The WWII wartime Survey of Antimalarial Drugs centered at Johns Hopkins solidly identified SN-7618 (SN = Survey Number) or chloroquine as the drug of choice for malaria. Dr. EK Marshall at Johns Hopkins actually coined the name chloroquine in Nov 1945.

# Resources

- CDC Malaria Hotline Number
  - 404-332-4555 (24 hrs a day)
- CDC guidelines for malaria
  - <http://www.cdc.gov/travel/malinfo.htm>
- CDC guidelines for travel with outbreak information
  - <http://www.cdc.gov/travel/travel.html>
- Online blood film knowledge testing
  - <http://www.rph.wa.gov.au/labs/haem/malaria/index.html>  
(This web site is presented by the Division of Laboratory Medicine at Royal Perth Hospital)
- Nick White. The Treatment of Malaria. *N Engl J Med* 1996;335:800-806
- Djimde et al. A Molecular Marker for Chloroquine-Resistant Falciparum Malaria. *N Engl J Med* 2001;344:257-63