

Announcements

- Register for the Epi-Tech Trainings:
 1. Log-on or Request log-on ID/password: <https://tiny.army.mil/r/zB8A/CME>
 2. Register for Epi-Tech Surveillance Training: <https://tiny.army.mil/r/LEAid/EpiTechFY15>
- Please enter your name/service and e-mail into the chat box to the left or email the disease epidemiology program at: usarmy.apg.medcom-phc.mbx.disease-epidemiologyprogram13@mail.mil
 - You will receive a confirmation email within the next 48 hours with your attendance record
- Please mute your phones and DO NOT place us on hold. Press *6 to mute/unmute your phone.

Malaria

By

CPT Susan N Gosine



“If you think you are too small to make a difference, try spending the night with a mosquito” Dalai Lama

Malaria -- Learning Objectives

- Describe the lifecycle the Plasmodium spp.
- Distinguish between the different Plasmodium spp.
- Describe vector as well as signs and symptoms of Malaria.
- Differentiate between Malaria and other tropical diseases with similar signs and symptoms.
- Determine and recommended chemoprophylaxis and treatment protocols.

Malaria – Table of Contents

- History and Overview
- Epidemiology
- Pathogenesis and clinical presentation
- Differential diagnosis
- Treatment and prophylaxis
- Future challenges
- Summary (**Prevent Malaria**... think prophylaxis
Treat think disease
Prevent recrudescence)

History of Malaria

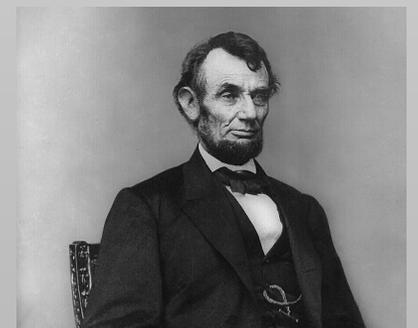
(Italian, mal'aria, "Bad air")

- 2700 BC: First described by the Chinese.
- Responsible for the decline of many Roman city states
- 400 BC: Hippocrates notes the various fevers of man, distinguishing the intermittent malarial fever from the continuous fever of other infectious diseases.
- 500 BC (?): The Sushruta/Susruta: First medical treatise to describe malarial fever and attribute it to the bites of certain insects.
- 340 CE: Artemisinins (sp**) from the Qinghao plant is used by the Chinese to treat malaria.
- 1880: French army doctor described the malaria parasite
- 1897-1898: Mosquitoes are shown to be the vectors of malaria



Historical Notables who succumbed to Malaria

- Alexander the Great is believed to have died of malaria in 323 BC
- Genghis Khan, is believed to have suffered from a malaria like illness in the spring of 1227.
- Dante, Italian poet died of malaria 1321.
- Christopher Columbus
- Roman Emperor Charles V supposedly died of malaria in 1558
- George Washington, (1st President, 1789-1797): Developed his first bout with malaria in Virginia in 1749 at age 17, periodic attacks, recorded in 1752, 1761, 1784, and 1798.
- Abraham Lincoln (16th President, 1861-1865) In youth had periodic bouts of malaria
- Theodore Roosevelt (26th President, 1901-1909) acquired malaria during a visit to Brazil in 1914
- John F. Kennedy (35th President, 1961-1963) acquired malaria during World War II, about 1943
- Mother Theresa, while visiting Delhi in 1993

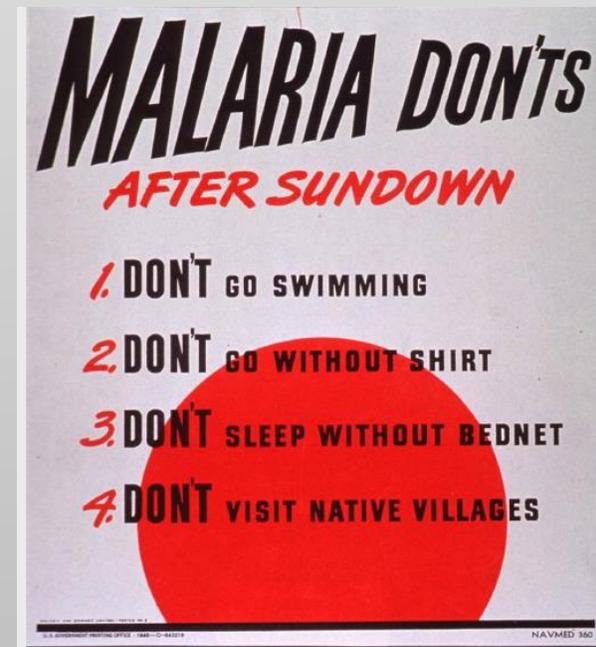
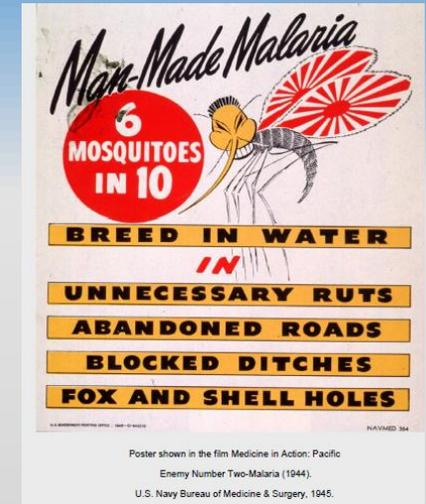


US Military History of Malaria

(<http://history.amedd.army.mil/booksdocs/wwii/Malaria/chapter1.htm>)

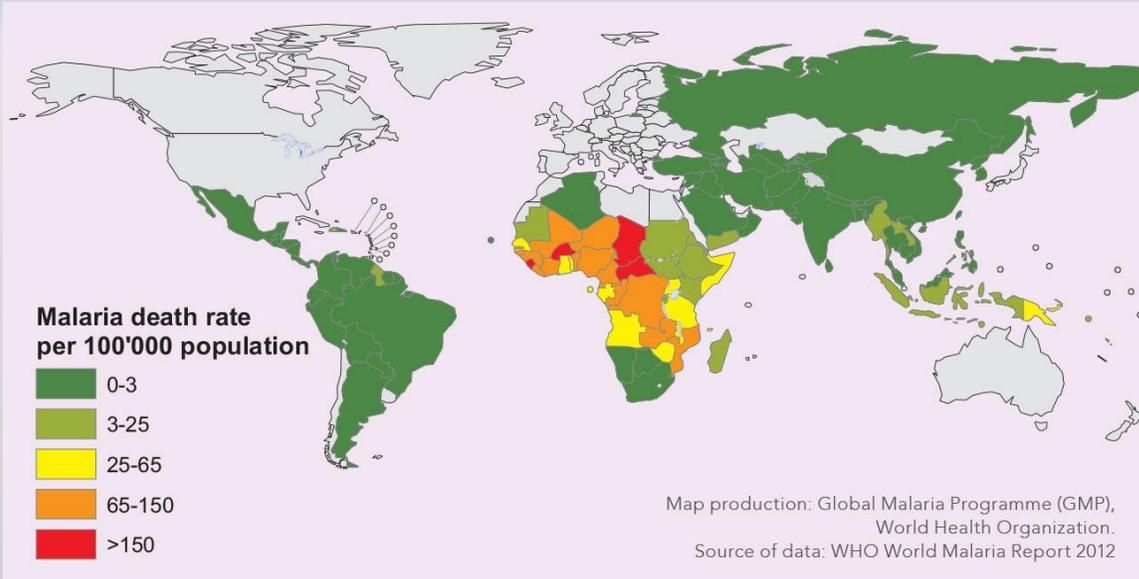
- American civil war (1861-1865) malaria accounted for about 10,000 deaths. It is estimated that 50% of the white soldiers and 80% of the non-white soldiers were sickened with malaria annually.
- During WWI and WWII one of the biggest causes of DNBI was Malaria . *“This will be a long war if for every 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. 60,000 U.S. troops died in Africa and the South Pacific from malaria.
- Korean War (1950–1953): U.S. military hospitals saw as many as 629 cases per week. More than 3,000 cases of malaria were documented in U.S. troops during this time.
- Vietnam War (1962–1975): Malaria felled more combatants during the war than bullets. Over 40,000 cases of Malaria were reported in US Army between 1965-1975. The U.S. Army establishes a malaria drug research program to combat Malaria in deployed US troops.
- In 1967, Project 523 – a secret military project – begins the research that would discover artemisinin.
- Operation Restore Hope (1992–1994): Malaria was the No. 1 cause of casualties among US troops.
- Malaria in Afghanistan, Iraq, and Liberia/Africa: Malaria is still a cause for concern when deployed to these countries. (<http://www.malariasite.com/wars-victims/>)
- 2015: *“Army officials say three troops contracted malaria in Liberia between October and November (2014) and two more were suspected of having a malaria infection.”*
(<http://www.militarytimes.com/story/military/benefits/health-care/2015/04/23/us-military-ebola-deployment-malaria/26236769/>)

<http://www.npr.org/2011/09/01/139641878/at-walter-reed-military-medicine-fights-malaria>



<http://flashbak.com/japs-japes-and-dr-seus-us-anti-malaria-warning-posters-from-world-war-2-36536/>

Overview



- 3.2 billion people are at risk of malaria.
- In 2013, there were about 198 million malaria cases
- Estimated 584 000 malaria deaths (prevention and control measures have led to a reduction in malaria mortality rates by 47% globally since 2000 and by 54% in the WHO African Region.)

*WHO Malaria facts <http://www.who.int/features/factfiles/malaria/en/>

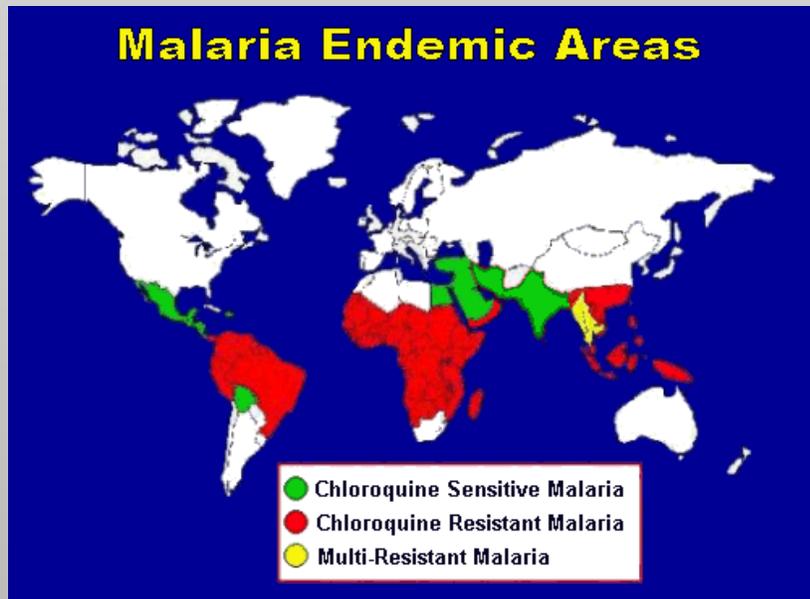
People living in the poorest countries are the most vulnerable to malaria. In 2013, 90% of all malaria deaths (525,600) occurred in the WHO African Region, mostly among children under 5 years of age.

(There are 525,600 minutes in a year)

Malaria is usually restricted to tropical and subtropical areas and altitudes below 1,500 m

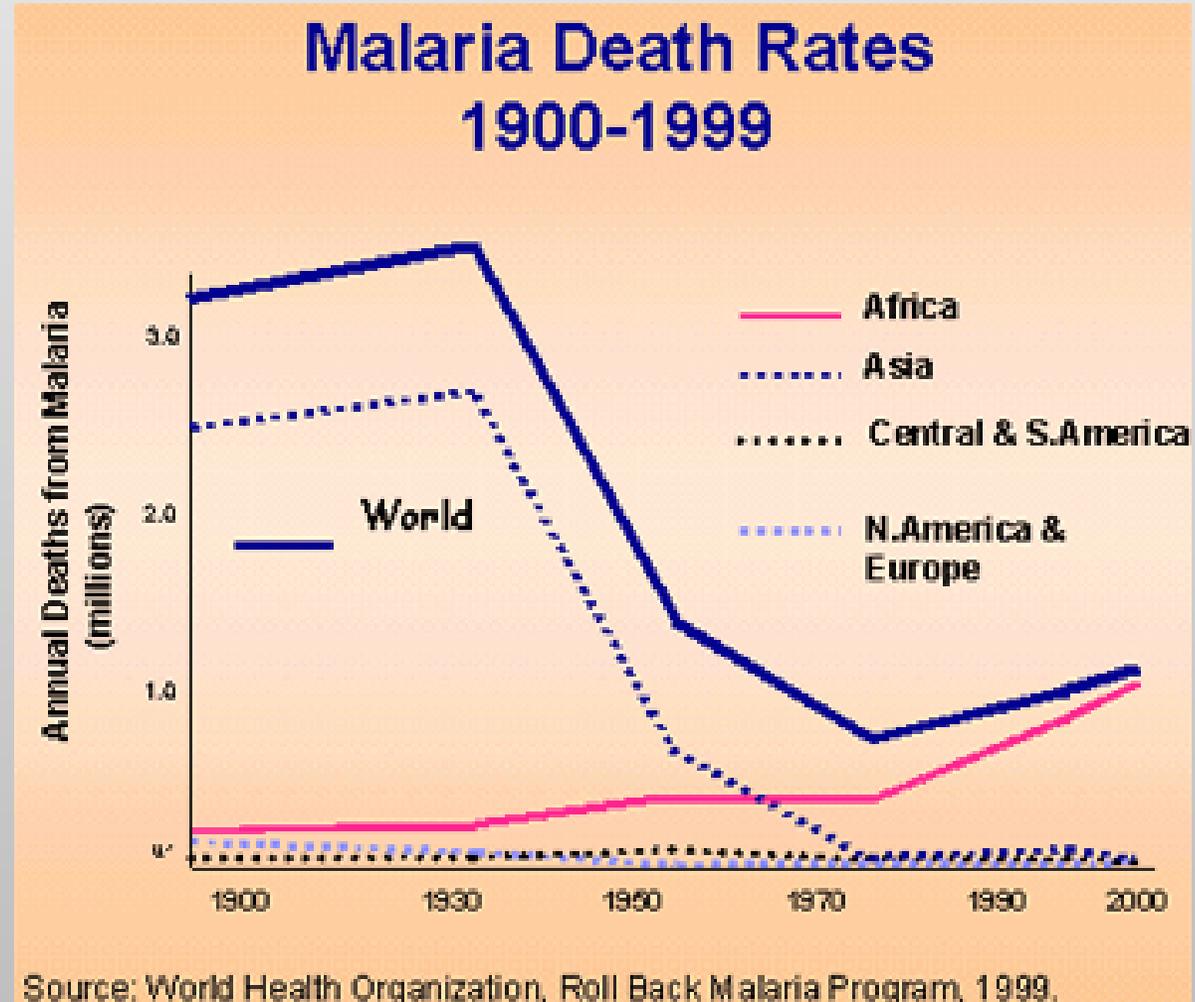
Malaria is an increasing problem due to (re-emerging disease)

- resurgence in some areas
- drug resistance (↑ mortality)



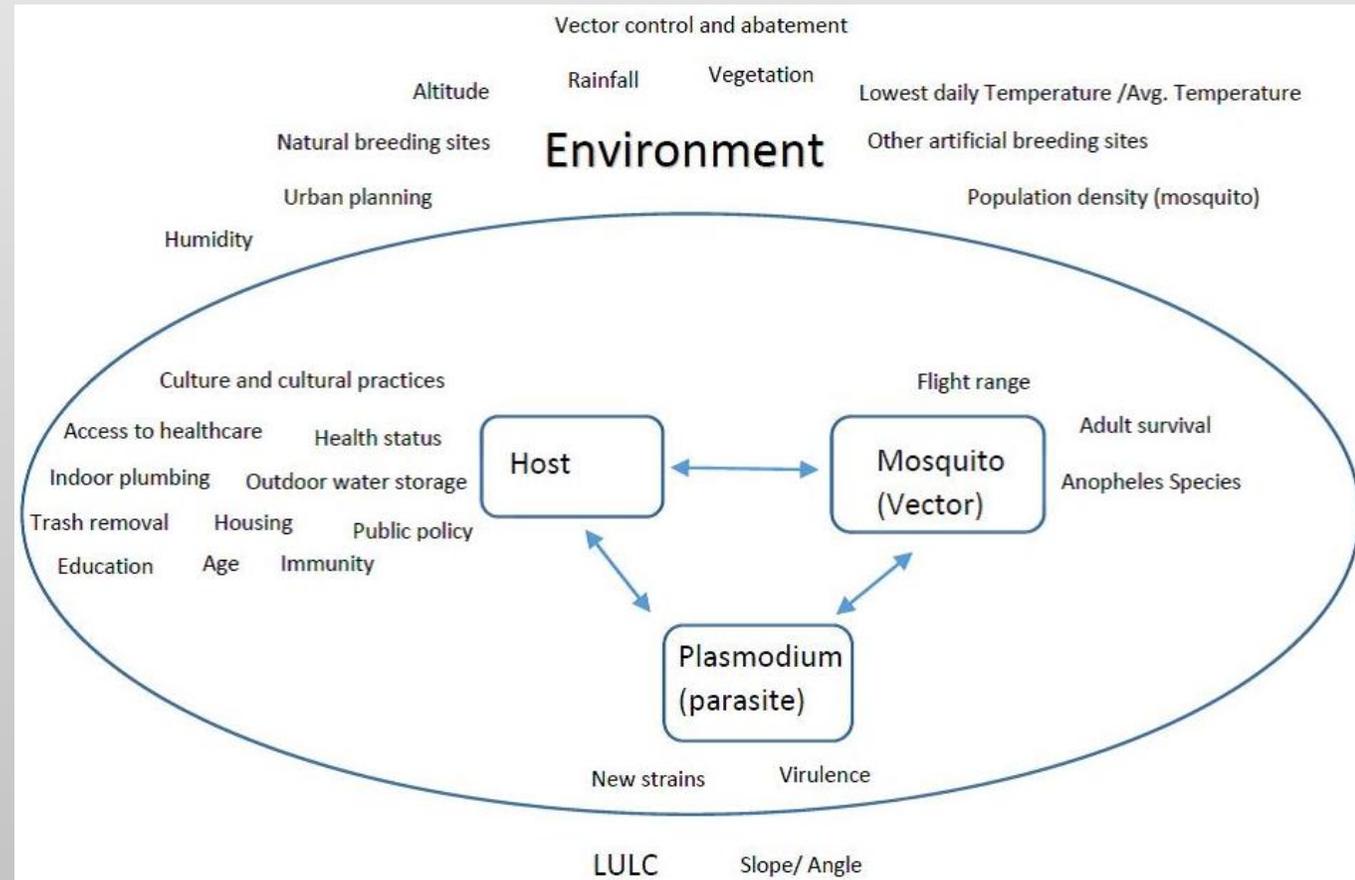
Malaria Trends

Whilst most of the world is reducing deaths due to Malaria, the malaria death rates in Africa continues to rise ☹.



Malaria and the Infectious Disease Triangle

- Need **host, pathogen/parasite & vector** to produce disease
- Multiple **external/environmental** factors can influence this cycle
 - Reservoir
 - Abiotic conditions (temp, rain)
 - Culture & behavior

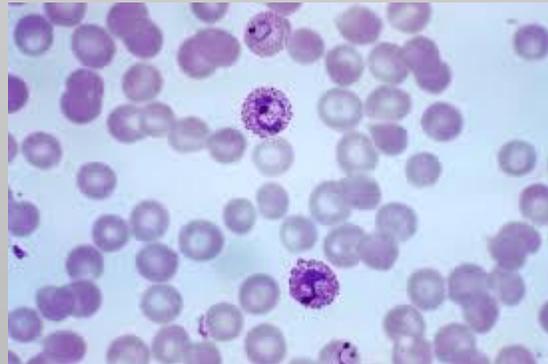
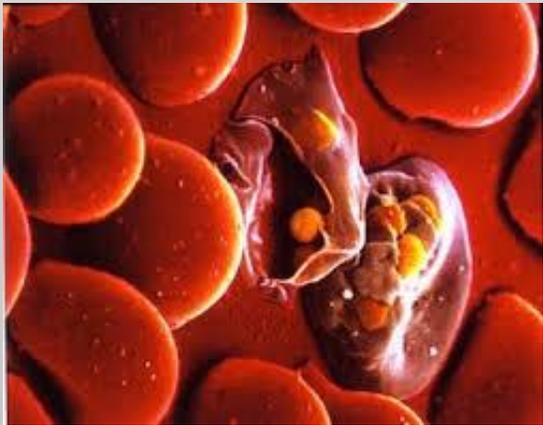


Vector and Causative Agent

- transmitted by Anopheline mosquitoes
- causative agent (**parasite** ☹)

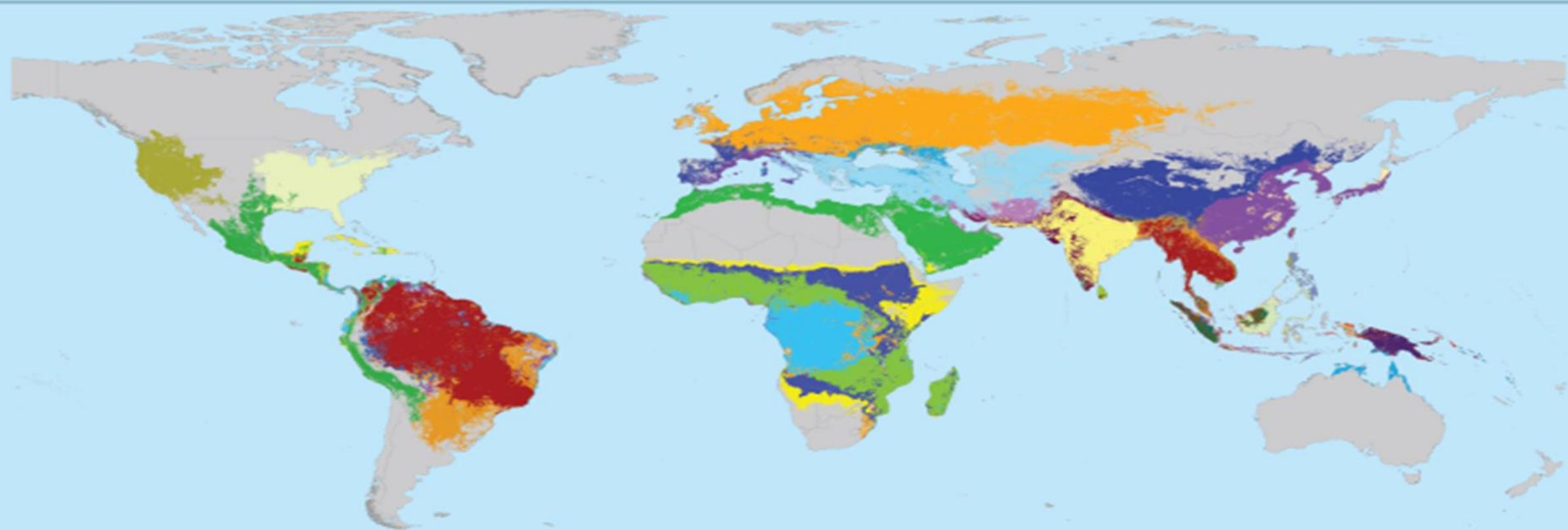
Plasmodium species

- protozoan parasite
- member of Apicomplexa
- 4 species infecting humans



- *P. falciparum*
- *P. vivax*
- *P. malariae*
- *P. ovale*

A global map of dominant malaria vector species



The Americas

- *An. darlingi*
- *An. equasalis*
- *An. albivittatus s.l.*
- *An. marajoara*
- *An. nuneztovari s.l.*
- *An. pseudopunctipennis*
- *An. albimanus*
- *An. quadrimaculatus s.l.*
- *An. freeborni*

Euro. & M.East

- *An. superpictus*
- *An. sergentii*
- *An. sacharovi*
- *An. messeae*
- *An. labranchiae*
- *An. atroparvus*

Africa

- *An. arabiensis;*
An. funestus;
An. gambiae
- *An. arabiensis;*
An. funestus
- *An. funestus;*
An. gambiae
- *An. gambiae*
- *An. funestus*
- *An. arabiensis*

India/Western Asia

- *An. culicifacies s.l.;*
An. stephensi;
An. fluviatilis s.l.
- *An. fluviatilis s.l.*
- *An. stephensi*
- *An. culicifacies s.l.*

South-East Asia & Pacific

- *An. farauti s.l.;*
An. kolensis;
An. punctulatus s.l.
- *An. dirus s.l.;*
An. minimus s.l.
- *An. lesteri; An. sinensis*
- *An. balabacensis*
- *An. barbirostris s.l.*
- *An. dirus s.l.*
- *An. farauti s.l.*
- *An. flavirostris*
- *An. kolensis*
- *An. lesteri*
- *An. leucosphyrus/fatens*
- *An. maculatus*
- *An. minimus s.l.*
- *An. punctulatus s.l.*
- *An. sinensis*
- *An. sundaicus s.l.*

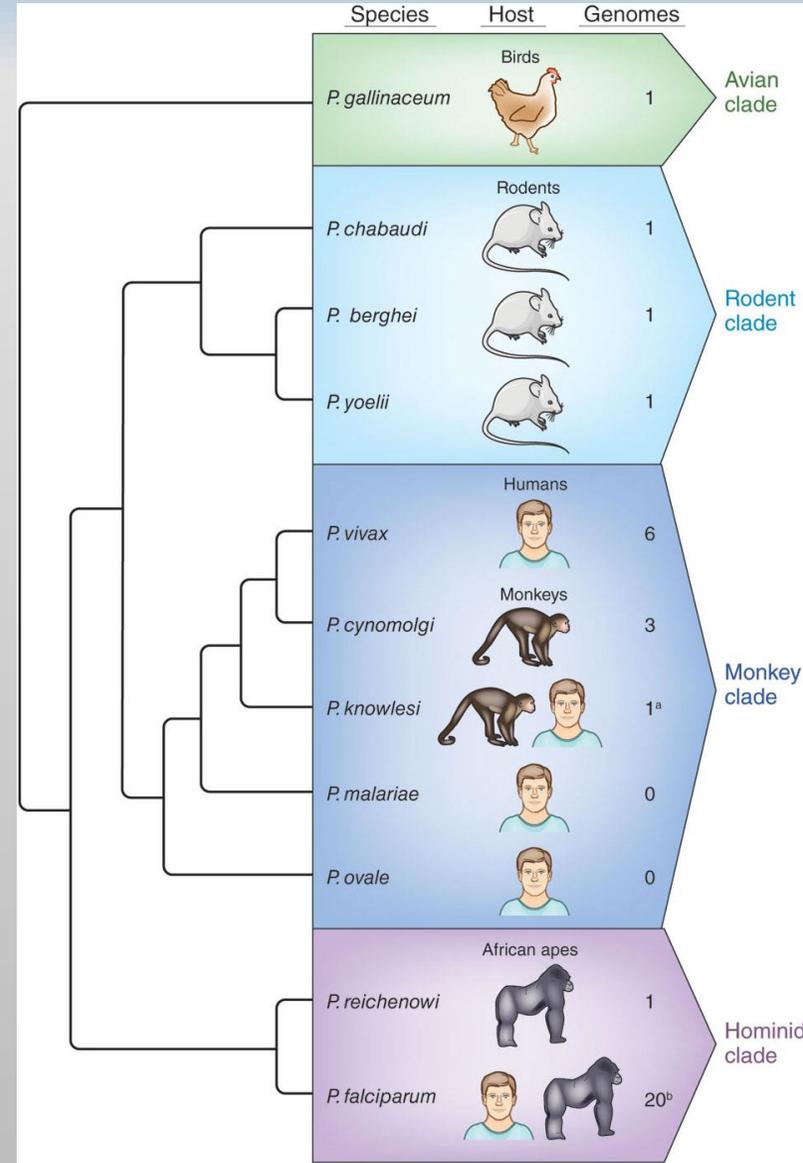


Plasmodia spp. Phylogeny



Has been identified in human malaria cases

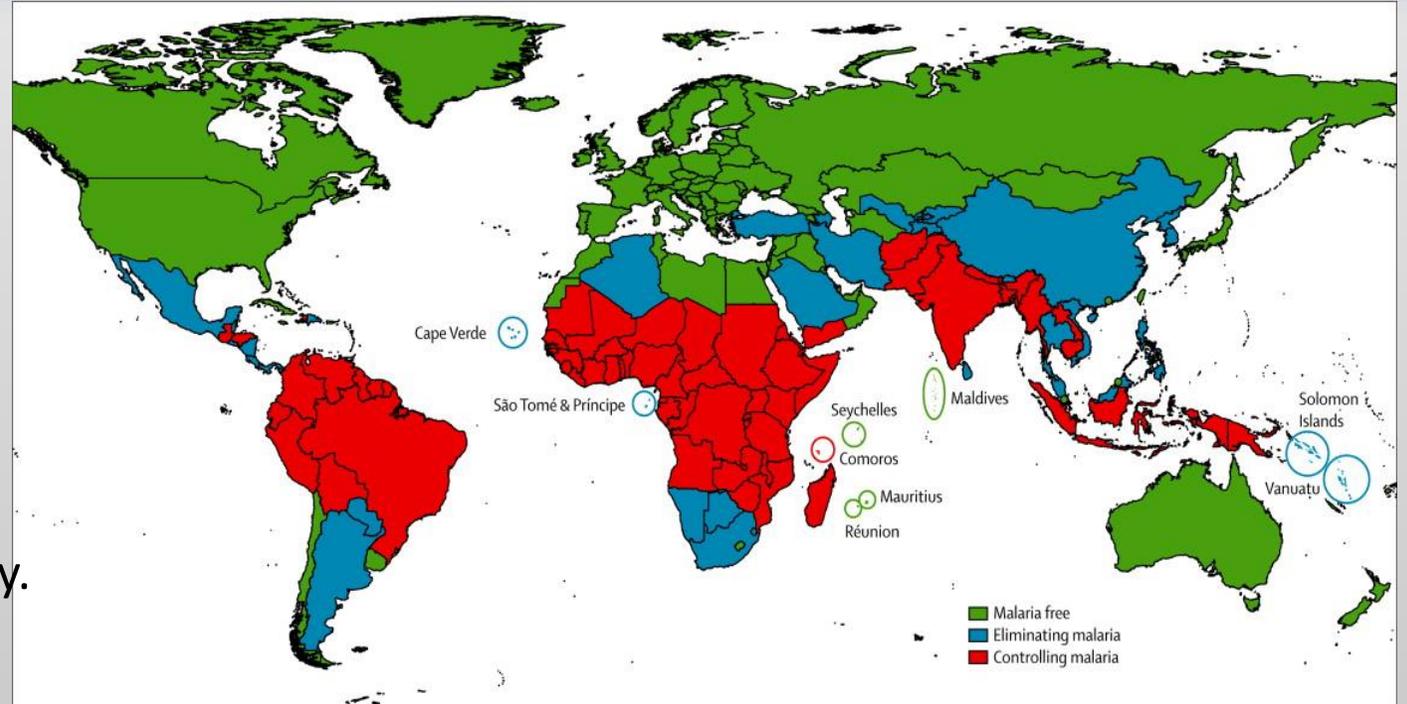
Known to infect Humans and cause Malaria



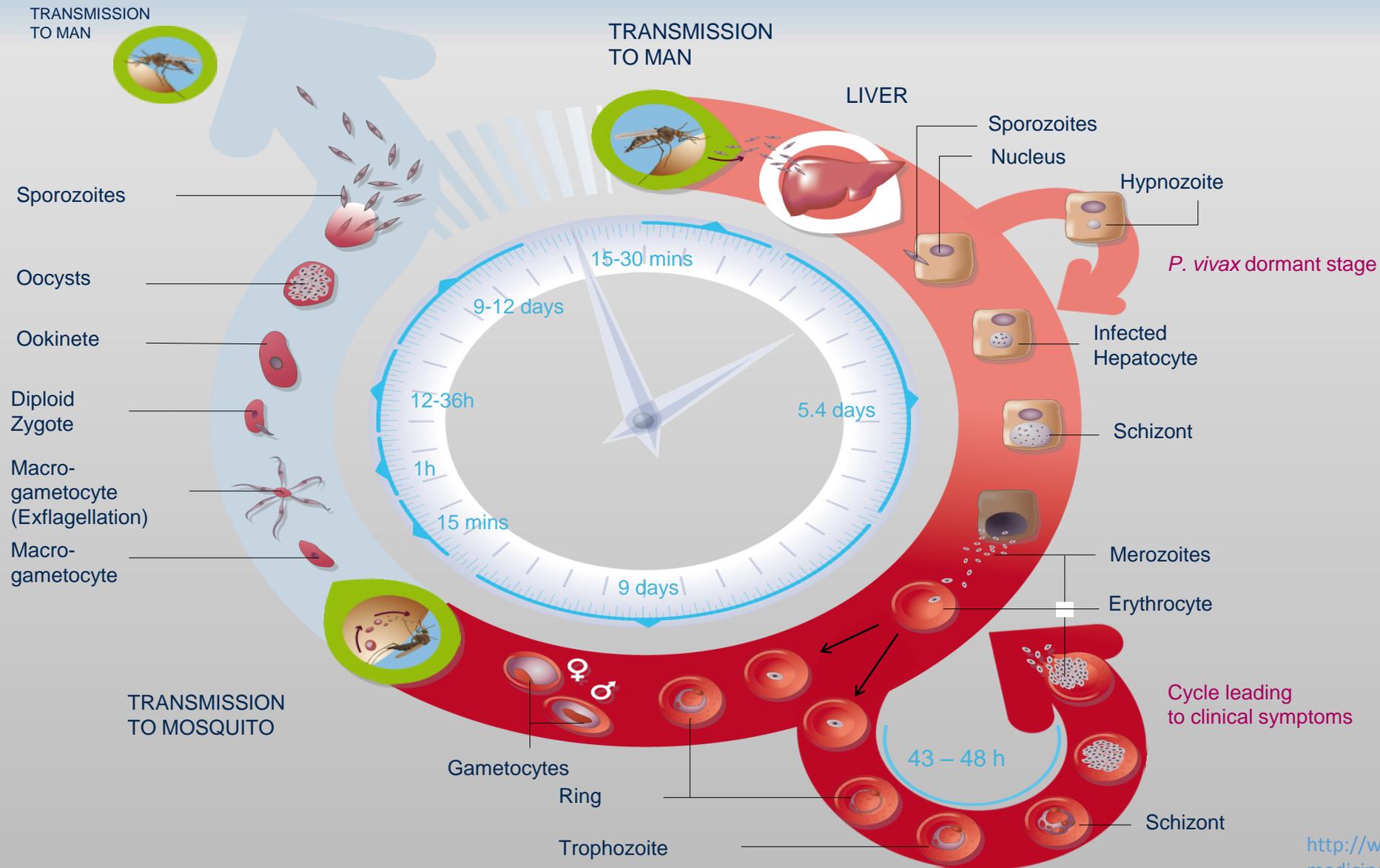
?= Plasmodia of uncertain phylogenetic placement

Geographical Distribution of Malaria Parasite

- *P. vivax*
 - Most common except in Africa. Occurs in temperate and tropical areas.
- *P. falciparum*
 - Tropical, holoendemic in much of Africa.
- *P. malariae*
 - Global, but very randomly spread; patchy.
- *P. ovale*
 - Mainly in tropical Africa and Oceania.
- *P. knowlesi*
 - Malaysia, Southeast Asia



Lifecycle of the malaria parasite



Malaria: Clinical Characteristics

Uncomplicated malaria

- Fever 96%
- Chills 96%
- Headache 79%
- Muscle Pain 60%
- Palpable liver 33%
- Palpable Spleen 28%
- Nausea or vomiting 23%
- Abdominal pain/diarrhea 6%



Is it Malaria?

Other diseases?

Dengue/Chikungunya/Leptospira/Malaria

Fever

1-2 days
remission: 1-2 without fever, y-relapse for 1-2 days
DENGUE/CHIKUNGUNYA

4-7 days
remission for : 1-2 days and relapse
LEPTOSPIROSIS

Daily or on Alternate Days
presume Malaria or other fever

Joint Pain

Severe joint pain and swelling in the extremities
Chikungunya

Mild joint pain/severe muscle pain
Dengue or Leptospira

no joint pain
malaria or other fever

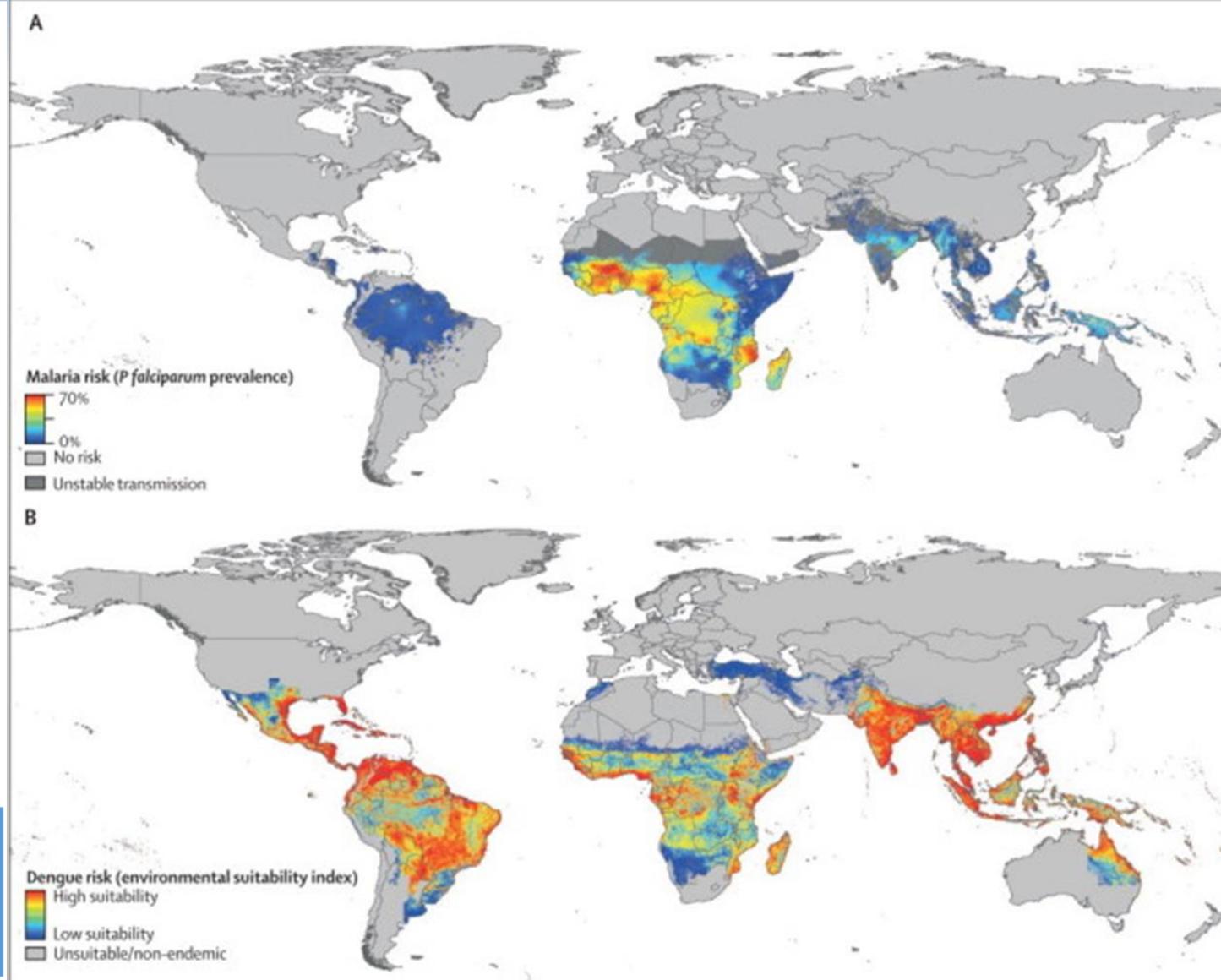
Rash

Over face, chest from day1-3 of fever
Non hemorrhagic
CHIKUNGUNYA

Over legs and trunk from Day 3-4 may become hemorrhagic
DENGUE

Over legs From Day 4-6 hemorrhagic
LEPTOSPIRA

No rash
Malaria or other fever



Diagnostic Tests for Malaria

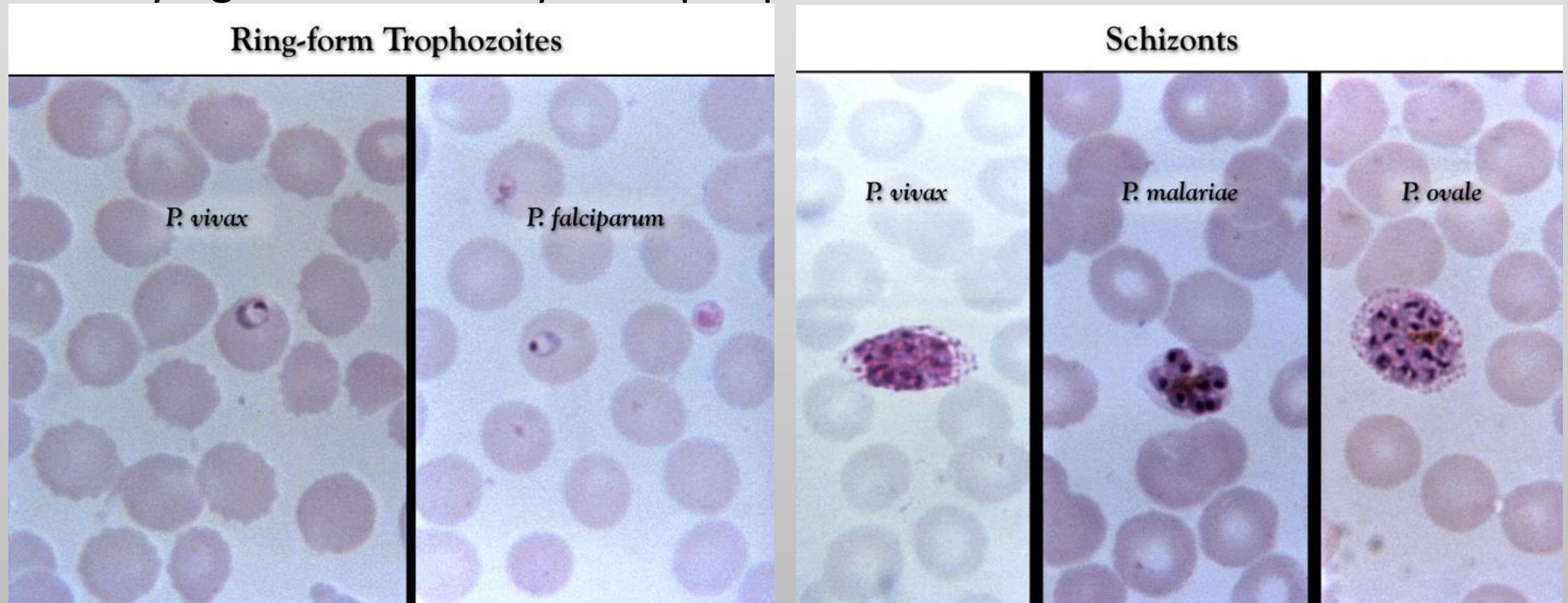
There are different diagnostic tests available for malaria.

- Microscopy – Gold Standard
 - Thick and thin smears
- Antigen detection
 - Rapid diagnostic tests (RDTs)
 - Army uses BinaxNow®.
(*P. falciparum* Sensitivity: 99.7% Specificity: 94.2%*
P. vivax Sensitivity: 93.5% Specificity: 99.8%)
- Molecular Diagnosis
 - Polymerase chain reaction (PCR)
- Serology
 - Indirect fluorescent antibody test (IFA)



Malaria - Diagnosis

Identifying Plasmodium *sp.* in a peripheral blood smear.



Malaria Drugs

- **Quinine**- In 1820, two young French chemists, Pierre Pelletier and Joseph Caventou, isolated the alkaloids quinine and cinchonine from cinchona bark.
- **Artemisinin**- by itself has a poor bioavailability so many semisynthetic derivatives have been created. Artemisinin is a derivative from the Qinghao plant that the Chinese used for fevers.
- **Resochin/Chloroquine**- was initially rejected as being too toxic . Was retested after WWII and renamed **Chloroquine** .Found to be one the most effective antimalarial drugs of the time.
- **Doxycycline** - Member of the tetracycline antibiotic group. Due to its many uses Doxycycline tends to be more readily available and cheaper than other antimalarial drugs.
- **Mefloquine** - Lariam (brand name), shown to have rare but serious neuropsychiatric problems.
- **Primaquine** - The most effective medicine for preventing *P.vivax*.
- **Malarone** - A combination of Atovaquone and Proguanil.
- **Fansidar** - Combination of sulfadoxine/ pyrimethamine.

Quinine and Artemisinin are the most effective drugs available today.

Malaria Prevention – Non-pharmaceutical

- Personal protective measures
 - Army uniform – worn properly and treated with permethrin
 - DEET
 - Bednets



Drugs used for Malaria

- Prophylaxis

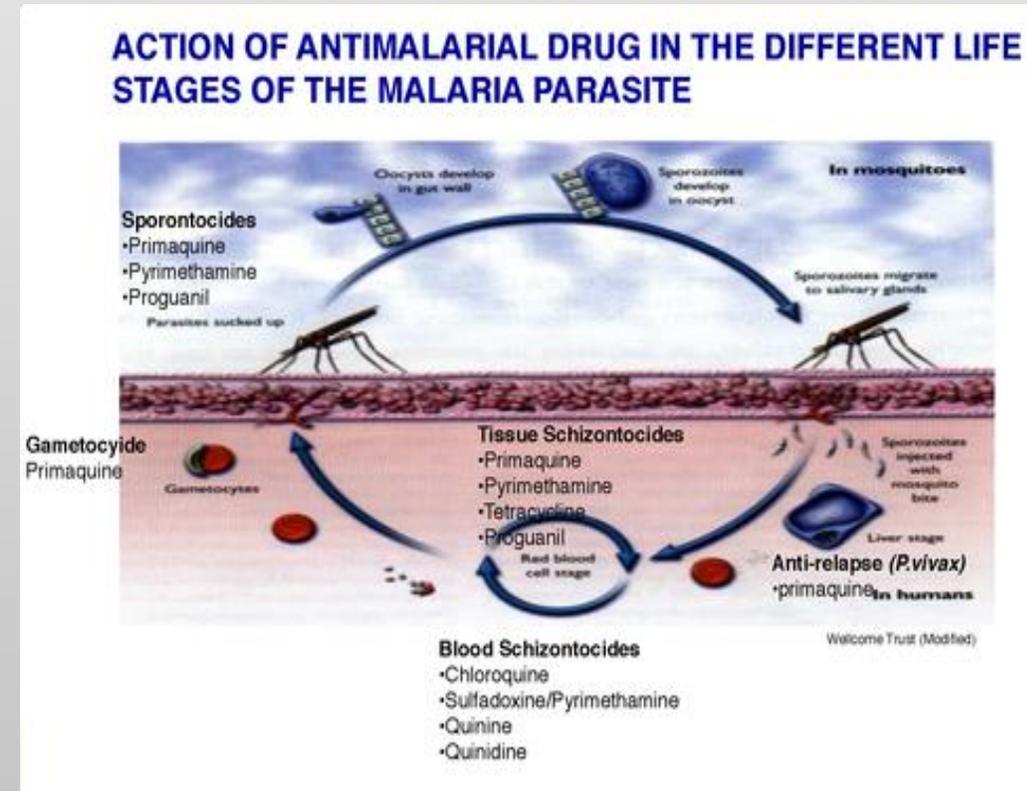
- Chloroquine, Doxycycline, Chloroquine+Proguanil

- Clinical treatment

- Quinine, Chloroquine, Artemisinin combinations, Sulfadoxine + Pyrimethamine, Atovaquone +Proguanil (malarone)
- Primaquine, DHA-piperaquine

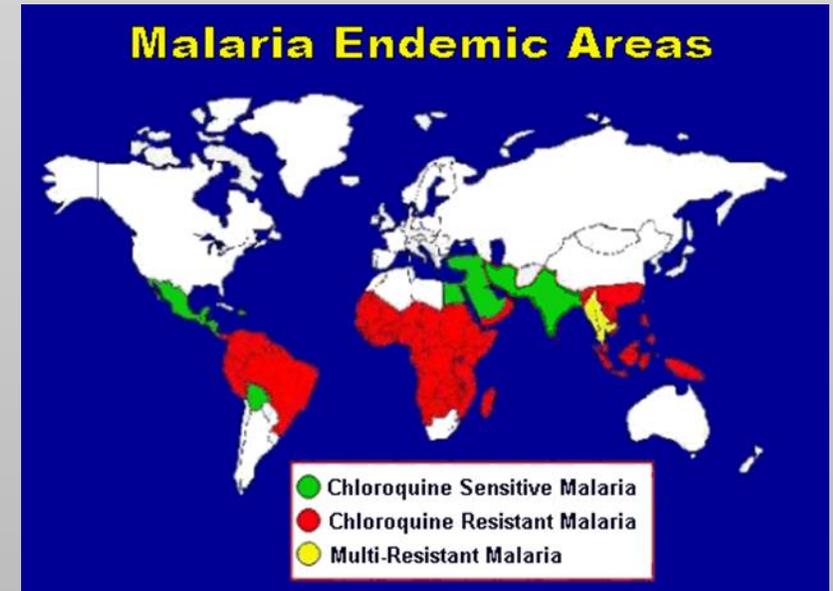
- Vector control

- Indoor residual spray of DDT
- Insecticide-impregnated bednets



Resistance to anti-Malarials

- For various reasons including; inadequate doses, improper adherence, mutation and evolution many Malaria strains are becoming resistant to drugs.
- **Chloroquine** the cheapest of the therapies is also the most widely resisted. Spread to nearly all areas of the world where falciparum malaria is endemic. Some vivax malaria has been showing resistance to chloroquine in some countries.
- Resistance has been shown to other anti-Malarials, mefloquine and quinine in some countries but has not spread worldwide.



Synthetic anti-malarials

- Primaquine: treat latent liver stages of *P. vivax* and *P. ovale*
- Chloroquine
 - chloroquine became one of the two principal weapons in the global malaria control campaign in the 1950. The other was DDT.
- Proguanil
- Amodiaquine
- Sulfadoxine/Pyrimethamine.

TAKE an ounce of the best jefuits bark, Virginian fnake-root, and orange-peel, of each half an ounce ; bruise them all together, and infuse for five or six days in a bottle of brandy, Holland gin, or any good spirit ; afterwards pour off the clear liquor, and take a wine-glafs of it twice or thrice a-day. This indeed is recommending a dram ; but the bitter ingredients in a great measure take off the ill effects of the spirit.

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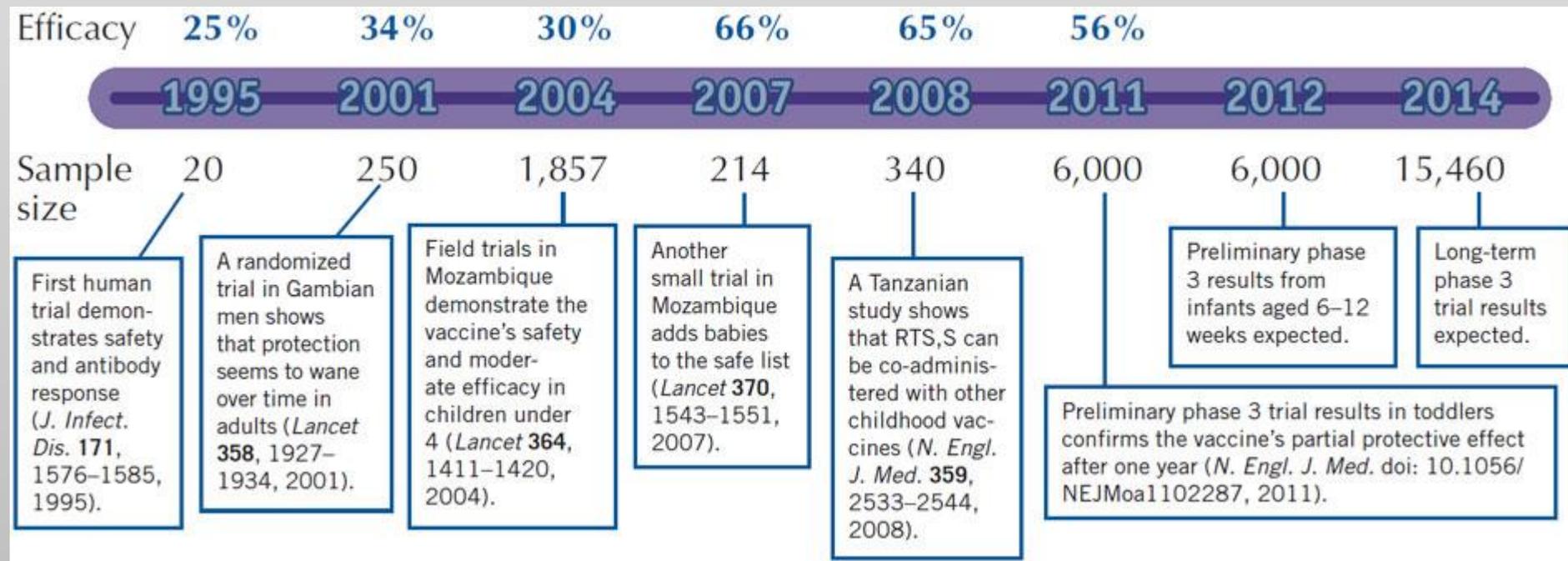
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Immunity

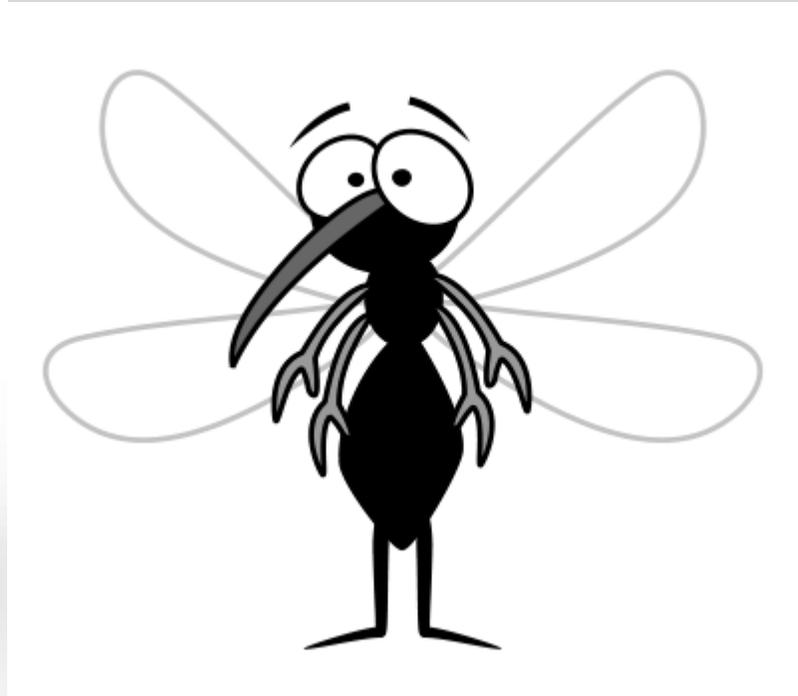
- Natural immunity
 - sickle cell anemia and beta-thalassaemia.
 - Lack in Duffy antigens on the surface of blood cells is resistant to infection from vivax.
- Acquired immunity
 - The course of malaria strongly depends on the degree of immunity of the infected individual. Complete sterile immunity is never reached, most adults in malaria endemic areas have partial immunity (semi-immunity).
 - Immunity is proportional to the age, the cumulative number of malaria episodes and time spent continuously in a malaria endemic region.
 - Repeated exposure
 - Strain specific immunity

Breaking news

- First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

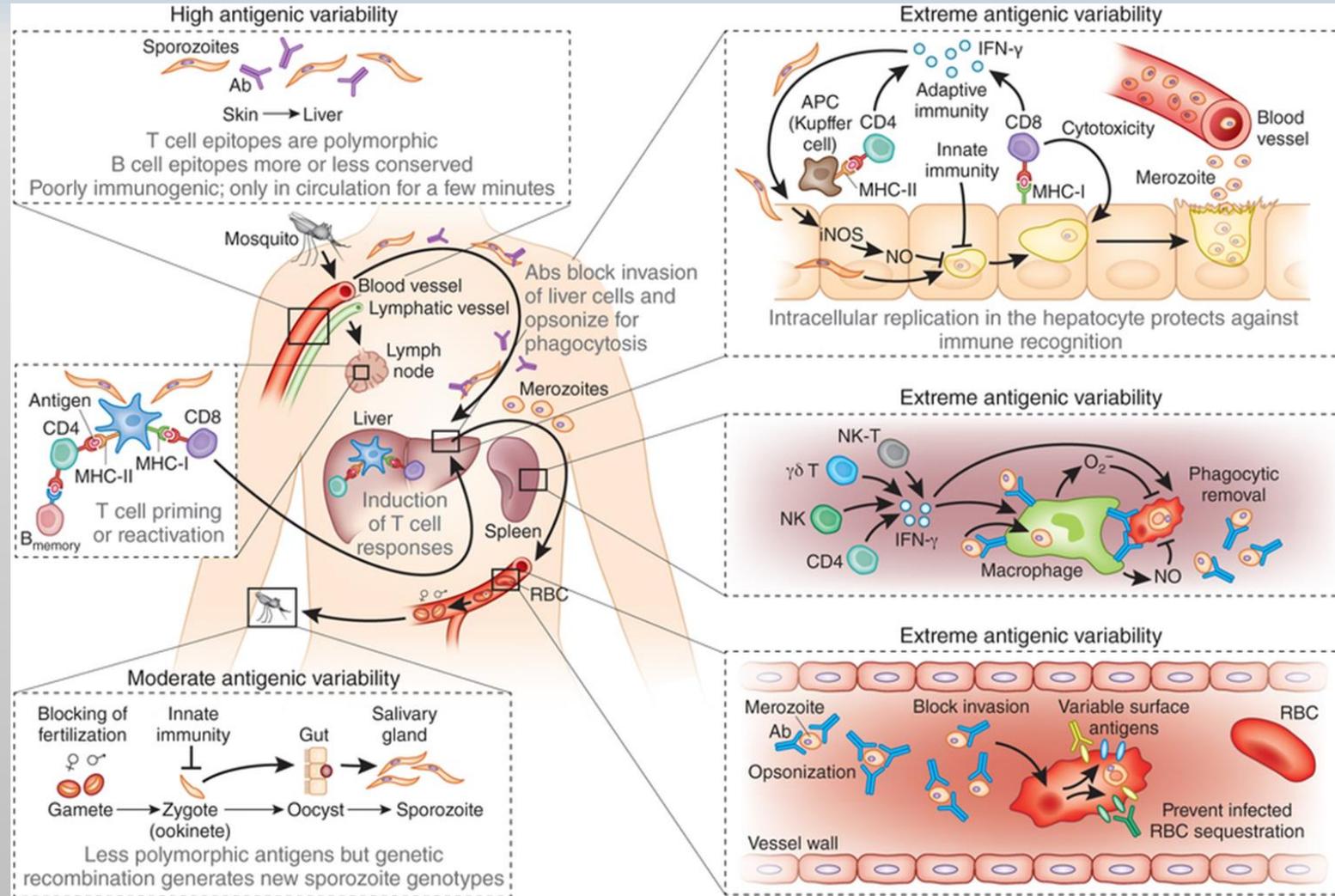


Questions??



These are my questions to you...

- Does the life cycle of *Plasmodium* tell you what kinds of control strategies are needed to manage the malaria problem?
- What are the biggest differences between *vivax* and *falciparum* malaria?
- Why do you think we have had a hard time developing a vaccine? See top illustration.



Resources

- Navy
- http://www.med.navy.mil/sites/nmrc/Pages/id_m.htm
 - http://www.public.navy.mil/surfor/Documents/6230_2.pdf
 - http://www.public.navy.mil/surfor/Documents/6250_1_NMCPHC_TM.pdf
 - <http://www.health.mil/~media/MHS/Policy%20Files/Import/13-002.ashx>
 - <http://www.health.mil/~media/MHS/Policy%20Files/Import/09-017.ashx>
 - <http://www.med.navy.mil/sites/nmcphc/program-and-policy-support/Pages/Malaria-Prevention-and-Control.aspx>

- Air Force
- http://www.phsource.us/PH/PARA/Chapter_9.htm

- Army
- http://wrair-www.army.mil/ReAndDevelop_InfectDisRe_MalariaResearch.aspx
 - <http://www.africom.mil/malaria>
 - <http://www.afpmb.org/sites/default/files/pubs/techguides/tg36.pdf>
 - http://www.armyg1.army.mil/militarypersonnel/PPG/PPG_22MAY2012.pdf

- CDC
- <http://www.cdc.gov/malaria/travelers/index.html>
 - <http://www.cdc.gov/parasites/cme/malaria/>

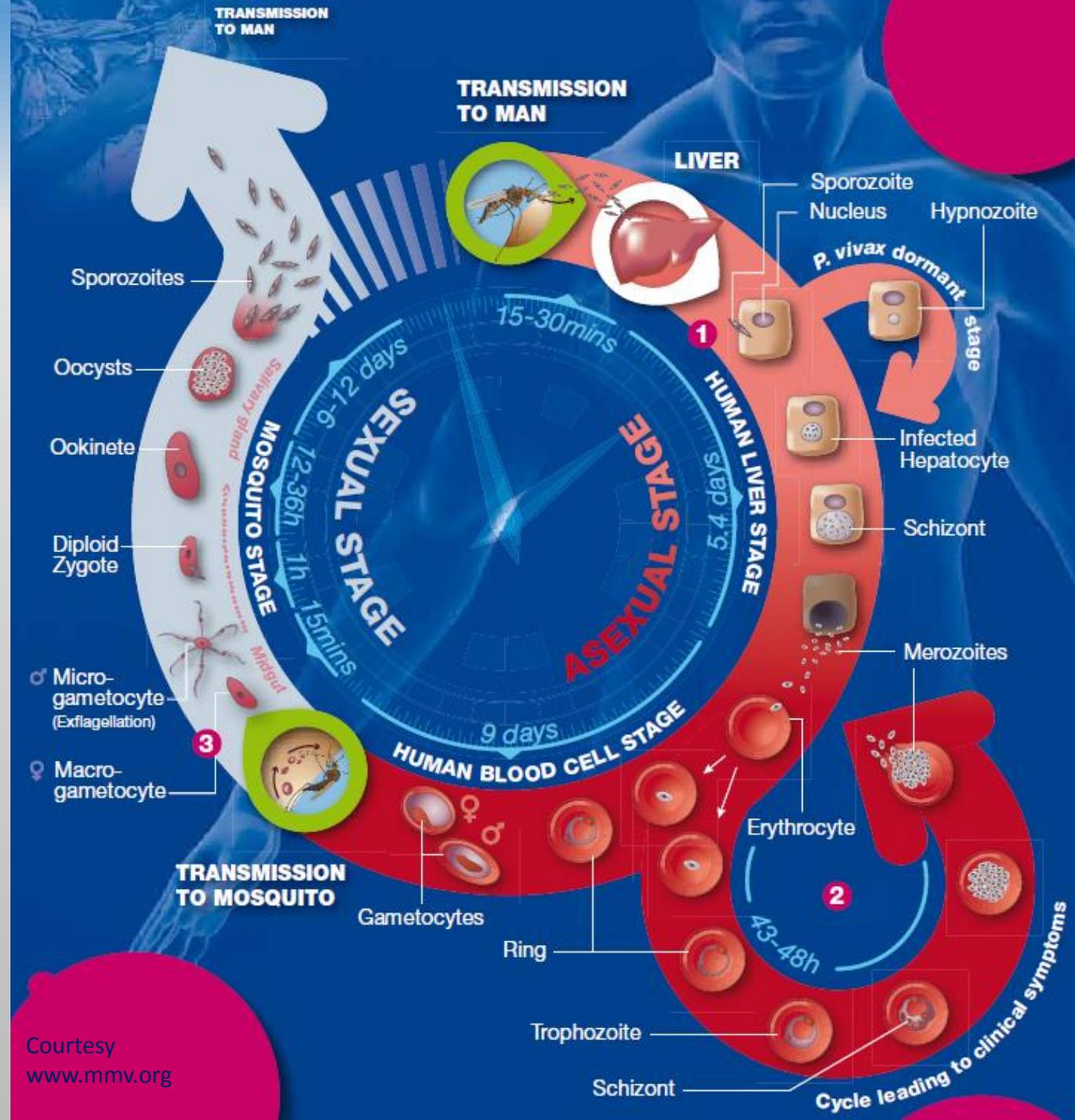
- Other
- Deployment Health
- <http://www.pdhealth.mil/malaria.asp>

Contact Information

- **Army: USAPHC – Disease Epidemiology Program**
Aberdeen Proving Ground – MD
Comm: (410) 436-7605 DSN: 584-7605
usarmy.apg.medcom-phc.mbx.disease-epidemiologyprogram13@mail.mil
- **Navy: Contact your cognizant NEPMU**
NEPMU2: COMM: (757) 950-6600; DSN: (312) 377-6600
Email: usn.hampton-roads.navhospporsva.list.nepmu2norfolk-threatassess@mail.mil
NEPMU5: COMM: (619) 556-7070; DSN (312) 526-7070
Email: HealthSurveillance@med.navy.mil
NEPMU6: COMM: (808) 471-0237; DSN: (315) 471-0237
Email: usn.jbphh.navenpvntmedusixhi.list.nepmu6@mail.mil
NEPMU7: COMM (int): 011-34-956-82-2230 (local): 722-2230; DSN: 94-314-727-2230
Email: NEPMU7@eu.navy.mil
- **Air Force: Contact your MAJCOM PH or USAFSAM/PHR**
USAFSAM / PHR / Epidemiology Consult Service
Wright-Patterson AFB, Ohio
Comm: (937) 938-3207 DSN: 798-3207
episervices@wpafb.af.mil

Life cycle of *Plasmodium spp.*

- sporozoites injected during mosquito feeding
- invade liver cells
- exoerythrocytic schizogony (merozoites)
- merozoites invade RBCs
- repeated erythrocytic schizogony cycles (end of human infective stage)
- gametocytes infect mosquito
- fusion of gametes in gut
- sporogony on gut wall in mosquito hemocoel
- sporozoites invade salivary glands



Courtesy
www.mmv.org

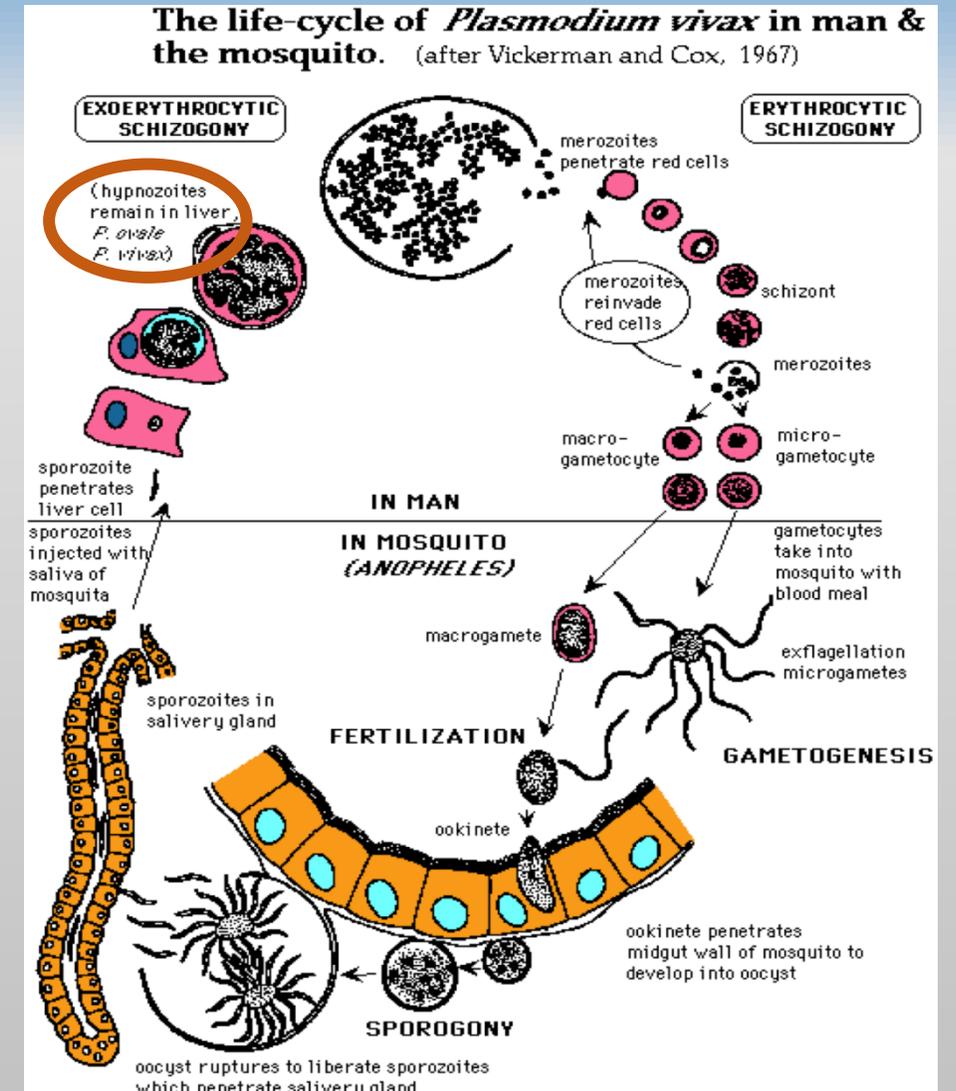
The times depicted on diagram here is for *P. falciparum* only

Life cycle of *Plasmodium vivax*

- exhibit delayed replication (ie, dormant)
- merozoites produced months after initial infection
- only *P. vivax* and *P. ovale*

relapse = hypnozoite

recrudescence = subpatent



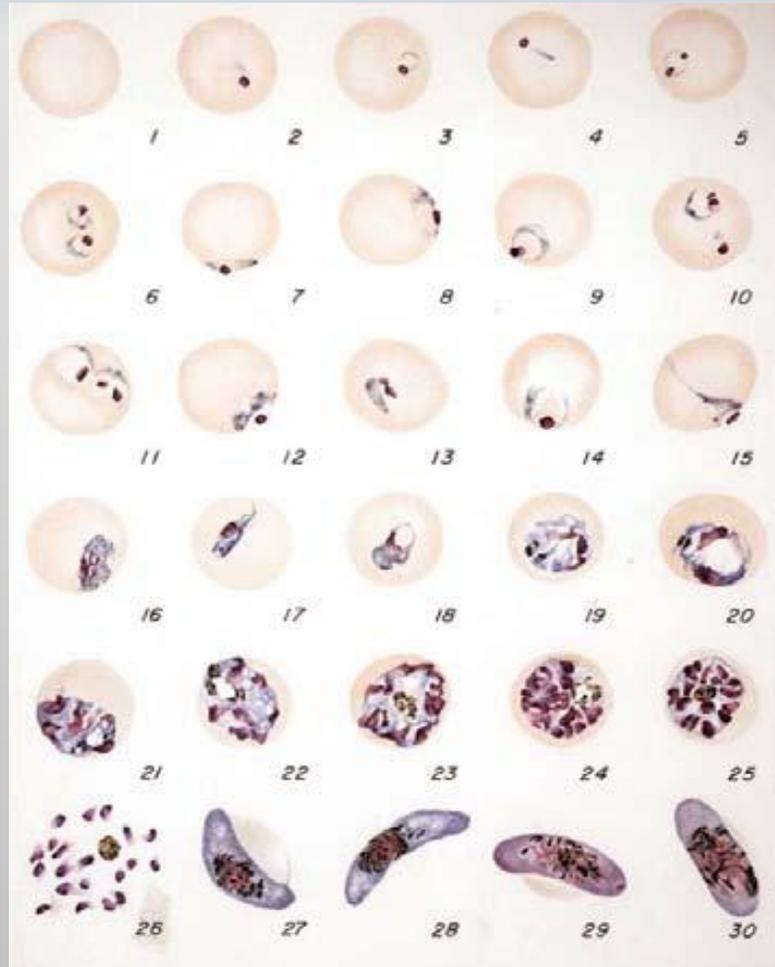
*Hypnozoites can remain in the liver

Lifecycle summarized

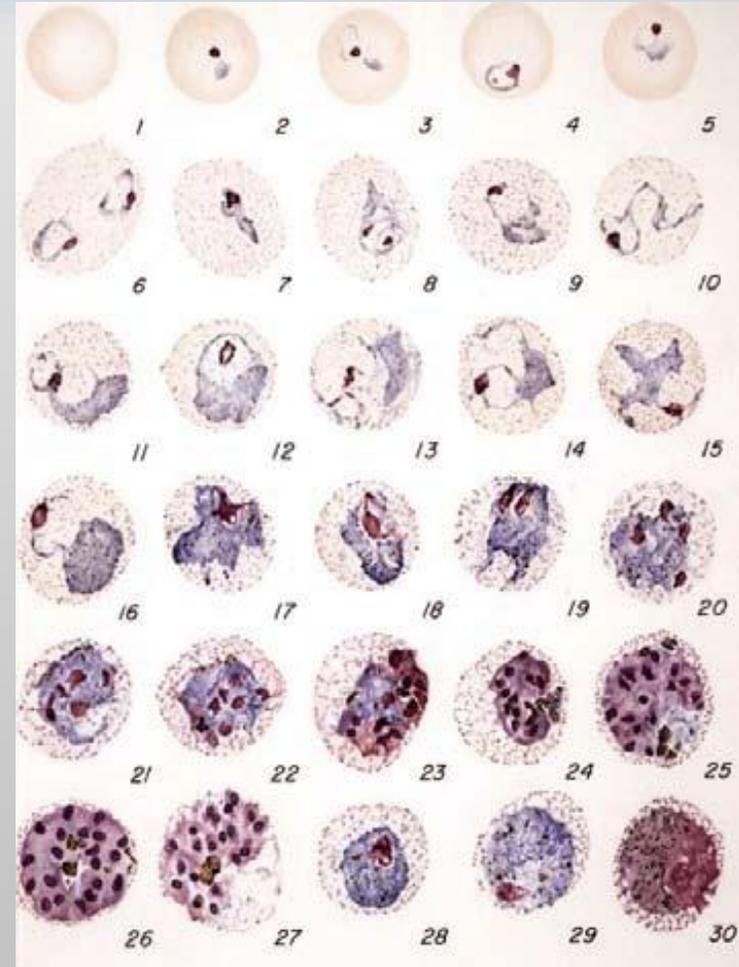
- Caused by a protozoan species, *Plasmodium spp.*, (*P. falciparum* is the most dangerous).
- Life cycle alternates between anopheline mosquito and man
- Female mosquito become infected with haploid gametocytes during blood meal of an infected individual.
- Fertilization takes place in the mosquito's gut.
- Resulting diploid ookinete leaves mosquito gut.
- Sporogony develops in mosquito hemocoel;
- Sporogony develop into an oocyst, which ruptures liberating sporozoites that migrate to the insect's salivary gland.
- Sporozoites are injected to human host when mosquito injects saliva during blood meal.
- Sporozoites develop into merozoites that enter the blood stream and infect red blood cells (RBCs).
- Merozoites reproduce in the RBCs, lysing them in the process (produces the clinical characteristic bouts of fever and chills)
- Re-invade more RBCs; finally they
- Produce gametocytes that are capable of infecting another mosquito during a blood meal, thereby perpetuating the cycle.

To summarize, *P. falciparum* is an extracellular parasite in mosquitos and an intracellular parasite in man.

Plasmodium falciparum



Plasmodium vivax



Comparative chart of malaria parasites

Phase/Status	<i>P. vivax</i>	<i>P. falciparum</i>	<i>P. ovale</i>	<i>P. malariae</i>
Exoerythrocytic cycle	May persist several years (4-5)	One or a few generation not more than 7 months	One or a few generations.	May persist several years (20-30)
No. merozoites in RBC's	12-24	8-18	8	6-12
Merozoites	Attack young red blood cells. 8,000 - 20,000/mm ³	Attack all ages 500,000/mm ³ (10% of RBC's)	Like <i>P. vivax</i> except exoerythrocytic phase short.	Attack aging RBC's 10,000/mm ³
Clinical paroxysms	Every day, then every other day.	48 hours for schizogony. RBC's tend to agglutinate. Thrombi and emboli not uncommon. Parasitized RBC's tend to concentrate in capillaries in many organs. Trophozoites decrease gametocytes increase.	Mild attacks of short duration	72- hour intervals

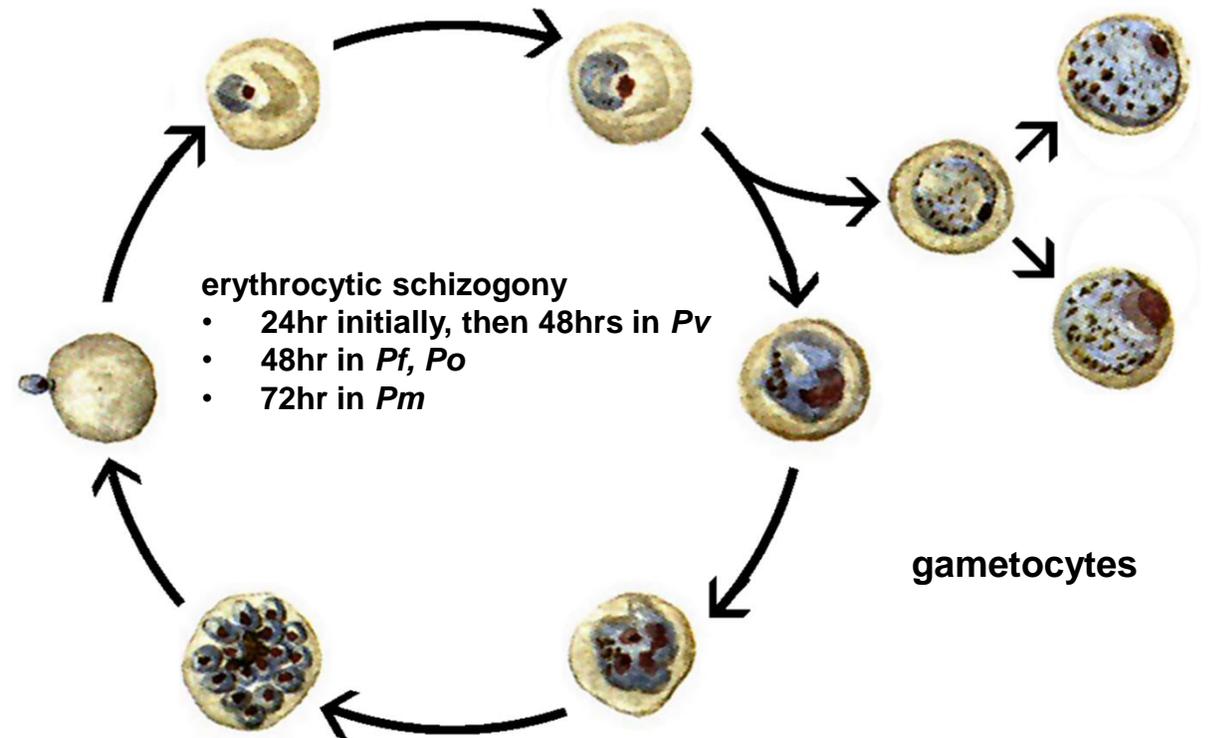


Table 1. Cost, Convenience, and Primary Clinical Application of Antimalarial Therapies.

Therapy	Cost (\$)*	No. of Doses	Duration of Therapy	Application
Chloroquine	0.11	3	48 hr	Blood-stage schizonticide
Sulfadoxine–pyrimethamine	0.14	1	Single dose	Blood-stage schizonticide
Quinine	0.97	21	7 days	Blood-stage schizonticide
Mefloquine	2.55	1	Single dose	Blood-stage schizonticide
Atovaquone–chloroguanide	48.00†	3	48 hr	Blood-stage schizonticide
Artemether–lumefantrine	9.12‡	6	48 hr	Blood-stage schizonticide, gametocytocide
Artesunate–mefloquine	5.00§	6	48 hr	Blood-stage schizonticide, gametocytocide
Artesunate–sulfadoxine–pyrimethamine	2.40¶	3	48 hr	Blood-stage schizonticide, gametocytocide
Artesunate–amodiaquine	2.00¶	3	48 hr	Blood-stage schizonticide, gametocytocide
Primaquine	1.68	7–14	7 days–8 wk	Tissue-stage schizonticide, gametocytocide

* Unless otherwise indicated, the cost shown is the cost, in 2003 U.S. dollars, of medication for one adult treatment regimen, purchased in bulk, according to the International Drug Price Indicator Guide (IDPIG) (<http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=dmp&language=English>).

† U.S. commercial sources were surveyed; the cost is not available from the IDPIG.

‡ The cost shown is from the IDPIG; the combination is available through the World Health Organization (WHO) to qualified purchasers at a cost of \$2.40 per adult treatment regimen.

§ The cost shown is from the WHO.

¶ The cost shown is from Arrow et al.⁸