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.
Make it easier to change the pictures: use the Selection Pane to temporarily hide a Picture Placeholder. (Home tab, Select, Selection Pane). Click the eye icon to hide or show an object.

To change a sample image, select the picture and delete it. Now click the Pictures icon in the placeholder to insert your own image. If you don't see the Pictures icon, click the Reset button (Home tab, Slides, Reset).

The animation is already done for you; just copy and paste the slide into your existing presentation.

Sample pictures courtesy of Bill Staples.

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

• 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/)

• 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.)

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.

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*
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

**TRANSMISSION TO MAN**

- Sporozoites
- Nucleus
- Hypnozoite
- Infected Hepatocyte
- Schizont
- Merozoites
- Erythrocyte
- Trophozoite
- Ring
- Ring

**TRANSMISSION TO MOSQUITO**

- Gametocytes
- Macro-gametocyte (Exflagellation)
- Macro-gametocyte
- Diploid Zygote
- Ookinete
- Oocysts
- Sporozoites

**LIVER**

- P. vivax dormant stage
- Cycle leading to clinical symptoms
- 9-12 days
- 12-36h
- 1h
- 15 mins
- 9-12 days
- 15-30 mins
- 9-12 days
- 5.4 days

http://www.mmv.org/malaria-medicines/parasite-lifecycle
# Malaria: Clinical Characteristics

## Uncomplicated malaria

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>96%</td>
</tr>
<tr>
<td>Chills</td>
<td>96%</td>
</tr>
<tr>
<td>Headache</td>
<td>79%</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>60%</td>
</tr>
<tr>
<td>Palpable liver</td>
<td>33%</td>
</tr>
<tr>
<td>Palpable Spleen</td>
<td>28%</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>23%</td>
</tr>
<tr>
<td>Abdominal pain/diarrhea</td>
<td>6%</td>
</tr>
</tbody>
</table>

Is it Malaria?  Other diseases?

Dengue/Chikungunya/Leptospiro/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 Leptospiro

- Rash
  - Over face, chest from day 1-3 of fever
    - Non hemorrhagic Chikungunya
  - Over legs and trunk from Day 3-4 may become hemorrhagic
    - Dengue
  - Over legs from Day 4-6 hemorrhagic
    - Leptospiro
  - No rash
    - Malaria or other fever

DOI: http://dx.doi.org/10.1016/S1473-3099(12)70246-3  The Lancet,
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.

http://phil.cdc.gov/phil/details.asp
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.
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* tells 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.health.mil/~/media/MHS/Policy%20Files/Import/13-002.ashx
- http://www.health.mil/~/media/MHS/Policy%20Files/Import/09-017.ashx

Air Force

Army
- http://www.africom.mil/malaria

CDC
- http://www.cdc.gov/parasites/cme/malaria/

Other

Deployment Health
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
  NEPMUS5: 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
  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

The times depicted on diagram here is for *P. falciparum* only.
Life cycle of *Plasmodium vivax*

- exhibit delayed replication (i.e., 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.
- Sporogeny develops in mosquito hemocoel;
- Sporogeny 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 mosquitoes and an intracellular parasite in man.
Plasmodium falciparum

Plasmodium vivax
Comparative chart of malaria parasites

<table>
<thead>
<tr>
<th>Phase/Status</th>
<th><em>P. vivax</em></th>
<th><em>P. falciparum</em></th>
<th><em>P. ovale</em></th>
<th><em>P. malariae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exoerythrocytic cycle</td>
<td>May persist several years (4-5)</td>
<td>One or a few generation not more than 7 months</td>
<td>One or a few generations.</td>
<td>May persist several years (20-30)</td>
</tr>
<tr>
<td>No. merozoites in RBC's</td>
<td>12-24</td>
<td>8-18</td>
<td>8</td>
<td>6-12</td>
</tr>
<tr>
<td>Merozoites</td>
<td>Attack young red blood cells. 8,000 - 20,000/mm³</td>
<td>Attack all ages 500,000/mm³ (10% of RBC's)</td>
<td>Like <em>P. vivax</em> except exoerythrocytic phase short.</td>
<td>Attack aging RBC's 10,000/mm³</td>
</tr>
<tr>
<td>Clinical paroxysms</td>
<td>Every day, then every other day. RBC's tend to agglutinate.</td>
<td>48 hours for schizogony.</td>
<td>Mild attacks of short duration</td>
<td>72-hour intervals</td>
</tr>
<tr>
<td></td>
<td>Thrombi and emboli not uncommon. Parasitized RBC's tend to concentrate in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>capillaries in many organs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trophozoites decrease gametocytes increase.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **erythrocytic schizogony**
  - 24hr initially, then 48hrs in *Pv*
  - 48hr in *Pf, Po*
  - 72hr in *Pm*
Table 1. Cost, Convenience, and Primary Clinical Application of Antimalarial Therapies.

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

* 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 (IDP/IG) (http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=drp&language=English).
† U.S. commercial sources were surveyed; the cost is not available from the IDP/G.
‡ The cost shown is from the IDP/G; 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."