

Apicomplexan basics:

- There are two major “groups,” the ones transmitted by contamination, and the vector-borne ones.
- Both asexual and sexual reproduction occur (unlike the protists we have discussed so far).
- Some important species are zoonotic.
- This phylum is named for ultrastructural features of the infective stages.
- Some species are highly opportunistic.

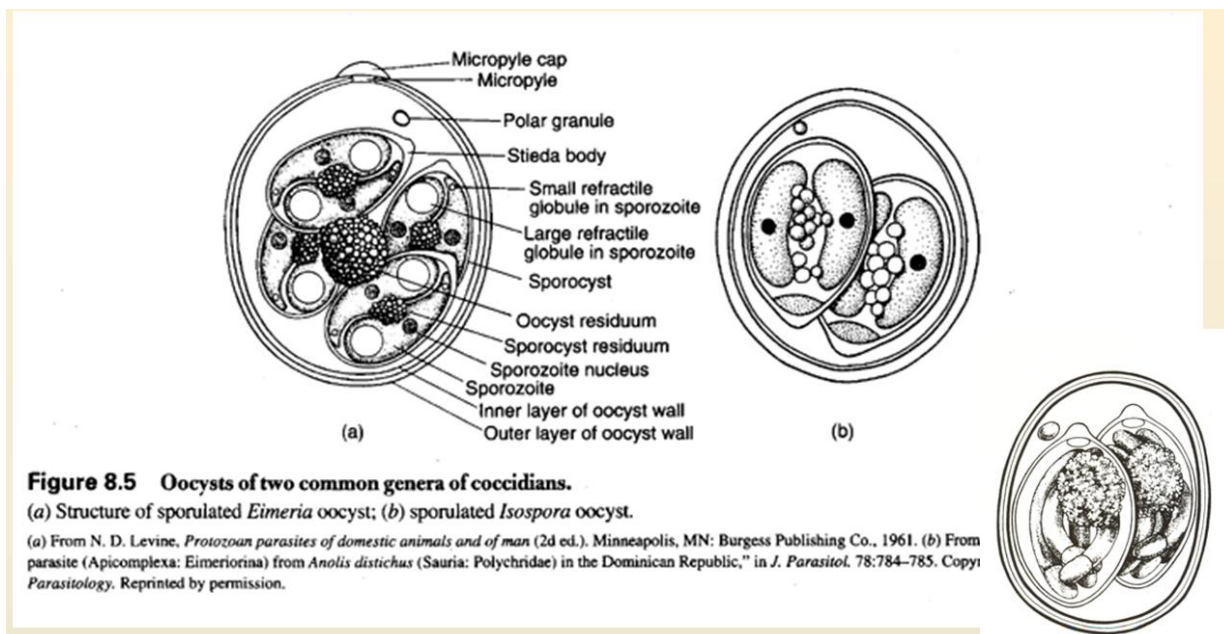
Apicomplexa - Examples

- *Eimeria* and *Isospora*
- *Toxoplasma* (*T. gondii*)
- *Cryptosporidium*
- *Cyclospora*

- *Neospora* - Neosporosis is an important neuromuscular disease of domestic dogs worldwide. The causative parasite, *Neospora caninum*, cycles between canine definitive hosts and herbivore intermediate hosts, most notably cattle. Congenital *N. caninum* infections occur in both cattle and dogs.
 - Oocysts (environmental stages formed in canine intestinal epithelium and passed with the feces)
 - Tachyzoites (rapidly dividing stages that actively invade tissues)
 - Bradyzoites (slowly dividing stages that encyst within tissues)

- *Sarcocystis* *S. neurona* cause equine protozoan myeloencephalitis , EPM -30 years to work out the life cycle of this neurological disorder.

Structure of coccidian oocysts (two common genera)



Life Cycle - See slides and handout.

Gregarine General characteristics

1. A large, specious group of apicomplexans that usually reside in the intestinal tract or body cavity of invertebrates or lower chordates
2. Mature gamonts typically large and usually develop extracellularly
3. Sporozoites, merozoites, and gamonts often possess an anterior adhesive organ
 - A. epimerite (apical anchoring structure)
4. Syzygy (pairing of two gametes prior to fertilization. In gregarines, this usually occurs end-to-end).

Gregarina cuneata (Suborder: Septatorina)

Oocysts ingested by larval beetles (mealworms), *Tenebrio molitor*.

Similar species in mealworms include *Gregarina niphandrodes* (in the adult beetle), *Gregarina polymorpha* (in the larvae), and *Gregarina steini* (in the larvae).

Cryptosporidium

GI watery diarrhea and or respiratory infection, live in gastrointestinal or respiratory epithelial cells (very small 2-6 um oocysts in feces)

Molecularly closer to gregarines -explains their resistance to medications given for coccidians.

Treatment includes: replacing electrolytes, nitazoxanide, and basic palliative care.

Cryptosporidium spp. infect over 150 different species of mammals.

The poultry industry and zoos must deal with *Cryptosporidium spp.*

Milwaukee, WI there were 403,000 **reported** cases of *Cryptosporidium* (out of ~1.6 million people) in 1993 epidemic.

Costs associated with outbreak:

Severity	Medical \$	Productivity loss	Total \$
Mild (354,600)	790,760	40,212,000	41,020,000
Moderate (44,000)	2,710,800	18,176,000	20,887,000
Severe (4,400)	28,153,000	6,201,400	43,355,000
Total	31,655,000	64,589,000	96,244,000

Cyclospora sp. causes cyclosporiasis. It causes watery diarrhea and is endemic in tropical and subtropical regions. It is fecal-orally transmitted. Unwashed produce and contaminated water spread *Cyclospora sp.*

Some of the major impacts of diarrheal illnesses caused, in part, by *Cyclospora spp.* and *Cryptosporidium spp.* occur in young children. In developing countries nearly a quarter of the deaths of children less than 5 years old are due to diarrhea. Additionally, correlations of early childhood diarrhea and cognitive dysfunction have proven to be statistically significant.

Correlations of early childhood (0-2) diarrhea (# days) with cognitive dysfunction @ 6-9 years:

Cognitive test	R (n)	P
McCarthy Draw-A-Design	-0.49(26)	0.012
Backward WISC-III Digit Span	-0.64(10)	0.049
WISC-III Scaled Coding	-0.69(10)	0.031
Forward WISC-III Digit Span	-0.17(26)	0.419
WPPSI-R Mazes 5-11	0.05(26)	0.802

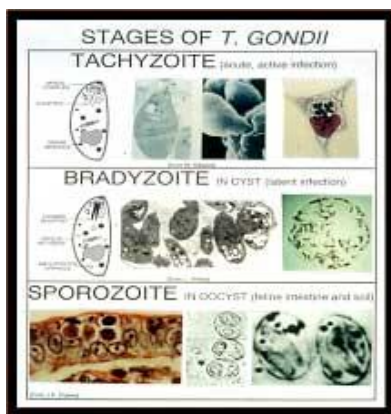
D. Guerrant et al., 1999, Am. J. Trop. Med. Hyg. 61: 707-713

Toxoplasma gondii

It is and obligate intracellular, parasitic protozoan that can infect nearly all endotherms, but the only definitive hosts are in the family Felidae.

Slide 43. The left shows a bradyzoite cyst with the dense cyst wall surrounding the bradyzoites. The right shows tachyzoites inside the **parasitophorous vacuole**. Bradyzoites will slowly reproduce asexually in the cyst and tachyzoites will rapidly reproduce asexually.

Generally, individuals are asymptomatic, may have malaise or flu-like symptoms. Additionally, some individuals can have cognitive changes, especially a lack of avoidance of cat sign. Research includes studies looking into links between *Toxoplasma gondii* infections and schizophrenia, Parkinson's, and Alzheimer's.



"Manipulation Hypothesis" rodents change in behavior and this leads them to mostly be preyed upon by cats, i.e. less aversion to cats/cat sign. There is epigenetic remodeling in neurons which govern the associated behavior.

Humans who are infected are not as adverse to cat pee. While those uninfected are still adverse per Flegr, J; Lenochová, P; Hodný, Z; Vondrová, M (2011). "Fatal attraction phenomenon in

humans – cat odour attractiveness increased for *Toxoplasma*-infected men while decreased for infected women".

What are the signs and symptoms of toxoplasmosis?

Symptoms of the infection vary.

- Most people who become infected with *Toxoplasma gondii* are not aware of it.
- Some people who have toxoplasmosis may feel as if they have the "flu" with swollen lymph glands or muscle aches and pains that last for a month or more.
- Severe toxoplasmosis, causing damage to the brain, eyes, or other organs, can develop from an acute *Toxoplasma gondii* infection or one that had occurred earlier in life and is now reactivated. Severe cases are more likely in individuals who have weak immune systems, though occasionally, even persons with healthy immune systems may experience eye damage from toxoplasmosis. *Toxoplasma gondii* can be fatal in patients with AIDS. This was a major cause of death in early AIDS patients. Treatment is essential for survival for AIDS patients.
- Signs and symptoms of ocular toxoplasmosis can include reduced vision, blurred vision, pain (often with bright light), redness of the eye, and sometimes tearing.
- Most infants who are infected while still in the womb have no symptoms at birth, but they may develop symptoms later in life. A small percentage of infected newborns have serious eye or brain damage at birth.

Who is at risk for developing severe toxoplasmosis?

People who are most likely to develop severe toxoplasmosis include:

- Infants born to mothers who are newly infected with *Toxoplasma gondii* during or just before pregnancy. - If the mother was infected prior to pregnancy, there is virtually no risk of fetal infection, as long as she remains **immunocompetent**.
- Persons with severely weakened immune systems, such as individuals with AIDS, those taking certain types of chemotherapy, and those who have recently received an organ transplant.

How do people get toxoplasmosis?

A *Toxoplasma* infection occurs by:

- Eating undercooked, contaminated meat (especially pork, lamb, and venison).

- Accidental ingestion of undercooked, contaminated meat after handling it and not washing hands thoroughly.
- Eating food that was contaminated by knives, utensils, cutting boards and other foods that have had contact with raw, contaminated meat.
- Drinking water contaminated with *Toxoplasma gondii*.
- Accidentally swallowing the parasite through contact with cat feces that contain *Toxoplasma*. This might happen by
 1. cleaning a cat's litter box when the cat has shed *Toxoplasma* in its feces
 2. touching or ingesting anything that has come into contact with cat feces that contain *Toxoplasma*
 3. accidentally ingesting contaminated soil (e.g., not washing hands after gardening or eating unwashed fruits or vegetables from a garden)
- Mother-to-child (congenital) transmission.
- Receiving an infected organ transplant or infected blood via transfusion, though this is rare.

Prevention

- Peel or wash fruits and vegetables thoroughly before eating.
- Do not eat raw or undercooked oysters, mussels, or clams (these may be contaminated with *Toxoplasma* that has washed into sea water).
- Wash cutting boards, dishes, counters, utensils, and hands with hot soapy water after contact with raw meat, poultry, seafood, or unwashed fruits or vegetables.
- Wear gloves when gardening and during any contact with soil or sand because it might be contaminated with cat feces that contain *Toxoplasma*. Wash hands with soap and warm water after gardening or contact with soil or sand.
- Teach children the importance of washing hands to prevent infection.

-----Phylum Apicomplexa

Order Heamosporida

Family Plasmodiidae

Genus *Plasmodium* (produces hemozoin – a pigment produced by *Plasmodium* spp. in host cells.

Members of the genus *Plasmodium* are considered "High-yield" parasites. *Plasmodium* spp. are the causative agent of malaria.

The *Plasmodium* spp. that cause malaria in humans are:

- *P. vivax*
 - Benign tertian malaria (48 hours)
 - Flourishes in temperate regions
 - 40% of malaria world wide
 - Cannot infect RBC without Duffy antigen
 - Separate infections common

- *P. ovale*
 - Biologically similar to *P. vivax*
 - Can** infect people who are negative for the Duffy blood group (FY/FY).
 - Especially prevalent in West Africa

- *P. malariae*
 - Quartian malaria (72 hours)
 - Localized, but global distribution
 - Low parasitemia
 - Merozoites only infect aging RBCs
 - Relapses recorded up to 53 years

- *P. falciparum*
 - Malignant tertian malaria
 - Eradicated in the U.S.
 - Highest mortality rate
 - Releases glycoprotein that makes RBCs sticky (Rosettes)
 - Can have multiple infections
 - No hypnozoites, so no relapses

Double ring trophozoites

Up to 65% of the RBCs can be infected

Untreated patients usually die within a month

Vector

Anopheles spp.:

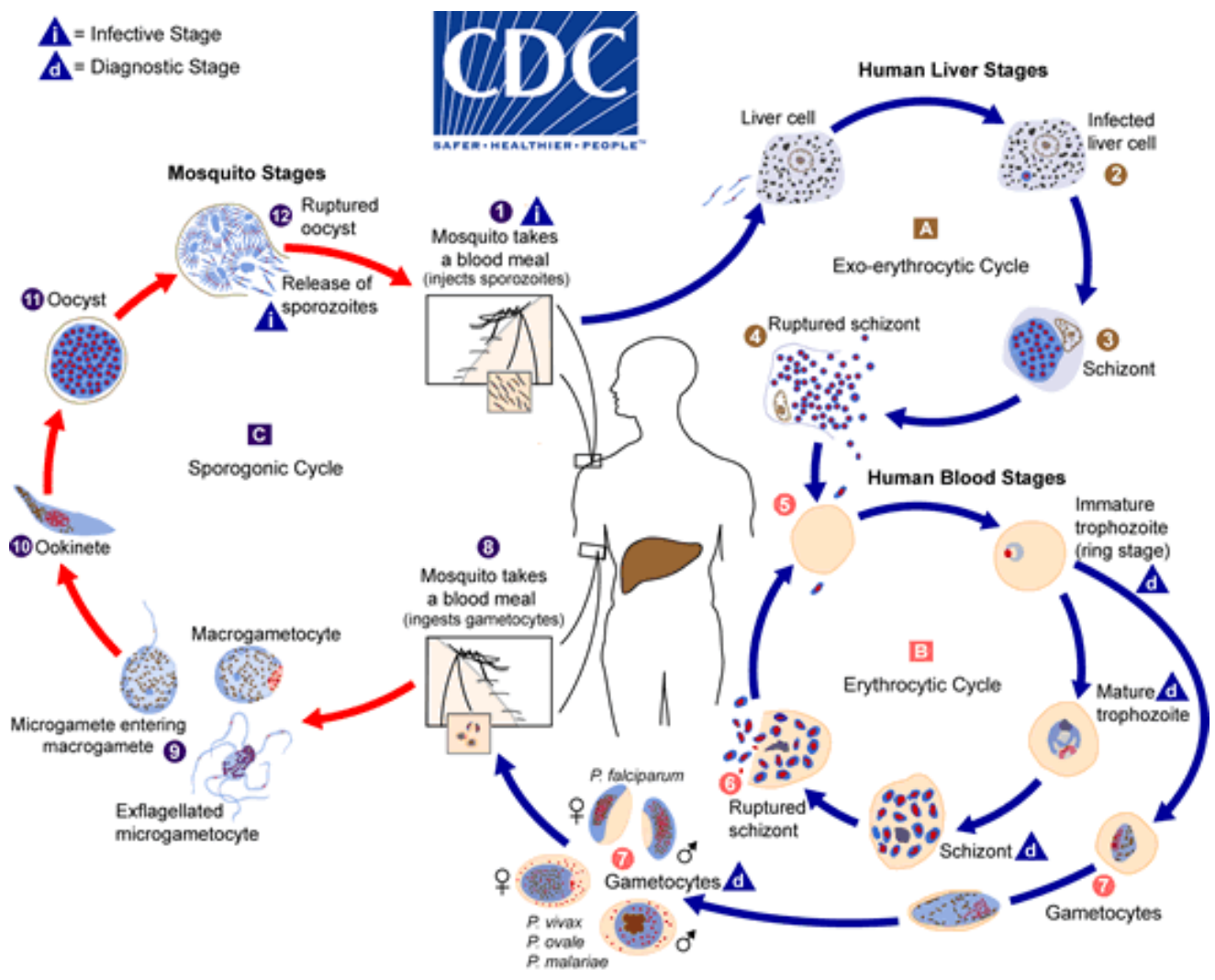
- Eggs are laid singly on the water and have floats
- Larvae do not have a siphon
- Resting position is at an angle to surface.

- Breeding locations
 - Standing water
 - Heavy vegetation
 - Heavy shade

- Only female mosquitoes bite. Aside from blood both sexes live on nectar, but one or more blood meals are needed by the female for egg laying, because there is very little protein in nectar.

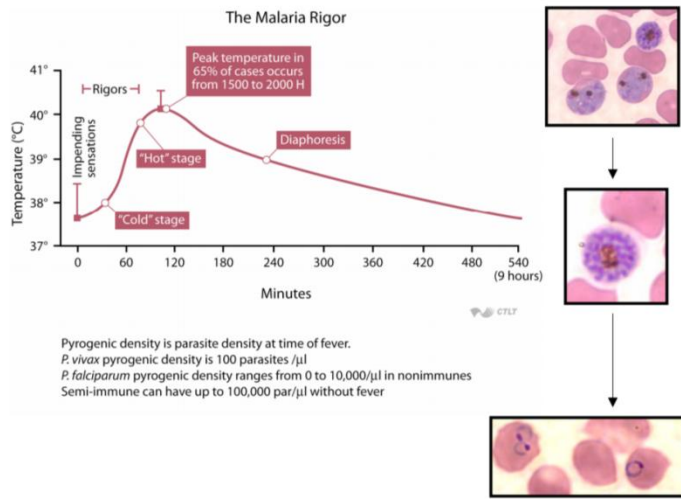
- Mosquitoes of the genera *Culex*, *Anopheles*, *Culiseta*, *Mansonia* and *Aedes* may act as vectors. The known vectors for human malaria belong to the genus *Anopheles*. Bird malaria is commonly carried by species belonging to the genus *Culex*.

Life Cycle



Geography and Paroxysms

See Slides 23-25 and 26 -28, respectively.

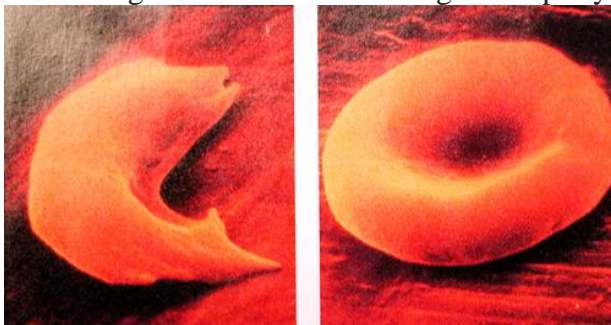


Areas of Resistance to *P. vivax*

See Slides 29-30.

Genetic Resistance

- Sickle cell offers selective advantage against *P. falciparum*. Persons with sickle cells have short life expectancy. Sickle cell disease takes a progressive toll on the body, raising the risk of infection, organ damage and stroke, and of acute chest syndrome, a life-threatening event in which the lungs fill rapidly with fluid.



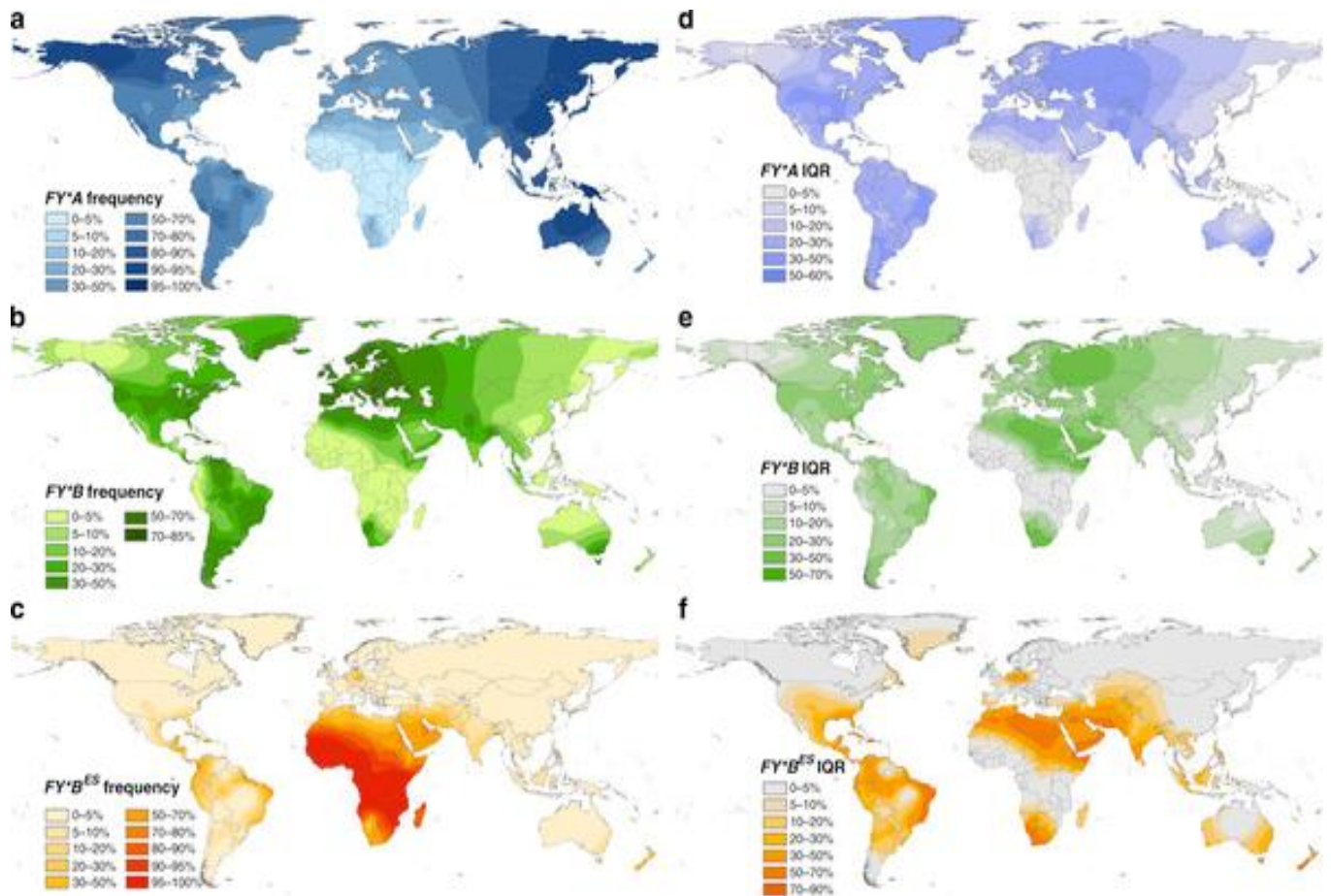
Sickle cell

Normal RBC

- The Duffy blood group system is a type of human blood with glycoproteins called Fy antigens on the surface of the red blood cells (RBC). There are 4 possible Fy phenotypes:

Fy^{a+b+} , Fy^{a+b-} , Fy^{a-b+} , and Fy^{a-b-} . The Fy^{a-b-} (Fy/Fy) genetic blood group occurs in nearly 70 percent of individuals of African descent. Because the Duffy antigens are not expressed in the Fy/Fy phenotype (there are no receptors to which malarial parasites can bind) the null condition is associated with some degree of protection against some forms of [malaria](#). Research indicates that the increased frequency of the Fy/Fy phenotype in West Africans and African Americans is the result of [natural selection](#) for disease resistance.

Duffy blood group system



History:

Keypoints:

- 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.
- • 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. • “mal aria” = bad air.
- • French: “paludisme” = rooted in swamp
 - Symptoms of malaria were described in the ancient Chinese writing Nei Ching. It was edited by Emperor Huang Ti
 - Hippocrates noted quotidian, tertian, and quartan fevers with splenomegaly.
 - Herodotus (2500-2424bc) Egyptian fisherman arranged nets to keep mosquitoes away
 - Medieval England - more crusaders taken out by malaria than fighting
 - Slave trade and colonial soldiers brought malaria to Europe and was devastating in the New World:
 - It is thought Spanish conquistadors and their slaves brought malaria to the New World.
 - 1880: Laveran identified pigment in body of living parasite in 26 patients. He is credited with describing the etiologic agent of malaria
 - In 1898 Ronald Ross demonstrated the existence of *Plasmodium* in the wall of the midgut and salivary glands of a *Culex* mosquito. For this discovery he won the Nobel Prize in 1902. Italian professor Giovanni Battista Grassi showed that human malaria could only be transmitted by *Anopheles* mosquitoes.
 - Sir William Gorgas was the first to successfully use bednets, anti-malarials, and mosquito control measures to prevent large-scale malaria infections. He did this as the Director of Sanitation during the construction of the Panama canal.
 - 1948: Shortt and Garnham describe exoerythrocytic stages of human malaria parasites

Disease burden

According to the latest WHO estimates, released in September 2015, there were 214 million cases of malaria in 2015 and 438 000 deaths.

Malaria in the United States gone due, in large part, to the spraying of dichlorodiphenyltrichloroethane (DDT).

Estimates of 100-659 million infected world wide –just humans.

Malaria treatment : available drugs

- Quinine.
- Chloroquine.
- Artemesinin products eg Artemether, artether, artesunate.
- Mefloquine.
- Antibiotics eg doxycycline, clindamycin, azithromycin.

