Lecture 13: Malaria

P. falciparum

"Eradicate Malaria by Spraying."
Indian Malaria Eradication Programme, [ca. 1960]. Poster.
Origins of malaria

• References to the unique periodic fevers of malaria are found throughout recorded history, beginning in 2700 BC in China
• The term malaria originates from Medieval Italian:
  – mala aria - bad air – swampy air was thought to cause it (close, but no vector)
• The disease was formerly called ague or marsh fever due to its association with swamps.

• Probably arose in Africa and evolved with us from primate ancestors

• 30 million year old mosquitoes of the right vector (Anopheles) trapped in amber
**Origins of malaria**

- Malaria affects birds, lizards, rodents, non-human primates and humans
  - Technically, in human malaria, the mosquito vector is the “definitive host” because the parasite reproduces in them (apologies to the Lyme group)
  - Malaria (*Plasmodium*) needs an anopheline mosquito and a vertebrate host to complete its cycle
  - The life cycle complexity and tight species associations suggest co-evolution
**Origins of malaria**

- Human malaria is caused by one of four species of a parasitic protozoan in the genus *Plasmodium*
  - *falciparum*
  - *vivax*
  - *malariae*
  - *ovale*

- Of these *P. falciparum* (also known as cerebral malaria) is the most lethal
  - estimated to cause 200 million clinical cases, and 1-3 million deaths (including many children) every year world-wide.
Wolfe et al., 1998 EID vol.4(2), figure 2

Split between Pre and Pfa estimated around 6-10 mya, consistent with human/chimp split estimate (Escalante and Ayala, 1994, PNAS)

- **P. reichenowi** (Pre) is from chimpanzees
- **P. gallinacium** (Pga) is from birds
- **P. berghei** (Pbe) and **P. yoelii** (Pyo) are from rodents.

**P. falciparum**
**P. vivax**
**P. malariae**
Macaques
**P. simium and brasilianum** from NWP
The Tropics as usual
Malaria worldwide

- Each year 350–500 million cases of malaria occur worldwide, and over one million people die, most of them young children in sub-Saharan Africa.
- In areas of Africa with high malaria transmission, an estimated 990,000 people died of malaria in 1995
  - over 2700 deaths per day, or a death every 30 seconds.
- One bite from an infected mosquito can mean weeks of fever and exhaustion, preventing children from going to school and adults from working to provide for their families.
  - Estimated 5-fold reduction in GDP in malarious countries
  - Estimated $12 billion loss to Africa annually due to malaria
- Close to 90% of malaria cases occur in Africa.

Sources: UNICEF, World Health Organization (WHO)
Malaria worldwide

• 41% of the world's population live in areas where malaria is transmitted (e.g., parts of Africa, Asia, the Middle East, Central and South America, Hispaniola, and Oceania).

• In 2002, malaria was the 4th cause of death in children in developing countries, after perinatal conditions (conditions occurring around the time of birth), lower respiratory infections (pneumonias), and diarrheal diseases.
  – Malaria caused 10.7% of all children's deaths in developing countries.

• In Malawi in 2001, malaria accounted for 22% of all hospital admissions, 26% of all outpatient visits, and 28% of all hospital deaths.
  – Since many people won’t go to hospital, real estimates are hard
Malaria at home

• Every year, nearly 1,500 cases of malaria are reported in the United States.

• Most of these cases occur in U.S. residents who become infected while traveling abroad.
  – 1,337 cases of malaria, including 8 deaths, were reported for 2002 in the United States, even though malaria has been eradicated in this country since the early 1950's
  – Of the 1,337 malaria cases reported for 2002 in the United States, all but five were imported, i.e., acquired in malaria-endemic countries.

• During 1963-1999, 93 cases of transfusion-transmitted malaria were reported in the United States
  – approximately two thirds of these cases could have been prevented if the implicated donors had been deferred according to established guidelines.

Source: CDC
Malaria at home

• Between 1957 and 2003, in the United States, 63 outbreaks of locally transmitted mosquito-borne malaria have occurred
  – local mosquitoes become infected by biting persons carrying malaria parasites (acquired in endemic areas) and then transmit malaria to local residents.

• Of the ten species of Anopheles mosquitoes found in the United States, the two species that were responsible for malaria transmission prior to eradication (Anopheles quadrimaculatus in the east and An. freeborni in the west) are still widely prevalent

• 92.7% of U.S. malaria deaths 1963-2001 were P. falciparum

• New York 1930s – Heroin needles maintained malaria, dealers started cutting ‘their wares’ with Quininine

Source: CDC
Malaria transmission

- The **sporozoites** from the mosquito salivary gland are injected into the human as the mosquito must inject anticoagulant saliva to ensure an even flowing meal.
- Once in the human bloodstream, the **sporozoites** arrive in the liver and penetrate **hepatocytes**, where they remain for 9-16 days, multiplying within the cells.
- Next they return to the blood and penetrate red blood cells, in which they produce either **merozoites**, which reinfect the liver, or **micro- and macrogametocytes**, which have no further activity within the human host.
- Another mosquito arriving to feed on the blood may suck up these gametocytes into its gut, where **exflagellation** of **microgametocytes** occurs, and the **macrogametocytes** are fertilized.
- The resulting **ookinete** penetrates the wall of a cell in the midgut, where it develops into an **oocyst**.
- **Sporogeny** within the **oocyst** produce many **sporozoites** and, when the **oocyst** ruptures, the **sporozoites** migrate to the **salivary gland**, for injection into another host.

Malaria transmission – what causes the symptoms?

• Malaria in the blood cell eats the hemoglobin, causing anemia
  – Dizziness, light-headedness, weakness, arthralgia (general joint aches)
  – Body responds with a spikey fever – different species cause different temperatures, cycles and durations

• Also alters the cell surface, making it “sticky”, so it sticks to blood vessel walls, causing further anemia and blockage of capillaries in the brain – cerebral malaria

• *P. vivax* and *P. ovale* can hang out in the liver for a long time and periodically re-emerge
  – Longest recorded incubation of *vivax* is 30 years
  – They can also go straight from there, and rip up the liver cells – causes hepatitis issues

• Malaria can clog up lots of organs – the spleen, the liver, the brain, the kidneys
  – Renal failure can manifest as “Blackwater Fever” wherein the hemoglobin from ruptured cells appears in the urine

• Cerebral issues cause developmental problems in children, especially from repeated infections
• Four Nobel prizes have been awarded for work associated with malaria:
  Sir Ronald Ross (1902)
  Charles Louis Alphonse Laveran (1907)
  Julius Wagner-Jauregg (1927)
  Paul Hermann Muller (1948)
• Working in India in 1858, Dr. Ross watched through a microscope the mechanism through which mosquitoes spread malaria.
  • Figured it out for humans, and bird to bird
• Laveran, working in Algeria in the 1880s, saw the parasites in red blood cells, and identified the protozoan as fundamental to causing the disease
• Jauregg used malaria to infect syphilis patients, using the fever and quinine to ‘burn’ syphilis out of the brain, while (mostly) not killing the patient with malaria
• Muller ‘rediscovered’ DDT as a useful mosquito preventative

1940s DDT indoors
Antimalarial drugs and strategies

- Quinine, plant-derived, works pretty well, also carcinogenic
  - From the cinchona tree (South America, 17th century).
  - Causes fever of its own – also contributes to Blackwater Fever

- Newer plant-derived artemisinin from the Qinghao plant (*Artemisia annua* L, China, 4th century) has become commercially available in the last decade
  - Resistance is already emerging in some *falciparum*

- Chloroquine was used for a long time, but the application was not controlled properly, and led to resistance
  - Also led to problems of secondary anemia and iatrogenic fevers, and consequent HIV transmission from blood transfusions

Sources: UNICEF, World Health Organization (WHO)
Antimalarial drugs and strategies

• Frequent and heavy doses of antibiotics, such as Doxycyclin
  – Fine for short tourist visits, impossible over the longterm

• Larium® - Mefloquine – another antimalarial, stronger than Chloroquine
  – Lots of neurological complications
  – Not a longterm drug – high toxicity
  – Mefloquine resistance

• Malarone® - Atovaquone-proguanil
  – Not the greatest stuff to take
  – Still (?) what they hand out to US travellers going to Africa, mostly

• The average cost for potentially life-saving treatments of malaria are estimated to be
  – US$0.13 for chloroquine
  – US$0.14 for sulfadoxine-pyrimethamine
  – US$2.68 for a 7-day course of quinine.

Sources: UNICEF, World Health Organization (WHO)
Antimalarial drugs and strategies

- Black market or OTC distribution of anti-malarials causes a suite of problems
  - Inappropriate application to all fevers
  - Non-compliance with full dosage

- Issues of availability versus compliance
  - Huge pharma question – worth investing if you can’t charge much?

- No way of supervising distribution and quality
  - A survey in Southeast Asia in 1999-2000 showed that of 104 shop-bought samples purportedly containing the antimalarial drug artemisin, 38% contained no artemisin.

- Kruger National Park tourist shop sells antimalarials next to the aspirin

Sources: UNICEF, World Health Organization (WHO)
Malaria transmission cases

- Residents of Asembo Bay (Western Kenya) were bitten 60-300 times a year by a malaria-carrying mosquito in the 1990's, before control measures (including the use of insecticide-treated bed nets) were put in place.

- 84% of the blood transfusions given in March-June 2000 in a major hospital in Kinshasa (Democratic Republic of Congo) were for anemia caused by malaria.

- Pregnant women have increased susceptibility to *Plasmodium falciparum* malaria; in malaria-endemic countries, *P. falciparum* contributes to 8-14% of low birth weight, which in turn decreases the chance of a baby’s survival.

Sources: UNICEF, World Health Organization (WHO)
**Antimalarial drugs and strategies**

- The best cure is prevention, and the best prevention is mosquito bed nets

- Netting protects people from mosquitoes while they sleep at night, when the mosquitoes come out.

- Back to bednets
  - Late 90’s – realization that DDT spraying wasn’t going to work, conversion of habitat into anopheline-friendly environments was on the rise
  - *P. falciparum* was resistant to everything
  - Vaccines, mosquito-blocking, mild-strain strategies, dead-end mosquitoes – not ready yet

- Permethrin (insecticide) treated nets really work, when used properly
  - Tucking in your bed net is complicated, and you have to stay away from the edges

Sources: UNICEF, World Health Organization (WHO)
My hotel room,
Entebbe, Uganda, 2007
**Antimalarial drugs and strategies**


- The cost for a bed net is $6, but since people in Africa often sleep two or more to a bed, the cost per person is about $3.

- Ideally, every person in the affected areas of Africa would be provided with a bed net.

- Besides saving lives, this would be an excellent economic investment, as the cost of malaria to Africans in lost productivity alone is estimated in the billions of dollars each year.

- Project HOPE sells bed nets to tea plantation owners to give to their workers
  - top-down strategy

Sources: UNICEF, World Health Organization (WHO)
Antimalarial drugs and strategies

- Spraying?
- WHO recommends DDT spraying again
  - Is working in parts of Mozambique where nothing else will
  - Indoor sprays are toxic, but there’s a tradeoff
  - Selection for indoor anophelines means that inside-wall sprays are needed
  - Fungal sprays are being employed in some places
  - Resistance to chemical sprays happens fast

Sources: UNICEF, World Health Organization (WHO)
Co-evolution and selection on humans

- Sickle-cell anemia
  - Hemoglobin molecules in the blood cell stick together, blood cell goes sickle shaped
  - Cells don’t look right and get taken off by the immune system
  - May happen before the cells release merozoites or gametocytes
  - Homozygous sickle-cell causes pre-adolescent mortality
  - But up to 10% of population carry the genes in high endemicity areas
  - 4 haplotypes of sickle have arisen, suggesting it is a selected advantage
  - Other mutations of HBB gene cause novel hemoglobin types which have a similar mode to cut the cycle – emerged in SE Asia and Western Africa
Co-evolution and selection on humans

- Blood disorders – Thalassemias
  - 50% reduction in clinical malaria in Liberia

- Duffy antigens
  - Absence of the antigens prevent *P. vivax* entering cells
  - Code for absence is rare in Europeans and Americans and common in West and Central Africans

- MHC molecule implicated in getting T cells to trigger B cells to recognize malaria
  - Fulani in Burkina Faso have lower malaria than their neighbors
  - Seem to have the right MHC
Avian Malaria

- Many birds can serve as a definitive host for *Plasmodium*.

- *Plasmodium* can be pathogenic to penguins, domestic poultry, ducks, canaries, falcons, and pigeons, but is most commonly carried asymptotically by passerine birds.

- *Plasmodium* may exploit several genera of mosquitoes (*Culex, Anopheles, Culiceta, Mansonia*, and *Aedes*) as vectors and intermediate hosts.

- Avian malaria has a worldwide distribution and is of great economic significance is to the poultry industry.

- Organisms such as *P. gallinaceum, P. juxtanucleare* and *P. durae* may cause up to 90% mortality in poultry.

- Incidentally, birds with avian malaria have been used as model systems for studying the pathogenesis and treatment of malaria in humans.

http://www.vet.uga.edu/vpp/clerk/jennings/index.php
Avian malaria and Hawaii

- Many bird species are in decline due to habitat loss and introduced predators in Hawaii
- Before Europeans got to Hawaii, there were no vectors for malaria
  - First mosquito introduction in 1826
  - 1800s – avian pox and early 20th century, avian malaria
  - It is thought that the introduction of rare birds from captivity to try to ‘re-stock’ the wild population, may have been the source of avian malaria
  - Wild populations were completely naïve to the malarias and huge epidemics swept through the natural populations
- Can only survive higher up mountains (volcano cones), where the temperature is too cool for the mosquito vector
  - Global warming is pushing the temperature band higher
  - Feral pigs are creating new mosquito habitat in the forest with rooting

Avian malaria and Hawaii – honeycreepers

December, 2004: An extremely rare Hawaiian bird has died in captivity, possibly marking the extinction of its species only 31 years after it was first discovered.

• The Po'o-uli, which was suffering from avian malaria, belonged to one of the world's most threatened bird families - the Hawaiian honeycreepers.

• Thirteen other honeycreeper species have already died out, in what some are calling Hawaii's extinction crisis.

• Failed plans
  • The small, stocky, brown Po'o-uli (Malamprosops phaeosoma) was first discovered in 1973, in Maui's Ko'olau Forest Reserve. Even then it was desperately endangered, with an estimated population of fewer than 200 individuals.
  • Since then, its decline has been steep. In 1995, fewer than seven birds were known and by 1997 that number had dropped to just three individuals.

• Search efforts
  • A hunt began for the two remaining birds - believed to be a male and a female - but they have not been seen for nearly a year and hopes for their survival are slim.

http://news.bbc.co.uk/1/hi/sci/tech/4066077.stm
Other diseases that bite – Cuba and Panama

• In 1899, after the Americans occupied Cuba during the Spanish-American War, Dr. Walter Reed traveled to Havana to combat yellow fever.
• Using brave volunteers, Dr. Reed demonstrated that yellow fever could only be spread by the *Aedes aegypti* mosquito.
• To rid the island of *Aedes aegypti*, households in Havana were ordered to dump ever container of water of pay a $10 fine.
• Cleanup squads fumigated houses, drained swamps, and poured oil into ditches.
• By 1902, yellow fever was eliminated from Cuba.

• The Panama Canal could not have been built had not the mosquitoes been eradicated by Dr. William Crawford Gorgas.
• The United States spent $3.50 on every one of the 100,000 workers in the Panama Canal Zone to rid mosquitoes from a 100-square mile strip of land.
• Yellow fever was eliminated by 1906.
• The incidence of malaria was reduced from 800 out of every 1,000 workers in 1906 to 16 out of 1,000 in 1916.
Other diseases that bite – the US mosquito forecast

- According to Matt Yates, president of the American Mosquito Control Association, there is a new menace called *Aedes albopictus*, the Asian tiger mosquito.
  - Tiger mosquito first discovered in the United States in 1985 in Houston, Texas
  - Considered to be a competent vector of yellow fever, and therefore, can bring jungle yellow fever to urban areas.
  - In addition, this mosquito may spread encephalitis.

- *Culex pipens*
  - This mosquito can be dangerous, particularly in Florida, because is spreads St. Louis encephalitis.
  - *C. pipens* is also a threat to dogs because of heart worms.

- The California salt marsh mosquito, *Aedes squimiger*, an important human pest in coastal California, was previously not suspected to be a vector of human pathogens.
  - Recent research suggests this pest as a new vector of California encephalitis.

- In addition, the Pacific coastal states are threatened by the Jamestown Canyon virus, which was isolated in three species of snowpool mosquitoes.

- And there’s many more on the horizon – range shifts and global warming

Source: American Mosquito Control Association, Pest Management Magazine, April 1992
What’s the risk?

• Anopheline mosquitoes – 380 species, 60 can transmit malarias
  – The primary vectors of human malaria in the Americas are *A. quadrimaculatus, A. freeborni, A. hermsi*; the potential vectors are *A. pseudopunctipennis, A. punctipennis, A. albimanus* and *A. crucians.*
  – *A. darlingi* subgroup in South America - despite eradication with DDT in the 1980s infected hundreds of thousands of people flooding into the Amazon region to look for gold and gems
  – *A. gambiae* in Africa is the aggressive night-feeder that took over from endemic mosquitoes, probably with the rise of agriculture
    • They CLING

• Plasmodium > 100 species of malaria (most non-human)
  – Many are endemic and low impact
  – Introduced to naïve populations, they can decimate

• Plasmodium is clearly able to adapt to new mosquito species

• Global warming is moving mosquitoes
  – Birds and rodents and humans all live quite close together in parts of the world…
Is this a zoonotic problem?

- Which host or vector should we ‘control’?
- Chemical arms race versus tried and true methods?
- One malaria does NOT fit all
  - Latin America tends to be chronic
  - Sub-Saharan Africa tends to be fatal
    - Different economic impacts, similar problems