Malaria

I. Introduction

Although we've spent a little time right at the beginning with diseases caused by organisms other than bacteria and viruses, most of those weren't terribly serious.

- That is, if we look just at # of people getting sick or dying.

- Now we get to one of the biggest killers of people in the world. It is neither virus or bacteria.

    - It is caused by a protozoan.

Malaria has also been around for an awfully long time.

- We have evidence that it's been around for over 50,000 years, and almost certainly much longer than that.

    - DNA evidence indicates it may have been around for 100's of millions of years.

- Because the disease is so serious, humans have actually “evolved” resistance to malaria.

- It affects not just humans, but also many other animals (though these are different species of malaria).

- It affects between 400 and 515 million people every year.

    - It kills between 1 and 3 million people every year.

    - As such, it's one of the three biggest killers of people every year (together with AIDS and tuberculosis).

- While it may not have quite the same dramatic impact as smallpox or the plague, over the years it's probably killed more people than anything else.

    - It's also affected history innumerable times:

        - Numerous attempts to conquer Rome failed because the besieging army came down with malaria.

        - The revolutionary war impacted both sides (one of the first expenses for Washington's army was for quinine).

        - Napoleon successfully attempted to use malaria in biological warfare by inundating part of the Dutch countryside so that British troops would come down with malaria (it resulted in over 3950 deaths).

        - over 1,000,000 soldiers in the Civil war came down with malaria. 10,000 died.

- there are numerous other examples.

II. Cause.

A protozoan parasite.

- Actually, four different parasites, but all of the same Genus.

- *Plasmodium falciparum, P. malariae, P. ovale,* and *P. vivax*

Generally, a mosquito of the Genus Anopheles will transmit malaria. Here are the details:

- A mosquito will bite an infected person and pick up gametocytes.

- These will change into male or female gametes (think sperm and egg).

    - These will then “fuse”, produce an oocyst which then releases lots of sporozoites which move to the salivary gland of the mosquito.

    - They are then injected when the mosquito feeds.

- From here the sporozoites move to the liver where they infect liver cells and change into merozoites.

    - These merozoites then spread out through the body and invade red blood cells.

- Merozoites do most of the damage:

    - They enter a red blood cell, reproduce, and then rupture the red blood cell. Each new merozoite then goes on to invade a new red blood cell to begin the cycle all over again.

    - A few merozoites will develop into gametocytes and start the cycle over.

III. Symptoms.

After infection, the “incubation” period is usually 10 days to 4 weeks. But a range of 7 days to one year is possible.

Some symptoms of malaria may be confused with the flu:

- fever, chills, shaking, headache, muscle aches, tiredness

- sometimes nausea, vomiting & diarrhea.

- this makes it difficult to diagnose (more later) in countries like the U.S. where malaria is uncommon (most cases are in travelers from infected areas).

- depending on the type of malaria, these symptoms can get much worse.

- often (particularly with non-*P. falciparum* malaria) one gets recurring fevers.

    - these match up pretty well with the times that the red blood cells lyse (burst open).

        - at this time, lots of damage is done and lots of toxins are released.

    - these fevers may be every 48 hours or every 72 hours depending on the type of malaria.

        - in between, one can be feeling relatively normal, though subsequent episodes can become worse.

- often, other organs can become involved as well:

    - kidneys start to malfunction due to the large amount of hemoglobin released with the blood.

    - cerebral malaria - involvement of the brain

        - this can often be fatal within 1 - 3 days and has an associated mortality of between 25 - 50%.

        - It's not clear what causes this, though two ideas are the blockage of blood vessels going to the brain (due to all the dead red blood cells) or the release of toxins that may cause the immune system to overreact.

            - In both cases it's possible that the blood-brain barrier may disintegrate.

    - in general, for malaria, if symptoms become severe, mortality is over 20%.

    - *P. falciparum* causes the most sever symptoms by far.

    - *P. vivax* and *P. ovale* may cause chronic malaria (the parasite stays dormant in the liver and may come out months or years later).

        - *P. malariae* causes less sever symptoms and can become chronic, though not in the same way.

If a person survives the initial fevers and other symptoms of malaria, they may often gain some degree of immunity (though not so much with *P. vivax* and *P. ovale* in their recurring forms).

Regardless, it usually isn't complete immunity, and often only lessons the severity of the symptoms and keeps the parasite from running amok.

IV. Immune system response.

Unfortunately the immune system doesn't get a good chance to respond.

- Most of the life cycle of the parasite is spent inside red blood cells, where the parasite can hide from the immune system (infected liver cells are similar).

- The spleen apparently can destroy infected red blood cells, but according to some sources infected red blood cells can “stick” to blood vessels thus preventing them from getting to the spleen.

- The parasite also seems to have the ability to change it's antigens, and keep ahead of the immune system.

- Still, there does seem to be some type of immune response:

    - The immune response seems to involve macrophages, T-cells (particularly in the liver) and antibodies.

    - Some immunity is also gained by babies from their mother's breast milk.

V. Cure, treatment & prevention.

Fortunately there is a cure for malaria:

Antimalaria compounds are available and will kill the parasite:

- Chloroquine is cheap and easily available.

- It will eliminate any parasites in the blood.

- However, it may not eliminate parasites living in the liver.

- To do this, another drug, primaquine, is often used.

Chloroquine is also used for prophylaxis (to prevent malaria).

- For travelers, it's recommended to start prophylaxis before leaving for areas where malaria is endemic, and then to continue prophylaxis for a while after getting back.

Of course, the problem is that the malaria parasites are fighting back.

- There are some parts of the world where resistance to chloroquine is high and other drugs must be used.

- fortunately there are other drugs, so malaria can still be cured and treated

    - however, other drugs are often more expensive.

The problem is getting the drugs to people who have difficulty getting to any type of pharmacy or doctor.

- that and the cost of the drug.

- consider that prophylaxis is not a cure - if one lives in endemic areas one has to take the drugs week after week.

    - recently, in some countries, counterfeit drugs have also shown up. They're hard to tell apart from the regular drugs and have led to deaths.

Vaccines are not available yet. Despite years of effort, the progress towards a malaria vaccine has been about as successful as the progress towards an AIDS vaccine.

- Some promising studies from the 1960's showed about a 60% efficacy for a vaccine made from attenuated (with radiation) sporozoites in mice. No luck with this one yet.

- One study indicated that to get a similar benefit in humans, a human would have to be exposed to over 1000 bites from infected irradiated mosquitoes.

    - this seems totally silly, but still, some progress to "simulate" 1000 bites had been made and it's possible this may actually get somewhere.

- There are numerous different vaccines that are being worked on, and some may even be ready for trial.

    - But right at the moment there's nothing easily available yet.

Insecticides:

- Don't underestimate this. They're the reason we don't have malaria in the United States.

    - Malaria was eliminated in the United States due to DDT. Yes, DDT.

    - Think what you will, but DDT did have some benefits.

    - But it was an ecological disaster, and due to this (and increasing resistance to DDT by insects), DDT is now banned in the U.S.

        - Overseas it's still allowed, though only in carefully controlled situations:

            - Spraying the inside of buildings (walls, ceilings, etc.) will kill mosquitoes and is rather effective.

            - This also doesn't affect the environment nearly as much as what we used to do (just spray it everywhere).

    - Other insecticides are also available, but are more expensive than DDT.

- mosquito nets are also very effective

- if you ever travel in areas with lots of malaria, use the mosquito nets!! There's no reason not to.

- even better is to combine mosquito nets with insecticides:

  - coating the net with insecticide will kill mosquitoes when they make contact with the net.

- bedclothes/sheets can also be impregnated with insecticide.

Others:

- recently sterile mosquitoes have been released. This shows some promise as this prevents offspring.

- work is being done to breed mosquitoes that are resistant to the parasite.

  - wouldn't get rid of the mosquitoes, but definitely better than nothing.

- better education:

  - a lot of people in areas with endemic malaria just assume they have malaria when they get sick and start taking drugs.

    - this has increased resistance (obviously).

    - it would be good to have better diagnostics and better enumeration of the symptoms.

  - similarly, in the U.S. (or Europe) where malaria is not that common, many doctors fail to recognize it, causing the opposite problem.

VI. Diagnosis & history.

The connection between mosquitoes and malaria took a long time to figure out.

People knew it was more common near water (particularly swamps), and even the name (malaria) refers to the “bad air” near swamps.

- The parasite was discovered in red blood cells in 1880 by a Frenchman, Charles Louis Alphonse Laveran (who won the Nobel prize in 1907).

- Carlos Finlay (yellow fever!) suggested mosquitoes may be transmitting diseases.

- Finally Sir Ronald Ross in 1898 in India proved that mosquitoes transmit malaria. He received the Nobel prize in 1902.

Laveran detected the parasite in red blood cells, and this is still the preferred (and cheapest) way to diagnose malaria:

- take a little blood (usually from the fingers, not through the veins)

- make a blood smear, and observe. The parasites should be easy to see IF YOU KNOW WHAT YOU'RE DOING!

- by taking more than one blood smear one can often also figure out what kind of malaria a person has since they all look a little different.

- more advanced tests are available, but (believe it or not) are not as accurate as the good old blood smear.

    - but they might be appropriate if no microscopy is not available or if no one who knows what they're doing is around.

VII. Genetics.

Malaria has been around for a long time, and some humans have evolved resistance to malaria.

The most famous example is probably Sickle cell anemia:

- This is an example of something called incomplete dominance.

    - it not the usual dominant/recessive.

    - homozygous individuals either:

        - don't get sickle cell (but get malaria)

        - get sickle cell (which is often fatal)

    - heterozygotes are generally normal but much more resistant to malaria. Their cells will sickle under poor oxygen conditions, or when attacked by the malaria parasite (*and the infected cells get destroyed*).

    - heterozygotes have a distinct advantage.

        - it's a bit strange, since both homozygote conditions are at a disadvantage.

        - due to the way genetics work, we can't guarantee only heterzyogotes in every generation.

And it's not just sickle cell - a number of other mutations have arisen that help humans fight off malaria:

- A group of recessive mutations called thalassaemias occur in areas with lots of malaria, particularly the Mediterranean.

- It's not clear how this might work, but it's associated with a 50% decrease in getting malaria.

- It does cause anemia, though, so it's considered a genetic disease

A lack of something called Duffy antigens confers resistance to *P. vivax* (*P. vivax* uses these antigens to get into red blood cells).

- It's common in areas with high incidence of *P. vivax*.

Glucose 6 dehydrogenase deficiency:

- this deficiency can cause red blood cells to break down in response to various environmental queues.

    - e.g. certain beans

- But it seems to confer increased resistance to severe malaria.

- Strangely, it also causes problems (hemolytic anemia) if a person with this deficiency takes primaquine.

    - Usually, if primaquine is needed, a test for this deficiency is done.

Others:

- various mutations to hemoglobin

- possibly also some special immune system mutations

In short, malaria is so serious and has been around so long that we've piled up mutations to help fight it off.

- not just one or two, but a whole bunch!

- of course, we can be pretty sure that the malaria parasite isn't standing still all this time. It's bound to be evolving it's own counterstrategies (and this has probably been going on for millions of years!)

VIII. Current Status & miscellaneous.

As usual, malaria affects mostly the third world, in particular Africa.

According to one estimate, the economic impact of malaria on Africa exceeds 12 billion dollars a year.

- This wouldn't be so bad for a rich country, but the countries in Africa don't have that big a budget.

- It's thought that malaria is making large contributions the continuing poverty in Africa.

Unfortunately, being a disease of the rest of the world, until recently not much effort was put into finding better treatments and/or vaccines.

- A lot of folks have recently highlighted the suffering caused by malaria:

    - The chairman of Micro$oft, Bill Gates and his wife Melinda have contributed almost a billion dollars to the fight against malaria.

        - (doesn't change the fact that Windows is a lousy operating system......)

    - (incidentally, although there's been a lot of press for the U.S. government and its contributions to malaria, the total numbers aren't a whole lot higher than what Bill & Melinda Gates have done.)

    - Other sources and governments have also made contributions, and this has helped to get some sorely needed research done.

Finally, what about AIDS and malaria?

Apparently, if someone with AIDS develops malaria, the HIV becomes about 10 times as common in the blood as in other folks.

- This makes it much more likely that that person can pass on the HIV.

- Estimates are that tens of thousands of HIV infections may be due to this "synergy" between AIDS and malaria.

The reverse doesn't seem to be true (HIV doesn't make malaria worse).