Understanding Epidemics
Section 3: Malaria & Modelling

PART B: Biology

Contents:

Vector and parasite

Malaria is caused by a type of parasite that is carried by a type of mosquito. The mosquito is the vector of the disease.

In total there are over 150 named species of the parasite *Plasmodium*, but only four of these species can transmit malaria to humans: *P.falciparum* (the most deadly) , *P.vivax*, *P.ovale*, and *P.malariae*.

Apart from *P. malariae* that can cause malaria in higher primates, these parasites can't cause malaria in animals, only in humans.

Animals can also get malaria but this is caused by other species of *Plasmodium* and these cannot cause malaria in humans.

The malaria parasite is transmitted to humans by mosquitos (it is transmitted when an infected mosquito bites a human). However, not all species of mosquito can carry the parasite responsible for causing malaria in humans.

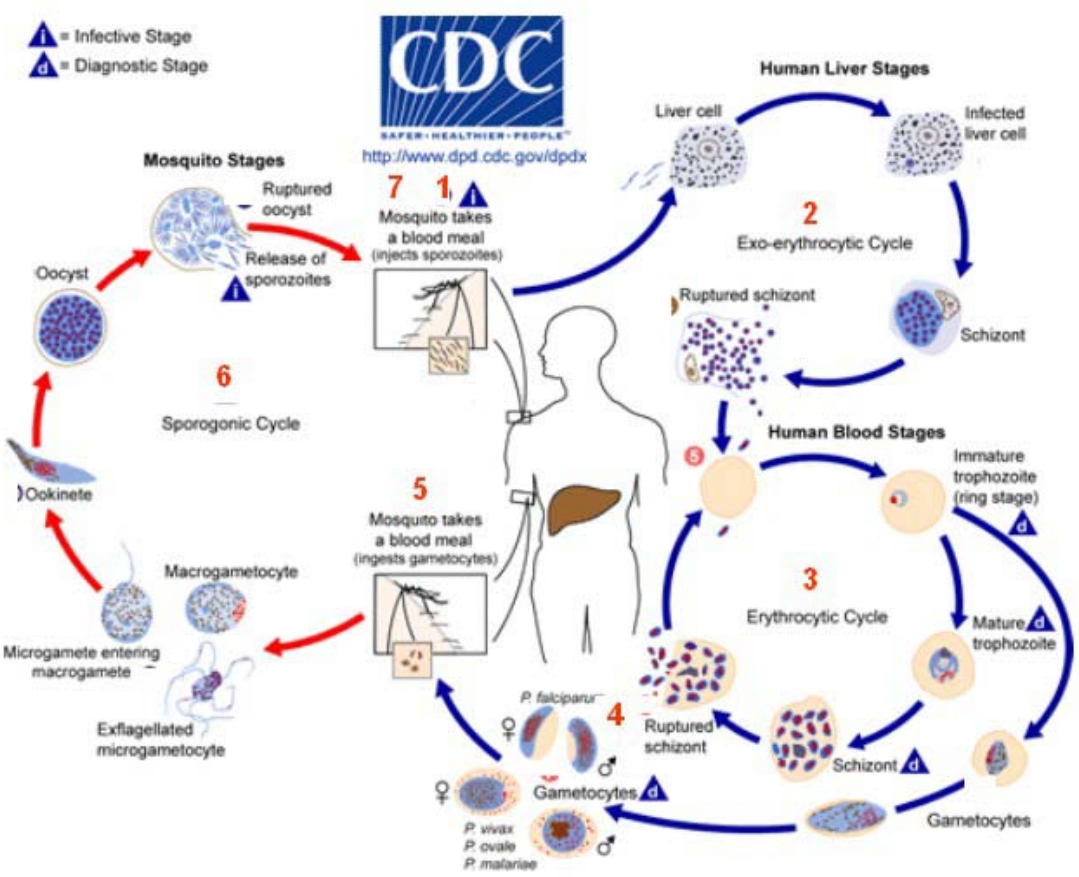
The mosquitoes which can carry the malaria parasite are *Anopheles* species mosquitoes. There are about 400 species of this mosquito of which just over 40 species are important transmitters of the malaria parasite to humans.

The key mosquitoes for tropical Africa are *Anopheles arabiensis,* normally written *A. arabiensis, A. funestus and A. gambiae .*

Given the number of deaths annually, in excess of one million, caused through infectious mosquito bites, the *Anopheles* should earn the title of 'the species which kills most people.' Sharks kill only 6 humans per year in comparison.

Biology of the malaria parasite

The exact development of the parasite depends in part on the type of parasite. The diagram below shows the general development stages of the malaria parasite in both the vector (mosquito) and the host (human).



The stages:

Stage 1: bite from infected mosquito

At this stage, a female *Anopheles* mosquito who is infected with the malaria parasite bites an uninfected human. As it takes the blood meal the mosquito injects sporozoites (the single cell form of the parasite) which have been in the salivary glands of the mosquito into the human.

Only the female mosquitoes bite humans as they need the blood meal for protein to allow them to develop eggs.

Stage 2: exoerythrocytic stage

Stage 2 is called the exoerythrocytic cycle. Erythrocytic means 'in the red blood cells', so EXOerythrocytic means outside the red blood cells. This stage is therefore the stage in the parasite lifecycle which takes place outside the red blood cells.

In stage 1 the mosquito injected sporozoites into the human. Some of these will be killed by the body's immune system, but those which aren't move to the liver where they develop and multiply and release merozoites into the blood stream.

Stage 3: erythrocytic stage

Stage three is the stage which ocurrs in the red blood cells (RBCs) and is called the erythrocytic cycle.

In this cycle the merozoites which have been released from the liver attach to RBCs and develop and multiply further.

The merozoites produced as a result of this development are found in the blood about 9-12 days after the person has been infected (this depends on the strain of parasite). This delay in time means that the symptoms of malaria also don't occur until over a week after being bitten, and also, a person is not infectious immediately.

There are three stages to the development of the merozoites in the RBCs.

1. First the RBCs become infected by the merozoites
2. Secondly, the merozoites develop into trophozoites.
3. The parasite continues to develop and forms schizonts. Schizonts are cells which contain many merozoites. The schizont cells eventually rupture and the merozoites are released into the blood stream. These merozoites then continue to develop in the same way.

This cycle, from meroziote - trophozoite - schizont - cell rupture and release of merozoites occurs about every 48-72 hours depending on the strain of parasite. Symptoms occur at the point when the RBCs eupture and so tend to occur in a cycle.

It is what happens at this stage of the parasite cycle which can cause death in humans. The parasite causes death by a number of means.

- When the RBCs which have been infected and become schizonts rupture, this can cause shock due to loss of water and electrolytes. Becuase there's not enough fluid, blood pressure falls and the vital organs don't get enough blood.

- The rupture of blood cells also leads to the release of large amounts of residue pigments that are very toxic and can lead to kidney failure.

- The invasion of red blood cells leads to haemolytic anaemia (a severe form of anaemia caused by the breakdown of RBCs) that can lead to heart failure in infants because the heart has to work harder as the body is not getting enough oxygen.

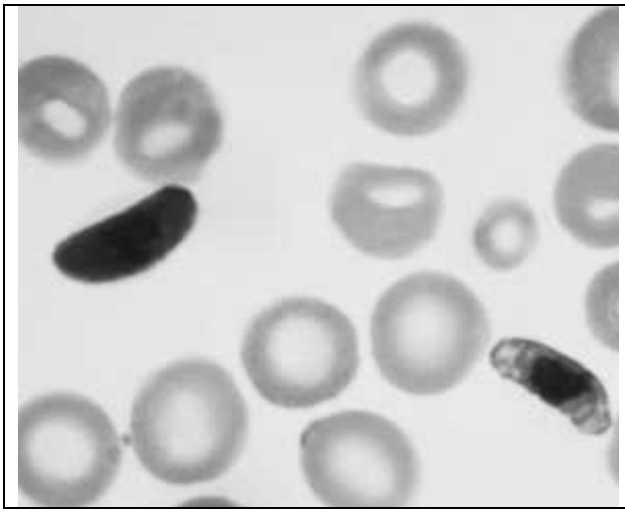
- Infected blood cells can block capillaries and thus affect circulation in major organs brain, lungs, kidneys leads to organ failure and death.

Stage 4: Gametogony

In the previous stages the reproduction of the parasite has been asexual - that is there are no male or female forms.

After a while, some of the merozoites which are released when a schizont ruptures develop into gametocytes (male and female forms of the parasite) instead of continuing the asexual reproduction cycle described in stage 3.

The male form is called a microgametocyte, and the female form is called a macrogametocyte.



The image on the left shows both a macro- and a micro-gametocyte.

The Microgametocyte (male) is on the right, and the macrogametocyte (female) is on the left.

Microgametocytes are usually smaller and less common than macrogametocytes.

Once this stage is entered and gametocytes have developed, the person is infective (i.e. can infect others).

Stage 5: bite from uninfected mosquito

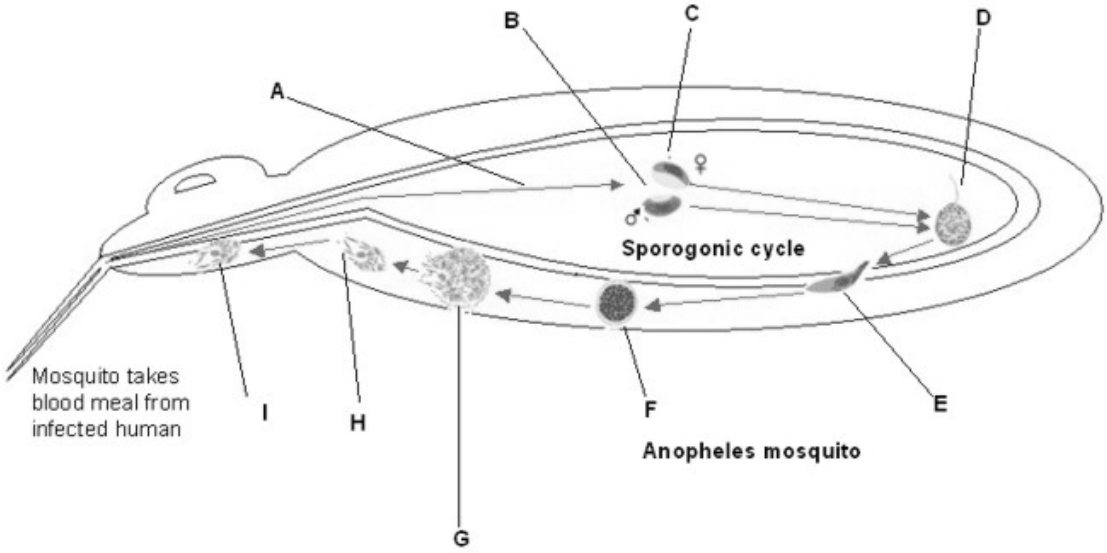
Stage 4 was the final stage of the *Plasmodium* lifecycle to take place in the host (human). From stage 5 onwards, the lifecycle continues in the vector (mosquito).

Although it is important to note that the human cycle (stages 2-4) continue to happen.

Stage 5, like stage 1 involves a female *Anopheles* mosquito taking a blood meal from a human. However, whilst in stage 1 the mosquito was infected and the human uninfected, in stage 5 it is the human who is infected and the mosquito which is uninfected.

As the mosquito feeds off the infected human, it ingests the *gametocytes* which developed in stage 4.

Stage 6: Sporogonic cycle



The diagram above shows the sporogonic cycle. This is the part of the lifecycle of the parasite which occurs in the vector (mosquito).

As in the host (human) the parasite develops and multiplies inside the mosquito. However, whilst this reproduction was asexual in the human, in the mosquito it is sexual.

The stages of the cycle are (the letters correspond to the diagram above):

A. As the mosquito feeds on the infected human, the gametocytes which developed in the human in stage 4 are ingested by the mosquito - they enter the mosquito's stomach.

B. The male gametocytes are called microgametocytes.

C. The female gametocytes are called macrogametocytes.

D. When the micro- and macro-gametocytes come together, fertilization occurs and a zygote is formed.

E. This zygote elongates and becomes a ookinate which can penetrate (go through) the mosquito's midgut wall, leaving the stomach.

F. These ookinates develop into oocysts which contain lots of sporozoites.

G. After a while the oocysts rupture, releasing the sporozoites.

H. The released sporozoites move to the salivary glands of the mosquito.

I. Next time the mosquito takes a blood meal these sporozoites are injected into the human and the cycle begins again at stage 1.

Stage 7: bite by infected mosquito

Stage 7 is the same as stage 1, an infectd mosquito bites an uninfected person and the cycle begins again.

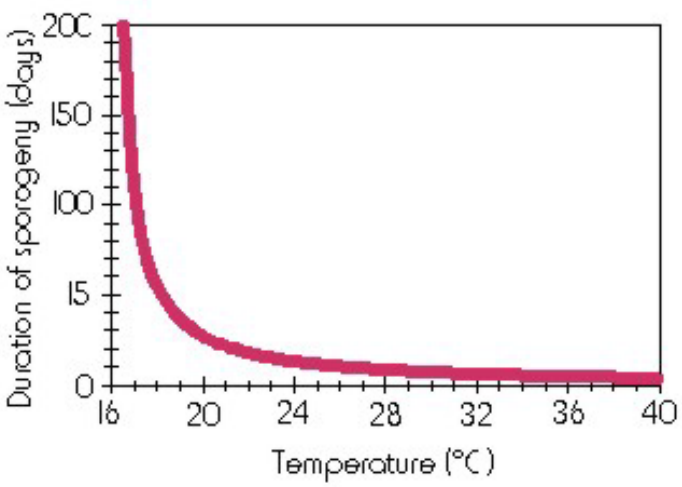
Even though the stages are numbered from one to seven, the cycle doesn't necessarily have to start at one. In fact stages 1 and 7 are the same (just different people).

The mosquito bite at stage 1 is from a mosquito which has already been infected so stages 5 and 6 must have already happened due to biting an already infected human. But if we start at stage 5, the human needs to have already been infected so stages 1 - 4 must have already occurred. Which came first? It is a bit of a chicken and egg puzzle!

Development time

The development time in the human host is about two weeks and in the vector it depends on the temperature.

The graph below shows the relationship between the ambient temperature (oC) and the length of the sporogonic cycle (development of the parasite within the mosquito) in days.



The graph begins at 16^{o}C as this is the lowest temperature at which parasite development takes place.

This relationship needs to be considered closely linked to the affect of temperature on mosquito survival (see the adult stage of the mosquito cycle below), as the mosquito needs to survive long enough for the sporogonic cycle to take place.

The ideal temperature is around 20^{o}C and so sporogeny generally takes about 10 days.

Further details on this temperature dependence are discussed in the modelling section.

Biology of the Anopheles mosquito lifecycle

Only the female mosquitoes transmit malaria as only they need the blood meal for protein to allow them to develop their eggs.

The development cycle of the mosquito is called the gonotrophic cycle. There are four stages to this cycle:

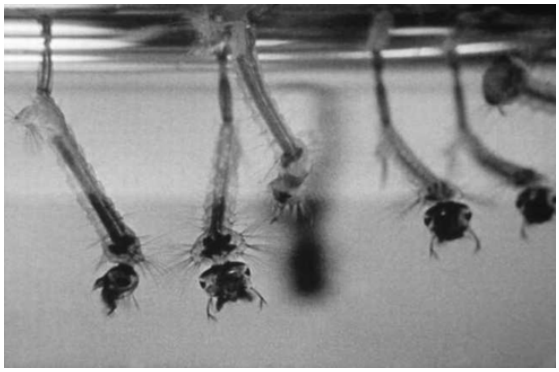
Eggs

After taking a blood meal the female mosquito rests for about 2-3 days while the eggs develop. The eggs are then oviposited in water which can be anywhere from a bike tyre to an irrigated field or slow moving irrigation channel.

Each female lays about 50-200 eggs each oviposition. The eggs have floats on them so that they stay at the water's suface. The time it takes for the eggs to hatch depends on temperature (longer time in colder temperatures). It usually takes about 2-3 days (but can be up to3 weeks).

Larvae

Mosquitoes require a body of still water as this is where the eggs develop.

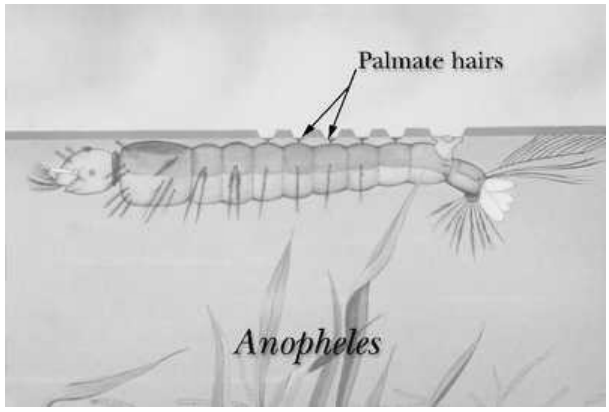


Mosquito larvae of most species (but not all) have a prominent breathing siphon (tube). You can see this in the picture on the left.

The larvae rest suspended diagonally from the water surface, while the end of their siphon tube penetrates the surface, this allows the larvae to access their air supply. It works a bit like a snorkel.

Anopheles are however one of the species which don't have these siphons.

Instead they lie suspended horizontally (parallel to the water's surface). They have small hairs which keep them attached to the water's surface and therefore able to breathe. You can see these on the diagram on the right.



Pupae

The next stage in mosquito development is pupae. They are comma shaped, and as with the larvae they stay at the surface of the water in order to breathe.

During this stage, the eyes, legs and wings develop and after a few days in this stage, the surface cracks and the adult mosquito emerges.

Adults

The time it takes from egg to adult varies according to the temperature, but it is usually about 10-14 days in tropical countries.

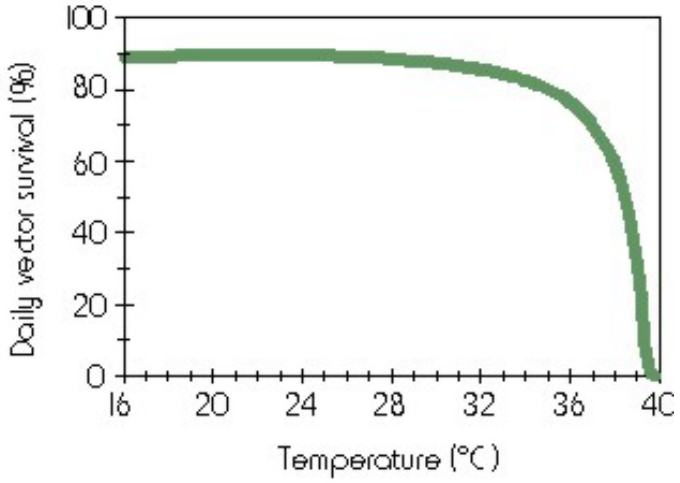
Adult mosquitoes usually mate a few days after emerging from the pupae. The male mosquitoes form large swarms and the females fly into these in order to mate.

It is only the females who take blood meals. Male mosquitoes feed on sugar and so get this from nectar and any other readily available sources of sugar. Females also feed on sugar, but they need the protein from the blood in order to develop the eggs.

After feeding, egg development takes about 2-3 days and the female rests and doesn't feed during this time. After the eggs are laid the cycle starts again and the female mates and seeks another blood meal.

The length of time a mosquito lives for is dependent on temperature. For male mosquitoes it is usually a week, and for females usually up to 2 weeks.

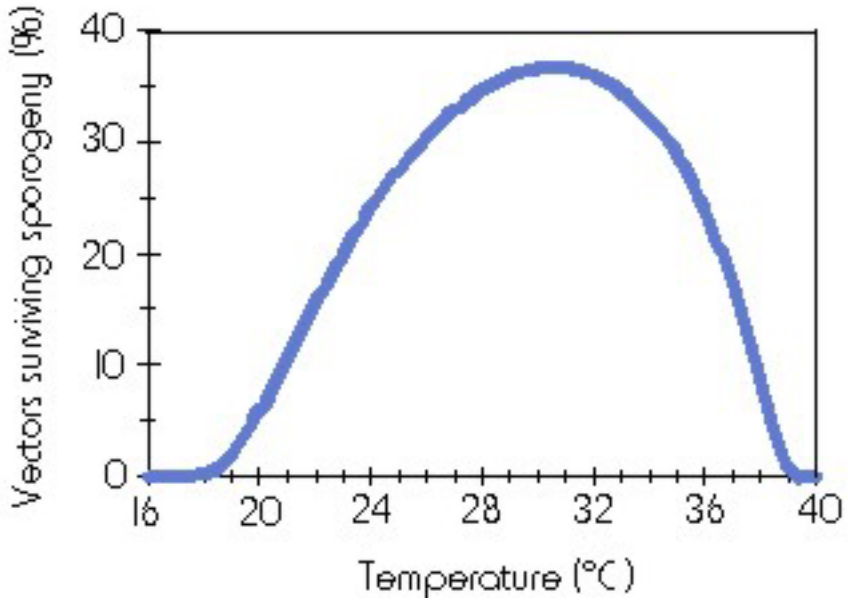
The graph below shows the percentage of mosquitoes who survive for a day or more depending on temperature.



This is very important for malaria rates as if the female mosquito doesn't live long enough for the sporogonic cycle to occur (the development of the parasite within the mosquito) then malaria won't be transmitted.

As the length of the sporogonic cycle depends on temperature too, there is a very delicate temperature balance between mosquito survival, sporogonic cycle length and malaria transmission.

This relationship is shown in the graph below. It shows the percentage of mosquitoes which survive through the whole sporogonic cycle depending on temperature.



If the temperature isn't right, either the parasite won't develop or the mosquito will die before the sporogonic cycle has completed and she has taken another meal and so malaria will not spread.

Understanding this relationship is important for prediciting transmission and is discussed more in the modelling pages.

This development cycle, from eggs to adults, depends on the water temperature. The eggs mature and the mosquitoes emerge and the cycle begins again.