Host-Pathogen Interaction (Immunology)
Prof. Himanshu Kumar
Laboratory of Immunology and Infectious Disease Biology
Department of Biological Sciences
Indian Institute of Science Education and Research (IISER) – Bhopal

Lecture - 79
Introduction to the Parasite Infection – Malaria

Hi. So we have learned various host pathogen interaction and in that series we have learned about the host virus interaction, host bacteria infection. We have learned about the host fungal infection and now we are reaching towards end and we will learn about the host parasite interaction. So, you know there are variety of parasites and these parasites are causing quite serious diseases in human as well as in some animals as well.

So we are going to discuss about these parasites. So, in this session, first I will introduce about parasites and then we will take one parasitic disease which you are very well aware that is malaria, we will take this malaria in great detail. So after that we will discuss also about African sleeping sickness which is also a quite serious disease and we will finish this course. So let us begin with the parasites.

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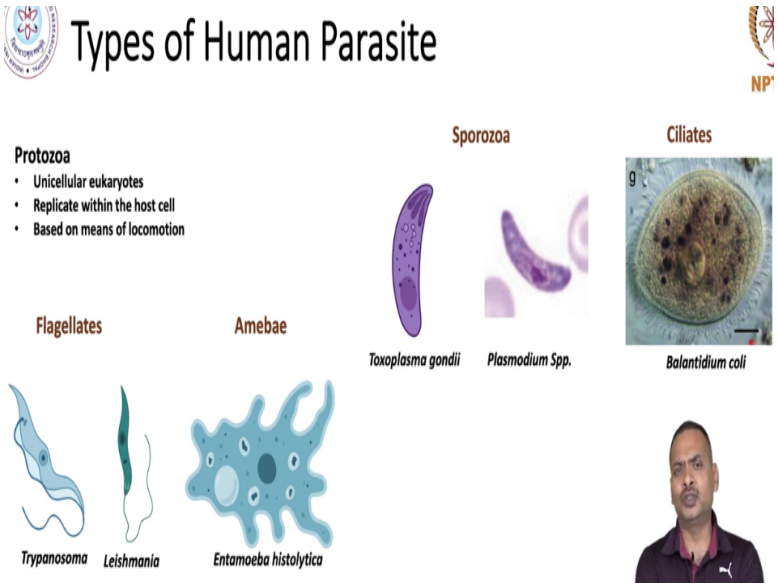

So there are two major kinds of human parasites. So one parasite we categorized as a protozoa and probably you are aware that protozoa is a unicellular eukaryotes. They have a proper nucleus that is why we call it as eukaryotes. They replicate within the host, these parasitic protozoa they replicate within the host. There are also various free living protozoa right like

paramecium, probably you might have studied in class 10th or 12th standard or there are amoeba.

But the parasite which we are going to discuss or I am going to discuss is we are going to talk about those protozoa which is causing disease in human. So these parasites or these protozoa parasite more precisely replicate within the host cell and based on means of locomotion, so these parasites move, there are various kinds of movements. These parasites are categorized in four major groups. The first is flagellates.

Here you can see that these flagellates are having one flagella which is used for the locomotion, for movement of these parasites. Here you can see there are two very important examples shown that is Trypanosoma and Leishmania. So, these cause very complicated diseases and they are basically parasite in human. If they will reach in the human, then that will cause the disease. Another is amebae, so these amebae are like amoeba.

And they basically move in the host through one specialized system which we call it as the pseudopodia. They have pseudopodia in order to make a movement. And one best example, one best parasitic protozoa is the Entamoeba histolytica, here you can see this Entamoeba histolytica. Another is a Sporozoa. So these Sporozoa they do not have any flagella, they do not have pseudopodia, so they basically glide.

Here you can see there are two very good examples, one is Toxoplasma gondii which again cause the disease and Plasmodium species. There are various plasmodium species which cause a disease in human that is known as malaria. There is the last group of this parasitic protozoa is ciliates. So these ciliates are having numerous cilia. So, these numerous cilia are used for the movement and the one best example is Balantidium coli.

This causes disease but this disease is quite rare, so we are not going to discuss anything about the Balantidium coli. I am just showing as one of a ciliate protozoa parasite.

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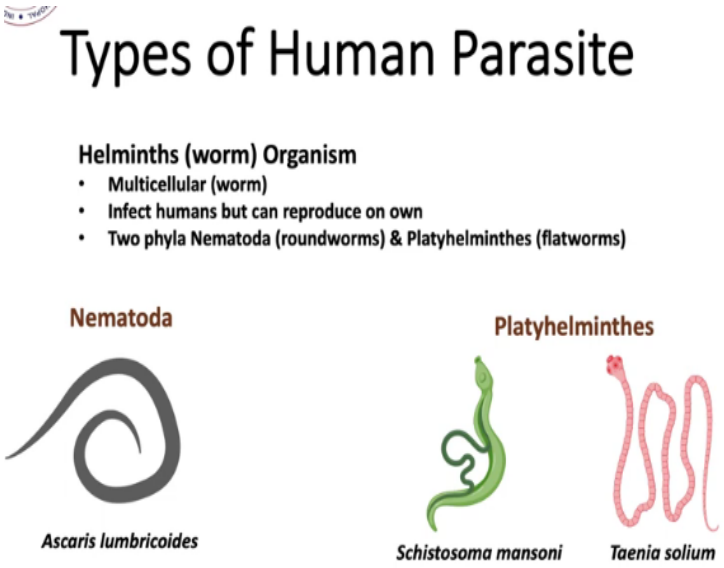

Another major group of parasites are here you can see we call it as helminths or worm, woarm infection. So these helminths in general they are multicellular and please note the protozoa is microscopic, they are not microscopic, they are quite big parasite. They are big parasite present in the host, So helminths are macro parasite and they are multicellular, they are woarm basically. They infect human but can reproduce by own.

There are two major phyla of these helminths, one we call it as Nematodes. So nematodes are basically here you can see that there is one very good example that is Ascaris lumbricoides, we also call it as a round worm, so their cross section will give the round appearance. And another is flat helminths, a flat worm. So this flat worm if you make a cross section you will see a flat kind of architect.

The two best examples for this group of animal or parasite are Schistosoma mansoni and another is Taenia solium and we also call tinea solium as a tape worm. It is a very long parasite and if they infect the human they reside in our body and that cause a variety of serious problems. So this is about the parasite. Now I will introduce about a few terms which is important in case of parasite biology.

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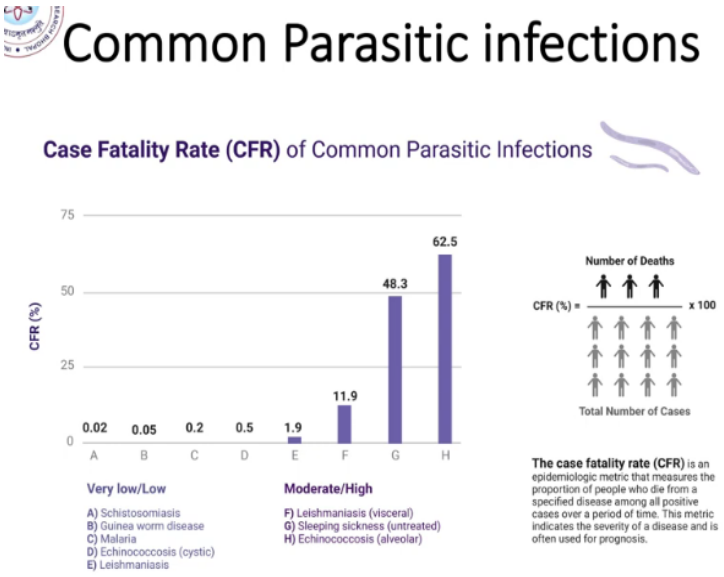

So common parasitic infection, here you can see that there is a term known as case fatality rate, it is a common parasitic infection and what is the case fatality rate. This is an epidemiologic metric that measure the portion of people, here you can see the portion of people who died from a specific disease, let us take the example of malaria. So there are the people who died by this malaria, died from a specific disease among all positive cases over a period of time.

This metric indicates the severity of a disease and is often used for prognosis. Here you can see that there are some diseases like leishmaniasis, sleeping sickness, echinococcosis infection, so they have a very high case fatality rate, so this is little threatening number compared to the other parasitic infection like schistosomiasis, guinea worm disease, malaria, there is echinococcosis, leishmaniasis, so all these compared to these three diseases are quite having a risk.

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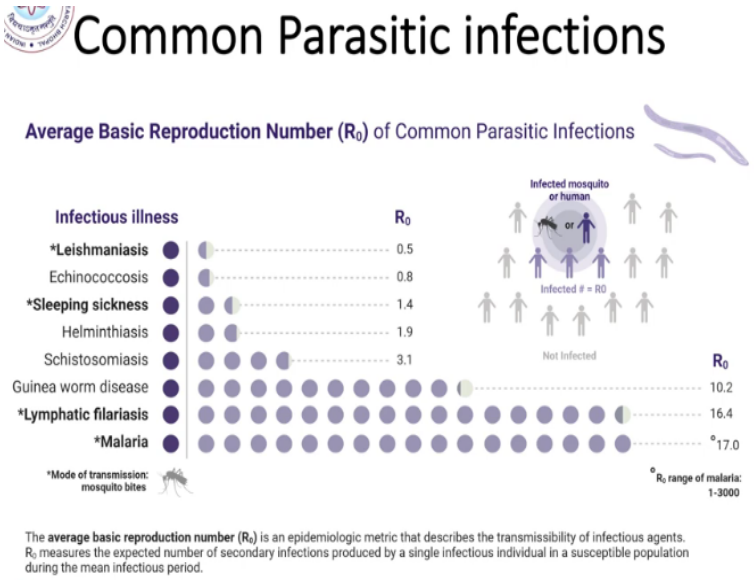

Another term which is used is average basic reproduction number. Again, it is a used in case of a common parasitic infection and what is average basic reproduction number is it is represented as R0 ~~naught~~, R 0 is a epidemiologic metric that describes the transmission ability of infectious agent. R 0 measures the expected number of secondary infection produced by a single infectious individual in a susceptible population during mean infectious period.

And here you can see that malaria has a very high average basic reproduction number. It has about 17 compared to the other parasitic disease like leishmaniasis, sleeping sickness, lymphatic filariasis, so and so. So now this is just a general introduction about the parasitic infection or the disease caused by parasites, a very brief introduction. Now I will move to parasitic disease, first we will discuss about malaria.

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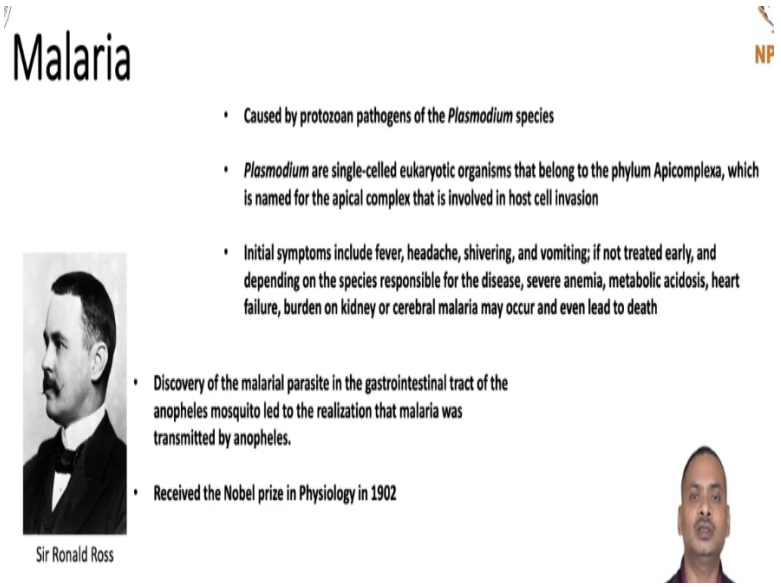

So you probably all are aware that this malaria is caused by Plasmodium species which is a protozoa and this Plasmodium are single celled eukaryotic organism. It is a single celled eukaryotic organism that belongs to the phylum Apicomplexa which is named for the apical complex, so at apical part there is a complex that is involved in host invasion. So initial symptom of malaria is quite wide range and that includes fever.

The fever is very high and this is a periodic fever, headache, shivering, vomiting. If not treated early and depending on the species responsible for the disease severe anemia can happen. I will give the detail in subsequent slide and the link how the severe anemia is happening and all those things and I will discuss once you will learn about the life cycle of this plasmodium species, then it is easy to understand, here just you remember this symptom.

Severe anemia, metabolic acidosis, heart failure, so I will explain you how the heart failure can take place if there is an infection of plasmodium, burden on kidney or cerebral malaria may occur and even lead to death. So, some of this plasmodium infected individual they also die by this disease, it is quite severe. The discovery of this malarial parasite is in gastrointestinal tract of the anopheles, female anopheles mosquito, led to realization that malaria was transmitted by these female anopheles.

And this was done by Sir Ronald Ross, you probably are aware, and for this work he received the Nobel prize in physiology in 1902.

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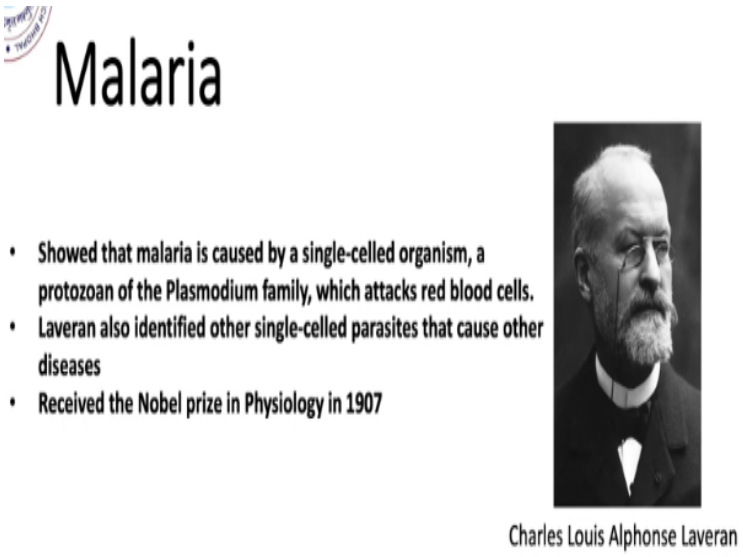

This is a Charles Louis Alphonse Laveran, he showed the malaria is caused by single celled organism, a protozoan of Plasmodium family which attacks the red blood cells. And he also identified other single celled parasite that cause other diseases and for all these works he received the Nobel prize in 1907. So this is a just a simple introduction about these workers.

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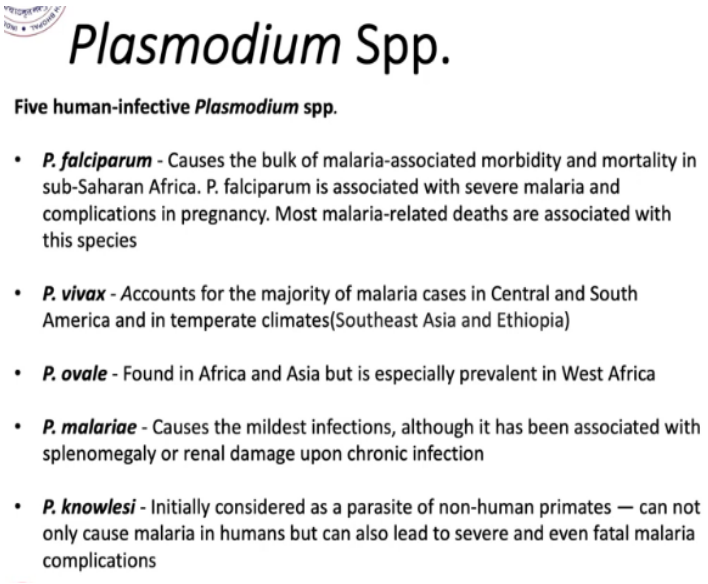

So basically, there are several species of Plasmodium and here you can see that there are five human infective Plasmodium species which I am going to discuss. The first is Plasmodium falciparum. This is quite dangerous and causes the bulk of malaria associated morbidity and mortality. So this is responsible for most of my mortalities associated with Plasmodium falciparum.

In sub-Saharan Africa the Plasmodium falciparum is associated with the severe malaria and complication in pregnancy. If the pregnant woman is infected with a Plasmodium falciparum it is a very complex situation. Most malaria-related death are associated with this species as I told you. Another is Plasmodium vivax. It is account for majority of malaria cases in Central and South America and in temperate climate that is Southeast Asia and Ethiopia.

Another is Plasmodium ovale. This is found in Africa and Asia, but especially prevalent in west Africa. Another is Plasmodium malariae, causes the mildest infection among all. Although it has been associated with splenomegaly, splenomegaly is a situation where the size of a spleen is enlarged. Once I will explain you the life cycle, then you can understand how this splenomegaly can take place or renal damage, so they also damage the kidneys upon chronic infection.

The last is the Plasmodium knowlesi, initially considered as a parasite of non-human primate, but cannot only cause malaria in human but can also lead to severe and even fetal malaria complication. So these are the five species which are mainly associated with malaria disease.

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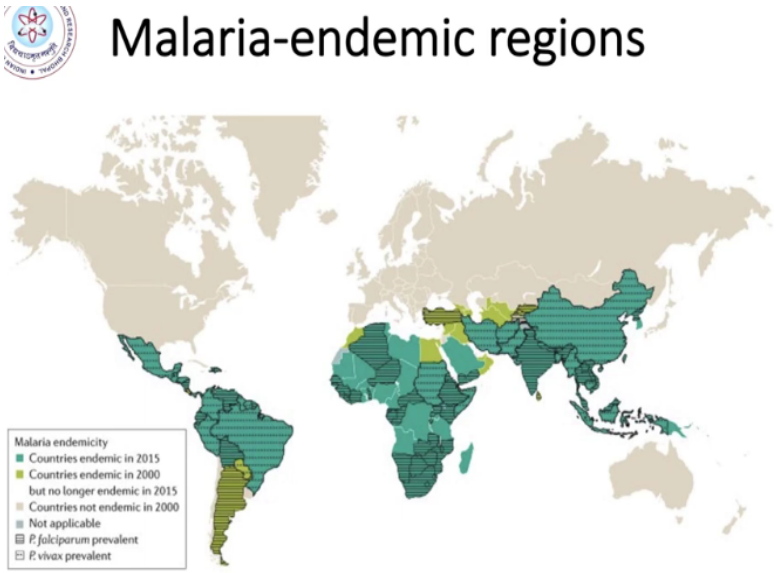

So this is malaria endemic region. Here you can see that near the equator this disease is quite prominent.

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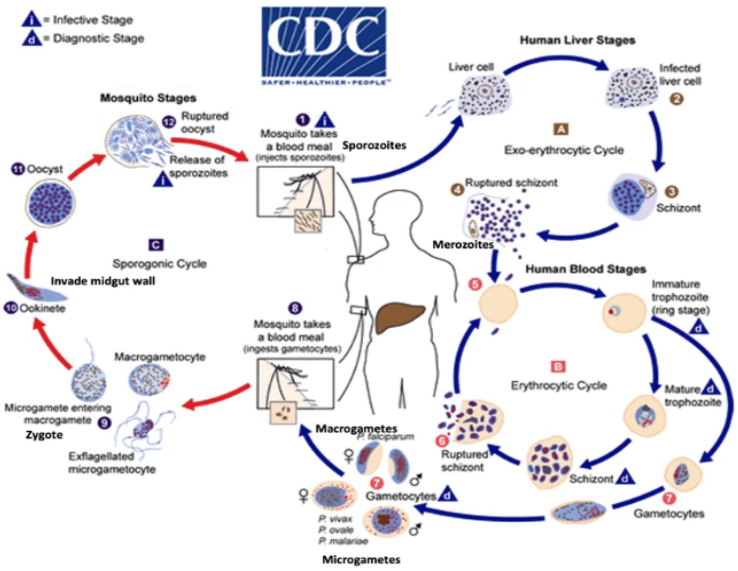

Now I will discuss about the life cycle of malaria parasite and here you can see that this malaria parasite life cycle involves two hosts. So during a blood meal, a malaria infected female anopheles mosquito inoculate the sporozoite into human host, here you can see that the mosquito is inoculating the sporozoites in the human, the infected female anopheles. This is

inoculating the sporozoite, this is the infective form of malaria which is present in salivary gland of mosquito.

So you know that when mosquito bites they throw the saliva in order to stop the coagulation of blood. So this sporozoite infect, so as soon as this sporozoite go into the human body this is sporozoite immediately disappear from the blood and they infect the liver cells and then they are over there, these sporozoite will mature into schizonts. Here you can see there is schizont, this is a schizont, which is basically present in the liver and which ruptures and release the merozoite, here you can see this is merozoite which is released from these liver cells.

So these merozoites basically can persist in liver and cause relapse by invading the blood stream weeks or even year later. So, for some species particularly the Plasmodium vivax and Plasmodium ovale it is present in the liver in the form of hypnozoites and these hypnozoites will be remain in there, it is something like they are present in latent state. But for another species after this initial replication in liver which we also call it as exoerythrocytic cycle.

Here you can see there is exoerythrocytic cycle. Exoerythrocytic cycle it means that out of the RBC, so they are replicating not in RBC, they are replicating in liver. So after this initial replication in liver that is exoerythrocytic cycle, the parasite undergo asexual multiplication in erythrocyte, here you can see that this merozoites are infecting the RBCs and now they will initiate erythrocytic cycle, here you can see there is a erythrocytic cycle.

And then this merozoites infect RBC and the ring stage trophozoite, here you can see that there is a ring stage trophozoite mature into the schizont which rupture and release the merozoites. Again they will release, so over there they will increase in number and then again they will release the schizonts and this will again infect the RBC. So some parasite differentiate into sexual erythrocytic cycle or gametes.

Here you can see that this bifurcates into two kinds of cycle, one is asexual reproduction and another is sexual reproduction where this will form the gamete gametocytes. So, blood stage parasites are responsible for clinical manifestation of the disease. Here you can see that these gametocytes are matured and then they will make microgametes which is male gamete and this is a macro gamete which is a female gamete and these gametes are present near the skin, blood vessels in the skin.

And when again a female anopheles will bite then these gametocytes male and female are ingested by the anopheles. Here you can see that after bite this is again ingested by the female anopheles mosquito during blood meal. So they take the blood meal, so these gametes will also transport it. The parasite multiplication in the mosquito is known as a sporogonic cycle. Here you can see there is a sporogonic cycle.

While in the mosquito's stomach, so all these things will happen in mosquito's stomach, the microgamete penetrate the macrogamete and generate the zygote, here you can see there is a generation of zygote. The zygote in turn become a motile and elongated ookinete, here you can see this will be a ookinete, which evade the mid gut wall of mosquito where they develop into oocyst. Here you can see they will penetrate and develop into the oocyst.

The oocyst grows, rupture and release sporozoites, here you can see there is a release of sporozoite, which make their way to mosquito's salivary gland. Inoculation of the sporozoite into new human host perpetuate the malaria life cycle. So in that way this malaria life cycle is keep on going on. So after this life cycle and other information, I have a very beautiful video and which is showing the life cycle of this malaria parasite in human host as well as in mosquito host. Anyway, so I will give you more detail in subsequent slides.

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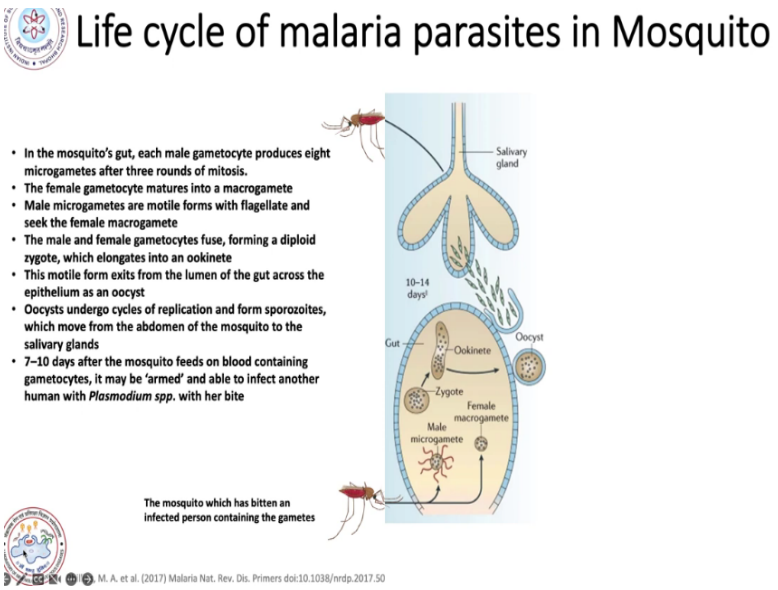

Here you can see that life cycle of malaria parasite in mosquito, I will give you little more detail about the life cycle of malaria parasite in mosquito host. So in mosquito's gut, here you can visualize in mosquito gut each male gametocyte produces eight microgamete. after three

rounds of mitosis. The female gametocytes mature into macrogamete. Male microgamete are motile forms with a flagellate and seek the female macrogamete.

The male and female gametocytes fuse forming a deployed zygote. Here you can see there is a formation of zygote which now elongate into ookinete, I have explained you in previous slide also. This motile form exits from the lumen of the gut across the epithelium as an oocyst. Oocysts undergo cycle of replication and form sporozoites which move from abdomen, basically from a stomach of mosquito to the salivary gland.

Seven to 10 days after the mosquito feed on blood containing gametocyte it may be armed and able to infect another human with Plasmodium species with her bite. So, this is all life cycle of this malaria parasite in human host as well as in mosquito host.

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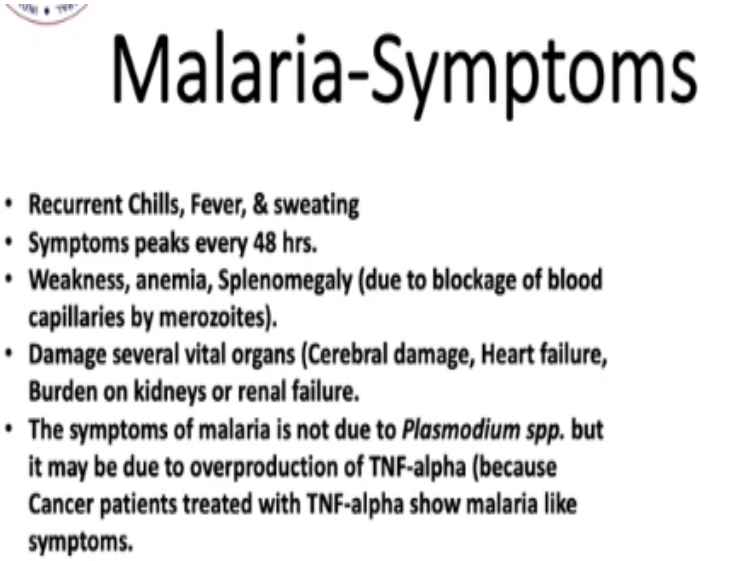

Now I will discuss about the malaria symptoms. I gave you some malaria symptoms in beginning of malaria. So here I will explain you why some symptoms are appearing. So of course, it is causing the recurrent chill, fever and sweating. So when these merozoites are released in RBCs there will be a release of merozoites. So at that time there will be a peak of fever, there will be a chill and fever.

And this is a kind of cyclic manner because when the merozoites, merozoites are not keep on releasing. So they are released every about 36 to 48 hours, so at that time the symptom will peak So as you can see that these parasites can infect the red blood cells or erythrocyte so that causes the anemia, the Plasmodium infection can cause the anemia and there is a

splenomegaly. So, splenomegaly you can understand all blood borne antigen are moving through the spleen.

So since this blood is loaded with the antigen so spleen is not able to handle, so that is why there is increase in size of spleen and that result to the splenomegaly. And it is also due to the blockage of blood capillaries by merozoites. So basically when this is happening then that damages several vital organs. You can understand that cerebral damage there could be a damage in brain and this is again why because they will block the capillaries.

So whatever the blood supplying arteries are there they will be blocked, right. Since it is blocked and there is no supply of blood that may cause the cerebral damage and due to this blockage that can also cause the heart failure. You know that all blood is filtering in the kidneys, so since the blood is loaded with these parasites so that may also block the kidneys so that result to the renal failure. The symptom of malaria is not due to Plasmodium species but it may be due to overproduction.

It has been shown that there is an overproduction of cytokines kind of thing. There is over production of TNF alpha. This is why we are saying because the cancer patient treated with TNF alpha shows malaria-like symptom. So in some cancer, we treat the cancer by TNF and those patients show like a malaria symptom that is why we can say that this is due to the overproduction of TNF alpha.

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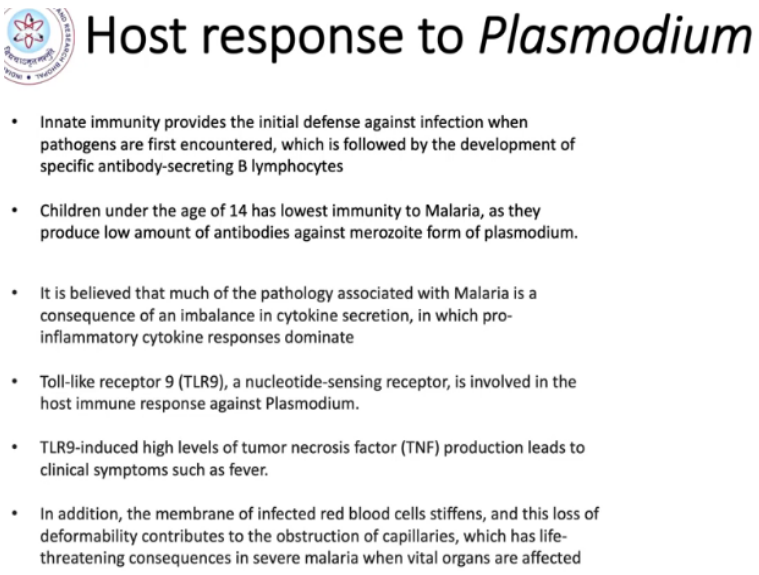

So host response to the Plasmodium. So innate immunity provides the initial defense against infection when pathogens are first encountered, when pathogen is coming to the host, which is followed by development of a specific antibody secreting B lymphocytes. So the younger children, children under age of 14 has a lowest immunity to malaria and that is why there is lot of motility associated with younger children, lowest immunity to malaria as they produce low amount of antibody against the merozoite form of this Plasmodium.

You remember that there is a release of merozoite once this sporozoite infect the liver cell, they make ~~me~~ merozoites. It is believed that much of pathology associated with malaria is a consequence of imbalance of cytokine. Imbalance of cytokine or cytokine production in which pro-inflammatory cytokine response dominates. It is believed that TLR9 nucleotide sensing receptor is involved in host immune response against Plasmodium.

So this hemoglobin is converted into one another form which we call it as hemozoin. So this hemozoin is sensed by the TLR9 and that may involve in production of more pro-inflammatory cytokines. So TLR9 induces high level of TNF alpha production leads to the clinical symptom such as fever. In addition, the membrane of infected RBC, so once they infect the RBC, this RBC turn to very sticky.

And this infected RBC make a stiffness and it loses its deformity contribute to the obstruction in capillaries, blood capillaries which has life-threatening consequences in severe malaria when vital organs are affected. So, once it will stiffen then it will not go into the capillaries and then there will be no blood supply, and if there is no blood supply then that will cause the cerebral damage, that may cause the heart failure and that may cause the kidney failure.

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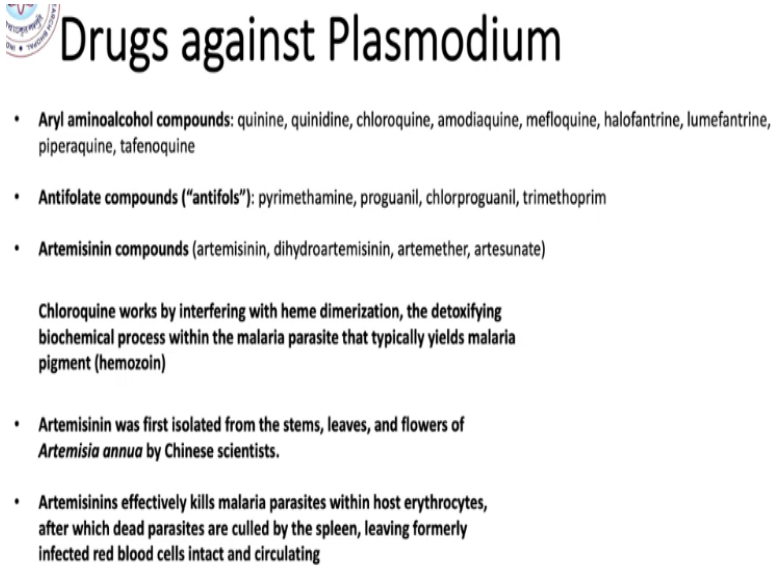

So there are drugs against Plasmodium like aryl aminoalcohol compound which is basically quinine. There are various forms of quinines, here you can see quinine, chloroquine and there are several molecules. Antifolate compounds, antifols, are also used in treatment of Plasmodium. Artemisinin compounds, you know this work was done by Youyou from China and she received Nobel prize in 2015.

So this is quite effective against the Plasmodium infection. So chloroquine work by interfering with heme dimerization, the detoxifying biochemical process within the malaria parasite that typically yield malaria pigment hemozoin. Artemisinin was first isolated from stems, leaves and flowers of Artemisia annua by Chinese scientist, her name is Youyou 2015. So Artemisinin effectively kills malaria parasite within host erythrocyte.

After which the dead parasites are culled by the spleen, leaving formally infected RBCs intact and circulating. So here I have a video and you can watch the life cycle of this malaria parasite. **(Video Starts: 35:29) (Video Ends: 39:30)** So I hope you have enjoyed this video and now I hope you can see the life cycle in mosquito host. **(Video Starts: 39:41) (Video Ends: 43:31).**

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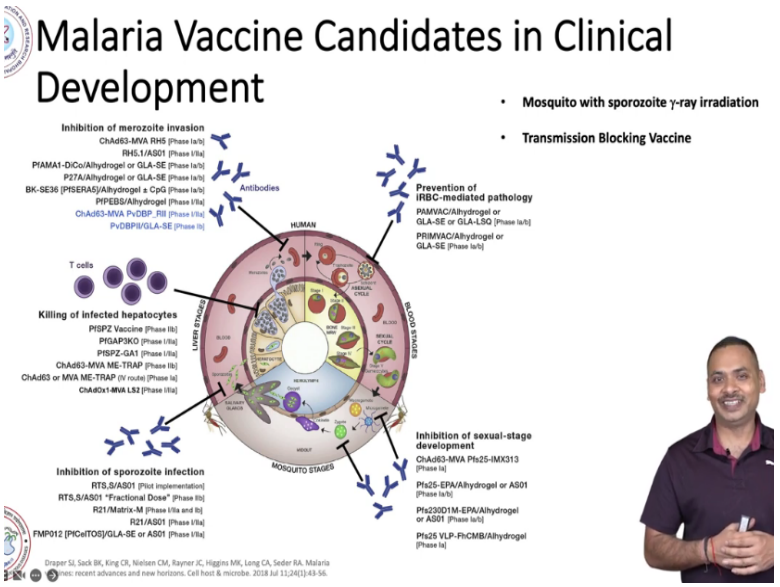

I hope you have enjoyed that video and now you are very well clear about the life cycle of this malaria or Plasmodium species in human as well as in mosquito host. So let us discuss about the malaria vaccine. There are so many, huge global effort is going on in order to make a malaria vaccine here. You can see some of the detail and I would also like to introduce with one very interesting concept.

So what people have tried, they have irradiated the mosquito, the female anopheles with this sporozoites. They irradiated with gamma rays and then they allowed to infect the human host and then they were really infected with this is sporozoites and it has been shown that this is giving a very good protection. However, if you see this is technically very challenging, you need to make a mosquito and then this mosquito need to be irradiated and this mosquito need to bite the human host.

So in a small setting it may be possible, but in a population it is almost impossible, right. You need to make a mosquito and then you need to irradiate and then this mosquito should bite you, so this is little complicated. Another concept is this transmission blocking vaccine. So, this is also very interesting concept in vaccine biology. Here what we do we purify the antigen from the parasite and from that stage of parasite which is present in mosquito, not in human.

Please remember the stage the antigens which is present only in mosquito host. So, what we can do, we can purify those antigens and then we can challenge the human by those antigens. So what will happen? Then there will be a generation of antibody against that antigen. So

when the malarial parasite, when this malaria containing mosquito will bite and then they will take the gametes, so at that time what will happen they will take the blood as well as antibody.

So this antibody will remain in the mosquito gut and this will be effective, and once in mosquito the stage will come and that antigen will express then these antibody can interact and then they can neutralize those parasites. So this is the concept of transmission blocking vaccine. So there are several candidate antigens for this transmission blocking vaccine and people are trying, so maybe in future we will have some good news.

And we will have a protection against the malarial parasite. So with this, I am stopping this session and I will take one more session and that will be the last session and I will discuss about the African sleeping sickness. Thank you.