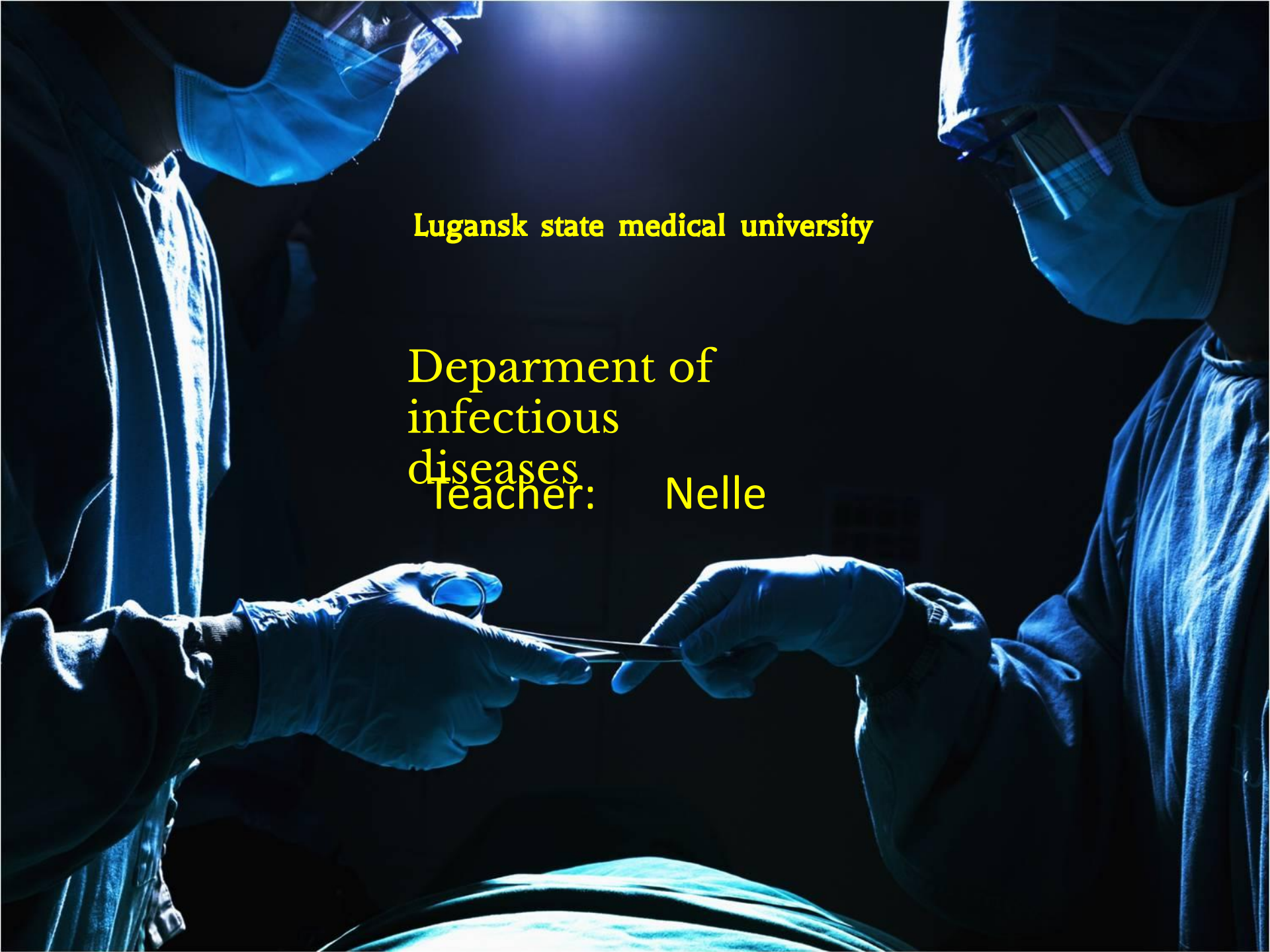

Lugansk state medical university
Deparment of infectious diseases
Teacher: Nelle

ABOUT MYSELF

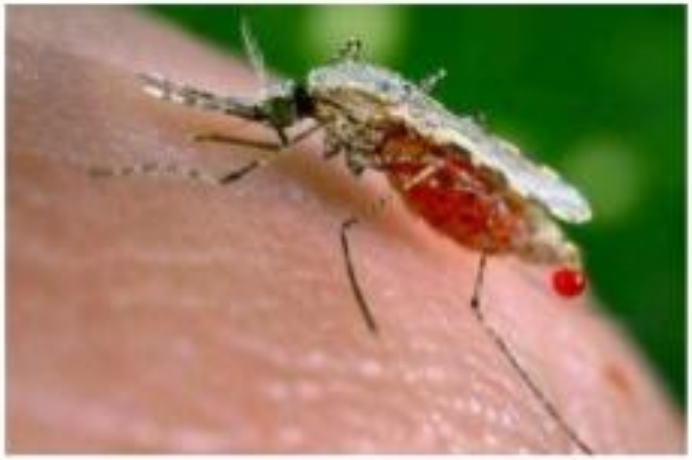
AJAY . GUNDAWAR

GROUP:18A

COURSE: 5TH

Adult

Anopheles



Aedes

Malaria

Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a group of single-celled microorganism) belonging to the genus *Plasmodium*.

The disease is transmitted most commonly by an infected female *Anopheles* mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood. The parasites travel to the liver where they mature and reproduce.

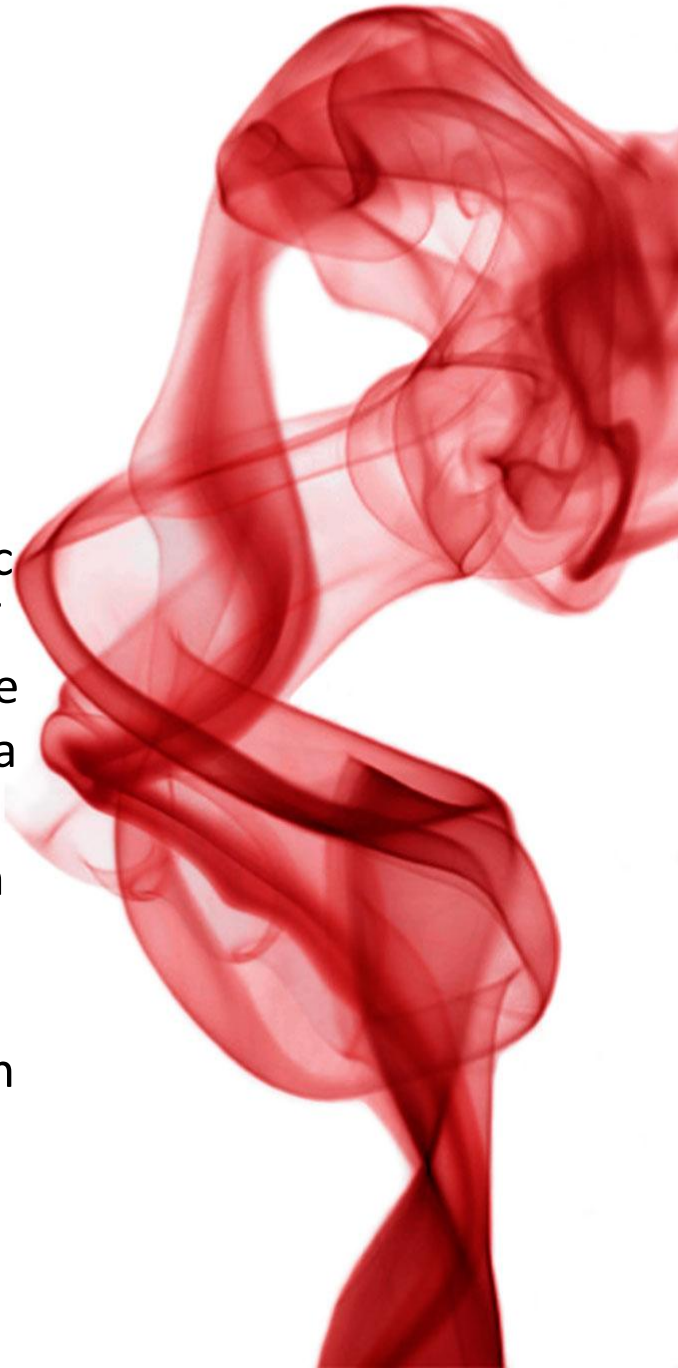
Five species of *Plasmodium* can infect and be spread by humans.[1] Most deaths are caused by:

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

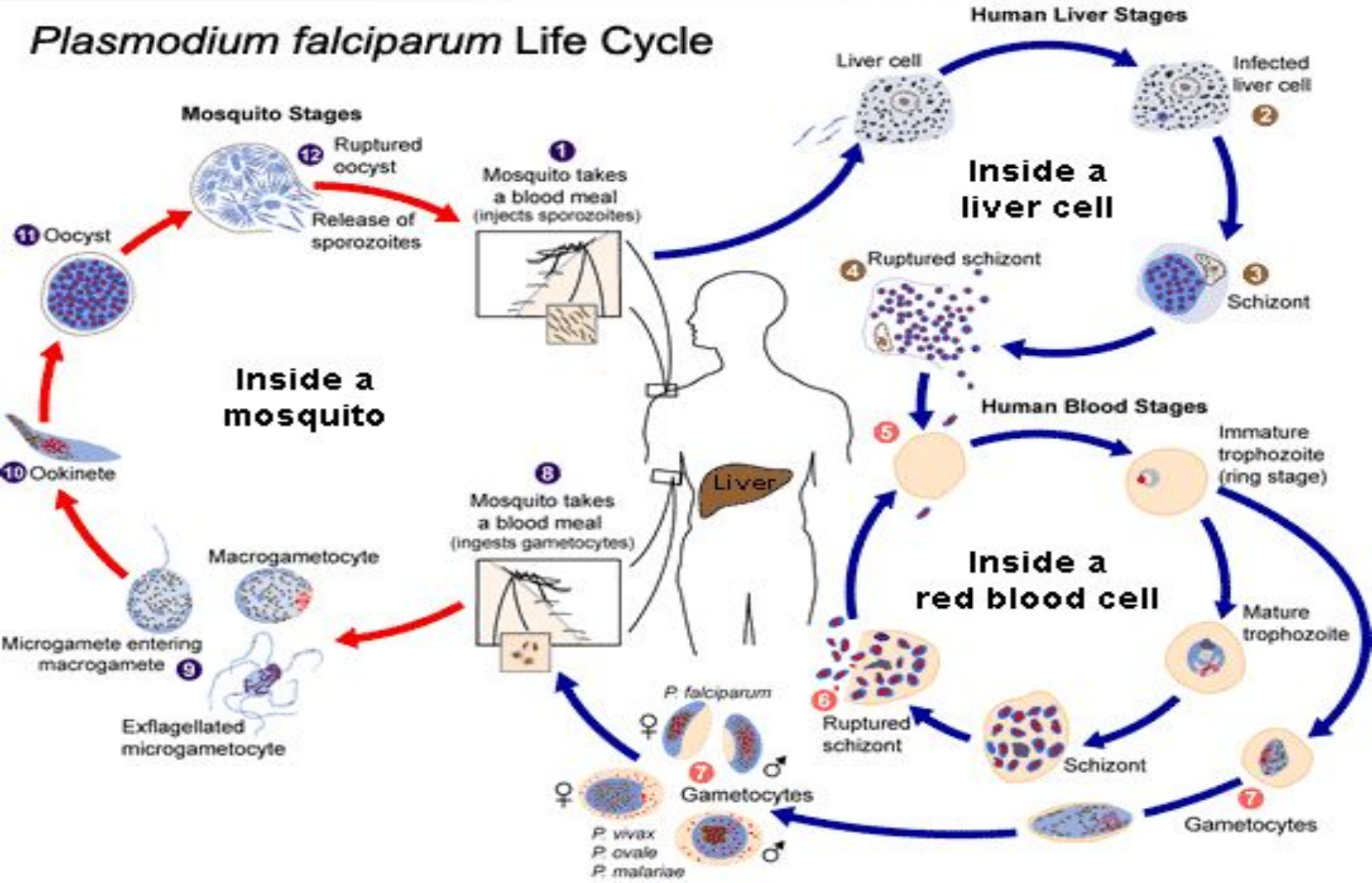
generally cause a milder form of malaria

Plasmodium Falciparum - Malaria

Plasmodium falciparum is the *Plasmodium* species responsible for 85 % of the malaria cases. The three less common and less dangerous *Plasmodium* species are: *P. ovale*,*P. malariae* and *P. vivax*. Malaria infects over 200 million people annually, mostly in poor tropical and subtropical countries of Africa. It is the deadliest parasitic disease killing over one million people each year. 90 % of the deaths occur south of the Sahara desert and most are under five-year-old children. In addition to Africa, malaria occurs in South and Southeast Asia, Central and South America, the Caribbean and the Middle East. Even within tropical and subtropical areas, malaria does not usually occur at high altitudes (over 1500 meters), during colder seasons, in countries of successful malaria programs or in deserts.



Life cycle


Plasmodium falciparum Life Cycle
Human Liver Stages
Liver cell
Infected liver cell
2
Inside a liver cell
Mosquito Stages
12 Ruptured oocyst
Release of sporozoites
1 Mosquito takes a blood meal (injects sporozoites)
11 Oocyst
4 Ruptured schizont
3 Schizont
Inside a mosquito
Human Blood Stages
5
Immature trophozoite (ring stage)
10 Ookinete
8 Mosquito takes a blood meal (ingests gametocytes)
Liver
Macrogametocyte
Inside a red blood cell
Mature trophozoite
Microgamete entering macrogamete 9
Exflagellated microgametocyte
P. falciparum
6 Ruptured schizont
Schizont
7 Gametocytes
Gametocytes
P. vivax
P. ovale
P. malariae

Malaria is carried by *Anopheles* mosquitoes. Of the over 400 *Anopheles* species, only 30–40 can transmit malaria. The infection starts, when a female mosquito injects (in her saliva) "sporozoites" (one form of *P. falciparum*) into **human** skin while taking a blood meal. A sporozoite travels (in the bloodstream) into the liver where it invades a liver cell. It matures into a "schizont" (mother cell) which produces 30000–40000 "merozoites" (daughter cells) within six days. The merozoites burst out and invade red blood cells. Within two days one merozoite transforms into a trophozoite, then into a schizont and finally 8–24 new merozoites burst out from the schizont and the red cell as it ruptures. Then the merozoites invade new red cells. *P. falciparum* can prevent an infected red cell from going to the spleen (the organ where old and damaged red cells are destroyed) by sending adhesive proteins to the cell membrane of the red cell. The proteins make the red cell to stick to small blood vessel walls. This poses a threat for the human host since the clustered red cells might create a blockage in the circulation system. A merozoite can also develop into a "gametocyte" which is the stage that can infect a **mosquito**. There are two kinds of gametocytes: males (microgametes) and females (macrogametes). They get ingested by a mosquito, when it drinks infected blood. Inside the mosquito's midgut, male and female gametocytes merge into "zygotes" which then develop into "ookinetes." The motile ookinetes penetrate the midgut wall and develop into "oocysts." The cysts eventually release sporozoites, which migrate into the salivary glands where they get injected into humans. The development inside a mosquito takes about two weeks and only after that time can the mosquito transmit the disease. *P. falciparum* cannot complete its life cycle at temperatures below 20 °C.

Pathogenesis

Transmission of *P. falciparum* occurs between humans and Anopheles mosquitoes. Mosquito vectors pass malaria from host to host. The parasite can infect the mosquitoes through the in take of human blood or a human may be infected by the mosquito's injection of saliva. Once the mosquito becomes infected with*Plasmodium falciparum* it transfers the disease to each new host it penetrates. Humans can rarely transfer the parasite between each other. There have been rare cases of contaminated transfused blood infecting the recipient, but seldom does this occur because of screening that takes place pre-blood donation. Mothers can also pass *P. falciparum* to their child during birth, this is also a seldom occurrence.

Infectious Dose, Incubation, Colonization

Symptoms of Malaria typically begin 8-25 days following infection however, in a few cases it can take up to a year. The late onset of incubation is due to taking an inadequate amount of anti-malaria medication. The infectious dose is not precisely known, but it is understood to be a very low number. Malaria can be observed months to years after first set of symptoms are observed. This is due to the parasites ability to lie dormant in liver cells until the environment is right for a relapse. This is mainly seen in *P.vivax* and *P. ovale*, rather then *P. falciparum*. The parasite colonizes in the liver and is then released into the blood stream and enters erythrocytes.

Epidemiology

- The key to Malaria-endemic is Anopheles the mosquito's ability to live in a certain area. Temperature is also important having to stay above 20 degrees Celsius. The main areas of *P. falciparum* are South America, Africa, India, and few parts of Indonesia. The ideal location for transmission is along the equator in a warmer region. Transmission will not occur in high altitudes, colder seasons, and deserts. Malaria is considered to have arisen since the beginning of mankind, but was first discovered in blood in 1880 and found to be transmitted by mosquitoes in 1889. There are four common species of Malaria of which P. falciparum is the most severe. *Plasmodium falciparum* continues to increase in drug-resistant populations and insecticide-resistant mosquitoes leading to the prediction that the disease will only worsen over

Virulence Factors

- PfEMP1,*P. falciparum* erythrocye membrane protein 1, is an adhesive ligand protein which is created inside of a *P. falciparum* infected erythrocyte and presented on the surface. PfEMP1 is known as a knob and is encoded by the multigene segment, Var. The protein is responsible for sequestration within the vital organs. In some case were sequestration occurs in the brain this will lead to the cerebral form of malaria. Each *Plasmodium falciparum* has multiple versions of PfEMP1 with which it can alter its appearance by changing to another PfEMP1 when the immune system begins to create antibodies for the original PfEMP1 in a process known as antigenic variation. Changing of adherence molecules also means a change in the receptor on the epithelial. The change in receptor is hypothesized to possibly change the disease outcome.
- RIFIN, repetitive interspersed family, is considered the most abundant multigene family. PfEMP1 along with RIFIN is considered a crucial cornerstones for the virulence of *Plasmodium falciparum* mainly due to its ability to avoid immune response through antigenic variability. RIFIN is also presented on the outer membrane of a parasite infected erythrocye as an adherence factor.
- Rosettes are uninfected red blood cells that form clumps with Malaria-infected erythrocytes. Clumping occurs when particularly sticky PfEMP1 attach to other red blood cells. Only a minority of *P. falciparum*actually creates rosettes, but when they do they are known to be linked to severe malaria.[
- Malaria pigment (hemozoin) is released during erythrocyte rupture, causing the uncomplicated symptoms of malaria such as chills and fever.

Symptoms

After being bitten by an infected mosquito, symptoms usually begin within 10–30 days. Malaria can be uncomplicated or severe. Symptoms of **uncomplicated malaria** might include:

-chills

-diarrhea

-fever

-headaches

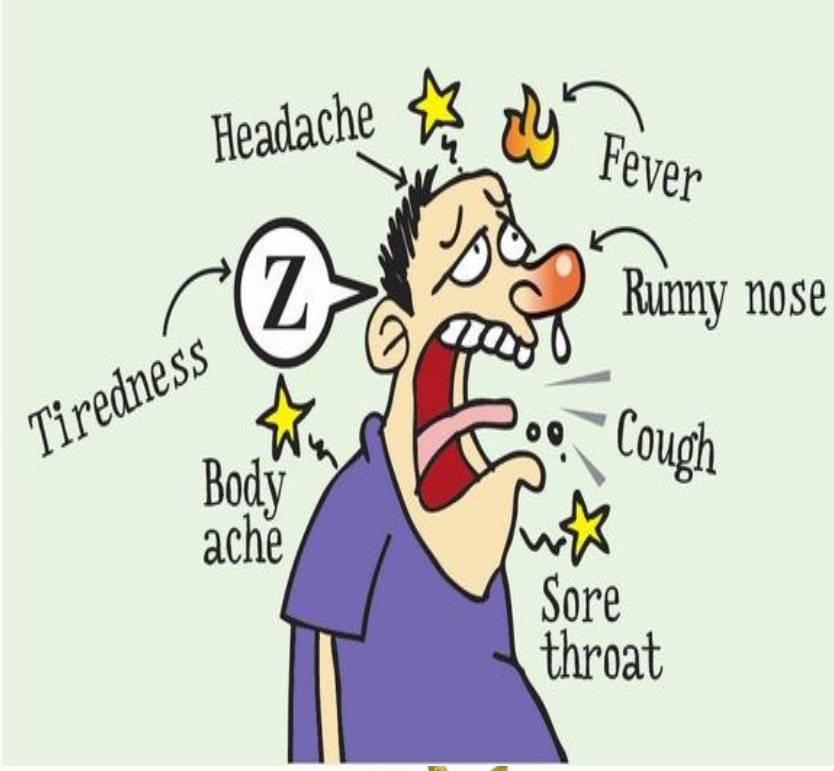
-muscle pain

-nausea

-sweating

-vomiting

-weakness.



- Some less noticeable manifestations:
  - enlargement of the spleen or liver
  - increased breathing frequency
  - mild anemia
  - mild jaundice (yellowish eye whites and skin).

- The disease can turn into severe malaria, if there are serious organ failures or abnormalities in the bloodstream or metabolism. Symptoms of **severe malaria** might include:
  - breathing difficulties
  - coma
  - confusion
  - death
  - focal neurologic signs
  - seizures
  - severe anemia.

- Some less noticeable manifestations:
- abnormalities in blood coagulation
- hemoglobin in the urine
- high acidity of the blood
- hypoglycemia (low blood glucose)
- low blood pressure
- kidney failure.

- During pregnancy malaria can lead to premature baby delivery or delivery of a low-birth-weight baby. The infant can get the parasite from the mother and develop the disease. Central nervous system involvement (cerebral malaria) can cause (especially in small children) blindness, deafness, speech difficulty, paralyses and trouble with movements.

Diagnosis

- Malaria is usually diagnosed by examining a blood sample under a microscope. There are also test kits that detect antigens of *P. falciparum* in the patient's blood. These immunologic tests are known as rapid diagnostic tests (RDTs). RDTs can detect two different malaria antigens, one for *P. falciparum* and the other is found in all four human malaria species. RDTs usually show results in about 20 minutes. It is a good alternative to microscopy, when reliable microscopic diagnosis cannot be done. RDT might not detect some infections, if there are not enough malaria parasites in the patient's blood. A negative RDT result can be followed up by microscopy. If a patient with positive RDT result is not responding to treatment, another blood sample should be taken. This time using microscopy to determine whether the medicine was appropriate for the*Plasmodium* species.
- Diagnosis can be challenging for many reasons:
- Some health workers in developing countries are insufficiently trained and supervised.
- The microscopes and reagents might be of poor quality and the supply of electricity might be unreliable.
- Some health workers save blood samples until a qualified person is available to perform the microscopy. This delay results sometimes as incorrect diagnosis.
- Many malaria endemic communities do not have the proper diagnostic tools such as microscopes and RDTs.

- Rapid and accurate diagnosis using microscopic examination of blood smears is the most precise way to determine *Plasmodium falciparum* as the disease. CDC provides various references for microscope diagnosis along with serology, PCR, and drug resistance testing. Each species of P. falciparum has distinctive characteristics that can be see under a microscope. In only early form, trophozites and gametocytes of *P.falciparum*are seen in the blood as ring form inside the erythrocyte. There are normally multiple parasites in one erythrocytes appearing as

Treatment

- Most malaria deaths occur in rural areas. Quick progression from illness to death can be prevented by fast and effective medication. Patients who have uncomplicated malaria can visit a nearby hospital to get treated and then go home to rest. In emergency cases rectal artesunate drug can be given as a first line treatment (if they cannot be treated orally). Patients with severe malaria can be hospitalized for many days. When treating a malaria patient, the following should be taken into account:
  - age and size of the person (to give the correct amount of medication)
  - drug allergies or other medications taken by the patient
  - health condition, when starting the treatment
  - where the person was infected (what *Plasmodium* species is likely to be responsible and what drug is needed).

The best line of defense against any form of malaria is preventative treatment, antimalarial, taken properly before, during, and after exposure to parasite.

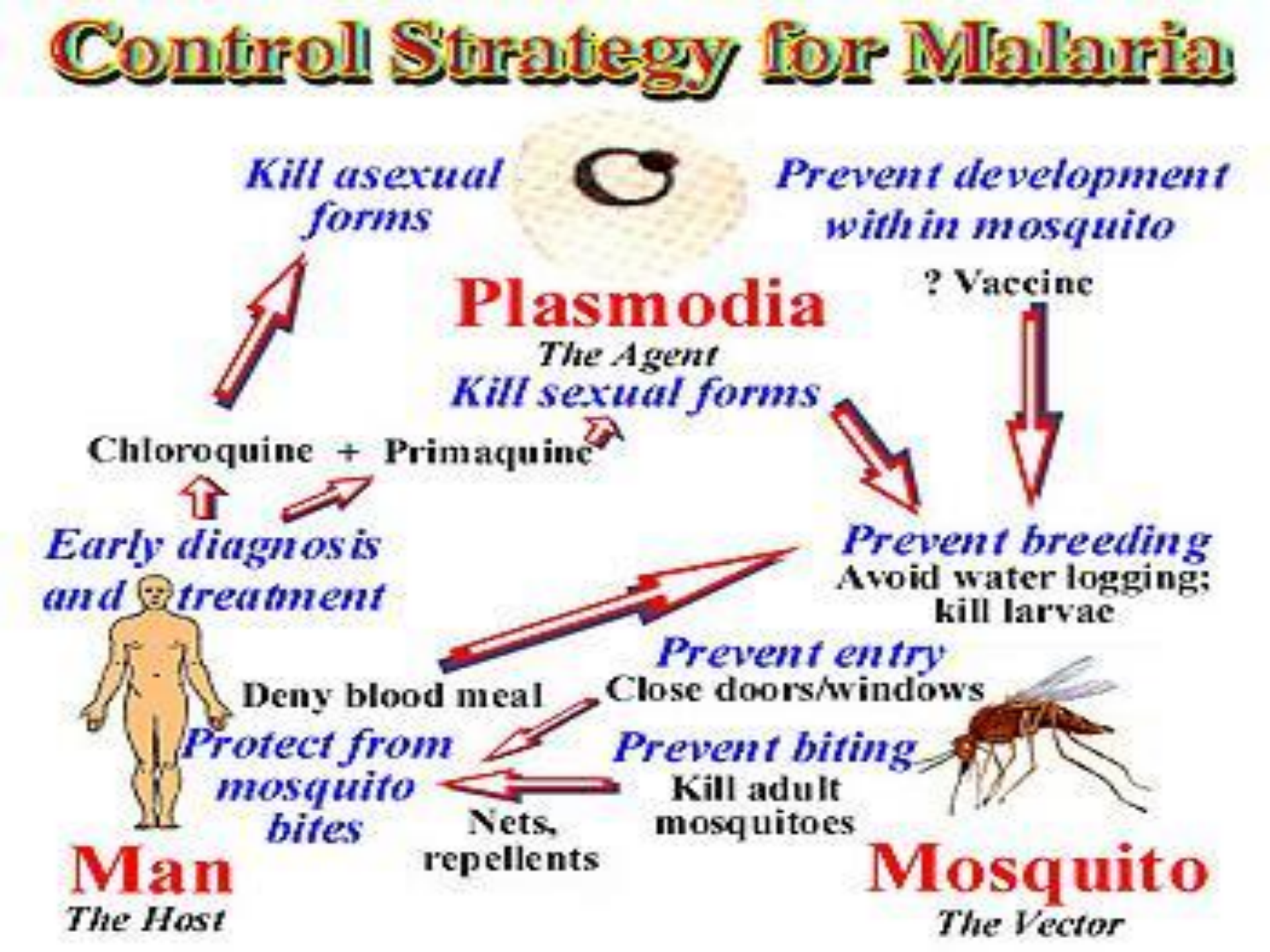
- *P. falciparum* and *P. vivax* have been confirmed to be resistant (in some areas) to many antimalarial drugs. For example, chloroquine resistant strain of *P. falciparum* has spread to most endemic areas.
- Listed below are some drugs that are usually recommended by national malaria control programs. They might not be effective in many parts of the world due to drug resistant strains.
  - artemesinin-containing combination treatments (for example, artemether-lumefantrine, artesunate-amodiaquine)
  - atovaquone-proguanil
  - chloroquine
  - doxycycline
  - mefloquine
  - quinine
  - sulfadoxine-pyrimethamine.

- Primaquine, is used as an adjunct against certain *Plasmodium* species. It is active against the dormant liver forms (hypnozoites which are rare/nonexistent with *P. falciparum*). Primaquine is not recommended for people who are deficient in glucose-6-phosphate dehydrogenase or for pregnant women. Treating all people simultaneously in a population can prevent major malaria epidemics. Unfortunately it can also increase drug resistance of the parasite and complications in those who are glucose-6-phosphate dehydrogenase deficient.

Prevention

Insecticide-treated **bed nets** may reduce deaths of children under 5 years up to 20 % (according to trials in several African communities). *Anopheles* mosquitoes usually feed during the night so you can protect yourself by sleeping under a bed net. If everyone in a community has a bed net, the occurrence of malaria can be reduced. Bed nets are usually made of polyester but sometimes cotton, polyethylene, or polypropylene is used instead. All bed nets are treated with pyrethroid insecticides, which have are low health risks to humans but are toxic to insects even at low doses. Pyrethroids do not rapidly wear off, unless exposed to sunlight or washed. "Long-lasting insecticide-treated bed nets" maintain effective levels of insecticide for three years or more. Bed net donations can be made through organizations such as Nothing But Nets and Malaria No More. The price of one bed net is only a few US dollars (which is often too expensive for people in developing countries).

Control Strategy for Malaria



Many malaria-carrying mosquitoes are endophilic, meaning that they typically rest inside the house after taking a blood meal. **Indoor Residual Spraying** of the walls and other surfaces can kill them reducing the chances that infected mosquitoes spread the disease from one household to another.

Humans living in areas where malaria is common can become partially immune. Travelers, young children, women having their first or second pregnancy and those who are weakened by other diseases (such as AIDS) have little to no immunity against malaria.

Recommendations for pregnant women living in malaria endemic areas:

- Eat iron and folate supplements to prevent anemia.
- Get a curative dose of an antimalarial drug at least twice during pregnancy (starting from the second trimester).
- Sleep under an insecticide-treated bed net.

The **number of mosquitoes may be controlled** by eliminating mosquito larvae before they reach adulthood. Rainfall forms water puddles where mosquitoes lay their eggs and aquatic larvae develop into adults in a few days. Draining or removal of small puddles can reduce the number of mosquitoes near populations. Chemical insecticides can also be applied but might harm the environment. Other methods applied to water:

- insect growth regulators
- oil that suffocates the aquatic larvae
- toxins from the bacterium *Bacillus thuringiensis* var. *israelensis* (Bti)

Additional **personal protection** methods include:

-glass windows (a well-constructed house)

•repellent

•white or light-colored clothes covering most of the body.

Plasmodium vivax

is a protozoal parasite and a human pathogen. The most frequent and widely distributed cause of recurring (Benign tertian) malaria, *P. vivax* is one of the five species of malaria parasites that commonly infect humans. It is less virulent than*Plasmodium falciparum*, the deadliest of the five, but vivax malaria can lead to severe disease and death due to splenomegaly (a pathologically enlarged spleen).*P. vivax* is carried by the female *Anopheles* mosquito, since it is only the female of the species that bite.

On the pathogenesis of Plasmodium vivax malaria: perspectives from the Brazilian field.

Life-threatening Plasmodium vivax malaria cases, while uncommon, have been reported since the early 20th century. Unfortunately, the pathogenesis of these severe vivax malaria cases is still poorly understood. In Brazil, the proportion of vivax malaria cases has been steadily increasing, as have the number of cases presenting serious clinical complications. The most frequent syndromes associated with severe vivax malaria in Brazil are severe anaemia and acute respiratory distress. Additionally, P. vivax infection may also result in complications associated with pregnancy. Here, we review the latest findings on severe vivax malaria in Brazil. We also discuss how the development of targeted field research infrastructure in Brazil is providing clinical and ex vivo experimental data that benefits local and international efforts to understand the pathogenesis of P. vivax.

Plasmodium vivax and P. falciparum epidemiology in Gambella, south-west Ethiopia

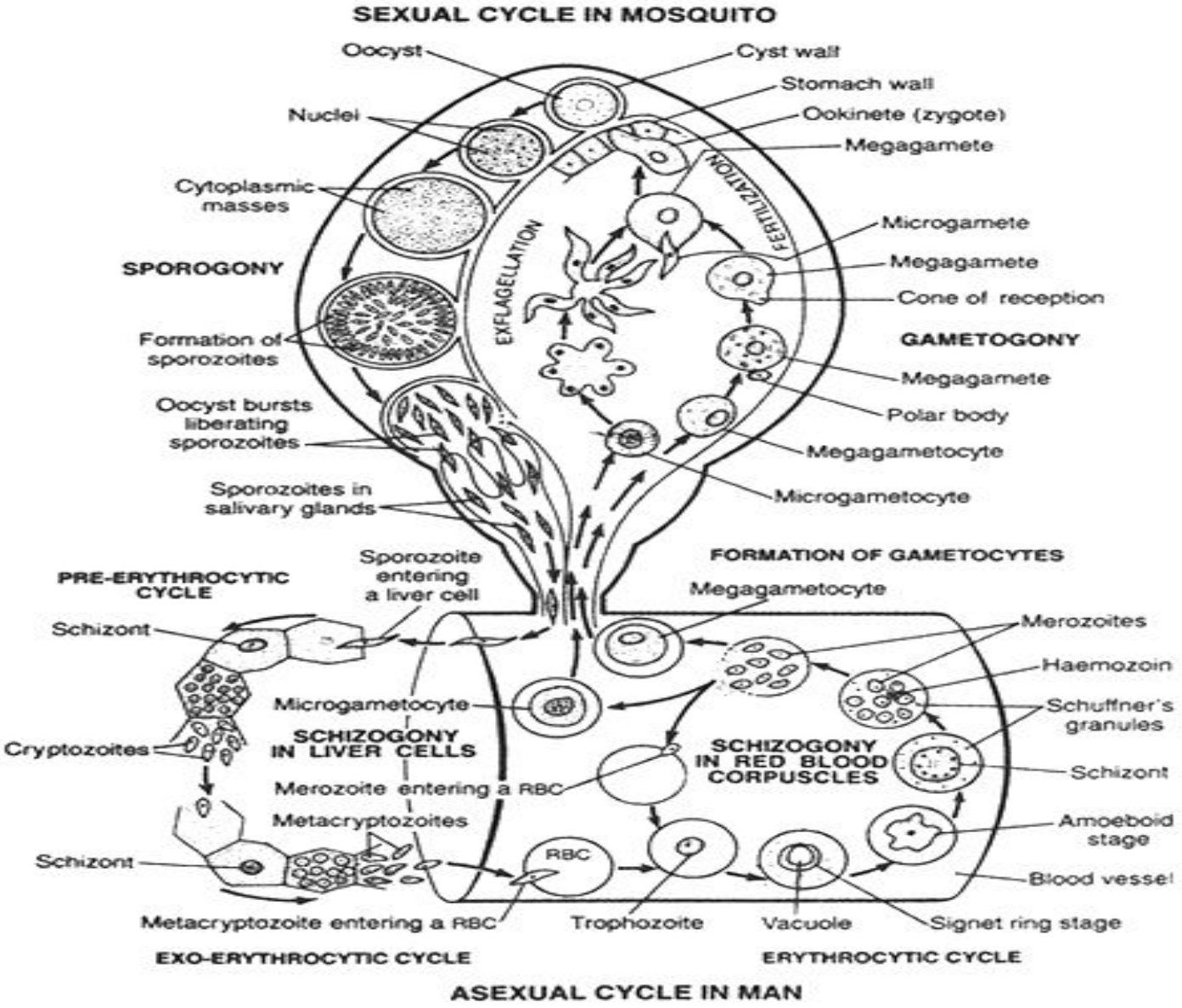
Plasmodium vivax and P. falciparum epidemiology were studied for parasitological and entomological samples collected during the period 1989 and 1990, respectively, from Gambella, South West Ethiopia. Of the total population examined (n = 1091), 147 (13.5%) were found to be positive for malaria parasites. Prevalence rates among males and females were 13.8% and 13.1%, respectively. Differences in the prevalence rates of malaria in the eleven villages were observed, the highest (33.3%) being in Ukuna 2 and the lowest (3.9%) in Ukuna 22. The dominant species of malaria found were both P. falciparum and P. vivax. 88.9% and 11.1% of the malaria cases of the general population were due to these parasites, respectively. It was also recognized that P. falciparum and P. vivax were prevalent in 81.6% and 18.4% of the Anuak population, respectively. The mosquito species responsible for malaria transmission were the indoor-resting A. gambiae s. l. and A. pharoensis. The parasite infection rates of these species were 0.76% and 0.46% and they were found to be the exclusive vectors of P. falciparum and P. vivax, respectively. The present findings are not in accord with the study results previously reported twenty years ago by Armstrong (1972) and Krafsur (1971). The most probable contributing factors for such switch of malaria transmission patterns were, the rehabilitation and resettlement programmes and agricultural activities undertaken in Gambella for the past 10 years that may have brought changes of the socio-economic situation and environmental factors.

Symptoms of Plasmodium vivax

Mouth becomes dry, nausea and loss of appetite

- Headache, muscular pain and joint pain
- Chill, fever (106° F) and sweating all every 48 hours.
- Chill to sweating lasts for 8-10 hours.
- Liver and spleen become enlarged.
- Due to loss of RBC’s anaemia is caused.

Life Cycle of Plasmodium vivax



Life cycle of *Plasmodium vivax*

- **Hosts:-**

- Plasmodium completes its lifecycle in two hosts (digenetic): Man and female Anopheles mosquito.
  - 1. Primary or definitive host:
- Female Anopheles mosquito is the primary host of Plasmodium in which it completes its sexual life cycle.
  - 2. Secondary or Intermediate host:
- Man is the secondary host of plasmodium in which it completes its asexual life cycle.
- The lifecycle of Plasmodium can be divided into three phases:
  - 1. Asexual sehizogony
  - 2. Sexual gamogony
  - 3. Asexual sporogony

- ASEXUAL CYCLE OF Plasmodium, IN MAN
- Infective form of Plasmodium is known as sporozoites. Sporozoites are 11-12µ long slender, uni-nucleated. Sickle-shaped structure present in the salivary glands of infected mosquito. When an infected female Anopheles mosquito bites a healthy man, a large number of sporozoites enter into the blood stream of man. Within half an hour, sporozoites enter the liver cells and undergo asexual multiplication called schizogony.

1. Asexual Schizogony:-

Schizogony is the asexual phase of reproduction of Plasmodium. It takes place in liver cells and RBC's of man. Schizogony can be divided into following phases:

a) Pre-erythrocytic schizogony

b) Exo-erythrocytic schizogony

c) Erythrocytic schizogony

d) Post- erythrocytic schizogony

a. Pre-erythrocytic schizogony:

In the liver cells, sporozoites grow to form a large and spherical schizont. Schizont divides by multiple fission and forms a large number of cryptozoites. They may either pass into the blood circulation to start erythrocytic schizogony or enter fresh liver cells to start Exo-erythrocytic schizogony. Pre-erythrocytic schizogony takes 8 days to complete.

- b. Exo-erythrocytic schizogony:
- After re-entering fresh liver cell each cryptozoites divides to form a large number of metacryptozoites similar to pre-erythrocytic schizogony.
- Meta-cryptozoites are two types:
- Smaller micro-metacryptozoites and larger macro-metacryptozoites. The micro-metacryptozoites enter the RBC's to start erythrocytic schizogony, while the macro-metacryptozoites invade fresh liver cells to continue exo-erythrocytic schizogony. It takes normally 4 days to complete.
- c. Erythrocytic schizogony:-
- As stated above, the erythrocytic schizogony begins when the RBC's of blood are attacked either by pre-erythrocytic cryptozoites or by exo-erythrocytic micro-metacryptozoites. It takes normally in 8 to 12 days after above 2 phases. Stages of erythrocytic schizogony are:
- **i. Trophozoite Stage:-**
- The merozoites (cryptozoites and micro- metacryptozoites) after entering into the blood stream, feed on erythrocytes, become rounded and modify into trophozoite

- **ii. Signet Ring Stage:-**
- As the merozoites grow a vacuole appears in the center and the nucleus is pushed to one side. It gives a ring like appearance and known as signet ring stage.
- The parasite ingests haemoglobin and decomposes it into protein and haematin. Protein is use as food whereas unused haematin forms toxic. Yellowish brown malarial pigment, haemozoin.
- **iii. Amoeboid Stage: -**
- As the signet ring parasite grows, vacuole disappears and the parasite becomes amoeboid in appearance, thrusting out pseudopodial processes. This stage is called amoeboid stage. At this stage RBC develops numerous granules, the Schuffner's granules.
- **iv. Schizont Stage:-**
- Parasite grows in size, becomes rounded and almost completely fills the RBC called Schizont.
- **v. Rosette Stage:-**
- The nucleus of schizont divides by multiple fission to form 6 to 24 daughter nuclei. These nuclei arrange at the periphery, while the toxic haemozoin granules accumulate at the center of RBC. It appears as a flower rose, so called rosette stage.
- Nuclei of rosette stage are surrounded by a little cytoplasm and are develop into merozoites. With the rupture of the RBC, these merozoites are liberated into the blood plasma along with toxic haemozoin. These normally attack fresh RBC's to repeat the erythrocytic cycle or may change into gametocytes. One complete erythrocytic cycle takes 48 hours in Plasmodium vivax.

d. Post-erythrocytic schizogony:-
Sometimes, some merozoites produced in erythrocytic schizogony reach the liver cells and undergo schizogony development in liver cells. This is called post-erythrocytic schizogony.

SEXUAL CYCLE OF Plasmodium in MAN

2. Sexual Gamogony:-
Formulation of gametocytes:
After many generations in about 4-5 is the blood some merozoites increase in size to form two types of gametocytes; larger macro (9-10µ), less numerous and contain large nucleus. Macro gametocytes are larger (10-12µ), more numerous and contain smaller nucleus.

SEXUAL CYCLE OF Plasmodium IN MOSQUITO

When a female Anopheles sucks the blood of a malaria patient, the gametocytes reach the stomach of mosquito and formation of gametes take palace as follows:

a. Gametogenesis (gemetogony) :

Process of formulation of gametes (male and female gametes).

i. Formulation of male gametes:

The nucleus of microgametocyte divides to form 6-8 daughter nuclei. The cytoplasm gives out same number of flagella like projections and daughter nuclei enter in each projection. These projections separate from the cytoplasm and form 6-8 haploid microgamete or male gametes. This process of formation of microgamete is called exflagellation.

ii. Formation of female gamete:-

The mega gametocyte undergoes some reorganization to form a single haploid mega gamete or female gamete which is ready for fertilization.

- b. Fertilization:
- The male gamete enters the female gamete through the fertilization cone formed at female gamete and form diploid zygote or synkaryon. Fusion is anisogamous.
- c. Ookinete stage:
- The zygote remains inactive for sometimes and then elongates into a worm like Ookinete or vermicule, which is motile. The Ookinete penetrates the stomach wall and comes to lie below its outer epithelial layer.
- d. Oocyst stage:
- The Ookinete gets enclosed in a cyst. The encysted zygote is called Oocyst. The Oocyet absorbs nourishment and grows in size.
- 3. Asexual Sporogony
- The nucleus of Oocyet divides repeatedly to form a large number of haploid daughter nuclei. At the same time, the cytoplasm develops vacuoles and gives numerous cytoplasmic masses. The daughter nuclei pass into each cytoplasmic mass and develop into slender sickle-shaped sporozoites are formed in each Oocyet. This phase of asexual multiplication is known as sporogony.
- Lastly, the Oocyet brusts and sporozoites are liberated into the haemolymph of the mosquito. They spread throughout the haemolymph and eventually reach the salivary glands and enter the duct of the hypopharyx. The mosquito is now becomes infective and sporozoites get inoculated or injected the human blood when the mosquito bites. The cycle is repeated.
- In mosquito whole sexual cycle is completed in 10-12 days.

Incubation period:

The period between infection and the appearance of first symptoms is called incubation period. It is about 10-14 days in Plasmodium vivax.

Pre-patent period:

The duration between the initial sporozoites infection and the first appearance of parasites in the blood is called as pre-patient period. It is about 8 days in Plasmodium vivax.

Control

- controlled by three ways
- 1. Destruction of vector
- 2. Prevention of infection(prophylaxis)
- 3. Treatment of patient
- 4. Public awareness

1. Destruction of vector (Anopheles mosquito)

- Mosquito can be killed by spraying DDT, BHC, Dieldrin, Malathion etc.
- Filling up ditches, gutters and pits where the mosquito breeds.
- Water surface can be poisoned by spreading kerosene oil, petroleum etc.
- A speedly flow of water prevents the mosquito larva and pupa flourishing.
- Biological control: Certain fishes (trouts, minnows, stickle back), ducks, dragon flies etc feed on larva and pupa of mosquito.

2. Prevention of infection (Prophylaxis)

- Use of mosquito nets.
- Screening doors, windows and ventilators.
- Using mosquito repellent creams (e.g. odomus), anti mosquito mat (e.g. Supermat) etc.

3. Treatment of patient:

There are several drugs that kill different stages of parasite in patient. The oldest drug is Quinine; Paludrine kills almost all stages of parasite. Daraprism (single dose of 25 mg) is the most effective drug.

Plasmodium ovale

Plasmodium ovale is a species of parasitic protozoa that causes tertian malaria in humans. It is one of several species of *Plasmodium*parasites that infect humans including *Plasmodium falciparum* and *Plasmodium vivax* which are responsible for most malarial infection. It is rare compared to these two parasites, and substantially less dangerous than *P. falciparum*.

P. ovale has recently been shown by genetic methods to consist of two subspecies, *P. ovale curtisi* and *P. ovale wallikeri*

- **Prepatent period.**Humans are the only natural hosts for *P. ovale*. Much of what is known about this parasite was obtained during malaria therapy of naïve patients over 60 years ago. The prepatent period is the interval between sporozoite inoculation and the first detection of parasites in the peripheral blood. Sinton et al. reported a mean prepatent period of about 15 days, whereas James et al. working with six different strains of the parasite, reported a mean of 13.6 days. The Donaldson strain exhibited prepatent periods of 12 to 20 days, with a mean of 15.3 days; for the Liberian strain, prepatent periods of 13.5 to 15 days have been reported . A retrospective examination of induced infections with *P. ovale*was made by Collins and Jeffery . These data were extracted from the records of patients that were given malaria therapy for the treatment of neurosyphilis between 1940 and 1963.
- Prior to the introduction of penicillin for the treatment of syphilis, malaria was one of the most effective treatments for the disease . The range in prepatent periods following sporozoite injection was 14 to 20 days. A listing of prepatent periods for 30 patients infected via sporozoites with the Donaldson and Liberian strains indicated prepatent periods of 12 to 20 days, with a median of 14.5 days.

Epidemiology

While it is frequently said that *P. ovale* is very limited in its range being limited to West Africa,the Philippines, eastern Indonesia, and Papua New Guinea, it has been reported
from Bangladesh , Cambodia, India, Thailand and Vietnam
The reported prevalence is low (<5%) with the exception of West Africa, where prevalences above 10% have been observed.
The epidemiology of this parasite is in need of updating because the most recent global map of its distribution was produced in 1969.
It has been estimated that there are about 15 million cases of infection each year with this parasite.

Clinical features

The prepatent period in the human ranges from 12 to 20 days. Some forms in the liver have delayed development and relapse may occur after periods of up to 4 years after infection.
The developmental cycle in the blood lasts approximately 49 h. An examination of records from induced infections indicated that there were an average of 10.3 fever episodes of > or = 101 °F (38,3 °C) and 4.5 fever episodes of > or = 104 °F (40,0 °C). Mean maximum parasite levels were 6,944/microl for sporozoite-induced infections and 7,310/microl for trophozoite-induced infections.

Diagnosis

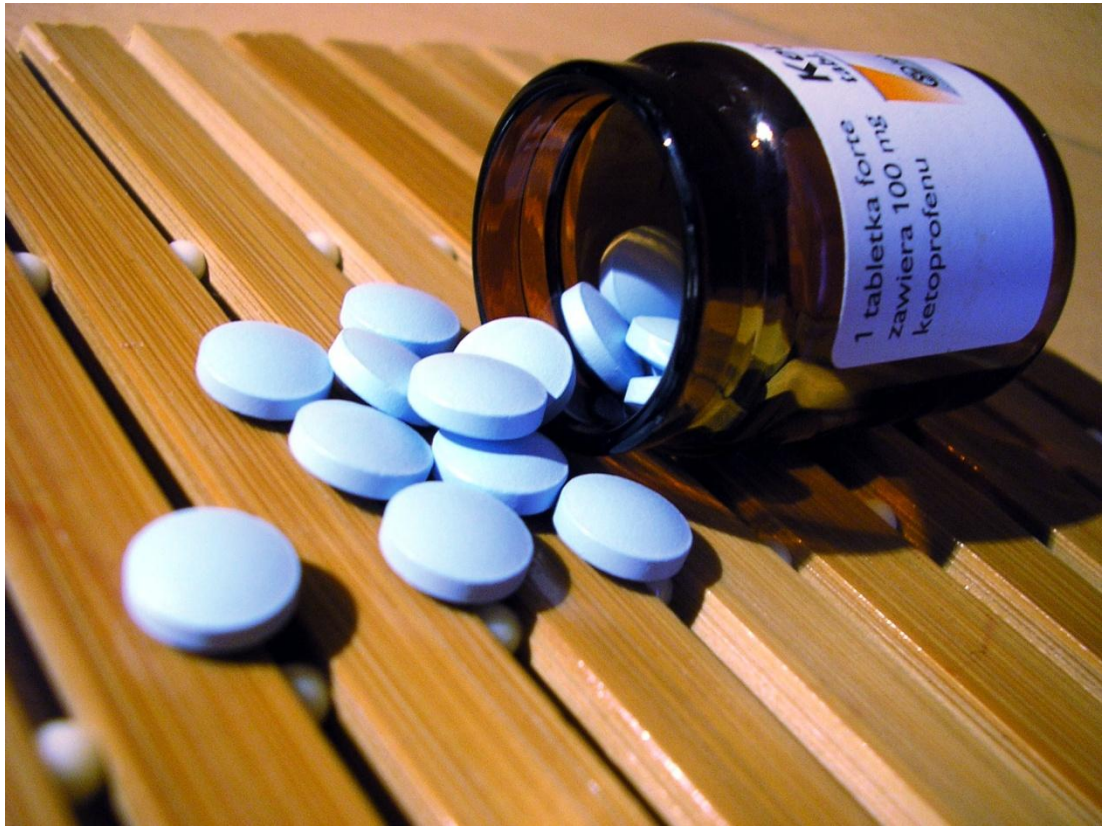
The microscopic appearance of *P. ovale* is very similar to that of *P. vivax* and if there are only a small number of parasites seen, it may be impossible to distinguish the two species on morphological grounds alone. There is no difference between the medical treatment of *P. ovale* and *P. vivax*, and therefore some laboratory diagnoses report "*P. vivax/ovale*", which is perfectly acceptable as treatment for the two are very similar. Schüffner's dots are seen on the surface of the parasitised red blood cell, but these are larger and darker than in *P. vivax* and are sometimes called James' dots or James' stippling. About twenty percent of the parasitised cells are oval in shape (hence the species name) and some of the oval cells also have fimbriated edges (the so-called "comet cell"). The mature schizonts of *P. ovale* never have more than twelve nuclei within them and this is the only reliable way of distinguishing between the two species.

P. vivax and *P. ovale* that has been sitting in EDTA for more than half-an-hour before the blood film is made will look very similar in appearance to *P. malariae*, which is an important reason to warn the laboratory immediately when the blood sample is drawn so they can process the sample as soon as it arrives.

Molecular tests (tests that look for DNA material from *P. ovale* in blood) must take into account the fact that there are two subspecies of ovale and tests designed for one subspecies may not necessarily detect the other

Treatment

Standard treatment is concurrent treatment with chloroquine and primaquine . The combination atovaquone-proguanil may be used in those patients who are unable to take chloroquine for whatever reason



Plasmodium malariae

Plasmodium malariae is a parasitic protozoa that causes malaria in humans. It is one of several species of *Plasmodium* parasites that infect humans including *Plasmodium falciparum* and *Plasmodium vivax* which are responsible for most malarial infection. While found worldwide, it is a so-called "benign malaria" and is not nearly as dangerous as that produced by *P. falciparum* or *P. vivax*. It causes feversthat recur at approximately three-day intervals (a *quartan fever*), longer than the two-day (tertian) intervals of the other malarial parasites, hence its alternate names **quartan fever** and **quartan malaria**

Epidemiology

Each year, approximately 500 million people will be infected with malaria worldwide Of those infected, roughly two million will die from the disease. Malaria is caused by six *Plasmodium* species: *Plasmodium falciparum*, *Plasmodium vivax, Plasmodium ovale curtisi*,*Plasmodium ovale wallikeri*, *Plasmodium malariae* and *Plasmodium knowlesi*. At any one time, an estimated 300 million people are said to be infected with at least one of these*Plasmodium* species and so there is a great need for the development of effective treatments for decreasing the yearly mortality and morbidity rates.

P. malariae is the one of the least studied of the six species that infect humans, in part because of its low prevalence and milder clinical manifestations compared to the other species. It is widespread throughout sub-Saharan Africa, much of southeast Asia, Indonesia, on many of the islands of the western Pacific and in areas of the Amazon Basin of South America. In endemic regions, prevalence ranges from less than 4% to more than 20%, but there is evidence that *P. malariae* infections are vastly underreported

Transmission

P. malariae can be maintained at very low infection rates among a sparse and mobile population because unlike the other *Plasmodium* parasites, it can remain in a human host for an extended period of time and still remain infectious to mosquitoes

Vector

The vector of transmission of the parasite is the female Anopheles mosquito, but many different species have been shown to transmit the parasite at least experimentally.Collins and Jeffrey report over thirty different types of species, which vary by geographic region.However, there are no animal reservoirs for *Plasmodium malariae*.

Incubation period

Information about the prepatent period, or the period of time between the infection of the parasite and demonstration of that parasite within the body, of *P. malariae* associated malaria is limited, but the data suggests that there is great variation, often the length of time depending on the strain of *P. malariae* parasite.[2] Usually, the prepatent period ranges from 16 to 59 days.

Morphology

The ring stages that are formed by the invasion of merozoites released by rupturing liver stage schizonts are the first stages that appear in the blood.The ring stages grow slowly but soon fill one-fourth to one-third of the parasitized cell.Pigment increases rapidly and the half-grown parasite may have from 30 to 50 jet-black granules. The parasite changes various shapes as it grows and stretches across the host cell to form the band form.

Clinical presentation in humans

Plasmodium malariae causes a chronic infection that in some cases can last a lifetime. The *P. malariae* parasite has several differences between it and the other *Plasmodium*parasites, one being that maximum parasite counts are usually low compared to those in patients infected with *P. falciparum* or *P. vivax.*The reason for this can be accounted for by the lower number of merozoites produced per erythrocytic cycle, the longer 72-hour developmental cycle (compared to the 48-hour cycle of *P. vivax* and *P. falciparum*), the preference for development in older erythrocytes and the resulting earlier development of immunity by the human host.Another defining feature of *P. malariae* is that the fever manifestations of the parasite are more moderate relative to those of *P. falciparum* and *P. vivax* and fevers show quartan periodicity.

Along with bouts of fever and more general clinical symptoms such as chills and nausea, **the presence of edema and the nephrotic syndrome** has been documented with some *P. malariae* infections. It has been suggested that immune complexes may cause structural glomerular damage and that renal disease may also occur. Although *P. malariae* alone has a low morbidity rate, it does contribute to the total morbidity caused by all *Plasmodium* species, as manifested in the incidences of anemia, low birth rate and reduced resistance to other infections.

Due to a similarity in the appearances of the pathogens, *P. knowlesi* infections are often misdiagnosed as *P. malariae* infections. Molecular analysis is usually required for an accurate diagnosis.

Diagnostics

The preferable method for diagnosis of *P. malariae* is through the examination of peripheral blood films stained with Giemsa stain.PCR techniques are also commonly used for diagnoses confirmation as well as to separate mixed *Plasmodium* infections. Even with these techniques, however, it may still be impossible to differentiate infections, as is the case in areas of South America where humans and monkeys coexist and *P. malariae* and *P. brasilianum* are not easily distinguishable

Life cycle

P. malariae is the only human malaria parasite that causes fevers that recur at approximately three-day intervals (therefore occurring evey fourth day, a *quartan fever*), longer than the two-day (*tertian*) intervals of the other malarial parasites.

Laboratory considerations

P. vivax and *P. ovale* sitting in EDTA for more than 30 minutes before the blood film is made will look very similar in appearance to *P. malariae*, which is an important reason to warn the laboratory immediately when the blood sample is drawn so they can process the sample as soon as it arrives.

Microscopically, the parasitised red blood cell (erythrocyte) is never enlarged and may even appear smaller than that of normal red blood cells. The cytoplasm is not decolorized and no dots are visible on the cell surface. The food vacuole is small and the parasite is compact. Cells seldom host more than one parasite. Band forms, where the parasite forms a thick band across the width of the infected cell, are characteristic of this species (and some would say is diagnostic). Large grains of malarial pigment are often seen in these parasites: more so than any other *Plasmodium* species, 8 merozoites

Management and therapy

Failure to detect some *P. malariae* infections has led to modifications of the species-specific primers and to efforts towards the development of real-time PCR assays .The development of such an assay has included the use of generic primers that target a highly conserved region of the 18S rRNA genes of the four human-infecting species of*Plasmodium*. This assay was found to be highly specific and sensitive. Although serologic tests are not specific enough for diagnostic purposes, they can be used as basic epidemiologic tools.The immunofluorescent-antibody (IFA) technique can be used to measure the presence of antibodies to *P. malariae*.. A pattern has emerged in which an infection of short duration causes a rapidly declining immune response, but upon re-infection or recrudescence, the IFA level rises significantly and remains present for many months or years.

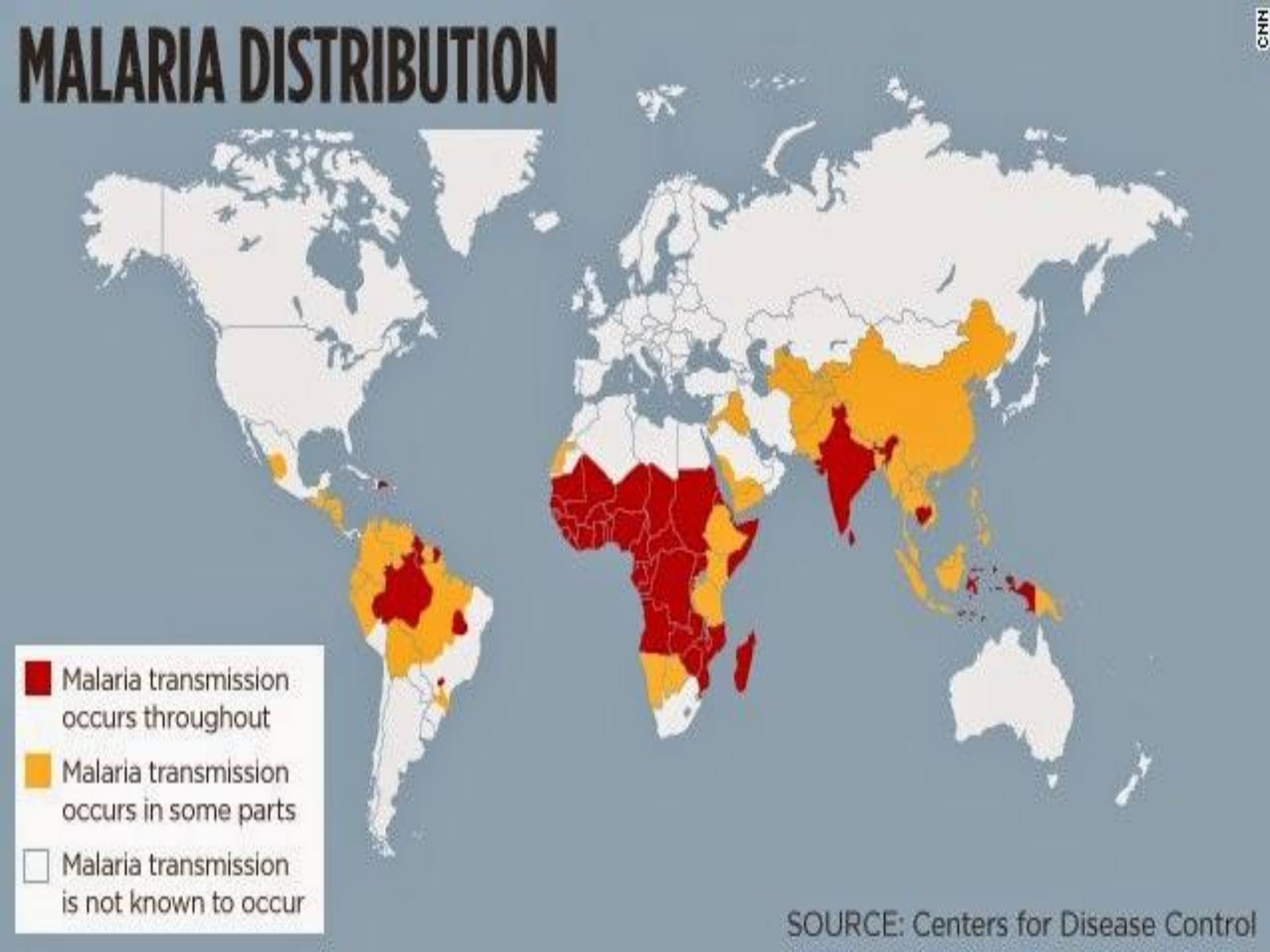
The increasing need to correctly identify *P. malariae* infection is underscored by its possible anti-malarial resistance. In a study by Müller-Stöver *et al.,* the researchers presented three patients who were found to be infected with the parasite after taking anti-malarial medications.[11] Given the slower pre-erythrocytic development and longer incubation period compared to the other malaria causing *Plasmodium* species, the researchers hypothesized that the anti-malarials may not be effective enough against the pre-erythrocytic stages of *P. malariae.*[11] They thought that further development of *P. malariae* can occur when plasma concentrations of the anti-malarials gradually decrease after the anti-malarial medications are taken. According to Dr. William E. Collins from the Center of Disease Control (CDC), chloroquines most commonly used for treatment and no evidence of resistance to this drug has been found.In that event, it is possible that the results from Müller-Stöver *et al.* provided isolated incidences.

Public health, prevention strategies and vaccines

The food vacuole is the specialized compartment that degrades hemoglobin during the asexual erythrocytic stage of the parasite.It is implied that effective drug treatments can be developed by targeting the proteolytic enzymes of the food vacuole. In a paper published in 1997, Westling *et al.* focused their attention on the aspartic endopeptidase class of enzymes, simply called plasmepsins. They sought to characterize the specificity for the enzymes cloned from *P. vivax* and *P. malariae.* Using substrate specificity studies and inhibitor analysis, it was found that the plasmepsins for *P. malariae* and *P. vivax* showed less specificity than that for *P. falciparum.* Unfortunately, this means that the development of a selective inhibitor for *P. malariae* may prove more challenging than the development of one for *P. falciparum.*Another study by Bruce *et al.*presented evidence that there may be regular genetic exchange within *P. malariae* populations. Six polymorphic genetic markers from *P. malariae* were isolated and analyzed in 70 samples of naturally acquired *P. malariae* infections from different parts of the world. The data showed a high level of multi-genotypic carriage in humans.

Both of these experiments illustrate that development of vaccine options will prove challenging, if not impossible. Dr. William Collins doubts that anyone is currently looking for possible vaccines for *P. malariae* and given the complexity of the parasite it can be inferred why. He states that very few studies are conducted with this parasite, perhaps as a result of its perceived low morbidity and prevalence. Collins sights the great restrictions of studies with chimpanzees and monkeys as a sizeable barrier.Since the*Plasmodium brasilianium* parasite that infects South American monkeys is thought to be an adapted form of *P. malariae,* more research with *P. brasilianium* may hold valuable insight into *P. malariae.*

MALARIA DISTRIBUTION



KEEP CALM AND THANK YOU FOR YOUR ATTENTION