RECENT ASPECT OF DRUG USED IN TREATMENT OF MALARIA

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ABSTRACT

Malaria is a serious and sometimes fatal disease caused by a parasite. Patients with malaria typically are very sick with high fevers, shaking chills, and flu-like illness. Four kinds of malaria parasites can infect humans: Plasmodium falciparum, P. vivax, P. ovale, and P. malariae.Infection with any of the malaria species can make a person feel very ill; infection with P. falciparum, if not promptly treated, may be fatal. Although malaria can be a fatal disease, illness and death from malaria are largely preventable.. Malaria is a leading cause of death and disease worldwide, especially in developing countries. Most deaths occur in young children. Since many countries with malaria are already among the poorer nations, the disease maintains a vicious cycle of disease and poverty. Malaria typically is found in warmer regions of the world -- in tropical and subtropical countries. Higher temperatures allow the Anopheles mosquito to thrive. Malaria parasites, which grow and develop inside the mosquito, need warmth to complete their growth before they are mature enough to be transmitted to humans. Usually, people get malaria by being bitten by an infected female Anopheles mosquito. Only Anopheles mosquitoes can transmit malaria and they must have been infected through a previous blood meal taken on an infected person. When a mosquito bites, a small amount of blood is taken in which contains the microscopic malaria parasites. The parasite grows and matures in the mosquito's gut for a week or more, then travels to the mosquito's salivary glands. When the mosquito next takes a blood meal, these parasites mix with the saliva and are injected into the bite. Once in the blood, the parasites travel to the liver and enter liver cells to grow and multiply. During this "incubation period", the infected person has no symptoms. After as few as 8 days or as long as several months, the parasites leave the liver cells and enter red blood cells. Once in the cells, they continue to grow and multiply. After they mature, the infected red blood cells rupture, freeing the parasites to attack and enter other red blood cells. Toxins released when the red cells burst are what cause the typical fever, chills, and flu-like malaria symptoms. If a mosquito bites this infected person and ingests certain types of malaria parasites ("gametocytes"), the cycle of transmission continues. Because the malaria parasite is found in red blood cells, malaria can also be transmitted through blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood. Malaria may also be transmitted from a mother to her fetus before or during delivery ("congenital" malaria). Malaria is not transmitted from person to person like a cold or the flu. You cannot get malaria from casual contact with malaria-infected people. Symptoms of malaria include fever and flu-like illness, including shaking chills, headache, muscle aches, and tiredness. Nausea, vomiting, and diarrhea may also occur. Malaria may cause anemia and jaundice (yellow coloring of

the skin and eyes) because of the loss of red blood cells. Infection with one type of malaria, Plasmodium falciparum, if not promptly treated, may cause kidney failure, seizures, mental confusion, coma, and death. For most people, symptoms begin 10 days to 4 weeks after infection, although a person may feel ill as early as 7 days or as late as 1 year later. Two kinds of malaria, P. vivax and P. ovale, can relapse. In P. vivax and P. ovale infections, some parasites can remain dormant in the liver for several months up to about 4 years after a person is bitten by an infected mosquito. When these parasites come out of hibernation and begin invading red blood cells ("relapse"), the person will become sick. Most people, at the beginning of the disease, have fever, sweats, chills, headaches, malaise, muscles aches, nausea and vomiting. Malaria can very rapidly become a severe and life-threatening disease. The surest way for you and your doctor to know whether you have malaria is to have a diagnostic test where a drop of your blood is examined under the microscope for the presence of malaria parasites. If you are sick and there is any suspicion of malaria (for example, if you have recently traveled in a malaria-risk area) the test should be performed without delay. The World Health Organization estimates that each year 300-500 million cases of malaria occur and more than 1 million people die of malaria.

INTRODUCTION

Malaria is an infectious disease caused by a parasite, Plasmodium, which infects red blood cells. Malaria is characterized by cycles of chills, fever, pain and sweating. Historical records suggest malaria has infected humans since the beginning of mankind. The name "mal 'aria" (meaning "bad air" in Italian) was first used in English in 1740 by H. Walpole when describing the disease. The term was shortened to "malaria" in the 20th century. C. Laveran in 1880 was the first to identify the parasites in human blood. In 1889, R. Ross discovered that mosquitoes transmitted malaria. Of the four species of malaria, the most serious type is Plasmodium falciparum malaria. It can be life-threatening. The other three species of malaria (P. vivax, P. malariae, and P. ovale) are generally less serious and are not life-threatening. The life cycle of the parasite is complicated (for life cycle details, see and involves two hosts, humans and Anopheles mosquitoes. The disease is transmitted to humans when an infected Anopheles mosquito bites a person and injects the malaria parasites (sporozoites) into the blood. Sporozoites travel through the bloodstream to the liver, mature, and eventually infect the human red blood cells. While in red blood cells, the parasites again develop until a mosquito takes a blood meal from an infected human and ingests human red blood cells containing the parasites. Then the parasites reach the Anopheles mosquito's stomach and eventually invade the mosquito salivary glands. When an Anopheles mosquito bites a human, these sporozoites complete and repeat the complex Plasmodium life cycle. P. ovale and P. vivax can further complicate the cycle by producing dormant stages (hypnozoites) that may not develop for weeks to years. Malaria is a particular problem and a major one in areas of Asia, Africa, and Central and South America. Unless precautions are taken, anyone living in or traveling to a country where malaria is present can get the disease. Malaria occurs in about 100 countries; approximately 40% of the world population is at risk for contracting malaria. To get information on countries that have current malaria infection problems, the CDC (Centers for Disease Control) has a constantly updated website that lists the problem areas in detail: Malaria is a particular problem and a major one in areas of Asia, Africa, and Central and South

America. Unless precautions are taken, anyone living in or traveling to a country where malaria is present can get the disease. Malaria occurs in about 100 countries; approximately 40% of the world population is at risk for contracting malaria. To get information on countries that have current malaria infection problems, the CDC (Centers for Disease Control) has a constantly updated website that lists the problem areas in detail: The period between the mosquito bite and the onset of the malarial illness is usually one to three weeks (seven to 21 days). This initial time period is highly variable as reports suggest that the range of incubation periods may range from four days to one year. The usual incubation period may be increased when a person has taken an inadequate course of malaria prevention medications. Certain types of malaria (P. vivax and P. ovale) parasites can also take much longer, as long as eight to 10 months, to cause symptoms. These parasites remain dormant (inactive or hibernating) in the liver cells during this time. Unfortunately, some of these dormant parasites can remain even after a patient recovers from malaria, so the patient can get sick again. This situation is termed relapsing malaria. Malaria may pose a serious threat to a pregnant woman and her pregnancy. Malaria infection in pregnant women may be more severe than in women who are not pregnant. Malaria may also increase the risk of problems with the pregnancy, including prematurity, abortion, and stillbirth. Statistics indicate that in sub-Saharan Africa, between 75,000-200,000 infants die from malaria per year; worldwide estimates indicate over 1 million children die from malaria each year. Therefore, all pregnant women who are living in or traveling to a malaria-risk area should consult a doctor and take prescription drugs (for example, sulfadoxine-pyrimethamine) to avoid contracting malaria. Treatment of malaria in the pregnant female is similar to the usual treatment described above; however, drugs such as primaquine (Primaquine), tetracycline (Achromycin, Sumycin), doxycycline, and halofantrine (Halfan) are not recommended as they may harm the fetus. In addition to monitoring the patient for anemia, an OB-GYN specialist is consulted for further management. All children, including young infants, living in or traveling to malaria-risk areas should take antimalarial drugs (for example, chloroquine and mefloquine [Lariam]). Although the recommendations for most antimalarial drugs are the same as for adults, it is crucial to use the correct dosage for the child. The dosage of drug depends on the age and weight of the child. Since an overdose of an antimalarial drug can be fatal, all antimalarial (and all other) drugs should be stored in childproof containers well out of the child's reach. If you are traveling to an area known to have malaria, find out which medications you need to take, and take them as prescribed. Current CDC recommendations suggest individuals begin taking antimalarial drugs about one to two weeks before traveling to a malaria infested area and for four weeks after leaving the area. Your doctor, travel clinic, or the health department can advise you as to what medicines to take to keep from getting malaria. Currently, there is no vaccine available for malaria, but researchers are trying to develop one. Malaria is a life-threatening parasitic disease transmitted by mosquitoes from person to person. When an infective mosquito bites, she transmits malaria parasites to her victim who falls ill. Other mosquitoes then pick up the parasite from the infected person and continue spreading the disease when biting other people. Today approximately 40% of the world's population mostly those living in the world’s poorest countries are at risk of malaria. The disease was once more widespread but it was successfully eliminated from many countries with temperate climates during the mid 20th

century. Today malaria is found throughout the tropical and sub-tropical regions of the world and causes more than 300 million acute illnesses and at least one million deaths annually.90% of deaths due to malaria occur in Africa south of the Sahara mostly among young children. Malaria kills an African child every 30 seconds. Many children who survive an episode of severe malaria may suffer from learning impairments or brain damage. Pregnant women and their unborn children are also particularly vulnerable to malaria, which is a major cause of prenatal mortality, low birth weight and maternal anemia. In sub-Saharan Africa, malaria affects mostly young children, with almost 3,000 dying every day - 20% of all deaths in children under 5 years of age. An estimated one million people in Africa die from malaria each year, 90% of these deaths occur in sub-Saharan Africa.71% of all deaths from malaria are in children under 5. A child's most vulnerable period begins at six months, when the mother's protective immunity wears off and before the infant has established its own robust immune system. Once infected a child's condition may deteriorate quickly and children can die within 48 hours after the first symptoms appear.Malaria kills an African child every 30 seconds. 300 to 500 million clinical cases of malaria are documented each year worldwide. The majority of infections in Africa are caused by Plasmodium falciparum, the most dangerous of the four human malaria parasites. Medical treatment should be sought immediately.The effectiveness of antimalarialdrugs differs with different species of the parasite and with different stages of theparasite's life cycle. Your physician will determine the treatment plan mostappropriate for your individual condition. Drugs include chloroquine, mefloquine, primaquine, quinine, pyrimethaminesulfadoxine (Fansidar), and anddoxycycline. Some plasmodiums have developed resistance to certain medications, and therefore, alternative medications will be prescribed for you.

CAUSES OF MALARIA

Malaria is a parasitic infection spread by Anopheles mosquitoes. The Plasmodium parasite that causes malaria is neither a virus nor a bacterium - it is a single-celled parasite that multiplies in red blood cells of humans as well as in the mosquito intestine. When the female feeds on an infected individual, male and female forms of the parasite are ingested from human blood. Subsequently, they meet and mate in the mosquito gut following which infective forms are passed into another human when the mosquito feeds again.

The World Health Organization led a successful campaign against the Anopheles mosquito in the 1950s and 1960s, cutting back their range dramatically. Lately the mosquito and the parasite have both made a comeback. Malaria now kills about two million people worldwide annually, making it the second most lethal infectious disease after tuberculosis. More than 300 million people are infected each year. It is especially dangerous for children and pregnant women.

Although the parasite has progressively developed resistance to several of our older antimalarial medications, we still have many safe and effective medications both for treatment and prevention (prophylaxis).

There are four species of Plasmodium parasite that can cause malaria: P. falciparum, P. vivax, P. ovale, and P. malariae. The first two types are the most common. Plasmodium falciparum is the most dangerous of these parasites because the infection can kill rapidly (within several days), whereas the other species cause illness but not death. Falciparum malaria is particularly frequent in sub-Saharan Africa and Oceania (Papaua New Guinea, Irian Jaya, and the Solomon Islands).

You can only get malaria if you're bitten by an infected mosquito, or receive infected blood from someone during a blood transfusion. Malaria can be transmitted from mother to child during pregnancy. The mosquitoes that carry Plasmodium parasite get it from biting a person or animal that's already been infected. The parasite then goes through various changes that enable it to infect the next creature the mosquito bites. Once it's in you, it multiplies in the liver and changes again, getting ready to infect the next mosquito that bites you. It then enters the bloodstream and invades red blood cells. Eventually, the infected red blood cells burst. This sends the parasites throughout the body and causes malaria symptoms.

Malaria has been with us long enough to have changed our genes. The reason why many people of African descent suffer from the blood disease sickle cell anemia is because the gene that causes it also confers some immunity to malaria. In Africa, therefore, people with a sickle cell gene are more likely to survive and have children. The same is true of thalassemia, a hereditary disease found in people of Mediterranean descent. Malaria is mainly caused by parasitic protozoa, which spends most of its life in the red blood cells of humans. Malaria is spread by the female Anopheles mosquito, which transmit the parasites by first ingesting them from an infected person's blood and then injecting the parasite in to an healthy person.

Malaria is caused by one of four protozoan species of the genus Plasmodium they are:

- Plasmodium falciparum.
- Plasmodium vivax.
- Plasmodium ovale.
- Plasmodium malariae.

After a bite from an infected mosquito, the parasite enters the person's bloodstream and travels to the liver where it grows and after that it multiplies the malaria. During this time when the parasite is in the liver, there are no visible symptoms and the victim doesn't feel sick.

Types of Malaria

There are three types of malarial fever that may be classified depending on symptoms or caused by the parasite. The leading symptoms are mainly same but their occurrence and duration do vary. They are

1) Tertian Fever.
2) Quartan Fever.
3) Malignant Fever.

Tertian Fever: The attacks surface on alternate days.

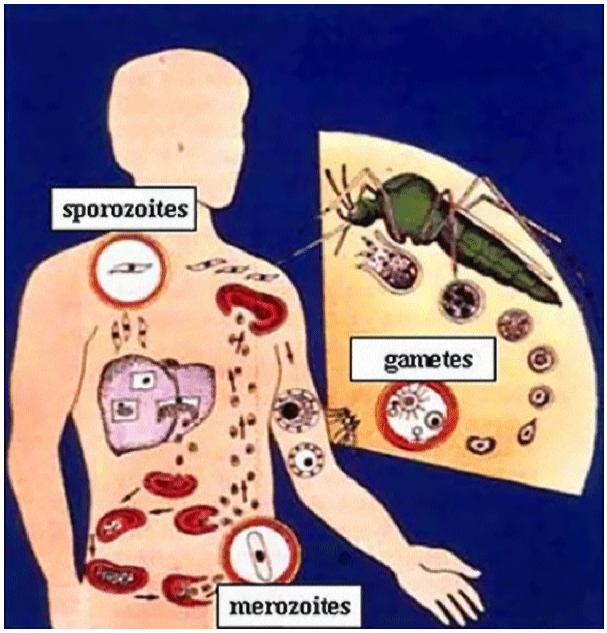
Quartan Fever: In this fever the attack of fever occurs after an interval of two days, i.e. if first attack of fever occurs on the first, another attack will occur on the 4th day, then 7th, 9th and so on.

Malignant Tertian: It is a variety of severe type of malarial fever when malignancy sets in and is, thus, the most severe and most alarming type of malarial fever.

The incubation period for malaria varies considerably. An incubation period is the time between the mosquito bite and the time symptoms of malaria begin to appear. The incubation period differs depending on the kind of parasite involved. There are following causes of Malaria:

- Female mosquitoes that carry the plasmodium parasite in their bodies transmit malaria.
- Rainfall is the leading cause of malaria epidemics as it creates high mosquito population.
- If the mosquito bites infected person then bites uninfected person then it may transfer those parasites to the uninfected person.

It can also be transmitted through blood transfusions.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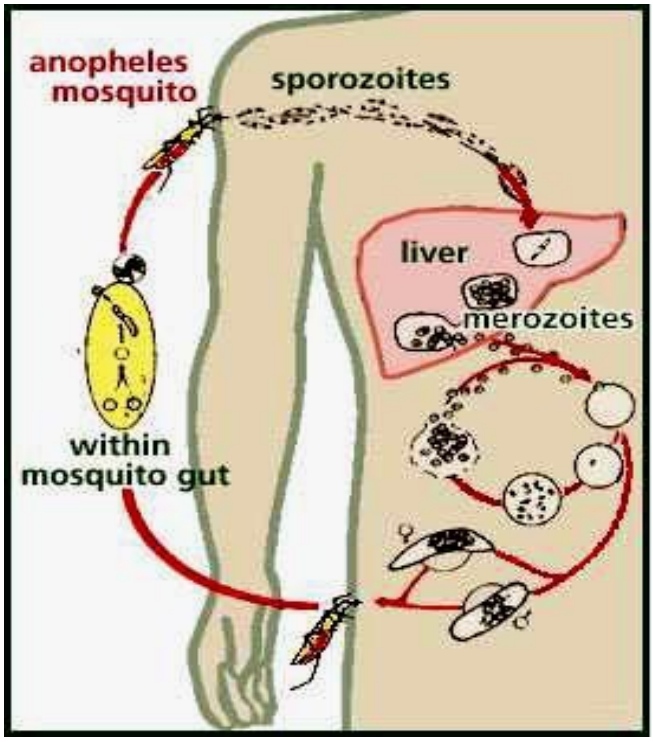

Figure-causes of malaria and transmission of malaria through mosquito

SYMPTOMS AND COMPLICATIONS OF MALARIA

Symptoms usually appear about 12 to 14 days after infection. People with malaria have the following symptoms:

- abdominal pain
- chills and sweats
- diarrhea, nausea, and vomiting (these symptoms only appear sometimes)
- headache
- high fevers
- low blood pressure causing dizziness if moving from a lying or sitting position to a standing position (also called *orthostatic hypotension*)
- muscle aches
- poor appetite

In people infected with *P. falciparum,* the following symptoms may also occur:

- anemia caused by the destruction of infected red blood cells
- extreme tiredness, delirium, unconsciousness, convulsions, and coma
- kidney failure
- pulmonary edema (a serious condition where fluid builds up in the lungs, which can lead to severe breathing problems)

DIAGNOSING MALARIA

You may have malaria if you have any fever during or after travel in malarial regions. See a doctor quickly, and get your blood tested to check if the parasite is present. The doctor will also check to see if you have an enlarged spleen, which sometimes accompanies the fever of malaria. Don't wait to get home for treatment if you get malaria abroad.

Plasmodium parasites in the blood are usually visible under the microscope. There are also simple dipstick tests (done by dipping a piece of paper with chemicals on it into your blood) that can be used to identify *P. falciparum*. Blood tests as well as liver and kidney function tests will be done to check the effects of the parasite on your system.

Treatment usually lasts for three to seven days, depending on the medication type. To get rid of the parasite, it's important to take the pills for the full length of time prescribed: don't stop taking the medication even if you feel better. If you experience intolerable side effects, your doctor can substitute another medication.

If you're travelling to a malarial region, you should take a course of preventive treatment. Medications similar to those used to cure malaria can prevent it if taken before, during, and after your trip. It's vital to take your pills as prescribed, even after you return home.

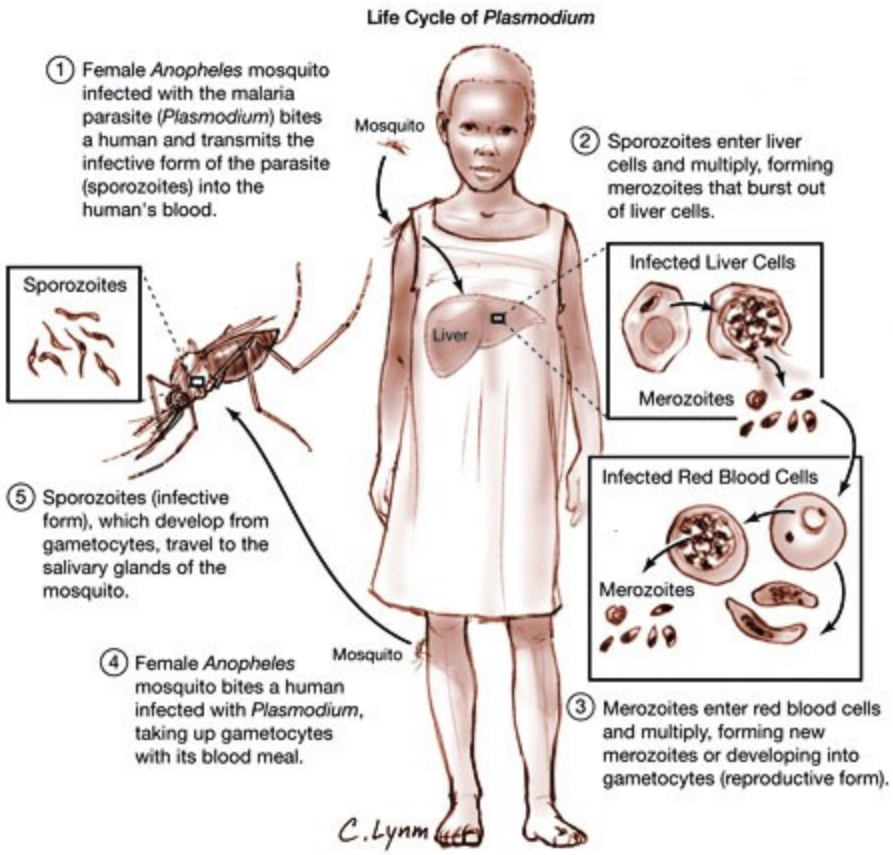

Figure-Life cycle of malaria

PREVENTIONS OF MALARIA

To get not infected from Malaria, First of all, a person should avoid being bitten by a mosquito carrying the malaria parasite. For that purpose some preventive measures need to be followed.

- Avoid travel to or through countries where malaria occurs (If possible). If you must go to areas where malaria occurs, take the prescribed preventive medicine.
- Have screens over cover windows and doors.
- Sleeping inside mosquito nets and use mosquito repellents of various forms.
- Spray mosquito repellents on clothing to prevent mosquitoes from biting through thin clothing.
- Staying indoors in well-screened areas between dusk and dawn.
- Wear long-sleeved shirts and long pants especially when you are outdoors.

Number of mosquitoes in and around the place of residence must be controlled. Public awareness building and joint effort in controlling mosquito population can be very effective way to prevent this disease.

DRUG USED IN TREATMENT OF MALARIA

Malaria is a common mosquito-borne parasitic infection characterized by fever, chills, and sweating. The disease is particularly severe in children below the age of 5 years. Malaria parasites have the capability of multiplying into thousands every few days after they enter the bloodstream and hence, the disease can quickly turn into an epidemic. Therefore, a little caution, correct diagnosis and timely treatment can help save you a lot of trouble. Malaria is spread by the bite of the female Anopheles mosquitoes, which are most active between dusk and dawn. In most people, the symptoms begin showing 10 days to four weeks after infection. A person contracts malaria when the parasites are transmitted from the mosquito's saliva into the person's bloodstream. Therefore, malaria cannot spread from direct contact with a person infected with malaria. Additionally, a person can be afflicted with malaria if he is receives infected blood during blood transfusion. Malaria is widespread in many parts of India throughout the year. However, the colder regions of northern India usually have lesser cases of the disease as mosquitoes do not thrive in low temperature areas. During the monsoon season (end June-mid September), however, cases of malaria shoot up as the warm humid weather and stagnant water provide the perfect breeding ground for mosquitoes. Most of the symptoms of malaria are similar to that of any other viral fever or flu, and even dengue or chikungunya. Therefore, if your child comes down with high fever and chills, you need to contact your doctor immediately. If your doctor suspects the symptoms to be that of malaria, he may request a blood test to confirm the diagnosis. Apart from medicines, your child will benefit from plenty of rest, light and healthy food and frequent sponging. The malaria infection may last up to 10 days, but if your child shows other symptoms such as convulsions, dehydration or loss of consciousness, hospitalization may be required. Ensure that your house and the surrounding areas are free of uncovered stagnant water that remain collected in old flower pots, vases, and air coolers or any other kind of clutter that you barely move or clean, especially during the monsoon season.Active malaria infection with *P. falciparum* is a medical emergency requiring hospitalization. Infection with *P. vivax*, *P. ovale* or *P. malariae* can often be treated on an outpatient basis. Treatment of malaria involves supportive measures as well as specific antimalarial drugs. When properly treated, someone with malaria can expect a complete recovery.[80]

Antimalarial drugs

Further information: Antimalarial drugs

There are several families of drugs used to treat malaria. Chloroquine is very cheap and, until recently, was very effective, which made it the antimalarial drug of choice for many years in most parts of the world. However, resistance of *Plasmodium falciparum* to chloroquine has spread recently from Asia to Africa, making the drug ineffective against the most dangerous Plasmodium strain in many affected regions of the world. In those areas where chloroquine is still effective it remains the first choice. Unfortunately, chloroquine-resistance is associated with reduced sensitivity to other drugs such as quinine and amodiaquine. There are several other substances which are used for treatment and, partially, for prevention (prophylaxis). Many drugs may be used for both purposes; larger doses are used to treat cases of malaria. Their deployment depends mainly on the frequency of resistant parasites in the area where the drug is used. One drug currently being investigated for possible use as an anti-malarial, especially for treatment of drug-resistant strains, is the beta blocker propranolol. Propranolol has been shown to block both *Plasmodium*'s ability to enter red blood cell and establish an infection, as well as parasite replication. A December 2006 study by Northwestern University researchers suggested that propranolol may reduce the dosages required for existing drugs to be effective against *P. falciparum* by 5- to 10-fold, suggesting a role in combination therapies.

Currently available anti-malarial drugs include:

- Artemether-lumefantrine (Therapy only, commercial names *Coartem* and *Riamet*)
- Artesunate-amodiaquine (Therapy only)
- Artesunate-mefloquine (Therapy only)
- Artesunate-Sulfadoxine/pyrimethamine (Therapy only)
- Atovaquone-proguanil, trade name Malarone (Therapy and prophylaxis)
- Quinine (Therapy only)
- Chloroquine (Therapy and prophylaxis; usefulness now reduced due to resistance)
- Cotrifazid (Therapy and prophylaxis)
- Doxycycline (Therapy and prophylaxis)
- Mefloquine, trade name Lariam (Therapy and prophylaxis)
- Primaquine (Therapy in *P. vivax* and *P. ovale* only; not for prophylaxis)
- Proguanil (Prophylaxis only)
- Sulfadoxine-pyrimethamine (Therapy; prophylaxis for semi-immune pregnant women in endemic countries as "Intermittent Preventive Treatment" - IPT)
- Hydroxychloroquine, trade name Plaquenil (Therapy and prophylaxis)

The development of drugs was facilitated when *Plasmodium falciparum* was successfully cultured. This allowed in vitro testing of new drug candidates. Extracts of the plant *Artemisia annua*, containing the compound artemisinin or semi-synthetic derivatives (a substance unrelated to quinine), offer over 90% efficacy rates, but their supply is not meeting demand. In 2007, the Bill & Melinda Gates Foundation contributed $13.6m to support research at the University of York to develop fast and high-yield strains of

artemisia, with researchers predicting an increase in yield of up to 1000% compared to current varieties. One study in Rwanda showed that children with uncomplicated P. falciparum malaria demonstrated fewer clinical and parasitological failures on post-treatment day 28 when amodiaquine was combined with artesunate, rather than administered alone (OR = 0.34). However, increased resistance to amodiaquine during this study period was also noted. Since 2001 the World Health Organization has recommended using artemisinin-based combination therapy (ACT) as first-line treatment for uncomplicated malaria in areas experiencing resistance to older medications. The most recent WHO treatment guidelines for malaria recommend four different ACTs. While numerous countries, including most African nations, have adopted the change in their official malaria treatment policies, cost remains a major barrier to ACT implementation. Because ACTs cost up to twenty times as much as older medications, they remain unaffordable in many malaria-endemic countries. The molecular target of artemisinin is controversial, although recent studies suggest that SERCA, a calcium pump in the endoplasmic reticulum may be associated with artemisinin resistance. Malaria parasites can develop resistance to artemisinin and resistance can be produced by mutation of SERCA. However, other studies suggest the mitochondrion is the major target for artemisinin and its analogs. In February 2002, the journal *Science* and other press outlets announced progress on a new treatment for infected individuals. A team of French and South African researchers had identified a new drug they were calling "G25". It cured malaria in test primates by blocking the ability of the parasite to copy itself within the red blood cells of its victims. In 2005 the same team of researchers published their research on achieving an oral form, which they refer to as "TE3" or "te3". As of early 2006, there is no information in the mainstream press as to when this family of drugs will become commercially available. In 1996, Professor Geoff McFadden stumbled upon the work of British biologist Ian Wilson, who had discovered that the plasmodia responsible for causing malaria retained parts of chloroplasts, an organelle usually found in plants, complete with their own functioning genomes. This led Professor McFadden to the realization that any number of herbicides may in fact be successful in the fight against malaria, and so he set about trialing large numbers of them, and enjoyed a 75% success rate. These "apicoplasts" are thought to have originated through the endosymbiosis of algaeand play a crucial role in fatty acid bio-synthesis in plasmodia. To date, 466 proteins have been found to be produced by apicoplasts and these are now being looked at as possible targets for novel anti-malarial drugs. Although effective anti-malarial drugs are on the market, the disease remains a threat to people living in endemic areas who have no proper and prompt access to effective drugs. Access to pharmacies and health facilities, as well as drug costs, are major obstacles. Medicines Sans Frontières estimates that the cost of treating a malaria-infected person in an endemic country was between US$0.25 and $2.40 per dose in 2002.

Counterfeit drugs

Sophisticated counterfeits have been found in several Asian countries such as Cambodia, China, Indonesia, Laos, Thailand, Vietnam and are an important cause of avoidable death in these countries. WHO have said that studies indicate that up to 40% of artesunate based malaria medications are counterfeit, especially in the Greater Mekong region and have established a rapid alert system to enable information about counterfeit drugs to be rapidly reported to the relevant authorities in participating countries. There is no reliable way for doctors or lay people to detect counterfeit drugs without help from a laboratory. Companies are attempting to combat the persistence of counterfeit drugs by using new technology to provide security from source to distribution.

Vector control

Before DDT, malaria was successfully eradicated or controlled also in several tropical areas by removing or poisoning the breeding grounds of the mosquitoes or the aquatic habitats of the larva stages, for example by filling or applying oil to places with standing water. These methods have seen little application in Africa for more than half a century. Efforts to eradicate malaria by eliminating mosquitoes have been successful in some areas. Malaria was once common in the United States and southern Europe, but the draining of wetland breeding grounds and better sanitation, in conjunction with the monitoring and treatment of infected humans, eliminated it from affluent regions. In 2002, there were 1,059 cases of malaria reported in the US, including eight deaths. In five of those cases, the disease was contracted in the United States. Malaria was eliminated from the northern parts of the USA in the early twentieth century, and the use of the pesticide DDT eliminated it from the South by 1951. In the 1950s and 1960s, there was a major public health effort to eradicate malaria worldwide by selectively targeting mosquitoes in areas where malaria was rampant. However, these efforts have so far failed to eradicate malaria in many parts of the developing world - the problem is most prevalent in Africa. Sterile insect technique is emerging as a potential mosquito control method. Progress towards transgenic, or genetically modified, insects suggest that wild mosquito populations could be made malaria-resistant. Researchers at Imperial College London created the world's first transgenic malaria mosquito, with the first plasmodium-resistant species announced by a team at Case Western Reserve University in Ohio in 2002. Successful replacement of existent populations with genetically modified populations relies upon a drive mechanism, such as transposable elements to allow for non-Mendelian inheritance of the gene of interest. However, this approach contains many difficulties and 34% of the malaria research and control community say that such an approach “will never fly”. Furthermore, such an approach is at least 5 to 10 years away from introduction and the progress which has been made in developing a vaccine could influence further research in genetic modification of malaria mosquitoes negatively.

On December 21, 2007, a study published in PLoS Pathogens found that the hemolytic C-type lectin CEL-III from *Cucumaria echinata*, a sea cucumber found in the Bay of Bengal,

impaired the development of the malaria parasite when produced by transgenic mosquitoes.[112][113] This could potentially be used one day to control malaria by using genetically modified mosquitoes refractory to the parasites, although the authors of the study recognize that there are numerous scientific and ethical problems to be overcome before such a control strategy could be implemented.

Prophylactic drugs

Several drugs, most of which are also used for treatment of malaria, can be taken preventively. Generally, these drugs are taken daily or weekly, at a lower dose than would be used for treatment of a person who had actually contracted the disease. Use of prophylactic drugs is seldom practical for full-time residents of malaria-endemic areas, and their use is usually restricted to short-term visitors and travelers to malarial regions. This is due to the cost of purchasing the drugs, negative side effects from long-term use, and because some effective anti-malarial drugs are difficult to obtain outside of wealthy nations. Quinine was used starting in the seventeenth century as a prophylactic against malaria. The development of more effective alternatives such as quinacrine, chloroquine, and primaquine in the twentieth century reduced the reliance on quinine. Today, quinine is still used to treat chloroquine resistant *Plasmodium falciparum*, as well as severe and cerebral stages of malaria, but is not generally used for prophylaxis. Samuel Hahnemann in the late 18th century noted that over-dosing of quinine leads to a symptomatic state very similar to that of malaria. This led him to develop the Law of Similars and homeopathy. Modern drugs used preventively include mefloquine (Lariam), doxycycline (available generically), and the combination of atovaquone and proguanil hydrochloride (Malarone). The choice of which drug to use depends on which drugs the parasites in the area are resistant to, as well as side-effects and other considerations. The prophylactic effect does not begin immediately upon starting taking the drugs, so people temporarily visiting malaria-endemic areas usually begin taking the drugs one to two weeks before arriving and must continue taking them for 4 weeks after leaving (with the exception of atovaquone proguanil that only needs be started 2 days prior and continued for 7 days afterwards).

Indoor residual spraying

Indoor residual spraying (IRS) is the practice of spraying insecticides on the interior walls of homes in malaria affected areas. After feeding, many mosquito species rest on a nearby surface while digesting the blood meal, so if the walls of dwellings have been coated with insecticides, the resting mosquitoes will be killed before they can bite another victim, transferring the malaria parasite. The first and historically the most popular insecticide used for IRS is DDT. While it was initially used exclusively to combat malaria, its use quickly spread to agriculture. In time, pest-control, rather than disease-control, came to dominate DDT use, and this large-scale agricultural use led to the evolution of resistant mosquitoes in many regions. If the use of DDT was limited agriculturally, DDT may be more effective now as a method of disease-control. The DDT resistance shown by Anopheles mosquitoes can be compared to antibiotic resistance shown by bacteria. The overuse of anti-bacterial soaps and antibiotics have led to antibiotic resistance in bacteria, similar to how overspraying of DDT on crops have led to DDT resistance in Anopheles mosquitoes.

During the 1960s, awareness of the negative consequences of its indiscriminate use increased ultimately leading to bans on agricultural applications of DDT in many countries in the 1970s.Though DDT has never been banned for use in malaria control and there are several other insecticides suitable for IRS, some advocates have claimed that bans are responsible for tens of millions of deaths in tropical countries where DDT had once been effective in controlling malaria. Furthermore, most of the problems associated with DDT use stem specifically from its industrial-scale application in agriculture, rather than its use in public health. The World Health Organization (WHO) currently advises the use of 12 different insecticides in IRS operations. These include DDT and a series of alternative insecticides (such as the pyrethroids permethrin and deltamethrin) to both combat malaria in areas where mosquitoes are DDT-resistant, and to slow the evolution of resistance. This public health use of small amounts of DDT is permitted under the Stockholm Convention on Persistent Organic Pollutants (POPs), which prohibits the agricultural use of DDT. However, because of its legacy, many developed countries discourage DDT use even in small quantities. One problem with all forms of Indoor Residual Spraying is insecticide resistance via evolution of mosquitos. According to a study published on Mosquito Behavior and Vector Control, mosquito breeds that are affected by IRS are endophilic species (Species which tend to rest and live indoors), and due to the irritation caused by spraying, their evolutionary descendants are trending towards becoming exophilic (Species which tend to rest and live out of doors), meaning that they are not as affected--if affected at all-- by the IRS, rendering it somewhat useless as a defense mechanism.

Mosquito nets and bedclothes

Mosquito nets help keep mosquitoes away from people and greatly reduce the infection and transmission of malaria. The nets are not a perfect barrier and they are often treated with an insecticide designed to kill the mosquito before it has time to search for a way past the net. Insecticide-treated nets (ITN) are estimated to be twice as effective as untreated nets,[104] and offer greater than 70% protection compared with no net.[120]. Although ITN are proven to be very effective against malaria, less than 2% of children in urban areas in Sub-Saharan Africa are protected by ITNs. Since the *Anopheles* mosquitoes feed at night, the preferred method is to hang a large "bed net" above the center of a bed such that it drapes down and covers the bed completely. The distribution of mosquito nets impregnated with insecticides such as permethrin or deltamethrin has been shown to be an extremely effective method of malaria prevention, and it is also one of the most cost-effective methods of prevention. These nets can often be obtained for around US$2.50 - $3.50 (2-3 euro) from the United Nations, the World Health Organization (WHO) and others. ITNs have been shown to be the most cost-effective prevention method against malaria and are part of WHO's Millennium Development Goals (MDGs).

For maximum effectiveness, the nets should be re-impregnated with insecticide every six months. This process poses a significant logistical problem in rural areas. New technologies like Olyset or DawaPlus allow for production of long-lasting insecticidal mosquito nets (LLINs), which release insecticide for approximately 5 years, and cost about US$5.50. ITNs protect people sleeping under the net and simultaneously kill mosquitoes that contact the net. Some protection is also provided to others by this method, including

people sleeping in the same room but not under the net. While distributing mosquito nets is a major component of malaria prevention; community education and awareness on the dangers of malaria are associated with distribution campaigns to make sure people who receive a net know how to use it. "Hang Up" campaigns such as the ones conducted by volunteers of the International Red Cross and Red Crescent Movement consist of visiting households that received a net at the end of the campaign or just before the rainy season, ensuring that the net is being used properly and that the people most vulnerable to malaria, such as young children and the elderly, sleep under it. A study conducted by the CDC in Sierra Leone showed a 22 percent increase in net utilization following a personal visit from a volunteer living in the same community promoting net usage. A study in Togo showed similar improvements. The cost of treating malaria is high relative to income and the illness results in lost wages. Mosquito nets are often unaffordable to people in developing countries, especially for those most at risk. Only 1 out of 20 people in Africa own a bed net. Although shipped into Africa mainly from Europe as free development help, the nets quickly become expensive trade goods. They are mainly used for fishing, and by combining hundreds of donated mosquito nets, whole river sections can be completely shut off, catching even the smallest fish. Nets are also often distributed though vaccine campaigns using voucher subsidies, such as the measles campaign for children.

A study among Afghan refugees in Pakistan found that treating top-sheets and chaddars (head coverings) with permethrin has similar effectiveness to using a treated net, but is much cheaper. Another alternative approach uses spores of the fungus *Beauveria bassiana*, sprayed on walls and bed nets, to kill mosquitoes. While some mosquitoes have developed resistance to chemicals, they have not been found to develop a resistance to fungal infections.

Vaccination

Vaccines for malaria are under development, with no completely effective vaccine yet available. The first promising studies demonstrating the potential for a malaria vaccine were performed in 1967 by immunizing mice with live, radiation-attenuated sporozoites, providing protection to about 60% of the mice upon subsequent injection with normal, viable sporozoites. Since the 1970s, there has been a considerable effort to develop similar vaccination strategies within humans. It was determined that an individual can be protected from a *P. falciparum* infection if they receive over 1000 bites from infected, irradiated mosquitoes.

It has been generally accepted that it is impractical to provide at-risk individuals with this vaccination strategy, but that has been recently challenged with work being done by Dr. Stephen Hoffman of Sanaria, one of the key researchers who originally sequenced the genome of *Plasmodium falciparum*. His work most recently has revolved around solving the logistical problem of isolating and preparing the parasites equivalent to 1000 irradiated mosquitoes for mass storage and inoculation of human beings. The company has recently received several multi-million dollar grants from the Bill & Melinda Gates Foundation and the U.S. government to begin early clinical studies in 2007 and 2008. The Seattle Biomedical Research Institute (SBRI), funded by the Malaria Vaccine Initiative, assures

potential volunteers that "the [2009] clinical trials won't be a life-threatening experience. While many volunteers [in Seattle] will actually contract malaria, the cloned strain used in the experiments can be quickly cured, and does not cause a recurring form of the disease." "Some participants will get experimental drugs or vaccines, while others will get placebo." Instead, much work has been performed to try and understand the immunological processes that provide protection after immunization with irradiated sporozoites. After the mouse vaccination study in 1967, it was hypothesized that the injected sporozoites themselves were being recognized by the immune system, which was in turn creating antibodies against the parasite. It was determined that the immune system was creating antibodies against the circumsporozoite protein (CSP) which coated the sporozoite. Moreover, antibodies against CSP prevented the sporozoite from invading hepatocytes. CSP was therefore chosen as the most promising protein on which to develop a vaccine against the malaria sporozoite. It is for these historical reasons that vaccines based on CSP are the most numerous of all malaria vaccines. Presently, there is a huge variety of vaccine candidates on the table. Pre-erythrocytic vaccines (vaccines that target the parasite before it reaches the blood), in particular vaccines based on CSP, make up the largest group of research for the malaria vaccine. Other vaccine candidates include: those that seek to induce immunity to the blood stages of the infection; those that seek to avoid more severe pathologies of malaria by preventing adherence of the parasite to blood venules and placenta; and transmission-blocking vaccines that would stop the development of the parasite in the mosquito right after the mosquito has taken a blood meal from an infected person. It is hoped that the sequencing of the *P. falciparum* genome will provide targets for new drugs or vaccines. The first vaccine developed that has undergone field trials, is the SPf66, developed by Manuel Elkin Patarroyo in 1987. It presents a combination of antigens from the sporozoite (using CS repeats) and merozoite parasites. During phase I trials a 75% efficacy rate was demonstrated and the vaccine appeared to be well tolerated by subjects and immunogenic. The phase IIb and III trials were less promising, with the efficacy falling to between 38.8% and 60.2%. A trial was carried out in Tanzania in 1993 demonstrating the efficacy to be 31% after a years follow up, however the most recent (though controversial) study in The Gambia did not show any effect. Despite the relatively long trial periods and the number of studies carried out, it is still not known how the SPf66 vaccine confers immunity; it therefore remains an unlikely solution to malaria. The CSP was the next vaccine developed that initially appeared promising enough to undergo trials. It is also based on the circumsporoziote protein, but additionally has the recombinant (Asn-Ala-Pro15Asn-Val-Asp-Pro)2-Leu-Arg(R32LR) protein covalently bound to a purified *Pseudomonas aeruginosa* toxin (A9). However at an early stage a complete lack of protective immunity was demonstrated in those inoculated. The study group used in Kenya had an 82% incidence of parasitaemia whilst the control group only had an 89% incidence. The vaccine intended to cause an increased T-lymphocyte response in those exposed, this was also not observed. The efficacy of Patarroyo's vaccine has been disputed with some US scientists concluding in The Lancet (1997) that "the vaccine was not effective and should be dropped" while the Colombian accused them of "arrogance" putting down their assertions to the fact that he came from a developing country. The RTS,S/AS02A vaccine is the candidate furthest along in vaccine trials. It is being developed by a partnership between the PATH Malaria Vaccine Initiative (a grantee of the Gates Foundation), the pharmaceutical company, GlaxoSmithKline, and the Walter Reed Army Institute of

Research In the vaccine, a portion of CSP has been fused to the immunogenic "S antigen" of the hepatitis B virus; this recombinant protein is injected alongside the potent AS02A adjuvant. In October 2004, the RTS,S/AS02A researchers announced results of a Phase IIb trial, indicating the vaccine reduced infection risk by approximately 30% and severity of infection by over 50%. The study looked at over 2,000 Mozambican children. More recent testing of the RTS,S/AS02A vaccine has focused on the safety and efficacy of administering it earlier in infancy: In October 2007, the researchers announced results of a phase I/IIb trial conducted on 214 Mozambican infants between the ages of 10 and 18 months in which the full three-dose course of the vaccine led to a 62% reduction of infection with no serious side-effects save some pain at the point of injection. Further research will delay this vaccine from commercial release until around 2011.

SOME HERBAL AND HOME REMEDIES FOR TREATMENT OF MALARIA

- Lime and lemon play a vital role in the treatment of quartan type of malarial fever. About three grams of lime and a juice of 1 lemon should be dissolved in about 60 ml of water. This mixture can be taken before you suspect the attack to take place.
- The herb *chirayata*, botanically known as Swertia chirata, is also beneficial in the treatment of intermittent type of malarial fevers. It helps in lowering the temperature. An infusion of the herb, prepared by immersing 15 gm of chirayata in 250 ml of hot water with aromatics like cloves and cinnamon, should be given in doses of 15 to 30 ml.
- Alum is also useful in malaria - First take a small amount of alum and then roast it over a hot plate. Now powder it. Half a teaspoon of this powder 0should be taken about four hours before the expected attack and half a teaspoon every two hours after it. This may help you in giving relief.
- The leaves of holy basil are also considered beneficial in the prevention of malaria. The juice of about eleven grams of leaves of holy basil mixed with three grams of powder of black pepper can be taken beneficially in the cold stage of the malarial fever. This will check the severity of the disease.

CONCLUSION

Malaria is a chronic disease. It affects the humans through mosquitoes. Malaria is caused by a parasite called Plasmodium. In the human body, the parasites multiply in the liver, and then infect red blood cells. It is prevalent mainly in tropical and sub-tropical regions. Many cases of malaria are considered today all over the world. Each year, there are approximately 515 million cases of malaria, killing between one and three million people,

the majority of whom are young children. It is most common disease and an enormous public health problem. Malaria affects 40% of world's population. 25 April is a day of unified commemoration of the global effort to provide effective control of malaria around the world. The child-patient should be kept in bed. He should be given plenty of fluids, especially orange juice diluted in warm water for the first few days of the treatment An ice bag should be applied to his head. Co-operative children can be given warm-water enema daily during this period to cleanse the bowels. After the fever has subsided, the patient may be placed for one or two days on an exclusive diet of fresh juicy fruits such as orange, grapes, grapefruit, apple, pineapple, mango and papaya. Milk may be added to the fruit-diet after this period and this diet may be continued for further few days. Thereafter, the patient may be allowed gradually to embark upon a well-balanced diet of natural foods, consisting of seeds, nuts and grains, vegetables and fruits, with emphasis on whole grains cereals, fresh fruits and raw or lightly-cooked vegetables.

- The child-patient should avoid tea, coffee, refined and processed foods, fried foods, condiments, pickles, white sugar, white flour and all products made from them. He should also avoid flesh foods.
- The best way to reduce temperature naturally, during the course of the fever, is by means of the cold pack, which can be applied to the whole body.

The best herbal treatment for malaria is tea made with 12 grams of dried holy basil leaves and 3 grams of black pepper powder, taken thrice a day. Honey, palm candy or sugar is optinals which can be added for taste. Promoting insecticide treated bed nets is one of the major breakthroughs of recent years – it is the realization that mosquito nets treated with insecticide give a much higher degree of protection against malaria. As well as stopping the bite, the net is a chemical death-trap for the mosquitoes drawn to the bait of the sleeping person. It therefore protects others living in the same house, and even in the same street or village. Properly used, insecticide treated nets can cut malaria transmission by at least 60% and child deaths by a fifth. But in 2006 very few of Africa's children are sleeping under insecticide treated nets. It is therefore clear that much of the world is not moving at the speed required to save the lives of innocent African children. The principal problem is the gap between what bed nets cost and what families can and will pay for them. Most malaria-carrying mosquitoes bite at night. Mosquito nets, if properly used and maintained, can provide a physical barrier to hungry mosquitoes. If treated with insecticide, the effectiveness of nets is greatly improved, generating a chemical halo that extends beyond the mosquito net itself. This tends to repel or deter mosquitoes from biting or shorten the mosquito's life span so that she cannot transmit malaria infection.

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