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Malaria: An Unseen Enemy Threatening to Mankind

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Abstract

The research work on malarial infection and malarial treatment has been increased tremendously over the years due to increased resistance of parasites to antimalarial drugs. To overcome the developed resistance, antimalarial drugs are used in combination. But eventually the amount of drugs administered increase with the resistance and extend to adverse effects. Many innovative, sophisticated delivery systems have been developed to increase the adequacy, competency and efficiency of antimalarial drugs. But it is predicted that these new inventions will also acquire resistance with time. Globally, it is seen that the countries which have low standards of hygiene have high levels of malarial infection. There are various antimalarial techniques developed and are slowly being adopted worldwide. But the first step is to maintain the hygiene and cleanliness so that mosquitoes will not harvest.

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Introduction

Historically, rise in cases of intermittent fever during rainy seasons which coincided with agricultural activities like sowing and harvesting led Romans and Greeks to believe that it is associated with swampy areas [1]. They presumed fevers to be a consequence of bad odour originating from marshy areas and thus termed it as malaria (mal=bad+ air) [1]. Malaria is a vector-borne infectious disease which is caused by unicellular parasitic protozoan belonging to genus *Plasmodium* [2]. The intracellular parasites, *Plasmodia*, have ability to infect and replicate intramurally in erythrocytes only after a clinically silent replication phase in the liver. In infectious condition around 156 types of *plasmodium* are present red blood cells of mammals (including humans), birds, reptiles, *etc.* [3].

Host of *Plasmodium*:

1- A vertebrate host in which reproduction is asexual (intermediate host): Human

2- A bloodsucking insect, sexual reproduction takes place (definitive host): Mosquito [4].

Female mosquitoes of genus *Anopheles* bites humans and transmit *plasmodium* parasite which causes malaria. *Anopheles* is derived from Greek word anopheles means useless. This life threatening disease is caused by five parasite species like *P. vivax, P. malariae, P. ovale, and P. falciparum.* and *P. knowlesi.* Recent study showed *P. knowlesi* found in monkey is responsible for malarial infection. Worldwide the parasite *P. falciparum* is more causal than *P. vivax* [2].

The human protozoa of the genus Plasmodium is classified as follows:

Domain: Eukaryota, Kingdom: Chromalveolata, Superphylum: Alveolata, Phylum: Apicomplexa, Class: Aconoidasida, Order: Haemosporida, Sub-order: Haemosporidiidea, Family: *Plamodiidea*, Genus: *Plamodia*, Sub-genus: *Plasmodium; Laverania,* Species: *P. falciparum, P. malariae, P. ovale, P. vivax, P. knowlesi*

Global Scenario

Globally *P. falciparum* is one of the pervasive malarial parasites found in African, south-east Asia and eastern Mediterranean regions. The malarial infection risk has increased drastically over a decade because of mosquito-bite, lack of sanitation, deficiency of antimalarial medicine and improper diagnosis [3].

The major drawback for malaria treatment is that symptoms are generally seen after 10-15 days after the mosquito bite in non-immune individual. The symptoms which are seen at initial stage are fever, headache and chills. These symptoms are not helped to recognise malaria at initial stage which is dependent on density of parasites in blood. This results in delayed treatment and spreading of infections in body. If the infection of *P. falciparum* is not treated within 24 h of infection, it may cause to death [4]. The countries which are affected by malaria are South Africa, India, South America, Brazil, Indonesian countries, Mexico and many more. *P. vivax* is presiding malarial parasite in most of the countries outside sub-Saharan Africa [5].

Life-cycle of Malarial Parasite

Gametocytes, the sexual stage of malarial parasite, get ingested in mosquito through its feed. These gametocytes in mosquito's body get converted to gametes which emerge and fertilize in midgut of mosquito [5]. This resulted to formation of zygotes which further develop into ookinetes. These ookinetes cross and lodge below the wall of midgut as oocytes followed by growth and division of oocytes to form thousands of active haploid called as sporozoites [6]. Depending on the malarial species these sporozoites break after 8 to 15 days and enter the salivary gland [7]. When mosquito bites, sporozoites enters the liver and invade hepatocytes in liver [8] which grows and divides within every single hepatocyte and forms haploids within 5 to 16 days[9]. These parasites exit liver as merozoites and enter the blood-stream. Parasites then grow and divide within erythrocytes and multiply continuously depending on the repetition of parasite's invasion in erythrocytes [10, 11]. If the parasite infection of blood is not treated properly, the male and female gametocyte would develop over a period of 2 weeks as shown in Figure 1.

Generally, the treatment for malaria is misleading. At the initial stage of disease, the common symptoms observed between malaria and dengue are fever, headache, vomiting and anaemia. Myalgia, rashes and leukopenia are seen in dengue patients irrespective of malarial patients [12].

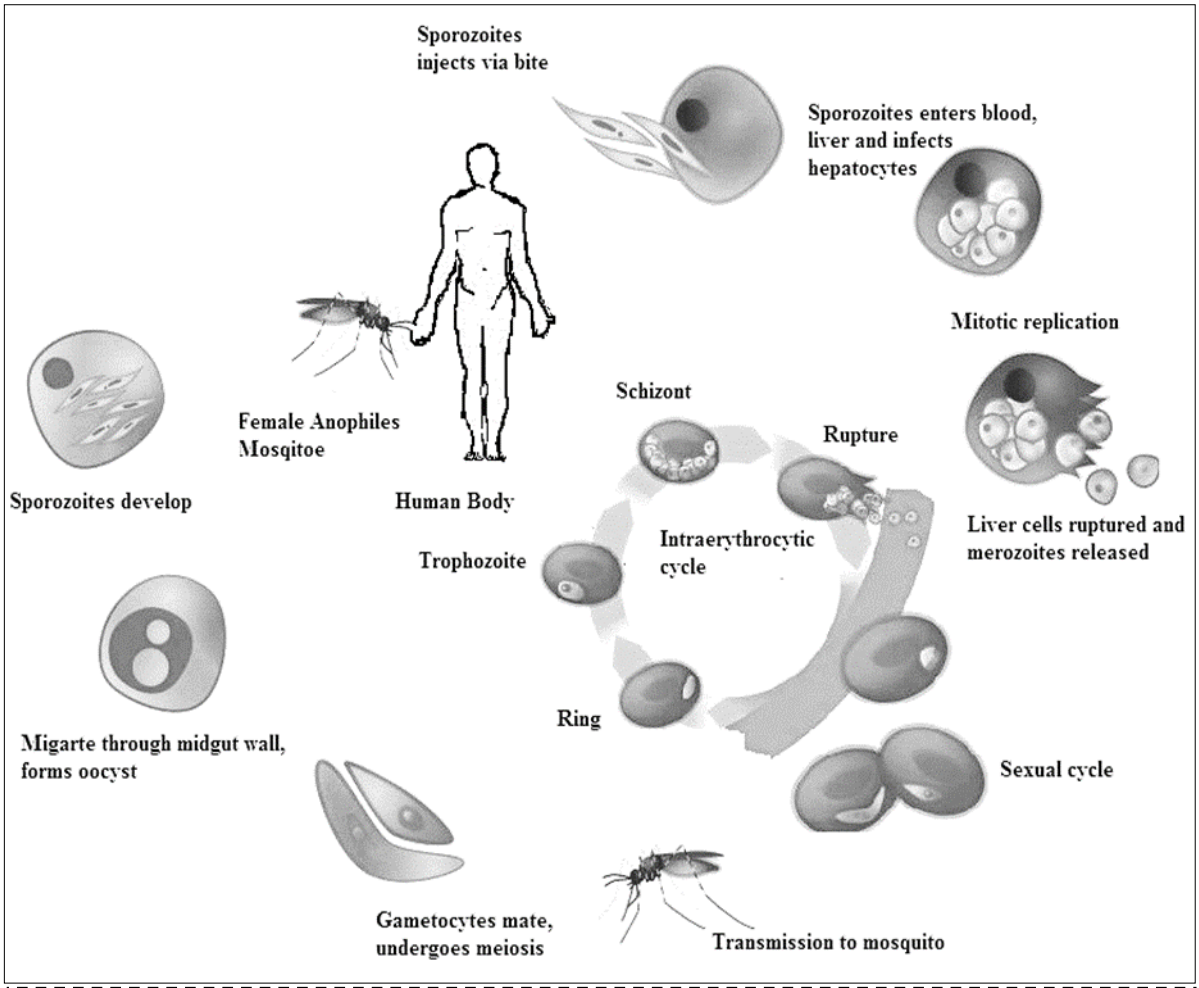

Figure 1. Life-cycle of malarial parasite

Diagnostic Tests

- Slide test: Few drops of blood are taken and spread on glass slide and then examined under a microscope by a trained laboratory technician. If *Plasmodium* organisms are visible in smears, then the slide is reported positive [13].
- Rapid Diagnosis Test (RDT): One drop of blood is placed on a test strip. A few drops of buffer solution are poured to the strip. Test is positive for malarial parasite *falciparum* if two lines appear. If one red line appears, the slide needs to be sent for laboratory testing, as the patient may have a less dangerous form, vivax malaria [14].
- Light microscopy: This test is species specific. It is limited because it requires a comparatively high amount of supervision and training, special equipment, trained personnel and electricity supply [15]. The sensitivity and specificity of this test depend on training and supervision.
- Fluorescent microscopy: It has advantages over light microscopy. The process is faster as compared to normal microscopy due to use of acridine orange dye. Special equipment, trained personnel, electricity supply is needed, also the dyes require dense parasites to show appropriate results are also limitations and also acridine orange is itself a hazardous material [16].

The advantage of RDT over slide test is that results can be obtained within a few minutes unlike slide test which may take a day or two.

Malaria has become one of the most devastating diseases according to report published by WHO (World Health Organization) in December 2016 which stated that half of the world's population is at risk of malaria. Around 212 million cases of malarial infection were encountered and 429 000 deaths by malaria in

2015.[17]

Anti-Mosquito Agents

The word anti-mosquito here states the different ways to prevent ourselves from mosquito's bite. There are various anti-mosquito techniques from conventional to newer sophisticated ways [18]. They are as follows: (Table 1)

Malarial Control Strategies of Different Nation:

Malaria is a global problem so different nations have adopted strategies to control and prevent malaria as follows:

Sub- Saharan Africa

In Sub-Saharan Africa, WHO recommends "intermittent preventive treatment in pregnancy" (IPTp) with sulfadoxine-pyrimethamine. This step is usually taken for the protection of women from the risk of malaria transmission, those who are living in areas of moderate to high-risk of malaria transmission. Also, the use of insecticide-treated nets for the prevention of malaria are used in Africa. It was reported that people slept under long-lasting insecticidal nets (LLINs) showed lower rates of malaria infection [31].

Malaysia

In Malaysia adopted strategies for vector control are selective and effective which include use of chemical insecticides, encouragement of personal safety, promotion of environmental measure and active community participation in vector control programmes. Techniques like use of automatic siphons, coconut husk packed drains, stone packing to prevent water logging, automatic drum sluice, tidal gates and timely entomological surveys are environmental measures for controlling malaria [32].

India

In India EDTP (Early case Determination and Prompt Treatment) is the main strategy to prevent and control malaria. Chloroquine is the recommended drug of choice under this programme. Other measures in controlling malaria include control on the vector by different methods like chemical control (use of sprays, Malathion fogging, etc), Biological control (use of larvivorous fish and biocides), personal prophylactic measures and spread of awareness through non-government organizations (NGOs) and workshops. Proper monitoring and implementation of the programme is the key to control malaria [33, 34].

Anti-Malarial Drugs

Antimalarial drugs can majorly be classified on the following basis:

A) Antimalarial activity

B) Structure

Classification Based on Antimalarial Activity of Drug is as Follows [35]:

1) Tissue Schizonticides for Casual Prophylaxis: Drugs acting on plasmodia's primary tissues after growing in liver initiate the erythrocytic stage and block the stage. The limitation to this is that it is more theoretical compared to clinical study. Examples: Pyrimethamine and Primaquine.

2) Tissue Schizonticides for Preventing Relapse: These drugs are parasite specific and act on hypnozoites of *P.vivax* and *P.ovale*. They help in preventing relapse by reactivation in liver. Examples: Pyrimathamine and Primaquine.

3) Blood Schizonticides: These drugs terminate the clinical attack of malaria by acting on blood forms of parasites. These are distinctively used for anti-malarial chemotherapy. Examples: Chloroquine, quinine, halofantrine.

4) Gametocytocides: These drugs prevent transmission of infection to other mosquitoes by destroying their sexual forms of parasites in blood. Example: Primaquine is active against all plasmodia.

5) Sporontocides: They prevent transmission by hindering the development of oocytes in mosquitoes. Examples: Primaquine, Chloroguanide.

Classification According to Structure:

The drugs are classified as [35,36]

1) Aryl Amino Alcohols: These are cinchona alkaloids. Examples: Quinine, quinidine.

2) 4- Aminoquinolines: Examples: Chloroquine and amodiaquine.

3) Folate Synthesis Inhibitors: These are type 1 competitive inhibitors of dihydropteroate synthase (example: sulphones and sulphonamides) and type 2 inhibitor of dihydrofolate reductase (example: proguanil,

Table 1. Description and limitations of anti-mosquito agents are summarized as follows:

Sr. No.	Anti-mosquito agent	Description	Limitations	References
1	Essential oils and plants	Primitively, aromatic plants were burnt or placed to keep the mosquitoes away. Other plants such as citron-ella, neem, tea tree, marigold, basil are also used. Oils such as lemon, eucalyptus, lavender, cinnamon, thyme, Greek catnip, citronella, tea tree, geraniol and neem are also used [13]. Apart from herbal sources cowdung is also used as natural mosquito repellent. Cowdung has high proportion of Menthol, Ammonia, Phenol, Indol and Formalin which are important factors in enhancing its mosquito repellent activity.	Longevity, efficacy, also few are grown specifically in certain geographical areas.	[19]
2	Nets	It's been proven that the most mosquito bites at dusk and dawn. So the proper protection like closure of windows, doors or using nets can help to prevent from a mosquito bite. This is one of the easiest ways to get prevented from mosquito bite. Insecticide treated nets are getting rapid attention due to their higher efficiency to repel mosquitoes.	Not feasible for the entire time. Blocks ventilation.	[20,21]
3	Coils	Mosquito coils were first introduced by Japanese entrepreneurs in early 1900. Coil contains pyrethroid insecticides.	Effective but produces smoke. Smoke produced causes irritation to eyes, throat and may trigger certain smoke induced allergies, breathing problem, headache and sneezing.	[22]
4	Liquid vaporizer	Many electrical products have been introduced which act as a mosquito repellent. It mainly contains an insecticide (transfluthrin), an anti-oxidant (butylated hydroxytoluene i.e. BHT) which prevents oxidation of active and fragrance to meet compliance. The mixture is prepared by dissolving all ingredients in deodorized kerosene to help for ease of vaporization. These liquids on moderate heat vaporize into the air and hence act as an anti-mosquito product. Natural liquid vaporizers are made from extracts of plant *Azadirachta indica, Vitex Negundo and Partheneum histerophorus* which have proven mosquito repellent action.	Effective action but in limited circulation. Needs continuous supply of electricity for its working. May cause nose irritation and breathing problem.	[22-25]

5	Fabric roll-on	These roll-on products contain pure eucalyptus oil and citronella oil. These plants were used in ancient time as mosquito repellent. This product does not stain clothes and provide protection for approximately 8 hrs. Few drops are to be applied on clothes. This product is 100 % natural and hence safe for babies.	Roll-ons reportedly do not have many side effects. The only problem associated is, it may stain the clothes, but gradually with time this has also overcome.	[26]
6	Sprays	These sprays contain mostly N, N-diethyl-meta-toluamide which is known as DEET and is an effective against repelling mosquitoes. But, now newer sprays have come which are gentler and safer than DEET. They contain lemon eucalyptus and picaridin and are more natural than DEET and hence periodic safer action.	Irritation, nausea and irritation.	[27]
7	Patches	These are naturally originated patches and are DEET free which resulted to side effects. They mainly contain eucalyptus oil, lemon oil, mint oil and citronella oil. These patches are stuck on clothes.	Skin irritation and difficulty for application	[28]
8	Electric bats	These are rechargeable electric bats and eco-friendly. The net of this bat is made of high conductible metal. An electric current passes through this net and kills the mosquito as it comes in contact with it.	Need electrical charging and probable risk of human accidents.	[29]
9	Mobile app	Anti-mosquito app is a unique app which emits high frequency ultrasound. This sound is disliked by most of the species of mosquitoes. Electronic or sonic mosquito repellent devices emit ultrasonic sound waves which is assumed to disrupt normal communication in between the pests and insects and also causes confusion and fear. This principle is used for repelling mosquitos and other insects.	Efficiency is very poor as a repellent.	[30]

pyrimethamine).

4) 8- Aminoquinolines: Example: Primaquine

5) Antimicrobials: Example: Tetracycline, doxycycline

6) Peroxides: Artemisinin derivatives such as artemether, arteether

7) Naphthoquinones: Example: Atovaquone

8) Iron Chelating Agent: Example: Desferrioxamine

(Table 2)

Combination Therapy of Antimalarials

The combination therapy means using more than one drug simultaneously, which vary if the mechanism of action and targets in the parasite are variable. This therapy does not include the use of non-anti-malarial drug to act for synergism with anti-malarial drug. Also, anti-malarial drugs which are used as fixed dose combinations (FDC) [38].

Need of Combination Therapy

Over the decades, resistance and relapse of malaria are increased due to resistant strain of plasmodium. Therefore, to overcome the combination therapy has been adopted to increase the efficacy and efficiency of antimalarial drugs [39].

Factors Prohibiting Combination Therapy

- Inadequate knowledge of drugs used for combination therapy.
- Cost of treatment.
- High dose administration and therefore increased risk of side effects and to certain extend resistance also.
- Less evidence of its effectiveness.
- Patient compliance.

Broadly Combination Therapy can be classified as Follows [40]

- Artemisinin-based combinations include artesunate plus chloroquine, artesunate plus amodiaquine, artemether plus lumefantrine.
- Non-artemisinin-based combinations include chloroquine plus sulfadoxine-pyrimethamine, atovaquone plus proguanil, quinine plus tetracycline, quinine plus doxycycline.
- Combinations in pipeline include naphthoquine plus dihydroartemisinin.

Novel Technologies in Anti-Material Treatment

1. Ligand Mediated Liposomes

The natures of phospholipid and drug are used for preparing liposomes to enhance encapsulation efficiency and stability. If the drug is hydrophilic it gets encapsulated in the hydrophilic cavity of the liposome and if the drug is lipophilic it gets encapsulated in the fatty acid bilayer of liposomes. A special ligand is attached to the surface of the formed liposomes to have targeted drug delivery system.

Chloroquine has developed resistance for malarial parasite over the years, Therefore, chloroquine embedded liposomes were prepared further to have targeted action. These liposomes had anti-erythrocyte antibody to have cell specific action and to increase the efficacy of drug and treatment. Pharmaceutical excipients used were phospholipids, chloroquine and anti-erythrocyte anti-body [41].

2. Drug Lipid Emulsions

In these preparations, emulsifier (such as egg-lecithin) is added to the water phase and dissolved. To this solution drug is added under constant stirring or the solution is homogenized. After a homogenous solution is formed, oil (such as soybean) and an antioxidant (such as α-tocopherol) are added. Antioxidants increase the oxidative stability of oil phase which resulted to emulsion. Both phases are gradually mixed and the homogenized to form a uniform emulsion. These lipid emulsions have average particle size of 200 nm and therefore more suitable to have parenteral administration. Other ingredients e.g. egg-lecithin, soybean oil, α-tocopherol and purified water [42].

3. Hybrid Drugs Delivery

The Iron (II) promoted trioxolane ring couples and splits with the beta elimination reaction. This enables a targeted drug delivery for malarial parasites. Haemoglobin degrades in the parasite's digestive vacuole and forms free heme which breaks the trioxolane ring. These hemes are targeted in the parasite and are present in large numbers in the parasite's digestive system and less in human plasma. For this targeted hybrid fragmentation, a masked retro

Table 2. Commonly used antimalarial drugs: The most commonly used antimalarial drugs are as follows [37]

Drug	Pharmacokinetic	Mechanism of action
Chloroquine	Absorption of drug is approximately 90 % from gastro-intestinal tract. It is also absorbed from intramuscular and subcutaneous sites. Volume of distribution is more. The maximum binding is with liver and then other body tissues. It is metabolized by liver and approximately 70 % is excreted unchanged. Initial half-life is 3 to 4 days, but as the drug is slowly released from tissues, it might extend to 1 to 2 months.	It accumulates in parasite infected erythrocytes. Inside parasite's lysosome it diffuses freely. pH of lysosome is acidic. Hence, it gets ionised and gets trapped in parasite. It also accumulates in food vacuoles of parasite. Thus, they inhibit peptide formation and decrease the supply of amino acid which is required for parasite's viability. Enzyme heme polymerase is also inhibited and thus the host heme is not converted to hemazoin. It also inhibits DNAs and RNAs by intercalation at high concentrations.
Artemisinin derivatives	It is extensively absorbed and rapidly metabolized and eliminated by bile.	It is a prodrug and rapidly metabolized to its active dihydroartemisinin. The breakdown of endoperoxide bridge of the artemisinin is catalysed by ferrous protoporphyrin-IV which is present in the food vacuole of parasite. The parasite membrane is damaged by covalent binding of highly reactive free radical to membrane protein.
Quinine	It is well absorbed from gastrointestinal tracts and extensively distributed in body tissues. It is metabolized primarily by the liver and excreted via urine. Half-life is approximately 10 to 11 h.	It has a blood schizonticidal and gametocytocidal activity. It's a weak base, hence gets accumulated in food vacuoles. It inhibits heme polymerase.
Proguanil	It is slowly but extensively absorbed from gastrointestinal tract. Elimination half-life is around 16 to 20 h. It is a prodrug which gets metabolized in liver to give active cycloguanil.	It is inhibit parasite's dihydrofolate reductase enzyme. Clinical attacks of *vivax* malaria are suppressed.

Sulfadoxine	It is bound to plasma protein by getting rapidly absorbed from the gut.	It inhibits synthesis of dihydropteroic acid by obstructing the use of p-amino benzoic acid. It has synergistic action with pyrimathamine.
Pyrimethamine	It is extensively absorbed by at a slow rate. Plasma half-life is around 80-95 h and excretion is via breast milk.	It inhibits dihydrofolate reductase enzyme. Hence the biosynthesis of purines and pyrimidines is hindered which is required for cell multiplication and synthesis of DNA. Hence, the nuclear division fails in erythrocytes and liver during a schizont formation stage.
Halofantrine	Bioavailability is less, but found to be more in the fed state. Cmax is achieved within 4 to 8 h. It is excreted via faeces.	It is similar to chloroquine and quinine.
Mefloquine	It is extensively absorbed and distributed in body tissues. It is highly protein bound. Elimination half-life is 2 to 3 weeks and mainly excreted through faeces. It undergoes enterohepatic circulation.	It form complexes with heme which interacts with plasmodia's components and damages its membrane.
Atovaquone	It attacks cytochrome bc1 complex known as complex III, in plasmodium parasite. It therefore inhibits mitochondrial electron transport. Various enzymes are linked to this electron transport. This metabolic effect finally results in inhibition of nucleic acid and ATP synthesis.	It interrupts the mitochondrial electron transport of mitochondria. This collapses the functions of mitochondrial membrane of plasmodia. Hence, hinders the synthesis of ATP and pyrimidine.
Quinacrine and Mepacrine	This drug is extensively absorbed, distributed but does not get bound to body tissues. It is metabolized by the liver and excreted via urine.	It acts as an erythrocytic schizonticides. But it is not used in practice since it is less effective than chloroquine.
Tetracyclines	Absorption is incomplete in the gut and hindered by antacids. It is majorly distributed in tissues, accumulated in spleen, liver, bone, bone marrow and enamel on unerupted teeth.	They are bacteriostatic agents. They bind to 30s ribosome sub-unit and inhibit protein synthesis.

Michael linker was embedded inside the ring. The heme iron eventually opens the ring which then unmasks the carbonyl function of the retro Michael linker by beta elimination to achieve targeted delivery [43].

4. Super Paramagnetic Nano Particles for Malarial DNA Vaccine

Due to limitations of DNA vaccines, the magnetofection is used by superparamagnetic nanoparticles. This vaccine encodes *Plasmodium* yoelii merozoite surface protein MSP119 which plays an important role in immunity of *Plasmodium*. The plasmid DNA containing membrane associates 19-kDa carboxyl-terminal fragment of merozoite surface protein 1 (PyMSP119) and was conjugated with superparamagnetic nanoparticles coated with polyethyleneimine polymer, with variable molar ratio of PEI nitrogen to DNA phosphate. In these complexes at pH 2, a larger number of amino acid groups got protonated and repelled inducing less aggregation. Similarly, at pH 4 and 7 these complexes were checked. At pH 4, better binding was shown better binding capacity also as compared at neutral pH [44].

5. Nanoparticles

In this technique, the poor bioavailability of antimalarial drug was enhanced by entrapping in carbohydrate structure of beta-cyclodextrin. This was then loaded on lecithin to form beta-cyclodextrin-drug-lecithin nanoparticles. The lecithin nanoparticles increased the bioavailability. Modified solvent evaporation method was used to prepare nanoparticles. Art ether have short plasma half-life and hence needs frequent dosing to maintain the blood plasma level. So, nanoparticles of this beta-cyclodextrin drug complexes improves therapeutic efficacy as well as the pharmacokinetic properties of the drug [45].

6. Sustained Release Copolymer of Drug

dl- lactic acid and glycolic acid were used to prepare copolymer in the ratio 1:3 respectively. Implantable controlled release formulation was prepared using 2,4- diamino-6-(2-napthysulfonyl)-quinazoline and copolymer. Two complexes were prepared using 16.7 % and 33.3% of drug by weight respectively. Spray drying technique was used to make these complexes and the size of complexes was achieved as 125 microns. Carboxymethyl cellulose (CMC) suspension of these complexes were prepared and injected in the scapular region of mice. The efficacy was measured for rodent malaria *Plasmodium berghei*. Evaluation was done using Rane antimalarial drug screening system. The duration of the release was studied by measuring the radioactivity of the excreted drug from urine and faeces. The prolonged release of drug was tested on infected mice which were survived for 14 weeks. The residual activities at the implant sites were 2 %, 13 % was obtained for 16.7 % and 33.3 % respectively for drug/ polymer preparations [46].

7. Transdermal Application

Transdermal application was studied using primaquine drug either in salt form or in free base form on hairless rats. Different vehicles were used and permeation was measured. Vehicles such Mygliol® 840 (M), propylene glycol, Transcutol® (T), Labrafac Hydrophile® (LH), and oleic acid. The most effective vehicle was Mygliol® 840 (M) which showed maximum therapeutic efficacy [47].

Improvement in Antimalarial Treatment

To improve the onset of action, efficacy and efficiency vaccines will be introduced. Many vaccine technologies have introduced for making anti-malarial vaccines such as community vaccination, novel adjuvants and vectored prime-boost regimes. Vaccines targeting different stages of the parasite's life-cycle were developed. Most effective vaccines were found against pre-erythrocytic stages. Currently, these vaccines are in phase-III clinical trials [48].

Budget for Prevention and Disease Control

The consideration of preventive measures will help in maintaining self- and surrounding- hygiene which will eventually save not only money also but also the pain of malarial symptoms. All the anti-malarial drugs are much costly and produce toxic effects when exposed to human body [49]. All other combination therapy and novel technologies eventually increase the cost of treatment. Geographically, if noted majority of the developing countries and underdeveloped countries are affected by malaria. So, in these countries cost of treatment becomes a crucial factor. The death rates have increased over a decade. If we consider the budget than preventive measures are much more economical as compared to the antimalarial treatment [50].

Resistant Drugs:

The drugs which are resistant to malarial treatment are [51,52]**:**

1. Chloroquine: It has acquired resistance in South America, Western, Eastern and Southern Africa, Indian Subcontinent, South-East Asia Oceania, East Asia (China). Incidence of resistance is variable but very common in most of the areas.

2. Quinine: It has acquired resistance in South America and South-East Asia Oceania. Resistance to this occurs infrequently.

3. Sulfadoxine-Pyrimethamine: It has acquired resistance in South America, Western, Eastern and Southern Africa, South-East Asia Oceania and East Asia (China). Incidence of resistance is reported, but very uncommon in most of the arears.

4. Mefloquine: It has acquired resistance in South America, Western Africa, South-East Asia Oceania. Incidence of resistance is reported but very uncommon in most of the areas.

Resistant strains:

P.falciparum and *P.vivax* are the most resistant strains.

Sanitation

The main cause of malaria is the poor level of sanitation and hygiene maintained. The main reason is a poor drainage system and uncovers water tanks. Educational programmes should be arranged in slums, rural areas where literacy rate is low to make them understand the cause and spread of diseases [53]. Latrines to be built with proper drainage facility. To empower health workers to train others in safe garbage and waste disposals. Proper water supply tanks to be installed at appropriate distance so that people reduce to store uncovered water. Integrated sanitation, hygiene and water program to be initiated by government. Hand washing stations should also be installed outside latrines. Also, all these precautions are also to be taken from door-to-door[54].

Recent technologies

Vaccines are under-development stage passed phase III trial. Vaccines will prove to be more effective in case of malaria. Vaccines undergo first-past metabolism and can be avoided completely when drugs can be immediately available in the systemic circulation and hence immediate action against malarial parasites [55]. Also, due to high resistance developed to the existing drugs targeted drug delivery systems will be more effective in future. Many targeted drug delivery systems are developing, but the only concern is the acceptance of pharma companies in scaling up these techniques. More efforts are built in globally by pharma companies to make this scale up easy and efficient [56].

Conclusions

Prevention is always considered better than curing any illness. Malaria is unseen enemy which is affecting maximum of world's population. Development of resistance to existing anti-malarial drugs can worsen the situation. Though combination therapy has been introduced, the patient compliance is less because of high exposure to drugs, increased side effects, chances of developing resistance and less cost effectiveness whereas, the preventive techniques are much more easily available, affordable and effective.

References:

1. http://www.nvbdcp.gov.in/malaria2.html
2. Shapiro HM, Apte SH, Chojnowski GM, Hänscheid T, Rebelo M, Grimberg BT, 2013. Cytometry in malaria—a practical replacement for microscopy? *Curr Protoc Cytom.* chapt 11:Unit 11.20..
3. WHO. World Malaria Report. Geneva: World Health Organization; 2014.
4. https://revisionworld.com/a2-level-level-revision/ geography/global-challenges-and-issues -0/health-and-welfare.
5. Antinori S, Galimberti L, Milazzo L and Corbellino M, 2012. Biology of Human Malaria Plasmodia Including *Plasmodium Knowlesi, Mediterr J Hematol Infect Dis*. 4(1).
6. Takken W, Knols BGJ, 1999. Odor-mediated behaviour of afrotropical malaria mosquitoes. *Ann Rev Entomol*. 44: 131-157.
7. Cardé RT, Gibson G, 2010. Host finding by female mosquitoes: mechanisms of orientation to host odours and other cues. In: Takken W, Knols BGJ, eds. Olfaction in vector-host interactions. *Wageningen Academic Publishers*. 115-140.
8. Verhuist NO, Qiu YT, Beijleved H, 2011. Composition

of human skin microbiota affects attractiveness to malaria mosquitoes. *PloS One*.

9. Baton LA, Ranford-Cartwright LC, 2005. Spreading the seeds of millionmurdering death: metamorphoses of malaria in the mosquito. *Trends Parasitol*. 21: 573-580.
10. Matuschewski K, 2006. Getting infectious: formation and maturation of Plasmodium sporozoites in the Anopheles vector. *Cell Microbiol*. 8:1547-1556.
11. Baldacci P, Menard R, 2004; The elusive malaria sporozoite in the mammalian host. Mol Microbiol 54: 298-306.
12. Druilhe P, Daubersies P, Patarapotikul J, Gentil C, Chene L, Chongsuphajaisiddhi T, 1998. A primary malarial infection is composed of a very wide range of genetically diverse but related parasites. *J Clin Invest*. 101: 2008–16.
13. Maguire JD, Lederman ER, Barcus MJ, O'Meara WA, Jordon RG, Duong S, Muth S, Sismadi P, Bangs MJ, Prescott WR, Baird JK, Wongsrichanalai C 2006. Production and validation of durable, high quality standardized malaria microscopy slides for teaching, testing and quality assurance during an era of declining diagnostic proficiency. *Malar J.* 5:92.
14. Chansuda Wongsrichanalai, Mazie J. Barcus, Sinuon Muth, Awalludin Sutamihardja, and Walther H. Wernsdorfer. A Review of Malaria Diagnostic Tools: Microscopy and Rapid Diagnostic Test (RDT) Defining and Defeating the Intolerable Burden of Malaria III: Progress and Perspectives: Supplement to Volume 77(6) of *American Journal of Tropical Medicine and Hygiene*.
15. Kawamoto F, 1991. Rapid diagnosis of malaria by fluorescence microscopy with light microscope and interference filter. *Lancet.* 337:200–202.
16. Sulzer AJ, Wilson M, Hall EC, 1969. Indirect fluorescent-antibody tests for parasitic diseases. An evaluation of a thick-smear antigen in the IFA test for malaria antibodies. *Am J Trop Med Hyg*. 18:199–205.
17. A guide for ASHA and other community volunteers in districts with a high burden of malaria, a book to detect, treat and prevent malaria, government of India, 2008.
18. Hill A, 2011. The Royal Society Publishing, Philosophical Transactions B. *Biological Sciences.* 366(1579): 2806-2814.
19. http://www.healthline.com/health/kinds-of-natural-mosquito-repellant#greek-catnip-oil6
20. Alexis R Sexton, 2011. Best practices for an insecticide-treated bed net distribution programme in sub-Saharan eastern Africa, *Malaria Journal*.
21. http://www.who.int/features/factfiles/malaria/en/
22. https://cameronwebb.wordpress.com/2015/05/01/are-mosquito-coils-making-us-sick/
23. http://www.allout.in/en-in/products/all-out-super-45-nights/tabs/ingredients
24. Yildiztekin T, Electric liquid vaporizer composition comprising para-menthane-3,8-diol. WO 2016175720 A1.
25. Sandbhor A, Pawale J, Ratnaparakhi P, Ghadage M and Theurkar S, 2014. Repellent Efficacy Against Mosquitoes Using Natural Biopesticide. *World Journal of Pharmaceutical research*. 3(2):1961-1967.
26. http://www.goodknight.in/fabric-roll
27. http://time.com/3856309/mosquito-repellent-bug-spray
28. http://www.peebuddy.in/product/bodyguard-premium-natural-anti-mosquito-patches-60 -patches-3-pack/
29. http://www.dhgate.com/reviews/mosquito-electric-bat-reviews.html
30. https://itunes.apple.com/in/app/anti-mosquito-sonic-repeller/id385921289?mt=8
31. www.who.int/mediacentre/news/releases/2016/malaria-control-africa/en/
32. Sanders KC, Rundi C, Jelip J, Rashman Y, 2014. Eliminating malaria in Malaysia: the role of partnerships between the public and commercial sectors in Sabah, *Malaria Journal.*
33. Pattanayak S, Sharma VP, Karla NL, Sharma RS, 1994. Malaria paradigms in India and control strategies. *Indian Journal Malariol*.31 (4):141-99.
34. http://www.wpro.who.int/emerging_diseases/documents/DC.Module5.pdf
35. https://www.malariasite.com/malaria-drugs/

36. Sharma K, Mishra S, Dubey A, 2017. Development of cowdung based herbal mosquito repellent; *Journal of Krishi Vigyan*. 6(1); 50-53.

37. Deshpande S, Kuppast B, 2016. 4-aminoquinolines: An Overview of Antimalarial Chemotherapy**.** *Medicinal Chemistry.* 6:1-11.

38. Hiasindh AA, Subahash Chandra P, 2016. Antimalarial drug resistance: An overview, *Trop Parasitol*. 6(1) 30-40.

39. Shende P, Desai P, Gaud RS, Dhumatkar R. (2016). Engineering of microcomplex of artemether and lumefantrine for effective drug treatment in malaria. *Artificial cells, nanomedicine, and biotechnology*, 1-11.

40. Christopher V P, 2007. Combination Therapy for Malaria: Mission Accomplished? *Clinical Infectious diseases*. 44(8):1075-1077.

41. Owais M, Varshney GC, Choudhury A, Chandra S, Gupta CM, 1995. Chloroquine Encapsulated in Malaria-Infected Erythrocyte-Specific Antibody-Bearing Liposomes Effectively Controls Chloroquine Resistant Plasmodium berghei Infections in Mice. A*ntimicrobial* agents *and chemotherapy*. 39:180–184.

42. Yufan M, Tingli L, Wen Z, Ying W, Ting C, Qibeng M, Tao C, 2014. Enhanced Antimalarial Activity by a Novel Artemether-Lumefantrine Lipid Emulsion for Parenteral Administration. *Antimicrobial agents and chemotherapy*. 58:5658-5665.

43. Mahajan S, Deu E, Lauterwassez E, Levya M, Ellman J, Bogyo M, Renslo A, 2011.A fragmenting hybrid approach for targeted delivery of multiple therapeutic agents to the malaria parasite. *Chem medchem*. 6(3):415-419.

44. Al-Deen F, Jenny H, Selomulya C, Charles M, Coppel R, 2011. Superparamagnetic nanoparticles for effective delivery of malarial DNA vaccine *Langmuir*. 7: 3703-3712.

45. Chadha R, Gupta S, Pathak N, 2011. Studies on the preparation and evaluation of antimalarial activity of Arteether and Complexed Arteether with beta-cyclodextrin loaded chitosan/lecithin nanoparticles. *Pharmaceutical nanotechnology*. 1: 204-212.

46. Wise D, Mc Cormick G, Willet G, Anderson LC, 1976. Sustained release of an antimalarial drug using a copolymer of glycolic/lactic acid. *Life sciences*. 6 (3):867-873.

47. Mayorga P, Couarraze G, Puisieux F, 1996. Formulation study of a transdermal delivery system of primaquine. *International journal of Pharmaceutics*. 132: 71-79.

48. Donnelly R, Thakur R,Woolfson D, 2011. Microneedle-based drug delivery systems: Microfabrication, drug delivery and safety. *Europe PubMed centre*. 17(4): 187-207.

49. Hill A, 2011. The Royal Society Publishing, Philosophical Transactions B. *Biological Sciences.* 366(1579): 2806-2814.

50. Nicholas Aflitto and Tom De Gomez, 2014. *Sonic Pest Repellents*. The University of Arizona Cooperative Extension.

51. Kantheti P, Kamari R, Dasari A, 2017. Use of Mosquito Repellent Devices- Problems and Prospects. *Int J Recent Sci Res*. 8(1):15279-15283.

52. http://www.nvbdcp.gov.in/malaria11.html

53. http://www.who.int/csr/resources/publications/drugresist/malaria.pdf

54. https://www.unicef.org/wash/index_wes_related.html

55. Greenwood BM, Fidock DA, Kyle DE, Kappe SH, Alonso PL, Collins FH, 2008. Malaria: progress, perils, and prospects for eradication. *J Clin Invest*. 118: 1266-76.

56. Krishna S, Bustamante L, Haynes RK, Staines HM, 2008. Artemisinins: their growing importance in medicine. *Trends Pharmacol Sci*. 29: 520-7.