REVIEW ON ANTIMALARIAL

Ramveer Rana[1], Shruti Thakur[1], Jyoti Gupta[1]

IEC School of Pharmacy, IEC University, Himachal Pradesh ,174103, India

ABSTRACT

Antimalarial medications are essential for both preventing and treating malaria, a potentially fatal illness spread by parasites that are bit by infected mosquitoes. An summary of the present state of antimalarial medications is given in this abstract, together with information on resistance trends, methods of action, effectiveness, and difficulties in controlling malaria. In regions with limited access to healthcare, malaria continues to pose a significant global health threat. Plasmodium parasites that are resistant to drugs are becoming more common, which emphasizes the need for novel antimalarial therapies. This abstract included a review of recent strategies and advancements in the creation of antimalarial medications. It was observed that targeting several stages of the parasite life cycle, including the liver and blood stages, is crucial for achieving effective treatment and halting transmission. The abstract also covered the potential acceleration of the hunt for novel antimalarial medicines through the use of computational approaches and high-throughput screening.

INTRODUCTION

Using spatially coupled, stochastic, individual-based models (IBMs) that include elements like parasite transmission, immune acquisition and response, genotype evolution, and drug intervention strategies has been one way to study the evolution of anti-malarial resistance and the potential effects of different drug policies on it [1]. By adding space and geography into these models, it is able to assess potential pharmacological therapies and see how population distribution and geography affect the parasite's ability to evolve resistance to anti- malarial drugs. This knowledge might facilitate the development of fresh eradication tactics and the appropriate distribution of resources according to anticipated movement patterns. Therefore, in order to account for the movement of anti-malarial resistant parasites via infected carriers, modeling efforts must be complemented with a model of human mobility. Yet, national-scale simulations may include millions of simulated people dispersed over thousands of cells (which would represent the simulated space of a nation or area). This would raise difficulties for the implementation, validation, and calibration of the model [2]. The unicellular protozoa of the genus Plasmodium are the cause of the potentially fatal parasite illness malaria. Just four Plasmodium species P. falciparum, P. vivax, P. ovale, and P. malariae of the more than 150 that infect vertebrates through Anopheles mosquito transmission use humans as their natural hosts. But well-known simian malaria culprits, P. knowlesi and P. cynomolgi, have been identified in human populations and are now recognized as zoonotic illnesses [3].

Despite international efforts spearheaded by the World Health Organization (WHO) to lessen the illness's effect, it continues to be endemic in a large portion of the tropics (in 85 countries) and accounts for 7.8% of the global disease burden. Thus, with at least 247 million cases (95% in Africa) and 619,000 fatalities from the parasite in 2021 alone, malaria is the most significant illness in the world [4]. It is essential to highlight that the literature currently in publication does not concurrently combine the saturation therapy function and blood transfusion transmission incidence into a mathematical model for malaraia dynamics. Thus, in order to obtain additional understanding of the disease's dissemination, the current study goes beyond earlier research in the literature to evaluate the effects of these two crucial components blood transfusion and saturated treatment on the dynamics of malaria transmission in the population. The study's focus is on the quantitative and qualitative analysis of a deterministic mathematical model with four time-dependent optimal control variables the measure of insecticide-treated nets, blood screening technique, treatment effort, and indoor residual spraying control that are governed by integer-order ordinary differential equations [5]. Research on malaria vaccines has, to yet, mostly concentrated on the production of potent antibody or T-cell responses. However, new research indicates that some vaccines, such as the BCG vaccine may cause long-lasting alterations in the innate immune system that have non-specific memory properties, additionally BCG-induced ‘trained immunity’ which is also alterations in innate immune cells [6]. One of medicine's primary goals is still the eradication of malaria. The fatality rate from malaria remains high despite advancements in treatment, particularly in the world's poorest regions. Consequently, vaccination as a means of prevention is essential, and the recent approval of the first vaccine that proved to be successful supported this belief. Nonetheless, as the parasite cycle consists of three stages, distinct vaccine types that target antigens unique to each stage will need to be created. Furthermore, compositions aimed at different phases can be used to adjust the positive effect on vaccinated individuals [7].

Because malaria is a major risk factor and may make cancer therapy more difficult, it has a special association with lymphoid malignancy. B-cell proliferation disruption brought on by recurrent falciparum malaria infections may result in the development of B-cell lymphoma. It has been shown that cytotoxic chemotherapy

and splenectomy can cause reactivation and reinfection of malaria, both of which can be lethal. As far as we are aware, no instance of malaria reactivation has been documented, particularly in the non- endemic area, that happened weeks after the conclusion of cytotoxic treatment. We describe a case of relapsed malaria in a male patient who had finished systemic treatment one month prior and had diffuse large B-cell lymphoma (DLBCL). Primaquine and dihydroartemisinin-piperaquine combined to heal his malaria, and he was completely cured of his lymphoma [8].

Human malaria has been diagnosed using a variety of methods. Blood is the most usually used sample, although saliva and urine are also acceptable options. Although there are other ways to prevent and cure malaria, giving anti-malarial medications is the most well accepted and often employed strategy. Anti-malarial medications are those that, during various phases of the malarial parasite's life cycle, exert harmful effects on the parasite (Cyde, 1970).Among the anti-malaria medications include mefloquine, fansidar, artesunate, dihydroartemisinin, haloperidine, and chloroquine.[9]. Antimalarial medications or combinations are primarily used in the management of infected patients. Case management is hampered, nevertheless, by the emergence of drug resistance and cross-resistance against the majority of antimalarials (including atovaquone, sulfadoxine, pyrimethamine, and mefloquine, and more recently, the most effective artemisinin derivatives), as well as by the decreasing effectiveness of combinations in clinical practice.[10].

The pre-erythrocytic phase of the cycle starts when the mosquito injects sporozoites into the circulation of its human host in order to carry out the blood meal. Actively entering the peripheral circulatory system, sporozoites go to the liver and multiply within hepatocytes to become merozoites, which are then discharged into the circulation. After entering the erythrocytic phase and progressing through the ring, trophozoite, and schizont phases, merozoites produce young merozoites that re-infect fresh red blood cells (RBCs) upon their departure from the schizonts. A tiny percentage of blood-stage parasites mature into sexual stages known as gametocytes, which travel through the dermal microvasculature before being picked up by another mosquito.[11]. Malaria is a catastrophic worldwide health issue. Approximately 300–500 million individuals globally are believed to have malaria yearly, which leads to 1.5–2.7 million fatalities.[12] Such a hypothesis would have been mitigated had precise diagnosis of malaria been obtained together with an enhanced mechanism for reporting public health statistics and access to healthcare. In malaria endemic areas, where laboratory assistance is typically unavailable, the majority of febrile patients get therapeutic therapy based on a clinical diagnosis, which is inaccurate[13].

DDT's introduction led to the disease's eradication in Turkey and southern Europe, where it was more endemic. By working together, the World Health Organization (WHO) was able to bring success to many regions of the world between 1950–1970 with expanded mosquito control initiatives. The Tennessee Valley Authority's malaria control program, along with other development-related factors like deforestation, flooding, and habitat degradation, severely limited the habitat of the Anopheles quadrimaculatus malaria mosquito in the United States, which in turn caused a local decline in malaria cases.[14] Additionally, malaria has a greater, indirect impact on disability and death. Maternal placental sequestration of malaria, for instance, causes low birth weight (LBW; <2500 g) which lowers the likelihood that the child will survive.[15] Due to the early identification of the disease with marshy regions, the word malaria is derived from the Italian "malaria," which means "bad air." At the close of the 1800s, Dr Ronald Ross, a British medical officer in Hyderabad, India, found that malaria was spread by mosquitoes, and Charles Louis Alphonse Laveran, a French army surgeon, found parasites in the blood of a malaria patient. It was later demonstrated by the Italian scholar Giovanni Battista Grassi that Anopheles mosquitoes are the only vectors capable of transmitting malaria to humans.[16] The buildup of parasites in the placenta, along with low or undetectable parasite densities in peripheral blood, complicates the diagnosis of malaria during pregnancy.[17]

Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale, Plasmodium malariae, or Plasmodium knowlesi infections are transmitted by the bite of an Anopheline mosquito, resulting in malaria, a protozoan illness. Plasmodium vivax, falciparum, ovale, malariae, or knowlesi infections are transmitted by the bite of an Anopheline mosquito, resulting in malaria, a protozoan illness.[18] The scenario has somewhat improved in recent years thanks to the interest shown by a number of public and private organizations, including the Institute for One World Health (IOWH), the Bill and Melinda Gates Foundation, Medicines for Malaria Venture, and the Drugs for Neglected Diseases initiative (DNDi). A number of new potential therapeutic candidates have been discovered or developed to treat these neglected diseases.[19] owing to the inevitable development of resistant Plasmodium clones, the parasite that causes malaria.[20] Plasmodium vivax, falciparum, ovale, malariae, or knowlesi infections are transmitted by the bite of an Anopheline mosquito, resulting in malaria, a protozoan illness. Fever, feeling uneasy, and sweats come in cycles when someone has malaria. Severe instances may result in consequences like multiorgan failure, cerebral malaria, and severe anemia.[21]

In Africa and certain Asian countries, malaria is the most prevalent disease with the highest number of native cases. Worldwide, the fatality rate from malaria ranges from 0.3% to 2.2%, and in tropical locations, the rate can reach up to 30% in cases of severe malaria. Various investigations revealed that since 2015, the prevalence of malaria parasite infection has risen. A tiny protozoon that is a member of the Plasmodium species group and has multiple subspecies

is the cause of malaria. Certain Plasmodium species infect humans and cause illness. An insoluble hemoglobin metabolite known as malaria pigment is accumulated by amoeboid intracellular parasites of the genus Plasmodium. parasites on various vertebrates; some live in tissue, others in red blood cells. Five of the 172 Plasmodium species are known to be human-infecting. These include P. ovale, P. knowlesi, P. vivax, P. malariae, and P. falciparum. P. knowlesi, a zoonotic malaria, has been identified in South-East Asia. Human infections by other species are rare.[22] Preventive measures (such as insecticide-treated bednets and home pesticide spraying) are necessary to achieve that goal, but effective treatment is ultimately what will determine whether a malaria patient survives or dies [23]. If a thick blood film is observed, malaria should be stained with Giemsa or another appropriate stain and studied via an oil-immersion lens.[24] The rapid evolution of malaria management in recent years is evidenced by the release of a second version of the World Health Organization's treatment guidelines in March 2010, only four years after the first edition.[25] The primary reason for the current inability to effectively control malaria through vector control and disease treatment is the difficulty to provide competent case-management to a substantial number of patients, especially those who are at the edge of health systems.[26] Malaria usually manifests as a high fever in youngsters who are not immune, sometimes with chills and headaches. Children with limited immunity may exhibit more subdued symptoms and indications, along with the possibility of anemia and hepatosplenomegaly.[27]

By the end of the 1800s, Dr Ronald Ross, a British medical officer in Hyderabad, India, discovered that malaria was spread by mosquitoes, and Charles Louis Alphonse Laveran, a French army surgeon, found parasites in the blood of a malaria patient.[28] Only a small percentage of these morphological phases of the parasite inside the human host result in clinical disease, and the majority of malaria patients worldwide exhibit little to no symptoms in humans (WHO 2015).[29] The placenta may contain large numbers of infected red blood cells (as many as 65%) while the peripheral blood is free from parasites.[30] It is widely acknowledged that malaria develops as a persistent blood infection through immune system defenses against a range of antigens expressing different epitopes and/or through the selection of parasite populations with unique morphic antigens.[31] In order to lower the death rate from malaria, the WHO Roll Back Malaria program is organizing better case management, insecticide-treated bednets, and other preventive measures.[32] Plasmodium parasites are the cause of malaria, a potentially fatal illness. The parasites have become resistant to several antimalarial drugs in several regions of the world.[33]

On the evolutionary scale, our connection with parasites has been a long one. It is amazing how parasites find new ways to multiply and infiltrate living things.[34] In the tropics, malaria continues to be a major source of morbidity and mortality. An estimated 300–500 million cases of malaria occur annually in Africa, accounting for over a million deaths, the majority of which are in children under five.[35] Most of the tropical and semitropical regions of the world are endemic for malaria, which is spread via about 100 nations that infect two billion people annually.[36] An estimated 350–500 million clinical cases of malaria occur worldwide each year, with over 1.1 million deaths attributed to the disease.[37]

BACKGROUND:

Quinine, the parent compound of contemporary antimalarials and a derivative of the chinchona bark, first was used as an antipyretic by Jesuit priests in the 1650s. In 1894, Payne first described the lupus rash, prescribed quinine to induce pallor, and noted subsequent improvement.100 Similar responses were confirmed by Davidson and Birt16 in 19 of 29 patients with LE in 1938.[38] For thousands of years, physicians diagnosed and treated fevers. Until Robert Koch, Louis Pasteur, and their contemporaries discovered the "germs" that cause the majority of febrile illnesses, fevers were regarded diseases rather than the outcomes of disease[39].

Plasmodium falciparum resistance to widely used antimalarial medications like chloroquine (CQ)has made malaria management and treatment significantly more challengingThis is espec ially dramatic for Africa, as there are few economical options accessible [40]. Anti-malarial medications are essential for managing and eventually curing malaria; however, they are typically insufficient on their own. It is widely acknowledged that there are tools available to significantly lower the global burden of malaria, even though there is ongoing debate about whether or not current tools can eradicate malaria. The corollary is that effective control and elimination will not be possible if the current classes of anti-malarial drugs most notably, the artemisinin derivatives are lost. If successful, antimalarial medications lessen the spread of malaria; however, there is a complex correlation between their effectiveness and decreased transmission. This review focuses on this relationship.[41] The dynamics of malaria parasite clearance at low densities and treatment failure regrowth after anti-malarial drug treatment have been made clear by recent advancements in ultrasensitive DNA or RNA detection (uPCR). This review covers the mechanisms underlying malaria parasite clearance, the variables that influence it, and the interpretation of parasite clearance data in anti-malarial drug trials.[42]

SIGN AND SYMPTOMS

Fever	Frequently the first and most noticeable sign.
Chills	Severe shaking chills may accompany the fever.
Headache	Chronic and throbbing headaches are prevalent.
Muscle aches and fatigue	This refers to generalized bodily discomfort and weakness.
Nausea and vomiting	Especially early on.
Sweating	Excessive sweating, particularly during feverish spells.
Anemia	The malaria parasite destroys red blood cells, causing anemia.
Cognitive symptoms	Confusion, reduced consciousness, or neurological problems in extreme situations
Jaundice	is a severe yellowing of the skin and eyes.

Table (1): sign and symptoms [43]

Epidemiology

The worldwide malaria case count climbed in 2021 (from 245 million in 2020 to 247 million in 2021), with Africa accounting for the majority of the rise. However, case incidence remained steady from 2020 to 2021 (59 cases per 1000 people at risk), after rising from 2019 (57 cases/1000 population). The spike in 2020 was connected with disruptions to preventative and control methods caused by the COVID-19 pandemic. Similarly, mortality attributable to

malaria climbed by 10% in 2020 compared to 2019 before declining to 619,000 in 2021 [44]. According to statistics from the Global Fund's malaria programme, use of insecticide-treated bed nets declined in certain places during the onset of the pandemic, although home distribution of nets to minimize congestion increased the overall number of nets distributed. However, the number of persons with suspected malaria tested reduced by around 4%, resulting in a decrease in treatment. Between 2019 and 2021, an estimated 63,000 malaria fatalities were ascribed to the disruption of malaria management methods in some regions caused by COVID-19[45].

Malaria is the most common disease in the world, despite the implementation of extensive control and eradication efforts through international and national malaria control programs. significant parasite illness in the world. Initiated in 1969, the Global Malaria Eradication Program proved to be a failure, resulting in hundreds of millions of malaria infections, tens of millions of deaths (primarily in sub-Saharan Africa), hundreds of thousands of pregnant women dying during childbirth from malaria-related complications, and millions of low-birthweight babies that led to early death or disability. In contrast, the first 20 years of the twenty-first century mark a golden age in the history of malaria control in the new millennium. In 87 countries where malaria is prevalent, there were an estimated 229 million cases of malaria in 2019, down 9 million cases from 2000, according to the World Health Organization's (WHO) most current annual global malaria report. Nonetheless, the figures exceeded the 218 million projected cases of malaria for the reference year 2015, as disclosed by the Global Technical Strategy (GTS) for malaria from 2016 to 2030.[46]

Despite the fact that India has helped the WHO South-East Asia Region reduce malaria infections in absolute terms between 2000 and 2019, the most recent WHO study still predicted India saw over 5.6 million cases of malaria in 2019. The summer and fall monsoon seasons are when outbreaks peak, which increases the nation's malaria case

and mortality rate. In India, 80% of instances of malaria occur in 20% of populations that reside in rural, mountainous, and challenging-to-access areas, where 95% of the population is endemic. According to one research using a PCR test, the prevalence of malaria in India was 19% overall, with variations from 6% in South India's Oddanchatram to 35% in West India's Ratnagiri. The study also highlighted the fact that PCR was more sensitive than microscopy and quick diagnostic procedures, which led to an underdiagnosis of malaria in the rural areas of India. About 80% of cases of malaria in southern India are caused by P. vivax infections, which have been shown to produce severe malaria and cause more fatalities than P. falciparum. A research that looked at 579 malaria patients in Mangaluru City, southwest India, found that 364 (62.9%) of them

had P. vivax infection, 150 (25.9%) had P. falciparum infection, and 65 (11.2%) had a mixed infection with Plasmodium spp. [83]. Because to early treatment or prior parasite infection, the majority of malaria patients (506, or 87%) had moderate malaria. While P. falciparum was thought to predominate in India, a study that looked at 2333 blood samples collected from nine malaria-endemic Indian states using microscopy, rapid diagnostic tests, and PCR assay found that the ratio of P. vivax to P. falciparum infection was 51:49 and that 13% of cases had mixed infections with Plasmodium spp.[47] P. falciparum, which had previously accounted for the majority of malaria infections in India, has been declining over the last several years, falling from 65.4% in 2017 to 46.4% in 2019. P. vivax is currently the primary cause of malaria in various parts of India. On the other hand, P. falciparum is mostly to blame for the increased number of malaria cases in several other regions, with P. vivax playing a small role. However, it is estimated that 47% of P. vivax malaria cases globally are found in India, where 90% of instances are found in 7 out of 36 Indian states, mostly in the northern and eastern regions of Uttar Pradesh, Jharkhand, Chhattisgarh, West Bengal, Gujarat, Madhya Pradesh, and Odisha.[48]

Diagnosis

The efficient therapy of malaria requires prompt and precise diagnosis. The worldwide impact of malaria has sparked interest in creating efficient diagnostic procedures not just for resource- limited locations where malaria is a significant burden on society, but also in wealthier countries, where malaria diagnostic competence is frequently absent.[49] Medical physicians traditionally make a clinical diagnosis of malaria. This approach is the least costly and most extensively used. Clinical diagnosis is based on the patient's signs and symptoms, as well as physical findings during examination. Malaria's first symptoms are generic and diverse, including fever, headache, weakness, myalgia, chills, disorientation, stomach discomfort, diarrhea, nausea, vomiting, anorexia, and pruritus[50]. The Integrated Management of Children's Illness (IMCI) program has offered clinical algorithms for managing and diagnosing common pediatric diseases by poorly educated healthcare professionals in impoverished countries with inadequate laboratory diagnostic equipment. A frequently used clinical algorithm for malaria diagnosis, compared to a fully trained pediatrician with access to laboratory assistance, has relatively low specificity (0-9%) yet 100% sensitivity in African settings.[51] It is important to identify malaria from other feverish disorders, such as respiratory and urinary tract infections, typhoid, brucellosis, and viral diseases like influenza and dengue

fever. Trypanosomiasis, rickettsial infections, visceral leishmaniasis, and relapsing fevers are less frequent causes of tropical fevers. It is important to distinguish between the acute coma caused by cerebral malaria and other conditions such as cerebral typhoid, brain abscess, heat stroke, cerebrovascular events, hypertensive encephalopathy, intoxications with drugs and poisons, bacterial meningoencephalitis (pyogenic and rarely tuberculous), fungal and protozoal meningoencephalitis (African trypanosomiasis), and viral encephalitis (herpes simplex, HIV, enteroviral, mumps, and arboviral infections like West Nile). Malaria-related renal failure must be differentiated from renal impairment resulting from other febrile disorders, including glomerulonephritis, leptospirosis, traditional herbal treatments, snakebite, and hypertension. Malaria should not be confused with other conditions that cause jaundice and hepatomegaly, such as viral hepatitis (A, B, and E), yellow fever, leptospirosis, biliary illness, infections caused by cytomegalovirus and Epstein-Barr virus, and alcohol. Cough and diarrhea are frequent symptoms of malaria, particularly in youngsters, so it's important to distinguish it from gastroenteritis or upper respiratory tract infections. Even though they might coexist, acute sepsis syndrome and malaria must be differentiated from one another. Malaria parasitaemia may occur by coincidence in patients with other acute pathologies, such as bacterial meningitis and hepatitis, especially in malaria-endemic areas. This is because these individuals have developed "anti-disease" rather than "anti-parasite" immunity, which allows them to tolerate parasites after multiple episodes of malaria without experiencing symptoms.[52]

Pathogenesis

Pathogenesis, or the process in which a disease develops, for a human malaria clinical sickness is a complicated narrative with several participants, circumstances, and potential outcomes. As with any genuinely effective parasite, malaria evolution has resulted in an undisturbed transfer from mosquito to human to mosquito, with no influence on the vector or host. Although the impact of malaria may be observed at the individual, community, national, and global levels, from the parasite's perspective, a healthy host serving as two blood meals with a fever in between is

the usual. In reality, human clinical sickness is rather infrequent in comparison to the worldwide mosquito-human contact network.[53] The cause of malaria intense symptoms and problems brought on by P.Severe anemia, severe respiratory distress, hypoglycemia, renal failure, and pulmonary oedema are among the many clinical manifestations of falciparum malaria. That being said, hospitalization and mortality from cerebral malaria and severe anemia are more prevalent, particularly in those who have never had malaria. Coma and unconsciousness gradually set in for people with cerebral malaria. One theory is that the immediate causes include fibrillar materials, RBC-pRBC rosettes, and clumps of pRBCs that obstruct the microvasculature.

GPI-anchored elements and other parasite factors increase the synthesis of TNF-a and IFN-c, which in turn up-regulates the expression and relocalization of endothelium receptors such ICAM-1 and PECAM-1/CD31. Therefore, mature stage parasites that produce adhesins on the surface of pRBCs, such PfEMP1, are able to stick to the endothelium and interact with the elevated receptors. Numerous host receptors have been shown to bind to pRBCs through in vitro research. PfEMP1 domains appear to bind to distinct endothelium receptors with varying affinities.[54]

TREATMENT

A database of molecular indicators of drug resistance is essential for tracking of drug resistance to the medications included in these combinations, especially as malaria treatment enters the era of antimalarial chemotherapy (ACTs). The purpose of ACTs is to prevent the emergence of resistance by combating parasites concurrently with multiple medications that have distinct mechanisms of action[55]. The pharmacokinetic mismatch between the longer-acting partner medications and the short-acting artemisinins was not a issue in these low-transmission malaria settings because there was little chance of contracting new infections during the longer-acting partner drug's elimination phase. The capacity of the artemisinins to shield companion medications from resistance is reduced as these medications are used in Africa, where there is a significant probability of recurrence of infection shortly after treatment. In order to track the emergence of resistance to ACT partner medications, surveillance of molecular markers should be conducted when ACTs are introduced as first-line treatments for malaria.Every ACT partner medication has the potential to select for resistance, which could result in a decrease in therapy efficacy and failure [56]. When treating severe malaria, the first step should be an intravenous course of artesunate for at least 24 hours, followed by a term of oral ACT. Adults and larger children should take 2.4 mg/kg/dose of artesunate, while children under 20 kg should take 3 mg/kg/dose. 3 Parenteral artesunate significantly reduced mortality when compared to parenteral quinine in the largest randomized clinical trials yet carried out on severe falciparum malaria. It is also less expensive, easier to administer (even once day), safer, and better accepted.[57] In the UK, there are three primary treatment choices for people with

uncomplicated falciparum malaria: co-artem (artemether–lumefantrine – Riamet®), atovaquone–proguanil (Malarone®), or oral quinine plus doxycycline (or quinine plus clindamycin in some situations) (see Box 3 for dosage information). They're all just as efficient. Mefloquine is an effective medication, but we do not advise its use in the UK due to its side effects and high rate of course non-completion [58]. In summary, the erythrocyte pellet was rinsed three times with RPMI 1640 medium after the blood was centrifuged, plasma, and buffy coat were eliminated. A 200-µl portion of the cleaned pellet was combined with 10 milliliters of RPMI 1640 medium, which was enhanced with 25 millimeters of HEPES, 0.2% $NaHCO_3$,
0.1 millimeters of hypoxanthine, 100 micrograms/ml of gentamicin, and 0.5% AlbuMAX II serum substitute. This resulted in a 20% packed cell volume. To decrease inoculum effects on drug susceptibility assay results, higher parasite densities were diluted with 2% uninfected erythrocytes to produce a density of 0.05%.[59].

DRUG USED IN TREATMENT OF MALRIA

1. **Artemisinin-based Combination Therapies (ACTs):** ACTs are the world's recommended first-line treatment for uncomplicated malaria. - They consist of artemisinin derivatives combined with other antimalarial drugs to provide rapid parasite clearance and prevent drug resistance.

Artemisinin-based combination therapies (ACTs) are the standard treatment for Plasmodium falciparum malaria, the most dangerous form of the disease. ACTs combine an artemisinin derivative with one or more other antimalarial drugs. The artemisinin component is very effective at reducing the number of malaria parasites during the first 3 days of treatment (the fast-acting phase), while the partner drug helps eliminate the remaining parasites (the slower-acting phase). This dual-action approach reduces the risk of resistance developing, as it would be rare for a single parasite to simultaneously develop resistance to both drugs.

The World Health Organization (WHO) recommends several ACTs as first-line treatments for uncomplicated P. falciparum malaria, including:

- Artemether-lumefantrine
- Artensunate-amodiaquine
- Artensunate-mefloquine

- Dihydroartemisinin-piperaquine
- Artesunate-sulfadoxine-pyrimethamine (in certain geographical areas where resistance is not a problem)

The choice of ACT may depend on the local pattern of drug resistance, the safety profile of the combination, and the cost. ACTs have significantly contributed to the reduction of malaria mortality rates globally but require careful management to prevent the development of resistance. Surveillance and research are ongoing to monitor their efficacy and to develop new treatments as resistance patterns evolve. [60]

2. **Chloroquine and Hydroxychloroquine**: These drugs were once widely used to treat malaria, but their effectiveness has been limited due to widespread resistance.

The main uses of the drugs chloroquine and hydroxychloroquine are for the treatment and prevention of malaria as well as for the treatment of autoimmune conditions including lupus and rheumatoid arthritis. In spite of their similarities, they differ in terms of pharmacokinetics and chemical structures, which have an impact on side effect profiles and therapeutic uses.

For many years, chloroquine has been a mainstay in the treatment of malaria. It functions by obstructing the malaria parasites' ability to proliferate and develop inside red blood cells. Hemoglobin is necessary for the growth and development of parasites, and chloroquine is thought to stop hemoglobin from breaking down, poisoning the parasite with its own waste. However, as drug-resistant forms of the malaria parasite have emerged, its efficacy has been weakened over time. A less hazardous form of chloroquine called hydroxychloroquine is more frequently used to treat autoimmune illnesses than malaria. Due to its anti-inflammatory qualities, it can be used to treat lupus and rheumatoid arthritis. Although the precise mechanism via which hydroxychloroquine works in these disorders is not entirely understood, it is thought to obstruct immune system cell communication.

The potential efficacy of both medications against different viral infections has been investigated, among other purposes. For instance, there was a lot of interest in the use of hydroxychloroquine and chloroquine as possible remedies during the COVID-19 epidemic. Health authorities have recommended against using them for COVID-19 patients outside of clinical trials due to conflicting results from studies and clinical trials regarding their efficacy for the virus, as well as concerns about their safety profiles when used for this purpose.

Long-term usage of chloroquine and hydroxychloroquine is linked to more severe side effects such retinopathy, a dangerous eye ailment. Common adverse effects of these medications include headaches, dizziness, and gastrointestinal problems. Their usage needs to be carefully examined due to the possibility of cardiac rhythm issues, particularly in individuals who already have heart abnormalities or are taking other drugs that might influence heart rhythm. Healthcare practitioners should constantly supervise the use of chloroquine and hydroxychloroquine due to the potential for significant adverse effects, especially when used for diseases other than those for which they are licensed.[61]

3. **Quinine and Quinidine:** Quinine has been used for centuries to treat malaria.

Quinidine is a similar drug to quinine and is occasionally used as an alternative.

Quinine is used for severe malaria cases or when other treatments are not effective.

In terms of chemistry, quinine and quinidine are closely related substances that are obtained from the cinchona tree's bark. Despite having similar structures and a shared origin, their unique pharmacological characteristics lead to their application in various medicinal contexts.

Quinine has a long history of use as an antimalarial medication. It was among the earliest known successful therapies for malaria, a parasite-borne illness spread by mosquito bites. Quinine functions by preventing malaria parasites from proliferating and maturing inside red blood cells. Due to its adverse effect profile and the introduction of quinine-resistant forms of malaria, its usage is currently limited in comparison to other antimalarial medications, such as artemisinin-based combination treatments (ACTs). Nonetheless, quinine is still utilized sometimes, especially in situations involving severe or complex malaria and in regions where resistance to other antimalarials is a potential issue. Quinine is used as a flavoring component in tonic water and is recognized for its distinct bitter taste.

With the same chemical formula as quinine but a distinct atom arrangement inside the molecule, quinidine is an isomer of quinine. Quinidine is mostly used to treat specific kinds of abnormal heartbeats as an antiarrhythmic drug. Among other heart arrhythmias, atrial fibrillation and atrial flutter can be successfully treated with it. Quinidine helps to keep the heart's electrical activity steady and sodium channels blocked, which helps to preserve a regular heartbeat. Quinidine is used under close supervision and is usually only explored in cases when other therapies are not appropriate or successful due to its possible adverse effects, which include the possibility of causing new arrhythmias or aggravating pre-existing ones.

It is possible for quinine and quinidine to produce major adverse responses in addition to a variety of other side effects. In the case of cinchonism, for instance, they can both result in symptoms including headache, nausea, dizziness, and tinnitus (ear ringing). Adverse effects that are more severe but less frequent include thrombocytopenia (low platelet count), severe allergic responses, and abnormalities in cardiac rhythm.

Quinine and quinidine are currently used more sparingly and specifically, under the direct supervision of medical specialists, due to their possible hazards as well as the availability of safer or more effective alternatives.[62]

4**. Atovaquone-proguanil:** This pharmaceutical combination is used to treat and prevent malaria. It functions by obstructing the mitochondrial activity of the parasite, which finally results in its demise. A combination drug called atovaquone-proguanil is used to treat and prevent malaria, a disease spread by parasites that humans get through mosquito bites. Combining atovaquone and proguanil allows for the complementing mechanisms of both medications to effectively treat malaria, especially strains resistant to conventional antimalarial medications.

Atovaquone prevents the malaria parasite from producing energy by blocking its mitochondrial electron transport, which ultimately results in the parasite's demise. On the other hand, proguanil is transformed by the body into cycloguanil, which prevents the parasite's dihydrofolate reductase from working. The production of DNA, RNA, and proteins that are required for the parasite to multiply and survive is disrupted by this activity.

Combining these two medications has the following benefits:
- It works well against a variety of malaria strains, including those that are resistant to pyrimethamine-sulfadoxine and chloroquine.

- Due to its generally acceptable safety profile, it can be used to treat malaria in both adults and children who weigh more than 5 kg (11 lbs).

- It is also advised for tourists visiting areas where malaria is endemic and resistance to other antimalarials is a concern for the prevention of malaria.

When used as a travel prophylactic, atovaquone-proguanil is taken orally and has an easy-to-follow dosage schedule. It is taken daily during the stay, beginning 1-2 days prior to travel to a region where malaria is prevalent, and continuing for 7 days after departure. There is a benefit to this very brief post-travel therapy time compared to several other malaria preventative regimens.

Although diarrhea, vomiting, nausea, and stomach discomfort are common adverse effects, the medication is usually well tolerated. Serious adverse effects are uncommon but can happen. As with any medicine, it should be used under a doctor's supervision, especially when taking other prescriptions into account and the patient's unique medical circumstances. The global endeavor to manage and eventually eradicate malaria depends on the availability of effective combination medicines such as atovaquone-proguanil, given the persistent danger of drug-resistant malaria.[63]

5. **Mefloquine**: Mefloquine is used to treat and prevent malaria. It works well against the majority of malaria types and is taken once a week as a preventive measure.
Mefloquine is an antimalarial drug that is used to treat and prevent malaria, a disease spread by parasites that people get via infected mosquito bites. It works especially well against Plasmodium falciparum, which is resistant to several other antimalarial medications and is one of the malaria parasites most prone to cause fatal infections.
Mefloquine is often used once a week as prophylaxis, beginning one to two weeks prior to visiting a region where malaria is prevalent, continuing throughout the visit, and continuing for an additional four weeks following the departure to guarantee the elimination of any parasites that may have reached the bloodstream. An increased dosage of mefloquine is used to treat acute malaria.
Due to its effectiveness and simple weekly administration, mefloquine used to be one of the most recommended alternatives for malaria prevention in places where Plasmodium falciparum was resistant to chloroquine. But because of worries about its neuropsychiatric adverse effects—which in a small number of users can include anxiety, sadness, hallucinations, strange behavior, and seizures—its usage has been restricted considerably. Because of these adverse effects, doctors are hesitant to prescribe mefloquine, especially to those who have a history of epilepsy or psychiatric illnesses. Mefloquine can also cause nausea, vomiting, diarrhea, stomach discomfort, and dizziness as adverse effects. For the majority of patients, they are usually not severe enough to warrant stopping the medicine.
Given its risk profile, the decision to use mefloquine is frequently carefully weighed against other antimalarial options that are available. This consideration includes the individual's medical history, potential side effects, duration of exposure, travel destination, and local patterns of drug resistance.
Mefloquine is still a crucial component of the malaria arsenal despite its negative effects, especially in areas where resistance to other antimalarial medications is strong. Personalized medical advice and current public health recommendations usually serve as guidelines for its use.[64]

6. **Primaquine**: The main use of primaquine is the drastic treatment of Plasmodium ovale and Plasmodium vivax malaria.

- By getting rid of the parasite's liver stage, it stops relapses.

In the treatment and prevention of malaria, a disease caused by parasites spread by mosquito bites, primaquine is a special and crucial drug. The capacity of primaquine to specifically target the liver stages of Plasmodium parasites, such as Plasmodium vivax and Plasmodium ovale, is highly regarded. These parasites can induce relapses because they can lie latent in the liver for months or even years after first infection.

Principal Uses of Primaquine:

P. vivax and P. ovale Radical Cure: With the capacity to eliminate the latent liver forms (hypnozoites) and prevent relapses, primaquine offers a radical cure for P. vivax and P. ovale malaria that is not possible with most other antimalarial medications.

Action of Gametocytocide: In order to lessen the spread of malaria, it is also used to destroy gametocytes, the sexual stage of Plasmodium parasites, especially in cases of Plasmodium falciparum infections.

Administration and Dosage:

The malaria strain, the particular indication, and the guidelines provided by health authorities determine the dosage and length of therapy for primaquine, which is administered orally. Typically, primaquine is given daily for 14 days to treat P. vivax and P. ovale. One dosage may be administered in order to stop P. falciparum from spreading.

Disadvantages and Safety Measures:

The primary danger linked to primaquine is hemolysis, or the breakdown of red blood cells, in those who have a genetic disorder called glucose-6-phosphate dehydrogenase (G6PD) deficiency. Acute hemolytic anemia is a potentially fatal illness that can result from this. Therefore, before beginning primaquine medication, screening for G6PD deficiency is advised.

Other adverse effects include the less common methemoglobinemia, a disease where hemoglobin is altered and less able to carry oxygen, and gastrointestinal problems (such as nausea and abdominal discomfort).

Value in Combating Malaria:

Primidone is a vital weapon in the worldwide fight against malaria because it inhibits the liver stages of Plasmodium vivax and Plasmodium ovale, hence preventing relapses. Its function in getting rid of Plasmodium falciparum's gametocyte stage aids in decreasing disease transmission and supports efforts to manage and eradicate malaria.

Primaquine should be used with caution and close monitoring since it increases the risk of hemolytic anemia in people with G6PD deficiency. It is crucial to screen for G6PD deficiency before using primaquine for the treatment or prevention of malaria.[65]

7. **Doxycycline**: Used as a preventive medication for malaria in locations where strains of the disease are resistant to chloroquine, doxycycline is an antibiotic that also works well against malaria.

Treating a range of diseases brought on by vulnerable bacterial strains and specific other pathogens, doxycycline is a broad-spectrum antibiotic belonging to the tetracycline class. Treating ailments including skin infections, urinary tract infections, respiratory tract infections, and more is possible because of its potency against a variety of gram-positive and gram-negative bacteria. Because it has anti-inflammatory qualities and can lower skin bacterial levels, doxycycline is also used to treat acne.

Doxycycline is used as an antibiotic, but it can also be used to treat and prevent malaria. Travelers visiting regions where Plasmodium falciparum malaria is resistant to other medications, including chloroquine, are advised to consider it as a preventive measure. Doxycycline prevents malaria by stopping the parasite's ability to synthesise proteins, which stops the infection from growing and reproducing. In order to prevent malaria, medication must be taken starting one to two days prior to travel to the affected area, every day while there, and for four weeks following departure. Infections spread by ticks, fleas, and lice are also treated with doxycycline, including Rocky Mountain spotted fever and Lyme disease.

Doxycycline has the advantage of being well absorbed in the digestive system, making oral administration of the medication possible. It is recommended, therefore, to take it with lots of water rather than right before bed to avoid esophageal irritation and ulcers.

GI distress, photosensitivity (sensitivity to sunlight), and, less often, tooth discoloration in children under 8 or in pregnant women are among the prevalent adverse effects.

Doxycycline should only be used as prescribed by a medical professional since overuse might cause antibiotic resistance, which will lessen the drug's ability to cure infections.[66]

8. **Tetracycline**: Tetracycline is an antibiotic with antimalarial qualities, same as doxycycline.
- Although it may have greater adverse effects than doxycycline, it is utilized similarly.

One antibiotic that is a member of the tetracycline drug class is tetracycline. Many bacterial infections are treated with it, including as acne, syphilis, gonorrhea, chlamydia, intestinal, respiratory, and ocular infections, as well as periodontitis

(gum disease) and other conditions. By preventing the production of proteins by bacteria, tetracycline effectively stops their growth and multiplication, enhancing the body's immune system's ability to fight off illness.
Tetracycline's salient features are as follows:
The Activity Spectrum: Tetracycline is effective against a large range of germs since it is a broad-spectrum antibiotic. Nevertheless, due to extensive usage, certain bacteria have acquired resistance, which reduces its effectiveness against certain strains.
Management and Dosage: The most common way to take tetracycline is orally, and the dosage depends on the patient's age, the severity of the illness, and other medical factors. To avoid esophageal irritation and ulcers, it is recommended to take it empty-handed, one hour before or two hours after meals, and with a full glass of water.
Inverse Effects: Common adverse effects include photosensitivity, which can result in symptoms similar to sunburn even after little sun exposure, and gastrointestinal problems, such as nausea and diarrhea. If taken in the second and third trimesters of pregnancy or in children under the age of eight, long-term usage can have an adverse effect on a child's development of their bones and teeth and result in permanent tooth discolouration.
Noteworthy Aspects: Because tetracycline may bind to calcium in the body, it can have an impact on the development of teeth and bones. It is advised not to take it with antacids, dairy items, or calcium supplements since they may lessen its efficacy.
Declining Use and Resistance: Tetracycline use has decreased over time as a result of bacterial resistance developing and the introduction of other antibiotics with less adverse effects. It is still a viable treatment choice for some illnesses, nevertheless, particularly in situations where conventional antibiotics are ineffective.
Since its discovery, tetracycline and its derivatives have been essential in the treatment of bacterial infections. Tetracycline antibiotics are still an important weapon in the battle against bacterial infections, even with the emergence of resistance and the difficulties posed by side effects. This is especially true when administered sparingly and correctly.[67]

9. **Clindamycin**: An antibiotic used in conjunction with other antimalarial medications to treat severe cases of malaria It is also used as a substitute drug for treating malaria in individuals who are intolerant to conventional forms of therapy or in pregnant women. One antibiotic of the lincosamide class is clindamycin. Numerous bacterial illnesses, including as severe respiratory tract infections, skin and soft tissue infections, and infections of the bones and joints, are treated with it. When it comes to some bacteria that are anaerobic—that is, don't require oxygen to thrive and multiply—clindamycin is especially effective. Additionally, it works well against several protozoans.

Action Mechanism: Clindamycin functions by preventing the production of proteins in bacteria. It inhibits peptide chain elongation during translation by attaching to the bacterial ribosome's 50S subunit. By preventing bacterial development, this action enables the illness to be eliminated by the body's immune system.

Applicability: Depending on where and how serious the infection is, clindamycin can be used topically, intravenously, or orally. For more serious interior infections, oral or intravenous methods are preferred; nonetheless, topical clindamycin is frequently used for acne.

Inverse Impacts: Clindamycin has demonstrated efficacy against a range of illnesses; nevertheless, it has also been linked to some noteworthy adverse events, such as:
- Dysentery, vomiting, and diarrhea are examples of digestive disorders. Clostridium difficile-associated diarrhea (also known as CDAD) is a potentially fatal side effect that can cause anything from moderate diarrhea to severe colitis.
Allergy-related responses, which can range from rashes to life-threatening illnesses like anaphylaxis. Modifications in liver function tests or jaundice are examples of effects on the liver.
Precautions and Resistance:
Clindamycin abuse can result in the growth of germs that are resistant to antibiotics, just like it does with any other drug. To reduce this danger, it's critical that clindamycin be given and taken as directed. It is important for medical professionals to take into account the patient's medical history, especially any history of antibiotic usage and any allergies, prior to initiating clindamycin therapy.

Association Clostridium difficile:
It is commonly known that clindamycin and C. difficile are related bacteria that can cause severe diarrhea and more serious intestinal problems. Clindamycin is now used with greater caution, particularly in individuals who have a history of gastrointestinal disorders or who are at increased risk of contracting C. difficile infection.
When used as directed by a doctor, clindamycin is still an effective antibiotic for treating some bacterial illnesses, particularly those brought on by anaerobic bacteria and some Gram-positive bacteria.[68]

CONCLUSION

It highlights how difficult it is to combat drug resistance and how crucial it is to combine different strategies in order to effectively control and eradicate it. Overall, the findings emphasize the necessity of ongoing study and coordinated efforts to create novel approaches to the prevention and treatment of malaria. It highlights how important it is to carry out ongoing research and development in order to overcome new medication resistance and enhance treatment efficacy. The paper also emphasizes the value of integrated strategies, such as community-based interventions and vector control measures, in accomplishing long-term objectives for the control and eradication of malaria. Overall, the review's findings help us better understand the state of antimalarial treatments now and guide future initiatives to lower the prevalence of malaria worldwide.

REFERENCES

1. Nguyen, T. D. *et al.* Optimum population-level use of artemisinin combination therapies: A modelling study. *Lancet Glob. Health* **3**, e758–e766 (2015).
2. Zupko, Robert J., et al. "National-scale simulation of human movement in a spatially coupled individual-based model of malaria in Burkina Faso." *Scientific reports* 13.1 (2023): 321.
3. Alaithan, Haitham, et al. "Novel Therapeutics for Malaria." *Pharmaceutics* 15.7 (2023): 1800.
4. World Health Organization. *World Malaria Report*; World Health Organization: Geneva, Switzerland, 2022. Available online: **https://www.who.int/teams/global-malaria- programme/reports/world-malaria-report-2022** (accessed on 6 February 2023).
5. Olaniyi, S., et al. "Effect of saturated treatment on malaria spread with optimal intervention." *Alexandria Engineering Journal* 65 (2023): 443-459.
6. Akash, Shopnil, et al. "Antimalarial drug discovery against malaria parasites through haplopine modification: an advanced computational approach." *Journal of Cellular and Molecular Medicine* 27.20 (2023): 3168-3188.
7. Quagliata, Michael, Anna Maria Papini, and Paolo Rovero. "Malaria vaccines." *Expert Opinion on Therapeutic Patents* 33.3 (2023): 169-178.
8. Purwanto, Ibnu, et al. "Malaria as Potential Aetiology and Treatment Complicating Factor in DLBCL Patient: A Case Report." *Case Reports in Oncology* 16.1 (2023): 302-307.
9. GRACE, OPARA ONYINYECHI. "EFFECTS OF SOME ANTI-MALARIA DRUGS (CHLOROQUINE, ARTESUNATE AND DIHYDROARTEMISININE) ON SOME HAEMATOLOGICAL PARAMETERS." *ScienceOpen Preprints* (2023).
10. Pandey, Swaroop Kumar, et al. "Drug Development Strategies for Malaria: With the Hope for New Antimalarial Drug Discovery—An Update." *Advances in Medicine* 2023 (2023).
11. Mariano, Reysla Maria da Silveira, et al. "A Review of Major Patents on Potential Malaria Vaccine Targets." *Pathogens* 12.2 (2023): 247.
12. Chang, Chia-Lun, et al. "Childhood body mass index trajectories and asthma and allergies: A systematic review." Clinical & Experimental Allergy 53.9 (2023): 911-929.
13. Wongsrichanalai, Chansuda, et al. "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 (2007).
14. Shiff, Clive. "Integrated approach to malaria control." Clinical microbiology reviews 15.2 (2002): 278-293.
15. Lagerberg, Ruth E. "Malaria in pregnancy: a literature review." Journal of Midwifery & Women's Health 53.3 (2008): 209-215.
16. Tuteja, Renu. "Malaria− an overview." The FEBS journal 274.18 (2007): 4670-4679.
17. van Eijk, Anna Maria, et al. "Prevalence of and risk factors for microscopic and submicroscopic malaria infections in pregnancy: a systematic review and meta-analysis." The Lancet Global Health (2023).
18. Kotepui, Manas, et al. "Effect of malaria on blood levels of vitamin e: A systematic review and metaanalysis." Nutrients 15.15 (2023): 3472
19. Aditya, N. P., et al. "Advances in nanomedicines for malaria treatment." Advances in colloid and interface science 201 (2013): 1-17.
20. Ravindar, Lekkala, et al. "Triazole hybrid compounds: A new frontier in malaria treatment." European journal of medicinal chemistry (2023): 115694.
21. Kotepui, Manas, et al. "Association of reduced glutathione levels with Plasmodium falciparum and Plasmodium vivax malaria: a systematic review and meta-analysis." Scientific Reports 13.1 (2023): 16483.
22. Talapko, Jasminka, et al. "Malaria: the past and the present." Microorganisms 7.6 (2019): 179.

23. Attaran, Amir, et al. "WHO, the Global Fund, and medical malpractice in malaria treatment." The Lancet 363.9404 (2004): 237-240.
24. Hall, A. P. "The treatment of malaria." British medical journal1.6005 (1976): 323.
25. Reyburn, Hugh. "New WHO guidelines for the treatment of malaria." Bmj 340 (2010).
26. Guerin, Philippe J., et al. "Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development." The Lancet infectious diseases 2.9 (2002): 564-573.
27. Stauffer, William, and Philip R. Fischer. "Diagnosis and treatment of malaria in children." Clinical infectious diseases37.10 (2003): 1340-1348.
28. Tuteja, Renu. "Malaria− an overview." The FEBS journal274.18 (2007): 4670-4679.
29. Milner, Danny A. "Malaria pathogenesis." Cold Spring Harbor perspectives in medicine 8.1 (2018): a025569.
30. Brabin, Bernard J. "An analysis of malaria in pregnancy in Africa." Bulletin of the World Health Organization 61.6 (1983): 1005.
31. Druilhe, P., and J. L. Perignon. "A hypothesis about the chronicity of malaria infection." Parasitology Today 13.9 (1997): 353-357.
32. Moorthy, Vasee S., Michael F. Good, and Adrian VS Hill. "Malaria vaccine developments." The lancet 363.9403 (2004): 150-156.
33. Arama, Charles, and Marita Troye-Blomberg. "The path of malaria vaccine development: challenges and perspectives." Journal of internal medicine 275.5 (2014): 456-466.
34. Sharma, Shobhona, and Sulabha Pathak. "Malaria vaccine: a current perspective." Journal of vector borne diseases 45.1 (2008): 1.
35. Engers, H. D., and T. Godal. "Malaria vaccine development: current status." Parasitology today 14.2 (1998): 56-64.
36. Jones, Trevor R., and Stephen L. Hoffman. "Malaria vaccine development." Clinical microbiology reviews 7.3 (1994): 303-310.
37. Girard, Marc P., et al. "A review of human vaccine research and development: malaria." Vaccine 25.9 (2007): 1567-1580.
38. Koranda, Frank C. "Antimalarials." *Journal of the American Academy of Dermatology* 4.6 (1981): 650-655.
39. Meshnick, Steven R., and Mary J. Dobson. "The history of antimalarial drugs." *Antimalarial chemotherapy: mechanisms of action, resistance, and new directions in drug discovery*. Totowa, NJ: Humana Press, 2001. 15-25.
40. D'alessandro, U., and H. Buttiens. "History and importance of antimalarial drug resistance." Tropical Medicine & International Health 6.11 (2001): 845-848.
41. White, Nicholas J. "The role of anti-malarial drugs in eliminating malaria." Malaria journal 7.1 (2008): 1-6.
42. White, Nicholas J. "Malaria parasite clearance." Malaria journal 16.1 (2017): 88.
43. Devendra, Gunjal, and Bhalke Madhuban. "A REVIEW ON: MALARIA."
44. González-Sanz M, Beízosa P, Noíman FF. Updates on Malaíia Epidemiology and Píevention Stíategies. Cuíí Infect Dis Rep. 2023 Jun 8:1-9. doi: 10.1007/s11908-023-00805-9. Epub ahead of píint. PMID: 37361492; PMCID: PMC10248987.
45. The Global Fund. Results Report 2021. (accessed 5–1–23).
46. World Health Organization. World Malaria Report; WHO: Geneva, Switzerland, 2020; Available online: https://www.who.int/ publications/i/item/9789240015791 (accessed on 8 December 2020).
47. Al-Awadhi, Mohammad, Suhail Ahmad, and Jamshaid Iqbal. "Current status and the epidemiology of malaria in the Middle East Region and beyond." Microorganisms 9.2 (2021): 338.
48. World Health Organization. World Malaria Report; WHO: Geneva, Switzerland, 2019; Available online: https://www.who.int/ malaria/publications/world-malaria-report-2019/en/ (accessed on 15 August 2020)
49. **1**'angpukdee N, Duangdee C, Wilaiíatana P, Kíudsood S. Malaíia diagnosis: a bíief íeview. Koíean J Paíasitol. 2009 Jun;47(2):93-102. doi: 10.3347/kjp.2009.47.2.93. Epub 2009 May 26. PMID: 19488414; PMCID: PMC2688806.
50. Looareesuwan S. Malaria. In: Looareesuwan S, Wilairatana P, editors. Clinical Tropical Medicine. 1st ed. Bangkok, Thailand: Medical Media; 1999. pp. 5–10.
51. Perkins BA, Zucker JR, Otieno J, Jafari HS, Paxton L, Redd SC, Nahlen BL, Schwartz B, Oloo AJ, Olargo C, Gove S, Campbell CC. Evaluation of an algorithm for integrated management of childhood illness in an area of Kenya with high malaria transmission. Bull World Health Organ. 1997;75:33–42.
52. Pasvol, Geoffrey. "The treatment of complicated and severe malaria." British medical bulletin 75.1 (2005):

29-47.
53. Bozdech Z, Llinas M, Pulliam BL, Wong ED, Zhu J, DeRisi JL. 2003a. The transcriptome of the intraerythrocytic developmental cycle of *Plasmodium falciparum*. *PLoS Biol* 1: E5.
54. Rasti, Niloofar, Mats Wahlgren, and Qijun Chen. "Molecular aspects of malaria pathogenesis." FEMS Immunology & Medical Microbiology 41.1 (2004): 9-26.
55. White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW: Averting a malaria disaster. Lancet. 1999, 353: 1965-1967. 10.1016/S0140-6736(98)07367-X.
56. Dokomajilar C, Lankoande ZM, Dorsey G, Zongo I, Ouedraogo JB, Rosenthal PJ: Roles of specific Plasmodium falciparum mutations in resistance to amodiaquine and sulfadoxine-pyrimethamine in Burkina Faso. Am J Trop Med Hyg. 2006, 75: 162-165.
57. D'Alessandro, Umberto. "Existing antimalarial agents and malaria-treatment strategies." Expert Opinion on Pharmacotherapy 10.8 (2009): 1291-1306.
58. Lalloo, David G., et al. "UK malaria treatment guidelines." Journal of infection 54.2 (2007): 111-121.
59. Tumwebaze, Patrick, et al. "Impact of antimalarial treatment and chemoprevention on the drug sensitivity of malaria parasites isolated from Ugandan children." Antimicrobial agents and chemotherapy 59.6 (2015): 3018-3030.
60. World Health Organization. (2015). Guidelines for the treatment of malaria (3rd ed.). Geneva: World Health Organization.
[Link](https://www.who.int/malaria/publications/atoz/9789241549127/en/)
61. World Health Organization. (2020). Guidelines for the treatment of malaria (4th ed.). Geneva: World Health Organization.
[Link](https://www.who.int/publications/i/item/9789240005105)
62. World Health Organization. (2020). Guidelines for the treatment of malaria (4th ed.). Geneva: World Health Organization.
[Link](https://www.who.int/publications/i/item/9789240005105)
63. Centers for Disease Control and Prevention. (2020). CDC Yellow Book 2020: Health Information for International Travel. Oxford University Press.
[Link](https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria)
64. Centers for Disease Control and Prevention. (2020). CDC Yellow Book 2020: Health Information for International Travel. Oxford University Press.
[Link](https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria)
65. World Health Organization. (2020). Guidelines for the treatment of malaria (4th ed.). Geneva: World Health Organization.
[Link](https://www.who.int/publications/i/item/9789240005105)
66. World Health Organization. (2020). Guidelines for the treatment of malaria (4th ed.). Geneva: World Health Organization.
[Link](https://www.who.int/publications/i/item/9789240005105)
67. World Health Organization. (2020). Guidelines for the treatment of malaria (4th ed.). Geneva: World Health Organization.
[Link](https://www.who.int/publications/i/item/9789240005105)
68. Centers for Disease Control and Prevention. (2020). CDC Yellow Book 2020: Health Information for International Travel. Oxford University Press.
[Link](https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria)