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Antimalarial Drug Resistance: A Synthesis of Evidence

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ABSTRACT

Malaria remains a major public health challenge, disproportionately affecting low- and middle-income countries, particularly in sub-Saharan Africa. Although significant progress has been achieved through vector control strategies and artemisinin-based combination therapies (ACTs), the spread of drug-resistant Plasmodium strains threatens malaria control and elimination efforts. Resistance to chloroquine, sulfadoxine-pyrimethamine, and, more recently, artemisinin and its partner drugs has been documented across endemic regions, driven by genetic mutations, drug pressure, and inadequate dosing. The emergence of artemisinin resistance, associated with mutations in the kelch13 (K13) propeller domain, is of particular concern given the reliance on ACTs as first-line therapy. This review synthesizes evidence on the history, mechanisms, and epidemiology of antimalarial drug resistance. It also discusses factors contributing to resistance, current therapeutic strategies, and the urgent need for surveillance, novel antimalarials, and integrated approaches to sustain malaria control and move toward elimination.

Keywords: Malaria; Antimalarial drugs; Drug resistance; Artemisinin; Plasmodium falciparum; and Public health.

INTRODUCTION

Since World War II, malaria morbidity and mortality have decreased in many regions, aided by insecticide-treated bed nets, indoor insecticide spraying, and artemisinin-based combination therapies (ACTs) [1]. These gains are threatened by the spread of resistance to artemisinin and ACT partner drugs, necessitating enhanced efforts to counter the development and spread of resistance [1]. Plasmodium parasites continue to pose a global health threat by frequently overcoming control measures and antimalarial drugs. An effective malaria vaccine would improve prospects for elimination and eradication, but no highly efficacious vaccine currently exists; consequently, appropriate use of antimalarial drugs remains essential for malaria control [2, 3]. Early identification of emerging resistance is crucial for devising strategies to prevent its spread. Malaria is a globally prevalent and lethal parasitic disease that infects almost half the world population. It is endemic and affects mainly developing countries, causing an estimated 247 million cases and 881,000 deaths every year, disproportionately affecting adults and children in sub-Saharan Africa [1]. The disease is caused by six recognized species of Plasmodium protozoa transmitted from person to person through the bite of Anopheles mosquitoes as vectors. Of the six Plasmodium species that infect humans, Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium knowlesi, and Plasmodium cynomolgi, Plasmodium falciparum is the most virulent and most prevalent species in Africa and the main contributor to malaria mortality.

Plasmodium spp [1] has a complex life cycle involving both the mosquito vector (sexual phase) and the human host (asexual phase). Transmission begins when an infected Anopheles mosquito releases sporozoites while biting and withdrawing blood from a human [3]. The sporozoites enter the liver cells and mature into hepatic merozoites, which eventually rupture, enter the bloodstream, and infect red blood cells (RBCs). Some of the merozoites mature into reproductive gametocytes within the blood. If another mosquito bites an infected person, the gametocytes enter the insect gut, mate, and further develop into transmissible sporozoites in the mosquito salivary glands [2]. The symptoms of the disease occur in the asexual blood stages and include chills and fever.

The main drug targets are therefore found either in the intra-erythrocytic parasite or in the metabolic pathways active in the parasite during this life-cycle stage [1, 2, 3].

Epidemiology of Malaria

Malaria remains a major health burden in many endemic regions around the world, particularly in the most impoverished areas of Africa and Asia, where life expectancy is low and health services are limited [3]. Malaria causes more than a million deaths each year, with 40% of the world's population at risk and greater than 500 million clinical cases annually [3]. Plasmodium falciparum is the major cause of malaria morbidity and mortality in Sub-Saharan Africa and is responsible for 2.7 million African deaths each year. In other parts of the world, such as South America and Asia, P. vivax, P. ovale, and P. malariae also cause substantial morbidity [5]. All species of malaria parasite can cause severe disease, particularly in children, when anaemia develops, and in pregnant women when the parasite infects the placenta. The burden of malaria may be underestimated, given that malaria infections are substantially associated with low birthweight and childhood cognitive impairment. Malaria transmission dynamics are governed by fluctuations in varied vector population densities, which can vary geographically [3].

Life Cycle of Plasmodium

Malaria remains a global burden that poses a risk to over 40% of the world's population and continues to claim over a million lives annually [5]. The disease is caused by protozoan parasites of the genus Plasmodium; of these, Plasmodium falciparum exerts the greatest toll. The life cycle of the parasite alternates between female Anopheles mosquitoes and vertebrate hosts. During a blood meal, an infective mosquito inoculates sporozoites into the skin of the vertebrate host [5]. The sporozoites migrate to the liver, where they invade hepatocytes and multiply asexually, producing thousands of merozoites. Merozoites then burst from hepatocytes, invade erythrocytes, and continue to multiply, resulting in the clinical manifestations of malaria. Some parasites differentiate into sexual blood stages, which are taken up by mosquitoes during a blood meal [4]. Within the mosquito, they develop into gametes, and sexual recombination occurs before invasion of the midgut wall. Developments from this stage eventually culminate in the production of sporozoites, which migrate to the salivary glands and restart the cycle by invading a new vertebrate host [4].

Antimalarial Drugs

The use of antimalarial drugs to prevent and treat malaria is a critical control and elimination strategy [2]. The main historical steps in the development of antimalarial drugs include the discovery of quinine, the introduction of chloroquine, and more recent developments involving antifolate drugs, atovaquone-proguanil, and artemisinin-based combination therapies (ACTs)[1]. Quinine controls the acute symptoms of malaria by killing Plasmodium parasites during the erythrocytic stage of the life cycle. Chloroquine, a synthetic derivative of quinine, affects the synthesis of hemozoin and the pyrimidine biosynthesis pathway. Although still widely used, chloroquine is no longer an effective treatment in many parts of the world owing to the development of drug resistance [5]. Other antimalarial drugs are based on sulphadoxine, pyrimethamine, atovaquone, and artemisinin [1, 2, 5].

History of Antimalarial Drug Development

The history of antimalarial drugs is extensive, spanning nearly a millennium. Quinine, derived from the bark of the cinchona tree, was the first drug with demonstrable activity against malaria and was used extensively throughout the eighteenth and nineteenth centuries before the identification and synthesis of other useful agents in the twentieth century [3]. Among the numerous drugs in widespread use or clinical trials today, only chloroquine, artemisinin, and related derivatives are broadly effective against the most lethal of human malarias, Plasmodium falciparum [1]. With the exception of the formulations derived from artesunate, these drugs act by inhibiting polymerization of ferriprotoporphyrin IX, a toxic byproduct of the parasite's digestion of the host hemoglobin. Artemisinin and its derivatives are used almost exclusively in combination therapies, such as artemether/lumefantrine or artesunate/sulfadoxine-pyrimethamine [6].

Current Antimalarial Treatments

Antimalarial drugs remain the cornerstone of global malaria control and elimination efforts [1]. The recent deployment of artemisinin-based combination therapies (ACTs) contributed to significant reductions in malaria burden over the past decade. However, the emergence and spread of artemisinin-resistant parasites in Southeast Asia, coupled with declining sensitivities to partner drugs, raise concerns about the sustainability of current treatment programs [1, 4]. Monitoring antimalarial efficacy and understanding resistance mechanisms through clinical studies, ex vivo or in vitro assays, and analyses of parasite polymorphisms are therefore critical to assess therapy effectiveness, anticipate the emergence of resistance to new agents, and guide policy decisions [1]. Chloroquine dominated malaria treatment from the 1950s until the 1980s. Its efficacy against Plasmodium falciparum malaria was superseded in the 1990s by sulfadoxine-pyrimethamine (SP). Systematic emergence of SP resistance along the Thai–Cambodia and Thai–Myanmar borders curtailed its utility by the turn of the 21st century. The introduction of ACTs in the early 2000s enabled a program of malaria elimination throughout the

Greater Mekong Subregion (GMS). However, the appearance of artemisinin resistance on the Thai–Cambodian border in 2008 led to rapid spread across the GMS. By 2013, nearly all malaria parasites in the region exhibited resistance to artemisinins and one or more partner drugs [4]. The progression of therapeutic options over five decades establishes the link between declining drug sensitivity and the subsequent replacement of the first-line agent. The current picture of malaria epidemiology showing the geographical extent of antimalarial drug resistance within the GMS betrays a serious threat to global malaria elimination endeavours [4]. The first detailed documentation of artemisinin resistance in Plasmodium falciparum malaria underscores the urgency of monitoring. Only concerted international efforts can safeguard the utility of highly effective antimalarials, preventing an unmanageable resurgence of malaria mortality and morbidity worldwide [4].

Mechanisms of Drug Action

Antimalarials act via several biochemical mechanisms, frequently targeting the Plasmodium digestive vacuole (DV) within the asexual blood stage parasite, where hemoglobin digestion takes place [3]. Hemoglobin is sequentially broken down into amino acids by different proteases, including aspartyl proteases (plasmepsins), cysteine proteases (falcipains), and metalloproteases (falcilysins) [4]. This degradation releases free heme, which is subsequently detoxified. Each step in the hemoglobin degradation pathway presents a potential target for antimalarial drugs. The key groups of compounds and their modes of action include several families of 8-aminoquinolines, amino-alcohols, aryl-amino alcohol compounds, 4-aminoquinolines, antifolate compounds, hydroxynaphtoquinone, sesquiterpenic lactone endoperoxides (peroxides), and antibiotics. The sites of anti-malarial drug action are associated with different cellular locations within the Plasmodium parasite, with a central focus on the DV [2]. A number of commercial drugs have exerted enormous pressure on the malaria parasites, selecting resistant organisms via several mechanisms of anti-malarial drug resistance [7]. Altered drug transport systems represent the most important mechanism of resistance, often through genetic alterations of ABC (ATP-binding cassette) transporter proteins. Alternatively, point mutations within the drug target enzymes decrease drug binding affinity without necessarily altering overall protein structure. Downregulation of enzymes involved in prodrug activation also contributes to the resistance phenomenon. The development of clinical resistance to antimalarial drugs during the 20th century corresponds, at least in part, to these established modes of drug action and the resulting selection for Plasmodium mutants [6].

Target Sites of Antimalarial Drugs

Malaria remains one of the major global diseases, especially in tropical underdeveloped countries. The Plasmodium species that infect humans are P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi. P. falciparum is the deadliest and most prevalent species worldwide, mainly distributed in sub-Saharan African countries. P. vivax is generally distributed in Latin America and countries of the Indian subcontinent and Southeast Asia [3]. The vector parasite interaction cycle begins with the introduction of the sporozoite into the human skin by the bite of an infected female Anopheles mosquito [2, 5]. The sporozoites first travel to liver cells, where they undergo replication and maturation into thousands of merozoites within the parasitophorous vacuole, initiating the hepatic stage [1]. In the 1940s, quinine was the only antimalarial drug used for the treatment of malaria. In the 1950s, chloroquine was introduced, but because of the emergence of drug-resistant Plasmodium strains, it was replaced by sulfadoxine-pyrimethamine, mefloquine, and lumefantrine. Currently, artemisinin combination therapies are the first-line drugs prescribed for the treatment of malaria [4]. These drugs bind to plasmodial proteins or compartments and consequently inhibit various metabolic and developmental pathways. For example, chloroquine is a blood schizonticidal agent and acts by blocking heme polymerization; atovaquone inhibits electron transport at the cytochrome bc1 complex in the mitochondrial membrane; antifolates, such as pyrimethamine and proguanil, target folic acid metabolism; artemisinin causes damage to the endoplasmic reticulum membrane [1, 2].

Biochemical Pathways Affected

Plasmodium falciparum resistance to antimalarial treatment is a pernicious and complex global health problem. Artemisinin-based combination therapy (ACT) is currently the front-line treatment for malaria worldwide, yet resistant parasites are steadily spreading throughout the Greater Mekong subregion, and the parasite has developed high-grade resistance to all widely used partner drugs in some settings [1]. The best hopes for achieving the elimination of malaria thus lie in curtailing the further dissemination of P. falciparum drug resistance and in mitigating the evolutionary paths by which it arises [2]. There is an urgent need to understand how artemisinin, its ACT partners, and candidate next-generation antimalarials kill P. falciparum, as well as to identify common pathways to resistance. Here, we collate emerging evidence in support of an integrated three-stage model for the asexual blood-stage growth of artemisinin-resistant parasites [2].

Emergence of Drug Resistance

Early drug treatments aided in World War II and encouraged exploration of other drugs to combat the problem. As Michael Chew's investigation showed [1], resistance appeared shortly after the launch of these drugs, although this may be exaggerated by the slow effect of malaria infections and the performance of these drugs at the outset. Chloroquine has been piggybacked onto other strategies in past decades because of its many beneficial properties, but repetitive use of chloroquine placed selective pressure on resistant parasites [1, 4]. This also held true for other antimalarial drugs, which range from natural products to synthetic compounds. Antimalarial drug resistance will likely continue to increase until new classes of effective drugs become widely available; however, these developments often take decades to reach implementation [4].

Historical Perspectives

Understanding the historical emergence of drug resistance in Plasmodium falciparum contributes valuable insights to the development of strategies for malaria control and eradication. Evidence for antimalarial drug resistance can be classified into three groups: clinical reports, in vitro assays, and molecular markers[1, 3]. Together, these provide an important baseline for control efforts. Key routes for introduction of new drugs involve: (i) new generations of classic antimalarial drugs, such as new-generation quinolines, and (ii) compounds with novel mechanisms of action, such as atovaquone [4]. The development of resistance in Plasmodium species was the inevitable consequence of chemotherapy, with early reports emerging during the 1960s. The parasite was several decades ahead of medical research [7]. Resistance to chloroquine and, later, to other drugs occurred quite rapidly. The origins of chloroquine resistance have been traced to Southeast Asia and South America in the late 1950s and early 1960s. Historical records of drug resistance in malaria parasites clearly demonstrate that Plasmodium falciparum is capable of developing resistance to chloroquine, antifolate drugs, resistance developed rapidly (10 years), and artemisinin and combination therapy [8].

Factors Contributing to Resistance

Several factors contribute to the emergence of drug resistance, including the presence of a drug-resistance mechanism within the parasite, spread of the resistant line of Plasmodium spp., suboptimal dosing, lack of effective drug concentrations following treatment, and the presence of continuous drug pressure [1]. Various mechanisms have evolved in Plasmodium to detoxify antimalarials and their metabolites [9]. The spread of a particular clone that has an inbuilt mechanism of resistance causes an outbreak of resistant malaria. Prescriptions of inadequate doses, which are unable to clear the parasites completely, lead to the emergence of resistance. Sub-therapeutic levels maintained in the blood for a long time may also be a contributory factor to the course of treatment. In 1889, Charles Laveran was the first to describe the presence of a parasite in the red blood cells [2]. In the same year, P. falciparum was identified by Golgi as the causative agent of malignant tertian malaria. Between the years 1934 and 1937, the related clinical symptoms of the disease were identified as being caused by P. vivax, P. ovale, and P. malariae. Plasmodium is an intracellular parasite, residing primarily inside the hepatocytes in the liver and in erythrocytes of the host. The parasite needs to pass through its complex life cycle, which involves sexual propagation in the female Anopheles mosquito (vector) and asexual propagation in the human host [4]. The disease progresses through two different phases in the human host. The primary stage (pre-erythrocytic phase) of infection occurs inside the hepatocytes, the liver cells, and the secondary stage (erythrocytic phase), inside the red cells. The pre-erythrocytic schizont produces many merozoites, which rupture after maturation, releasing the merozoites into the bloodstream. Merozoites immediately parasitize the erythrocytes and cause the clinical symptoms of malaria. In addition, a small number of pre-erythrocytic forms, designated as hypnozoites, remain in the host liver cells in P. vivax and P. falciparum infections [5].

Types of Drug Resistance

Chloroquine resistance was first reported in the late 1950s, towards the end of the 10-year malaria eradication program. Different factors contribute to the emergence of antimalarial drug resistance [2,3]. Importantly, the mechanism of antimalarial drug resistance depends on the mode of action of the drug on the parasite. Although artemisinin resistance in P falciparum malaria is not fully understood, it has been associated with mutations in the propeller domain of the Kelch-13 (K13) protein, which emerged on a de novo basis in Southeast Asia. Resistance to chloroquine currently exists in almost all P. falciparum malaria-endemic regions, with particular hot spots in areas of Southeast Asia and South America. The map illustrates the presence or absence of artesunate plus mefloquine resistance in the Greater Mekong Subregion. Antimalarial drug resistance serves as a crucial indicator of the efficacy of current therapeutic options and acts as an early warning system [2]. The evolution and spread of drug-resistant strains create significant obstacles and threaten malaria elimination programs. In many nations, the economic consequences of malaria, including hospital treatment and care costs, have made controlling the disease particularly challenging. Consequently, it is of paramount importance to regulate and implement appropriate policies based on this information [8, 9].

Resistance to Chloroquine

Chloroquine (CQ) was the mainstay of antimalarial therapy for decades. Initially, an effective and safe drug, resistant Plasmodium falciparum strains emerged in Thailand and Malaysia in the late 1950s and subsequently spread to most malaria-endemic countries, including India, beginning in 1973 [7,8]. In certain regions, such as Malawi and Gabon, the high-frequency presence of chloroquine-resistant genotypes has persisted for years following the drug's withdrawal from use [8]. A number of methods have been developed to assess in vitro sensitivity of P. falciparum to chloroquine. These include measurement of parasite growth inhibition via quantification of schizont maturation, incorporation of radiolabeled 3H-hypoxanthine, detection of parasite pLDH enzymatic activity, and evaluation of schizont maturation within red blood cells. The World Health Organization (WHO)-recommended micro-technique is based on the determination of CQ concentrations that inhibit schizont maturation; this method can be efficiently implemented in laboratories situated in areas exhibiting high levels of chloroquine resistance [7, 8].

Resistance to Artemisinin

The ACT combines artemisinins, which act rapidly but have short half-lives, with longer-acting partner drugs to eliminate remaining parasites [9, 10]. To prevent resistance development, artemisinins have been recommended in combined regimens for uncomplicated malaria. A 2005 WHO report warned against artemisinin resistance, and the following year recommended eliminating monotherapy. Impaired parasite responses to artemisinin have been recognized as a significant concern [9].

Resistance to Other Antimalarials

Resistance also emerged during the introduction of antifolates, and eventually all classes of antimalarial drugs proved vulnerable to it. More recent evidence indicates a geographical correlation between resistance to multiple antimalarial drugs and the emergence of resistance to artemisinin [6]. As a result of artemisinin resistance in the Greater Mekong Subregion, resistance to the combination partner drugs used in ACTs also emerged in this region, severely impacting the efficacy of ACTs and jeopardizing treatment options in this region. The descriptions of the resistance mechanisms that follow are synthesized from published evidence using the search strategy and selection criteria detailed in the overview [6, 2].

Geographical Distribution of Resistance

The distribution of antimalarial drug resistance exhibits marked spatial heterogeneity [11]. Sulfadoxine-pyrimethamine (SP) resistance was observed at detectable levels in all national trend series analyzed. National point estimates for childhood infection prevalence in 2010 signify that resistance remained highly prevalent in countries of East and Central Africa [10]. The Central African Republic and Equatorial Guinea appeared to lack significant SP resistance, whereas the absence of pertinent surveys precluded estimation in a few additional countries. Further projections, based on posterior draws and inputs of malaria endemicity in 2018, corroborate that SP resistance maintains a widespread presence throughout the sub-Saharan region [10, 11].

Regions Affected by Resistance

Data from various research and surveillance initiatives illustrate the extent of malaria drug resistance in different regions [11, 12]. Chloroquine resistance is present in much of Southeast Asia, and parts of South America and Africa, while artemisinin resistance is firmly established in the Greater Mekong Subregion (GMS) of Southeast Asia but remains unconfirmed in other parts of the world except for isolated cases in Guyana [10]. In Africa, resistance to sulfadoxine-pyrimethamine along the whole east and west coasts reached multiple national historical maxima in 2015–20. Continued surveillance of resistance is critical to ensure that drug policies remain effective and to detect resistant strains when they first emerge so that they may be contained [11].

Case Studies from Endemic Areas

The genesis of drug resistance is the failure to eliminate a single Plasmodium cell that harbors a mutant gene conferring a replicative advantage in the presence of the antimalarial drug [3]. This initial recrudescent event yields a little-studied resistance genotype that is poised to proliferate within the patient, the community, and the region. Statistical analyses performed on databases of malaria clinical trials enable the diversification, quantification, and regionalization of known resistance genotypes [3]. Intensively drug-treated patients in the Asia–Pacific region present a set of resistance genotypes that differs conspicuously from those exhibited by patients in Africa, highlighting the need to define the most efficient antimalarial therapy in specific endemic regions instead of assuming that a single regimen can be successfully deployed worldwide [3].

Impact of Drug Resistance

Reduced drug efficacy in malaria therapy increases morbidity and mortality and imposes substantial costs on health systems and affected households [1]. Quantity-and productivity-adjusted losses from malaria case management reach US$1.1 billion annually in Africa alone [4]. The indicated figures do not take into account the high cost of second-line, more effective treatments or the potential for additional outbreaks of resistant parasites.

Continued drug resistance threatens to jeopardize past gains in malaria control and presents an urgent call to strengthen existing monitoring and surveillance strategies, which underpin effective containment efforts [1, 4].

Public Health Implications

Antimalarial drug resistance poses a serious global threat to malaria control efforts and economic development [10]. The ongoing emergence and spread of drug resistance compromise treatment efficacy and can lead to increases in malaria mortality, socioeconomic hardship, and political instability [11]. Reliable methods for characterizing and quantifying resistance are therefore essential tools for public health officials and policy makers. Methods to monitor resistance along a spectrum of severity include quantifying parasitemia, measuring the fraction of parasite clearance, and dose-inhibition experiments [12]. Discarding parasite isolates on an individual basis has led to the collection of thousands of ex vivo isolates, which can be used to assess spatiotemporal variation in resistance. In the absence of dose-inhibition experiments, information about the mechanisms and pathways associated with resistance may still be retrieved from genome scans by analyzing parasite populations subjected to different levels of drug pressure [11, 12]. The insight provided by dose-inhibition experiments and genome-wide analyses on the mode of action of antimalarial drugs can also help identify novel candidate genetic markers to predict and track the future spread of resistance.

Economic Consequences

The economic consequences of resistance to antimalarial drugs create a substantial impediment to social and economic development at local, national, and regional scales and contribute to poverty and underdevelopment in afflicted countries [1, 9]. Malaria is already associated with untold human and economic losses 4. In an average year, approximately 300 million people suffer an acute form of the disease, 150–300 million suffer from chronic repercussions, and approximately 1.7–2.7 million fatalities have been attributed to malaria since 1996. Malaria can be both a consequence and a cause of poverty. Poor people tend to be less able to protect themselves and less able to afford treatment. Conversely, the economic and social consequences of malaria tend to perpetuate and deepen poverty and underdevelopment [3]. Malaria has strong and negative effects on both economic growth and poverty. Whereas widespread poverty probably contributes to the dissemination of malaria, the disease itself tends to perpetuate poverty. Analyses conducted at national levels show that lightly affected countries have experienced slightly higher growth rates than intensively affected countries [21]. Common diseases can sometimes have a bigger economic impact on poverty and development because of their incapacitating but nonfatal nature [8].

Monitoring and Surveillance

Methods for monitoring the emergence and spread of antimalarial drug resistance include mapping clinical treatment efficacy, evaluating ex vivo and in vitro drug susceptibility, and tracking molecular markers of resistance. The Worldwide Antimalarial Resistance Network (WWARN) aggregates available data sets from diverse geographical regions to enhance understanding of resistance patterns [13]. Sustained surveillance, aligned with ongoing deployment of new compounds, is required to anticipate and respond to emerging resistance and to guide corresponding adjustments in treatment policies. The ongoing effectiveness of antimalarial treatments depends on early detection of drug resistance and timely changes in therapeutic strategies [14]. Variations in the scale, coverage, quality, and accessibility of interventions, coupled with heterogeneous levels of human population immunity, considerably influence local selection pressures and the emergence of drug resistance. The continued efficacy of artemisinin-based combination therapy is increasingly threatened by emerging resistance in many regions. Integrating enhanced surveillance with research and development of innovative agents, vaccines, and vector-control methods is imperative for the eventual eradication of malaria [13, 14].

Methods for Tracking Resistance

Clinical and in vitro drug efficacy studies have proven invaluable in monitoring the progression of resistance. Areas with emerging drug resistance are first identified through clinical efficacy trials of antimalarials. These studies evaluate the drug's ability to clear parasitemia rapidly and prevent recrudescence, both of which are indicative of resistance [13, 14]. In vitro susceptibility assays are employed to evaluate the sensitivity of the parasite to various antimalarial drugs across different geographical regions [12]. Such assays offer the advantage of using considerable quantities of the drug and testing its effects on various life stages of the parasite, particularly the blood stages. However, the time-consuming nature and high costs of these assays have limited their application in routine surveillance [10, 17]. Nevertheless, in vitro studies are particularly useful in analyzing the parasite's susceptibility to new antimalarial compounds before they are subjected to clinical trials. Postclinical era monitoring demands the integration of various surveillance methods, including pharmacovigilance, pharmacokinetics, and clinical efficacy, in vitro/ex vivo testing, and molecular markers of drug resistance. Network organizations like the Worldwide Antimalarial Resistance Network (WWARN) provide free and interactive web-based platforms that display epidemiological maps of up-to-date resistance scenarios for both Plasmodium falciparum and P. vivax. Monitoring the status and development of resistance not only aids in the

formulation of policies to control malaria but also fosters a deeper investigation into the underlying causes of resistance and the search for novel antimalarials. Detecting early emergence of resistance can prompt effective preventive strategies and enhance the efficiency of existing drugs involved in malaria control [15, 18].

Global Surveillance Networks

As resistance to artemisinin has spread from Southeast Asia to sub-Saharan Africa, it has become imperative to monitor its development across the continents where malaria is endemic [14]. In addition to the strategies that have traditionally been used to track the evolution of drug efficacy and perturbations in parasitological profiles, several global networks that routinely collect and analyse resistance-related information have been established [15]. These groups provide an important resource for the rapid dissemination of knowledge that can support policy revision and development [14]. The Worldwide Antimalarial Resistance Network, for example, aggregates circulating data on clinical response, molecular markers, and in vitro drug-susceptibility profiles that can be accessed in the form of searchable databases. The network also provides recommended protocols for the investigation of resistance at a range of epidemiological scales [15]. Comparable international initiatives that seek to improve data-sharing platforms can be found at various geographic levels. The summary that follows highlights their scope and status.

Strategies to Combat Resistance

A major challenge in controlling malaria is the increasing resistance of Plasmodium parasites to antimalarial drugs, which has often been a reaction to the active pharmaceutical ingredients of those drugs. Hence, the development of new drugs is the paramount aim of modern antimalarial drug research [1, 14]. Another important activity in this field is the study of the Plasmodium genome, which might lead to the definition of new drug target groups that have control over the respective stage in the parasite cycle. In addition, the development of an antimalarial vaccine would be the ultimate prevail against malaria [1, 15]. Malaria is preventable by vaccines, although no vaccine has been made commercially available for human use. Patients should be treated with appropriate antimalarial drugs and should complete the course of treatment. Several types of drug therapy are available [10]. The World Health Organization recommends combination therapy treatment using more than one drug at the same time for malaria. The use of more than one drug kills more parasites, reduces treatment time, and lowers the chances of developing drug resistance [16].

Development of New Drugs

New antimalarial drugs are presently under development. Efforts focus on combating resistance and improving treatment protocols [16]. The World Health Organization (WHO) emphasizes the importance of developing new medications and calls for discontinuing single-drug artemisinin treatments because of resistance concerns. Research and guidelines undergo continuous updates to enhance malaria control and treatment strategies [15]. For example, in a phase II dosing study of cipargamin monotherapy, about two-thirds of patients who experienced recrudescence carried a mutation in PfATP4. To model resistance risk, stakeholders have established an in vitro minimum inoculum of resistance plus a resistance threshold. All compounds tested that selectively inhibit a parasite target can generate some level of resistance in vitro within 60 days. Consequently, novel antimalarial therapies are expected to be developed as combination treatments to minimize resistance risk [17]. The spread of Plasmodium falciparum resistance highlights the need for drugs with novel modes of action. Natural product–driven malaria drug discovery faces challenges such as reliable access, variable supply, and mixture complexity, and recent high-throughput screens have failed to identify high-quality hits. Most new antimalarial drugs are discovered via phenotypic and target-based screening of small synthetic molecules. In phenotypic screening, large libraries are tested against cultured parasites to determine their in vitro activity [16, 17].

Combination Therapy Approaches

Monotherapy with antimalarial drugs is often considered suboptimal, as the parasite can easily develop resistance mutations and be selected against the administered drug. Advancements in the understanding of mechanisms of action, the development of techniques determining the pharmacological activity of drugs, and the acquisition of clinical experience concerning the mechanisms and time frames for resistance development have led to an increasing use of combination therapy in malaria [16]. Specific advantages include synergistic or additive effects, a reduction in the transmission rate of malaria, a reduction in the overall use of drugs, and potential benefits in terms of re-expansion of the susceptible parasite population [17]. However, there exist important disadvantages; these include the fact that some combinations of drugs exacerbate adverse effects, that the use of multiple drugs is more costly, and that certain combinations require different modes of administration and cannot be given to certain populations. Novel approaches, such as hybrid molecules, have also been studied but have yet to reach the market. Hybrid molecules consist of two different groups of compounds bound by a linker, combining two different pharmacophores into a single molecule [18].

Vaccination Efforts

"Vaccination Efforts." The success of a malaria vaccine could transform control efforts. A wide pipeline of vaccine candidates is under evaluation, and the World Health Organization (WHO) recommends the phase 3 RTS, S/AS01 vaccine for infants and children in areas of moderate-to-high transmission [18]. "Weighing the Risks" Until the last century, all antimalarial drugs were single compounds acquired through chemical synthesis, extraction from medicinal plants, or fermentation of natural products. Many of these attacks involve detoxification, a pathway specific to Plasmodium and other blood-feeding protozoa. A limited number of these compounds is currently available, many of which were first discovered over 50 years ago [4].

Future Directions in Research

The emergence of resistance to antimalarial drugs continues to threaten malaria control and eradication programmes worldwide. Strategies to combat resistance include the development of new drugs and more effective combinations against multiple targets, the development of a vaccine, improved monitoring and surveillance, and better management of the supply and use of antimalarial drugs [11, 1]. Newly identified molecular targets may aid the development of new antimalarial therapies, but few have yet led to new treatments. Advances in understanding biochemical functions of key metabolic pathways in the parasite and the molecular basis of resistance enable new approaches for designing inhibitors of essential enzymes and for developing agents specific for resistant parasites. The emergence and spread of artemisinin resistance has resurrected older antimalarial drugs in some places and created demand for new combinations. The emergence and spread of artemisinin resistance in Southeast Asia has sparked renewed interest in the study of Plasmodium genomics [1]. Studies of parasite genome-wide variation provide data of sufficient resolution to compare epidemiological trends of movement and selection in human and parasite populations and to reveal and monitor shapes of parasite population structure that affect the spread of resistance. These approaches promise to provide scientifically objective metrics to guide policy and control and elimination programmes. Maintaining and strengthening the commitment to malaria elimination and sustained budgeting of these programmes remains a profound challenge [19]. Meanwhile, drug resistance continues to evolve and spread with remarkable ability, even under conditions of weakened selection. Accordingly, the development of more sustainable outlooks, working upstream of mechanistic understanding of resistance with complementary approaches to guide the use of drugs currently and to shape the drugs of the future when they emerge, remains a priority focus of malaria transmission and resistance research [19, 1].

Innovative Approaches to Drug Development

The development of novel antimalarial agents has involved exploring natural products, large compound libraries, artemisinin derivatives, anticancer agents, and established drugs from other indications [17]. Effective new agents differ from existing drugs, exhibit efficacy against artemisinin-resistant parasites, reduce transmission, and display low propensity for resistance. Compounds with transmission-blocking activity combined with therapeutic potential are of interest in curing both malaria and transmission dynamics [17]. In a phase II dosing study of cipargamin monotherapy, approximately two-thirds of patients who experienced recrudescence carried a G358S mutation in PfATP4, implying selection of this resistance variant. Over the past five years, data on new target proposals, identification of new chemical classes active against parasite proliferation, and a fresh understanding of Plasmodium biology have created an unparalleled research environment. New antimalarial therapies are expected to be deployed as combination treatments to minimize resistance risk [17].

Genomic Studies on Plasmodium

Advanced whole-genome sequencing technologies provide valuable information about the genetic structure of the various malaria parasite populations [20]. The sequencing of multiple parasite genomes is a critical step toward the development of new drugs and vaccines, as it allows one to scan the entire genome and identify potential new antigens and drug targets [20]. Whole-genome sequencing studies have aided in the identification of molecular markers and better characterization of certain target genes across geographical regions and malaria parasite populations, enabling a deeper understanding of the genetic basis of drug resistance. Genome-wide in vitro analysis has been used to identify potential genetic markers and better characterize certain target genes. In addition, studies based on whole-genome sequencing of laboratory and clinical isolates can help to understand the population genetics of Plasmodium falciparum better [20].

Policy Recommendations

The fight against antimalarial drug resistance requires strengthened national health-care systems that solicit the needs and perspectives of local communities, enforced through sufficient financial and human resources, mechanisms for accountability, and strong political will. International collaboration facilitates partnership and can help in case of local shortcomings [4].

Strengthening Health Systems

Effective antimalarial drug policy depends on political commitment and sustained funding to enable an appropriate regulatory framework. Health systems influence the accessibility, affordability, availability, and acceptability of antimalarials to populations that need them. Insufficient availability and quality of treatment can increase the risk of drug resistance developing [10]. The capacity to operate comprehensive therapeutic efficacy studies, with a quality-assured system to monitor drug resistance in vivo, is integral to national treatment policy implementation. High-quality laboratory and investigative infrastructure are needed to monitor the most informative molecular markers of resistance [14]. Actively engaged health systems, with mechanisms to monitor the efficacy of existing drugs, protected supply of quality-assured antimalarials, systems to regulate inappropriate treatment, and programmes to promote and monitor adherence, are best positioned to contain resistant parasites [10]. Reporting of drug efficacy and molecular surveillance data to the WHO ensures their proper application in evidence-based treatment guidelines. Considerable emphasis has been placed on increasing the accessibility, availability, and affordability of artemisinin-combination therapy since the pre-qualification of these medicines by the WHO. Ongoing efforts point to the need for continued focus on improving the effectiveness of ACTs in resource-limited and vulnerable communities, in the context of service delivery strategies that motivate practitioner adherence [11]. Strengthening national and global health systems is needed to address the spread of P. falciparum resistant to antimalarial drugs [10, 11, 14].

International Collaboration

International collaboration to address antimalarial drug resistance has been inadequate. Much more international coordination and cooperation are essential to facilitate the rapid exchange of study plans, epidemiological and molecular data, parasite materials, and drugs to further prepare for an aggressive global response that quickly curtails the spread of the new resistance threat before it becomes an intractable problem [15]. The sharing of protocols to standardize the collection of data and samples can improve coordination and cooperation among the many ongoing research efforts, facilitate the adoption of new approaches, and enhance quality control of research methods to prevent 'false alarms' [10]. The International Centers of Excellence for Malaria Research (ICEMR) network is actively contributing to the monitoring of drug efficacy and to studies addressing the emergence of resistance. Together, clinical and laboratory studies (ex vivo/in vitro drug assays, level of parasitaemia and parasite clearance, and characterization of molecular markers of drug resistance) provide comprehensive assessments of the effectiveness of antimalarial therapies, the ability to predict the emergence of resistance, and the means to design the timely formulation of appropriate local drug policies [1]. Synthesis of the worldwide antimalarial efficacy data, including information from published and unpublished clinical studies, can provide a more comprehensive view of temporal and geographical patterns of the evolution of drug resistance and the evidence needed to anticipate geographical movements [15].

Ethical Considerations

Public health threats, such as the continued evolution and spread of antimicrobial resistance, also give rise to distinct ethical challenges at the international, national, and local levels [22]. Ensuring equitable access to treatment and containment technologies and to the research and development of new, effective, affordable tools is an ethical responsibility. Current priorities to address malaria drug resistance include universal availability of diagnostic support, targeted, locally effective treatments before multi-resistant strains emerge, and increased research and development of new antimalarials. Universal access to these resources would not only address prevailing injustices but also help prevent future harms upstream [21]. Several malaria control strategies, such as long-lasting insecticidal nets, prompt access to diagnosis and treatment, mass drug administrations, mass screenings and treatment, and the use of primaquine or tafenoquine, pose additional ethical issues, which require careful balancing of public health goals and respect for individual liberties. Screening to exclude asymptomatic carriers from non-endemic areas aims primarily to benefit the individual through treatment and to prevent outbreaks of malaria, so restricting individual liberty thus appears well justified if the conditions for such screening (e.g., local absence of malaria, local vulnerability, and an acceptable screening test) are met. Screening may be an important component in preventing the spread of artemisinin combination therapy (ACT) resistance, as evidenced by the screening of Cambodian peacekeeping troops before deployment to Africa [21]. A clear ethical framework should guide decision-making about screening programs. It should clarify why testing is chosen over other approaches and set limits to ensure screening does not create unnecessary burdens, such as undue restrictions on migrants' choices, discrimination, or stigma for individuals who test positive or other disadvantages for groups coming from high-prevalence areas [22]. The circumstances in which a mass drug administration might be cost-effective and beneficial to eradication have not yet been clearly defined. Notwithstanding that triple ACTs might eventually become attractive in Africa, the primary objective in deploying these new therapies in the foreseeable future should remain slowing down the increasing emergence of resistance to ACTs [21, 22].

Access to Treatment

Treatment of symptomatic malaria became a routine component of the clinical and public health response following the Second World War. Access to treatment varies greatly by country, with the lowest levels reported in African countries [2]. Antimalarial drugs eventually generated resistance that led to their removal from use; for example, chloroquine, sulfadoxine-pyrimethamine, and mefloquine have all been removed for this reason. Managing resistance represents a critical component of the control effort because of its potential to induce treatment failure [21]. Distributing multiple first-line therapies (MFT) simultaneously in the population remains a key strategy to manage resistance for uncomplicated falciparum malaria. MFT can maintain high treatment levels while simultaneously lowering the selection pressure that renders monotherapies ineffective [20]. Although implementing such a strategy requires careful design, it is widely recognized as preferable in many endemic settings because of its ability to curtail resistance emergence. MFT has proved feasible in practice, but even in contexts of apparent success, it remains prudent to proceed with caution and to await further analyses [2].

Research Ethics in Malaria Studies

Ethical considerations form a critical component of antimalarial research and efforts to control drug resistance. Ensuring proper ethical review and adherence to guidelines protects participants and secures reliable results that support malaria control and public health [3]. Challenges posed by resistance call for transparent and responsible research practices. Assessment of parasite survival in the field informs the fitness of resistant variants and associated risk factors at the population level, but such analyses remain challenging [3]. Filling this knowledge gap is essential, as the fitness of resistant and sensitive parasites is shaped by contrasting ecological environments [3]. The International Centers of Excellence for Malaria Research (ICEMR) provide an opportunity to establish a concerted evidence base based on data sets comprising a broad spectrum of ecological settings in Africa, South America, and Asia [22]. Variation in the interplay between drug resistance and fitness originates from the contrasting epidemiological, immunological, and ecological differences influencing each site [1]. Factors including drug selection pressure, herd immunity, and transmission intensity affect the in-host competition and outcome of mixed infections and contribute to the differential fitness of resistant and sensitive parasites in the wild. Vector control strategies may modify the transmission setting and further impact the prevalence of resistant infections. Detailed comparison of multiple data sets will foster the identification of common patterns, which will guide the formulation of appropriate strategies to contain resistance on a global scale [1, 3]

CONCLUSION

The evolution and spread of antimalarial drug resistance remain one of the greatest obstacles to global malaria control and elimination. From chloroquine and sulfadoxine-pyrimethamine to the current threat of artemisinin resistance, the parasite has consistently demonstrated its ability to adapt under selective drug pressure. Evidence shows that resistance arises through a complex interplay of genetic mutations, altered biochemical pathways, and programmatic factors such as suboptimal dosing and widespread drug pressure. While ACTs remain effective in many regions, declining efficacy in Southeast Asia underscores the urgent need for continuous molecular surveillance, the development of novel therapeutic agents, and integration with non-pharmaceutical interventions such as vector control and vaccines. Strengthening health systems, improving access to effective treatments, and fostering international collaboration will be critical to prevent a resurgence in malaria morbidity and mortality. Safeguarding antimalarial efficacy is not only a scientific and medical challenge but also a public health imperative for achieving long-term malaria elimination.

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