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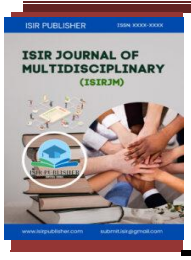

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ANTI MALARIAL DRUG RESISTANCE: A MAJOR THREAT IN COMBATTING MALARIA

By

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Abstract

Antimalarial drug resistance remains a critical threat to global malaria control, with profound implications for public health and economic stability in endemic regions such as Nigeria. Resistance to first-line antimalarial, compromises efforts to reduce malaria-related morbidity and mortality. Nigeria, bearing one of the highest global malaria burdens, faces significant challenges as resistance exacerbates healthcare costs and strains limited resources. This paper examines the threat posed by antimalarial drug resistance in Nigeria and beyond, including its impact on treatment efficacy, increased disease burden, and long-term economic consequences. Higher treatment costs, prolonged illness, and reduced productivity, the socio-economic toll on communities is substantial. Therefore there is need to strengthened surveillance systems, effective drug policies, and investment in research and development of novel antimalarial and also vaccines.

Keywords:. *Malaria, Plasmodium falciparum, Antimalarial drugs, Drug failure, Resistance,*

INTRODUCTION

Malaria is a life-threatening disease caused by *Plasmodium* parasites that are transmitted to humans through the bites of infected female Anopheles mosquitoes. The disease is a principal infectious disease that continues to be a worldwide cause of mortality in endemic countries such as Nigeria (World Health Organization, 2021). Nearly half of the world's population is at risk of malaria (WHO, 2017). In Nigeria alone, malaria remains a leading cause of morbidity and mortality, with over 200,000 deaths annually attributed to the disease (WHO, 2020). The spatial correlation between poverty and malaria remains pronounced, with both conditions predominantly affecting tropical and subtropical regions, underscoring the complex interplay between socioeconomic factors and malaria prevalence (Bennett *et al.,* 2020). In addition, the disease imposes a significant economic burden on countries with high transmission rates, leading to a growth penalty of up to 1.3% annually (WHO, 2014). The disease affects both personal and public expenditures, including spending on prevention, treatment, and healthcare infrastructure (WHO, 2019). In some countries, malaria accounts for a substantial portion of public health expenditure and outpatient visits (Roll Back Malaria, 2015).The economic impact of malaria hinders regional economic growth and exacerbates Gross Domestic Product disparities between affected and unaffected countries (WHO, 2014).

Prevention and treatment of malaria rely mainly on the use of synthetic drugs (WHO, 2022), these drugs kill the parasites in the bloodstream, preventing them from multiplying, or reducing the severity of symptoms (Center for Disease Control, 2022). Common antimalarial drugs include Chloroquine, Mefloquine (Lariam), and Artemisinin-based Combination Therapies (ACTs) such as Artemether-Lumefantrine (Coartem) and Artesunate-Mefloquine (ASMQ) (National Institute of Allergy and Infectious Diseases, 2022). Sulfadoxine-Pyrimethamine (SP) and Artemisinin-based Combination Therapy (ACT) are the current recommended drugs for the treatments of uncomplicated malaria (WHO, 2017). SP is an Antifolate combination that inhibits folic acid synthesis, effective against *Plasmodium falciparum*. ACTs combine an Artemisinin derivative with a partner drug, rapidly killing the parasite. These combination therapies are highly effective against *P. falciparum*, well-tolerated, and reduce transmission.

Unfortunately several reports indicate that, the parasite has developed resistance to almost all classes of antimalarial drugs, including the most recently recommended Artemesinin. Antimalarial resistance is a growing concern worldwide, and

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in the case of malaria, the development of resistance in *Plasmodium falciparum* poses a significant public health challenge. The overuse and misuse of antimalarial drugs, particularly Chloroquine and Sulfadoxine-Pyrimethamine (SP), have accelerated the development of resistant strains, complicating malaria control efforts globally (Oladipo *et al.*, 2017). In Nigeria, one of the most malaria-endemic countries in the world, resistance to Chloroquine was first reported in the 1990s, and resistance to SP has also spread widely across the country (Kumar *et al.*, 2018; Oladipo *et al.*, 2017). More recently, resistance to Artemisinin-based Combination Therapies (ACTs), the frontline treatment for malaria, has emerged in several regions, including parts of Nigeria, highlighting the urgent need for continued surveillance and novel treatment strategies (Roper *et al.*, 2019). In light of the ongoing threat posed by drug resistance, this paper examined the major setbacks due to drug-resistant malaria-parasite and its implications for public health.

Methodology

This review adopts a systematic approach to synthesize and analyze existing literature on antimalarial drug resistance, with a specific focus on its threat and economic impact. A comprehensive search was conducted across academic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant peer-reviewed articles, reports, and reviews. Grey literature, such as governmental and non-governmental organization reports, were also included. Search terms included combinations of keywords such as antimalarial drug resistance, malaria in Nigeria, economic impact of malaria, and Artemisinin resistance. Studies were included if they focused on malaria and antimalarial drug resistance in Nigeria or sub-Saharan Africa, addressed economic impacts, treatment outcomes, or resistance mechanisms, and published in English within the last 11 years (2013–20240) Studies were excluded if they did not provide empirical data, were anecdotal, or focused exclusively on laboratory or preclinical studies without field applicability.

Drug resistance and drug failure

In 1967, WHO defined 'drug resistance' as the ability of a parasite strain to survive or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the tolerance of the subject (WHO, 1967). This definition was later modified to include the sentence: "The form of the drug active against the parasite must be able to gain access to the parasite or the infected erythrocyte for the duration of the time necessary for its normal action" (Paloque, et.al., 2016). Although the decreased sensitivity of malaria to antimalarial drugs was first reported about a century ago in association with quinine, the term drug resistance malaria was rarely used, resistance was not considered as a major problem until the late 1950s, after Chloroquine resistance emerged (Harald *et al*.,2010). Despite many years of research, for many drugs, the mechanisms by which they work, and how parasites develop resistance to them is, not completely understood (Cravo *et al*.,2006).

The consequences of drug resistance are severe, leading to increased morbidity, mortality, and healthcare costs. The spread of resistant *Plasmodium falciparum* strains exacerbates this burden, rendering existing treatments less effective and leading to higher rates of treatment failure and complications. To address this challenge, it is crucial to use antimalarial drugs judiciously, enhance diagnostic accuracy, and invest in research to develop new treatment options. Effective surveillance, as well as adherence to treatment guidelines, will be key to preventing further resistance and ensuring that antimalarial drugs remain effective in the fight against malaria.

Drug failure occurs when a drug does not work as expected due to factors such as improper use, poor absorption, or the parasite's inability to respond to the drug's action. Resistance, on the other hand, involves genetic changes in the parasite that allow it to survive and reproduce even in the presence of a normally effective drug.

Antimalarial Drugs and Emergence of Resistance

Antimalarial drug resistance has been a persistent and evolving challenge in malaria control. The earliest antimalarial drug, quinine, derived from the cinchona tree, was introduced in Europe in the 1600s and served as the primary malaria treatment until the 20th century, despite occasional reports of resistance (Dye-Braumuller & Kanyangarara, 2021). In the 1930s, Chloroquine was developed as a synthetic alternative; however, widespread use led to resistance emerging by the 1950s and 1960s. This prompted the development of combination therapies like Sulfadoxine-Pyrimethamine (SP), yet resistance to SP spread rapidly across Africa and Asia (Dye-Braumuller & Kanyangarara, 2021). Efforts to combat resistance led to the discovery of Artemisinin in the 1970s, derived from the *Artemisia annua* plant. Its combination-based formulations (ACTs) have been crucial in treating resistant malaria strains and remain one of the most effective treatments available (Dye-Braumuller & Kanyangarara, 2021). However, resistance to SP and ACTs is now emerging, especially in Africa and Southeast Asia, intensifying concerns about treatment efficacy and public health impact. Factors like drug misuse and inadequate adherence to treatment regimens have accelerated resistance, posing serious implications for global health security, as treatment failures and increased mortality rates become more frequent (Talisuna, 2020; Hanson, 2022).

Types of Antimalarial Drug Resistance

Antimalarial drug resistance is classified into three types: Resistance Type I (RI), Resistance Type II (RII), and Resistance Type III (RIII). In Resistance Type I, there is an initial clearance of the parasite following treatment; however, the parasite reappears within a month after the onset of treatment. This re-emergence is often due to reduced drug accumulation or parasite adaptation mechanisms (Fidock et al., 2018). In Resistance Type II, parasitemia initially decreases following treatment, but the parasite fails to be fully cleared, and there is a subsequent rise in parasitemia. This resistance is typically associated with reduced drug efficacy due to mutations that impair drug-target interactions, leading

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to a partial therapeutic response (Dhorda et al., 2019). Resistance Type III represents the most severe form of resistance, where there is no significant change in parasite load despite treatment, indicating a complete failure of the drug to exert its therapeutic effect. This type of resistance is often linked to critical mutations in genes that affect drug targets, rendering the parasite largely unresponsive to the treatment (Witkowski et al., 2020).

In respect to Drug development:Type 1 antimalarial drug resistance refers to resistance to 4-aminoquinolines, such as Chloroquine (CQ) and amodiaquine (AQ), which is mediated by mutations in the *Plasmodium falciparum* Chloroquine resistance transporter (PfCRT) gene (WHO, 2019). Mutations in PfCRT lead to reduced drug accumulation in the parasite, causing decreased efficacy of CQ and AQ (Fidock *et al.*, 2018). The most common mutation associated with Type 1 resistance is the K76T mutation in PfCRT (*Mwai et al.*, 2020). Type 1 resistance has been reported in various parts of the world, including Africa, Asia, and Latin America, and its spread has contributed to the decline in efficacy of CQ and AQ (Dhorda *et al.*, 2019). The global surveillance of antimalarial drug resistance is crucial to monitor and manage resistance (WHO, 2020). Sidhu *et al.* (2019) conducted a comprehensive review of the literature on Chloroquine resistance in *Plasmodium falciparum*, synthesizing findings on the molecular mechanisms underlying resistance, including the role of mutations in the PfCRT gene, and emphasizing the critical need to understand these mechanisms in order to develop innovative and effective treatment strategies to combat malaria.

Type 2 antimalarial drug resistance refers to resistance to antifolate drugs, such as Sulfadoxine-Pyrimethamine (SP) and trimethoprim-sulfamethoxazole mediated by mutations in the *Plasmodium falciparum* dihydrofolate reductase (PfDHFR) and dihydropteroate synthase (PfDHPS) genes (Dhorda *et al.*, 2019). Mutations in PfDHFR and PfDHPS lead to reduced binding affinity of antifolate drugs, causing decreased efficacy, with the most common mutations being S108N and A16V in PfDHFR, and S436A, A437G, and K540E in PfDHPS (Mwai *et al.*, 2020). The spread of type 2 resistance has been reported in various parts of the world, including Africa, Asia, and Latin America, contributing to the decline in efficacy of Sulfadoxine-Pyrimethamine and Trimethoprim-Sulfamethoxazole (WHO, 2019). Global surveillance of antimalarial drug resistance is crucial to monitor and manage resistance, with studies highlighting the need for continued vigilance and development of effective treatment strategies (Dhorda *et al.*, 2019).

type 3 antimalarial drug resistance refers to resistance to Artemisinin-based combination therapies (ACTs), specifically the Artemisinin component, mediated by mutations in the *Plasmodium falciparum* kelch13 (Pfkelch13) gene (Witkowski *et al.*, 2020). Mutations in Pfkelch13 lead to reduced susceptibility to Artemisinin, causing decreased efficacy of ACTs, with the most common mutations being C580Y, R539T, and Y493H (Imwong *et al.*, 2020).

The spread of type 3 resistance has been reported in Southeast Asia, particularly in Cambodia, Laos, and Myanmar, raising concerns about the spread of resistance to other regions (WHO, 2020). The emergence of Artemisinin resistance highlights the need for continued monitoring and development of effective treatment strategies to combat malaria.

2.3 Global Distribution of Resistant Malaria Parasite

The global distribution of resistant *Plasmodium falciparum* parasites is of significant concern, as it directly impacts the efficacy of antimalarial treatments and poses challenges for malaria control programs worldwide. Drug resistance in malaria has been observed in several regions, with varying patterns of resistance emerging over time" (WHO, 2020; Dhorda et al., 2019). Resistance to 4-aminoquinolines, such as Chloroquine (CQ) and Amodiaquine (AQ), has been widespread across many parts of the world, particularly in sub-Saharan Africa, Southeast Asia, and Latin America. Initially, Chloroquine was the mainstay of malaria treatment; however, its efficacy started declining in the 1950s, primarily due to mutations in the *Plasmodium falciparum* Chloroquine resistance transporter (*PfCRT*) gene. These mutations lead to reduced accumulation of the drug inside the parasite, resulting in treatment failure (Fidock et al., 2018; Mwai et al., 2020). The most common mutation associated with this resistance is the K76T mutation in *PfCRT*, which is prevalent in regions like West and Central Africa (Dhorda et al., 2019). Despite the global effort to control Chloroquine resistance, it has contributed to a decline in the efficacy of CQ and AQ in these regions, necessitating the development of alternative therapies.

Resistance to antifolate drugs, such as Sulfadoxine-Pyrimethamine (SP) and trimethoprim-sulfamethoxazole, is also a significant issue in regions such as sub-Saharan Africa, Southeast Asia, and parts of Latin America. Mutations in the *PfDHFR* and *PfDHPS* genes, which encode for the enzymes dihydrofolate reductase and dihydropteroate synthase, respectively, result in reduced drug efficacy (Mwai et al., 2020). In particular, mutations such as S108N and A16V in *PfDHFR* and S436A, A437G, and K540E in *PfDHPS* have been linked to increased resistance (Dhorda et al., 2019). In regions like East Africa and Southeast Asia, the widespread use of Sulfadoxine-Pyrimethamine for intermittent preventive treatment has further exacerbated resistance, leading to reduced effectiveness of the drug combinations in controlling malaria (WHO, 2020).

Resistance to Artemisinin-based combination therapies (ACTs), particularly the Artemisinin component, has become one of the most urgent challenges in malaria treatment. Resistance has been most prominently observed in Southeast Asia, particularly in Cambodia, Laos, Myanmar, and Thailand, where mutations in the *Pfkelch13* gene have been linked to delayed parasite clearance after Artemisinin treatment (Imwong et al., 2020; Witkowski et al., 2020). The emergence of Artemisinin resistance has raised significant concerns about its potential spread to other parts of the world, including sub-Saharan Africa, which is home to the highest burden of malaria cases. In response, the World Health

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Organization (WHO) has called for enhanced surveillance and monitoring of drug resistance in these regions to prevent the spread of resistant parasites (WHO, 2020). Global efforts to control malaria, such as the widespread distribution of insecticide-treated nets and the use of ACTs, have contributed to a significant reduction in malaria incidence in many regions. However, the emergence of drug-resistant *Plasmodium falciparum* poses a major threat to these gains. The rise of Artemisinin resistance, in particular, has created a situation where new treatments are urgently needed. The spread of resistance to both older and newer drugs highlight the need for novel therapies and improved drug combinations that can overcome these resistance mechanisms. Furthermore, the socio-economic factors and inadequate access to healthcare in endemic areas continue to complicate the situation, making global malaria control efforts even more challenging (WHO, 2020; Dhorda et al., 2019).

Global distribution of resistance malaria. WHO, 2023

- Countries with relatively low resistance
- Countries with relatively medium resistance
- Countries with relatively high resistance

Antimalarial Resistance Regional Hotspots

The global spread of drug-resistant *Plasmodium falciparum* parasites is a major concern for malaria control worldwide, particularly in specific regions where resistance has emerged more prominently. Southeast Asia has long been a hotspot for the development of drug resistance, particularly to Artemisinin-based combination therapies ACTs (White 2019). Resistance to Artemisinin, first identified in western Cambodia, has spread to neighboring countries such as Thailand, Myanmar, Laos, and Vietnam. Mutations in the *Plasmodium falciparum* kelch13 (Pfkelch13) gene are key drivers of this resistance, leading to delayed parasite clearance following treatment. This region is a critical area for global malaria control because Southeast Asia has historically been a source of new antimalarial treatments. The emergence of Artemisinin resistance here is alarming as it could potentially spread to other regions, especially Africa, where the malaria burden is highest (Witkowski et al., 2020; WHO, 2020; Imwong et al., 2020).

In sub-Saharan Africa, which bears the greatest burden of malaria, resistance to older antimalarial drugs such as Chloroquine (CQ) and Sulfadoxine-Pyrimethamine (SP) has been well documented. Mutations in the *PfCRT* gene are responsible for Chloroquine resistance, contributing to the declining efficacy of this drug across East and Central Africa (Mwai et al., 2020; Fidock et al., 2018). While Artemisinin resistance has been less prominent in Africa, there are growing concerns as signs of delayed parasite clearance have been observed in some areas, particularly along the border with Southeast Asia. Continued surveillance is essential to monitor these trends and ensure the effectiveness of current treatments (Dhorda et al., 2019; WHO, 2020).

Latin America, though not as heavily impacted by malaria as Africa and Southeast Asia, has experienced reports of drug resistance in regions like the Amazon basin. Resistance to drugs like Chloroquine and Sulfadoxine-Pyrimethamine has been linked to the use of monotherapies and inadequate treatment regimens. Given the geographical proximity to the southern United States, there is concern that drug-resistant malaria could spread northward, exacerbating challenges for malaria control in the Americas (WHO, 2019; Dhorda et al., 2019).

In India, resistance to Chloroquine and other first-line treatments has been a significant concern. Mutations in the *PfCRT* gene have led to decreased drug efficacy, while recent reports of delayed parasite clearance in eastern and northeastern India have raised fears of the emergence of Artemisinin resistance similar to that seen in Southeast Asia. With India's large population and substantial malaria burden, this development is troubling and could potentially spread to neighboring countries (Dhorda et al., 2019; WHO, 2020).

These regional hotspots—Southeast Asia, sub-Saharan Africa, Latin America, and India—are critical to global efforts to combat malaria (Beale 2018). Their role in the spread of drug resistance underscores the importance of sustained surveillance, development of new treatments, and international collaboration to prevent further resistance. As resistance continues to spread in these regions, it poses a serious threat to global malaria control and calls for urgent action to prevent its further dissemination (WHO, 2020; Mwai et al., 2020).

Setback due to Resistance species.

Antimalarial drug resistance is an escalating global health issue that significantly impacts the effectiveness of treatment, complicates malaria control efforts, and leads to increased morbidity and mortality. Resistance has been observed in several antimalarial drugs, including Chloroquine, Sulfadoxine-Pyrimethamine (SP), and Artemisinin-based combination therapies (ACTs), which are currently the first-line treatments for *Plasmodium falciparum* malaria (Oladipo, Adebayo, & Odaibo, 2017; Roper, Pearce, & Nosten, 2019). The widespread resistance to Chloroquine and SP has prompted the adoption of ACTs, but emerging resistance to these drugs is further jeopardizing malaria control, with studies indicating a decrease in their efficacy (Kumar, Dutta, & Singh, 2018).

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In countries like Nigeria, resistance to Chloroquine and SP has become a major concern, resulting in a growing reliance on ACTs. However, even ACTs are now facing challenges, as resistance to Artemisinin has been documented in certain parts of the country, with concerning trends emerging (Plowe et al., 2019). Resistance mechanisms, such as mutations in the *Plasmodium falciparum* kelch13 gene, have been identified as contributors to reduced Artemisinin sensitivity, threatening the global effectiveness of ACTs (Witkowski et al., 2020). The persistence of drug-resistant malaria parasites prolongs illness, increases the likelihood of severe malaria, and poses a greater risk of transmission, as infected individuals harboring resistant strains can unknowingly spread the parasite to others through mosquito vectors.

The consequences of antimalarial resistance are particularly evident in countries like Nigeria and across West Africa, where declining drug efficacy has been documented in recent studies. In southwestern Nigeria, the effectiveness of SP plummeted from 100% to approximately 50% within five years, underscoring the urgent need for alternative treatments and continuous monitoring of resistance patterns (Adebayo et al., 2021). Similarly, studies in Kenya reported a significant drop in the efficacy of ACTs, from 95% to 70% over a three-year period, highlighting the critical need for tailored interventions to combat drug resistance (Ajayi et al., 2013).

These trends emphasize the importance of comprehensive malaria control strategies that prioritize the development of new therapies while strengthening surveillance systems to detect and track emerging resistance patterns. Without such measures, the global fight against malaria will face increasingly difficult challenges (National Malaria Elimination Programme, 2021).

Increase in morbidity and Mortality

In Nigeria, resistance to Chloroquine, sulfadoxine-pyrimethamine, and even Artemisinin-based combination therapies (ACTs) has been documented, threatening the effectiveness of standard treatments (Odaibo, 2017). As resistance spreads, these antimalarial drugs, which were once highly effective, become less capable of clearing the parasite from the body, leading to prolonged illness and an increase in the number of severe malaria cases. This decline in treatment efficacy undermines malaria control efforts, particularly in regions where the disease burden is highest, contributing to a rise in mortality rates and hindering the goal of malaria elimination (Nosten, 2019).

The impact of antimalarial drug resistance extends far beyond clinical health issues, contributing to prolonged illness, increased risk of severe malaria, and heightened morbidity. These consequences place a considerable economic burden on both individuals and communities, as households face repeated medical expenses and potential loss of income due to illness. Vulnerable populations particularly children and pregnant women are disproportionately affected by drug resistance, increasing their susceptibility to severe malaria, anemia, and related complications. This situation is well-documented in studies focused on West Africa, where resistance against common treatments exacerbates these risks (Anyanwu *et al.,* 2017).

In addition, reduced treatment efficacy due to antimalarial drug resistance has led to increased morbidity and mortality rates, posing a significant threat to global health (Nosten & White, 2018). Drug-resistant parasites can survive and multiply despite treatment, leading to prolonged illness and increased risk of severe malaria, which can result in long-term health consequences, such as organ damage and disability (Roper *et al.,* 2019). Mortality rates also rise as treatment efficacy declines, with severe complications such as cerebral malaria, organ failure, and eventually death becoming more common outcomes, especially among high-risk groups (Ajayi *et al.,* 2020). This burden is evident in Nigeria, where antimalarial resistance intensifies malaria's impact, escalating the prevalence of life-threatening conditions and straining the already limited healthcare infrastructure (Kumar *et al.,* 2018; National Malaria Elimination Programme, 2021). Studies show that the resistance-driven increase in mortality and severe disease further amplifies healthcare costs and impedes sustainable progress in reducing malaria prevalence (Roper, 2019).

The impact of reduced treatment efficacy is particularly concerning because it increases the burden on healthcare systems already struggling to address the high incidence of malaria. In areas like Nigeria, where *Plasmodium falciparum* is the predominant malaria parasite, drug-resistant strains prolong the duration of illness, making it harder to manage cases effectively (National Malaria Elimination Programme, 2021). As patients remain infected longer, there is a greater risk of developing severe complications, including anemia, cerebral malaria, and organ failure, all of which significantly increase healthcare costs and burden local healthcare infrastructure. This situation worsens as more cases of resistant malaria emerge, leading to a vicious cycle that exacerbates the health crisis and impedes progress in malaria control (Singh, 2018).

The increased morbidity and mortality rates resulting from drug-resistant malaria have far-reaching economic and social implications, not only impacting individuals' health but also burdening entire communities and healthcare systems. In Nigeria, for example, the economic burden of malaria is substantial. Malaria-related illness leads to loss of productivity as people, particularly in the working-age population, are unable to attend work or school due to sickness. This loss of labor contributes to a decrease in household income and affects the broader economy, especially in regions where malaria is endemic. In addition, the cost of medical treatment for malaria increases, as drug-resistant strains require more expensive or extended treatments. This can drain household savings, leaving families in financial hardship and potentially pushing them deeper into poverty (National Malaria Elimination Programme, 2021).

The economic impact of the disease is even more pronounced. In sub-Saharan Africa, malaria is responsible for a significant proportion of healthcare expenditures, with households often

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spending a substantial portion of their income on malaria treatment, which becomes even more costly as resistance develops (Oladipo, 2017). For example, a study in Mozambique found that the economic burden of malaria was particularly heavy on rural households, which spent much of their income on medical care for malaria, as well as on transportation costs to seek treatment (Alonso *et al.*, 2019).

Globally, the rising rates of drug-resistant malaria are increasing the strain on healthcare systems, particularly in malaria-endemic regions. Healthcare providers are now faced with the challenge of managing more complicated and prolonged cases of malaria, which require more intensive care and longer hospital stays, thereby exhausting limited healthcare resources. The increased pressure on health systems can lead to reduced availability of essential services for other diseases, creating a ripple effect that undermines overall public health (Roper, 2019). The increased cost of treatment and the financial burden on health systems have a broader economic impact, with national economies losing billions of dollars each year due to malaria-related morbidity and mortality. The rising rates of drug resistance only exacerbate this financial strain, making it a critical issue not only for public health but for global economic stability (Plowe *et al.*, 2019).

Increase in malaria transmission

The spread of drug-resistant malaria parasites has made it much harder to control the transmission of malaria, especially in countries like Nigeria, where the disease is most prevalent. As *Plasmodium falciparum* parasites become resistant to commonly used antimalarial drugs, such as Sulfadoxine-Pyrimethamine and Chloroquine, treatments become less effective. This means that malaria stays in the body longer, giving the parasites more time to multiply and be passed on to mosquitoes. In Nigeria, for instance, resistance to Sulfadoxine-Pyrimethamine has been growing, which means that people are staying infected for longer periods. This not only worsens their health but also increases the risk that mosquitoes will pick up the parasite and pass it on to others (Oladipo, Adebayo, & Odaibo, 2017). The longer someone remains infected, the greater the chances that the disease will spread.

In many parts of Nigeria, malaria continues to be caused primarily by *Plasmodium falciparum*, and resistance to treatment is becoming more common (Roper, 2019). This has led to an increase in treatment failures, especially in rural areas where access to the latest medicines is limited. For example, despite widespread use of Artemisinin-based combination therapies (ACTs), drug-resistant strains of malaria are beginning to emerge in some regions. This is causing delays in treatment and allowing the parasite to persist in the body longer, which not only harms the individual but also increases the likelihood of transmission (Ajayi *et al.*, 2020). Essentially, the longer the infection lasts, the more likely it is that mosquitoes will become infected and carry the disease to other people, continuing the cycle of transmission (Roper, Pearce, & Nosten, 2019).

This problem is not just confined to Nigeria but is a growing concern across sub-Saharan Africa. Resistance to Sulfadoxine-Pyrimethamine, which is also used to prevent malaria in pregnant women, has been reported in several countries, making it harder to protect the most vulnerable populations (Anto *et al.*, 2019). When people stay sick for longer periods, their risk of passing malaria on to others increases, leading to higher transmission rates. This situation highlights the urgency of addressing drug resistance because the longer the parasites can survive in the body, the more they contribute to the spread of malaria, which ultimately sets back efforts to control the disease (Alonso *et al.*, 2019).

On top of that, drug-resistant parasites tend to produce more gametocytes, the form of the parasite that is passed on to mosquitoes. Tinto et al. (2018) found that these resistant parasites produce higher numbers of gametocytes, which increases the chances of the parasite being picked up by mosquitoes and then transmitted to others. This makes the problem even worse because the longer a person is infected and the more gametocytes they produce, the more mosquitoes can spread the disease, even to people who aren't showing symptoms.

The risk of malaria spreading is also made worse by the fact that the mosquitoes that carry the disease are very efficient, even when there are low levels of the parasite in someone's body. Akhwale et al. (2019) point out that mosquitoes like *Anopheles gambiae* can transmit the parasite even when the parasite load is low, meaning people who might not even know they're infected can still pass the disease on. This makes controlling malaria more difficult because it's not just people with obvious symptoms who are spreading it everyone with malaria, even mild cases, can play a role in transmission. Together, drug resistance and these efficient mosquitoes make it much harder to stop the spread of malaria, even with existing treatments.

This increasing risk of transmission has serious consequences for efforts to control and eliminate malaria. WHO (2019) has emphasized how urgent it is to develop new treatments and improve healthcare systems to address the growing threat of drug-resistant malaria. With parasites becoming harder to treat and mosquitoes continuing to spread the disease, the goal of eliminating malaria becomes more difficult every day. To make progress, we need better tools, treatments, and healthcare access, particularly in places like sub-Saharan Africa where malaria remains a major health concern.

Reduced Effectiveness of Combination Therapies

The rise of antimalarial drug resistance has significantly reduced the effectiveness of combination therapies, posing a major challenge to malaria control and elimination efforts (Plowe *et al.*, 2019). Artemisinin-based combination therapies (ACTs), which were once highly successful in treating malaria, are now less effective due to the development of drug-resistant parasites (Roper *et al.*, 2019). This loss of effectiveness is due to the ability of these resistant parasites to survive and multiply even in the presence of treatment, leading to prolonged illness, a higher risk of severe malaria,

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and increased mortality rates (Ouattara *et al.,* 2019). As treatment failure becomes more common, the implications for malaria control are significant. The spread of drug-resistant parasites results in higher transmission rates, which fuels the ongoing cycle of malaria, making efforts to control and eliminate the disease even more difficult (Akhwale *et al.*, 2019). The reduced efficacy of combination therapies also has serious public health consequences, including increased rates of illness and death, as well as a greater economic burden on affected individuals and communities (Tinto *et al.*, 2018). These challenges underscore the urgent need for new and more effective treatments to combat malaria, as well as for strengthening healthcare systems and improving malaria surveillance. Only by addressing these issues can we hope to reduce the impact of drug resistance and continue to make progress toward malaria control and elimination (WHO, 2019). The declining effectiveness of combination therapies not only threatens public health but also reverses the gains made in the fight against malaria (Roper *et al.,* 2019). Therefore, it is crucial to develop new treatment options, reinforce healthcare infrastructure, and improve malaria monitoring to ensure ongoing success in combating this deadly disease (Plowe *et al.*, 2019).

Delayed Parasite Clearance

Delayed parasite clearance refers to the slow clearance of malaria parasites from the bloodstream, even after treatment has been initiated (Stepniewska *et al.,* 2010). This phenomenon is a major concern, as it can lead to prolonged illness, increased transmission, and the development of drug resistance (Dondorp *et al.,* 2011). When parasites are not cleared quickly, they can continue to multiply and cause harm, making treatment more challenging (Sutherland *et al.*, 2017). Delayed parasite clearance can be caused by various factors, including drug resistance, inadequate dosage, or poor-quality drugs (White *et al.*, 2014). Inadequate dosage or poor-quality drugs can also contribute to delayed parasite clearance, as they may not provide sufficient antimalarial activity to clear the parasites (Baird *et al.,* 2012). Prolonged illness can lead to increased morbidity and mortality, as well as increased healthcare costs (Hansen *et al.,* 2013). Increased transmission can lead to outbreaks and epidemics, making it harder to control the spread of malaria (Cairns *et al.,* 2012). The development of drug resistance can also make treatment more challenging, as it reduces the effectiveness of available antimalarial drugs (Talisuna *et al.,* 2012). Addressing delayed parasite clearance requires a multifaceted approach, including monitoring treatment efficacy, using combination therapies, ensuring quality drugs, and adhering to treatment guidelines and protocols (WHO, 2019). Monitoring treatment efficacy can help identify areas where treatment is failing, allowing for swift action to be taken (Flegg *et al.,* 2018). Combination therapies can also help delay the development of resistance, while ensuring quality drugs and adhering to treatment guidelines can help ensure effective treatment (Kakolwa *et al.*, 2018).

Economic impact of Antimalarial Drug Resistance

The rise in malaria transmission due to drug resistance puts a serious strain on the economy and society. As malaria becomes harder to treat and spreads more easily, healthcare costs go up. In Nigeria, for example, malaria makes up about 60% of outpatient visits and 30% of hospital admissions, placing a huge burden on the healthcare system (Oguche *et al.,* 2014). As more people get sick, the cost of treatment increases, and medical resources become stretched.

Malaria also leads to a significant loss in productivity. Each year, malaria is responsible for the loss of over 200 million workdays in sub-Saharan Africa (WHO, 2020). In Nigeria, the cost of lost productivity due to malaria is estimated to be about $1 billion annually (Ajayi *et al.,* 2020). This happens because people miss work, are less productive when they do show up, or spend time seeking treatment. For many families, especially those in low-income communities, this financial burden can push them deeper into poverty.

On top of the direct costs, malaria also puts a heavy load on the healthcare system. As more people get sick, This not only affects people with malaria but also slows down the treatment of other diseases. The overall impact is that the resources needed to improve health and living conditions are drained, making it harder to combat poverty and promote development in areas where malaria is most common (Alonso *et al.*, 2019).

Conclusion

Drug resistance poses a formidable threat to malaria control and elimination efforts, as it compromises the efficacy of antimalarial drugs, leading to treatment failure, increased morbidity, and mortality. The emergence of resistance to Artemisinin, raises concerns about the long-term effectiveness of current treatments. If not addressed, drug resistance could undo the advances made in malaria control, resulting in more cases of the disease. The consequences of reduced treatment efficacy are far-reaching, with significant implications for malaria control and elimination efforts. It is essential to develop and deploy new, effective treatments to address the growing threat of drug-resistant malaria. In addition, strengthening drug resistance monitoring and surveillance systems is crucial to track the emergence of drug-resistant parasites and inform treatment policies.

Recommendation

i. Accelerate Research and Development of New Antimalarial Drugs: There is an urgent need to develop new antimalarial drugs with novel mechanisms of action to combat resistance. Governments, pharmaceutical companies, and research institutions should collaborate to accelerate research and development of new drugs.

ii. Implement Effective Malaria Treatment and Monitoring Programs: Healthcare providers should be trained to use antimalarial drugs rationally, and treatment outcomes should be monitored to detect resistance early. This includes using Artemisinin combination

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therapy (ACT) and monitoring for resistance markers.

iii. Enhance Malaria Surveillance and Data Sharing: Improved surveillance and data sharing are critical to tracking resistance and informing treatment policies. National malaria control programs should strengthen surveillance systems, share data, and collaborate with international partners to stay ahead of resistance.

iv. Clear and simple instructions on treatment administration should always be provided this will help patients understand how to take their medication correctly in other to avoid drugs misuse. This can be achieved by using local language, avoiding medical jargon, and providing step-by-step guidance.

v. The importance of completing the full treatment course should always be explained to the patients. This will make them understand the risks of not finishing their medication, including the development of drug resistance.

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