Decoding the Puzzle: Factors Shaping the Potential Emergence of Artemisinin Combination Therapy Resistance in Nigeria- A review of Literature

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ABSTRACT

Background:

Falciparum malaria accounted for 99% of cases in Africa, 77% in the Western Pacific Region, 66% in Southeast Asia, 58% in the Eastern Mediterranean Region, and 36% in America of the anticipated 216 million cases of the disease in 2016. The use of artemisinin-based combination therapies (ACTs), which combine an artemisinin derivative with a partner drug, in the treatment of uncomplicated malaria has largely been responsible for the significant reduction in malaria-related mortality in Nigeria. ACTs have played a significant role in the 18% decline in the incidence of malaria cases from 2010 to 2016. However, this progress is seriously threatened by the reduced clinical efficacy of artemisinins, which is characterised by delayed parasite clearance and a high rate of recrudescence, as reported in 2008 in Western Cambodia. Furthermore, resistance to partner drugs has been shown in some instances to be facilitated by pre-existing decreased susceptibility to the artemisinin component of the ACT. A major concern is not only the spread of these multidrug-resistant parasite in Nigeria but also their possible appearance in Sub-Saharan Africa the continent most affected by malaria, as has been the case in the past with parasite resistance to other antimalarial treatments.

Conclusion

It is therefore essential to understand the factors that are implicated in the possible development of ACT drug resistance, the underlying mechanisms and regulations that can reduce the development and spread of ACT resistance in Nigeria

INTRODUCTION

An estimated 3.2 billion people, or about half of the world's population, live in countries that are tropical or subtropical, where malaria is endemic [1]. Falciparum malaria accounted for 99% of cases in Africa, 77% in the Western Pacific Region, 66% in Southeast Asia, 58% in the Eastern Mediterranean Region, and 36% in America of the 216 million cases of the disease in 2016 [2]. Sub-Saharan Africa accounted for over 91% of the 445,000 malaria-related deaths worldwide in 2016, with children under five accounting for the majority of these deaths [2,3]. Thus, the current efforts to reduce the global burden of malaria are threatened by the rapid emergence and spread of *P. falciparum* resistance to ACTs including artemisinin derivatives and their partner drugs [4,5,6,7,8].

Artemisinin is a potent antimalarial agent derived from the plant *Artemisia annua*, commonly known as sweet wormwood. It is highly effective against *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria [9]. Artemisinin and its derivatives (artesunate, artemether, and dihydroartemisinin) exert their antimalarial effect through the generation of reactive oxygen species (ROS). Upon entering the parasite, the endoperoxide bridge in the artemisinin molecule is cleaved by iron, releasing free radicals. These reactive intermediates damage the parasite's proteins and membranes, leading to its death [10]. Artemisinin is well absorbed orally, but its bioavailability can be variable due to its poor solubility and instability in the gastrointestinal tract [11]. After absorption, artemisinin is widely distributed in body tissues. It crosses the blood-brain barrier, making it effective against cerebral malaria [9]. Artemisinin is metabolized primarily in the liver by the cytochrome P450 enzyme system. Its derivatives are rapidly converted to the active metabolite dihydroartemisinin [12]. The metabolites of artemisinin are excreted primarily in the urine. The half-life of artemisinin is relatively short, ranging from 2 to 4 hours [12]. Artemisinin is used primarily in combination therapies (ACTs) to enhance efficacy and reduce the risk of resistance. Common combinations include artemether-lumefantrine and artesunate-mefloquine. ACTs are recommended for the treatment of uncomplicated and severe malaria, including multidrug-resistant strains of *Plasmodium falciparum* [13]. Artemisinin and its derivatives are generally well-tolerated. Common side effects include gastrointestinal disturbances (nausea, vomiting, diarrhea), headache, and dizziness. Rare but serious adverse effects can include cardiotoxicity and neurotoxicity, particularly with prolonged use [9].

Antimalarial drug resistance is the ability of malaria parasites to survive or multiply despite exposure to antimalarial agents, rendering them less effective or ineffective in treating malaria infections. This develops when parasites acquire genetic mutations that confer protection against the active principles of antimalarial drugs, allowing survival and proliferation despite treatment [14,15]. The epidemiology of antimalarial resistance in Nigeria is characterized by the presence of resistance to multiple classes of antimalarial drugs, posing significant challenge to malaria

control efforts in the country [16]. Artemisinin Combination Therapies (ACTs) have been reported to fall into the category of antimalarial drugs with reduced efficacy [17]. A study conducted in Kano state, Nigeria which consists of three primary health care centres showed the development of TIER 1 Artemisinin combination therapy resistance [18]. Artemisinin Combination Therapy (ACT) resistance is thus referred to as the reduced effectiveness or failure of Artemisinin Combination Therapy in treating malaria-related to infections due to the emergence of resistance to artemisinin and/or its partner drugs [19]. ACT is a frontline treatment for uncomplicated malaria recommended by the World Health Organization (WHO) and is composed of an artemisinin derivative combined with one or more longer-acting antimalarial drugs [20]. ACT resistance can lead to treatment failure, recurrent infections, and the spread of resistant parasite strains within populations. Consequently, ACT resistance poses a significant threat to malaria control efforts and can undermine the effectiveness of key antimalarial interventions [21]. The key factors responsible for the development of Artemisinin combination therapy resistance are drug pressure, incomplete treatment, substandard drugs, poor drug quality, vector resistance, population movement, concurrent administration of antagonists, genetic factors and poor health care infrastructure in Nigeria typically manifesting as delayed parasite clearance after treatment with artemisinin-based drugs, particularly artemisinin monotherapy [17,22]. This delayed clearance can result in prolonged fever and parasitemia, leading to increased transmission of resistant parasites and potential treatment failure. Resistance to partner drugs in ACT can also occur, further compromising treatment efficacy [22,23]. In addition, genetic factors have been implicated in artemisinin resistance, thus pathologically linking it with mutations in the Plasmodium falciparum kelch13 (Pfkelch13) gene, although other genetic factors may also contribute. Pfkelch13 mutations reduce the susceptibility of malaria parasites to artemisinin derivatives, allowing them to survive and multiply despite drug treatment [23,24,25]. Thus, ACT resistance poses a significant threat to malaria control efforts, as it undermines the effectiveness of first-line treatments and can lead to increased morbidity, mortality, and the spread of resistant parasite strains. Surveillance, monitoring, and research efforts are essential for detecting and tracking ACT resistance, informing treatment policies, and developing strategies to combat resistance and preserve the efficacy of artemisinin-based therapies [26,27].

Epidemiology of Antimalarial Resistance in Nigeria

The epidemiology of antimalarial resistance in Nigeria is characterized by the presence of resistance to multiple classes of antimalarial drugs, which poses a significant challenge to malaria control efforts in the country. These malaria control efforts in Nigeria require a coordinated approach involving government agencies, healthcare providers, community organizations, and international partners to effectively combat the burden of malaria and reduce its impact on public health and

socioeconomic development [28]. Chloroquine resistance in Nigeria has been a significant challenge in the country's efforts to control malaria. It was first documented in the late 1970s in the southwestern region of the country. Over subsequent decades, resistance spread rapidly, becoming widespread across Nigeria and leading to its eventual withdrawal as the first-line treatment for uncomplicated malaria [29,30.] The prevalence of chloroquine resistance varies geographically within Nigeria, with higher levels of resistance observed in some regions compared to others [31,32]. Several studies have reported varying levels of chloroquine resistance across different states and ecological zones, influenced by factors such as local drug use practices [33,34], parasite genetic diversity [35,36,37,38,39,40,41], and historical treatment patterns [42,43]. Likewise, SP resistance prevalence varies across different regions of Nigeria [44,45,46,47]. Numerous studies have reported varying levels of SP resistance, with higher resistance rates observed in some areas compared to others [44,45,46,47]. Thus, the potential for artemisinin resistance to emerge and spread in Nigeria remains a concern, especially given its emergence in the Greater Mekong Subregion of Southeast Asia, in the horn of Africa and East Africa [48]. Malaria-related mortality rates in Nigeria have declined over the years, thanks to efforts to scale up malaria control interventions such as insecticide-treated bed nets, indoor residual spraying, and access to artemisinin-based combination therapies (ACTs) [49]. However, antimalarial resistance can still contribute to malaria-related deaths by reducing the efficacy of first-line treatment options and delaying effective parasite clearance [17,50,51]. Children under five years of age and pregnant women are particularly vulnerable to severe malaria and malaria-related deaths, and antimalarial resistance can exacerbate this vulnerability by compromising treatment effectiveness [50,51].

Factors Implicated in the Possible Development of Artemisinin Combination Therapy Resistance in Nigeria

Several factors can influence the development of Artemisinin Combination Therapy (ACT) in Nigeria:

Malaria Burden

The prevalence [52] and severity [53] of malaria in Nigeria drives the need for effective treatments like ACT. The high malaria burden in Nigeria significantly contributes to the risk of Artemisinin Combination Therapy (ACT) resistance. The extensive use of ACT in a region with a high malaria burden increases the selective pressure on the parasite population, potentially leading to the emergence of resistant strains. In areas with a high malaria burden, incomplete or inadequate treatment courses may occur due to initial reduction in severity of symptoms and drug affordability, fostering an environment for a development of resistance [54]. In addition, unregulated access to antimalarial drugs and self-medication can lead to inappropriate use, contributing to the development of resistance. The intensity of malaria transmission affects the frequency of exposure to the parasite, influencing the development and spread of resistance [55,56]. Furthermore, Nigeria's proximity to other

countries with varying malaria control measures may contribute to the cross-border spread of resistant parasites (transboundary diseases) [57,58,59]. Lastly, environmental factors, such as temperature and rainfall, influence mosquito abundance and malaria transmission, potentially affecting the dynamics of resistance development [60].

Drug Resistance

Resistance to numerous antimalarial drugs has a significant impact on the potential development of Artemisinin Combination Therapy (ACT) resistance in Nigeria. Previous use of antimalarial drugs like chloroquine and sulfadoxine-pyrimethamine has led to the emergence and spread of resistance in Nigeria. The continued use of these drugs, despite their reduced effectiveness, can exert selective pressure on the parasite population, potentially leading to resistance against newer drugs like artemisinin [61]. Likewise, resistance to one antimalarial drug can confer cross-resistance to other drugs within the same class or with similar mechanisms of action. Thus, if parasites develop resistance to one of the components of ACT, they may also exhibit reduced susceptibility to artemisinin or its partner drugs [62,63]. In addition, inadequate treatment, or failure to complete full treatment courses can contribute to the selection of drug-resistant parasites that potentially leads to an incomplete clearance of parasites which allows resistant strains to proliferate and spread within the population [64,65]. Furthermore, the presence of substandard or counterfeit antimalarial drugs in the market can undermine treatment efficacy and contribute to the development of drug resistance. These deny patients exposure to optimal doses or ineffective formulations, promoting the survival of resistant parasites [66,67,68]. Lastly, Nigeria's role as a hub for international travel and trade increases the risk of imported drug-resistant parasites from neighboring countries or regions where resistance is prevalent. This can introduce resistant strains into local parasite populations, further complicating malaria control efforts [69].

Absence of Government Support

Government support plays a crucial role in influencing the potential development of Artemisinin Combination Therapy (ACT) resistance in Nigeria. Adequate government funding is essential for implementing comprehensive malaria control programs, including the procurement of quality-assured ACT drugs as Insufficient funding may lead to the use of substandard or counterfeit drugs, which can contribute to the emergence of resistance [70,71,72]. Government regulatory agencies can enforce quality standards for antimalarial drugs, monitor drug distribution channels, and crack down on the circulation of counterfeit medications. Likewise, strong regulatory oversight, such as policy formulations on transboundary and endemic diseases, helps ensure the effectiveness of ACT and reduces the risk of resistance due to substandard drugs. Government support is necessary for building and maintaining healthcare infrastructure, including access to healthcare facilities, trained personnel, and diagnostic tools [73]. In addition, Government-led public awareness and education campaigns

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are crucial for promoting understanding of malaria, its transmission, prevention, and the importance of proper treatment with ACTs [74]. Well-informed communities are more likely to use ACT appropriately, reducing the risk of resistance due to misuse or overuse of drugs [74]. Finally, government investment in research and development fosters innovation in antimalarial therapies, including the development of new ACT formulations or alternative treatments. Research efforts supported by the government can help address emerging resistance and prolong the effectiveness of malaria treatment in Nigeria. Government-led surveillance programs can systematically monitor drug efficacy, track the prevalence of resistance markers in parasite populations, and detect early signs of resistance emergence. Timely surveillance data allows for prompt interventions to mitigate resistance and prevent its spread.

Inadequate Healthcare Infrastructure

Access to healthcare facilities, trained personnel, and diagnostic tools are essential for the proper administration and monitoring of ACT, as inadequate healthcare infrastructure can exacerbate the risk of Artemisinin Combination Therapy (ACT) resistance in Nigeria [75]. In regions with poor healthcare infrastructure, access to quality-assured ACT drugs may be limited. This can lead to the use of substandard or counterfeit medications, which not only compromises patient outcomes but also contributes to the development of drug resistance [76]. Inadequate healthcare infrastructure may limit access to accurate diagnostic tools for malaria, such as rapid diagnostic tests (RDTs) or microscopy [77]. Without proper diagnosis, there is a risk of overuse or misuse of ACT, as patients may be treated empirically, leading to unnecessary drug pressure and potential resistance [78,79]. Inefficient drug distribution systems can lead to stockouts or irregular availability of ACT drugs in healthcare facilities. Patients may resort to purchasing drugs from unregulated sources, increasing the likelihood of using substandard or counterfeit drugs and contributing to resistance development. In settings with inadequate healthcare infrastructure, patients may face barriers to accessing healthcare services or may receive incomplete or incorrect treatment regimens [80]. Furthermore, poor treatment compliance can result in the persistence of parasites and the selection of resistant strains. In the absence of robust healthcare infrastructure, there may be limited capacity for monitoring drug efficacy, tracking resistance patterns, and conducting surveillance of malaria cases [80,81]. This may hamper efforts at early detection and response to emerging resistance allowing an unchecked spread

Lack of Public Awareness and Education

Community awareness and education campaigns via television, social media etc e.g. for pregnant mothers at antenatal clinics and for the general populace, are necessary to ensure proper usage of ACT and reduce the risk of resistance as the lack of public awareness and education can contribute to the potential development of Artemisinin Combination Therapy (ACT) resistance in Nigeria. Without proper education, individuals

may misuse or overuse ACT drugs, such as taking incomplete regimen, missed dose-recontinued dose, suboptimal dosage such as body weight dosage miscalculation, usage of children dose for adults and vice-versa, sharing medications, or using them for conditions other than malaria [82]. This improper use can lead to treatment failure and the selection of drug-resistant parasites. Lack of awareness about malaria symptoms, prevention methods, and the importance of seeking prompt treatment may result in delays in seeking healthcare. This results in some communities having preference for traditional remedies over modern healthcare practices. Without education on the effectiveness of ACT and the dangers of relying solely on traditional remedies, individuals may not seek appropriate treatment or may delay seeking care until the disease becomes severe [83]. The dissemination of misinformation or misconceptions about malaria and its treatment can undermine public trust in ACT and promote alternative, ineffective treatments. This can lead to inconsistent use of ACT and contribute to the emergence of resistance [84].

Lack of Collaboration with Global Health Organizations

Partnerships with organizations like the World Health Organization (WHO) can provide expertise, resources, and support for the development and implementation of ACT programs as the lack of collaboration with global health organizations can have detrimental effects on the potential development of Artemisinin Combination Therapy (ACT) resistance in Nigeria [82]. Collaboration with global health organizations provides access to resources, expertise, and support in the form of funding, research, and technical assistance. Without such collaboration, Nigeria may face malaria control programs implementation challenges effective and research forays in strategic resistance combat developments [82,83]. Similarly, global health organizations often play a key role in monitoring and response-time dependent emerging health threats, including ACT drug resistance without active collaboration. Nigeria has no statistical and epidemiological data to assess demographic information on ACT drug resistance and interventions to address evolving resistance patterns. In addition, global collaboration enhances the capacity for robust surveillance systems as lack of collaboration may result in less effective surveillance, making it difficult to track the spread of resistance, identify hotspots, and implement timely interventions. Collaboration fosters coordinated research efforts and information sharing, helping to accelerate the development of new antimalarial drugs and treatment strategies. Without collaboration, research efforts may be fragmented, slowing down progress in addressing resistance challenges. Global health organizations often contribute to the development of evidence-based policies. Lack of collaboration may lead to a disconnect between global best practices and local strategies, potentially hindering the effectiveness of malaria control efforts and increasing the risk of resistance. Collaborative efforts often involve advocacy and awareness campaigns on a global scale without which

may culminate in struggle for international advocacy thereby limiting the visibility of challenges posed and potential support reducing effects for malaria control efforts [82].

Poor Research and Development Protocols

Continued research into new drug formulations, dosages, and delivery methods can improve the efficacy and accessibility of ACT in Nigeria suggestive that poor research and development (R&D) protocols may be contributory in potential Artemisinin Combination Therapy (ACT) resistance development in Nigeria [84,85]. Inadequate R&D investment and protocols may consequent in limited innovation in antimalarial drug development as without new and improved treatment options, reliance on existing ACT regimens may also lead to increased drug pressure and the selection of resistant parasites [86,87]. Similarly, inefficient protocols may delay patterns identification in emerging resistance or new resistance mechanisms; This can hinder the timely implementation of strategies to mitigate resistance and prevent its spread. Poorly designed protocols may substrate to suboptimal drug formulations, including inadequate dosages, systemic bioavailability and ineffective drug combinations [85,86,87]. In addition, insufficient R&D efforts may produce a lack of alternative treatment options to ACT as without viable alternatives, healthcare providers may have limited options for managing cases of ACT treatment failure or resistance, exacerbating the spread of resistant parasites. Further, weak protocols can undermine drug efficacy monitoring efforts , resistance markers tracking, and malaria cases surveillance conduction [86,87]. Lastly, inadequate surveillance and monitoring systems limit the ability to detect resistance early and institute appropriate interventions. It is therefore important to note that research endeavor notwithstanding, poor dissemination and translation of research findings into policy and practice can impede efforts to address drug resistance, without effective translation mechanisms, valuable research insights may not be utilizable in malaria control strategies [86,87].

Mechanistic Contributors to Artemisinin Combination Therapy resistance

Understanding the mechanisms in Artemisinin Combination Therapy resistance is crucial for monitoring resistance patterns, developing strategies to combat resistance, and designing new antimalarial therapies that can overcome resistance mechanisms [88]. Surveillance, molecular studies, and clinical trials are essential for elucidating the underlying mechanisms of ACT resistance and guiding effective malaria control efforts. Artemisinin Combination Therapy (ACT) resistance involves complex mechanisms that can arise due to several factors.

Reduced Artemisinin Sensitivity

Resistance to artemisinin, the core component of ACT, is a key factor in the development of Artemisinin Combination Therapy (ACT) resistance. Artemisinin derivatives, such as artemether and artesunate, are the cornerstone of ACT and are highly effective against the malaria parasite. However, when parasites

exhibit decreased sensitivity to artemisinin, it can lead to treatment failure and the emergence of resistance [22,88,89,90]. Artemisinins are characterized by their rapid onset of action and ability to clear malaria parasites from the bloodstream within hours. Reduced sensitivity to artemisinin results in slower parasite clearance rates, prolonging the time taken to eliminate parasites from the body. Persistent parasitemia increases the risk of recrudescence and treatment failure [91,92,93]. In addition, parasites with reduced sensitivity to artemisinin are better able to survive the initial drug exposure. This prolonged survival allows parasites to replicate and propagate, increasing their numbers and the likelihood of developing resistance-associated mutations. The selective pressure exerted by artemisinin treatment on parasite populations with reduced sensitivity drives the selection of resistant strains [92,93]. Consequently, reduced Artemisinin sensitivity may be accompanied by changes in parasite biology, such as alterations in metabolic pathways or gene expression patterns. These changes can confer resistance traits and enable parasites to evade the effects of artemisinin more effectively. These parasites may also exhibit cross-resistance to other antimalarial drugs, including the partner drugs used in ACT [94,95,96]. Thus, complicating treatment options and limiting the effectiveness of combination therapies, further exacerbating resistance development.

Altered Drug Metabolism

Resistance to ACT can involve changes in the metabolism of artemisinin and its partner drugs within the parasite as alterations in drug metabolism pathways can result in reduced efficacy or increased tolerance to the drugs, contributing to treatment failure [97]. Altered Artemisinin metabolism plays a significant role in development of (ACT) resistance. Artesunate and artemether undergo reductive activation, primarily facilitated by heme and iron within the malaria parasite. Alterations in this activation process can reduce the conversion of artemisinin into its active form, diminishing its efficacy against the parasite [97,98]. Some resistant parasites may upregulate detoxification pathways to metabolize and eliminate artemisinin more efficiently. This enhanced detoxification can reduce the concentration of active drug within the parasite, leading to decreased efficacy and treatment failure. These changes in the metabolic pathways within the parasite implicate the enzymes involved in drug metabolism [99,100,101]. Mutations or alterations in these metabolic enzymes can impact the metabolism and efficacy of artemisinin derivatives thereby contributing to resistance. In ACT, artemisinin is typically coformulated with partner drugs, such as lumefantrine or mefloquine. Altered metabolism of artemisinin can affect the pharmacokinetics and metabolism of these partner drugs, potentially influencing their efficacy and contributing to treatment failure [(102)].

Efflux Pump Activation

Efflux pump activation plays a significant role in (ACT) resistance by reducing the intracellular concentration of active drugs within the malaria parasite. These efflux pumps are proteins located in the parasite's cell

membrane that actively transport molecules, including drugs, out of the parasite's cell. When activated, these pumps can rapidly remove artemisinin and its derivatives from the parasite's intracellular compartment, reducing the concentration of active drug available to kill the parasite thereby limiting their effectiveness. Reduced intracellular drug levels make it more difficult to achieve the threshold concentration required to kill the parasite, leading to treatment failure and the emergence of resistance [103,104]. Efflux pumps are often associated with multidrug resistance, where parasites become resistant to multiple antimalarial drugs simultaneously. Activation of efflux pumps can confer cross-resistance to other drugs used in ACT, such as the partner drugs like lumefantrine or mefloquine, further compromising treatment efficacy [105,106]. The presence of efflux pump-mediated resistance creates selective pressure for the survival and proliferation of parasites that are less susceptible to artemisinin and its derivatives. Over time, this selective pressure can lead to the emergence and spread of resistant parasite strains within the population. Efflux pump-mediated resistance may also confer cross-resistance to other structurally unrelated drugs, not just those used in ACT. This broadens the spectrum of resistance and limits treatment options, complicating efforts to control malaria [105,106].

Mutations in Drug Targets

Resistance to ACT can also arise through mutations in the molecular targets of artemisinin and its partner drugs [35,36]. Mutations in these targets, such as the PfKelch13 gene associated with artemisinin resistance, can alter drug binding and interfere with drug action, leading to treatment failure. Mutations in the target of artemisinin, specifically the PfKelch13 gene, play a crucial role in Artemisinin Combination Therapy (ACT) resistance. Mutations in the PfKelch13 gene have been identified as molecular markers associated with artemisinin resistance in Plasmodium falciparum, the parasite responsible for most cases of malaria. These mutations are correlated with delayed parasite clearance rates following artemisinin treatment. Mutations in PfKelch13 can affect the parasite's response to artemisinin by altering the function of the Kelch13 protein [35,36,37]. This can result in delayed or incomplete clearance of parasites from the bloodstream, leading to treatment failure and the emergence of resistance. One hypothesis suggests that mutations in PfKelch13 disrupt the protein's interaction with partner proteins involved in protein degradation pathways, leading to impaired clearance of damaged proteins and increased parasite survival in the presence of artemisinin. PfKelch13 mutations have been associated with reduced susceptibility to partner drugs used in ACT, such as lumefantrine and mefloquine. This suggests a potential role for PfKelch13 mutations in promoting multidrug resistance and complicating treatment outcomes in cases of ACT failure. The prevalence of PfKelch13 mutations varies geographically, with higher frequencies observed in regions where artemisinin resistance has been documented, such as Southeast Asia. Surveillance of PfKelch13 mutations can provide valuable

insights into the spread of artemisinin resistance and guide malaria control efforts [107,108].

Quiescence and Dormancy of Malaria Parasite

In response to artemisinin exposure, some parasites may enter a dormant or quiescent state, reducing their susceptibility to drug action. These dormant parasites, commonly at the schizont stage, can later resume growth and cause recurrent infections, contributing to resistance development. The phenomenon of malaria parasite dormancy and quiescence can contribute to Artemisinin Combination Therapy (ACT) resistance. Dormant or quiescent parasites can enter a state of metabolic inactivity, making them less susceptible to the rapid action of artemisinin derivatives. While artemisinins are highly effective against actively replicating parasites, dormant parasites may remain unaffected by the drug, allowing them to survive treatment [109,110,111]. Dormant parasites have the potential to re-activate and resume replication following the completion of artemisinin treatment. These re-activated parasites can contribute to recurrent infections and treatment failure, even after apparent initial clearance of parasites from the bloodstream. These parasites can serve as reservoirs for future infections, maintaining the parasite population within the host and facilitating the spread of resistant strains [112,113]. In addition, these dormant parasites may persist in various host tissues, including the liver, where they can evade drug exposure and contribute to resistance development. Dormant parasites may exhibit increased tolerance to environmental stressors, including drug exposure, nutrient deprivation, and immune responses. This enhanced resilience can enable dormant parasites to survive under adverse conditions, including artemisinin treatment, contributing to the development of resistance. Parasites in dormant or quiescent states may undergo changes in gene expression patterns, including upregulation of stress response genes and downregulation of genes associated with metabolic activity and replication. These alterations in gene expression can influence parasite behavior and survival mechanisms, potentially impacting drug susceptibility and resistance [114,115].

Host Immune Response

Immune-mediated mechanisms may play a role in parasite clearance, and variations in host immune factors can affect treatment outcomes and the development of resistance. The host immune response can influence (ACT) resistance in several way; this mechanism plays a critical role in clearing malaria parasites from the bloodstream, complementing the action of antimalarial drugs. A robust immune response can help eliminate parasites more effectively, reducing the parasite burden and contributing to treatment success and influence the pharmacokinetics and efficacy of antimalarial drugs [116]. In cases where parasites survive initial drug treatment, the host immune response can target and clear residual parasites. Immune-mediated clearance mechanisms, such as phagocytosis by macrophages and antibody-mediated killing,

can help eliminate parasites that survive artemisinin exposure, reducing the risk of recurrence and treatment failure, including artemisinin derivatives. Immune factors such as cytokines, chemokines, and inflammatory mediators can alter drug metabolism, distribution, and clearance, potentially impacting treatment outcomes and susceptibility to resistance [116]. The host immune response exerts selective pressure on parasite populations thus favoring the survival and proliferation of parasites that are less susceptible to immune attack [106]. This immune selection pressure can contribute to the emergence and spread of resistant parasite strains, including those resistant to ACT [106]. The effectiveness of ACT can vary depending on the host's immune status. Immunocompromised individuals, such as those with HIV/AIDS or other immunodeficiencies, may have impaired immune responses to malaria parasites, reducing the efficacy of ACT and increasing the risk of treatment failure and resistance development. Artemisinin derivatives have been reported to possess immunomodulatory properties, including effects on cytokine production, immune cell function, and inflammatory responses. These immunomodulatory effects may influence the host immune response to malaria parasites and impact treatment outcomes [117].

Regulations to Prevent Artemisinin Combination Therapy Resistance in Nigeria

The implementation of regulations and strategies that prevents the ACT resistance in Nigeria can strengthen its malaria control efforts, mitigating the risk of ACT resistance, and safeguarding the effectiveness of artemisinin-based treatments in combating malaria. To prevent Artemisinin Combination Therapy (ACT) resistance in Nigeria, several regulations and strategies can be implemented, such as:

Regulation of Drug Quality

Strict regulations ensure the quality, safety, and efficacy of ACT drugs that are available in the market. These regulations involve rigorous testing and monitoring of drug formulations to prevent the circulation of substandard or counterfeit medications which may contribute to resistance. It plays crucial roles in preventing (ACT) resistance in Nigeria; regulatory authorities establish and enforce standards for the quality of ACT drugs, ensuring that they contain the correct concentration combinations of artemisinin and partner drugs. This oversight helps maintain the efficacy of ACT, preventing underdosing that could contribute to resistance [118,119]. In addition, stringent regulations help prevent the circulation of substandard or counterfeit ACT drugs. Substandard drugs may contain inadequate amounts of active ingredients, while counterfeit drugs may not contain any effective antimalarial components other than Artemisinin as indicated on its label and contributory to treatment failure and the emergence of resistance [120,121,122]. Similarly, regulatory agencies set guidelines for good manufacturing practices (GMP) to ensure the quality, safety, and consistency of ACT formulations. Regular inspections and adherence to GMP standards help maintain the

integrity of the manufacturing process, reducing the likelihood of variations that could impact drug quality [123,124]. Furthermore, regulations govern the importation, distribution, and sale of ACT drugs. By monitoring these channels, regulatory authorities can prevent the infiltration of substandard or counterfeit drugs into the market. This oversight is crucial for maintaining the quality of drugs available to healthcare providers and the public. Drug quality regulations often align with pharmacopeial standards, which specify the acceptable levels of purity, strength, and quality for pharmaceutical ingredients. Compliance with these standards ensures that ACT drugs meet internationally recognized benchmarks for quality and effectiveness. In particular, regulatory agencies engage in post-market surveillance to monitor the quality of ACT drugs already in circulation. This involves ongoing testing and inspections to identify and address any issues that may arise after the drugs have entered the market. Finally, regulatory bodies play a role in educating manufacturers, distributors, and healthcare providers about the importance of adhering to quality standards. Strict enforcement of regulations, including penalties for non-compliance, acts as a deterrent against the production and distribution of poor-quality ACT drugs [125].

Adherence to Treatment Guidelines

Adherence to Nigerian national treatment guidelines for malaria management, including proper dosing, duration of treatment, and use of combination therapies should be promoted [126]. This is essential in preventing Artemisinin Combination Therapy (ACT) resistance in that it provides standardized protocols for the use of ACT, including appropriate dosing regimens and treatment durations. Adherence to these guidelines ensures that patients receive the most effective treatment, minimizing the risk of inadequate drug exposure and the development of resistance [127]. In addition, proper dosing and treatment durations reduce the likelihood of suboptimal drug concentrations, which can promote the selection of resistant parasites and allows healthcare providers to mitigate the risk of resistance development. Likewise, adherence to treatment guidelines helps prevent underdosing of ACT, which can occur if healthcare providers prescribe lower-than-recommended doses or if patients do not complete the full course of treatment. Underdosing allows parasites to survive and potentially develop resistance to artemisinin and its partner drugs [128]. Furthermore, malaria treatment guidelines emphasize the use of ACT as the first-line treatment for uncomplicated malaria. It discourages monotherapy with artemisinin derivatives and ensures that ACT is used in combination with partner drugs, reducing the likelihood of resistance emergence. In particular, it promotes standardized care practices across healthcare facilities and providers. Consistent adherence to guidelines ensures that patients receive uniform and evidence-based treatment, regardless of their location or healthcare provider. This also reduces variability in treatment practices and contributes to more effective malaria control efforts [129].

Surveillance and Monitoring

Regular monitoring allows for timely interventions, adjustment of treatment protocols, and containment of resistance spread. This plays a crucial role in the prevention of Artemisinin Combination Therapy (ACT) resistance in Nigeria. First of all, surveillance systems monitor the efficacy of ACT by tracking treatment outcomes and detecting early signs of resistance emergence. Monitoring parasite clearance rates and treatment failure rates can provide valuable indicators of changes in drug susceptibility and resistance patterns, allowing for prompt intervention [26,27]. Secondly, surveillance data helps identify geographic areas or populations with higher rates of treatment failure or drug resistance and outbreak areas. This information allows health authorities to target interventions, such as intensified monitoring, alternative treatment strategies, or targeted education campaigns, to areas at greatest risk of resistance development. Similarly, molecular surveillance involves monitoring genetic markers associated with ACT resistance, such as mutations in the PfKelch13 gene. By tracking the prevalence of resistance markers in parasite populations, surveillance systems can detect emerging resistance trends and inform treatment guidelines and strategies accordingly. Consequently, surveillance efforts assess adherence to treatment guidelines and evaluate the quality of ACT administration in healthcare settings. Monitoring treatment practices helps identify gaps in adherence, inappropriate prescribing practices, or issues with drug quality that may contribute to resistance development. In particular, surveillance systems monitor imported malaria cases, including those from neighboring countries or regions with known resistance. Detecting imported cases with resistance markers helps prevent the introduction and spread of resistant parasite strains within Nigeria, supporting containment effort [130]. Furthermore, surveillance and monitoring data are integrated into health information systems, allowing for real-time analysis, reporting, and decision-making. Timely dissemination of surveillance findings to policymakers, healthcare providers, and stakeholders facilitates evidence-based decision-making and responsive interventions. Thus, surveillance programmes build local capacity for data collection, analysis, and interpretation through training of healthcare workers and laboratory personnel. Strengthening surveillance capabilities ensures the sustainability of monitoring efforts and enhances Nigeria's ability to detect and respond to resistance threats effectively [131].

Antimicrobial Stewardship

Antimicrobial stewardship programmes include educating healthcare providers and the public about the importance of proper diagnosis, treatment compliance, and avoiding self-medication. It helps prevent artemisinin Combination Therapy (ACT) resistance in Nigeria by promoting the rational use of antimalarial drugs and minimizing the emergence of resistance. By promoting appropriate prescribing practices, these stewardship programmes help prevent unnecessary use of antimalarial drugs, reducing the selective pressure for resistance

development. In addition, antimicrobial stewardship efforts discourage overuse and misuse of ACT, such as prescribing antimalarials for non-malarial febrile illnesses or using ACT as first-line treatment without proper diagnosis. By limiting unnecessary drug exposure, stewardship programmes minimize the risk of resistance selection and spread. In particular, antimicrobial stewardship programmes advocate for the use of diagnostic testing, such as rapid diagnostic tests (RDTs) or microscopy, to confirm malaria diagnosis before initiating treatment. By ensuring accurate diagnosis, stewardship efforts help target ACT use to confirm cases of malaria, reducing unnecessary drug pressure on parasite populations [131]. Furthermore, antimicrobial stewardship initiatives work to combat the use of antimalarial monotherapy, including artemisinin monotherapy, which increases the risk of resistance development. Stewardship programs advocate for the use of ACT as the preferred treatment regimen and discourage the use of artemisinin derivatives as standalone therapies. Consequently, antimicrobial stewardship programs monitor antimalarial prescribing patterns, treatment outcomes, and resistance trends to identify areas of concern and implement targeted interventions. By integrating surveillance data into stewardship efforts, healthcare providers can adapt treatment strategies and containment measures in response to emerging resistance threats. Likewise, antimicrobial stewardship initiatives provide education and training to healthcare providers, pharmacists, and the public about the importance of rational antimalarial drug use, antimicrobial resistance, and malaria prevention strategies. By raising awareness and promoting behavior change, stewardship programs empower stakeholders to contribute to resistance prevention efforts. Thus, antimicrobial stewardship efforts involve collaboration with government agencies, professional organizations, and community stakeholders to advocate for policy changes, resource allocation, and investment in malaria control programs. By advocating for evidence-based policies and strategies, stewardship programs help create an enabling environment for resistance prevention [132].

Regulation of Drug Distribution

The regulation of drug distribution plays a critical role in preventing Artemisinin Combination Therapy (ACT) resistance in Nigeria by ensuring the quality, availability, and appropriate use of antimalarial medications such that regulatory oversight of drug distribution channels ensures that ACT drugs distributed within Nigeria meet stringent quality standards. By enforcing regulations on drug importation, manufacturing, storage, and distribution, regulatory authorities can prevent the circulation of substandard or counterfeit medications that may contribute to resistance development. In addition, regulation of drug distribution channels helps control access to ACT drugs, ensuring that they are only available through authorized healthcare facilities and licensed pharmacies [121,123]. This reduces the likelihood of inappropriate use, overuse, or stockpiling of antimalarial medications, which can promote resistance emergence. Likewise, regulation of drug distribution prevents the parallel importation

of ACT drugs from unregulated sources or neighboring countries. Unauthorized importation can lead to the introduction of substandard or counterfeit drugs into the market, undermining efforts to control resistance and ensure treatment efficacy. Regulatory agencies monitor the supply chains of ACT drugs to ensure compliance with quality standards and good distribution practices. By tracking the movement of drugs from manufacturers to end-users, regulators can identify and address vulnerabilities in the distribution system that may compromise drug quality or integrity. In particular, regulation of drug distribution enforces licensing requirements for wholesalers, distributors, and retailers involved in the distribution of ACT drugs. Licensing ensures that distribution entities meet specified criteria for storage facilities, handling practices, and personnel qualifications, reducing the risk of drug contamination or degradation that could impact efficacy. Regulatory agencies crackdown on illicit drug trade and unauthorized vendors selling counterfeit or substandard ACT drugs by conducting inspections, raids, and enforcement actions, regulators deter illegal drug trafficking activities and protect public health by ensuring access to quality-assured medications [123,124]. Thus, the regulation of drug distribution channels includes public awareness campaigns to educate consumers about the risks of purchasing counterfeit or substandard drugs from unlicensed sources. By raising awareness about the importance of obtaining ACT drugs from authorized sources, regulators empower consumers to make informed decisions and avoid counterfeit medications [122].

Public Awareness and Education

Public awareness and education play a crucial role in the prevention of Artemisinin Combination Therapy (ACT) resistance in Nigeria by empowering individuals, communities, and healthcare providers to make informed decisions and take appropriate actions [133]. First of all, public education campaigns raise awareness about malaria transmission, risk factors, and preventive measures, such as the use of insecticide-treated bed nets, indoor residual spraying, and environmental sanitation. By promoting malaria prevention strategies, education efforts reduce the incidence of malaria and the need for ACT treatment, thereby lowering the selective pressure for resistance development [133,134]. Secondly, education initiatives educate healthcare providers and the public about the importance of proper use of ACT, including adherence to treatment guidelines, completion of full treatment courses, and avoidance of self-medication. By promoting appropriate ACT use, education efforts minimize the risk of inadequate drug exposure and resistance emergence. Likewise, public awareness campaigns emphasize the importance of early diagnosis and prompt treatment of malaria to prevent severe illness and complications. By encouraging early healthcare-seeking behavior, education efforts reduce the risk of untreated malaria infections and the potential for resistance development. In particular, public education campaigns raise awareness about the concept of drug resistance, including the factors contributing to resistance

development and the consequences of ineffective treatment. By educating the public about the importance of preserving the effectiveness of ACT, awareness efforts foster a sense of responsibility and collective action in combating resistance. In addition, education initiatives provide training and resources to healthcare providers on the proper diagnosis, treatment, and management of malaria, including the rational use of ACT. By empowering healthcare providers with knowledge and skills, education efforts improve the quality of care and minimize factors contributing to resistance emergence [133]. Furthermore, public awareness campaigns engage communities in malaria control efforts, fostering community ownership and participation in prevention activities. By mobilizing community members to take proactive measures against malaria, awareness efforts create a supportive environment for resistance prevention. Therefore, education initiatives address myths and misconceptions about malaria treatment and resistance, promoting evidence-based information and dispelling misinformation. By correcting misconceptions, awareness efforts improve treatment-seeking behavior and adherence to ACT, reducing the risk of resistance development [134].

Collaboration with Global Health Partners

Collaboration with global health partners plays a crucial role in the prevention of Artemisinin Combination Therapy (ACT) resistance in Nigeria by leveraging resources, expertise, and best practices to strengthen malaria control efforts. It contributes to ACT resistance prevention through global health partners provision of financial support, technical assistance, and resources to bolster Nigeria's malaria control programs. Funding from organizations such as the Global Fund, the World Bank, and bilateral donors helps support the procurement of ACT drugs, diagnostic tools, insecticide-treated bed nets, and other essential supplies for malaria prevention and treatment. In addition, global health partners offer technical expertise and capacity-building support to strengthen Nigeria's healthcare infrastructure, laboratory facilities, and surveillance systems [135,136]. Through training programs, mentorship, and knowledge exchange initiatives, global partners help build local capacity for malaria diagnosis, treatment, and surveillance, enhancing Nigeria's ability to detect and respond to resistance threats. In particular, collaboration with global health partners facilitates research collaboration and data sharing initiatives to better understand the dynamics of ACT resistance and inform evidence-based interventions. Joint research projects, epidemiological studies, and surveillance networks enable the sharing of data, samples, and best practices, fostering a collaborative approach to resistance prevention and control. Furthermore, global health partners support Nigeria in developing and implementing evidence-based policies, guidelines, and strategic plans for malaria control [135]. By providing technical assistance, policy analysis, and advocacy support, global partners help align national malaria control efforts with international standards and best practices, ensuring a coordinated and effective

response to resistance threats [136]. Collaboration with global health partners facilitates coordination and alignment of multisectoral efforts to combat malaria, including partnerships with government agencies, non-governmental organizations, academic institutions, and private sector stakeholders. By fostering collaboration and synergy among diverse stakeholders, global partnerships strengthen Nigeria's malaria control efforts and maximize impact. Global health partners support the introduction and adoption of new tools and technologies for malaria prevention, diagnosis, and treatment. This includes the rollout of innovative diagnostic tests, insecticide-treated bed nets, and antimalarial drugs, as well as the development of new vector control strategies and drug formulations to address emerging resistance challenges [137].

Research and Development

Research and development (R&D) play a crucial role in the prevention of Artemisinin Combination Therapy (ACT) resistance in Nigeria by advancing our understanding of resistance mechanisms, informing evidence-based interventions, and developing innovative strategies to combat resistance. It contributes to resistance prevention in that research efforts aim to elucidate the molecular mechanisms underlying ACT resistance, including mutations in the PfKelch13 gene and other genetic determinants of resistance. By studying resistance mechanisms, researchers can identify molecular markers, pathways, and targets for resistance surveillance, diagnosis, and intervention [135]. In addition, research initiatives monitor the prevalence and spread of ACT resistance through surveillance networks, epidemiological studies, and molecular surveillance of resistance markers. By tracking resistance trends, geographic hotspots, and emerging resistance threats, researchers can inform targeted interventions and containment strategies to prevent further spread. Furthermore, research evaluates the efficacy, pharmacokinetics, and pharmacodynamics of ACT drugs in different population groups and malaria endemic settings. By assessing treatment outcomes, drug concentrations, and resistance profiles, researchers can optimize treatment regimens, dosing strategies, and drug combinations to maximize effectiveness and minimize resistance selection. In particular, research explores alternative antimalarial therapies, drug combinations, and novel drug candidates to address emerging resistance challenges. By screening for new drug leads, repurposing existing drugs, or developing synergistic combinations, researchers can expand the armamentarium of antimalarial treatments and mitigate. Research investigates innovative vector control strategies, such as insecticide resistance management, larval control, and environmental interventions, to reduce malaria transmission and limit the spread of resistant parasites. By targeting both the parasite and its vector, researchers can disrupt the malaria transmission cycle and complement drug-based interventions. Likewise, research examines behavioral and socioeconomic factors influencing malaria treatment-seeking behavior, adherence to ACT, and community engagement in resistance prevention efforts

[135]. By understanding social determinants of health, researchers can design context-specific interventions, communication strategies, and community empowerment initiatives to promote effective malaria control practices [136,137].

Conclusion

There are numerous factors that can contribute to the development of ACT resistance in Nigeria. In addition, surveillance, molecular studies, and clinical trials are essential for elucidating the underlying mechanisms of ACT resistance. Thus, addressing these factors requires a multifaceted approach, including strengthening drug quality control measures, promoting adherence to treatment guidelines, enhancing surveillance of resistance markers, and improving healthcare infrastructure and access to quality-assured medications. Collaboration between government agencies, healthcare providers, researchers, and international partners is essential for effective resistance prevention and containment in Nigeria.

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