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Malaria: A Driving Force to the Emergence and the Global Spread of Antibiotics Resistance

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Abstract

Malaria and bacteraemia are significant public health concerns and economic threats. In Africa, the intensity for simultaneous transmission and co-infection of *Plasmodium spp* and other bacteria pathogens are extremely high. It is believed that malaria suppress the immune system and enable the translocation of bacteria in the gastrointestinal tract to other cellular compartments in the body. Some of the factors that contributed to the co-emergence of these pathogens are poor access to clean water, sanitation and hygiene (WASH), poor infection control measures, inefficient health care systems. In addition, the similarities in the clinical signs and symptoms of these febrile diseases and the fact that the etiologic diagnostic testing can be complex, costly, and limited are the reasons why clinicians in resource-constrained setting often prescribe antibiotics empirically prior to or without laboratory testing to prevent severe outcomes in any patient hospitalized with malaria. However, this indiscriminate use of antibiotics has been identified as the driving force for antibiotic resistance, which is already at alarming rate in malaria endemic nations. In developed countries where malaria had been previously eradicated, there are increasing reports of imported malaria with concurrent bacteraemia. In this review, we emphasized the role of malaria in the indiscriminate use of antibiotics and the fact that eliminating malaria in Africa is one of the best strategies to address the emergence and the global spread of multi-drug resistance organisms.

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Introduction

Malaria is a life-threatening disease of global concern. Infection in human predominantly occurs in tropical and subtropical regions lacking adequate health care facilities and effective control measures [1] [2]. Of all the Malaria parasites, *P. falciparum* and *P. vivax* – pose the greatest threats with the later common in sub-Saharan Africa and is one of the most common causes of fever in many malarial endemic countries and in travellers returning from those countries [3].

In 2022 alone, an estimated 249 million malarial cases and 608, 000 deaths were reported in 85 countries [4]. In Africa, the intensity for simultaneous transmission and co-infection of *Plasmodium spp* and other bacteria pathogens such as *Salmonella spp.*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* are extremely high. Basically, diseases caused by these bacterial pathogens have over-lapping clinical signs and symptoms with malaria thereby posing serious diagnostic challenges in

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resource constrained environments where symptom-based diagnosis is relied on [5] [6] Consequently, an attempt to treat malaria could lead to the misuse of different antibiotics, this could be recognized as one of the drivers of antibiotics resistance bacteria. Antibiotic resistance (AR) bacteria acquired in this process could be disseminated locally and internationally through mobility of humans, animals and formites.

Co-infection of Malaria and Bacteraemia

In low- middle-income countries, there exist co-circulation of various infectious agents leading to increasing susceptibility of individuals to contracting different diseases concurrently. Co-infection of bacterial pathogens such as *Salmonella spp*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* and *Plasmodium spp* are the two causes of febrile diseases. Malaria is thought to increase susceptibility of bacteraemia to intestinal translocation by impairment of gastrointestinal barrier defences and immune response with increased erythrophagocytosis [5] [7] [8].

Complications from Malaria among children across Africa often results in Invasive Bacterial Infection (IBI). Evidence of this concomitant interaction between *Plasmodium* and Bacteraemia was a systematic review that covers 7,208 children with severe Malaria across Africa. It was revealed that the mean prevalence of IBI among these children was 6.4% [9]. Indeed, the co-existence of malaria parasitaemia and bacteraemia usually increases the risk of morbidity and mortality among children in malaria-endemic regions, as it is difficult to distinguish clinically between severe malaria and sepsis. As a therapeutic guideline for children with severe malaria, the WHO recommended concomitant antimalarial and broad-spectrum antibacterial treatment especially where bacterial meningitis and evidence of aspiration cannot be ruled out [10] [11]. In contrast, it was believed that concurrent bacteraemia is uncommon in adults hospitalized with *Plasmodium* infection. As a result, adults with severe malaria are not encouraged to take antibacterial and antimalarial medications simultaneously. This approach is important to prevent the development and spread of multi-drug resistance genotypes in *Plasmodium falciparum* and bacteria pathogens [12] [10] [13] [14] [15]. However, a study from Myanmar hospital conducted on 87 patients admitted with diagnosed *falciparum* malaria showed that 15% of the victims were bacteraemia on admission [16]. Another meta-analysis report on co-infection of bacteraemia in malaria patients covering 37 and 6 studies across Africa and Asia continents respectively gave 7.6% total prevalence of IBI. Africa, with the highest burden of malaria carried 9.1% prevalence while Asia got 6.1% incidence. This study also gave the pooled prevalence of bacteraemia in adults and children to be 10.3% (6 studies) and 9.1% (27 studies) respectively [5]. As against WHO guidelines on malaria treatment, clinicians in resource-limited settings, where etiologic diagnostic testing can be complex, costly, and limited, antibiotics are often prescribed empirically prior to or without a laboratory testing to prevent severe outcomes in any patient hospitalized with malaria. In addition, the overlapping in the clinical signs and symptoms of these febrile diseases often result in diagnosis challenges and antibiotics are one of the few affordable adjunctive treatments that is widely available in these settings. However, this strategy has potential shortcomings: indiscriminate use of antibiotics increases health care costs and the risk of drug side effects, while driving AR, which is already at concerning levels in sub-Saharan Africa [17] [18].

Phylosophy of Indiscriminate use of Antibiotics in Malaria-endemic Regions

Antibiotics are group of medications useful in the treatment and prevention of diseases caused by bacteria. Antibiotics use ranged from 33% for patients in the Western Pacific Region, to 83% in the

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Eastern Mediterranean and the African Regions. Increasing bacterial resistance to antibiotics can occur spontaneously through mutation, but has accelerated greatly through a number of other factors such as; indiscriminate use of antibiotics, poor access to clean water, sanitation and hygiene (WASH), poor infection control measures, lack or poor diagnosis, inefficient Antimicrobial Resistance (AMR) surveillance programs and lack of proper regulations especially in agricultural sectors [19] [20] [21].

This increasing AMR pose a significant concern of both public health and economical threats. Globally, deaths from drug-resistant infections currently claim around 700,000 lives annually, and by 2050 this figure is projected to rise to 10 million with Africa accounting for 4.5 million, if appropriate actions are not taken. In addition, the World Bank estimates that by 2050, AMR could result in US$ 1 trillion additional healthcare costs, and US$ 3.4 trillion gross domestic product (GDP) losses per year by 2030 [22] [23]. Addressing this monster requires urgent and holistic interventions at national and international levels. As a matter of fact, the top of the WHO laid down strategies is to address all infections that may result in inappropriate use of antimicrobial agents [22]. With an estimated 249 million cases and 608,000 deaths in 2022, the similarities in the clinical signs and symptoms to other febrile diseases and the poor health care facilities in the endemic regions, undoubtedly, malaria remains the leading parasitaemia suspect that contribute to the emergence and spread of antibiotics resistance pathogens [24] [25]. Corroborating this assertion was the research conducted in Tororo, a historically high malaria transmission area of Uganda. The investigators observed that after the implementation of highly effective malaria control interventions, the incidence of antibiotics treatment reduced significantly. This was attributed to fewer episodes of symptomatic malaria and fever which were previously treated with antibiotics [26]. In this regard, it could be reasonably assumed that, effective malaria control strategies will reduce the indiscriminate use of antibiotics and hence downward trends in the development and spread of antibiotic-resistant bacteria.

Global Spread of Malaria and Multidrug-resistance Organisms

For several decades ago, localized transmission of malaria has been eliminated in many developed countries of the world, while some nations are advancing towards its eradication. However, this success has been threatened by the continuous increase in long-distance travel and recent large migratory movements from malaria high transmission nations. Consequently, this phenomenon has resulted in an increased incidences of imported malaria cases in most of these non-endemic countries [27] [28]. Factors such as; variability in disease recognition, diagnostic capabilities, reporting protocols and adherence to those reporting protocols and population travel patterns are responsible for the variation in the reported incidence of imported malaria case [29]. Official data revealed that European countries contributed approximately 70% of the global burden. Indeed, the percentage of incidence increased from 14% to 86% throughout the last decade with France accounting for 50% of the total imported cases. The United States got approximately 15% of global imported malaria episodes. In both scenarios, *P. falciparum* from sub-Saharan Africa was identified as the major etiological agent responsible for such imported malaria incidence. This imported parasitaemia requires special and urgent interventions because of the potentially high mortality, delayed diagnosis, high cost of treatment and the risk of secondary local transmission owing to the limited awareness among medical experts in nonendemic countries [30] [31] [32].

Similar to the occurrence in sub-Saharan Africa, some of the events of imported malaria have been accompanied with concurrent bacteraemia diagnosis. For instance, In Italy and Germany, a co-infection rates of 13% (9/70) and 16% (41/264) were reported among patients hospitalized with malaria respectively [8]. One might presume that, individuals diagnosed with this imported *Plasmodium*

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infection, having exposed to the risk factors such as; contaminated water and food, and prior exposure to antibiotics, could be a reservoir for carriage and distribution of drug-resistant *Enterobacteriaceae*. Apart from being an important commensal of human gastro-intestinal tract, *E. coli* has been reported as an important reservoir of antimicrobial resistance genes, that can be transferred to other pathogenic species through horizontal gene transfer. Indeed, by means of its virulence factors, pathogenic species of *E. coli* has been associated with diverse intestinal and extraintestinal illnesses such as; diarrhoea, dysentery, urinary tract infections and meningitis [33] [34] [35].

In the United States, the Department of Health and Human Services has declared the necessity to take national action and to strengthen surveillance systems in order to combat the spread of antimicrobial resistance. In line with this, drug resistance *Enterobacteriaceae* have been designated as 'urgent threat' or 'priority 1' pathogens by the US Centers for Disease Control and Prevention (CDC) and the WHO [35].

Conclusion

Malaria is a life-threatening infectious disease of public health concerns, with African regions accounting for high share of the global malaria burden. *Plasmodium* infection suppress the immune system and increases the translocation of bacteria in the gut thereby increasing the susceptibility of children and adult to concurrent bacteraemia, often with severe outcomes. For effective therapeutic strategy, the WHO recommended simultaneous use of antimalarial and broad-spectrum antibacterial treatment in children with severe malaria. However, this practice is strongly condemned in adults, with a view to preventing the abuse of the medications. Despite this, several factors such as; diagnosis difficulties, similarities in the clinical signs and symptoms of these febrile diseases and limited access to quality health facilities, the act of taking antimalaria concurrently with antibiotics has become a common practice among adult in resource-constrained malaria endemic regions. Unfortunately, this act of indiscriminate use of antibiotic has been identified as the driving force for antibiotic resistance, which is already at concerning levels in malaria endemic areas.

Due to globalization, there have been an increased exportation of malaria cases from the endemic nations to developed countries where malaria has been previously eradicated. In comparison to what is obtained in sub-Saharan Africa, this imported malarial incidences have been accompanied with bacteraemia in some hospitalized patients.

In line with the WHO frontline strategy to address all infections that may result in inappropriate use of antimicrobial agents, we stand to reason that defeating *Plasmodium* infection in sub-Saharan Africa will go a long way in addressing the emergence and the global spread of MDRO and their genetic factors. Honestly, we can only take comfort in the fact that, reduction in the level of global malaria events is complementary to reduction in global bacterial infection.

Authors Contribution

ROM conceptualized the paper, which was developed further in discussion with DI. Both authors collated articles for review and contributed to the preparation of the final version, and provided consent for submission.

Declarations

Competing Interests: The authors declare no competing interests.

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Abbreviations

P. falciparum - Plasmodium falciparum; P. vivax - Plasmodium vivax; WASH - Water and Sanitation Hygiene; AR - Antibiotics Resistance; IBI - Invasive Bacterial Infection; WHO - World Health Organisation; MDRO - Multi-Drug Resistance Organisms

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