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Review

Factors Driving Malaria Transmission in Sub-Saharan Africa

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【Abstract】

Malaria is a major public health problem in sub-Saharan Africa. According to the World Health Organization, in 2018, this region suffered 93% of the global malaria cases and 94% of the global malaria deaths. In the literature on malaria transmission, there are reports of some successes in the reduction of malaria cases between 2000 and 2015. These successes were largely attributable to a combination of preventive and curative measures, including vector control using long-lasting insecticide-treated nets, indoor residual spraying, and larval source management, and improved malaria diagnostics and chemotherapeutics. However, further significant reduction in malaria transmission after 2015 remained a major challenge. Malaria control gains were stalled and cases began to rise in 2016. The major challenges to malaria control include the application of inappropriate approaches (i.e., "one-size-fits-all" approaches) and lack of political commitment by sub-Saharan African national governments. The World Health Organization and Roll Back Malaria Partnership is now encouraging country-focused and country-led plans for the implementation of comprehensive actions against malaria at individual country levels. This mini-review aimed to describe factors influencing continued malaria transmission in sub-Saharan Africa

Key words: Malaria, Malaria transmission, Influencing factors, Sub-Saharan Africa.

総　説

サハラ砂漠以南のアフリカにおけるマラリア感染を促進する要因

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【要　旨】

マラリアはサハラ以南のアフリカの主要な公衆衛生問題である。2018 年、世界のマラリア症例の 93%、マラリアによる死亡の 94%が世界保健機関のアフリカ地域で発生した。とりわけ 5 歳未満の子供、妊婦、HIV/AIDS 陽性者、へき地にくらす人々は最もマラリアに脆弱な集団である。マラリア症例数は 2000 年から 2015 年の間に著明に減少し、対策が成功していることが多くの文献によって示されている。これは主に、長期残効型蚊帳、屋内残留噴霧、幼虫発生源の同定を用いた媒介蚊対策とマラリアの診断、治療法の改善によるものである。しかし、2015 年以降マラリア対策の進展はそれ以前と比べ停滞し、2016 年から症例数が増加し始めた。マラリア対策の主な課題は、アプローチを不適切に用いること（"one-size-fits-all" approaches）やサハラ以南のアフリカによる政治的なコミットメントの欠如である。世界保健機関とロールバックマラリアのパートナーシップは、各国の事情に合わせたマラリアに対する包括的な行動を実施するために、国主導で計画を立てることを強調している。このミニレビューは、サハラ以南のアフリカにおけるマラリア流行の持続に影響を与える因子について概説する。

キーワード：マラリア、マラリア伝搬、影響因子、アフリカ

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1. Introduction

Malaria is a life-threatening disease caused by protozoan parasites of the genus *Plasmodium*. The disease is transmitted through the bites of infected female *Anopheles* mosquitoes. To date, there are five plasmodia species known to cause malaria in humans. Among them, two species, *P. falciparum* and *P. vivax*, are the most common and present the greatest threat to humans. Malaria is a global health problem, affecting nearly half of the world's population and is currently endemic in 76 countries (Figure 1). According to the World Health Organization (WHO), it is estimated that, in 2018, 228 million people suffered from malaria and 405,000 people died from the disease globally (WHO, 2019). Nearly 93% of the malaria cases and 94% of the deaths occurred in sub-Saharan Africa (SSA) where *P. falciparum* is the predominant species (WHO, 2019). Currently, six African countries account for more than half of all malaria cases worldwide. These include Nigeria (25%), the Democratic Republic of the Congo (12%), Uganda (5%), and Côte d'Ivoire, Mozambique, and Niger (4% each) (WHO, 2019).

Previously, for a period of about 15 years, concerted and aggressive malaria control efforts significantly decreased the global malaria burden (Hemingway et al., 2016). In 2015, a *Nature* report by Bhatt and colleagues indicated that between 2000 and 2015, an estimated 663 million clinical malaria cases were prevented (Bhatt et al., 2015). Insecticide-treated nets (ITNs) averted 68% of malaria cases, making it the most effective malaria control tool available, compared with artemisinin-based combination therapy and indoor residual spraying, which averted 22% and 10% cases, respectively. The remarkable progress presented an increase in the number of countries nearing malaria elimination worldwide (WHO, 2018b). On the African continent, Egypt and Morocco have been malaria-free since 2000, and Algeria, achieved elimination status in 2016 (WHO, 2019). More countries in SSA, including Botswana, Cape Verde, Comoros, South Africa, and Swaziland promised

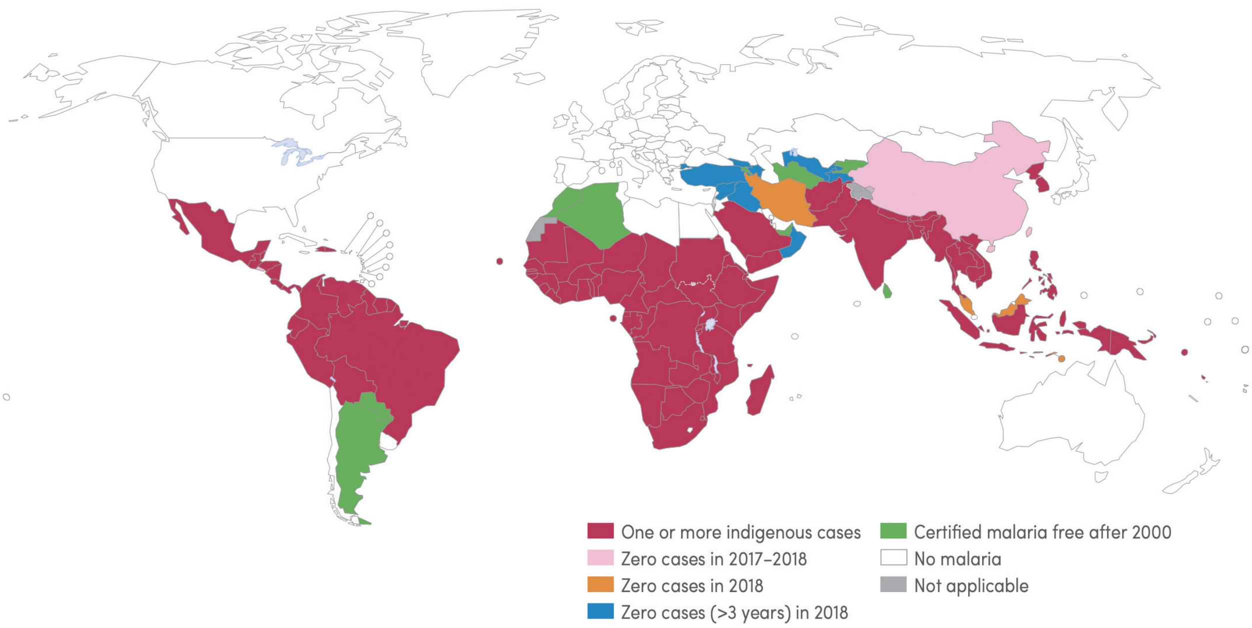

Figure 1: Countries with indigenous malaria cases in 2018. Countries with zero indigenous cases over at least the past 3 consecutive years are considered as having eliminated malaria (World Malaria Report 2019)

malaria elimination by 2020 (WHO, 2018b). However, despite the sustained global efforts, gains in malaria control especially in Africa have plateaued, and most elimination strategies so far remain seriously challenged (Bashir, Nyakoe, & van der Sande, 2019; Nkumama, O'Meara, & Osier, 2017). The WHO reported significant increases in the number of malaria cases (from 211 million to 216 million) in 2016 (WHO, 2017b). Moreover, countries, including Burkina Fasso, Cameroon, Democratic Republic of the Congo, Ghana, Mali, Mozambique, Niger, Nigeria, Uganda, and the Republic of Tanzania still have significantly high malaria burden, and have missed the WHO Global Technical Strategy for Malaria elimination 2020 aimed at reducing malaria incidence and deaths by 40% (WHO, 2018b).

While malaria control strategies employed in the SSA region have been previously explored (Segun, Shohaimi, Nallapan, Lamidi-Sarumoh, & Salari, 2020; WHO, 2019), the need for a thorough understanding of the factors that influence continued malaria transmission in the region remains. The deciphering of these factors would promote discovery of novel malaria control strategies and improve the once effective current interventions. Therefore, this mini-review aimed at delineating factors driving continued malaria transmission in SSA despite ongoing control strategies. We grouped these factors into six categories: (i) environmental and behavioral factors, (ii) socioeconomic factors, (iii) poor health systems, (iv) funding constraints, (v) lowered sensitivity of mosquito vectors to insecticides, and (vi) emerging antimalarial drug resistance in Africa.

2. Factors contributing to the stability of malaria transmission in sub-Saharan Africa

2.1 Environmental and behavioral factors

The environment and human behavior play critical roles in malaria transmission in Africa (Obed Matundura Ogega. & Alobo, 2020). Climate-related factors, including temperature, rainfall, and humidity, encourage survival of the mosquito vector (Metelmann et al., 2019; Nsoesie et al., 2016). Africa is located in the tropics, where the climate is warm, wet, and humid. The wet season collects stagnant water, which is a good breeding ground for mosquito vectors. Different *Anopheles* species prefer different aquatic habitats. Some prefer small, shallow collections of fresh water, such as puddles and hoof prints that are abundant around homesteads. Others breed in large, stagnant water bodies. In addition to the rainy season, warm temperatures further promote mosquito breeding. Increasing evidence has shown that global warming is likely to increase the seasons and geographical extents for malaria transmission, resulting in more cases and new malaria hotspots (Himeidan & Kweka, 2012; Karungu et al., 2019; Kristie L Ebi., 2018; Peterson, 2009). Temperatures ranging from 24℃ to 25℃ were reported to be optimal for the maturation of the aquatic stages of the *Anopheles* mosquito vector, and appropriate for the completion of the parasite's life cycle in the vector host (Arab, Jackson, & Kongoli, 2014; Mordecai et al., 2013). Statistical modelling of the effects of weather on malaria occurrence in Abuja, Nigeria, revealed that relative humidity was a factor that influenced malaria epidemics, however the most significant influence was temperature (Segun et al., 2020).

With regard to behavior, Hernández-Valencia et al. (Hernandez-Valencia, Rincon, Marin, Naranjo-Diaz, & Correa, 2020) recently reported the impact of landscape fragmentation on mosquito abundance and diversity. The authors observed that activities that modified the landscaope structure and land cover composition generated changes that effected the spatial distribution and composition of Anopheles mosquitoes and impacted malaria distribution in the region. Practices of landscape fragmentation for example rice farming allow collection of stagnant water promoting mosquito breeding and subsequent increase in malaria infections.

Therefore, climate and ecological factors that favor mosquito vector breeding and completion of the parasite's lifecycle, coupled with the mosquito vector prioritizing feeding on humans other than animals for survival, could, at least in part, justify the over 90% burden of malaria infections in SSA.

2.2 Socioeconomic factors

For long, poverty has undeniably been a significant contributor to stabilized malaria transmission in Africa. Poorer and marginalized communities suffer more malaria and related consequences than more economically advantaged communities. Several factors that favor malaria transmission interrelate malaria and poverty. These factors include low household income, low education and health awareness, poor housing, malnutrition and nutrition deficiencies, socio-cultural barriers, and inequalities in accessing quality malaria treatment. Low household income and low education or health awareness directly or indirectly hamper efficient consumption of health services akin to malaria control. In fact, a relationship between low income and the incidence of febrile infections was reported (Filmer, 2005). The poor are also often less exposed to information, education, and communication materials such as printed posters and flyers as well as the media (newspapers, radio, or television). When resources such as the aforementioned are available, more often than not they are difficult to comprehend due to the low literacy levels in the communities. Hence, low literacy levels as well as general lack of health information and awareness among the poor maybe directly associated with reduced demand for health care.

Additionally, low household income translates into poor food security and malnutrition. Children in poor communities tend to suffer from chronic malnutrition due to poor protein and calorie intake and micronutrient deficiencies. WHO estimates that 60% of childhood deaths in developing countries occur in underweight children (WHO, 2020). More still, malnutrition is associated with reduced immunity and increased malaria morbidity and mortality (Caulfield, Richard, & Black, 2004; WHO, 2020).

Another important poverty-related factor of malaria transmission is poor housing. By and large, living conditions in Africa are considered poor and characterized by inadequate housing and overcrowding. Several housing structures, temporary or semi-permanent, are made from readily available materials and offer easier mosquito entry compared with permanent structures with screened outlets (Tusting et al., 2015; Wanzirah et al., 2015). In addition, some homes are overcrowded and have family living spaces in close proximity to domestic animal shelters. The warm animal body temperatures in the shelters attract mosquito vectors, enhancing malaria transmission (Lindsay et al., 2003). Overcrowding has also been associated with an increased risk of malaria infection; the mosquitoes are attracted by the high carbon dioxide concentration generated in such circumstances (Alton C., 2004).

Additionally, health workers, especially in the public sectors of these African poorer countries, are reluctant to practice in rural and remote health districts or units. The health districts or units simultaneously suffer shortages in the supply of essential medicines and equipment, leading to reduced quality of patient care and limited confidence in the health system. Unfortunately, most attempts for seeking alternative private healthcare are frustrated by substandard service delivery and the rampant marketing of expired antimalarial drugs in the region.

2.3 Poor health systems

The WHO-proposed a structure for an effective health care system consisting of six core components: (i) service delivery, (ii) health care workforce, (iii) health care information systems, (iv) medicine and technology, (v) financing, and (vi) leadership/governance (WHO, 2007). However, most African countries cannot conform to the proposed framework due to several challenges, including lack of political will, poor leadership, and inadequate or insufficient human and other resources for the public health sector. Further challenges often include corruption, lack of evidence-based interventions, poor health service delivery, poor training of health care workers, and inadequate health information systems (Oleribe et al., 2019). The core of these challenges includes poor funding, poor leadership, and lack of political will by the national governments.

Skilled manpower is an important pillar of efficient health care services, and, in Africa, shortages in skilled workers are often due to unfavorable government policies, especially those regarding education/training and employment. The WHO recognizes that to a greater extent, low health workforce contributes to the disproportionately high share of the global malaria burden in Africa (WHO, 2017a). In most African countries, limited allocation of resources, including logistical supplies and health workers to the public health sector, is coupled with poor working conditions and inadequate remuneration. Reduced manpower results in staff burnout, reduced professional commitment, poor job performance, and more health care workers moving to private practice (Omaswa, 2014). Additionally, the shortages in medical supplies, including drugs and other medicaments, often breed corruption within the system and drive patients to seek illegal or outsourced healthcare. Moreover, the outsourced or alternative care especially in rural communities is dominated by low cadres and sometimes unprofessional staff who often contribute to poor malaria case management and indiscriminate use of drugs. It has been reported that most fevers are diagnosed as malaria by these unprofessional staff, leading to unnecessary use of antimalarial drugs. This eventually creates drug pressure that leads to selection of drug resistant parasites. Subsequently compromising the efficacy of the few available drugs in malaria treatment (Awor, Wamani, Bwire, Jagoe, & Peterson, 2012). Hence, poor government policies greatly impact health care service delivery, especially in rural African communities, leading to poor health outcomes and impeding the achievement of national and global malaria control targets.

2.4 Funding constraints

Malaria control and elimination requires consistent and sustainable support for core interventions, such as vector control, case management, and chemoprevention measures (e.g., intermittent preventive treatment in pregnancy). Any interruption in the continuity of these interventions directly and negatively affects malaria transmission control efforts. The majority of funding for malaria control in the poor African countries is unfortunately dependent on external donor funding. From 2010 to 2018, about 70% of the funding for malaria control worldwide was provided by international agencies (WHO, 2018a, 2019). Governments in endemic countries contributed only 30%. Since 2010, malaria funding has plateaued at US$2.5 to 3 billion annually, and from 2015 to 2016, 34 African countries experienced reduced funding from the international community. In 2018, the US$2.7 billion funding allocated to malaria control fell short of the US$ 5 billion required to achieve 2025 and 2030 Global Technical Strategy goals (WHO, 2019) and governments of endemic countries only contributed US$ 800 million. Even when member states of the African Union (a continental union consisting of 55 member states) pledged to provide at least 15% of domestic budgets to control disease, less than 10% of the governments upheld their pledge. Compounding this problem is the fact that the limited foreign monetary funds donated to the African governments to fight malaria are often swindled or misappropriated by government officials. One example of this is the reported misuse of global fund funding for HIV/AIDS, tuberculosis, and malaria programs in some SSA countries in 2011 (TheGlobalFund, 2011). The non-prioritization of health care service delivery, corruption, and financial abuse in the African governments profoundly reflects the lack of political will to fight malaria.

Low funding and reduced budgeting significantly impact malaria control coverage and the performance of health systems. For example, in 2018, ITN coverage was only 54%, indicating that half of the vulnerable people, such as pregnant mothers and children, did not sleep under ITNs. This situation resulted in persistently high malaria morbidity and mortality in these populations (WHO, 2018b). Therefore, to achieve the global targets of malaria elimination, funding from both international agencies and local governments should be increased and equitably allocated for sustainable and efficient application of all malaria control interventions. It is also critical that SSA local governments show more commitment to malaria control by dealing more severely with the corruption and misuse of funds meant for disease control in accordance with the local and international laws and regulations governing the affected agencies and institutions.

2.5 Resistance of mosquito vectors to insecticides

Resistance of malaria vectors to the commonly used insecticides, including pyrethroids, organophosphates, carbamates, rare organochlorine dichlorodiphenyltri chloroethane, threaten malaria control and elimination efforts. During the period of 2010 to 2018, 73 countries confirmed insecticide resistance to at least one insecticide in at least one malaria vector species (WHO, 2019). Of these, 26 countries reported insecticide resistance to all 4 main insecticide classes (pyrethroids, organophosphates, carbamates, and organochlorine dichlorodiphenyltri chloroethane) in at least one vector species, and 18 countries reported resistance to three insecticide classes. The percentage of confirmed resistance to pyrethroids is 85%; organochlorines, 81.5%; carbamates, 68%; and organophosphates, 56% (WHO, 2019).

Pyrethroids are currently the only insecticides used in treating bed nets for vector control. The use of ITNs reportedly averted 68% of 663 million malaria cases between 2000 to 2015 (Bhatt et al., 2015), and recently, the WHO indicated that increased ITN use reduced malaria incidence rates by more than 50% in Africa (WHO, 2017b). However, emerging resistance threatens these gains and could, in part, explain the observed escalation in malaria cases in Africa (Churcher, Lissenden, Griffin, Worrall, & Ranson, 2016). Although insecticides are currently notable drivers of low malaria transmission in regions with susceptible vector populations, their efficacy in regions with resistant *Anopheles* vectors is limited. Some studies have shown that even low levels of insecticide resistance contribute to the propagation of malaria infections (Churcher et al., 2016). In contrast, several areas in Africa with moderate to high insecticide resistance have reported effective reduction of malaria infections (Alout, Labbe, Chandre, & Cohuet, 2017; Kleinschmidt et al., 2018). Future research is crucial to better understand this discrepancy, which may be largely attributable to the ITN physical barrier between mosquitos and humans.

Besides emerging insecticide resistance, there are other challenges to malaria vector control. For instance, although most malaria vectors feed and rest indoors, there are some vectors that have developed behavioral plasticity in an effort to evade insecticides. These vectors may choose to feed indoors but rest outdoors on surfaces not protected by insecticides. Moreover, some vectors may completely invade new territories where they adapt to altered breeding and feeding patterns. For example, some vectors primarily not only feed on humans but also on animals (Alout et al., 2017; Hemingway et al., 2016; Nkumama et al., 2017). Such behavior establishes extra-domiciliary malaria transmission.

2.6 Emerging antimalarial drug resistance in Africa

Like the above-mentioned insecticides for vector control, drugs used to treat and/or prevent malaria are threatened by resistance. Resistance to previously used drugs like chloroquine and related aminoquinolines, as well as antifolates has been documented (Mita, Tanabe, & Kita, 2009). Currently, the recommended treatment for malaria is artemisinin-based combination therapy. Artemisinin-based combination therapy reportedly averted 22% of 663 million malaria cases between 2000 and 2015 (Bhatt et al., 2015). However, resistance to artemisinin, defined as delayed parasite clearance, has emerged and is currently confirmed in 5 countries South east Asia (SEA); Thailand, Cambodia, Myanmar, Laos and China (WHO, 2019). The clinical phenotype of artemisinin resistance is associated with mutations in the kelch13 gene (Ariey et al., 2014), and increased parasite survival in the ring survival assay (Witkowski, Amaratunga, et al., 2013; Witkowski, Khim, et al., 2013). Delayed parasite clearance phenotype alone does not lead to treatment failure but decreases the efficacy of the partner drug. At the moment, the decreased efficacy of partner drugs i.e. mefloquine (Wongsrichanalai & Meshnick, 2008) and piperaquine (Witkowski, Khim, et al., 2013) have led to treatment failure in some countries in Southeast Asia. Therefore, it is increasingly worrisome that the observed drug resistance in Southeast Asia might spread to Africa either following a path previously taken by chloroquine resistance (Mita et al., 2009) or emerging independently in the region. In 2018, we reported for the first time, the emergence of *in vitro* artemisinin resistance in Africa among four (4/194) isolates obtained between 2014 and 2016 (Ikeda et al., 2018). One of these parasites carried the kelch13 A675V mutation associated with artemisinin resistance observed in Southeast Asia (WWARN, 2019). This mutation has also been reported in some African countries. For instance, among 5% of isolates from four sites in Northern Uganda (Asua et al., 2019) and one isolate in Rwanda (Tacoli et al., 2016). There are also warning signs of declining artemisinin-based combination therapy efficacy in some African countries, including Uganda, Kenya, Angola, and the Democratic Republic of Congo (Borrmann et al., 2011; Plucinski et al., 2017; Plucinski et al., 2015; Yeka et al., 2016). The establishment of antimalarial drug resistance increases propagation of the malaria parasites amid the absence of immediate effective alternatives, which results in increased malaria cases and related deaths in the most vulnerable groups.

3. Conclusion

Global efforts against malaria continue unabated amid reassurances of the possibility of reprising past progress in control and the achievement of set targets by both the WHO and all stakeholders. There are many challenges, particularly in highly endemic regions. We have presented the most likely factors driving the stability of malaria transmission in SSA. Although environmental factors such as climate change cannot be overlooked, most challenges are related to human behavior, the political will of national governments, and poverty. It is crucial that the national governments of African countries focus more on the efficient implementation of available effective malaria control measures and on improving the economy of their populations. Sub-Saharan African national governments must take on the disease burden and translate political commitment into equitable appropriation of available resources and tangible actions that save lives. Africans must also adequately protect themselves from malaria through knowledge, proper practices, and attitude change. Malaria control strategies are often designed and guided by donor governments and/or agencies, leaving the region's national governments with only implementation responsibility. Although such strategies are well intended, they are usually "one-size-fits-all" approaches that may not be effective in certain situations. More effective strategies that are tailored to resolve country-specific challenges are recommended. For example, African countries need to spearhead research and surveillance to identify and utilize vector control measures that are effective in their individual countries. Also, African governments should plan for sustaining malaria control interventions. For instance, strategies such as indoor residual spraying are implemented in cycles. Missing subsequent rounds of IRS due to lack of funds is followed by a surge in malaria transmission. Frustrating the little gains in malaria control. Therefore, prioritizing deployment of effective control tools for maximum impact is paramount. Furthermore, a more effectively coordinated intersectoral collaboration between health and other sectors (e.g., the environment, agriculture, and education) could comprehensively strengthen malaria control in sub-Saharan Africa.

Conflicts of interest

The authors declare no conflicts of interest.

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