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Review Article

Malaria can become a Big Threat in Urban Areas of Ethiopia and Somewhere Else in Africa

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Abstract

According to a recent publication in BioMed Research International, malaria can be a significant public health issue in Ethiopia and elsewhere in Africa. Malaria currently looks to be increasing in a number of locations where it was previously under control, according to this paper written by Tekalign., *et al* [1]. *Anopheles stephensi's* emergence in Africa [1] and the influence of the COVID-19 pandemic on prevention and control efforts [2] were mentioned in the literature as contributing factors to this problem. Malaria is responsible for about 10% of all diseases in Africa. Nearly 70% of Ethiopia is affected, with 52% of the population at risk. Tekalign., *et al.* also discussed various difficulties with malaria preventive and treatment methods, such as partial resistance to artemisinin. Additionally, gaps in the novel therapeutic pipeline and prospective alternatives such medicinal plants were considered [1]. The goal of this remark was to further explain the impact of malaria, the challenges associated with its preventive, control, and treatment strategies, as well as to address recent events and potential future directions.

Keywords: *Malaria; Ethiopia; Africa, Anopheles stephensi*

Introduction

Current and future prevalence of malaria in Africa

The World Health Organization (WHO) reported that, notably in sub-Saharan Africa (high burden countries), progress in reducing the global burden of malaria has slowed or stopped in recent years [3]. Africa accounts for over 96% of the annual global morbidity and mortality from malaria. Malaria continued to harm young children and pregnant mothers in Africa. It accounts for 20% of all fatalities in children under the age of five in Africa [1]. In Ethiopia, it was discovered that the combined prevalence of malaria among adults (13.61%) was higher than that of the general population and almost on par with that of pregnant women [4]. The Ethiopian Federal Ministry of Health (FMoH) clarified in Amharic at a meeting on November 17, 2022 that malaria is widely distributed throughout the nation and that the positivity rate was 26% [5]. The prevalence of malaria was 20.7% in Mizan-Tepi University Teaching Hospital, Southwest Ethiopia, demonstrating that the disease continues to pose a serious threat to local residents [6]. In a conference conducted on November 29, 2022,

the health department of the Bench-Sheko zone in southwest Ethiopia reported that out of 82,000 suspected malaria cases, 45,000 cases were confirmed to be positive for the disease within a period of 4 months. This demonstrates that the current malaria prevalence is more than 50% at the zonal level [7]. According to a facility-based cross-sectional study conducted in Northwest Ethiopia, malaria significantly contributes to febrile illnesses (29% of participants had a *Plasmodium* species infection) [8]. Throughout the past few decades, land use changes have accelerated all over the world. Through changes in ecology and environment, this phenomenon may have significant effects on the regional and temporal distribution of vector-borne illnesses, including malaria [1]. Important drivers of malaria risk and transmission in Ethiopia include housing conditions, altitude, climate, and environmental changes brought on by the construction of infrastructures, dams, and agricultural projects. Some investigations have found malaria in places higher than 2000 meters above sea level (masl), despite the fact that areas between 1600 and 2000 masl are typically epidemic-prone hypo-endemic zones for the disease. In northern Ethiopia, households in villages with irrigation micro-dams experienced a malaria incidence of roughly 32% compared to 19% in communities without micro-dams. In lowland and midland ecological environments, where the nation has recently considered expanding its large-scale irrigated agriculture, the adverse consequences are even more noticeable. Additionally, the highlands of Ethiopia, particularly Addis Ababa, are becoming conducive to malaria because of rising temperatures, which is expected to increase the prevalence of the disease. According to a case study conducted in northern Ethiopia, the region appropriate for malaria transmission may rise by 94 to 114% by 2050 as a result of climate change. By 2070, up to 130 million individuals nationwide could be at risk of malaria, which could result in significant economic losses. Furthermore, the risk of increased *Plasmodium falciparum* and *vivax* transmission in Africa, especially Ethiopia, is enhanced due to the appearance of new vectors like the *A. stephensi* [9]. As per Hamlet., *et al*. the number of *falciparum* malaria cases per year might rise by 50% in the absence of any new measures. In Djibouti, malaria cases have multiplied 30-fold since the first *A. stephensi* detection in 2012 [10].

Emergence of *A. stephensi* and malaria control challenges in Africa

The mosquito species *A. gambiae* has been regarded as the most hazardous and prevalent in rural parts of Africa. Malaria is usually thought of as a disease of the countryside because the majority of African *Anopheles* mosquitoes breed in rural areas. However, *A. stephensi*, the primary malaria mosquito in India, has been found in Djibouti, Ethiopia (Diredawa, Oromia, Somali, and Afar), Sudan, Somalia, and Nigerian cities and towns. Therefore, malaria has the potential to worsen in urban Ethiopia and elsewhere in Africa [1,10]. According to Sinka., *et al.* over 126 million people in cities across Africa could be at risk of acquiring malaria due to close association of *A. stephensi* with man-made habitats [11]. The spread of this invasive malaria vector poses a significant threat to efforts to improve global health in Africa. It is an efficient vector of *P. vivax* and *falciparum* and is may be a vector of zoonotic *Plasmodium* species. The expansion of *A. stephensi* as a result of zoophilic (choose animals), exophagic (feed outdoors), and exophilic (rest outdoors) preferences is a further threat to malaria prevention and control in Africa, according to the World Malaria Report [1].

A. stephensi has demonstrated resistance to insecticides, delaying the elimination of this vector by this technique. The malarial mosquitoes that are native to Africa love to bite individuals when they are asleep inside their homes. However, *A. stephensi* can bite in the early evening. People aren't actually in bed when it comes looking for a meal, so bed nets don't offer the same level of protection. In addition, this vector favors eating its blood meal outside. If it does bite indoors, it leaves quickly and avoids being sprayed with insecticides. According to a laboratory study conducted in Ethiopia, *A. stephensi* is resistant to a variety of insecticide classes, most notably pyrethroids (the only class recommended by the WHO, to date, for use in nets) [12-14]. The malaria parasite is becoming harder to detect as well as harder to kill [11]. Rapid diagnostic tests (RDTs) for malaria are becoming less and less reliable as isolates lacking the histidine rich protein-2 (HRP2) antigen have been discovered in the Amazon, India, Africa, and Asia regions. Furthermore, due to the fact that this vector often nests in artificial water storage areas (plastic tanks, cisterns, barrels, discarded tyres and plastic containers), malaria transmission can persist for a very long period. Many people conserve water due to an unreliable water supply. This concern is most pressing in metropolitan and periurban regions, where there is a high population density, poor access to medical care, inadequate vector control, and a constant

need to stock up on water. It is not unexpected that *A. stephensi* frequently coexists with *A. aegypti*, a significant dengue vector in urban Africa. Furthermore, solid waste disposal is frequently problematic in these locations, which increases the potential for the breeding of these vectors. These demonstrate that some areas are susceptible to malaria epidemics. Despite being primarily an urban vector, *A. stephensi* may expand its biological range into more rural locations when habitats like streams and irrigation ditches are abundant [1,15]. In conclusion, a molecular biologist at Ethiopia's Armauer Hansen Research Institute describes *A. stephensi* as a three to meet-the medicine resistance, the diagnostic resistance, and the extremely effective vector [12]. These circumstances added a new barrier to stopping the spread of malaria and made it more difficult to combat the disease.

Malaria treatment difficulties

The four doses of Mosquirix® vaccination (RTS, S vaccine) only achieve a 30% reduction in malaria mortality in children. Accepting this constraint, a substantial domestic or international budget or money is needed to implement a malaria immunization campaign in Africa. In addition, the malaria vaccine is not available for adults [1]. These worries and the emergence of insecticide-resistant malaria vectors (described above) highlight the reliance on chemotherapy that is now in place. However, a significant issue is the establishment of resistance among frequently used antimalarial medications. Globally, the Greater Mekong subregion and numerous countries in Africa, particularly Eritrea, Rwanda, and Uganda, have been found to have parasite resistance to artemisinin. It is anticipated that the partial artemisinin resistance would spread to the partner agents used in artemisinin-based combination therapy (ACT). High rates of treatment failure can result from resistance to both artemisinin and the partner drugs used in ACT therapy regimens, as has been observed lately in some areas of the Greater Mekong subregion. Recent findings from Africa indicate that parasites are becoming more resistant to artemisinin. Additionally, there are concerning indications that some parasites may be resistant to partner drugs [16].

According to Sema and Waktola, more than nine studies in Ethiopia documented malaria treatment failures [17]. Deressa., *et al*. observed 8% late parasitological failures in Dembia district, Northwest Ethiopia [18]. Concerns about the strength and therapeutic efficacy of the currently available anti-malarial medications have been raised by the rise of drug-resistant malaria. In all of Ethiopia's malarious regions, there exist parasites that are multi-drug resistant. Also from Ethiopia, reports of *vivax* malaria that is chloroquine-resistant have been made. The development of parasites that are resistant to drugs, particularly *falciparum*, makes it difficult to implement malaria containment measures. *Falciparum* has among the species developed resistance to almost every antimalarial agent that is currently on the market. As with *falciparum*, the emergence of *vivax* that is resistant to both chloroquine (CQ) and primaquine (PQ) may eventually cause a resurgence of *vivax* malaria [17]. There has been an increase in the prevalence of specific single nucleotide polymorphisms (SNPs) connected to artemether-lumefantrine (AL) use since the drug's introduction in Jimma, Ethiopia, in 2006. *Vivax* had a lot of CQ resistance indicators [19]. Recent findings by Hailemeskel., *et al*. that a high level of the mutant *P. falciparum* chloroquine resistance transporter (*Pfcrt*-76T) allele is present in *P. vivax* co-endemic sites (Adama, Babile, Benishangul-Gumuz, and Gambella) suggest that CQ usage in areas where both *falciparum* and *vivax* are endemic needs to be re-evaluated. In this investigation, the *P. falciparum* multidrug resistance 1 (*Pfmdr1*-N86) allele was shown to be present in a higher percentage (77.3 - 100%) across all study sites [20].

Current antimalarial medication resistance is a result of several things. Some of them include the *Plasmodium* mutation rate, the overall parasite load, the drug strength chosen, treatment compliance, and poor adherence to treatment. The development of resistance is aided by ineffective dosage, a poor pharmacokinetic profile, and counterfeit medications (falsified antimalarials without active components) that result in exposure of parasites to the insufficient drugs [21]. Self-treatment is common in Ethiopia. Therefore, patients may be forced to purchase and take half of the antiplasmodial drug dosage as a result of market price inflation that has occurred both locally and globally. Because malaria transmission persists for a very long period after the appearance of *A. stephensi*, several re-infections are typical. Hence, as a result of the parasites being exposed to the drugs repeatedly due to recurrent therapy and treating large numbers of malaria-infected persons, the present antimalarial agents may become less and less effective secondary to the development of resistance parasites.

Innovative measures and prospective directions

For the protection of native mosquitoes, we can keep using bed nets and indoor sprays because they are still out there [12]. It was believed that ACTs remain the best available treatment for uncomplicated *falciparum* malaria. But there is currently no one tool that can completely address the malaria problem. Innovative new techniques are essential. These include novel vector control strategies and insecticides, improved diagnostics, and more potent medications, among other tools [3]. Regaining momentum and reaching the WHO's goals of a 90% decrease in malaria case incidence and mortality rates by 2030 will call for, among other things, renewed global attention, greater funding, ongoing research, and development of new interventions. Researchers are working on a number of breakthroughs in the field of vector management that will help the fight against the disease. It was shown by Fongnikin., *et al*. and Vatandoost., *et al*. that indoor residual spraying with Fludora® Fusion (a combination of deltamethrin and clothianidin) caused high and protracted mortality in carbamate- and pyrethroid-resistant malaria vectors, primarily because of the clothianidin component [22,23]. In a recent large trial, the new Interceptor G2 nets, which are treated with a pyrethroid and a different class of chemical called chlorfenapyr that hasn't previously been used for vector control, significantly outperformed pyrethroid-only nets at preventing malaria. The usage of attractive targeted sugar bait (ATSB), an outdoor bait station that attracts and kills mosquitoes, was also suggested. Spatial repellents, which release volatile chemicals into the air and alter mosquito behavior, are another breakthrough that might lessen some of the difficulties of indoor spraying. Endectocides like ivermectin, which humans can consume to have an impact on mosquitoes that bite them indoors, outdoors, daytime, and night-time, represent another new frontier. Mosquito genetic engineering and the use of radiation to sterilise insects are two more promising novel techniques. If you release a male genetically altered mosquito, it will diminish the female's ability to reproduce, resulting in no offspring and a decline in population [24].

In urban areas, eliminating standing water, sealing water containers firmly with polystyrene beads, and using larvicides in storage containers can help stop mosquitoes from laying eggs [12]. In order to strengthen and improve malaria prevention, control, and treatment efforts, community mobilization and awareness-raising efforts should be conducted through local and national public media, such as television and radio [8]. Countries in Africa should mobilize their resources and involve stakeholders (environment, health, education, local councils, trade and industry, agriculture, housing and finance) in order to improve the capacity of their surveillance (vector and drug resistance monitoring through advanced training and use of molecular and sequencing techniques), diagnostic, protective, and curative systems of malaria in addition to showing solidarity with international organizations caring about malaria containment and elimination. Environmental management and sanitation organizations may be particularly important for better waste management and a reduction in mosquito breeding. On the other hand, the ministries of education can support community- and school-based educational efforts that help localities identify and control the risk factors connected to the vectors [15]. Because *A. stephensi* breeds where mosquitoes that transmit dengue, chikungunya, and yellow fever also do, attempts to control one would also control the others. *A. stephensi* has recently undergone genomic sequencing, which has uncovered at least 29 previously unknown genes that provide them insecticide resistance. This finding may make it possible to stop the spread of malaria in Asia and Africa [25]. Regular malaria control efforts can be complemented by preventive chemotherapies like mass drug administration (MDA), post-discharge malaria chemoprevention (PDMC), perennial malaria chemoprevention (PMC), seasonal malaria chemoprevention (SMC), intermittent preventive treatment of malaria in pregnancy (IPTp), and school-aged children (IPTsc). Early detection and treatment of malaria infections could reduce transmission [2].

The existence of artemisinin partial resistance emphasizes the necessity for a robust antiplasmodial agent's pipeline attributing compounds with new mechanisms of action. While we await novel compounds from the new drug development pipeline (seven of which are in translational and human exploratory studies), they might fail at later stages of the pipeline. As a result, searching for new antiplasmodial compounds should be a continuous activity to treat resistant malaria infections. In the discovery of novel antimalarials, medicinal plants are valuable resources [1]. We showed that Ethiopian medicinal plants like *Maytenus gracilipes* and *Maesa lanceolata* [1] have promising antimalarial activity. Therefore, much work needs to be done to include or translate traditional Ethiopian insecticides, insect repellents, and antimalarials into modern medicine. The use of already available medications in the form of triple ACTs, which combine an artemis-

inin with two partner drugs such as DHA-piperaquine and mefloquine, however, may be a better option [21]. To reduce drug pressure through preventative measures, the WHO recommended improving and better regulating the use of diagnostics and therapies [16]. It is also suggested that clinical efficacy studies be used to continue monitoring the effectiveness of the present antimalarials in order to make early decisions on treatment strategies.

Conclusion

In order to effectively drive and eradicate malaria today, integrated and multi-sectorial responses should be put in place. These include producing standardized data on drug efficacy, promoting equitable access to high-quality diagnostics and medications, ensuring optimal vector control coverage and developing novel diagnostic, preventive, and treatment tools to reduce malaria infection and transmission.

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