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REVIEW

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Enhancing malaria elimination in high-transmission settings: the synergy of concurrent vector control and chemotherapy

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Abstract

Background Malaria elimination, defined as interrupting local transmission and reducing cases to zero, is a critical public health goal. While a dual parasite-vector approach is essential, the path to elimination is complex and marked by both progress and setbacks. Despite renewed commitment and initiatives like the "High Burden High Impact" approach, challenges persist, particularly in sub-Saharan Africa. These include shifting epidemiological profiles, weak health systems, drug and insecticide resistance, and emerging global issues. Effective elimination, therefore, requires a multi-pronged approach, scaling-up a package of interventions tailored to transmission intensity, including prompt treatment with ACT, IPTp for pregnant women, vector control measures like IRS and LLINs, and robust community engagement. Ultimately, a combination of contextually appropriate strategies, implemented synergistically, will be crucial to breaking the transmission cycle and achieving sustained malaria elimination. This report aims to review the available evidence on the strategies and deployment of current tools targeting vectors and parasites in resource-limited settings, focusing on sub-Saharan Africa.

Recent findings Combining malaria interventions can create a synergistic effect, where the combined impact is greater than the sum of individual interventions. For example, simulations show benefits from combining MDA and IRS, vaccines and bed nets, or the RTS,S vaccine with perennial malaria chemotherapy. However, synergistic effects are not always guaranteed; some combinations, like LLINs and IRS, may not provide additional benefit. Conversely, combining IRS and MDA, or SMC with seasonal malaria vaccination, has demonstrated increased protective effects. Therefore, successful elimination efforts depend on country-specific factors including malaria burden, political commitment, and health system capacity. However, significant biological and operational challenges remain, which may necessitate contextually appropriate approaches to achieve malaria elimination.

Conclusion Synergistic intervention effects are crucial, but implementation context is paramount. While combining malaria interventions can be highly effective, not all combinations yield equal results. Thus, tailoring strategies to the specific local context and transmission dynamics is essential for maximizing impact. Moreover, successful malaria elimination is heavily reliant robust health systems and understanding the biological and operational challenges. Consequently, adaptable, evidence-based strategies are required to overcome these obstacles and achieve lasting progress toward malaria elimination.

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Background

Malaria elimination, defined as the interruption of local transmission, that is reducing the rate of malaria cases to zero of a specified parasite in a defined geographical area [1] is a critical public health goal. This ambitious

undertaking, championed by the World Health Organization (WHO) and the global health community, requires an approach that concurrently targets both the parasite and the mosquito vector [1]. This renewed path to malaria elimination is driven by the devastating impact of malaria on individuals and communities and demands a concerted global effort [2] to develop strategies that will combat the disease. To this end, in 2017, recognizing the urgent need for renewed action, the WHO and the Roll Back Malaria (RBM) Partnership to End Malaria launched the "High Burden High Impact" initiative [3]. This targeted, country-led malaria response served as a massive wake-up call, refocusing global attention on the countries hardest hit by malaria to change course and improve strategies for combating the disease. Indeed, there was a clear need to alter the trajectory and accelerate efforts towards elimination [4].

Historically, in 1955, the WHO launched the Global Malaria Eradication Programme (GMEP) and recommended the use of indoor residual spraying (IRS) with dichlorodiphenyltrichloroethane (DDT), to achieve the higher goals of eradication [5]. Initially, encouraged by the early success of using DDT against malaria, the WHO embarked on the GMEP with the goal of reducing malaria cases and deaths significantly, aiming at eventually eradicating the disease completely. However, GMEP faced numerous obstacles, which led to a failure to achieve its goal of eradication resulting in a resurgence of malaria in some areas in the 1960s [7, 8]. Consequently, the campaign was discontinued when it was recognised that eradication was not achievable with the available means in many areas, although the long-term goal remained unchanged [6]. Subsequently, during the 1970s and 1980s, due to economic and financial crises, international support for malaria control declined rapidly[7]. The decline in funding led to marked increase in malaria cases worldwide [5]. In some regions, mosquitoes became resistant to DDT and parasites became resistant to chloroquine (ref). Nevertheless, in the past decade, following increasing demands from endemic countries and promising results from scaling-up of control activities, interest in malaria elimination and the long-term goal of eradication has received international political and financial support [8, 9]. For example, in 2007, there was a renewed call for malaria eradication and a consultative process to define a research and development agenda for malaria eradication (malERA) was established [10]. Ultimately, lessons learned from the GMEP (1955–1969) highlight the fact that no single strategy can be applicable everywhere and that a long-term commitment with a flexible strategy that includes community involvement, integration with health systems, and the development of agile surveillance systems is needed [7].

The complexity of malaria elimination

Eliminating malaria presents a complex challenge as the epidemiological profile is constantly shifting, marked by periods of decline and resurgence [11, 12]. Indeed, the burden of disease in each geographical area, measured as transmission intensity, directly impacts the feasibility of effective deployment of interventions [13]. Essentially, high transmission areas require potentially more intensive interventions compared to low transmission areas to achieve significant impact. Furthermore, major challenges to sustaining malaria control and progressing towards elimination [14] in many sub-Saharan African (SSA) countries exist at the health systems level. These include inadequate healthcare resources, weak health systems, inadequate utilization of drugs for malaria prevention, inappropriate case management, and inadequate epidemic preparedness and response (ref). Adding to this complexity, the increasing threat of artemisinin resistance and the rising prevalence of insecticide-resistant mosquitoes [15], coupled with an inadequate understanding of malaria epidemiology, pose significant obstacles to malaria elimination efforts. Moreover, many emerging challenges such as poverty, increased outdoor transmission, climate change, new emerging vectors have led to continued high malaria incidence rates in many African countries[16, 17]. Despite these challenges, prospects for malaria control have improved. Consequently, with due attention to these underlying challenges, continued progress toward the elimination of malaria is expected.

A multi-pronged path to malaria elimination

The strategy for optimizing control interventions in a country or region should be based on data from the local settings [18]. Indeed, no single intervention can effectively eliminate malaria (12), [19], especially in high-transmission settings. Therefore, effective and efficient scale-up of a package of interventions which includes early treatment of malaria cases with artemisinin-based combination therapy (ACT), intermittent preventive treatment for pregnant women (IPTp), and interventions that reduce human-vector contact, such as indoor residual spraying (IRS) or use of long-lasting insecticidal nets (LLINs) [20], and including community engagements [21], must be rolled out to the degree of malaria transmission intensity. For instance, the application of different malaria control strategies and measures at different epidemic stages such as intensive malaria control, consolidating gains in malaria control, and preventing re-establishment of transmission helped Guangzhou, China to eliminate indigenous malaria infections [22]. However, in sub-Saharan Africa, countries are still navigating how best to move from control to pre-elimination and from

pre-elimination to elimination. Several African countries are employing diverse strategies in their pursuit of malaria elimination. For example, some advocate for integrated control across all epidemiological settings [23], while others favour dynamic, adaptive responses tailored to their evolving situation [24]. Still others have adopted a stepwise approach, initially targeting low-transmission areas and progressively expanding their efforts [25]. Consequently, achieving significant and lasting elimination across the continent will require proactive approaches, and applied in combination to interrupt transmission [26]. Ultimately, a multi-pronged approach while utilizing a mix of interventions to break the transmission cycle and achieve sustained progress will be required if countries are to move to elimination.

Current tools for malaria control and elimination

Vector control

• Long-lasting insecticidal nets (LLINs) are defined as treated nets which retain insecticidal activity for at least 3 years under field conditions [27]. Because they are treated with insecticides, LLINs provide personal protection against mosquito bites while sleeping. Consequently, widespread use of LLINs significantly reduces the risk of infection, particularly for vulnerable populations like children and pregnant women. Indeed, the use of LLINs is the primary strategy employed for the prevention of malaria in endemic countries throughout the world. Historically, LLIN distribution was aimed at pregnant women and children under 5 years. While these groups are severely impacted by malaria, they do not represent the major population groups harbouring the asymptomatic parasite pool.

• Indoor residual spraying (IRS) involves applying long-lasting insecticides to the walls and ceilings of houses. This creates a protective barrier that kills mosquitoes upon contact, significantly reducing their population and their potential to transmit malaria. Specifically, the primary effects of IRS towards curtailing malaria transmission are twofold: first, to reduce the lifespan of vector mosquitoes so that they can no longer transmit malaria parasites from one person to another, and second, to reduce the density of the vector mosquitoes [28]. Furthermore, the strategy for applying IRS is to deploy it in relation to transmission ecology, malaria endemicity, cost and logistics, as recommended by the WHO [29, 30]. Consequently, in many sub-Saharan African countries like Uganda, the emphasis for implementing IRS is placed on epidemic-prone areas, high transmission settings and high-risk situations, such as camps for internally displaced persons or refuges.

Case management

In the early 2000s, 20 African countries transitioned to the use of ACT in response to WHO recommendation [31, 32]. This shift was driven by the growing drug resistance of malaria parasites to monotherapies, such as chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) in most African countries, including Uganda, by the late 1990s [33]. Consequently, during 2004 to 2006, National Malaria Control Programmes in most African countries implemented the new malaria treatment policy [34]. This implementation involved revising national malaria case-management guidelines, providing in-service training for health workers, and ensuring the provision of ACT to governments by a few development agencies, such as the Global Fund to fight HIV/AIDS, TB and Malaria, and the President's Malaria Initiative (PMI).

Mass drug administration

Mass drug administration (MDA) involves the empiric administration of a therapeutic anti-malarial regimen to an entire population, or targeted groups, at the same time, regardless of symptoms [35]. The aim of this strategy is to rapidly reduce parasite prevalence and interrupt transmission chains. For instance, MDA has been used successfully to control and eliminate *Plasmodium falciparum* and *Plasmodium vivax* malaria in the past, and is considered as part of a comprehensive malaria elimination strategy [36]. Moreover, its effective implementation using ACT, has shown to be safe, unrelated to the emergence of drug resistance and may play an important role in sufficiently lowering the malaria burden [37]. However, the emergence and spread of drug resistance is a feared consequence of MDA, but it has been suggested that because the population is treated in a similar time frame, it provides homogeneity in drug concentration profiles. This homogeneity, in turn, suggests that it limits the spread of resistance because drug concentrations are diminishing in the treatment community as a whole [38]. Nevertheless, MDA given repeatedly, to the entire population successfully reduced malaria burden in settings with low to medium, medium to high transmission settings in Africa [39–41]. Ultimately, repeated rounds of MDA to the entire population are important for elimination attempts to achieve parasite clearance from the population for longer than the life span of the mosquito [42, 43].

Malaria vaccination

Recently, the WHO approved two malaria vaccines, RTS,S/AS01 and R21/Matrix-M, for use to protect infants from severe malaria [44, 45]. The RTS,S/AS01 vaccines has demonstrated programmatic feasibility

and effectiveness in three African countries, including Ghana, Kenya and Malawi [46]. To this end, the WHO prioritizes the use of malaria vaccines in moderate-to-high transmission settings for higher impact. However, this advancement faces limitations including the need for trained personnel, coverage and uptake, and cold chain challenges [47–49], and knowledge about a malaria vaccine [50]. Moreover, these vaccines are also relatively expensive, making a four-dose course over two years a significant financial burden.

Synergistic effect of interventions in malaria elimination

The synergistic effect of malaria interventions refers to the interaction of two or more interventions that produce a combined effect greater than the sum of each if deployed separately. Simulations, for example, have demonstrated a cooperative synergistic effect of combining vaccines and bed nets, synchronously deploying MDA and IRS, result in impacts that exceed those achieved when the campaigns are deployed in isolation [51, 52]. Similarly, other modelling studies have shown benefits from combining the RTS,S vaccine with perennial malaria chemotherapy (PMC) for children under two years in areas with high malaria burden and perennial transmission [53]. Notably, there is mixed evidence on synergistic effects of malaria control tools. For instance, combining LLIN and IRS, both intervention targeting the human-vector contact, indicates no additive effect on malaria prevalence [54]. Yet studies that synchronously implemented IRS and MDA indicate a protective effect greater than when IRS was given alone [55, 56] among children under five years. Additionally, other studies have also shown that combining seasonal Malaria Chemoprevention (SMC) with seasonal malaria vaccination has a better protective effect than either intervention given alone[57–59]. Therefore, tailoring strategies to the specific context and transmission dynamics to benefit from synergistic effects of current tools is crucial for each high burden setting. Moreover, it is also important to note that elimination efforts are based on factors specific to the country's context, such as epidemiological criteria for malaria burden, natural borders of disease, political and financial commitment to elimination, and sufficient health system and surveillance capacity to manage elimination programmes.

Challenges

Implementing and sustaining malaria control and elimination programmes in high burden countries presents several biological and operational challenges. Specifically, biological factors where malaria parasites and their mosquito vectors constantly evolve to resist drug and insecticides [60]. Additionally, the efficacy of available vaccines do not provide complete protection against malaria, the genetic diversity of *Plasmodium* parasites [61, 62]. Furthermore, social, demographic, cultural, and behavioural beliefs and practices, and weak health systems need to be considered to achieve the global elimination of malaria parasites [14]. Moreover, it is paramount to address the lack of adequate financing, and effects of climate change. Consequently, these biological challenges, coupled with operational challenges related to the health system, call for approaches that can contextually address them to move towards malaria elimination.

Conclusion

In conclusion, the fight against malaria demands a nuanced and adaptable approach. While combining interventions holds great promise for synergistic effects, achieving more than the sum of individual efforts, success is not guaranteed. For instance, strategic combinations like MDA and IRS, or SMC and seasonal malaria vaccination, have shown promise. However, other combinations, such as LLINs and IRS, may offer limited additional benefits. Therefore, tailoring interventions to specific context and transmission dynamics is crucial for maximizing impact. Furthermore, successful malaria elimination hinges on national-level factors. These include disease burden, political will, and robust health systems. Moreover, significant biological and operational challenges remain. Specifically, evolving drug and insecticide resistance, limited vaccine efficacy, and weak health systems, coupled with socioeconomic factors, necessitate contextually appropriate, multifaceted strategies to achieve lasting malaria elimination. Ultimately, the key takeaway is that a flexible, evidence-based approach, combining the right interventions in the right context, is paramount to making continued progress against this devastating disease.

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R.M wrote the main manuscript text. All authors reviewed the manuscript.

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Declarations

Competing interests

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