Countries can hold the line against antimalarial resistance in Africa - but we must act now.

Originally published in Jeune Afrique, Nov 23 in French: En Afrique, la résistance aux antipaludiques n'est pas une fatalité - Jeune Afrique

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Throughout the 1980s and 90s, Africa faced a worrying challenge: chloroquine, the first-line treatment for malaria, was quickly becoming ineffective. Another drug introduced around this time - sulfadoxine/pyrimethamine (or SP) – soon met a similar fate. In the early 2000s, however, the global malaria community responded by rolling out a new family of malaria medicines - artemisinin-based combination treatments (ACTs).

ACTs have since transformed the fight against malaria in Africa, working alongside insecticide-treated nets and other vector control tools to contribute to a rapid decline in malaria cases and resulting deaths. Indeed, over 2 billion malaria cases have been prevented globally since the start of the century, and the malaria mortality rate in Africa has declined by over 60%.[1]

Although six ACTs are currently recommended by WHO, artemether-lumefantrine (AL) is currently used to treat between 80-90% of malaria cases on the continent. It is very affordable, costing around $0.26 for a paediatric dose and around $0.60 for adults. As the most widely-used first-line treatment in Africa, the continent is heavily reliant on AL to keep the disease at bay.

However, today the effectiveness of AL is also under threat; since 2020, several studies have confirmed the emergence of partial artemisinin resistance – a delay in the time it takes for treatments to successfully clear the parasite - in a growing number of African countries, notably Rwanda, Uganda, Tanzania and Ethiopia.[2,3,4] This presents a significant threat to efforts to control and eliminate malaria in Africa. Indeed, researchers at Imperial College London have estimated that if partial resistance to artemisinin becomes widespread, we can expect to see 16 million additional cases of malaria recorded each year, costing the African continent approximately US $1 billion annually.[5]

The world simply cannot afford the cost of inaction on antimalarial resistance. Full-blown artemisinin resistance would be a public health catastrophe and in response, the World Health Organization (WHO) has raised the alarm on this threat, calling on the malaria community to respond urgently. In 2022, it launched its Strategy to Respond to Antimalarial Drug Resistance in Africa, which includes a raft of measures including strengthened surveillance, enhanced vector control measures, and increased research and innovation. Whilst novel alternatives to ACTs are in development, they are some years away and, meanwhile, solutions are needed today.

Diversifying the use of available malaria drugs with the multiple first-line treatment approach

One recommendation in the WHO's strategy that can be implemented now is to diversify the use of ACTs to reduce dependence on AL and maximise the useful therapeutic life of existing drugs. While AL is a particularly cost-effective and familiar option, there are already a range of alternative medicines that can be used to tackle malaria on the African continent, to reduce pressure on AL and protect the effectiveness of artemisinin.

One approach to diversification is the deployment of multiple first-line treatments (MFT). This involves the use of two or more first-line drugs to make it harder for parasites to develop resistance and can be deployed in a

[1] World Health Organization: World Malaria Report 2022

[2] Ebong C, *et al.* Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria and prevalence of molecular markers associated with artemisinin and partner drug resistance in Uganda. *Malar J.* 2021. PMID: 34952573.

[3] Uwimana A et al. Association of Plasmodium falciparum kelch13 R561H genotypes with delayed parasite clearance in Rwanda: an open-label, single-arm, multicentre, therapeutic efficacy study. *Lancet Infect Dis* 2021 April 14.

[4] Bayih, A. G. *et al.* A unique Plasmodium falciparum K13 gene mutation in Northwest Ethiopia. *Am. J. Trop. Med. Hyg.* 94, 132–135 (2016).

[5] Slater, H.C., Griffin, J.T., Ghani, A.C. et al. Assessing the potential impact of artemisinin and partner drug resistance in sub-Saharan Africa. Malar J 15, 10 (2016) (as referenced in the WHO Strategy to Respond to Antimalarial Drug Resistance in Africa).

number of different ways. One way is the **rotational approach,** in which first-line antimalarial treatments are rotated at regular intervals. Other approaches include **stratification**, in which different treatments are given to different patient groups (for example, children under 5 receive drug A, older children and adults get drug B, and pregnant women are offered drug C) and **geographical variation** (e.g. different treatments are delivered in adjacent districts or regions to reduce drug pressure on a single ACT). While MFT has not yet been delivered at national scale, promising pilot studies completed in Burkina Faso and Kenya in 2020 and 2022, respectively, have confirmed both the feasibility and acceptability of MFT and have provided a model for other countries to use in their own contexts.

Key considerations when delivering MFT

Both pilot studies focused heavily on the practical aspects of implementation. Proactive stakeholder involvement, comprehensive and regular training of all healthcare workers in the use of "new" drugs, revision of relevant reporting tools and robust co-ordination of logistics with national and district medicines stores were found to be crucial to successful deployment.

Alternative treatments may cost more than AL, so overall drug commodity costs may also be higher. To address this challenge, partners including MMV, MedAccess, the Medicines for All institute, and the Bill & Melinda Gates Foundation are working with generics companies to reduce the prices of other ACTs in the short to mid-term by reducing the costs of Active Pharmaceutical Ingredients (APIs) and increasing generic manufacturing capacity. The longer-term objective is to achieve greater price parity between different ACTs.

However, given the threat of ACT resistance, initial modest increases in drug and logistical costs must be balanced against the cost of inaction, which could be to erase decades of progress against malaria.

The scientific rationale for the effectiveness of MFT in mitigating resistance is also based on modelling work which, though robust, has not yet been validated 'in the real world'. For this reason, a key recommendation resulting from the pilot studies is that countries deploying MFT programmes in future include monitoring of resistance markers to assess the real-life impact of MFT. Such large-scale data generation from real-life delivery will be invaluable for informing future normative guidance, both at WHO and national levels.

A collaborative, country-led response to resistance

The engagement of countries, researchers and the wider community will be critical to the successful delivery of MFT across the continent to delay the spread of artemisinin resistance in Africa as long as possible. Cross-country collaboration will be key to share learnings and ensure MFT programmes are co-ordinated effectively across country borders. To address this need, the ALARM (the African Leadership for ACT Resistance Mitigation) partnership was founded in April 2023, bringing together 13 African countries and partners committed to developing country-led plans to deploy MFT at scale.

Antimalarial resistance poses a major threat to the fight against malaria, and deploying MFT is a critical step for African countries to delay resistance and preserve the effectiveness of current treatments for as long as possible. African leadership will also be critical in the context of safeguarding or protecting the efficacy of currently available antimalarial drugs. The time to act is now.