Artemisinin-resistant malaria and a prevention strategy

Francis M Malwal
University of Juba, College of Medicine, Department of Pharmacology

Correspondence:
Francis M Malwal
francismalwal@gmail.com

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Abstract

Malaria is a widely spread infectious disease and claims many lives annually in the African region. Therefore, prevention and effective therapy are significantly crucial for the successful reduction of malaria morbidity and mortality. However, recently emerging artemisinin-resistant parasites in Southeast Asia, South America, and Rwanda have raised concern globally. Studies have established that artemisinin-resistant is associated with a mutation in the Kelch13 (K13) propeller domain of malaria parasites. This mutation delays malaria parasite clearance from the bloodstream to more than three days following ACT's therapy.

The objective of this paper is to alert authorities and researchers to the upcoming threat of artemisinin-resistant and recommend prevention strategies. Health authorities need to invest more in malaria prevention, enforcing existing laws, monitoring emerging resistance, and its impacts. Moreover, healthcare professionals can play a vital role by adhering to malaria treatment guidelines, avoiding monotherapy, and promoting antimalarial adherence

Keywords: Artemisinin, resistant, malaria, prevention, strategy

Introduction

Globally, malaria is the most widely spread infectious disease, with 228 million cases and an estimated 405,000 deaths in 2018. Unfortunately, the African region carries a disproportionately high share of the malaria burden.[1] For instance, in 2018, almost 93% of malaria cases and 94% of deaths were from the African region. *Plasmodium falciparum* is responsible for 99.7% of malaria cases in Africa making this region the most affected in the world.[1]

The campaign of the World Health Organization (WHO) to eradicate malaria began in the 1950s. Despite this effort, drug-resistant parasites developed and resulted in the failure of response to chloroquine in endemic areas. The development of chloroquine-resistance prompted the WHO to introduce an artemisinin-based combination therapy (ACTs).[2]

Currently, the ACTs are recommended by the WHO as the first and second-line therapy of uncomplicated P. falciparum malaria and chloroquine-resistant *P. vivax* malaria.[1]

However, recently emerging parasite resistance to artemisinin in Southeast Asian countries and Rwanda has raised concerns globally since there is no alternative drug to replace ACTs if they become ineffective.[3, 4]

This review article focuses mainly on artemisinin resistance because of its significant role in the treatment of P. falciparum malaria and what should be done to slow down artemisinin resistance.

Artemisinin-based Combination Therapy (ACTs)

ACTs combine an artemisinin derivative with a partner drug (companion drugs). The artemisinin derivatives include dihydroartemisinin, artesunate, and artemether: partner drugs include lumefantrine, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, piperaquine, and chlorproguanil/dapsone.[5]

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The ACTs have dual actions (immediate and long) against malaria parasites. While the fast-acting artemisinin derivative clears the parasites from the bloodstream within three days of ACT's therapy, the long-acting partner drug clears the remaining parasites. This synergism has made ACTs the most efficacious antimalarial drugs with a profound record of morbidity and mortality reduction. [6]

Artemisinin Resistance (AR)

Artemisinin-resistance (AR) defines a delay in malaria parasite clearance from the bloodstream following ACTs treatment. Consequently, the artemisinin compound becomes less effective in clearing malaria parasites within three days.[4]

Recent studies have established that parasites' resistance mechanism developed against the artemisinin compound is associated with a mutation in the Kelch13 (K13) propeller domain of malaria parasites, affecting only the parasites' ring stage in humans.[4,7] Parasites carrying K13 have been reported in Southeast Asia, South America and Rwanda.[8, 9]

It is important to note that recent molecular studies have shown that the partial artemisinin-resistance in Rwanda emerged independently and did not come from South Asia.[4] The emerging artemisinin resistance in Rwanda was associated with poor treatment practice, inadequate adherence to the prescribed antimalarials, the widespread use of artemisinin-based monotherapy, and substandard drugs.[4]

It is important to note that ACTs are still significantly efficacious antimalarial drugs and can cure malaria as long as the partner drug is still effective.[4] However, the slow clearance of parasites from the bloodstream of a patient treated with ACTs adds significant dependence on a companion drug, increasing the parasite's chances to develop resistance to ACTs and subsequently causing treatment failure.

The main strength of ACTs is embodied in the dual-effect as a deterrent mechanism against parasite resistance. Unfortunately, this defence mechanism began to crack in Southeast Asia, where ACTs have started to fail, and the emergence of mutated parasites in Rwanda. All these are signs of the inevitable development of artemisinin resistance. The world should think about alternative plans before the storm hits Africa, where the global burden of malaria morbidity and mortality is greatest.

Prevention strategy

The development of new treatment takes enormous efforts and resources. However, many strategies can be applied here, starting from the African health authorities and their partners, healthcare professions, and population. The health authorities need to focus more on fighting malaria through prevention, outlawing substandard drugs as well as enforcing existing laws, monitoring emerging resistance, and assessing their clinical impacts in collaboration with international partners.

Moreover, healthcare professionals can play a vital role by adhering to malaria treatment protocols and guidelines, avoiding monotherapy, and promoting adherence to prescribed medications and reporting to authorities any suspicious cases of treatment failure. Finally, the population needs to continue prevention measures such as using mosquito nets and mosquito repellent, and adhering to a prescribed medication.

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Additional Resource

World Health Organization. Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010-2019)