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## **Major Challenges of Standard Antimalarial Drugs**

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## Abstract

Malaria is a parasitic disease caused by protozoa of the genus *Plasmodium*. Early and effective treatment of malaria is the cornerstone of malaria control. However, the number of available and effective antimalarial drugs is quickly dwindling may be due to standard antimalarial drugs are facing different avoidable challenges those may negatively affect its efficacy. This review tried to assess some major challenge of standard antimalarial drugs. Inaccessibility of proper health care services and effective diagnoses leads to delayed diagnosis and treatment that result with patient death. Self-treatment without confirmed diagnosis, treatment with substandard drugs and improper usage of the drug expose the parasite to sub-therapeutic level. Treatment with monotherapies is easy for the parasite to overcome and develop resistance. The knowledge of the society on every aspect of malaria has its own influence on the malaria control strategy. Therefore, ensuring that drugs are taken properly only for treating those with a definitive diagnosis at a sufficient dose and for a sufficient duration reduces this risk. Understanding of the social, cultural and behavioral issues relating to treatment and prevention of malaria is crucial; the views of the community should be sought and incorporated into any control measures to make the participation of the community meaningful.

**Key words:** Antimalarial, Standard drug, Major challenges

## **Introduction**

Malaria is the most important parasitic disease and endemic in parts of Asia, Africa, Central and South America, Oceania, and certain Caribbean islands [1]. Globally the number of malaria cases is 214 million in 2015 and 88% of the cases occurred in Africa. Malaria caused mortality is 438,000 in 2015 and 90% of the death is occurred in the WHO African region. In East and some areas of southern Africa about 313 million people are at some risk for malaria, with 254 million at high risk [2]. It is believed that human malaria parasites originated in Africa thousands of years ago and spread to nearly all of the tropical, sub-tropical and temperate regions of the world with expansion of agriculture and related activities [3]. Even if it is a preventable and treatable infectious disease, it affects hundreds of millions of people primarily in the developing world [4]. Populations living in sub-Saharan Africa have the highest risk of acquiring malaria than all geographical regions [5]. In addition to resistance standard antimalarial drugs are facing different challenges against their efficacy. This review tried to summarize different challenges from different perspective.

## **Accessibility of health care**

Accessibility of formal healthcare services has multiple barriers and unfortunately these are likely to fall most on the poor that have the majority of malaria cases [6]. Equitable and sustainable access to high-quality and effectively functioning health systems has yet to be achieved across malarious areas [7]. Poverty can be reason as well as result of Malaria disease, and many at risk populations live in extremely remote areas [8]. Poor rural families may live kilometers from the nearest healthcare facility; have least access to these preventative measures and less able to afford treatment [9]. Accessibility of health care services has three main strategies: early diagnosis and prompt treatment; selective vector control and epidemic prevention and control [10].

The constraints of accessing formal healthcare include socioeconomic status, limitation of knowledge, distance from health services, transport costs, treatment costs, opportunity costs and difficulties to get funds to attend health centers [11-12]. Sometimes, the indirect costs of care exceed the direct costs [13]. These healthcare accessing barriers may lead to delayed diagnosis

or none at all and severe illness with significant associated morbidity and mortality in low-income settings [14-15]. Delayed diagnosis and death due to inaccessibility of health care services may lead to lack of confidence of the society on the curing potential of the drug [16]. Increasing access to health care services is considered central to improving the health of populations, reduce disease transmission, access to malaria diagnosis and treatment as well has great contribution in keeping the treating ability of the standard drugs [17 & 12].

### **Cost (Treatment and/or Opportunity)**

Most malaria-endemic countries are developing nations with limited financial resources and malaria has serious negative macroeconomic effects on these areas [7 & 4]. Therefore, Economic limitations can be challenge against malaria control for individuals and at the governmental level [11]. As mentioned above, the economic burden of the disease is vast. According to Kokwaro, up to 40% of African health budgets are spent on malaria each year, and on average, malaria stricken family loses a quarter of its income through loss of earnings and the cost of treating and preventing the disease [13]. Malaria causes an average loss of 1.3% of economic growth per year in Africa [18].

Access to malaria treatments is highly affected by the availability, price, and affordability of diagnosis and effective antimalarial drugs [19]. More expensive direct cost of drugs and hospital admissions, the costs of seeking treatment, opportunistic cost and the indirect costs of lost productivity are among the burden of health care accessibility in terms of increased costs [20]. Moreover, intangible costs such as psychological stress and loss of confidence in a health system that fails to deliver a cure [21]. During the time of prevalence of malaria (i.e. rainy season) in most parts of Africa the opportunity costs become highest and the transport is most difficult [6]. As Hetzel mentioned, much of this burden falls on the poor society and exacerbates already existing transmission and prevalence [11].

### **Antimalarial drugs Resistance**

Antimalarial drug resistance is strictly defined as the ability of a parasite strain to survive and/or multiply, despite the administration and absorption of drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the subject [22]. It is more difficult to quantify the burden caused specifically by antimalarial drug resistance. The ultimate

pressing problem that challenges malaria control in many endemic countries is the resistance of *Plasmodium* against different anti-malarial drug [10]. Some best available data from Africa estimate that the demise of Chloroquine (CQ) is the main reasonable factor contributing for the rise of malaria specific mortality [23].

Measuring the impact of antimalarial drug resistance is difficult, since the impact may not be recognized until it is severe, especially in high transmission areas. This is partly because routine health information systems grossly underestimate the magnitude of the problem [21]. Drug resistance arises due to several reasons, the first and one of the core causative reasons, as Saeed stated, is a result of changes occurring spontaneously in specific parasite genes. The other contributory reason is pharmaco-kinetics of the drugs i.e. half-life [2]. The other major reason for the rapid spread of resistance is widespread use of antimalarial drugs [24]. The resistant parasite to the given chemotherapeutic agent increases in the population by the process known as drug selection [25-26].

### **Diagnosis as Precondition for drug treatment**

Even though microscopy is the base for malaria diagnosis in health services, due to the scarcity of laboratory facilities, it has been common practice for several years to base diagnosis of malaria mainly on clinical signs and symptoms [27], and results in a large degree of unnecessary use of antimalarials [11]. According to Kokwaro, in the majority of African people antimalarial are used to treat patients without malaria based on symptoms because malaria with confirmed diagnosis is lower than (less than 20%) other regions of the world [13]. The overlap of clinical signs and symptoms and non-specific nature of these symptoms make difficult to distinguish malaria from other febrile illnesses [5]. Diagnoses of malaria on clinical grounds alone have led to substantial over-diagnosis that jeopardizes the effectiveness of available anti-malarial drugs [27].

It is well known that malaria diagnosis is mostly based on microscopy, which requires a power source, a microscope, staining solution, and a well-trained technician [5]. Even in the availability of microscope, it has only a limited impact on treatment decisions. Several studies demonstrate that both positive and half of negative slides inevitably given an antimalarial [6]. Even in countries with high incidence rates of malaria the accuracy of clinical diagnosis is poor due to

co-infections and/or overlapping of clinical symptoms with other tropical diseases [24]. In some laboratory technicians the accuracy of slide reading was low, and the negative predictive value (being dependent on prevalence) was in excess, that leads to providing an antimalarial on the basis of a negative slide [28]. The WHO guidelines in 2009, recommend that antimalarial should be given to febrile patients with confirmed malaria by laboratory or RDT [9].

### **Mono-therapies**

Treating malaria patient with effective antimalarial drugs can avoid almost all deaths due to malaria [29]. Mono-therapies were highly effective in the 1960s and had gradually lost their efficacy due to drug resistance, particularly in Asia and subsequently in East Africa, but most clinicians were restricted to it for a long time [11]. Emergence and spread of drug resistance can be aggravated by the misuse of antimalarial mono-therapies [12], because it is easier for the parasite to overcome the obstacles presented by a single drug and adapt than combination of drugs bring together [11].

Constant exposure of the parasite to mono-therapies could accelerate parasite resistance to that specific drug. One of the indications from the Thai-Cambodia border, due to high and longer exposure to Artemisinin mono-therapies, malaria parasite is becoming increasingly resistant to it [27]. In response to increasing burden of malaria caused by parasite resistance to the conventional antimalarial medicines WHO in 2001, recommended the use of ACTs in countries where *P. falciparum* malaria is resistant to the conventional antimalarial medicines. ACTs provide the highest cure rates and could reduce the spread of drug resistance [30-31].

### **Drug quality**

Studies in some countries report that the majority of some of antimalarial drugs being fakes and these drugs are wide spreading in South-East Asia and Africa [6]. As Kinung'hi *et al.*, mentioned, sub-standard drugs have already penetrated the African market to certain degree but in some place it is much more, for instance 35% of antimalarial drugs sold in six major African cities were substandard [24]. These fakes place a major technical and law-enforcement challenge and are highly sophisticated in convincing packaging, holograms and marketing [20].

If fake antimalarial drugs penetrate the market to a higher degree, they may precipitate a collapse of confidence on other effective drugs [24]. Every malaria patient treated with fake antimalarial

drugs is in danger of progressing to severe illness and in some cases of dying. As Whitty *et al.* mentioned, the WHO (2007) estimated that 200, 000 malaria-related deaths worldwide could have been avoided if antimalarial drugs were of high quality and administered properly [6].

### **Therapeutic levels**

In the development and spread of resistance the half-life of the drug is believed to be an important factor [10]. The exposure of malarial parasites to sub-therapeutic levels of antimalarial drugs may kill sensitive parasites but allow parasites with a resistance mutation to survive, reproduce and spread [32]. The tendency to become ineffective due to parasite resistance is greater with longer half-life compounds even if they have the capacity to be “post treatment prophylaxis” [25]. Taking long half-life drug that remains in the patient’s blood at low levels for weeks aggravate the risk of resistance because it exposes any newly introduced malarial parasites to sub-therapeutic levels [26].

Self-treatment without prescribed dose and pattern will facilitate exposure of the malarial parasites to sub-therapeutic levels [12]. Appropriate taking of drug, in dose and duration, in some community is poor. Most of the peoples stop taking the drug before complete treatment if they feel cured [11]. Individual patient may be harmful to society health benefits because as more parasites are exposed to sub-therapeutic drug levels, development of resistance will be greater [13]. Such burdens can be reduced by using shorter half-life drugs and by restricting the use of the first line drug to patients with confirmed malaria [26].

### **People’s Knowledge, Attitude and Practices about malaria treatment**

Malaria control campaign also influenced by socio-cultural factors like community perceptions and practices related to causation, transmission, prevention and treatment malaria [6]. Incorrect beliefs or inappropriate behavior can interfere with the effectiveness of a control measure especially with chemotherapy [10]. These issues are particularly important in tropical areas where malaria control options are limited because of the parasite and vector resistance to antimalarial drugs and insecticides, respectively [33]. Some society may have inadequate knowledge and miss understanding about every aspect of malaria [10].

In some society there is confirmation of the hypothesis that malaria is a disease of the poor [26]. In some community proper drug utilization is poor [11]. Some rural communities may not know



or bother about resistance of the parasite for the drug, and they rely on ineffective antimalarial drugs without seeking an alternative [34]. Sometimes the symptoms of different disease have similarity. In such cases, the patient may take antimalarial drug based on the symptoms without any confirmation of the disease [35]. Some society members trust CQ as effective antimalarial drugs due to its bitter taste. Other effective drugs are not trusted since they are not bitter [33]. This may indicate that they are not psychologically ready to accept and use physician ordered effective non-bitter drug. In such cases, according to Maslove *et al.*, for the success of specific control measures an understanding of the communities' beliefs and behavior is crucial [36].

### Self-treatment

The misuse of antimalarial drugs has been largely neglected for several years. Home management of malaria in the form of self-treatment after self-diagnosis based on presumptive symptoms is almost always chosen especially in areas with high transmission [26]. Inadequacies of healthcare facilities and delivery of services, inaccessibility of the health-care facilities, inefficiency of health service, high cost, waiting time, lack of drugs, social distance of health workers, and the high burden of malaria itself are among the main reasons for wide spreading of self-medication especially in rural communities [34 & 37].

Drugs for self-treatment can be obtained from a variety of sources such as government health institutions, mission clinics, local drug vendors, and open markets [30]. In some malarious areas most medicines do not need mandatory prescriptions and more of the malaria patients buy antimalarial drugs freely from drug shops for self-treatment [34]. The main drawback of looking for treatment at formal health care facilities after taking medications is favoring the chance of false negatives, as the parasites can be inactive or scanty in the peripheral blood [37]. Therefore identification of personal modifiable risk behaviors is important in planning approaches to prevent and control the disease [24].

### Antimalarial herbal medicines

According to several reports about 80% of world's populations still depend on traditional medicine as primary source for the treatment of diseases. In ethno-medical practices malaria ranks as the most important disease treated with herbal remedies [38] because they are easily affordable treatments in most malarial regions [39]. Accessibility and diversity of indigenous

plants in tropical and sub-tropical regions, and also acceptability from cultural and spiritual perspective makes these herbal medicines the most convenient solution [24].

Furthermore, distances from health care and socioeconomic status are among the influencing factors to choose informal sources for treatment [40]. Some people seek care from formal healthcare at the late episode of illness because informal healthcare drug sources are seen as important first tiers of care not as an alternatives [37]. The use of traditional medicines developed from similar basic chemical compounds and Pharmo-kinetic with standard antimalarial drugs can increase the rate of resistance development; there may be cross-resistance to each other [13 & 40].



## **Summary**

Effective diagnosis and treatment is the key for malaria control. Inaccessible and unaffordable health care services and diagnoses, restricting to mono-therapies, therapeutic level of the drug, self-treatment, substandard drugs and social misperception are among the major challenges of standard antimalarial drugs. These challenges, besides their contribution to the emergence and development of drug resistance they can be hindrance for accessibility and affordability of the drug. Therefore, integrated endeavor from different disciplines along with concerned bodies is needed in averting these challenges and to be successful in malaria control. Systematic surveillance and monitoring of the drug efficacy; improving accessibility and affordability of health care services, advancing laboratory standard with the appropriate material and good skilled technicians, using combination therapies are the major appropriate solutions. Furthermore, creating awareness of the society on every aspect of malaria, controlling fake drugs and scientific research on traditional antimalarial medicines has greater value and play positive role in the success of the malaria control campaign.

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