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Adaptive Drug Resistance in Malaria Parasite: A Threat to Malaria Elimination Agenda?

Moses Okpeku

Abstract

Malaria is a global disease of importance, especially in the sub-Saharan African region, where malaria accounts for great losses economically and to life. Fight to eliminate this disease has resulted in reduced disease burden in many places where the diseases is endemic. Elimination strategies in most places is focus on the use of treated nets and drug application. Exposure of malaria parasites to anti-malaria drugs have led to the evolution of drug resistance in both parasites and host. Development of drug resistance vary but, studies on adaptive drug resistance has implications and consequences. Our knowledge of this consequences are limited but important for the pursuit of an uninterrupted malaria elimination agenda. This chapter draws our attention to this risks and recommends interventions.

Keywords: adaptive resistance, drug-resistance, malaria, plasmodium, parasite

1. Introduction

1.1 Malaria - a global infectious disease

Malaria is a global deadly communicable disease [1], caused by plasmodium species, an apicomplexan microbe transmitted by the mosquito vector. Five major plasmodia parasites (*P falciparum*, *P vivax*, *P ovale*, *P malariae* and *P knowlesi*) have been implicated in malaria infections [2]. Of these, *Plasmodium falciparum* (*P. falciparum*) and *Plasmodium vivax* (*P. vivax*) are more widely distributed [3]. In sub-Saharan Africa, *P. falciparum* is the cause of most malaria cases while *P. vivax* is reported to cause most of the malaria cases in Asia; *P. falciparum* cause more fatal disease [4].

In 2019 alone, about 229 million positive malaria infections were reported globally, mortality from was estimated at about 409,000, with children under 5 years accounting for about 67% of death [5]. The disease is common among in poor communities [6], especially rural communities of the underdeveloped/ developing countries of the world. Economic, social and health importance of this disease in terms of loss of life (particularly; young children), reduction in productivity of affected adult population, and negative social and health implication of the disease makes it one of the high ranking microbial, infectious disease in the world.

1.2 Malaria elimination agenda

Among the diseases which have great public health impact, malaria is a significant public health concern [7–9]. The fight to eliminate malaria is an aged long battle globally. Elimination programmes were launched after the Second World War [6], with chloroquine as the major frontline anti-malaria drug [10] and Dichlorodiphenyltrichloroethane DDT used for vector control [11]. Malaria elimination efforts in Africa began with the World Health Organisation (WHO) roll back malaria initiatives started in 1998 [1]; these efforts focused on entomology control (to reduce transmitting vectors) using indoor insecticides, and treated mosquito nets introduced for protection and prevention [6].

The success of these elimination programmes is why over one hundred countries have been awarded malaria free status [12] and thirty-four others accorded elimination status [13], and most malaria endemic countries working very hard towards the attainment of elimination status. Today the disease burden continues to decrease across the world [14] relative to the era, before the launch of the global elimination programmes.

Success stories leading to this elimination stage in malaria control had been heavily dependent on traditional entomology surveillance and drug use. However, the plasmodium is a ubiquitous parasites that has evolved, complex systems of survival [15]. Among these survival strategies is the development of drug resistance to nearly all know malaria drugs. Resistance to chloroquine (the major frontline medicine for the treatment of malaria) was reported and widespread [13] long before the roll-back-malaria initiatives. Better understanding of the biology of the parasites and the life cycle led to the development of a range of other anti-malaria drugs some of which are still actively being used, but resistance to almost all know malaria drugs have been reported [16–19].

Drug resistance vary, and is transferable from pathogen to host [20]. Of the different types of drug resistance, adaptive drug resistance is usually not permanent, but is capable of producing strains of parasites not targeted by known drugs. This chapter aims at reviewing the different types of drug resistance with focus on adaptive drug resistance in plasmodium and the implication to malaria elimination programme.

2. Brief history of anti-malaria drug resistance

The fight against drug resistance in pathogenic microbes is global. The life of these microbes are so inter-twined with human wellness that if overlooked could be very costly in terms of treatment cost and loss of life. As efforts are being up-scaled towards malaria elimination, the issue of drug resistance continues to surface as a major challenge to cope with. This is because the malaria parasite continues to evolve and regularly develop mechanisms for surviving the toxic effect of drugs. These mechanisms result with fixed mutations in the genetic architecture that confers fitness and resistance to withstand or evade targeting drugs, thereby hindering or completely preventing binding between drug compounds and their target.

The history of evolution of drug resistance in plasmodium dates back to the 1930s when chloroquine (CQ) resistance in *P. falciparum* arose independently in Columbia and Thailand [21], and rapidly spread throughout the world. Research efforts to truncate this spread led to the development of different variants of malaria drugs to replace CQ. However, the plasmodium in it's unique way continue to adapt and evolve new mutations for survival and resistance to drugs which are harmful to it [22]. Advances in molecular technology has made it possible to

Mutation sites associated with drug resistance in plasmodium	References
Mutation resulting in polymorphism at the position 76 (K76T) in the transmembrane protein, known as <i>Plasmodium falciparum</i> chloroquine resistance transporter (PfCRT).	[23, 24]
The N86Y and Y184F amino-terminal mutations falciparum multidrug resistance transporter 1 (PfMDR1) has been implicated commonly in CQ and other anti-malaria drug resistance in Asian and African parasites.	[17, 25, 26]
Mutation of dihydrofolate reductase (DHFR) associated with <i>Plasmodium falciparum</i> sulfadoxine-pyrimethamine resistance.	[27]
Mutation of dihydropteroate synthetase (DHPS) enzymes implicated in <i>Plasmodium falciparum</i> sulfadoxine-pyrimethamine resistance.	[27]
mutations in <i>pvm-dr1</i> , <i>pvcrt-o</i> , <i>pvdhfr</i> , and <i>pvdhps</i> genes in temperate-zone of <i>P. vivax</i> associated with malaria drug resistance	[28, 29]

Table 1.
Common mutations associated with P. falciparum malaria drug resistance.

uncover different mutations in the plasmodium parasites associated with drug resistance (**Table 1**). Evolution of these mutations are dynamic and difficult could be difficult to track and eliminate, especially when novel parasite results, against which known anti-malaria drugs is ineffective.

3. Drug resistance types: how much do we know in plasmodium?

Drug resistance types include Intrinsic, acquired and adaptive resistance. Intrinsic drug resistance is a natural phenomenon, and an innate ability in pathogen for resisting drug or harmful substance without prior record of susceptibility [30, 31], pathogens do not necessarily develop mutation for this to occur [32]. Acquired drug resistance builds up in human host, and makes them unresponsive to a drug that should normally eliminate known pathogenic parasite from the host system [33], these are both stable forms of drug resistance. Adaptive resistance [34, 35] develops in a pathogen in response to stimuli [36]. While “intrinsic and acquired resistance are stable and can be transmitted vertically to subsequent generations “[32] adaptive resistance is temporal, unstable, and is often lost ([17]; [37]). [38] observed that “unstable adaptation contains modulation of gene expression, which results in phenotypic changes due to changes in environmental markers that are sensed by the microorganisms” but it is not certain how long this resistance is, or could be sustained [39]. Adaptive resistance is acquired through mutation and binding genetic plasticity that enables transfer of genes [20] from parasites to host. These different mode of drug resistance have been extensively studied and reported for bacteria [36, 40–42], but not much is seen in literature regarding adaptive resistance in plasmodium.

4. Adaptive drug resistance has implications and consequences

Development of drug resistance interferes with disease control, increase the cost of treatment and management of control programs and if not quickly address could thwart control programmes. The evolution of drug resistance in malaria parasites have been a focus of many research but there is a dearth of information regarding adaptive resistance in malaria parasite and the consequence in their human hosts. It is quite understandable since adaptive resistance only confers a temporal resistance

and is reversible. Although temporal and reversible, The possibility of mutation and evolution of a unique strain of parasite is possible, on which known drugs would be ineffective. However, the period between active activation of adaptive resistance in plasmodium, the product of activation (whether lethal or not, or novel and insensitive to known drugs or not), the consequence in gene transfer to host and a host of other factors are unknown.

5. Discovering and tackling adaptive drug resistance in plasmodium: recommendations

Evolution of resistance to drugs is a survival mechanism influenced by many factors that produce mutation in the parasites. Common among causes of resistance is exposure to non-lethal doses of anti-malaria drugs [15]. Malaria parasites have unique ability to evolving mechanisms for evading the immune response in humans [43] and they are actively evolving resistance to anti-plasmodia drugs [44]. But there is a dearth of information are to the effect of plasmodia resistance to drug, especially adaptive resistance, which though is temporal, could influence the development of novel plasmodium stains not targeted by currently available anti-malaria drug. This development is a threat to malaria elimination agenda and should not be encouraged.

A host of resistance gene markers in plasmodium for drug resistance is an active field of malaria research [16, 18, 19, 45, 46], and still counting, but not much is written about the role or influence of adaptive resistance on these markers this is a conspicuous research gap in malaria biology and genetics requiring urgent attention. Selective sweep resulting in sudden change in an advantageous gene under strong positive selection [47] has been reported as product of evolution of resistance to drug. It is possible to scanning the genome for signature of selective sweeps, to identify genes undergoing adaptive evolution [48]. Similar studies revealed the mutations in presently known markers used in the study of malaria drug resistance [49–52], but none is focused on adaptive resistance. This kind of studies leverage of the NEXT GENERATION sequencing technology which is very limited and still very expensive in developing countries, especially in countries with no direct funding of research by government, where malaria is endemic.

6. Pertinent questions and suggestions for the way forward

Is adaptive resistance in malaria parasites a challenge? Does it have a significant influence on combating and elimination of malaria particularly in malaria endemic regions in Africa? Understanding the effects of adaptive malaria drug resistance, in plasmodium, the vector and the human host will greatly contribute to malaria elimination agenda and reposition the malaria elimination programmes across the world with focus on sub-Saharan Africa as the hub. In addition, different populations respond differently to the same drugs. These differential responses are influenced by genetic variability in different ethnic groups within a population, which in turn can be associated with variation in resistance to given drugs. Identification of genes and gene pathways involved in adaptive resistance is also vital for developing markers for prediction and diagnosis and should be pursued.

Kim and Schneider [48] observed that, “by examining selective sweeps in many endemic areas with different demographic and epidemiologic characteristics” it would be possible to identify factors associated with adaptive resistance to malaria drugs and track epidemiological variables [53–56] for transmission

and development of treatment regimes, accurate drug prescription and be able to determine costs of resistance. Understanding the implication and consequences of adaptive resistance alongside other forms of drug resistances will play significant role in policy formulation and implementation for disease control, give vivid picture of how to manage malaria control and modelling of disease transmission.

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