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Review

Resistance to antimalarial drugs: An endless world war against *Plasmodium* that we risk losing

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ABSTRACT

The objective of this review was to describe the 'state of the art' of *Plasmodium falciparum* resistance to the main antimalarial drugs. A brief note on *Plasmodium vivax* is also included. Resistance of *P. falciparum* to the various antimalarials has a long history of hits and misses. During the last 60 years, the pace at which this parasite has developed resistance to antimalarial drugs has exceeded the pace at which new drugs have been developed. In the last decade, the introduction of artemisinin-based combination therapies (ACTs) as a first-line drug treatment for non-complicated *P. falciparum* malaria had led to extraordinary results in disease control, especially in sub-Saharan Africa. However, the emergence and spread of resistance to artemisinin in Southeast Asia jeopardise these results. In conclusion, the possible spread of artemisinin resistance in Africa should be considered as an epochal disaster.

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1. Introduction

Malaria is the major parasitic disease of humans in the world and is a major health problem affecting developing countries. Worldwide malaria morbidity is currently estimated at over 250 million clinical cases and ca. 700 000 deaths each year, most of them being children aged <5 years [1], and the global burden of malaria expressed in disability-adjusted life-years is estimated at 83 million [2]. Few other infectious diseases place such a burden on social, economic and healthcare systems in developing countries [2]. Malaria is transmitted by bites from infected female anopheline mosquitoes and is caused by a protozoan infection by five species of the genus *Plasmodium*, namely *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi* ([3] and references therein). *Plasmodium knowlesi* is a malaria parasite of primates that, since

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2004, is recognised as the fifth human malaria species [4], although only transmission from monkeys to humans via mosquito vectors (i.e. zoonosis) is recognised so far. *Plasmodium knowlesi* is a major cause of malaria in Malaysia, particularly on the island of Borneo, but case reports of this infection have also been documented in China, Thailand, Myanmar and other neighbouring countries [5]. Severe forms of malaria due to *P. knowlesi* have been reported recently in the literature [6].

The signs and symptoms of malaria and their severity in humans are due to the asexual blood stage of the malaria parasite and are quite diverse, with a wide range of outcomes and pathologies. Symptoms may include fever (which may be alternating), tachycardia, rigours and sweating as well as severe features such as cerebral involvement and multiorgan failure [7]. Morbidity and mortality are mostly due to *P. falciparum* infection causing the severe disease syndrome known as cerebral malaria, which is associated with a high mortality rate. However, it has become clear that *P. vivax* is also responsible for a dramatic toll in many endemic areas except Africa. Cerebral malaria and severe respiratory distress due to *P. vivax* infections were recently reported from different settings, with severe disease peaking at an earlier age than in infections due to *P. falciparum* [8–11]. Since sequestration of *P. vivax*-infected red blood cells was only recently reported [12–14], the mechanisms at the origin of these complications are still a matter of debate.

As there is still no effective vaccine available, malaria treatment and prophylaxis are dependent on drugs. Unfortunately, most of the drugs available for the treatment of malaria (Table 1) have lost efficacy worldwide owing to resistance. Even artemisinin-based combination therapies (ACTs), currently the most effective antimalarial treatment, have been associated with decreased efficacy and emerging drug resistance [15,16].

Here, a 'state of the art' of *P. falciparum* resistance to the main antimalarial drugs is presented, including a short history of drug resistance and a brief note on resistance to anti-*P. vivax* drugs.

2. A short history of antimalarial resistance

The oldest antimalarial is quinine, an aryl amino alcohol extract from the bark of *Cinchona officinalis*, a plant native to South America. It was introduced to Europe by the Jesuits as 'Jesuits powder' and was subsequently isolated in 1820 in France from the bark of the cinchona. From that moment, quinine became the treatment of choice for intermittent fevers worldwide [17]. Primaquine (PMQ) was produced during and after the First and Second World Wars, whilst chloroquine (CQ) made its appearance in the frame of antimalarials in 1934 [18]. After the Second World War, CQ was the drug of choice to threat *P. falciparum* malaria and was employed in mass drug administration in the Global Malaria Eradication Campaign launched by the World Health Organisation (WHO) in 1955 [19].

The first mention of resistance to quinine was in an article published in 1910 in the journal *Memórias do Instituto Oswaldo Cruz* [20], but it can be considered as an anecdotal report.

Resistance of *P. falciparum* to CQ has emerged separately in four endemic areas of the world in different years: in 1957, CQ resistance was reported at the Thai–Cambodian border [21]; in 1960 CQ-resistant *P. falciparum* strains were identified in Venezuela and Colombia [22]; and finally in 1976 cases of CQ resistance were reported in Papua New Guinea [23] (Box 1).

In Africa, the first report of CQ resistance was in 1978, and by 1983 it had spread to Sudan, Uganda, Zambia and Malawi [24,25]. The first African country to replace CQ with sulfadoxine/pyrimethamine (SP) was Malawi in 1993, and the use of CQ as an antimalarial was discontinued in all African countries in subsequent years [26].

Different to the gradual appearance of CQ resistance, resistance to the alternative drugs introduced to treat CQ-resistant strains emerged in some cases relatively rapidly. In 1967 the combination SP was introduced in Thailand and SP resistance was reported the same year, spreading throughout Southeast Asia, and in the late 1980s it appeared in Africa. Mefloquine resistance was first

Table 1
Treatment of malaria.

First-line antimalarial treatment	Second-line antimalarial treatment
Treatment of uncomplicated *Plasmodium falciparum* malaria	
Artemisinin-based combination therapies (ACTs)	Artesunate plus tetracycline or doxycycline or clindamycin
Dihydroartemisinin plus piperaquine is an option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide.	Quinine plus tetracycline or doxycycline or clindamycin
The following ACTs are also recommended:	
Artemether plus lumefantrine;	
Artesunate plus amodiaquine;	
Artesunate plus mefloquine;	
Artesunate plus sulfadoxine/pyrimethamine	
Treatment of severe malaria	
For adults: artesunate (i.v. or i.m.)	Artemether or quinine is an acceptable alternative if parenteral artesunate is not available
For children: artesunate (i.v. or i.m.)	
Treatment of uncomplicated *Plasmodium vivax* malaria	
Chloroquine combined with primaquine.	
In areas with chloroquine-resistant *P. vivax*, ACT (exception artesunate + sulfadoxine/pyrimethamine) in combination with primaquine	
Pregnancy	
First trimester	
Quinine plus clindamycin	
Second and third trimesters	
ACTs known to be effective in the country/region or artesunate plus clindamycin	
Lactating women	
Standard antimalarial treatment (including ACTs) except for dapsone, primaquine and tetracyclines	
Infants and young children	
ACTs	

i.v., intravenous; i.m., intramuscular.