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History and importance of antimalarial drug resistance

U. D'Alessandro and H. Buttiëns

Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium

Summary The emergence of *Plasmodium falciparum* resistance to widely used antimalarial drugs such as chloroquine (CQ) has made malaria control and treatment much more difficult. This is particularly dramatic for Africa, as few affordable alternatives are available. Drug pressure has been identified as one of the key factors for the emergence and spread of resistance. The contribution of the extensive use and misuse of antimalarial drugs to the selection of resistant parasites became particularly evident during the Global Malaria Eradication campaign, launched by World Health Organization (WHO) in 1955. The first reports confirming *P. falciparum* resistance to CQ came almost simultaneously in the early 1960s from South America and South-East Asia, where direct or indirect (through use of medicated cooking salt) mass drug administration (MDA) had been implemented. Similar approaches were very limited in Africa, where *P. falciparum* resistance to CQ was first reported from the eastern region in the late 1970s and spread progressively west. Most African countries still rely heavily on CQ as first-line treatment despite various levels of resistance, although some states have changed to sulphadoxine-pyrimethamine (SP) as the first-line drug. Unfortunately, the predicted SP useful therapeutic life might be very short, probably because of its prolonged half-life, causing a higher probability of selecting resistant strains and a consequent fast development of resistance. CQ resistance is not evenly distributed and important differences can be found within and between countries. It seems to have spread more rapidly in East than in West Africa. Considering the high level of CQ use in West Africa, other factors such as intensity of transmission, population immunity or population movements should be considered when explaining the different levels of resistance. Understanding such factors may help us in devising strategies to contain the spread of drug resistance.

keywords Africa, antimalarial resistance, chloroquine, strategies, sulphadoxine-pyremethamine

correspondence U. D'Alessandro, Prince Leopold Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium. E-mail: udalessandro@proto.itg.be

Introduction

Despite considerable efforts during last century to eradicate or control *Plasmodium falciparum* malaria, it remains the most prevalent and devastating parasitic disease in the tropics (WHO 1993). Worldwide, it causes 300–500 million clinical cases, more than 80% of which live in sub-Saharan Africa. A conservative estimate puts the yearly malaria mortality burden at around 1 million deaths, 90% in sub-Saharan Africa. In the last decades, malaria control and treatment has been complicated by the rapid emergence of resistance to widely used antimalarial drugs such as chloroquine (CQ). This is particularly dramatic for the African continent, as few cheap and safe alternative drugs to CQ are available.

Drug pressure has been identified as one of the key factors in the emergence of resistance to antimalarial drugs. Selection of resistant strains can occur when a drug is misused (Wernsdorfer 1991, 1994) or used alone extensively. Readily absorbed drugs with a long half-life, such as mefloquine and sulphadoxine-pyrimethamine (SP), can permit effective single-dose treatment of malaria and the following chemoprophylactic period prevents infection for several weeks and may be important in recovery from anaemia. However, these drugs are likely to exert undesirable drug pressure for a long time once their concentrations drop below the critical threshold and may select resistant parasites. This has been shown in Kenya where potent selective pressure for resistance operates even under conditions of supervised drug administration and optimal dosage (Watkins *et al.* 1997). This is why drug

combinations have recently been proposed to delay the emergence and spread of drug resistance (White & Olliaro 1996; White 1998, 1999), an approach already used for highly drug-resistant infectious diseases such as tuberculosis or AIDS. The first consequence of using drugs in combination is that the starting frequencies of malaria parasites resistant to all the components are much reduced, such that the evolution of resistance is delayed compared with when its components are used alone. The second consequence is that the resistant combinations will be broken down much more frequently during recombination in meiosis: the greater the number of genes required to encode resistance, the greater the rate of loss (Hastings & D'Alessandro 2000). In practice, the emergence and spread of resistant strains should be delayed and the useful therapeutic life (UTL) of the combination should be much longer than its single components.

The past

The contribution of monotherapy and misuse of antimalarial drugs to the emergence of drug resistance became particularly evident during the Global Malaria Eradication campaign launched in 1955 by WHO. At the beginning, the campaign's strategy was mainly based on DDT indoor spraying, whose insecticide properties would interrupt malaria transmission by decreasing the survival of potentially infected mosquitoes. However, the first reports of insecticide resistance (to dieldrin) in *Anopheles gambiae* in Nigeria prompted the Second African Malaria Conference held in Lagos in 1955 to stress the importance of obtaining the complete interruption of local transmission as quickly as possible (Bruce-Chwatt 1956). Therefore, the use of chemotherapeutic methods in association with residual insecticides was recommended whenever the rapid elimination of malaria was thought to be possible. Although it is unclear what has been the role of mass drug administration (MDA) on the emergence of antimalarial drug resistance, it has clearly shown that widespread use of a drug can select resistant parasites.

Direct MDA with available antimalarial drugs such as pyrimethamine or CQ was not easy to implement. Several problems were identified: it was difficult to obtain an accurate census and to persuade the mostly asymptomatic population to comply with the drug therapy. Complete coverage of the population was almost impossible to achieve. The introduction of cooking salt medicated with an antimalarial drug (indirect MDA) was in this regard a more feasible method (WHO 1961). But soon it became clear that these interventions, besides the operational difficulties, could easily select resistant parasites. In a few Kenyan villages, MDA with monthly pyrimethamine initially decreased the parasite prevalence but was followed by the emergence of parasites showing increased tolerance to the drug: sensitive parasites were rapidly replaced by resistant ones that disappeared when the administration of monthly pyrimethamine was stopped (Clyde & Shute 1954; Avery 1958). A similar observation was reported from Ghana, although in this case it was explained by the irregular ingestion of tablets (Charles *et al.* 1962).

The use of medicated salt had the disadvantage of not covering infants and small children and it was also associated with the emergence of resistance (WHO 1961). Interventions based on the introduction of pyrimethamine-medicated salt were implemented, among others, in The Netherlands, New Guinea, Brazil and Cambodia (Eyles *et al.* 1963). Usually, despite an initial decrease, parasite rates returned back to pre-operational levels within a period of 6 months. In New Guinea, the emergence of pyrimethamine resistance, unsatisfactory distribution of medicated salt and underestimation of the salt ration were identified as major causes for failure (WHO 1961). Better results were reported with CQ-medicated salt from Guyana (Giglioli *et al.* 1967) and Uganda (Hall & Wilks 1967), where parasite rates decreased. In general, the widespread use of medicated salt produced a wide variation of drug levels in the population because of the great variation in salt intake and the (clandestine) use of non-medicated salt. This resulted in a very high selection pressure that induced an almost instantaneous *P. falciparum* resistance to pyrimethamine. CQ seemed to induce resistance less easily. However, the first cases of CQ-resistant strains originated from or near areas where CQ-medicated salt had been distributed (Payne 1988).

The first reports of confirmed *P. falciparum* resistance (RI) to CQ came, almost simultaneously, from South America (Colombia, Brazil, Venezuela in 1960) (Moore & Lanier 1961; Wernsdorfer & Payne 1991) and South-east Asia (Thailand, Kampuchea in 1961) (Hartinuta *et al.* 1962). In 1973, CQ resistance had been reported in several countries in South America (Brazil, Colombia, Guyana and Venezuela) and in Asia (Burma, Cambodia, Malaysia, Philippines, Thailand and Vietnam) but not in sub-Saharan Africa (WHO 1973). In Africa, *P. falciparum* CQ resistance was firstly reported from the eastern region, in Kenya (Fogh *et al.* 1979) and Tanzania (Campbell *et al.* 1979), in the late 1970s and it spread from east to west. A few years later, the number of countries with at least RI CQ resistance had increased considerably in Africa (Burundi, Comores, Gabon, Kenya, Madagascar, Malawi, Sudan, Uganda, Tanzania, Zaire [(eastern part), Zambia], South America (Brazil, Colombia, Guyana, Venezuela, Bolivia Ecuador, French Guyana, Panama, Suriname), Asia (Burma, Cambodia, Malaysia, Philippines, Thailand,

Vietnam, Bangladesh, China, East Timor, India, Indonesia, Lao's PDR, Papua New Guinea) and Oceania (Solomon Islands, Vanuatu) (WHO 1984). By 1989, the distribution of CQ resistance was almost identical to that of *P. falciparum* (Wernsdorfer & Payne 1991).

Current situation of CQ and SP resistance in Africa

CQ, the cheapest and most widely available antimalarial drug in the market, is still extensively used in many African countries despite various levels of resistance. In response to prevailing CQ resistance, Malawi, Kenya, Botswana and South Africa have changed the first-line drug from CQ to SP and other countries might follow soon. However, the UTL predicted for SP might be very short probably because of its prolonged half-life, causing a higher probability of selecting resistant strains and consequent rapid development of resistance (Nzila *et al*. 2000). This is why new alternative drugs or new approaches, such as drug combinations, are urgently needed.

Levels of resistance can vary widely between and within countries. In Kenya, for example, there were major differences in CQ resistance between the North, where malaria transmission is low, and the south-west, where transmission is intense. In the early 1990s, CQ resistance (positive slide on day 14 after treatment) was about 18% around Lake Turkana (Clarke *et al*. 1996) while in Kisumu, on the shores of Lake Victoria, it was around 70% (RII and RIII) (Bloland *et al*. 1993). This kind of situation represents a real dilemma for health managers needing to decide whether and with which drug to change the country's antimalarial drug policy. Such a change constitutes a major undertaking that can take several years before being fully operational. In optimal conditions the 'reaction time' has been estimated to be at least 2 years (Baudon 1995). Once the decision of changing the first-line drug is taken, there is no way back. However, it has always been difficult to give detailed guidelines or to establish a threshold at which a change should be implemented because this depends on several factors such as the cost of the drug and compliance.

CQ resistance seems to have spread more rapidly in East than in West Africa. In Uganda CQ resistance has reached such high levels (up to 44% clinical failure in one of the sentinel sites in 1998) in just a few years that the country recently decided to change its drug policy (Bakyaita *et al*. 2000). In West Africa, the level of CQ resistance seems still relatively low by comparison. For example, a study using *in vivo* tests in 1997–99 at the Centre Muraz in Bobo Dioulasso, Burkina Faso, reported CQ clinical failure rates under 20% (Coulibaly 2000). In Mali, a recent study reports a level of CQ parasitological resistance (RI + RII + RIII) of 14% (Djimdé *et al*. 2001). If drug pressure were the only determining factor, resistance should be extremely high in Mali because of high CQ use and misuse by the local population (Théra *et al*. 2000). Other factors such as the intensity of transmission, the population immunity or the population movements should be considered (Hastings & D'Alessandro 2000). Understanding these may help us devise strategies to contain the spread of drug resistance.

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