Milestones in Drug Therapy
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Treatment and Prevention of Malaria

Antimalarial Drug Chemistry, Action and Use

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HMS dedicates this book to his wife, Zoë, and children,
Talia, Luca and Oren and SK to Yasmin's memory
and Karim, and to the rest of his exceptional family.

Preface

Malaria is a devastating disease that extracts huge health and economic costs from the poorest countries in endemic regions. Malaria is caused by single celled parasites, belonging to the genus *Plasmodium* that have infected humans (and related primates) for thousands of years. In its different specific and clinical guises, malaria is one of the strongest selective forces to have shaped our recent evolution. These parasites have already evaded one attempt at eradication in the mid twentieth century. Now, there are renewed attempts to control and eventually eradicate what remains one of the world's biggest killers.

With ambitious new targets set to reduce the global burden of malaria, we must urgently develop new tools for disease control, as well as optimising and re-evaluating our current tools. An indispensable part of controlling malaria is the capability of treating the disease effectively, despite the ability of this highly mutable parasite to develop resistance sooner or later to all classes of antimalarials. Understanding of how antimalarial drugs might work, how best to use them and how to assess for resistance to them has expanded considerably in the past few years. This book aims to capture these recent advances in our understanding of all antimalarial classes, and discuss how this information is pertinent for treating patients.

The introductory chapter details the disease, its current political, financial and technical context, alongside the policies and tools required to make eradication a possibility. Subsequent chapters cover the history, chemistry, mechanisms of action and resistance, preclinical and clinical use, pharmacokinetics and safety and tolerability of our current antimalarial drug armamentarium. Each chapter reflects the unique perspectives of its expert authors, and often describes new ideas and directions for study. There is particular emphasis on artemisinins (and related next generation peroxides) that have become the frontline treatment for malaria, as part of artemisinin-based combination therapies (ACTs). The artemisinins may have become established in ACTs in the past decade, but they are now being challenged by the potential for resistance that has recently been described and is only just being defined.

Other chapters authoritatively discuss our antimalarial drug development pipeline and how this is being shaped by public/private partnerships; molecular markers

of antimalarial drug resistance, their use in monitoring treatment failures and the insights they provide into the action of these drugs; malaria prevention strategies, including chemoprophylaxis, where the risk of catching malaria is balanced against the risk of side effects of drugs and the critical use of diagnostics to improve the identification of malaria and to refine treatment strategies.

The treatment and prevention of malaria is a fascinating and complex subject – made all the more interesting now that malaria eradication is back on the global agenda. We hope that readers will be stimulated by this volume and that they may find its contents useful in dealing with malaria.

London, United Kingdom

Henry M. Staines
Sanjeev Krishna

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Antimalarial Drugs and the Control and Elimination of Malaria

Karen I. Barnes

Abstract Malaria remains a massive global public health problem despite being readily preventable and treatable. The past decade has seen unprecedented levels of political, technical and financial support that have facilitated the scaling-up of malaria control interventions, particularly the implementation of artemisinin-based combination therapy (ACT) policies. During this window of opportunity for reducing the burden of malaria globally and possibly eventually eliminating malaria, attention now needs to be focussed on ensuring that countries select and implement treatment policies that are not only highly effective, but will also have a prolonged useful therapeutic life, reduce malaria transmission safely and effectively and, where applicable, be active against *P. vivax*. To reduce the probability of resistance, antimalarials should be used in quality-assured fixed-dose combinations and treatment doses need to be optimised on the basis of pharmacokinetic assessments conducted within therapeutic efficacy studies in each key target population. As important is ensuring optimal targeting and adherence with these treatment policies.

1 Introduction

Malaria is a massive global public health problem. Nearly half the world's population lives at risk of malaria, which causes an estimated one million deaths and 450 million *Plasmodium falciparum* and 390 million *P. vivax* cases each year [1, 2]. Those with malaria also carry an increased burden of HIV/AIDS, measles, respiratory tract infections, diarrhoea, malnutrition and anaemia [3]. Malaria in pregnancy increases the infant risk of low birth weight, abortions and stillbirths, in addition to

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the maternal burdens of anaemia, severe malaria and maternal mortality [4]. The indirect burden of malaria includes its adverse effects on education, worker productivity and investment. It has been estimated that malaria costs Africa $12 billion per year, with a fivefold reduction in per capita gross domestic product (GDP) after controlling for other socio-economic determinants [5].

Efforts to reduce malaria morbidity and mortality include control of the mosquito vector (using insecticide-treated bed nets and indoor residual spraying) and prompt treatment with effective antimalarials. Unprecedented levels of political, technical and financial support have facilitated the scaling-up of malaria control interventions, particularly changes in malaria treatment policy from the inexpensive yet failing monotherapies, chloroquine and sulfadoxine–pyrimethamine, to the recommended artemisinin-based combination therapies (ACTs). ACTs are generally considered as the best current treatment of uncomplicated falciparum malaria [6], as they have high cure rates, have more rapid parasite clearance times and have the potential to reduce both antimalarial resistance and malaria transmission. Over the last decade, the bar for recommending an antimalarial regimen as policy for uncomplicated falciparum malaria was raised from requiring an adequate clinical and parasitological response (ACPR) rate at 14 days of merely 75%, to at least 95% at $\geq$28 days [6]. Fortunately, there are now a number of ACTs in most settings that meet this stringent criterion. While most malaria endemic countries have adopted ACT policies, the implementation of these policies has been slower.

The extent to which malaria can be eradicated in the foreseeable future is a subject of active debate, but it is generally agreed that the tools are available to reduce the global burden of malaria substantially. How these tools are selected and, more importantly, deployed will be critical in determining the success achieved. Optimising the impact of ACTs on the control and eventual elimination of malaria depends on careful selection of the regimen implemented. In addition to the usual considerations of effectiveness, safety and cost, treatment policy selection should consider the likely useful therapeutic life (the time until ACPR rates at $\geq$28 days decrease below 90%), impact on malaria transmission and, where relevant, efficacy against non-falciparum malaria. As important are the selection of evidence-based dosage regimens that are appropriate for each key target population, especially young children and pregnant women [7], and optimising the implementation strategies deployed to ensure high coverage and adherence rates among those with malaria, while limiting use among those with non-malarial febrile illnesses [8].

2 Malaria: The Basics

All malaria is transmitted by female mosquitoes of the genus *Anopheles*. Humans are mainly infected by four species of *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, although human infections with the monkey malaria parasite, *P. knowlesi* have also been reported recently in the forested regions of Southeast Asia [9]. The majority of all human malaria cases are caused by

P. falciparum and *P. vivax*, although the burden of *P. ovale* and *malariae* are poorly defined. Although almost all severe malaria is caused by *P. falciparum*, severe disease and malaria-related deaths have also been reported with *P. vivax* and *P. knowlesi*.

The sporozoite form of the parasite is inoculated into humans when bitten by an infected female *Anopholes* mosquito. Sporozoites rapidly enter the liver cells where they multiply to form thousands of merozoites. These then enter the bloodstream where they invade red blood cells and multiply to form new merozoites. Infected red blood cells burst, releasing merozoites that infect new red blood cells. This is referred to as the asexual blood stage, the stage of the plasmodial life cycle that causes the clinical signs and symptoms of malaria. Some merozoites that invade the red blood cells develop into gametocytes, the sexual stages of the parasite. Gametocytes are ingested by the mosquito when it takes a blood meal. In the mosquito gut, the gametocytes develop into gametes and fuse to form a zygote. After fertilisation, the zygote transforms into a motile ookinete, which penetrates the mosquito stomach wall and becomes an oocyst. The oocyst divides to produce sporozoites, which move into the salivary glands, from where another human can be infected when the mosquito takes a blood meal (Fig. 1).

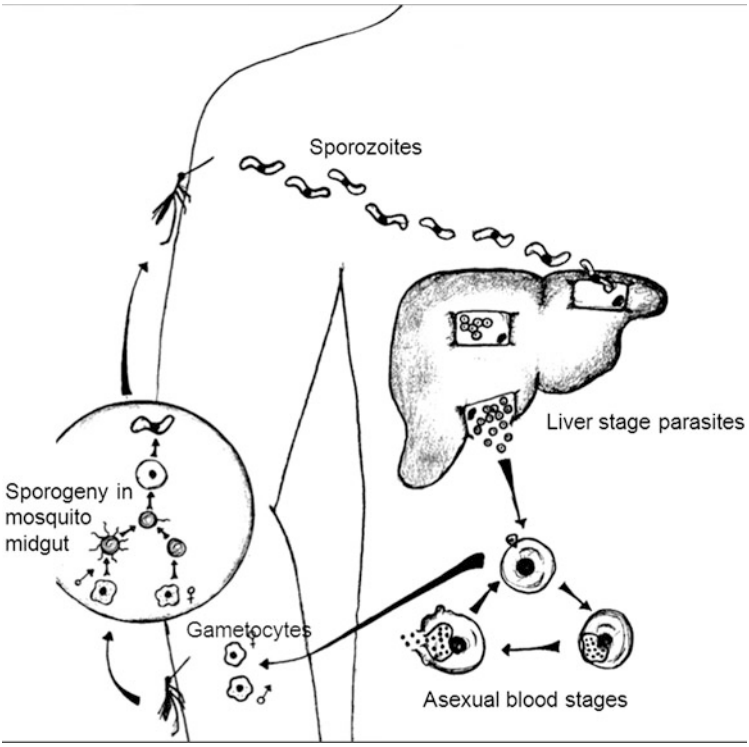

Fig. 1 The lifecycle of the malaria parasite in the human host and *Anopholene* mosquito vector

Malaria transmission rates are determined by the parasite reservoir in a community and the abundance and behaviour of the mosquito vectors [10]. The probability of a mosquito being infected depends on the prevalence, duration and density of viable gametocyte carriage in the human host, although additional immunological factors also affect transmissibility [11]. There are many factors that can lead to an increase in the duration and density of *P. falciparum* gametocyte carriage. Most of these are not well defined, but gametocyte numbers increase with the density and duration of asexual parasitaemia (emphasising the importance of prompt treatment), anaemia and drug resistance [11, 12].

3 Treating Malaria to Prevent Transmission

While eliminating the asexual stages of plasmodial infections is the focus of treatment of individual symptomatic patients, at a population level, limiting the transmission of malaria, and in particular, the transmission of resistant parasites is pivotal for decreasing the community's burden of malaria. In considering antimalarial drug effects on transmissibility, three different components need to be considered (a) activity against asexual stages and early gametocytes, (b) activity against mature infectious gametocytes and (c) sporontocidal effects in the mosquito [13].

Early access to effective treatment of the asexual blood stage can reduce the incidence and prevalence of malaria in a community, although the effects are greater in areas of low transmission where a higher proportion of the infectious reservoir is in non-immune and thus symptomatic individuals, who are more likely to seek antimalarial treatment [13]. However, achieving malaria control and eventually elimination requires a complete parasitological cure, including killing of the parasites in the sexual (gametocyte) stages that are responsible for malaria transmission [11, 14]. *P. falciparum* gametocytes are relatively insensitive to most antimalarials, other than the artemisinins and primaquine [15]. It has been suggested that artemisinins predominantly inhibit gametocyte development, whereas primaquine accelerates gametocyte clearance in *P. falciparum* malaria [16]. ACTs have the advantage of being the only antimalarials currently available that rapidly reduce both asexual and gametocyte stages of *P. falciparum*. When compared with amodiaquine plus sulfadoxine–pyrimethamine treatment, ACTs reduced the duration of gametocyte carriage (quantified using nucleic acid sequence-based amplification) fourfold [17]. The large-scale deployment of ACTs contributed to a marked reduction in the number of malaria cases seen in a number of countries, mostly in areas of low to moderate intensity transmission [18–23].

As the effect of the artemisinins on *P. falciparum* gametocytes is not complete, patients treated with artemisinins can still transmit malaria [24–26]. Mature gametocytes are resistant to almost all of the antimalarial drugs that affect the asexual stages and the only licenced drug that can ensure complete killing of *P. falciparum* gametocytes is primaquine. This 8-aminoquinoline is very effective

in preventing transmission, even when administered as a single dose. The addition of primaquine to artesunate plus sulfadoxine–pyrimethamine in Tanzania, when compared with artesunate plus sulfadoxine–pyrimethamine alone, resulted in a further fourfold reduction of the duration of gametocyte carriage [17], and an even greater reduction in sub-microscopic gametocytaemia [27]. However, primaquine may cause methaemoglobinaemia and haemolysis, which can be severe and occasionally life threatening. Haemolysis occurs most frequently (but not only) in patients with certain glucose-6-phosphate dehydrogenase (G6PD)-deficiency variants, particularly when a prolonged course of treatment is used. Primaquine is contraindicated in pregnancy, lactation, infants and young children and in those with haemolytic anaemia, methaemoglobinaemia or severe G6PD deficiency. As G6PD-deficient variants protect against *P. falciparum* and *vivax* malaria, this abnormality is most prevalent in malaria-endemic areas [6, 28–32]. The key operational question now is whether the benefits of adding primaquine (probably as a single dose) to ACTs in order to further reduce transmission exceed the risks. Unfortunately, there are remarkably limited data available to inform this decision, as summarised by Baird [33]: "Despite more than 50 years of continuous use in millions of people annually as the only drug available for its therapeutic indication, it is not known how primaquine acts or how it should be taken."

Lastly, atovaquone and the antifolate antimalarials reduce transmission by decreasing the formation of sporozoites in the *Anopheline* mosquito. For antifolates, this effect is reduced by antifolate resistance, creating a further transmission advantage for resistant parasites [13]. Also, atovaquone–proguanil offers the further benefit of acting as a causal prophylactic agent, but atovaquone rapidly selects for the *cytochrome b* mutation associated with high-level resistance. The possible role of atovaquone–proguanil alone or in combination with artesunate in attempts to contain or eliminate malaria deserves further study.

4 Antimalarial Resistance: The Major Threat to Malaria Control and Elimination

Parasite resistance to antimalarial medicines is a major threat to achieving malaria control and eventual elimination. Antimalarial resistance in *P. falciparum* parasites results in an enormous public health and economic burden. The rise in malaria-related hospital admissions and malaria mortality across west, east and southern Africa during the 1990s is largely accounted for by the continued use of the cheap monotherapies, chloroquine and sulfadoxine–pyrimethamine, despite widespread high levels of resistance [34–37]. Lower levels of resistance are associated with return of illness, anaemia and increased gametocyte carriage (which fuels malaria transmission, particularly of the resistant parasites) and a higher risk of treatment failure in subsequent infections [38, 39]. Parasite resistance has been documented for all classes of antimalarials, including – in the Southeast Asian epicentre of drug

resistance along the Thai–Cambodian border – the artemisinin derivatives [40, 41]. If the efficacy of the artemisinin derivatives is lost, then effective control and elimination will not be possible with currently available tools [13]. Despite these concerns, the artemisinin-resistance phenotype has been poorly characterised, and the contribution of host factors remains to be defined. The key features of the artemisinin-resistant phenotype are prolonged parasite clearance times, despite apparently adequate drug exposure, and even dose escalation [42, 43]. Although molecular markers for artemisinin resistance remain elusive, a genetic basis for this clinical phenotype has been proposed recently based on its high heritability [44]. The recent declines in the clinical effectiveness of all antimalarial drugs, including the artemisinins, have prompted suggestions to revise the definitions of antimalarial drug resistance to include a category for extensively drug-resistant (XDR) malaria, as this approach has proved useful in tuberculosis for individual patient care and for public health [45].

Antimalarial resistance spreads when parasites are exposed to the selective window of drug concentrations that are sufficient to kill sensitive but not resistant parasites [7] (Fig. 2). Drugs with longer terminal elimination half-lives have the advantage of providing a longer post-treatment prophylactic effect, which appears to be important for their action in intermittent preventive therapy (IPT) in high-risk groups such as pregnant women, infants and young children. However, these long-acting antimalarials have the disadvantage of residual concentrations inhibiting sensitive parasites far longer than resistant parasites, thus fuelling the spread of resistance. The window of selection is prolonged with an increase in resistance or in the terminal elimination half-life (unless these terminal concentrations are too low even to kill sensitive parasites) (Fig. 2).

Antimalarial resistance spreads because gametocyte carriage and infectivity to mosquitoes is consistently higher in patients infected with drug-resistant compared with drug-sensitive parasites. An increase in gametocyte numbers has been identified as the first indication that an antimalarial is beginning to fail and emphasises the need for the treatment policy implemented to include drugs that will kill the sexual stages [12, 13]. Combining antimalarials with differing modes of action is expected to reduce the probability of a resistant (mutant) parasite surviving treatment [46]. Despite their mismatched elimination half-lives, ACTs are preferred to other combination therapies given their potential to reduce malaria transmission – due to their rapid clearance of asexual parasites together with their partial gametocidal activity [6]. The gametocyte-reducing effect of widespread use of artesunate plus mefloquine therapy has resulted not only in the sustained decrease in malaria transmission described above, but also in decreased mefloquine resistance in northwest Thailand, an area of low-intensity malaria transmission notorious for multi-drug resistance [18, 47]. By contrast, the first and only effort to date in Africa documenting the routine large-scale surveillance of temporal changes in resistance after successful implementation of an ACT treatment policy, found that systematic deployment of artesunate plus sulfadoxine–pyrimethamine had not delayed the spread of sulfadoxine–pyrimethamine resistance and may in fact have contributed to the rapid increase in the proportion of parasites carrying quintuple

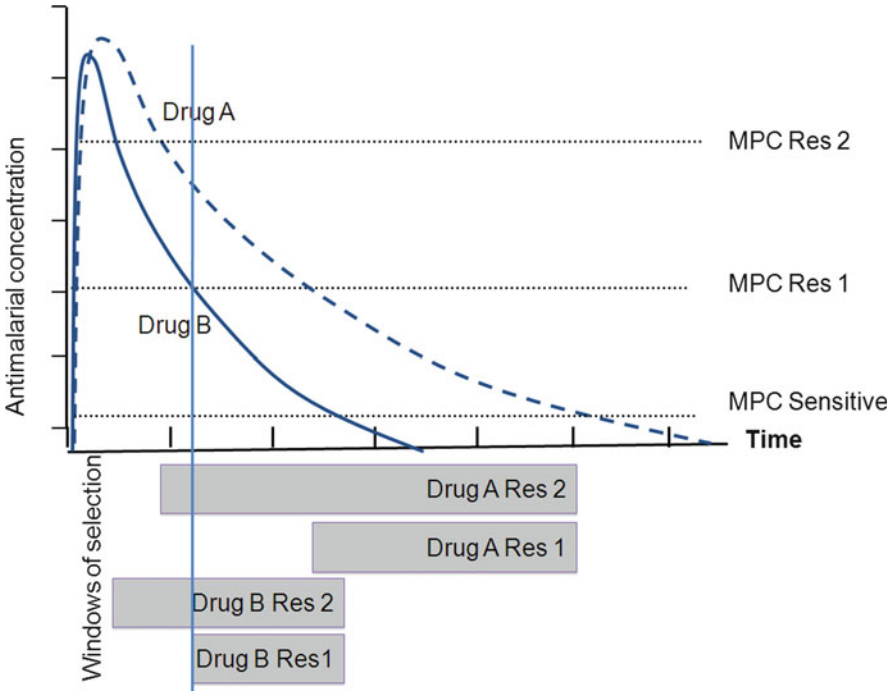

Fig. 2 Resistance selection by drugs with long elimination half-lives. The *curves* show antimalarial drug concentrations over time for Drug A (*dashed line*) and Drug B (*solid line*). The Window of Selection is the time when antimalarial concentrations are sufficient to clear sensitive but not resistant parasites. The three *dotted lines* show hypothetical minimum parasiticidal concentrations (MPCs) needed for clearing sensitive, partially resistant (Res 1) and highly resistant (Res 2) parasites. The duration of the window of selection increases with (a) increasing levels of resistance, so is longer for highly resistant than for partially resistant parasites, and (b) terminal elimination half-life, so is longer for Drug A than for Drug B

dihydrofolate reductase and *dihydropteroate synthetase* resistance markers from 11 to 75% over the 5-year study period [48]. Transmission of sulfadoxine–pyrimethamine resistance occurs intrinsically more readily than with mefloquine, probably since mefloquine resistance confers a survival disadvantage, while this does not appear to be the case with sulfadoxine–pyrimethamine.

A further challenge to limiting the rate of spread of ACT resistance is that expanding ACT access is necessary for reducing malaria morbidity and mortality. To be accessed promptly, ACTs need to be available near the home. With recent efforts to reduce the costs of ACTs dramatically, this is becoming achievable even in the poorest communities. However, such ready access creates creates the opportunity for widespread and indiscriminate use of antimalarials, which exerts a strong selective pressure towards resistant parasites towards high levels of resistance [42]. This could be addressed by limiting ACT use to those with a confirmed malaria diagnosis [6]. While 78 malaria-endemic countries (33 in Africa) have a policy that

patients of all ages with suspected malaria should receive a diagnostic test before treatment, this policy is only implemented in a minority of African cases – but is used in more than 80% of suspected cases outside Africa [23]. Other challenges to the effective targeting of ACTs are that only 38 countries (16 in Africa) are deploying rapid diagnostic tests at a community level and that ACTs continue to be used by those with negative malaria tests [23, 49].

Continued use of artemisinin-based monotherapy is considered a major factor in resistance to the artemisinins emerging and spreading, emphasising the importance of oral artemisinins being used only in combination with an effective longer acting antimalarial. This makes fixed dose artemisinin-based combinations highly preferable to loose tablets or blister-packed combinations [6]. To this end, the WHO recommends the withdrawal of all oral artemisinin-based monotherapies from the market [23, 42]. Others have argued that oral artesunate monotherapies are still needed, but should be reserved for use as a 7-day treatment course for patients with uncomplicated hyperparasitaemia and pregnant women in areas of multi-drug resistance [50].

De novo antimalarial drug resistance is most likely to occur in hyperparasitaemic patients who are non-immune, particularly if their antimalarial drug exposure is inadequate [51]. In hyperparasitaemic patients, parasite populations are larger and recrudescence rates following treatment are high [52]. Drug exposure can be inadequate due to sub-standard antimalarial quality, poor adherence, vomiting, unusual pharmacokinetic behaviour or underdosing [7]. Current antimalarial dosing recommendations are generally based on the lowest effective dose seen in dose-finding studies, which are conducted early in a drug's therapeutic life and thus before parasite resistance has become apparent [7]. Recommending the lowest effective dose, while justified in terms of cost and safety/tolerability, might not be the wisest choice as this is likely to select for resistant parasites. For example, mathematical modelling suggests that, if the recommended 25-mg/kg mefloquine dose had been deployed initially, instead of 15 mg/kg, then mefloquine resistance could have been delayed [53]. Furthermore, the relationship between the drug concentrations actually achieved with the recommended antimalarial dosage regimen and the therapeutic response needs to be reassessed once resistance starts to develop because, by definition, the minimum concentrations required to clear these resistant parasites has increased [7]. Current dose recommendations also almost invariably assume that the same weight-adjusted (milligram per kilogram) dose is effective for all key target population groups [7]. This approach encourages resistance selection, particularly in patients with high parasite burdens and low drug levels [51]. These are often young children or pregnant women who lack immunity and so generally have higher parasite densities, and whose larger apparent volumes of distribution and higher apparent clearance rates result in sub-optimal drug concentrations for many antimalarials [7, 51]. Despite extensive use for four decades, it has only been recognised recently that the currently recommended doses of both sulfadoxine–pyrimethamine and chloroquine achieve substantially lower plasma drug concentrations in young children than in older patients [54, 55]. Children given the recommended dosage regimens are similarly at increased risk of

inadequate exposure to both lumefantrine and piperaquine [56, 57]. Similarly, physiological changes in pregnancy result in decreased exposure to a number of key antimalarial drugs, including the artemisinins, sulfadoxine, lumefantrine and mefloquine [7]; no data on the pharmacokinetics of amodiaquine or piperaquine in pregnancy has been published yet.

To reduce the probability of resistance, quality-assured fixed-dose combination antimalarials should be used, treatment doses need to be optimised on the basis of pharmacokinetic assessments conducted within therapeutic efficacy studies in each key target population and patients with heavy parasite burdens have to be identified and receive sufficient treatment to prevent recrudescence [51].

5 *P. vivax*: A Particular Challenge to Malaria Elimination

The focus of malaria control programmes has, to date, been largely on *P. falciparum* because this is the major cause of severe malaria and malaria mortality, especially in sub-Saharan Africa. However, once elimination becomes the target, *P. vivax* needs to be given much more attention [58]. It has a more widespread distribution and infects 130–435 million people a year amongst a population at risk of approximately 2.85 billion, mostly in Central and Southeast Asia [33, 59]. *P. vivax* can undergo sporogeny in mosquitoes at lower temperatures than *P. falciparum* and forms a latent liver stage, the hypnozoite, which initiates relapses (Fig. 1) [60]. Gametocytes of *P. vivax* appear in the circulation at the same time as the asexual stages and, although killed by the antimalarial drugs that are effective against the asexual blood stages (unlike *P. falciparum*), *P. vivax* transmits well at very low parasite densities, so transmission can already have occurred before a patient has become symptomatic and sought treatment [13]. These factors, together with the low priority given by policy makers, funders and researchers to these infections that have been mislabelled "benign" [61], explain why *P. vivax* malaria is so widespread and is significantly more difficult to control or eliminate than falciparum malaria.

The asexual stages of *P. vivax* are increasingly resistant to chloroquine but remain highly sensitive to the artemisinins [6, 16]. Amodiaquine, mefloquine, piperaquine, lumefantrine, sulfadoxine-pyrimethamine and quinine are also effective in the treatment of chloroquine-resistant asexual blood stages of *P. vivax* [6, 16, 62–64]. ACTs are the preferred treatment in areas where falciparum malaria is also endemic or *P. vivax* is chloroquine resistant [6]. However, ACTs do not provide a radical cure.

Primaquine is the only radically curative drug for *P. vivax* (and *P. ovale*) malaria; it prevents relapse by clearing the hypnozoite stage when given as a 14-day course [65]. This prolonged treatment course compromises adherence and safety, with the main risk being haemolysis (as noted above). Supervision of this long course of therapy markedly reduces the risk of relapse, and almost all reports of primaquine resistant malaria are associated with lack of such supervision [66].

6 Progress Towards Malaria Control and Eventual Elimination

There has been substantial progress in reducing the burden of malaria globally over the last 60 years, with the number of countries that are malaria-free increasing from nine in 1945 to 108 today [58]. More than one-third of the 108 malaria-endemic countries documented reductions in malaria cases of >50% in 2009 compared with 2000, including 11 countries and one area in Africa and 32 countries in other regions [23]. These impressive results occurred in countries that achieved high coverage with their vector control and ACT treatment programmes. These successes have fuelled a wave of optimism that has led to renewed commitments to achieving the ambitious goal of progressively reducing the burden of malaria, leading eventually to global eradication[1], as outlined in the Roll Back Malaria Global Malaria Action Plan. This entails three components (a) effective malaria control[2] to reduce malaria morbidity in the majority of malaria-endemic countries by scaling-up and then sustaining appropriate vector and parasite control interventions, (b) progressive elimination[3] from the margins of malaria transmission, to "shrink the malaria map", and (c) research to bring forward better drugs, diagnostics, insecticides, vaccines and other tools, as well as inform policy and improve operational implementation of effective strategies [58, 67, 68]. Better drugs are needed for elimination-specific indications such as mass treatment, curing asymptomatic infections, curing relapsing liver stages of *P. vivax* and *P. ovale* and preventing transmission [69].

The ACT coverage rates (i.e. the proportion of parasitaemic patients that promptly receives an adequate dose and duration of ACT treatment) need to be high to impact on malaria transmission and the spread of resistance. One of the major deterrents to ensuring widespread access to ACTs is their cost – being tenfold more expensive than chloroquine and sulfadoxine–pyrimethamine monotherapies. The patients and governments that most need ACTs can least afford them [70]. Fortunately, international funding commitments for malaria have increased from around US$ 0.3 billion in 2003 to US$ 1.8 billion in 2010 [23], due to greater commitments by the US President's Malaria Initiative, the World Bank and primarily the emergence of the Global Fund and more recently, its innovative Affordable Medicines Facility for malaria (AMFm). This increased financial, technical and political support is resulting in dramatic scale-up of malaria control interventions in many settings and measurable reductions in malaria burden.

In general, the number of cases fell least in countries with the highest malaria incidence rates, with the notable exceptions of Zanzibar (United Republic of

[1] Malaria eradication is the permanent reduction to zero of the worldwide incidence of malaria infection caused by a specific agent; i.e. applies to a particular malaria parasite species.

[2] Malaria control is reducing the disease burden to a level at which it is no longer a public health problem.

[3] Malaria elimination is interrupting local mosquito-borne malaria transmission in a defined geographical area, i.e. zero incidence of locally contracted cases.

Tanzania), Zambia, Eritrea, Rwanda and Sao Tome and Principe, that illustrate that dramatic reductions in malaria morbidity and mortality can also be achieved in areas with a high malaria incidence [18–23, 71]. Similar results have also been seen in more limited geographic areas of the high malaria burden countries of Equatorial Guinea (Bioko Island), the Gambia, Kenya and Mozambique [72–75].

There is evidence from Bioko Island (Equatorial Guinea), Kenya, Sao Tome and Principe, Zanzibar and Zambia that large decreases in malaria cases and deaths have been mirrored by steep declines in all-cause deaths in children under 5 years of age [20, 71, 73, 74], suggesting that intensive malaria control in African countries could play an important role in not only achieving the Millennium Development Goal 6 of reducing malaria incidence and death rates, but also the Millennium Development Goal 4 of reducing all-cause childhood mortality by two-thirds by 2015 [76].

In 2009, however, there was evidence of an increase in malaria cases in three countries that had previously reported dramatic reductions in malaria burden (Rwanda, Sao Tome and Principe and Zambia) [23]. These resurgences highlight the fragility of malaria control and the critical importance of sustaining control interventions and surveillance rigorously – particularly in areas that have historically carried a high malaria burden.

At the other end of the malaria transmission intensity spectrum, tangible progress is being made. In 2010, both Morocco and Turkmenistan were certified as having achieved malaria elimination [23]. At least another 27 countries are working towards malaria elimination; nine countries have interrupted transmission and are in the phase of preventing re-introduction of malaria; ten countries are implementing nationwide elimination programmes and eight countries are in the pre-elimination phase [23]. In Botswana, Cape Verde, Namibia, Sao Tome and Principe, South Africa and Swaziland, large initial decreases in the number of malaria cases have been sustained but remain at 10–25% of those reported in 2000 [19, 22, 71]. However, the few remaining cases are proving more difficult to prevent, to detect and treat promptly, and additional interventions are likely to be necessary for further reductions in malaria morbidity to be achieved. Encouraging results of additive benefit are starting to be seen in studies evaluating the combination of indoor residual spraying with insecticide-treated bed-net deployment [77] and of adding primaquine to ACTs [17, 27].

Since the current levels of international financial support for malaria control fall far short of the estimated US$ 6 billion required annually to ensure maximal impact worldwide [56], it seems even less likely that international funding will be sustained for the long haul required to achieve the more expensive and ambitious yet possible goal of malaria eradication. As the risk of malaria decreases, the behaviour of patients, caregivers, healthcare providers and funders become less likely to take the steps needed to reduce the malaria burden further until it is eventually eliminated. Effective information, education and communication campaigns, strong programmes monitoring the impact of malaria control interventions on disease burden, good governance and coherent advocacy (that acknowledges the many demands on limited financial and especially human resources in malaria endemic

countries) are important tools for encouraging ongoing support, once there are only a few locally transmitted malaria cases.

The goals and strategies required to achieve elimination of the parasite from low-transmission settings are very different for those needed for reducing malaria morbidity and mortality in high-transmission settings. In an elimination programme, treatment of a sufficient number of infected subjects in a community to interrupt transmission becomes the primary goal. In order to interrupt transmission, the individuals who are parasitaemic (infected) and – more importantly in terms of elimination – gametocytaemic (infectious) need to be treated even if they are asymptomatic. Two possible approaches to this objective can be adopted – mass screening and treatment of both infected and infectious individuals (regardless of whether nor not they are symptomatic), or mass drug administration (MDA) given to as large a proportion of the population as possible on the grounds that this will cover a higher proportion of those infected. The lack of a rapid diagnostic method that is suitable for field use and sensitive enough for diagnosing the lower limit of parasite and gametocyte densities able to cause and transmit malaria is currently a major obstacle to using mass screening and treatment in malaria elimination.

MDA is the administration of a complete treatment course of antimalarial medicines to every individual in a geographically defined area on a specific day. MDA is not recommended by the World Health Organization, as there is no evidence of long-term benefits in large population groups [6]. An analysis of 19 MDA projects carried out over the period 1932–1999 found only one study in the small island population ($n = 718$) of Aneityum, Vanuatu, where MDA might have contributed to the elimination of *P. falciparum* and *P. vivax* malaria [78, 79]. MDA has been highly effective in reducing parasite prevalence to a very low level, but parasitaemia soon rebounds to its previous level once MDA is stopped, as seen in Garki, Nigeria and Nicaragua [78]. Mass treatment with ACTs alone is unlikely to be sufficient for malaria elimination – and primaquine and/or atovaquone–proguanil may be worth adding. In this context, drug safety should be given priority as drugs are given to a large number of people who are not infected. Thus, more evidence is needed on the risk:benefit profile of atovaquone–proguanil and primaquine to inform mass treatment approaches in the context of malaria elimination programmes [58]. Lessons should also be learnt from the lasting legacy of MDA of chloroquine and pyrimethamine: the rapid selection of resistant parasites.

7 Conclusions

Prompt effective antimalarial treatment is and will remain pivotal in achieving malaria control and eventually elimination. The past decade has seen remarkable progress being made in the fight against malaria. Almost all countries in which *P. falciparum* malaria is endemic have adopted ACT policies. High ACT coverage, together with the scaling-up of effective vector control interventions, has resulted in documented reductions in malaria cases of >50% in 2008 compared with 2000 in

43 of the 108 malaria-endemic countries. Unprecedented levels of financial, technical and political support have made this possible. During this window of opportunity for reducing the burden of malaria globally and possibly eventually eliminating malaria, attention now needs to be focussed on ensuring that countries select treatment policies that not only achieve cure rates >95% [65], but that are also likely to have a prolonged useful therapeutic life, reduce malaria transmission safely and effectively and, where applicable, are also active against *P. vivax*. As important is ensuring optimal targeting, dosing and adherence with these policies.

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4-Aminoquinolines: Chloroquine, Amodiaquine and Next-Generation Analogues

Paul M. O'Neill, Victoria E. Barton, Stephen A. Ward, and James Chadwick

Abstract For several decades, the 4-aminoquinolines chloroquine (CQ) and amodiaquine (AQ) were considered the most important drugs for the control and eradication of malaria. The success of this class has been based on excellent clinical efficacy, limited host toxicity, ease of use and simple, cost-effective synthesis. Importantly, chloroquine therapy is affordable enough for use in the developing world. However, its value has seriously diminished since the emergence of widespread parasite resistance in every region where *P. falciparum* is prevalent. Recent medicinal chemistry campaigns have resulted in the development of short-chain chloroquine analogues (AQ-13), organometallic antimalarials (ferroquine) and the "fusion" antimalarial trioxaquine (SAR116242). Projects to reduce the toxicity of AQ have resulted in the development of metabolically stable AQ analogues (isoquine/*N-tert*-butyl isoquine). In addition to these developments, older 4-aminoquinolines such as piperaquine and the related aza-acridine derivative pyronaridine continue to be developed. It is the aim of this chapter to review 4-aminoquinoline structure–activity relationships and medicinal chemistry developments in the field and consider the future therapeutic value of CQ and AQ.

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1 History and Development

Quinine **1**, a member of the *cinchona* alkaloid family, is one of the oldest antimalarial agents and was first extracted from *cinchona* tree bark in the late 1600s. The *cinchona* species is native to the Andean region of South America, but when its therapeutic potential was realised, Dutch and British colonialists quickly established plantations in their south-east Asian colonies. These plantations were lost to the Japanese during World War II, stimulating research for synthetic analogues based on the quinine template, such as the 4-aminoquinoline chloroquine (CQ **2**, Fig. 1) [1].

A thorough historical review of CQ (in honour of chloroquine's 75th birthday) is available elsewhere [2]. In short, CQ was first synthesized in 1934 and became the most widely used antimalarial drug by the 1940s [3]. The success of this class has been based on excellent clinical efficacy, limited host toxicity, ease of use and simple, cost-effective synthesis. Importantly, CQ treatment has always been affordable – as little as USD 0.10 in Africa [4]. However, the value of quinoline-based antimalarials has been seriously eroded in recent years, mainly as a result of the development and spread of parasite resistance [5].

Although much of the current research effort is directed towards the identification of novel chemotherapeutic targets, we still do not fully understand the mode of action and the complete mechanism of resistance to the quinoline compounds, knowledge that would greatly assist the design of novel, potent and inexpensive alternative quinoline antimalarials. The search for novel quinoline-based antimalarials with pharmacological benefits superseding those provided by CQ has continued throughout the later part of the twentieth century and the early part of this century since the emergence of CQ resistance.

Comprehensive reviews on the pharmacology [6] and structure activity relationships [7] have been published previously, so will be only mentioned briefly. It is the aim of this chapter to review developments in the field that have led to the next-generation 4-aminoquinolines in the development "pipeline", in addition to discussion of the future therapeutic value of CQ and amodiaquine (AQ). We will begin with studies directed towards an understanding of the molecular mechanism of action of this important class of drug.

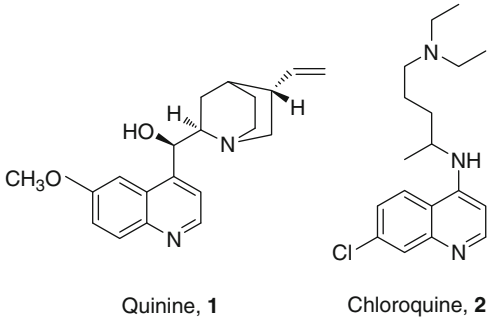

Fig. 1 Quinine **1** and related 4-aminoquinoline antimalarial chloroquine, **2**