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Role of Quinine in prevention and treatment of malaria A historical, structural and adverse effect Review

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Abstract
Great progress has been made in recent years to reduce the high level of suffering caused by malaria worldwide. Notably, the use of insecticide treated mosquito nets for malaria prevention and antimalarial drugs with the use of artemisinin-based combination therapy (ACT) for malaria treatment have made a significant impact. This article reviews the role, structural pictographs and side-effects of quinine, comparison of all quinine used so far and their discoveries and properties. It's role in prevention and Elimination and its side-effects. Quinine remains an important antimalarial drug almost 410 years after its effectiveness was first documented.However it's continued use is challenged by its poor tolerability, poor compliance with complex dosing regimes. But still quinine are used as second line of defense against malariainfection ,when ACT (artemisinin-based combination therapy)are unavailable. Lastly ,in pregnancy, quinine continues to play a critical role in management of malaria, especially in the first trimester, and it will remain a mainstay of treatment until safer alternatives become available.

Keywords malaria, quinine , ACT

I. Background

According to the latest World malaria report, there were 241 million cases of malaria in 2020 compared to 227 million cases in 2019.The increase in figures emphasizes that there must not be complacency with the current treatment and prevention strategies [2,3]. This review aims to summarize most common quinines used to treat malaria.

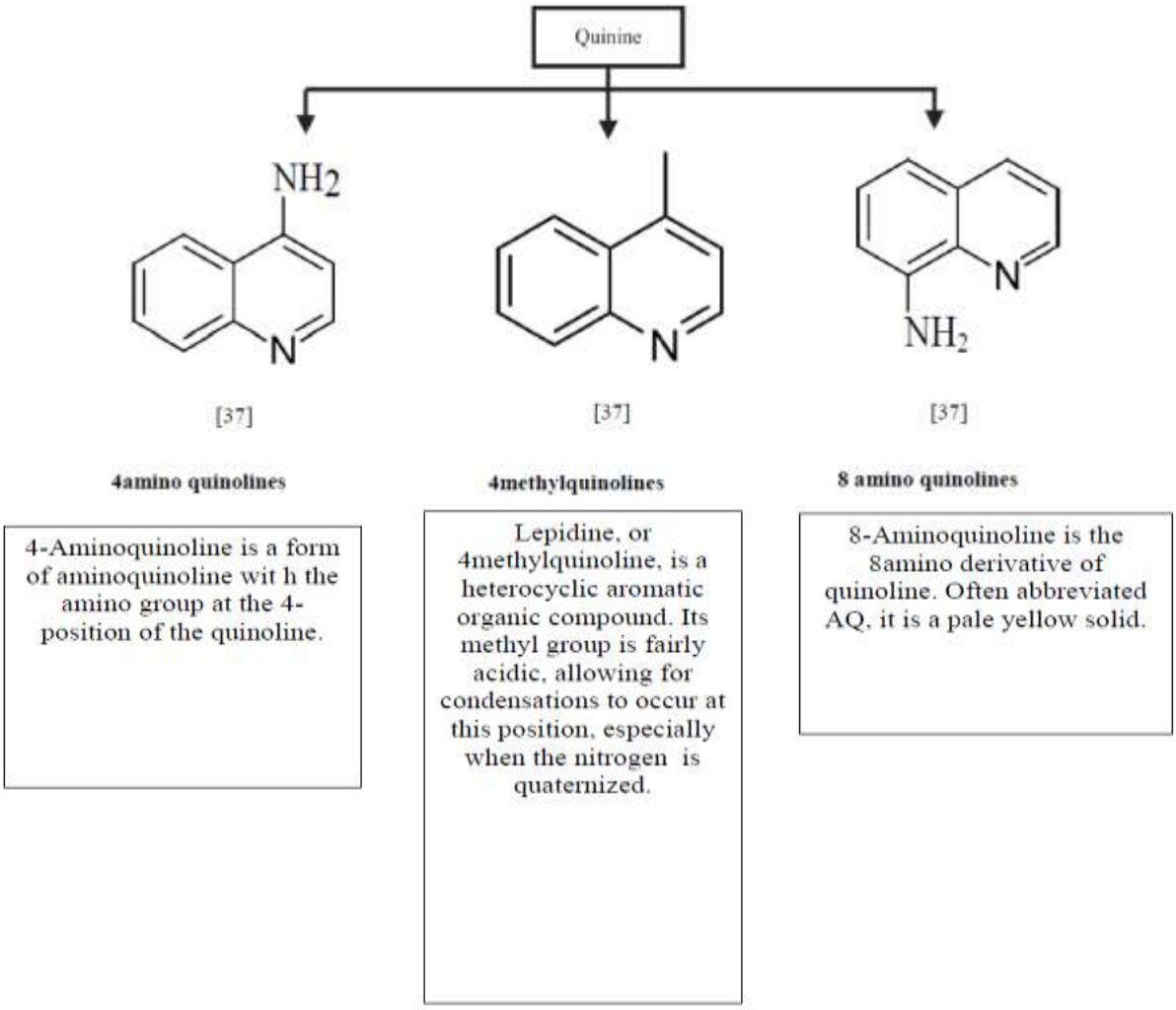
Quinine and it's Properties

Quinine is a cinchona alkaloid that belongs to the aryl amino alcohol group of drugs. It is an extremely basic compound and is, therefore, always presented as a salt [4]. Various preparations exist, including the hydrochloride, dihydrochloride, sulphate, bisulphate, and gluconate salts; of these the dihydrochloride is the most widely used. Quinine has rapid schizonticidal action against intra-erythrocytic malaria parasites. It is also gametocytocidal for Plasmodium vivax and Plasmodium malariae,but not for Plasmodium falciparum.Quinine also has analgesic,but not antipyretic properties. The anti-malarial mechanism of action of quinine is unknown. Quinine is rapidly absorbed both orally and parenterally, reaching peak concentrations within 1-3 hours[5]. It is distributed throughout the body fluids and is highly protein bound,mainly to alpha-1 acid glycoprotein. The binding capacity in plasma is concentration dependent, but also depends on the levels of alpha-1 acid glycoprotein, which therefore makes comparisons between different studies difficult [6]. Quinine readily crosses the placental barrier and is also found in cerebral spinal fluid.

Excretion is rapid- 80% of the administered drug is eliminated by hepatic biotransformation and the remaining 20% is excreted unchanged by the kidney [7-8]. The half life of quinine ranges between 11-18 hours [9, 10].Several pharmacokinetic characteristics of quinine differ according to the age of the subject and are also affected by malaria. The volume of distribution is less in young children than in adults, and the rate of elimination is slower in the elderly than in young adults. In patients with acute malaria the volume of distribution is reduced and systemic clearance is slower than in healthy subjects; these changes are proportional to the severity of the disease. As a result, plasma quinine levels are higher in patients with malaria. Protein binding of quinine is increased in patients with malaria as a result of an increased circulating concentration of alpha-1 acid glycoprotein [11]. Quinine has a low therapeutic index,and adverse effects with its use are substantial [12]. The side effects commonly seen at therapeutic concentrations are referred to as cinchonism, with mild forms including tinnitus, slight impairment of hearing, headache and nausea. Impairment of hearing is usually concentration dependent and reversible [13]. More severe manifestations include vertigo, vomiting, abdominal pain, diarrhea, marked auditory loss, and visual symptoms, including loss of vision. Hypotension

may occur if the drug is given too rapidly, and venous thrombosis may occur following intravenous injections [7]. Intramuscular administration is painful and may cause sterile abscesses. Hypoglycaemia is yet another common side effect of quinine therapy [11, 16] and is a particular problem in pregnant women[17]. Hypoglycaemia has been reported to occur in up to 32% of patients receiving quinine therapy[16]. However in more recent studies, hypoglycaemia occurred in only 3% of adults and 2.8% of African children receiving quinine [18,19]. Less frequent but more serious side effects of quinine therapy include skin eruptions, asthma, thrombocytopaenia, hepatic injury and psychosis [20].

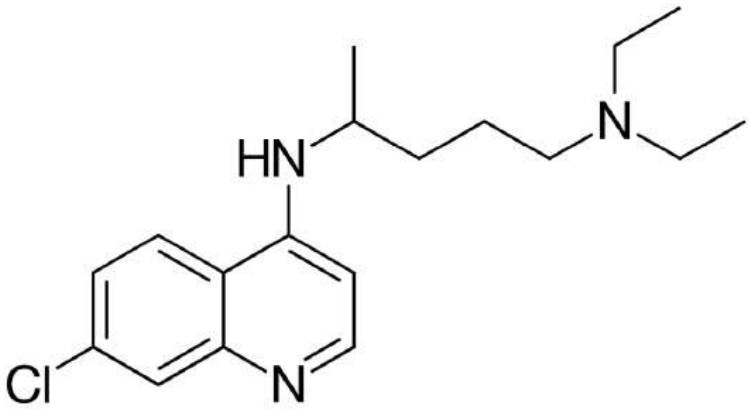
Types of quinine [14,15]



A. 4aminoquinolines

1. Chloroquine

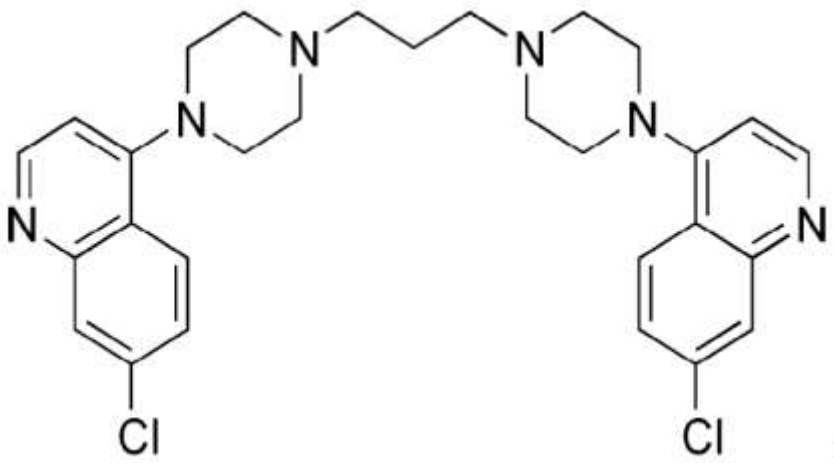
Chloroquine During the 1940s, chloroquine (CQ) was used to treat all forms of malaria with few side effects [21]. Resistance to CQ was first reported in the 1950s and over the years many strains of malaria have developed resistance. Indeed, resistant strains (Kl, 7GB, W2, Dd2, etc.) of the malaria parasite are now used in potency evaluation assays as away of showing efficacy [22]. Chloroquine is on the MLEM for the treatment of P. vivax in regions where resistance has not developed.



[37]

Side effects
Include blurred vision, nausea, vomiting, abdominal cramps, headache, diarrhea, swelling legs/ankles, shortness of breath, pale lips/ nails/skin, muscle weakness, easy bruising/ bleeding, hearing and mental problems. [23] [24]

2. Piperaquine
Piperaquine Piperaquine was developed in the 1960s as a part of the Chinese National Malaria Elimination Programme [25]. Initially used throughout China as a replacement forchloroquine, resistance led to its diminished use as a monotherapy. While the MoA of piperaquine is not completely understood, studies have suggested that it acts by accumulating in the digestive vacuole and inhibiting haem detoxification through the binding of haem-containing species [26]. These days, piperaquine is used as a partner drug with dihydroartemisinin (commonly sold under the trade nameEurartesim).

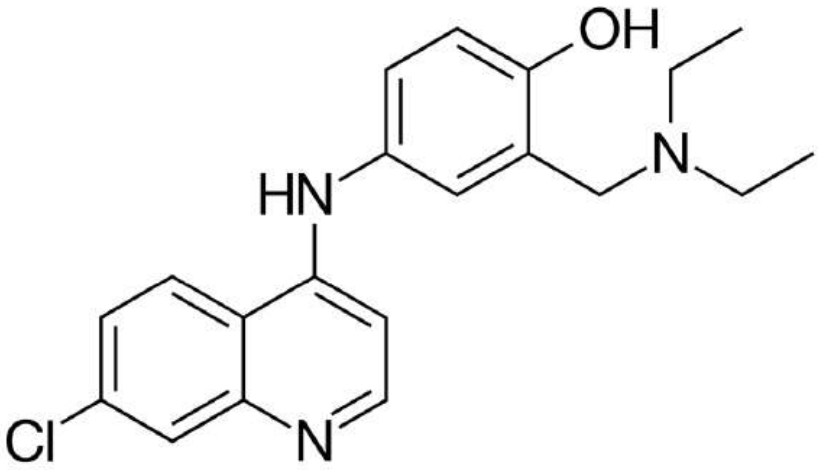


[37]

Side Effects
Palpitations, Atrial arrhythmias (altered heart rate), Cough, Breathlessness, Nausea, Vomiting, Weakness [27]* possibility of choreoathetosis as an adverse effect.

3. Amodiaquinine
Amodiaquine was first synthesized in 1948 [28]. It is mainly used for the treatment of uncomplicated P.

falciparum malaria when used in combination with artesunate and is commonly sold under the trade name Camoquine or Coarsucam. Similar to chloroquine, amodiaquine's MoA is thought to involve complexation with haem and inhibition of haemozoin formation [29].



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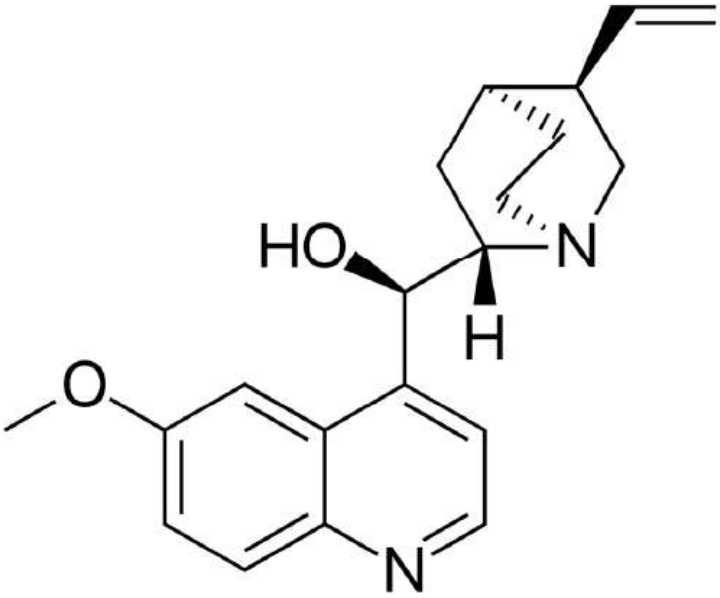
Side Effects

Amodiaquine has been linked to severe cases of acute hepatitis which can be fatal, for which reason it is recommended for use only as treatment and not for prophylaxis against malaria. [30]

A. Methanolquinolines

1. Quinine

First isolated from the bark of the cinchona tree in 1820,quinine has been used as one of the most effective treatments for malaria to date[31]. Resistance was f irst reported in the 1980s [32] and as of 2006, quinine is no longer used as a front-line treatment for malaria but is still on the WHO's Model List of Essential Medicines (MLEM) [33] for the treatment of severe malaria in cases where artemisinins are not available.



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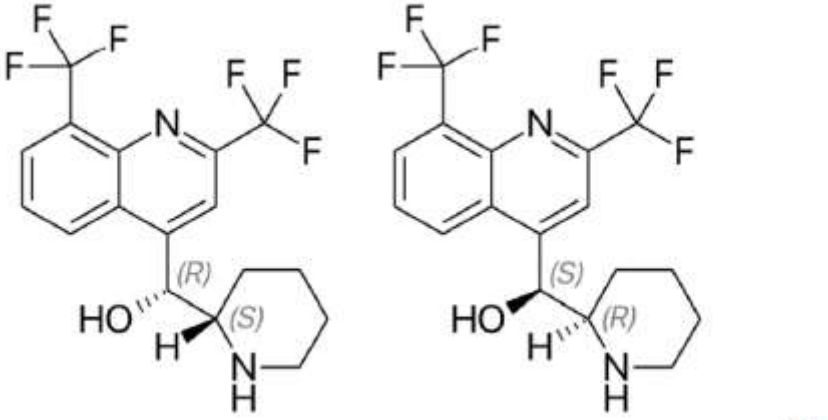
Side-effects

The most common adverse effects involve a group of symptoms called cinchonism, which can include headache, vasodilation and sweating, nausea, tinnitus, hearing impairment, vertigo or dizziness, blurred vision, and disturbance in color perception.[34][35][36]

1. Mefloquine

Mefloquine was developed in the 1970s by the United States Army [22] and is still used today, also being one of the medicines on the MLEM. Originally introduced for the treatment of chloroquine-resistant malaria, it has been used as both a curative and a prophylactic drug.Resistance was first reported in 1986 [38]. It is thought that the structurally related quinoline drugs (such as quinine, mepacrine, chloroquine and mefloquine) act through the disruption of haemoglobin digestion in the blood stage of the parasite [39]. These drugs are commonly used in combination with a complementary drug (e.g. mefloquine and artesunate, sold as Artequin) to reduce the chance of resistance development to the quinoline family of compounds. Mefloquine is commonly sold in its racemic form under the brand name Lariam, however it is no longer widely used due to the perception of central nervous system toxicity that has been suggested to affect a large number of its users [40].



[37]

Side Effects

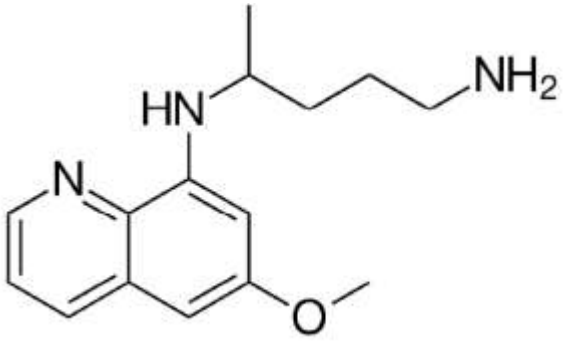
Common side effects include vomiting, diarrhea, headaches, and a rash.[41] Severe side effects requiring

hospitalization are rare,[42] but include mental health problems such as depression, hallucinations, anxiety and neurological side effects such as poor balance, seizures, and ringing in the ears.[41] Mefloquine is therefore notrecommended in people with a history of psychiatric disorders or epilepsy.[41]

B. 8aminoquinolines

1. Primaquine

Primaquine was firstly synthesized in 1946 in the USA, and is the most representative member of the anti-malarial 8 aminoquinolines. An expanding risk and range of endemic malaria threatens travelers. Primaquine is an old drug recently demonstrated to offer effective prophylaxis. Clinical trials conducted in Indonesia, Kenya, and Colombia showed that a primaquine base (30 mg per day) had protective efficacy against Plasmodium falciparum and Plasmodium vivax of 85%-93% Primaquine's major advantage over most drugs for chemoprophylaxis is that it does not have to be taken before entering or beyond 3 days after leaving a malarious area.[43]



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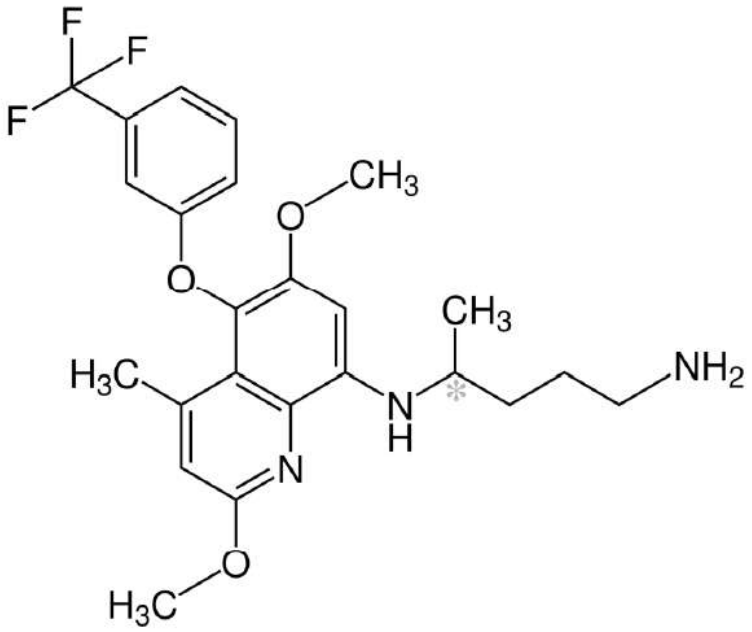
Side-effects
Heartburn,itching, skin rash,pain or discomfort in the chest, upper stomach, or
throat,stomach cramps. Hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) and methemoglobinemia in patients with nicotinamide adenine dinucleotide methemoglobin reductase deficiency have been reported[44]

2. Tafenoquine
Tafenoquine First discovered in 1978 at the Walter Reed Army Institute of Research, Tafenoquine (TQ) was recently approved by the United States Food and Drug Administration for use as the first new single dose for the radical treatment of P. vivax malaria in over 60 years [45]. TQ is thought to be a prod rug which is metabolized to the active quinine TQ, however the MoA is not well known [46]. It is currently sold under the brand name Krintafel.



[37]

Side-effects

Common side effects include vomiting, headache, and dizziness. [47] Other side effects may include methemoglobinemia, trouble sleeping, and anaphylaxis.[47] In people with G6PD deficiency, red blood cell breakdown may occur.[47] Use in pregnancy is not recommended. [47]

Quinine for malaria in pregnancy

Malaria in pregnancy causes several adverse outcomes that include maternal anaemia, intrauterine growth retardation, low birth weight, preterm deliveries and abortion. Prevention and treatment of malaria in pregnancy is, therefore, critical to avoid these adverse outcomes. In 2010 the WHO recommends the use of quinine plus clindamycin for treating malaria in the first trimester of pregnancy, as the safety of artemisinin compounds during this period is not yet established [48]. As most clinical trials exclude women in their first trimester of pregnancy, information on the efficacy and safety of anti-malarial drugs during this period is extremely limited. Evidence for the safety of quinine in pregnancy is mostly historical and there are few clinical trials published [49,50]. Clindamycin on the other hand has a good safety record in pregnancy [51] and its pharmacokinetic properties are usually unchanged by pregnancy [52]. The combination of quinine and clindamycin has proven highly efficacious against multidrugresistant strains of P. falciparum, with 42 day cure rates of 100% in one study [49]. The only concern with this combination is that it is usually not affordable for most resource limited settings. For the second and third trimester of pregnancy, quinine monotherapy seems to have unacceptably low efficacy in areas with multidrug resistant malaria when compared to ACT. The occurrence of adverse events experienced by the pregnant women was similar in all groups, although tinnitus was more frequent in the quinine group. In these studies, the considerably inferior efficacy of quinine was attributed to both drug resistance and to the varying pharmacokinetic properties of quinine during pregnancy. In Africa however, available evidence suggests that Plasmodium falciparum generally remains sensitive to quinine [53] and low cure rates with quinine monotherapy in pregnant women has been mainly attributed to poor compliance to treatment [54]. Thus in Africa, quinine monotherapy remains the most widely used treatment for malaria in the first trimester of pregnancy and is also considered safe during all trimesters of pregnancy. A study from Uganda provides important reassurance of continued efficacy of quinine monotherapy in these regions of Africa. In this study, quinine and artemetherlumefantrine had similar efficacy for the treatment of uncomplicated malaria in the second and third trimesters of pregnancy [55]. The evidence for safety of ACT use during the first trimester of pregnancy is currently limited [56]. Therefore, until more data become available, the recommendation to use quinine in the first trimester of pregnancy will remain and ACT should only be used in the second and third trimesters of pregnancy. Patient education and counseling will however be critical to promote compliance with therapy.

II. Conclusion

Although the rate of malaria related deaths has declined over the past few years, the progress is beginning to slow. With the recent emergence of resistance to current frontline artemisinin-based combination

therapy. Quinine continues to play a critical role in the management of malaria in the first trimester of pregnancy, and will remain so until safer alternatives become available. The continued use of quinine in the management of uncomplicated malaria is a concern. Clearly, the seven day duration of therapy and thrice daily administration of quinine present a major challenge to completion of therapy, leading to sub-optimal treatment outcomes. In these situations, ACT is a better option given the simplicity of dosing and shorter treatment duration. However, because of the frequent ACT stock outs, the rapid withdrawal of quinine as a treatment option for uncomplicated malaria cases is risky. The best approach would be, besides improving the supply system, to maintain quinine as a fall-back drug in case of ACT stock-outs or areunavailable.

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V. Author contribution

Entiremanuscriptwaswroteandsubmittedmyauthor

VI. Competing interests

Theauthordeclaresthathehavenocompetinginterests.

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