Limited Access to Drug in Malaria Control

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Malaria burden has severe impact on the world. Several arsenals, including the use of antimalarials, are in place to curb the malaria burden. Limited access to drugs ensures that patients do not get the right doses of the antimalarials in order to have an effective plasma concentration to kill the malaria parasites, which leads to treatment failure and overall reduction in malaria control via increased transmission rate.

malaria drug-pressure limited-access antimalarials treatment

1. Introduction

The control of malaria has stalled in the last five years [1][2]. There is need for a continuous review of the control strategies. Antimalarials remain one of the formidable tools in malaria control. Both reduced access to antimalarials by the populace and pressure from these drugs on malaria parasites are important factors that play different roles in the overall malaria control. Limited access to drug and drug pressure are two sides of a coin that can individually and/or collectively lead to treatment failure. While reduced access to drugs negatively impact malaria control via increased spread/transmission, drug pressure facilitates the generation of resistant *Plasmodium* which results in treatment failures, respectively. Some antimalarials such as chloroquine (CQ) have lost their place in malaria control due to resistance development, and this fate befalls several other antimalarials [3][4]. Treatment failure can result from drug resistance (often from drug pressure), high baseline parasite density, childhood (age less than five), incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality and drug interactions leading to decreased drug exposure [5]. Other factors that can lead to reduced access may include: cost of the drug, reduced or poor access to health facilities, lack of free drug or functional health insurance scheme, and some socio-cultural as well as religious characteristics of a people (e.g., religious beliefs and traditions).

2. Overview of the Current Antimalarial Portfolio

Before the advent of refined antimalarials, the use of herbs had been the hallmark of treatment, as exemplified by the *Cinchona* bark from which quinine was extracted and identified in 1820 by the French chemists, J. Pelletier and J. Caventou [6]. Today, several drugs are currently used for the treatment of malaria. These drugs, for convenience, are classified into four major classes: antifolates, quinolines (aryl-amino alcohols, 4-aminoquinolines, bis-quinoline and naphthyridine), hydroxynaphtoquinone and endoperoxides (**Table 1**). The antifolates interfere with folic acid synthesis which is essential in nucleic acid metabolism [7]. The commonest antifolates in use are pyrimethamine and sulfadoxine. The main mode of action of quinolines and endoperoxides is targeting of the heme detoxification process put in place during the digestion of hemoglobin by the parasite [8][9]. The quinolines are mainly represented

by chloroquine, mefloquine, amodiaquine, lumefantrine and quinine [10]. For the endoperoxides, artemisinin and its derivatives (artemether, artesunate, arteether) are the main examples.

Table 1. Antimalarial portfolio.

Antimalarials	Introduction Date	Resistance Date	Genetic Marker	Mechanism of Action	Mechanism of Resistance	References
Aryl-amino alcohol						
Quinine	1820	1910	Pfmdr1	Inhibition of heme detoxification	Gene amplification and mutation leading to drug efflux and/or non-binding to target site	[11]
Mefloquine	1977	1982	Pfmdr1			[12]
Lumefantrine	1976		Pfmdr1			[13]
4-aminoquinolines						
Chloroquine	1945	1957	Pfcrt, Pfmdr	Inhibition of heme detoxification and redox cycling of heme to and fro the cytosol	Gene mutation: efflux of molecules from food vacuole	[14][15]
Amodiaquine	1948	1990s	Pfcrt, Pfmdr			[13][16]
Bis-quinoline						
Piperaquine	1960s	2010	Pfcrt, Pfplasmepsin 2-3 copy number	Inhibition of heme detoxification and redox cycling of heme	Gene amplification	[17][18]

Antimalarials	Introduction Date	Resistance Date	Genetic Marker	Mechanism of Action	Mechanism of Resistance	References
				to and fro the cytosol		
Naphthyridine						
Pyronaridine	1980	-		Inhibition of heme detoxification		[19]
Antifolates						
Sulfadoxine	1937	1960s	Pfdhps	Inhibition of folate metabolism and DNA replication	Gene mutation leading to drug binding site modification	[20]
Proguanil/cycloguanil	1948	1949	Pfdhfr			[21]
Pyrimethamine	1952	1960s				
Endoperoxide						
Artemisinin and its derivatives (DHA, ATS, ATM)	1972	2008	PfKelch13	Inhibition of heme detoxification and C-C radical formation	Entry into quiescent state	[22]
Hydroxynaphtoquinones						
Atovaquone	1996	1996	Pfcytb	Competitive inhibition of	Modification of binding site on Complex	[21][23]

Antimalarials	Introduction Date	Resistance Date	Genetic Marker	Mechanism of Action	Mechanism of Resistance	References
				Complex iii of the ETC	iii/cytochrome b	
Tetracycline antibiotic						
Doxycycline	1967	[26]	SNPs in Pfmdt and PftetQ	Inhibition of protein, nucleotide and deoxynucleotide synthesis	Not yet described	[24][25]

Table 2. Artemisinin-based combinations therapies (ACTs) against *P. falciparum* recommended by the WHO [27][28][29].

ACTs	Region Used	Region of Reported ACT Failure
Artemether-lumefantrine (AL)	Africa, Americas and Middle East	Burkina Faso, Cambodia, Lao People's Democratic Republic, Thailand and Vietnam
Dihydroartemisinin-piperaquine (DHA-PPQ)	Southeast Asia, China and Africa	Cambodia, Lao People's Democratic Republic, Thailand and Vietnam
Artesunate-amodiaquine (AS-AQ)	West Africa	Indonesia, Cambodia
Artesunate-mefloquine (AS-MQ)	Southeast Asia and Americas	Cambodia, Lao People's Democratic Republic, Thailand and Vietnam
Artesunate-sulfadoxine-pyrimethamine (AS-SP)	Southeast Asia, Middle-East and South America	Northeastern India, Somalia and Sudan
Artesunate—pyronaridine (AS-PY)	Southeast Asia	Cambodia, Vietnam

ACTs	Region Used	Region of Reported ACT Failure [2].

Prevention is said to be better than cure. Some antimalarials can be used for chemoprevention. This reduces the risk of developing overt malaria signs and symptoms. This also reduces the mortality risk associated with malaria especially in children under five years, pregnant women and travelers, who do not live in malaria endemic countries. Atovaquone/proguanil and sulfadoxine/pyrimethamine are among the antimalarials that can be used in chemoprevention of malaria (**Table 1**) [30][31].

3. Limited Access to Drugs

For effective treatment of diseases, access to the right medications is a prerequisite, among several other factors. The availability of quality and affordable drugs in sufficient quantity is an essential element in universal health coverage. Several health agencies including the World Health Organization (WHO) have since their establishment worked to increase access to medications. Unfortunately, these efforts have been frustrated by a number of factors, ranging from economic to sheer wickedness on the part of businessmen. (**Figure 1**).

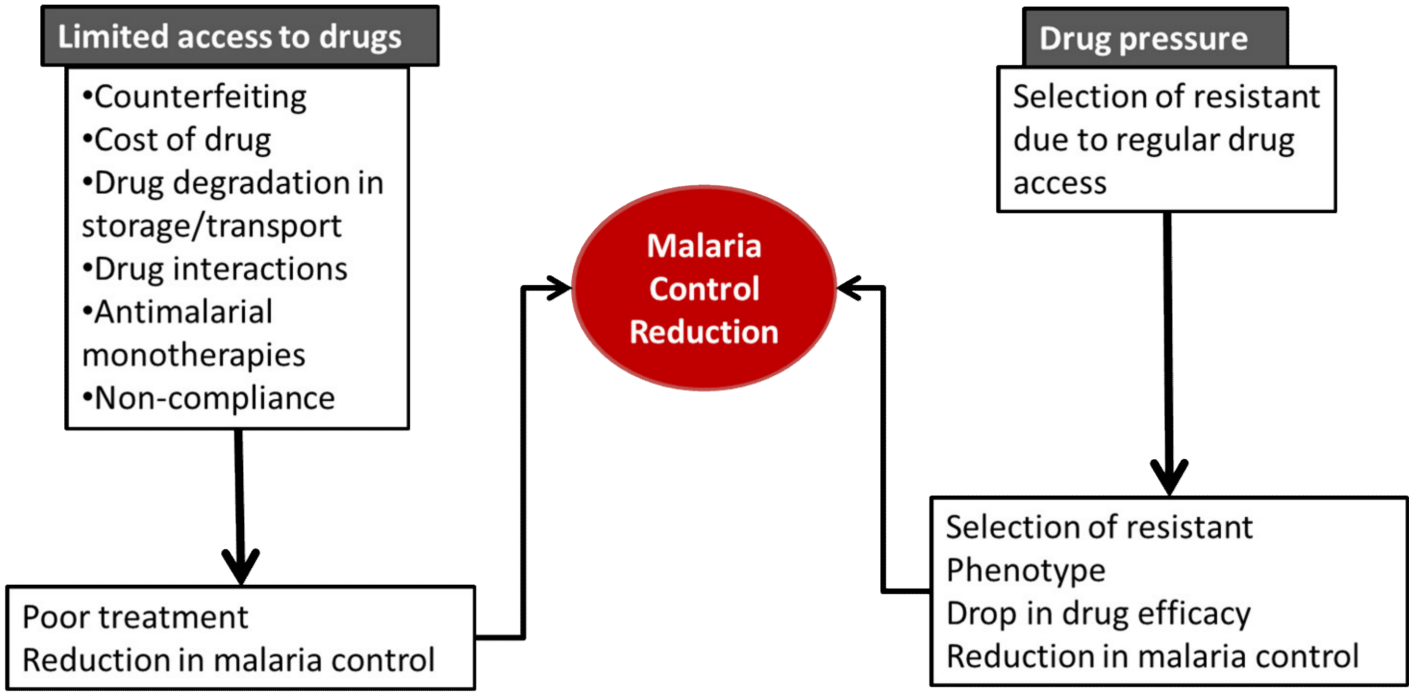

Figure 1. Impact of limited drug access and drug pressure on malaria control.

3.1. Counterfeiting/Drug Quality

The quality of drug refers to the suitability of either a drug substance or drug product for its intended use as described during an FDA international conference on Harmonization [32]. The quality of a drug is anchored on three features: identity, strength and purity for the intended use [33]. The quality of a drug must be assured and

maintained until it gets to the end users (patients). Regrettably, there is a great deal of interplay between drug manufacture and delivery to the end users which compromises the drug quality. Such interplay includes but not limited to: compromised drug manufacture (sub-therapeutic active ingredients, non-compatible excipients and lack of good manufacturing practices (GMP)). Inaccessibility and high price of quality ACTs, poor transportation and harsh storage conditions, wrong dispensing (mistakes by dispensers) as well as lack/or inadequate regulation from regulatory agencies, contribute immensely to counterfeiting of antimalarials. The use of poor quality antimalarials can cause a drop in efficacy and reduce parasite clearance, which are characteristics of drug resistance and eventual drug failure [34]. Drugs against infectious diseases such as malaria are among the most falsified drugs in the market especially in developing countries, which fall under malaria endemic regions. According to a WHO account, one in every ten drugs in developing countries are either substandard or falsified [35]. Quality tests conducted on some artemisinin derivatives in Africa failed the tests [36]. This calls for more regulation from the government of these affected countries to ensure strict compliance to GMP.

Even when the drugs meet the required standard after manufacture, the means of transportation to the pharmacies or hospitals are often inadequate. This is mostly the case with drugs that are unstable under certain temperature ranges. The impact of poor quality drugs is huge; about 122,000 deaths were estimated in children under five in sub-Sahara Africa and therefore should be taken seriously [37]. The counterfeiting of antimalarials limits the availability of the required amount of drugs for effective treatment and hence can culminate in treatment failure and reduction in malaria control.

3.2. Cost of Drug

Most, if not all, the novel antimalarials hit the market at exorbitant prices as premium brands. This adversely affects the affordability by the deserving masses, thereby limiting access to the drugs. Some patients may attempt to buy some doses. Consequently, there will be an incomplete or non-treatment of malaria across different categories of patients. Incomplete drug regimens can lead to treatment failure on subsequent administration of complete doses. Sometimes, the lack of resources from the patients can result in the use of less effective antimalarials.

Both non-treatment and incomplete treatment continually make the subjects harbors for the malaria parasites, which enhances transmission to other people, worsening malaria control. The WHO considers health insurance as a veritable tool in ameliorating the effect of the cost of essential drugs [38][39]. Ordinarily in developed countries, the cost burden of drugs are borne by health insurance; however, in most of the low-to-medium income countries (LMIC) where malaria is endemic, health insurance utilization or its awareness is still relatively low [40]. Most patients still pay for their drugs out of the pocket. Attention must be paid to the cost of drugs as treatment outcome or efficiency is tightly linked to the cost of prescription. The high cost of some antimalarials, especially ACTs, raises the risk of utilizing counterfeit or sub-standard brands due to switches at the pharmacy because of their cheapness. This can lead to treatment failure which may be progressive, affecting the regimen even when the right drugs are eventually used.

To ameliorate the impact of high cost of novel antimalarials, most malaria endemic countries benefit from antimalarial donations which are made available to malaria subjects free of charge. Increasing access to

antimalarials through reduced cost can improve the treatment outcome and reduce transmission significantly. This will reduce overall malaria burden.

3.3. Drug Storage/Transportation

Antimalarials remain viable at certain temperatures. However, this is not the case in the course of movement of these drugs to some rural communities. The drug gets to the end users in a degraded form with reduced efficacy. Improved means of transportation of drugs and storage can therefore retain the quality of drugs as they get to the end users. The right environmental controls such as temperature, light, and humidity, conditions of sanitation, ventilation, and segregation, which affect the drug stability and quality [41], must be regulated during drug transit and storage.

3.4. Drug Interactions

The drugs that reach the systemic circulation can be grossly affected by their interaction with substances ingested alongside the drugs. Such interactions affect the absorption, distribution, metabolism, and/or excretion of drugs, which can reduce the clinical efficacy of the drug. The interaction could be additive, synergistic or antagonistic. Such substances are mainly either food (drug-food interaction) or other drugs (drug-drug interaction). Synergistic interactions can improve the efficacy of the index drug. Antagonistic interactions can reduce the drugs available at the site of action, in other words, reducing access to the drug. For example, some antiviral and antibacterial agents administered concurrently with antimalarials result in antimalarial failure [42]. While some interactions decrease the availability and activity of some antimalarials, others may increase their activity [43][44]. For instance, imatinib or other Syk kinase inhibitors which potentiate artemisinin combination therapies [45]. Due to the interaction of antimalarials with other drugs or food, patients must seek proper medical counsel before taking any antimalarial with other drugs. The interaction of antimalarials and other substances is shown in **Table 3**.

Table 3. Drugs interacting with antimalarials.

Food/Drug	Class	Probable Mechanism of Interaction	Consequences
Indinavir, nelfinavir	Antiretroviral	Inhibits CYP3A4	May increase concentrations of ART and LUM
Imatinib	Anticancer	Inhibits Syk, Lyn, Bcr-Abl	Decrease artemisinin concentration and accelerate ART efficacy
Ritonavir	Antiretroviral	Inhibits CYP2D6	May increase concentrations of ART

Food/Drug	Class	Probable Mechanism of Interaction	Consequences
		and CYP3A4	and LUM
Ketoconazole	Antifungal	Inhibits CYP3A4	Shown to cause modest increase in concentration of ART and LUM
Fluconazole	Antifungal	Inhibits CYP3A4	May cause increase in concentration of ART and LUM
Rifampicin, isoniazid	Anti-tuberculosis	Induces CYP3A4	May decrease concentrations of ART and LUM
Nevirapine, efavirenz	Antiretrovirals	Induces CYP3A4	May decrease concentrations of ART and LUM
Phentytoin/phenobarbital /carbamazepine [43][44][45]	Anticonvulsants	Induces CYP3A4	May decrease concentrations of ART and LUM

mmended combination is artemisinin-based therapy (ACT) (**Table 2**), although other combinations such as atovaquone/proguanil and sulfadoxine/pyrimethamine are also available. Atovaquone/proguanil and sulfadoxine/pyrimathamine are used mainly in prophylaxis (malaria chemoprevention) in travelers and pregnant women, respectively [30][31]. The combination makes up for the shortcomings (such as short half-life of artemisinin) of each drug in the combination, ensuring effective exposure time [46]. The currently recommended six ACTs from WHO are: artemether-lumefantrine (AL), dihydroartemisinin-piperaquine (DHA-PPQ), artesunate-amodiaquine (AS-AQ), artesunate-mefloquine (AS-MQ), artesunate-sulfadoxine-pyrimethamine (AS-SP) and artesunate-pyronaridine (AS-PY) [28]. Regrettably, in some places and for some reasons, people still use these antimalarials as monotherapies. The exposure of the parasite to only one drug makes it easier for the parasite to develop resistance to such antimalarial drugs, leading to a reduction in malaria control. The effective use of these ACTs is therefore strongly advocated to improve access to drugs.

3.6. Hoarding of Drugs by Corrupt Officials

There are several malaria programs intended to increase access to drugs by different governmental and non-governmental agencies. These agencies either subsidize the drugs or make them entirely free [2]. These drugs go

through some middlemen before getting to the intended targets. Regrettably, sometimes the drugs get stockpiled in the hands of these middlemen, who do so for several reasons ranging from profit-making to sheer wickedness. They hoard the drug in order to resell them to make gains. This leaves the poor masses without the usually subsidized or free drugs.

References

1. World Health Organization. World Malaria Report 2019; WHO: Geneva, Switzerland, 2019; ISBN 9789241565721.
2. WHO. World Malaria Report 2020: 20 Years of Global Progress and Challenges; WHO: Geneva, Switzerland, 2020.
3. Payne, D. Spread of chloroquine resistance in Plasmodium falciparum. Parasitol. Today 1987, 3, 241–246.
4. Noedl, H.; Se, Y.; Schaecher, K.; Smith, B.L.; Socheat, D.; Fukuda, M.M. Evidence of artemisinin-resistant malaria in Western Cambodia. N. Engl. J. Med. 2008, 359, 2619–2620.
5. Bloland, P.B. Drug Resistance in Malaria (WHO/CDS/CSR/DRS/2001.4). Available online: https://www.who.int/csr/resources/publications/drugresist/malaria.pdf (accessed on 20 January 2021).
6. Willcox, M.L.; Bodeker, G. Traditional herbal medicines for malaria. Br. Med. J. 2004, 329, 1156–1159.
7. Nzila, A. The past, present and future of antifolates in the treatment of Plasmodium falciparum infection. J. Antimicrob. Chemother. 2006, 57, 1043–1054.
8. Robert, A.; Benoit-Vical, F.; Claparols, C.; Meunier, B. The antimalarial drug artemisinin alkylates heme in infected mice. Proc. Natl. Acad. Sci. USA 2005, 102, 13676–13680.
9. Sullivan, D.J.; Matile, H.; Ridley, R.G.; Goldberg, D.E. A common mechanism for blockade of heme polymerization by antimalarial quinolines. J. Biol. Chem. 1998, 273, 31103–31107.
10. Golden, E.B.; Cho, H.Y.; Hofman, F.M.; Louie, S.G.; Schönthal, A.H.; Chen, T.C. Quinoline-based antimalarial drugs: A novel class of autophagy inhibitors. Neurosurg. Focus 2015, 38, E12.
11. Sidhu, A.B.S.; Valderramos, S.G.; Fidock, D.A. pfmdr1 mutations contribute to quinine resistance and enhance mefloquine and artemisinin sensitivity in Plasmodium falciparum. Mol. Microbiol. 2005, 57, 913–926.
12. Price, R.N.; Uhlemann, A.C.; Brockman, A.; McGready, R.; Ashley, E.; Phaipun, L.; Patel, R.; Laing, K.; Looareesuwan, S.; White, N.J.; et al. Mefloquine resistance in Plasmodium falciparum and increased pfmdr1 gene copy number. Lancet 2004, 364, 438–447.

13. Holmgren, G.; Hamrin, J.; Svärd, J.; Mårtensson, A.; Gil, J.P.; Björkman, A. Selection of pfmdr1 mutations after amodiaquine monotherapy and amodiaquine plus artemisinin combination therapy in East Africa. Infect. Genet. Evol. 2007, 7, 562–569.
14. Pickard, A.L.; Wongsrichanalai, C.; Purfield, A.; Kamwendo, D.; Emery, K.; Zalewski, C.; Kawamoto, F.; Miller, R.S.; Meshnick, S.R. Resistance to antimalarials in Southeast Asia and genetic polymorphisms in pfmdr1. Antimicrob. Agents Chemother. 2003, 47, 2418–2423.
15. Martin, R.E.; Marchetti, R.V.; Cowan, A.I.; Howitt, S.M.; Bröer, S.; Kirk, K. Chloroquine transport via the malaria parasite's chloroquine resistance transporter. Science 2009, 325, 1680–1682.
16. Beshir, K.; Sutherland, C.J.; Merinopoulos, I.; Durrani, N.; Leslie, T.; Rowland, M.; Hallett, R.L. Amodiaquine resistance in Plasmodium falciparum malaria in Afghanistan is associated with the pfcrt SVMNT allele at codons 72 to 76. Antimicrob. Agents Chemother. 2010, 54, 3714–3716.
17. Witkowski, B.; Duru, V.; Khim, N.; Ross, L.S.; Saintpierre, B.; Beghain, J.; Chy, S.; Kim, S.; Ke, S.; Kloeung, N.; et al. A surrogate marker of piperaquine-resistant Plasmodium falciparum malaria: A phenotype–genotype association study. Lancet Infect. Dis. 2017, 17, 174–183.
18. Dhingra, S.K.; Small-Saunders, J.L.; Ménard, D.; Fidock, D.A. Plasmodium falciparum resistance to piperaquine driven by PfCRT. Lancet Infect. Dis. 2019, 19, 1168–1169.
19. Croft, S.L.; Duparc, S.; Arbe-Barnes, S.J.; Craft, J.C.; Shin, C.S.; Fleckenstein, L.; Borghini-Fuhrer, I.; Rim, H.J. Review of pyronaridine anti-malarial properties and product characteristics. Malar. J. 2012, 11, 270.
20. Hyde, J.E. Drug-resistant malaria—An insight. FEBS J. 2007, 274, 4688–4698.
21. Staines, H.M.; Burrow, R.; Teo, B.H.Y.; Ster, I.C.; Kremsner, P.G.; Krishna, S. Clinical implications of Plasmodium resistance to atovaquone/proguanil: A systematic review and meta-analysis. J. Antimicrob. Chemother. 2018, 73, 581–595.
22. Ariey, F.; Witkowski, B.; Amaratunga, C.; Beghain, J.; Langlois, A.C.; Khim, N.; Kim, S.; Duru, V.; Bouchier, C.; Ma, L.; et al. A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature 2014, 505, 50–55.
23. Musset, L.; Bouchaud, O.; Matheron, S.; Massias, L.; Le Bras, J. Clinical atovaquone-proguanil resistance of Plasmodium falciparum associated with cytochrome b codon 268 mutations. Microbes Infect. 2006, 8, 2599–2604.
24. Conrad, M.D.; Rosenthal, P.J. Antimalarial drug resistance in Africa: The calm before the storm? Lancet Infect. Dis. 2019, 19, e338–e351.
25. Gaillard, T.; Madamet, M.; Pradines, B. Tetracyclines in malaria. Malar. J. 2015, 14, 445.
26. Dipanjan, B.; Shivaprakash, G.; Balaji, O. Triple Combination Therapy and Drug Cycling—Tangential Strategies for Countering Artemisinin Resistance. Curr. Infect. Dis. Rep. 2017, 19, 25.

27. Gansané, A.; Moriarty, L.F.; Ménard, D.; Yerbanga, I.; Ouedraogo, E.; Sondo, P.; Kinda, R.; Tarama, C.; Soulama, E.; Tapsoba, M.; et al. Anti-malarial efficacy and resistance monitoring of artemether-lumefantrine and dihydroartemisinin-piperaquine shows inadequate efficacy in children in Burkina Faso, 2017–2018. Malar. J. 2021, 20, 48.
28. WHO Artemisinin Resistance and Artemisinin-Based Combination Therapy Efficacy (Status Report—August 2018). Available online: https://apps.who.int/iris/bitstream/handle/10665/274362/WHO-CDS-GMP-2018.18-eng.pdf?ua=1 (accessed on 26 December 2020).
29. WHO Report on Antimalarial Drug Efficacy, Resistance and Response: 10 Years of Surveillance (2010–2019). Available online: https://www.who.int/publications/i/item/9789240012813 (accessed on 27 December 2020).
30. McKeage, K.; Scott, L.J.; Borrmann, S.; De Vries, P.J.; Hutchinson, D.B.A.; Looareesuwan, S.; Nosten, F.; Price, R.; Shanks, G.D. Atovaquone/proguanil: A review of its use for the prophylaxis of Plasmodium falciparum malaria. Drugs 2003, 63, 597–623.
31. Deloron, P.; Bertin, G.; Briand, V.; Massougbodji, A.; Cot, M. Sulfadoxine/Pyrimethamine Intermittent Preventive Treatment for Malaria during Pregnancy. Emerg. Infect. Dis. 2010, 16, 1666.
32. FDA. Guidance for Industry: Q8(R2) Pharmaceutical Development|FDA. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8r2-pharmaceutical-development (accessed on 8 June 2021).
33. WHO. Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials. Available online: https://www.who.int/medicines/areas/quality_safety/quality_assurance/QualityAssurancePharmVol2.pdf (accessed on 24 June 2021).
34. WWARN. Access to Quality Antimalarials—Determining the Scale of the Problem. Worldwide Antimalarial Resistance Network. Available online: https://www.wwarn.org/news/news-articles/access-quality-antimalarials-determining-scale-problem (accessed on 8 June 2021).
35. WHO. 1 in 10 Medical Products in Developing Countries Is Substandard or Falsified. Available online: https://www.who.int/news-room/detail/28-11-2017-1-in-10-medical-products-in-developing-countries-is-substandard-or-falsified (accessed on 3 July 2021).
36. Amin, A.A.; Kokwaro, G.O. Antimalarial drug quality in Africa. J. Clin. Pharm. Ther. 2007, 32, 145–150.
37. Renschler, J.P.; Walters, K.M.; Newton, P.N.; Laxminarayan, R. Estimated under-five deaths associated with poor-quality antimalarials in sub-Saharan Africa. Am. J. Trop. Med. Hyg. 2015, 92, 119–126.

38. Spaan, E.; Mathijssen, J.; Tromp, N.; McBain, F.; ten Have, A.; Baltussen, R. The impact of health insurance in Africa and Asia: A systematic review. Bull. World Health Organ. 2012, 90, 685–692.
39. WHO. World Health Statistics 2010. Available online: https://apps.who.int/iris/handle/10665/44292 (accessed on 9 June 2021).
40. McIntyre, D.; Thiede, M.; Dahlgren, G.; Whitehead, M. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? Soc. Sci. Med. 2006, 62, 858–865.
41. Briscoe, C.J.; Hage, D.S. Factors affecting the stability of drugs and drug metabolites in biological matrices. Bioanalysis 2009, 1, 205–220.
42. Tarning, J.; Hoglund, R.M. Clinically Relevant Drug Interactions for Malaria. In Encyclopedia of Malaria; Kremsner, P.G., Krishna, S., Eds.; Springer: New York, NY, USA, 2019.
43. Kokwaro, G.; Mwai, L.; Nzila, A. Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. Expert Opin. Pharmacother. 2007, 8, 75–94.
44. Adedeji, W.A.; Balogun, T.; Fehintola, F.A.; Morse, G.D. Drug-Drug Interactions of Antimalarial Drugs. In Drug Interactions in Infectious Diseases: Antimicrobial Drug Interactions; Pai, M.P., Kiser, J.J., Gubbins, P.O., Rodvold, K.A., Eds.; Springer International Publishing: Cham, Switzerland, 2018; pp. 503–514.
45. Tsamesidis, I.; Reybier, K.; Marchetti, G.; Pau, M.C.; Virdis, P.; Fozza, C.; Nepveu, F.; Low, P.S.; Turrini, F.M.; Pantaleo, A. Syk Kinase Inhibitors Synergize with Artemisinins by Enhancing Oxidative Stress in Plasmodium falciparum-Parasitized Erythrocytes. Antioxidants 2020, 9, 753.
46. White, N. Antimalarial drug resistance and combination chemotherapy. Philos. Trans. R. Soc. B Biol. Sci. 1999, 354, 739–749.