

Availability, market share and price of quality assured artemisinin-based combination therapies in private drug outlets after over a decade of Copayment mechanism in Uganda.

Moses Ocan^{1*}, Winnie Nambatya², Caroline Otike³, Loyce Nakalembe⁴, Sam Nsobya⁵

Author affiliations

¹Department of Pharmacology & Therapeutics, College of Health Sciences, Makerere University, P. O. Box 7072, Kampala.

²Department of Clinical Pharmacy, College of Health Sciences, Makerere University, P. O. Box 7072, Kampala.

³Data Department, Joint Clinical Research Centre, Lubowa, P. O Box 10005, Kampala, Uganda

⁴Department of Pharmacology, Soroti University, P.O. Box 211, Soroti, Uganda

⁵Department of Pathology, College of Health Sciences, Makerere University, P.O. Box 7072, Kampala, Uganda

*Corresponding author: Moses Ocan, E-mail: ocanmoses@gmail.com; Tel: +256712234364

Abstract

Background: Malaria remains one of the leading causes of morbidity, and mortality in Uganda. A large proportion of malaria symptomatic patients seek healthcare in the private sector. However, availability and affordability are major barriers to access to effective treatment. The private sector copayment mechanism in Uganda aims to increase availability and affordability of antimalarial agents. Our study assessed the availability, price, and market share of quality assured artemisinin-based combination therapies (QAACTs) in private drug outlets after over a decade of copayment mechanism in the private sector in Uganda.

Methods: This was a cross-sectional survey of anti-malarial agents in private drug outlets in high (Tororo, and Apac districts) and low (Kabale and Mbarara districts) malaria transmission settings. Following the World Health Organization Health Action International (WHO/HAI) criteria, an audit of the antimalarial agents was done using a checklist to determine availability, price, and market share of QAACTs. Data was entered in Epi-data and analyzed in STATA ver 14.0 at 95% confidence level.

Results: A total of twenty-eight (28) private drug outlets (pharmacies and drug shops) were included in the survey. One in seven Artemisinin-based combination therapies (ACTs) in the drug outlets were quality assured (QAACTs). Artemether-lumefantrine (AL), 8.9% (11/124) and Artesunate-Amodiaquine (AQ), 7.3% (9/124) were the only QAACTs present in the drug outlets at the time of the survey. The majority, 86.1% (124/144) of antimalarial agents present in stock in the drug outlets were artemisinin based. The most common, 38.9% (56/144) ACT in the drug outlets was Dihydroartemisinin-Piperaquine (DHP). Most, 69.4% (100/144) of the antimalarial agents were in high malaria transmission settings. The cost of ACT antimalarial agents is high in the country, USD 1.4 (Artemether-Lumefantrine, AL), USD 2.4 (Dihydroartemisinin-Piperaquine, DP), the first line and second-line agents respectively for treatment of uncomplicated malaria in Uganda. There was a statistically significant difference between the dispensing price of the 'Green leaf' ACTs and the recommended price ($p < 0.001$).

Conclusion: Quality assured artemisinin-based combination therapies (QAACTs) are not common in private drug outlets in low and high malaria transmission settings. All the drug outlets had at least one ACT antimalarial agent present on the day of the survey. The dispensing price of QAACTs was significantly higher than the recommended markup price. There is need for awareness creation, surveillance, and monitoring of the implementation of Copayment mechanism in the country.

Key words: Quality assured artemisinin agents, non-artemisinin agents, malaria, cost, self-medication

Introduction

The World Health Organization (WHO) reported an overall increase in malaria burden globally of up to two million cases in 2020-2021 with most of the increase occurring in the WHO Africa region (1). Uganda is among the four countries including Nigeria, Democratic Republic of Congo and Mozambique that accounted for nearly half of all malaria cases globally in 2020-2021 (1). Malaria thus remains a disease of public health concern in Uganda accounting for 30-50% of all out-patient visits, and 15-20% of all hospital admissions (2). The healthcare system in Uganda like most other low-and middle-income countries (LMICs) is faced with multiple challenges including inadequate human resource and limited funding (3). The unreliable supply coupled with high costs of antimalarial agents in health facilities common in most LMICs potentially affect malaria treatment (4, 5). In Uganda, this is likely to be worsened by the high burden of malaria.

In most low-and middle-income countries (LMICs), over 60% of the population first seek treatment in the private sector (6). A study by Ocan *et al.*, (7) reported over half of population in northern Uganda accessing antimalarial agents over the counter in private drug outlets. The sector thus plays an integral role in the fight against malaria (8). Patients seeking malaria treatment in the private sector are however faced with multiple challenges including high cost, unreliable supply, and substandard antimalarial agents (5, 9). In most malaria affected countries price remains the leading contributor to limited access to antimalarial agents (5, 10). These potentially affects access to appropriate malaria treatment which potentially predisposes patients to adverse treatment outcomes including exacerbation of the current resistance to first-line antimalarial agents.

One of the key factors influencing access to appropriate malaria treatment is pricing of antimalarial agents (5). The Affordable medicines facility for malaria (AMFm) is a financing mechanism incorporating three elements; price reductions through negotiations with manufacturers of quality-assured ACTs (QAACTs), a buyer subsidy to the participating manufacturers, and interventions to support AMFm implementation and promote appropriate antimalarial use (11). Affordable Medicines Facility-malaria (AMFm), funded by three donors (UNITAID, the UK government and the Bill & Melinda Gates Foundation) was renamed as the

private sector co-payment mechanism and integrated into the existing Global Fund grants (12). The AMFm initiative is intended to improve availability, affordability, and access to quality assured artemisinin-based combination therapies (QAACts) in the private sector (13). Under the AMFm, public and private importers pay manufacturers a subsidized price between \$0.005 and \$ 0.22 per treatment course, representing 1-20% of the manufacturer price (14). The balance is then paid to the manufacturer via the co-payment fund (14). Uganda was part of the countries where the initiative was first piloted and subsequently implemented the Copayment mechanism following the AMFm transition period in 2013 (13).

Negotiations with manufacturers under the AMFm led to reductions in manufacturer price for sales to private-for-profit buyers of up to 29-78% depending on package size, bringing prices down to around the levels paid by public purchasers (15). This helped improve availability, affordability, and access to QAACts in the AMFm pilot countries. In Uganda the AMFm was replaced by Copayment mechanism following the end of the pilot period (13). The approved quality assured ACTs in Uganda include Artemether/lumefantrine, Artesunate/Amodiaquine, Dihydroartemisinin/piperaquine, and Artesunate/Pyronaridine (16, 17). Uganda is currently implementing 70% subsidy for all package sizes of QAACts (13). However, the impact of the Copayment mechanism in the private sector remains unclear. Therefore, this study assessed availability, price, and market share of quality assured artemisinin-based combination therapies (QAACt) in the private drug outlets in low and high malaria transmission settings in Uganda after over a decade of implementing Copayment mechanism.

Methods

Study design and setting

This was a cross-sectional study conducted in low (Kabale and Mbarara districts) and high (Apac and Tororo districts) malaria transmission settings. Data on antimalarial agents present in the drug outlets on the day of the survey was collected.

Sample size, drug outlet selection and sampling

In each district (Tororo, Apac, Mbarara and Kabale), a comprehensive list of the available private drug outlets was compiled using the National drug authority register of drug outlets. Additionally, a census was taken to identify all the private drug outlets (pharmacies and drug shops) in each district prior to data collection. All the drug outlets identified from the National drug authority register and the census were then included in the survey. Private drug outlets in this study are defined as for-profit licensed establishments that dispense medicines. Two research assistants, a pharmacist (KJ) and nurse (RK) conducted the antimalarial drug audit in the private drug outlets. Each of the research assistants separately visited different drug outlets in the study districts. At each drug outlet prior to data collection the research assistants introduced themselves and explained the study and provided approval letters from the Ethics committee, UNCST and local authorities. The research assistants obtained a written informed consent from the pharmacists/dispensers in each pharmacy prior to data collection which was done between 15th June 2021- 21st December 2021. In each study district, the research assistants moved from one drug outlet to the next until all the identified private drug outlets were covered.

Data collection

The WHO/HAI methodology was used for collection of data on availability and price of antimalarial agents. In each drug outlet, the dispenser/pharmacist was requested to show the research assistants all the antimalarial agents available in stock on the day of the survey. Additionally, a stock card and dispensing logs were also obtained and screened. An audit of the antimalarial agents that were provided, stock cards and dispensing logs was then done using a data collection checklist. The tool was pre-tested in drug outlets in Kampala city and validated. Data was collected for each identified anti-malarial agent in the drug outlet. The WHO list of antimalarial agents was used in identification of antimalarial agents present in stock during the day of the survey. Additionally, the Ministry of Health list of quality assured artemisinin-based agents in the country was also used in identifying QAACTs in the drug outlets. Data was collected on, drug outlet type, generic name, brand name, active ingredients and strengths,

formulation, quality assured ACT (having a green leaf logo), non-quality assured ACT (without a green leaf logo), manufacturer and country of manufacture, type of antimalarial (artemisinin or non-artemisinin based), location of drug outlet (transmission setting), and package size. The price of the antimalarial agents was collected from the dispensing logs and the dispenser/pharmacist.

During each data collection day, the lead researcher reviewed all the data collection forms and visited 20% of all the drug outlets for quality control checks. Any discrepancies in the data collection tool were rectified through discussion with the data collectors and consensus.

Data management and analysis

In this study, ACT antimalarial agents were classified into two categories: i) quality assured ACTs (QAACTs) are ACTs that comply with the Global Fund's ACT chemical regulation and have a green leaf logo printed on its label and ii) non-quality assured ACTs (non-QAACTs) which are ACTs without the green leaf logo on their labels. The Quality-assured ACTs were further divided into two categories: i) quality-assured first-line ACT (Artemether/Lumefantrine) and ii) quality-assured alternative first-line ACT (Artesunate/Amodiaquine) as per the national malaria treatment guidelines (18). Antimalarial availability was measured as the proportion of outlets with at least one anti-malarial agent present on the day of data collection (survey). Additionally, in each private drug outlet the proportion of specific anti-malarial categories present in stock during the day of the survey was also calculated. The prices of antimalarial agents in the drug outlets were converted to US dollars using the average annual exchange rate by the Bank of Uganda in 2021. The antimalarial price data at the time of data collection is reported in terms of adult equivalent doses, defined as the amount needed to treat a 60 kg adult (19).

Data was entered in EpiData *version* 4.2.0.0 and exported to STATA *version* 14.0 for cleaning and analysis. Antimalarial agents were summarized using frequencies and proportions, prevalence of antimalarial agents was also determined using proportions. Distribution of antimalarial agents across malaria transmission settings and type of drug outlet was compared using fisher's exact test of independence at 95% level of significance. Price of antimalarial agents was summarized using median and interquartile range.

Results

Descriptive results

A total of twenty-eight (28) drug outlets were included in the survey of which majority, 78.6% (22/28) were pharmacies. All the drug outlets in the study districts (Apac, Tororo, Mbarara and Kabale) had at least one antimalarial agent present in stock during the day of the survey. Of the 28 drug outlets visited in this study, majority 82.1% (23/28) had a minimum of 5 different kinds of antimalarial agents present on the day of the survey. Most, 69.4% (100/144) of the antimalarial agents were in high malaria transmission settings. The majority, 86% (124/144) of the antimalarial agents were tablet formulations. Twelve, 8.3% (12/144) of the artemisinin based antimalarial agents in the drug outlets were monotherapies (Table 1).

Antimalarial agents present in the drug outlets on the day of the survey.

A total of 144 antimalarial agents were present in the drug outlets on the day of the survey of which majority, 86.1% (124/144) were artemisinin-based agents. Of the Artemisinin based combination therapies, 61.1% (88/144) were in high malaria transmission settings and 68.8% (99/144) were found in pharmacies. For non-artemisinin based antimalarial agents, 8.3% (12/144) were in high malaria transmission setting and 11.1% (16/144) were in pharmacies.

Of the artemisinin-based agents, majority 90.3% (112/124) were Artemisinin-based combination therapies (ACTs). Artesunate was the most common artemisinin monotherapy, 8.9% (11/124). All the artemisinin monotherapies 9.7% (12/124) were injectables (Artemether and Artesunate). Over a third 35.4% (51/144) of the antimalarial agents were first-line ACTs (Artemether-lumefantrine, 29.2%: 42/144 and Artesunate-amodiaquine, 6.3%: 9/144). Most first-line ACTs, 26.4% (38/144), 25.7% (37/144) were in high malaria transmission setting and pharmacies respectively. Of the ACTs 70.2% (87/124), 66.9% (83/124) were present in pharmacies and high malaria transmission settings respectively. There was no statistically significant difference in the presence of ACTs in pharmacies and drug shops ($p=0.318$). However, there was a statistically significant difference in the distribution of ACTs based on setting ($p=0.03$).

Four batches, 2.8% of the Artemisinin based antimalarial agents available in stock in the drug outlets had passed their expiry date. Of the expired agents, three were artemisinin-based while one was a non-artemisinin-based agent (Table 1).

Availability of Quality Assured Artemisinin Combination therapies (QAACTs)

One in every seven Artemisinin-based combination therapies in the drug outlets were Quality Assured Artemisinin combination agents ('Green leaf ACTs'; QAACT). Most, 9.7% (12/124) of the QAACTs were in pharmacies. The QAACTs were common, 13.7% (17/124) in drug outlets in high malaria transmission settings. The QAACTs were significantly distributed in the pharmacies within the study settings ($p=0.031$). While there was no significant difference in the distribution of QAACTs by malaria transmission setting ($p=0.123$). Artemether-lumefantrine (AL), 8.9% (11/124) and Artesunate-Amodiaquine (AQ), 7.3% (9/124) were the only QAACTs present in drug outlets on the day of the survey. All the Artesunate/Amodiaquine agents in drug outlets were 'Green leaf' ACTs (Table 1).

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245 **Table 1: Antimalarial agents (N=144) in drug outlets in high and low malaria transmission settings in**
246 **Uganda**

Antimalarial category	Description	Overall n (%)	Low malaria transmission n (%)	High malaria transmission n (%)	p-value
Artemisinin monotherapies	Artesunate	11 (7.6)	6 (4.1)	5 (3.5)	1.00
	Artemether	1 (0.7)	1 (0.7)	0	
Non-Artemisinin based monotherapies	Chloroquine	2 (1.4)	1 (0.7)	1 (0.7)	1.00
	Quinine	8 (5.6)	3 (2.1)	5 (3.5)	
	Mefloquine	1 (0.7)	0	1 (0.7)	
Artemisinin-based combination therapies (ACTs)	Artemether/lumefantrine	42 (29.1)	13 (9)	29 (20.1)	0.213
	Artesunate/Amodiaquine	9 (6.3)	0	9 (6.3)	
	Dihydroartemisinin/Piperaquine	56 (38.9)	15 (10.4)	41 (28.5)	
	Artesunate /Mefloquine	2 (1.4)	1 (0.7)	1 (0.7)	
	Artesunate/Pyronaridine	3 (2.1)	0	3 (2.1)	
Non-Artemisinin based combination therapies	Atovaquone/Proguanil	2 (1.4)	1 (0.7)	1 (0.7)	1.00
	Sulfadoxine/Pyrimethamine	7 (4.9)	3 (2.1)	4 (2.8)	
Quality Assured ACTs (‘Green leaf ACTs	Artemether/lumefantrine	11 (7.6)	3 (2.1)	8 (5.5)	0.218
	Artesunate/Amodiaquine	9 (6.3)	0	9 (6.3)	
Expired antimalarial agents	Yes	4 (2.8)	1 (0.7)	3 (2.1)	1.00
	No	140 (97.2)	43 (29.9)	97 (67.3)	
Formulation	Powder	18 (12.5)	10 (6.9)	8 (5.5)	0.039
	Syrup	2 (1.4)	0	2 (1.4)	
	Tablets	124 (86.1)	34 (23.6)	90 (62.5)	

247 *ACTs: Artemisinin-based Combination therapies; n=sample size; %: percentage*

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Price of antimalarial agents in drug outlets in Uganda

Arterolane maleate/piperaquine phosphate combination had highest median price among the antimalarial combination agents, 4.9 USD. The median price for Artemether/lumefantrine (AL), the first line agent for uncomplicated malaria in Uganda was 1.4 USD. Dihydroartemisinin/Piperaquine (DP), the second-line agent for treatment of uncomplicated malaria in Uganda cost was sold at a median price of 1.7USD. Artesunate + Amodiaquine (AS+AQ), the second-line alternative agent for uncomplicated treatment of uncomplicated malaria in Uganda the median price was 2.1 USD (Table 2).

Table 2: Median price of oral antimalarial agents in drug outlets in Uganda

S/N	Generic name	Median price (USD)	IQR (USD)
1.	Artemether/Lumefantrine	1.4	0.9, 1.9
2.	Arterolane maleate/piperaquine Phosphate	4.9	2.4, 5.6
3.	Artesunate + Amodiaquine	0.8	0.7, 1.3
4.	Artesunate/Mefloquine	2.8	2, 4.2
5.	Chloroquine Phosphate	0.6	0.5, 0.8
6.	Dihydroartemisinin/Piperaquine	3.2	2.7, 4.2
7.	Mefloquine	1.1	0.7, 2.2
8.	Quinine sulphate	0.4	0.3, 0.4
9.	Sulfadoxine/Pyrimethamine	0.6	0.1, 0.4
10.	Atovaquone/Proguanil	1.9	1.8, 2.0
11.	Artesunate/Pyronaridine	2.2	0.1, 2.8
12.	Arterolane maleate/piperaquine Phosphate	4.9	2.4, 5.6

USD: US dollar, IQR: Interquartile range

Price mark-ups on quality assured artemisinin-based combination therapies (QAACTs) in drug outlets in Uganda

The median dispensing price for adult dose of quality assured (QAACT: 'Green leaf') first-line ACT for uncomplicated malaria, artemether-lumefantrine (AL) (20/120mg) was USD 0.98, which is higher than the recommended retail price by 10.2%. The median dispensing price for quality assured Artesunate/Amodiaquine (AQ) (25/67.5mg) was USD 0.7 which is higher than the recommended retail price by 57%. There was a statistically significant difference between the dispensing price of the 'Green leaf' ACTs and the recommended retail price ($p < 0.001$).

Discussion

The study found at least one antimalarial agent present in all drug outlets during the day of the survey. Additionally, Artemisinin-based combination therapies (ACTs) were the most common antimalarial agents in the drug outlets. This is unlike the findings of a previous study by O'Connell et al., (20) done in six sub-Saharan African countries that reported a low prevalence of ACTs in private sector. The implementation of Affordable medicines facility for malaria (AMFm) program could have influenced the difference in the findings of the two studies. A study by ACTwatch group *et al.*, (13), reported an increase on availability of ACTs following implementation of the AMFm-malaria program. The finding of our study is an indicator of wide availability of Artemisinin-based combination therapies (ACTs), the current cornerstone for malaria treatment in private drug outlets.

The immediate post AMFm pilot period was characterized by increases in the availability of QAACTs in the private sector in Uganda and all other countries where it was implemented (13, 14). However, our study found a low prevalence of QAACTs in private drug outlets after over a decade of implementing copayment mechanism following AMFm pilot period. This is like findings of a study by O'Connell et al., (20). The low availability of QAACTs in private drug outlets highlights the challenges of implementation of copayment mechanism especially lack of

supporting interventions like training of private sector healthcare personnel and behavioral change communication (13, 14).

The study did not find oral artemisinin-based monotherapies in the drug outlets. The injectable artemisinin monotherapies (Artesunate and Artemether) were however common. According to the National malaria case management guidelines, injectable artemisinin agents are indicated in the treatment of severe malaria and are to be used alongside oral ACTs. The use of oral artemisinin monotherapies in malaria treatment was reported in Southeast Asia as one of the drivers of artemisinin resistance development (21). Our findings are like those of a previous study by ACTwatch et al., (13) and O'Connell et al., (20) who reported not finding artemisinin-based monotherapies in sub-Saharan Africa. The objectives of the AMFm were to make the ACTs more available, accessible and to crowd out artemisinin monotherapies (13). The findings of our study could thus be due to the emphasis placed on the Artemisinin based combination therapies through the AMFm and Copayment mechanism in the country. In addition, the absence of artemisinin monotherapies in Uganda could be due to the World Health Organization (WHO) recommendation to malaria affected countries to ban importation and manufacture of these agents.

The study found non-artemisinin antimalarial agents in the drug outlets across the country. This is like the findings of a study by O'Connell et al., (20) which reported high prevalence of non-artemisinin agents in sub-Saharan African countries. Our study found, chloroquine, quinine and Sulphadoxine/Pyrimethamine (SP) as common non-artemisinin agents in drug outlets. Presence of non-artemisinin therapies in the private drug outlets could be due to their perceived effectiveness and familiarity from previous use coupled with provider behavior and beliefs (7, 22). Sulphadoxine/Pyrimethamine (SP) is recommended for use in prophylaxis against malaria in pregnancy (23). Additionally, Quinine is a second line agent in treatment of severe malaria in the country (18). However, the use of chloroquine was discontinued in 2006 (24) due to widespread resistance. The continued presence of chloroquine in private drug outlets is an indicator of access and use by communities in management of symptoms of malaria. Recent

studies in Uganda have reported persistence of *P. falciparum* resistance against chloroquine over two decades after discontinuation of its use in the country (25). Therefore, continued use of chloroquine by communities is likely to lead to inadequate treatment and increased risk of unwanted malaria treatment outcomes.

Dihydroartemisinin/Piperaquine (DP) and Artemether/lumefantrine (AL), the two most popular ACTs had a high median dispensing price for a full adult dose ranging from USD 1.4 – 2.4. The median price of the subsidized ACTs ('Green leaf ACTs') was also significantly higher than the non-subsidized agents. This is similar to the prices reported in a study by O'Connell et al., (20) done in six malaria endemic countries in sub-Saharan Africa. A previous study by Tougher et al., (14) also found no significant change in ACT prices following implementation of AMFm pilot program in Uganda. In a country where majority of the rural communities live under USD 1.0 a day, the reported prices of ACTs are potentially prohibitive. The reported high cost of ACTs potentially hinders access to appropriate and effective malaria treatment in the country. Recent studies in Uganda have reported high over-the-counter access of antimalarial agents which coupled with the high cost of ACTs could drive inappropriate use (7, 26). With the emerging artemisinin resistance, inappropriate use of ACTs is likely to exacerbate malaria parasite resistance in the country (27). The high cost of quality assured ACTs in the private sector despite government subsidy highlights the challenge of implementation of government programs especially in LMICs. There is thus need for regular monitoring of the implementation of copayment mechanism for improvement of availability and access to quality assured ACTs in the private sector.

The study had some limitations, the overt method used is likely to be affected by the pharmacists not reporting the actual practice in the pharmacy. However, the additional review of stock cards and drug dispensing logs in the pharmacies and drug shops helped collaborate the findings of the study.

Conclusion:

The results of our study indicate low prevalence of QAACTs in private drug outlets after over a decade of implementation of copayment mechanism in Uganda. Prices of both QAACTs and non-QAACTs remain high in private drug outlets (pharmacies and drug shops) despite the subsidies on QAACTs. There is need for consistent implementation of Copayment supporting interventions to help create demand for QAACTs among private sector health providers and the population. The Ministry of Health needs to conduct a review of the copayment mechanism to establish barriers to its implementation in the country.

Author contribution

Conceptualization of the study (MO and SN), data curation and formal analysis (CO), methodology and investigation (MO and LN), validation (WN), Writing-original draft preparation (MO), supervision (SN). All the authors reviewed and edited the final version of the manuscript.

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