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Determination of Concentration of Active Pharmaceutical Ingredients in Different Brands of Artemether/Lumefantrine Tablets Sold in the Pharmacies in Uganda

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ABSTRACT

Substandard, counterfeit and falsified antimalarial agents are a big challenge to effective malaria elimination interventions mainly in developing countries. In low-and middle-income countries (LMICs), the quality of antimalarial agents inclusive of AL is affected by several factors including insufficient regulation porous borders and limited funds. This study therefore focused evaluation of quality of different brands of fixed dose artemether/ lumefantrine tablets sold in Ugandan Pharmacies. This was an experimental study conducted using AL tablets obtained from different pharmacies in the different cities of Uganda purchased using mystery shopper method. The samples were screened for quality using visual inspection, assessed different physical quality parameters like weight variation, friability, disintegration and dissolution and content assay tests were also done both for the brands from the pharmacies and their correspondent LTR. The assay test was done using HPLC technique USP method. The samples were considered substandard if the API content was outside 90-110% range of the label claim. Data was analysed using descriptive statistics and presented as means with standard deviations and frequencies. Out of the 16 brands in the study, 14 brands (88%) passed the artemether assay and two brands failed at 89.8% and 110.2% of declared artemether content. For Lumefantrine assay, out of the 16 brands in the study, 14 brands (88%) passed the Lumefantrine assay except two brands (12%). The presence of A/L brands that are unregistered and the total assay failure of the brands of 18% for the AL tablets purchased causes alarm and the total assay failure of the brands of 18% for the AL tablets purchased calls for NDA to intensify on its operations to find out the conformity of the pharmacies to selling only registered medicines.

Keywords: Artemether Lumefantrine, Quality, Tablets

INTRODUCTION

Artemether Lumefantrine (AL) is the most commonly used Artemesinin Combination Therapy (ACT) in the management of uncomplicated *P. falciparum* malaria [1]. Both artemether and lumefantrine are blood schizontocides [2]. However, artemisinin also has some gametocytocidal activity resulting in a decrease in malarial parasite transmission [2]. Food enhances the absorption of both Artemether and Lumefantrine however, this effect is more pronounced for lumefantrine [3]. Therefore, there is a necessity for a standard African diet is adequate to ensure optimal efficacy for Artemether lumefantrine [3].

Artemether is a herbal remedy anciently used in Chinese for relapsing fever from *Artemisia annua*, alternatively called sweet *wormwood* [4]. Lumefantrine on the other hand is not from nature rather formed by chemical synthesis following research carried out in 1967 by the academy of Military Medical Sciences in Beijing China [5]. The initial approval of AL as an ACT to the market dates back to 1999 and has been used ever since then in the management of uncomplicated malaria worldwide [5]. The presence of unregistered antimalarial agents on the market has been reported in different parts of the world and the quality of these agents remains in question causing a great risk to the general population taking these agents [5].

Substandard and falsified antimalarials are very prevalent in countries considered as low and middle income (LMICS) at a rate of 19.1% [6] and have significant negative health and economic effect, with a high deaths burden, disability and wastage of money on cost-ineffective antimalarials leading to health inequities in Uganda [7]. Developing countries

including Uganda have over 25% of their medicines reported as counterfeit and substandard, these medicines lead to around 0.25 million deaths per year. However, treatment with good quality medicines can help reduce all these deaths [8].

Treating malaria with good quality antimalarials (artemether-lumefantrine) instead of counterfeits and substandard drugs can help to prevent the high death rates, morbidity due to consumption of poor-quality drugs [9]. The recommended first-line treatment for management of uncomplicated falciparum malaria a species that causes the most severe forms of malaria and subsequent deaths is fixed dose artemether lumefantrine [10]. AL is used in management of uncomplicated plasmodium falciparum malaria in Uganda however due to the presence of porous borders and unregulated private sector drug procurement, there may be poor quality artemether-lumefantrine on the market. Therefore, this study will focus on evaluating the quality of different brands of fixed-dose artemether-lumefantrine tablets on the Ugandan market.

METHODOLOGY

Study design

This was an experimental study which involved use of pharmacopoeias, compedial and non-compendia tests.

Study area

The study focussed on all the different brands of fixed dose artemether/ lumefantrine on the Ugandan market obtained from all the different ten cities that is Kampala the capital city, Jinja, Mbaale, Soroti, Lira, Gulu, Arua, Hoima, Mbarara, Masaka and Fortportal.

Study setting

The experimental procedures were carried out at the KIU-WC Pharmaceutics Laboratory that is for disintegration, thickness, friability, hardness and weight uniformity. Not only was the research done at KIU-WC pharmaceutics Laboratory but also at the analytical Research laboratory of Mbarara University of Science and Technology.

Inclusion criteria

All tablets claimed having artemether and lumefantrine were obtained from NDA licenced Pharmacies as well as batches of AL tablets left with at least three months to their expiry date were purchased reason aligned to avoid those with near expiry from expiring during storage before analysis. Sample with different products names at the same licenced drug outlet were obtained.

Exclusion criteria

Drug outlets with less or equal to 48 tablets of a batch of AL tablets were not purchased as these were the number of tablets needed for the study catering for all the involved tests and Samples of short expiry were not included also.

Sampling procedure

In this study, two aspects of sampling were involved, namely sampling pharmacies and sampling of tablets from different AL batches for laboratory testing.

Sample size determination of drug outlets

The formula for sample size determination for drug quality studies provided by [11] was used to calculate the number of private pharmacies to be sampled. WHO recommends that for a drug survey to be done across the country, the lowest number of Pharmacies from which drugs are to be obtained should be twenty (20). For this study, the following formula for sample size calculation was used:

The formula $sa = Px20$ was used [11].

Where;

Sa is the number of the private drug outlets sampled in the capital city

$P = n1/n$

n is the total number of private drug outlets in the country.

$n1$ is the list of private drug outlets in the capital city (Kampala) and 20 is the lowest number of private drug outlets to be selected.

The number of private drug outlets sampled in the selected geographical unit region (sb) $=20- sa$

Total number of private drug outlets in Kampala is 1106

Total number of private drug outlets in Uganda is 2193

$Sa= (1106/2193) \times 20$

$Sb=20- ((1152/2055) \times 20) = 10$ pharmacies.

Sb is the number of pharmacies from which the AL tablets were obtained from a given city other than the capital city Kampala.

Using the above formula, samples were collected from 10 pharmacies from each of the Cities NDA regions of Uganda cities that is Kampala the capital city, Jinja, Mbaale, Soroti, Lira, Gulu, Arua, Hoima, Mbarara, Masaka and Fortportal. Therefore, based on the calculation 110 Pharmacies were considered in the study.

Selection procedure for drug outlets

A stratified random method of sampling was used to select the various Pharmacies following calculation of the required sample size of drug outlets. This involved assigning random numbers to the Pharmacies in the City and these numbers were noted on small pieces of paper. The papers were then folded, placed in two different baskets, and shaken. One piece of paper was randomly taken at a time out of the basket and the number was written without replacement. In the basket private pharmacies 10 papers would be taken at random without replacing

and these were representative of be the Pharmacies that were considered in the study and it is from these Pharmacies that the drugs were bought.

Replacing of a Pharmacy was only to be done in a scenario where if during the time of data collection, it is found out that the Pharmacy is non-existent and the next on the list was to be selected.

Collection of AL tablets from the drug outlets

In order to reduce bias during sampling, mystery shoppers were used to purchase the AL tablets. The mystery shoppers were not informed of the study main goal and only instructed to collect samples. Different batches from different brands of tablets claimed to be containing artemether and lumefantrine were purchased from selected private pharmacies. 48 tablets of each batch and brand were bought. All brands were collected in cases where a drug outlet had more than one brand and/ or batch of AL tablets. The following information was written in a sampling form (Appendix I) upon drug buying, the facility code and type of the drug outlet, date of sampling, brand/ trade name and batch number of the sampled AL tablets, manufacturing date, expiry date country of origin, manufacturing company, will all be documented in a drug sampling form(appendix1). To ensure that drugs collected are protected from sunlight and moisture, all AL samples collected were packed and sealed in a well labelled envelope that was later packed in a polythene bag that is dark and water proof. The samples were transferred to Kampala International University Western Campus Pharmaceutics and Pharmaceutical Technology Laboratory where they had to be stored according to manufacturers' storage conditions stated on package pending laboratory analysis.

Materials used in weight uniformity determination

To determine the weight uniformity of the different brands of fixed dose AL, equipment like an analytical balance, weighting boats. The analytical balance was not only applied for weight uniformity determination but also to weigh solutes for the preparation of the mobile phase.

Materials used in content analysis and assay

The equipment in the analysis of uniformity of content were stainless steel HPLC Column, pH meter to be used to determine the pH of the mobile phase. Sonicator, Millipore apparatus for water filtration, Nylon membrane filters, filter paper, beakers, pipettes, spatulas, measuring cylinders, Vortexer, motor, and pestle.

Not only equipment was needed, several reagents were used inclusive of acetonitrile HPLC grade that was used as mobile phase A in assay and dissolution test. Hexane sulphonic acid sodium salt and sodium dihydrogen phosphate monohydrate (analytical grade) used to prepare the ion pair reagent (B-phase). Orthophosphoric acid (85%w/v) for pH adjustment of the ion pair reagent, 2-propanol (HPLC grade), and filtered distilled water as a solvent.

The artemether and lumefantrine reference standards (RS) were obtained from CIPLA Quality Chemical Industries Limited (Cipla QCIL), Uganda which was kept under the required storage condition that is temperature 2-8^{o}C and in a dark waterproof container with silica beads to absorb the moisture. These were applied in determination of the standard curves and calculating the quantity of artemether and lumefantrine in each batch.

Data management analysis

The generated laboratory results were kept in hard copies for safety and reference. Following HPLC analyses, resultant chromatograms generated were printed and filed. Data from chromatograms was entered in Microsoft excel before analysis.

For the data of the different physicochemical parameters that is from weight uniformity, average weight, standard deviation, and percentage relative standard deviations was calculated for each brand using standard formulae in Microsoft Excel. Not only for weight uniformity but also for friability, disintegration, hardness, thickness and dissolution was analysed using a standard formula in Microsoft excel.

Following assay, the area under the curve (AUC) obtained in the chromatograms of the samples and standard solutions during the assay of content was employed to auto-calculate the percentage amount of APIs

The amount of API in both the artemether and lumefantrine test assays was acceptable if the result was in the range of 90-110% of the declared amount as per international pharmacopeia.

To compare the assay results of both the Brand obtained from the general market and that obtained from the respective LTR, this was based on the difference or the similarity in the content following assay and a table showing the consistency (similarity of content) and inconsistency (difference in content) was obtained from the data set. Two pie charts showing the frequencies of occurrence of consistency or inconsistency were drawn from the data set for both Artemether AND Lumefantrine assays.

Ethical considerations

Ethical approval and clearance was obtained from Kampala international University Research and Ethics Committee. The identity of the drug outlets from which the drugs were obtained was protected by coding like A, B, C, D, E, F and so on. The different brands identity too was protected by use of codes

BAL1, BAL2, BAL3, BAL4 and so on. To minimise bias, mystery shoppers who were used in the study were not be from the same location of tablet collection. During running of the different laboratory experiments, protective gears were put on to avoid any direct exposure of the reagents and the body. After the experiment, the wastes from the experiment were disposed off as per the NDA guidelines of pharmaceutical waste disposal. Data obtained from the research will be published but the identity of the brands and the drug outlets will be protected by coding and this is how the data will be published.

RESULTS

Following assay of the different brands obtained from the market and their corresponding samples from the Local Technical Representatives, the following results from table 7 (Lumefantrine assay results) and 9 (Artemether assay results) were obtained and recorded. A brand was considered to have passed the assay test if the results obtained following the assay were within the range of 90-110%. Out of the 16 brands in the study, 15 brands (94%) passed the artemether assay for all those that were collected from the market including BAL10 that was obtained from the field but not existent at the LTR and only one brand BAL16 failed the artemether assay at 89.8% of declared artemether content of 20mg as it was at 17.96mg (Table 9). For Lumefantrine assay, out of the Out of the 16 brands in the study, 14 brands (88%) passed the Lumefantrine assay except two brands (12%) that is BAL9 and BAL10 that failed the Lumefantrine assay that had 110.8% and 114% Lumefantrine concentrations respectively (Table 7) therefore both of them were above the upper limit of the et ranges yet the International Pharmacopoeia specifies that AL samples should contain not less than 90.0% and not more than 110.0% of the amount of artemether and lumefantrine stated on the label [7]. An assay for the different samples of LTR brands corresponding to brands obtained from the market was too done and the results for both artemether and lumefantrine assay for the LTR samples were obtained, recorded and presented in tables 8 (lumefantrine LTR assay) and 10 (Artemether LTR assay). The results of assay of brands from the market and their corresponding LTR were compared and recorded as consistent, inconsistent or inconclusive. Consistent meant there was similarity between the content assay for brand collected from the market and the corresponding brand sample from the LTR. Inconsistent meant there was a difference between the content assay for brand collected from the market and the corresponding brand sample from the LTR. Inconclusive meant that there was no conclusion taken on either consistency or inconsistency between the content assay for brand collected from the market and the corresponding brand sample from the LTR as there was no sample obtained from the LTR at the time of study.

Table 1: Lumefantrine Assay Results

BRAND CODE	BRAND NAME	Lumefantrine label Strength (mg)	Assay result (mg)	% Lumefantrine content	Conclusion (90-110%)
BAL1	Coartem (20/120)	120	120.0	100.0	Passed
BAL2	Lumaren (20/120)	120	116.4	95.3	Passed
BAL3	Lumartem (20/120)	120	120.0	100.0	Passed
BAL4	Lumiter (20/120)	120	120.0	100.0	Passed
BAL5	Lartem (20/120)	120	120.0	100.0	Passed
BAL6	Roart (20/120)	120	120.0	100.0	Passed
BAL7	Lariacte (20/120)	120	120.0	100.0	Passed
BAL8	Artefan (20/120)	120	114.4	95.2	Passed
BAL9	Komefan (20/120)	120	133.0	110.8	Fail
BAL10	Combiart 20/120	120	136.8	114.0	Fail
BAL11	Lonart (20/120)	120	120.0	100.0	Passed
BAL12	Artefan Dispersible (20/120)	120	120.0	100.0	Passed
BAL13	Artefan 60/360)	360	343.1	95.3	Passed
BAL14	Artefan (80/480)	480	457.0	95.2	Passed
BAL15	Lumerex (80/480)	480	480.0	100.0	Passed
BAL16	Comether (20/120)	120	119.0	99.2	Passed

Table 2: LTR Lumefantrine Assay Results

LTR BRAND CODE	NAME	Content (mg)	Content (%)	Conclusion	Remark
LTR1	Coartem (20/120)	120.0	100.0	Passed	Consistent
LTR2	Lumartem (20/120)	116.4	95.3	Passed	Consistent
LTR3	Lumartem (20/120)	120.0	100.0	Passed	Consistent
LTR4	Lumiter (20/120)	120.0	100.0	Passed	Consistent
LTR5	Lartem (20/120)	120.0	100.0	Passed	Consistent
LTR6	Roart (20/120)	120.0	100.0	Passed	Consistent
LTR7	Lariacte (20/120)	120.0	100.0	Passed	Consistent
LTR8	Artefan (20/120)	114.4	95.2	Passed	Consistent
LTR9	Komefan (20/120)	119.0	99.2	Passed	Inconsistent
LTR10	Lonart (20/120)	120.0	100.0	Passed	Consistent
LTR11	Artefan Dispersible (20/120)	120.0	100.0	Passed	Consistent
LTR12	Artefan 60/360)	343.1	95.3	Passed	Consistent
LTR13	Artefan (80/480)	457.0	95.2	Passed	Consistent
LTR14	Lumerex (80/480)	480.0	100.0	Passed	Consistent
LTR15	Comether (20/120)	119.0	119.0	Passed	Consistent

BAL10 missing in LTR assay because it was not at the local technical representative at the time of the study

Table 3: Artemether assay results

BRAND CODE	BRAND NAME	Artemether label Srength (mg)	Assay result(mg)	% Lumefantrine content	Conclusion (90-110%)
BAL1	Coartem (20/120)	20	20.00	100	Passed
BAL2	Lumaren (20/120)	20	19.88	99.4	Passed
BAL3	Lumartem (20/120)	20	20.00	100.0	Passed
BAL4	Lumiter (20/120)	20	22.04	110.2	FAIL
BAL5	Lartem (20/120)	20	20.00	100.0	Passed
BAL6	Roart (20/120)	20	20.68	103.4	Passed
BAL7	Lariacte (20/120)	20	21.00	105.0	Passed
BAL8	Artefan (20/120)	20	20.56	102.8	Passed
BAL9	Komefan (20/120)	20	19.84	99.2	Passed
BAL10	Combiart 20/120	20	18.20	91.0	Passed
BAL11	Lonart (20/120)	20	20.00	100.0	Passed
BAL12	Artefan Dispersible (20/120)	20	20.00	100.0	Passed
BAL13	Artefan 60/360)	60	61.68	102.8	Passed
BAL14	Artefan (80/480)	80	80.24	100.3	Passed
BAL15	Lumerex (80/480)	80	80.00	100.0	Passed
BAL16	Comether (20/120)	20	17.96	89.8	FAIL

Table 4: Artemether LTR Assay Results

LTR BRAND CODE	NAME	Content (%)	Content (mg)	Conclusion	Remark
LTR1	Coartem (20/120)	100.0	20.00	Passed	Consistent
LTR2	Lumartem (20/120)	99.4	19.88	Passed	Consistent
LTR3	Lumartem (20/120)	100.0	20.00	Passed	Consistent
LTR4	Lumiter (20/120)	100.0	20.00	Passed	Inconsistent
LTR5	Lartem (20/120)	100.0	20.00	Passed	Consistent
LTR6	Roart (20/120)	103.4	20.68	Passed	Consistent
LTR7	Lariacte (20/120)	105.0	21.00	Passed	Consistent
LTR8	Artefan (20/120)	102.8	20.56	Passed	Consistent
LTR9	Komefan (20/120)	99.2	19.84	Passed	Consistent
LTR10	Lonart (20/120)	100.0	20.00	Passed	Consistent
LTR11	Artefan Dispersible (20/120)	100.0	20.00	Passed	Consistent
LTR12	Artefan 60/360)	102.8	61.68	Passed	Consistent
LTR13	Artefan (80/480)	100.3	80.24	Passed	Consistent
LTR14	Lumerex (80/480)	100.0	80.00	Passed	Consistent
LTR15	Comether (20/120)	95.0	19.00	Passed	Inconsistent

BAL10 missing in LTR assay because it was not at the local technical representative at the time of the study

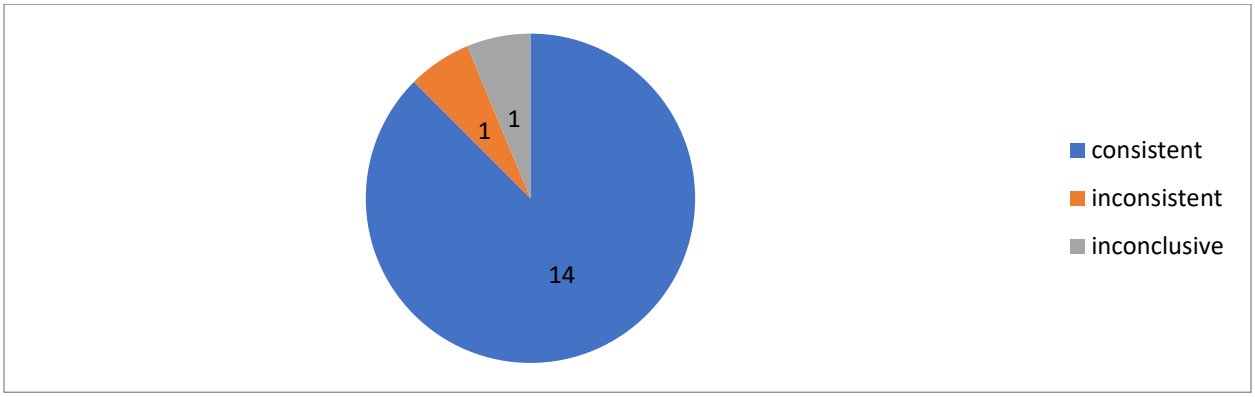

Figure 1: Frequency of Lumefantrine content similarity between brands collected from the market compared to those from LTR

Consistent: means there was similarity between the content assay for brand collected from the market and the corresponding brand sample from the LTR.

Inconsistent: means there was a difference between the content assay for brand collected from the market and the corresponding brand sample from the LTR.

Inconclusive: No conclusion taken on either consistency or inconsistency between the content assay for brand collected from the market and the corresponding brand sample from the LTR as there was no sample obtained from the LTR at the time of study.

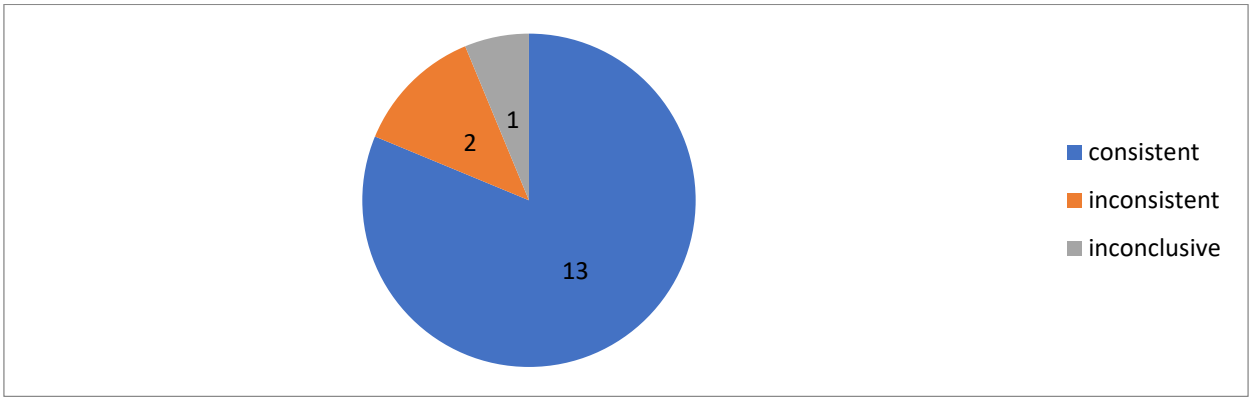

Figure 2: Frequency of Artemether content similarity between brands collected from the market compared to those from LTR

Consistent: means there was similarity between the content assay for brand collected from the market and the corresponding brand sample from the LTR.

Inconsistent: means there was a difference between the content assay for brand collected from the market and the corresponding brand sample from the LTR.

Inconclusive: No conclusion taken on either consistency or inconsistency between the content assay for brand collected from the market and the corresponding brand sample from the LTR as there was no sample obtained from the LTR at the time of study.

DISCUSSION

Out of the 16 brands in the study, 15 brands (94%) passed the artemether assay for all those that were collected from the market including BAL10 that was obtained from the field but not existent at the LTR and only one brand BAL16 failed the artemether assay at 89.8% of declared artemether content of 20mg as it was at 17.96mg (Table 9). For Lumefantrine assay, out of the Out of the 16 brands in the study, 14 brands (88%) passed the Lumefantrine assay except two brands (12%) that is BAL9 and BAL10 that failed the Lumefantrine assay that had 110.8% and 114% Lumefantrine concentrations respectively (Table 7) therefore both of them were above the upper limit of the set ranges yet the International Pharmacopoeia specifies that AL samples should contain not less than 90.0% and not more than 110.0% of the amount of artemether and lumefantrine stated on the label [12]. In all instances of assay failure, this is unacceptable because of the role artemether plays in this combination.

Artemether has a rapid effect on asexual erythrocytic stages and sexual gametocyte stages of the plasmodium parasite [13]. Through its effects to prevent gametocyte development, the drug is able to inhibit plasmodial transmission [14]. Therefore, low levels of artemether in the tablets as seen in batch one are associated with sub-optimal drug exposure resulting in incomplete elimination of the parasite biomass and subsequent recrudescence (The Worldwide Antimalarial Resistance Network (WWARN) DP Study Group, 2013). All these outcomes are very vital driving forces for the selection of parasites with reduced drug susceptibility [15-20]. Also overdosing can lead to drug toxicity and numerous adverse drug reactions which in turn may lead to death [15-20].

The failure to obtain one of the brands that was obtained from the market at the stipulated LTR raises a concern that is for BAL10 and its failure for Lumefantrine assay further raises more negative concerns where it was at 114% of the declared Lumefantrine concentration. This may imply that the private sector which is the main chain of medicine distribution in the country may be accessing antimalarials from an illegal market hence the need for more stringent regulation and inspection by the NDA. The total failure for the batches of brands for assay was 18% that, this percentage failure rate and the different reasons that could be leading to this need to be addressed promptly ranging from manufacture where the GMP may be is not followed to substandard and counterfeit medicines accessing the market and poor storage conditions.

Some of the factors that may have affected the quality of these antimalarials on market include; non-compliance of the manufactures with established Good Manufacturing Practices, storage conditions, insufficient regulatory performance and irregular inspection by the National regular authorities [15-20].

All batches collected from the Local technical representatives passed both Artemether and Lumefantrine assay test. Three brands collected from the market failing the assay test yet the ones obtained from the LTR passed the assay raises numerous concerns. These brands were BAL9 & BAL10 that failed Lumefantrine assay and BAL4 & BAL16 that failed Lumefantrine assay. The inconsistency in the assay results between brands obtained from the market and their correspondents from the LTRs maybe imperative of the following reasons like drugs on the general market could be reaching the market from unauthorised sources that are not LTR. Not only that but this may be due to poor storage at the adjacent premises on the market as poor storage can lead to degradation of the APIs in the drug formulation. Unfortunately, the storage conditions of these different brands were not evaluated in this study. Besides poor storage and drugs probably reaching the market from unauthorised sources, failure may also give an insight that counterfeits or substandard drugs are on the market. Having substandard and counterfeit medicines of unproven safety, efficacy and effectiveness possesses a serious negative health risk to the general population as with unproven safety this may result into undesired drug effects or even death.

CONCLUSION

The total assay failure of the brands of 18% for the AL tablets purchased t cannot be ignored. Also unregistered antimalarial agents exist in Ugandan drug market. These findings should give an insight to NDA to enhance post-market quality surveillance of not AL but for all drugs and health supplies in the country (Table 7, 8, 9 &10).

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