Journal Of Pharmacy And Pharmacological Research Vol. 3(1) pp. 11 - 21 August 2013
Available online http://www.globalresearchjournals.org/journal/jppr

Full Length Research.

Substandard rifampicin based anti-tuberculosis drugs common in Ugandan drug market.

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Accepted 30th May 2013.

Background: Tuberculosis (TB) is an important curable infectious disease in Uganda; its treatment however is facing a challenge of increasing drug resistance. Although Rifampicin containing Fixed-Dose Combination (R-FDC) drugs are a mainstay in TB treatment, about 1/5 are reportedly substandard in the global drug market.
Aim: To determine the quality of R-FDC and rifampicin single formulation anti-TB drugs in Kampala city, Uganda.
Method: Eight private and five public pharmacies were randomly selected, and drug samples purchased or obtained free of charge respectively. Drug quality was assessed using visual inspection, weight uniformity, dissolution, and assay.
Results: Fifteen batches of anti-TB drugs were collected, 13 R-FDC and 02 rifampicin single formulations. One batch of R-FDC collected from a public pharmacy was not assayed as it had passed its expiry date by the time of analysis. Of the samples analyzed, six batches of R-FDC and two of rifampicin single formulations were purchased from private pharmacies. The other six batches of R-FDC were obtained from public pharmacies. Ten samples (10/14: 71.4%) were not in the National Drug Register (NDR) of which eight were R-FDC and two rifampicin single formulations. Of the R-FDC drugs, four samples (4/12: 33.3%) failed the assay test and all were not in the NDR. All the R-FDC drug samples passed the dissolution, visual and weight uniformity tests. All rifampicin single formulations passed assay, visual, and weight uniformity tests while one failed the dissolution test.
Conclusion: Unregistered and sub-standard rifampicin anti-TB drugs are common in drug outlets in Ugandan drug market**.**

Key words: Rifampicin, Fixed-Dose Combination, Post-market quality, Drug quality, Assay**.**

Introduction

Tuberculosis (TB) is the world's leading curable infectious killer disease (WHO, 2008). The WHO estimated global TB prevalence as 14.4 million with the incidence of 363/100,000 population and 355/100,000 population in Africa and Uganda respectively (WHO, 2008). Uganda being one of the most highly TB burdened countries of the world is faced with the challenge of drug resistance to TB treatment. In a previous study by Bertzel, (1999), the reported rate of Multi-Drug Resistant TB (MDR-TB) in Uganda was 4.4 % in patients with a history of prior treatment and 0.7 % in patients with no history of prior treatment. A number of factors contribute to development of resistance to TB medications. Among these factors is substandard quality of TB medications and lack of patient supervision (Pecoul, 1999; Panchagnula, 2004).

Rifampicin (3-[4-methyl-1-piperazinyl] iminomethyl rifamycin SV) is a semi synthetic macro cyclic antibiotic derived from *Streptomyces mediterranei* (Martindale, 2002). It is one of the most effective anti-tuberculosis agents available and is bactericidal for both intra- and extra-cellular bacteria (Chambers, 2001).

In spite of the increased use of FDC drugs in TB treatment, initiatives by the global bodies such as WHO to combat TB through their use face challenges due to the reported presence of poor quality FDC anti-TB drugs on the global drug market (Pillai *et al*., 1999). A study by

Laserson, 2001 showed that 21% of rifampicin containing FDC anti-TB drugs is substandard in the global drug market. In a study done in Nigeria by Taylor *et al.*, (2001), 33% of rifampicin single-drug formulations supplied by Nigerian pharmacies were substandard. The quality of drugs in many less developed countries is inadequate (Behrens *et al.,* 2002). The market quality of rifampicin containing FDC anti-TB drugs have been of concern with respect to the poor bioavailability of rifampicin, and its instability (Pillai *et al.,* 1999).

This therefore calls for routine quality assessment of TB medications in the market to ensure that TB patients take drugs of acceptable quality if good treatment outcomes are to be assured.

In this study, we evaluated the quality of rifampicin containing FDC and single formulation anti-TB drugs sampled from pharmacies in Kampala city Uganda.

MATERIALS AND METHODS

Chemicals, reagents and anti-TB drugs

Rifampicin containing FDC anti-TB drugs registered in Uganda were obtained from the Human drug register of National Drug Authority (NDA). The rifampicin standard was a donation from the National Drug Quality Control Laboratory (NDQCL) of NDA. Acetonitrile (HPLC-grade) and methanol (pro analysis), were obtained from Scharlau Chemie; Spain. Potassium dihydrogen orthophosphate, Sodium hydroxide and ortho-phosphoric acid were obtained from Merck gmbH (Darmstadt, Germany). All other chemicals were analytical grade and were used without purification.

Study design and sample collection

This was a cross-sectional study. The study drugs were purchased from registered private dispensing pharmacies, and obtained free of charge from National Tuberculosis and Leprosy Program (NTLP)-TB treatment centers in Kampala city, Uganda. The drug outlets, private pharmacies and government TB treatment centers were randomly selected. The study was approved by the Makerere university faculty of medicine research ethics committee and the Uganda National Council for Science and Technology.

The number of drug outlets from which the drugs were sampled was calculated according to the World Health Organization (1999), Operational guide for National tuberculosis control Program (Hogerzeil, 1997). For a country wide drug survey, the minimum number of private drug outlets from which drugs are to be collected should be twenty (20) and forty (40) for government centers.

The formula, $S_a = Px20$ where, S_a is the number of the private pharmacies to be sampled in the city, and $P = n_1/n$ where, n_1 is the number of private pharmacies in the city (328) and n is the number of private pharmacies in the country (620); 20, is the minimum number of private pharmacies to be selected (WHO, 1999). And $Sa = Px40$ where, S_a is the number of public pharmacies to be sampled in the city, and $P = n_1/n$ where, n_1 is the number of public pharmacies in the city (36) and n is the number of public pharmacies in the country (113); 40, is the minimum number of public outlets to be selected (WHO, 1999).

The drugs were to be collected from eleven (11) private pharmacies and thirteen (13) public pharmacies at National Tuberculosis Treatment Program centers (NTLP-TB) selected using simple random sampling method.

Instrumentation and chromatographic conditions

The chromatographic analysis was carried out using a Schimadzu LC system (Hitachi, Japan) equipped with a photometric detector, a standard flow cell, a quaternary pump with a degasser, an auto sampler and column oven with Class-VP Ver. 6.1 software. The analytical column was an ODS1 (4.6 x 250 mm, 5µm, Waters, Ireland). The Mobile phase consisted of 40% acetonitrile in sodium phosphate buffer. The buffer was made by weighing and dissolving 1.4g of anhydrous dibasic sodium phosphate in 1 liter of distilled water. The pH was then adjusted to 6.8 using ortho-phosphoric acid 85%. The absorbance was monitored at 238 nm and elution was carried out at room temperature using a flow rate of 1.00 mL per min. Run time was set at 12 minutes.

Preparation and analytical procedure

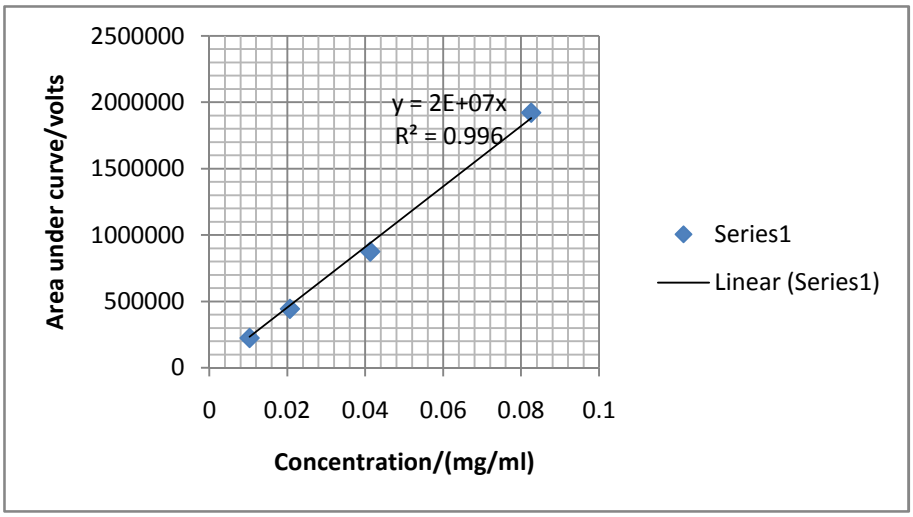
Twenty tablets or capsules were randomly picked from each sample and individually weighed. All the tablets were finely powdered together using a motor and pestle, or all the capsules contents were emptied and thoroughly mixed in a motor. An amount of the powder equivalent to 25mg of rifampicin was weighed in each case and dissolved in 50ml of the mobile phase. The mixture was sonicated for 10 minutes and the resultant solution was filtered. Two milliliters of the filtrate was separately transferred and diluted in two 25ml volumetric flasks with mobile phase. Ten microliters from each of the diluted solutions were injected into the chromatographic system. 10µl of the freshly prepared standard solution were injected in duplicate on each day of analysis. Fresh stock solutions of the samples and standards were prepared in a dark room. The drug samples were also analyzed in duplicate. Drug assays were performed in the department of Pharmacology and Therapeutics Makerere University.

Standards and calibration procedure

Rifampicin standard was prepared by weighing 25.8mg and dissolve in mobile phase using 50ml volumetric flask. The mixture was sonicated for ten (10) minutes and resultant solution filtered. 2 ml of the filtrate was diluted with mobile phase in a 25 ml volumetric flask.

A calibration curve with four calibration points was generated on each day of analysis and a regression equation with the slope, intercept and correlation coefficient (r^2) was generated using Microsoft excel program. The curve was used for calculating the drug concentrations.

Figure 1: Calibration curve



R^2 : Slope of the curve. Scale: vertical; 01 small square is equivalent to 100000 volts, Horizontal; 01 small square is equivalent to 0.004mg/ml of rifampicin.

Weight uniformity

Tablets

Twenty (n = 20) tablets were randomly selected from the different blister or strip packs of one sample and individually weighed using the analytical balance. The mean, standard deviation and percentage (%) Relative Standard Deviation (RSD) of the twenty tablets was calculated using Excel. The sample passed weight uniformity test if not more than two weights of the twenty individual tablets had more than 5 percent RSD (B.P 2009; U.S.P 32, 2009). This procedure was repeated for all the samples that were of tablet formulation.

Capsules

An intact capsule was randomly selected from the blister packs of the sample and weighed using the analytical balance. The capsule was then opened without losing any part of the shell and all the content emptied. The shells were then separately weighed. The weight of the content was the difference in the weight of the shell and the intact capsule. This was repeated for another nineteen randomly selected capsules of the same sample. The mean, Relative Standard Deviation (RSD) was calculated using Excel. The sample passed if not more than two weights of the twenty individual capsules had more than 5.0 percent RSD (B.P 2009; U.S.P 32, 2009). This procedure was repeated for all the samples that were of capsule formulation.

Drug dissolution

Six vessels of the electro lab tablet tester USP (XXIII) were filled with 900mls of 0.1M HCl solution and allowed to equilibrate at 37± 0.5°C. Rifampicin FDC tablets or capsules of each sample were each placed in six baskets. The baskets were then each fixed on six separate metallic rods corresponding to the six vessels. The metallic rods with the baskets were then lowered into the vessels until the baskets were fully submerged in the dilution medium and then rotated at 100rpm for 45 minutes. After 45 minutes the metallic rods automatically stopped rotating and 25mls of the medium in each vessel withdrawn from the middle of the vessel and filtered. The filtrate was left to equilibrate to room temperature for ten (10) minutes.

Dilution of the drug solutions (filtrate) for absorbance reading was done in accordance with Lambert beer's law. The dilutions of the filtrate were made in 50ml volumetric flasks. The required volume of the filtrate was transferred using a pipette to the flask then 10.0mls of potassium phosphate buffer was added and the flask filled to the mark with 0.1M HCl. The absorbances of the solutions were measured using a spectrophotometer at a wavelength of 475nm.

Absorbance of a corresponding concentration of the rifampicin standard prepared at the same time was also measured and percentage drug (rifampicin) dissolution calculated using the formulae below in accordance with Lambert beer's law. A sample passed the test if not less than 80.0 percent of the drug (rifampicin) goes into solution after 45 minutes (B.P 2009 and U.S.P 32, 2009).

Preparation of Rifampicin standard for dissolution test

Rifampicin reference substance (16.7mg) was weighed and transferred into a 50-ml volumetric flask. The powder was dissolved with 10ml of 0.1M HCl, sufficient amount of 0.1M HCl was added up to the mark. The solution was then sonicated for 45 minutes. The resultant solution was filtered discarding the first 5-ml of the filtrate. The filtrate was left to equilibrate to room temperature for 10 minutes. A quantity of the filtrate was transferred using a pipette and diluted in 50ml volumetric flask using 10.0mls of potassium phosphate buffer and 0.1M HCl. The dissolution test was done in Kampala Pharmaceutical Industries (1996) Uganda.

Table 1: Dilutions of rifampicin standard and quantities of the drug sample solutions used in the dissolution test

Rifampicin standard Weight taken (16.7mg)	Drug dilutions made based on rifampicin label claim 150mg	450mg	600mg
$\frac{16.7}{50} x \frac{4mls}{50}$	-	$\frac{450}{900} x \frac{2.5mls}{50}$	$\frac{600}{900} x \frac{10mls}{50} x \frac{10mls}{50}$
$\frac{16.7}{50} x \frac{5mls}{50}$	$\frac{150}{900} x \frac{10mls}{50}$	-	-

Formulae used in calculations

The percentage (%) drug content of the samples was calculated using a formula as per BP 27, 2009 and USP 32, 2009 specifications .

$$\text{Percentage (\%) drug content} = \frac{\text{AUC (Sample)}}{\text{AUC (Standard)}} \times \frac{\text{Concentration of standard}}{\text{Concnetration of sample}} \times \text{Potency of standard} \times 100$$

Where; AUC: Area under the Curve, and Potency of standard: 100%

The percentage rifampicin dissolution in the samples was calculated using a formula as per USP 32, 2009

$$\%\ dissolution = \frac{Absorbance\ (sample)}{Absorbance\ (standard)} \times \frac{Concentration\ (standard)}{Concentration\ (sample)} \times Potency\ of\ std\ x\ 100$$

Where; Absorbance of the standard = 0.455nm, (for dilution of 150/900 x 10/50) and 0.563nm (for dilution of 450/900 x 2.5/50 and 600/900 x 10/50 x 10/50). Potency of (Std) standard= 100 percent.

Results

The drugs were purposively purchased from eight (8) instead of eleven (11) private pharmacies since the batches already sampled from previous pharmacies were being encountered in subsequent pharmacies. The drugs were also collected from five (5) NTLP-TB treatment centers instead of thirteen (13) because at the time of drug collection there was drug stock outs in most NTLP-TB treatment centers in Kampala city. These were the only national TB treatment centers in the city that had drugs at the time and were located in each of the five administrative divisions of Kampala city.

Fifty (50) tablets or capsules per batch was purchased from private pharmacies and obtained free of charge from the NTLP-TB treatment centers. All the drugs were collected in black polythene bags and kept in clean dry drawers at room temperature in the laboratory in the department of pharmacology and therapeutics until analysis. Each batch of the rifampicin containing FDC anti-TB drugs in the market was collected only once from either the private pharmacies or NTLP-TB treatment centers in Kampala.

A total of 15 rifampicin containing formulations were sampled. Two samples were single formulation rifampicin capsules obtained from private pharmacies, one originated from East Africa and the other from Asia. Thirteen samples were FDC containing rifampicin, comprising of two-drug (6), three-drug (2) and four-drug (5) formulations, of which only, 12 FDC formulations were analyzed as one had reached expiry before analysis could be done. Most of the FDC drug samples (9/12, 75.0%) analyzed in this study were manufactured from Asia with only a few (3/12, 25.0%) manufactured from East Africa. Of the collected drug samples, 10/15 (66.7%) were not found in the National Drug Register (NDR), comprising of eight FDC and the two single formulations (Table 2). All the samples however passed visual inspection and weight uniformity tests with all the samples having less than 5.0% relative standard deviation (Table 3).

Table 2: Details of the rifampicin single-dose and Fixed Dose Combination formulation anti-tuberculosis drugs collected .

No.	Sample code	Registered In NDR	Stated APIs	Label Amount of APIs (mg)	Pharmacopeia standard label	Manufacture date	Expiry date	Origin
1.	A02T	Yes	R/H	150/100	B.P	08/2008	07/2011	Asia
2.	A03T	No	R/H	150/100	B.P	06/2007	05/2010	E.Africa
3.	A04T	Yes	R/H	150/100	B.P	08/2007	07/2010	Asia
4.	A05T	Yes	R/H	150/100	B.P	11/2007	10/2010	Asia
5.	A06T	No	R/H/Z/E	150/75/400/275	B.P	10/2006	09/2009	Asia
6.	A07T	No	R/H/Z/E	150/75/400/275	B.P	11/2007	10/2009	Asia
7.	B09T	No	R/H	600/300	U.S.P	03/2008	02/2010	Asia
8.	B10C	Yes	R/H	450/300	U.S.P	07/2007	06/2010	Asia
9.	B11T[a]	No	R/H/Z/E	150/75/400/275	U.S.P	07/2008	06/2010	Asia
10.	B12T[a]	No	R/H/E	150/75/275	U.S.P	05/2007	04/2009	Asia
11.	B13T[a]	No	R/H/Z/E	150/75/400/275	U.S.P	07/2008	06/2010	E.Africa
12.	B14T[a]	No	R/H/Z/E	150/75/400/275	U.S.P	07/2008	06/2010	E.Africa
13.	B15T[b]	Yes	R/H/E	150/75/400/275	U.S.P	04/2007	03/2009	Asia
14.	AS01C	No	R	150	B.P	04/2008	03/2011	E.Africa
15.	AS08C	No	R	300	B.P	08/2008	07/2011	Asia

A: Samples purchased from the private pharmacies in Kampala. B: Samples donated by the National Tuberculosis and Leprosy Treatment Program tuberculosis treatment centers in Kampala.
T - Tablets, C- Capsules, R - Rifampicin, H - Isoniazid, Z - Pyrazinamide, E - Ethambutol, B.P - British Pharmacopeia, U.S.P - United States Pharmacopeia, APIs: Active Pharmaceutical Ingredients, NDR – National Drug Register.
[a] These were drug samples labeled 'Ministry of Health' of a neighboring country.
[b] This drug sample was not analyzed since it had passed its expiry date by the time of analysis.

Table 3: Weight uniformity test results of the rifampicin containing Fixed Dose Combination tablet and capsule formulations

No.	Sample code	Mean weights (n = 20)/g	Standard deviation($x10^{-2}$)	Percentage RSD	Verdict
1.	A02T[c]	0.5	0.6	1.2	Pass
2.	A03T[c]	0.5	1.0	2.0	Pass
3.	A04T[c]	0.5	0.5	1.0	Pass
4.	A05T[c]	0.5	0.5	1.0	Pass
5.	A06T[e]	1.1	1.5	1.4	Pass
6.	A07T[e]	1.2	1.5	1.3	Pass
7.	B09T[c]	1.4	6.5	4.6	Pass
8.	B10C[c]	0.8	1.2	1.5	Pass
9.	B11T[e]	1.1	0.9	0.8	Pass
10.	B12T[d]	0.8	0.7	0.9	Pass
11.	B13T[e]	1.1	0.6	0.5	Pass
12.	B14T[e]	1.1	0.9	0.8	Pass

A - samples purchased from private pharmacies, B - Samples donated by the National Tuberculosis and Leprosy Treatment Program tuberculosis treatment centers in Kampala. T- Tablet, C - Capsule, S - Single dose capsules, RSD - Relative Standard Deviation. Sample passes the weight uniformity test if the percentage RSD is less than 5%
[c] Two drug combination (RH), [d] Three drug combination (RHE), [e] Four drug combination (RHZE),

Content and dissolution test results

Four (4/12: 33%) R-FDC anti-TB drug samples failed the assay test. All the samples that failed quality test were not in the National Drug Register. One of the samples that failed the assay test was from the NTLP-TB treatment center while the other three were from the private pharmacies. Of the samples which failed, three were 4-drug FDC samples of Asian origin purchased from private pharmacies, while the fourth was a 2-drug FDC sample manufactured from a neighboring East African country. Three failed samples had rifampicin content below the lower limit of 90.0%, while the fourth had more than the upper limit of 110.0% (Table 4). Of the R-FDC, the dissolution test was only performed on the 2-drug FDC samples and all passed, while of the single-formulation rifampicin capsules, one which was of East African origin failed the dissolution test.

Table 4: Content Test results of rifampicin analysis from the Fixed Dose Combination formulation samples

Sample No.	Sample code	Rifampicin label claim (mg)	Assayed rifampicin content (mg)	Content as % label claim	Verdict
1.	A02T[c]	150	165.0	110.0	Pass
2.	A03T[c]	150	169.5	113.0	Fail
3.	A04T[c]	150	151.4	100.9	Pass
4.	A05T[c]	150	140.9	93.9	Pass
5.	A06T[e]	150	124.8	83.2	Fail
6.	A07T[e]	150	118.4	78.9	Fail
7.	B09T[c]	600	619.4	102.7	Pass
8.	B10C[c]	450	462.2	102.7	Pass
9.	B11T[e]	150	111.5	74.3	Fail
10.	B12T[d]	150	155.4	103.6	Pass
11.	B13T[e]	150	156.0	104.0	Pass
12.	B14T[e]	150	158.9	105.9	Pass

A - samples purchased from private pharmacies in Kampala District, B - Samples donated by the National Tuberculosis and Leprosy Treatment Program tuberculosis treatment centers in Kampala. T - Tablet, C – Capsules, [c] Two drug combination (RH),
[d] Three drug combination (RHE),
[e] Four drug combination (RHZE),
Sample passed content test if the content as percentage of the label claim was between 90% – 110% (BP and USP 2009 specifications). All the samples that failed were not in the National Drug Register.

Rifampicin Single- formulation capsules

Two samples of rifampicin single- drug capsules (150mg and 300mg) were tested for percentage rifampicin dissolution. A dissolution test result of one sample was less than 80.0 percent; hence it failed the test as per B.P specifications (Table 5).

Table 5: Percentage dissolution of rifampicin single- drug capsules

Sample no	Sample code	Stated active ingredients	Percentage (%) dissolution			Pass/Fail (NLT 80.0 %, B.P)
			Lowest value	Median value	Highest value	
1.	AS01C	R (150mg)	71.6%	74.6%	96.7%	Fail
2.	AS08C	R (300mg)	83.7%	86.4%	87.8%	Pass

S: Single dose, C: Capsules, R: Rifampicin, NLT: Not Less Than, B.P: British Pharmacopoeia.

Chromatograms for Rifampicin standard and the different R-FDC anti-tuberculosis drugs

Figures 2, 3, 4, and 5 show the chromatograms of the standard and some of the various R-FDC anti-tuberculosis drugs that were analyzed in this study. The peak that was consistently eluting between 3-4 minutes could not be identified in this study since our interest was rifampicin which eluted between 5-6 minutes.

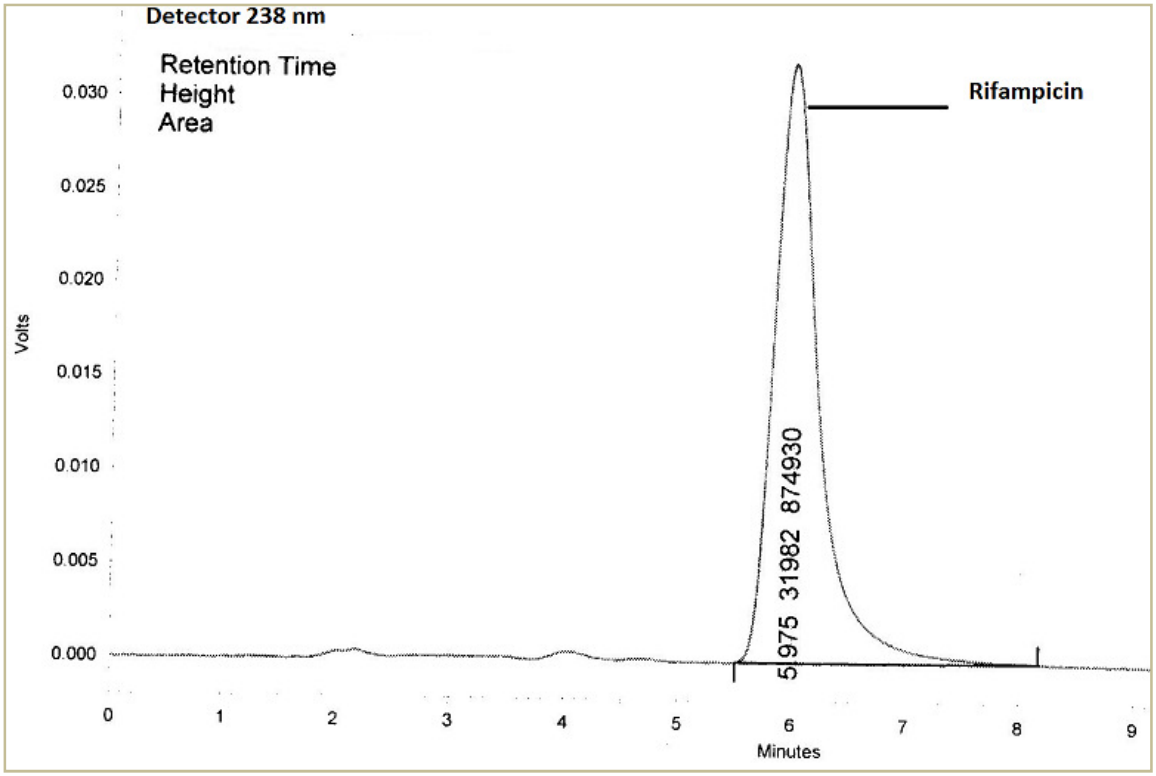


Figure 2: Rifampicin Standard chromatogram

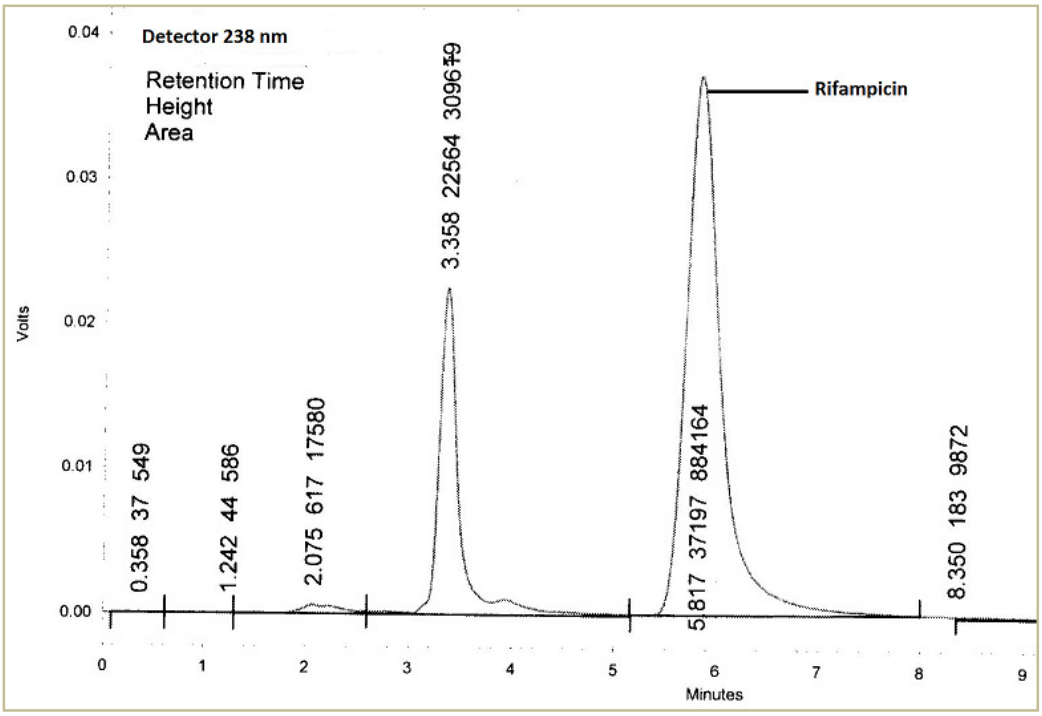


Figure 3: Two drug R-FDC (B09T) chromatogram

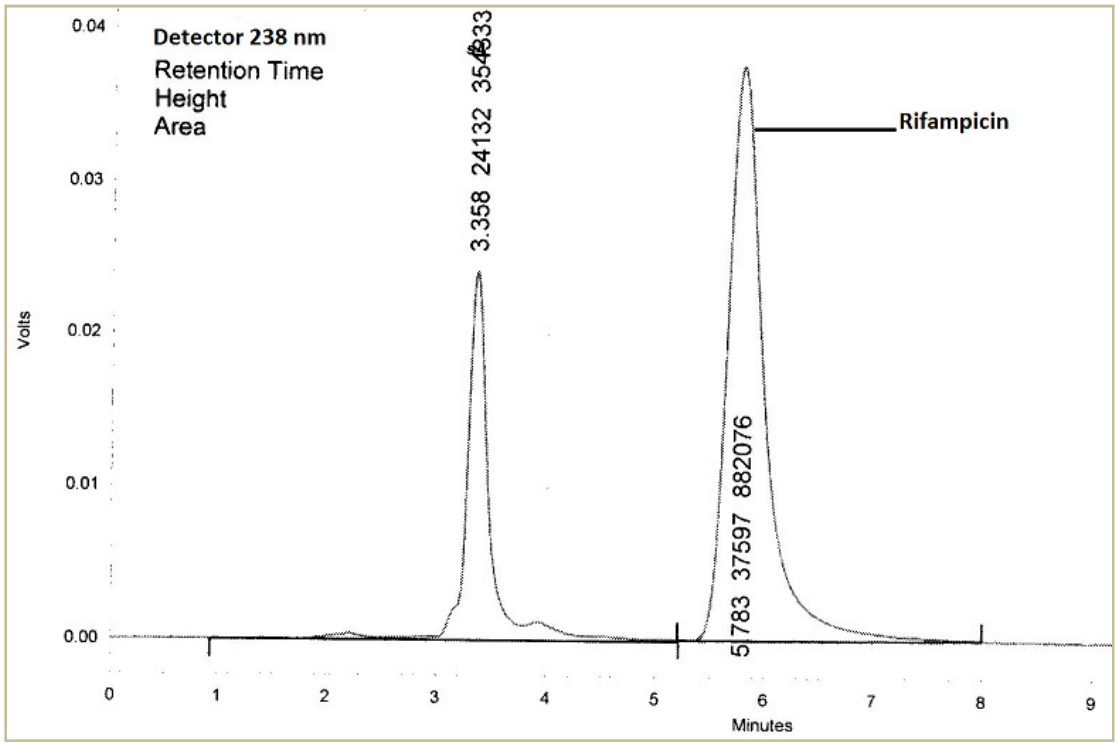


Figure 4: Three drug R-FDC (B12T) chromatogram

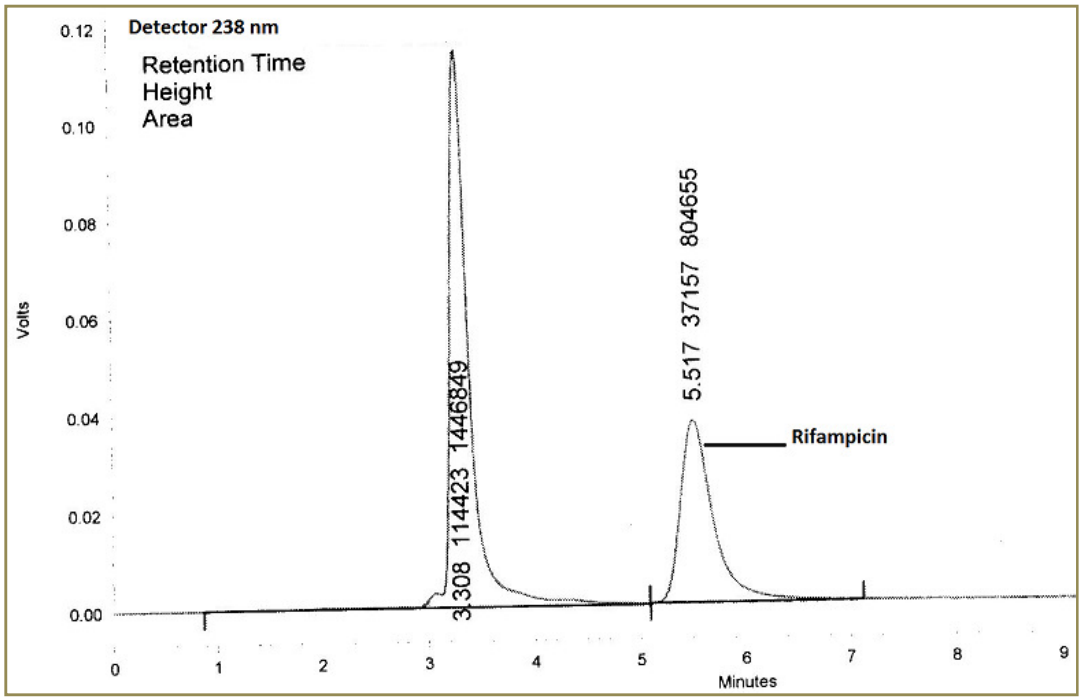


Figure 5: Four drug R-FDC (B11T) chromatogram

Discussion of results

The findings from this study showed that most rifampicin containing FDC anti-TB drugs in Kampala are mainly manufactured in Asia and they constituted the majority of drugs not found in the National Drug Register. This finding should be of concern to the National drug regulatory body since it clearly shows that these drugs are able to find their way into the Ugandan drug market by-passing the regulatory system. The risks these unregistered drugs pose cannot be understated since they also constituted the drug samples that were declared of poor quality. The proportion of poor quality FDC anti-TB drugs (33.3%) in this study surpassed what had been found in the world market, 21% in a study by Laserson, (2001) and in a Nigerian study by Taylor *et al*., (2001).

One of the R-FDC samples that failed the quality test was obtained from the NTLP-TB treatment center in Kampala however it was a donation to Uganda from the national government of a neighboring East African country. This brings into focus the dilemma of drug donations (Hogerzeil, 1997). The decision to allow these donated drugs to go into circulation through the national TB treatment centers could have been on the premise that the donating country had proof of their quality. This however in no excuse as to why the drugs should not have been tested for quality before their distribution to the treatment centers.

While the use of single formulation rifampicin is discouraged (WHO, 1999), the fact that they are readily available on sale in the private pharmacies is an indicator that they are in use probably for other indications other than for tuberculosis. Furthermore, they were not registered and one of them failed the quality test should raise a lot of concern not only for the regulating authorities but also for the TB patients and the general population. The possible drug pressure from use of these single formulations in other conditions would directly contribute to emergence and acceleration of resistance to rifampicin, as there are already reports of multidrug resistant tuberculosis in Uganda (Bertzel, 1999). The unsuspecting tuberculosis patients who take these drugs for other indications could be unduly exposing the TB causative organisms to sub-therapeutic rifampicin concentration as a result of taking these substandard drugs.

The findings of this study define the state of the drug market in the country as Kampala is the major Centre for drug importation and distribution to other parts of the country. The possibility of the porous nature of the

boarders may have contributed to the free entry of unregistered and substandard drugs into the Ugandan drug market, as all the drugs that failed the quality tests were those that were not on the National Drug Registry. This should raise concern for the population and the policy makers. However the fact that all the drug formulations passed the visual inspection test is an indication that these were probably genuine products, but the poor quality formulations raise issues of the manufacturing processes.

While WHO emphasizes that anti-TB drugs should not be sold in the private sector due to their lack of patient supervision (Panchagnula, 2004). During the sample collection, the study team was alarmed to note that anti-TB drugs could be purchased from the private pharmacies without a prescription, a practice that undermines any efforts to regulate the use of these drugs exclusively in patients diagnosed with tuberculosis. Substandard anti-TB drugs coupled with lack of patient supervision in the private sector are a twin challenge which should raise specific attention from drug regulatory bodies both locally and internationally if the risk and spread of resistance development is to be checked.

The study findings showed that 4-drug R-FDCs were more likely to have substandard rifampicin content than the other R-FDC drugs. The more number of drugs incorporated in a fixed dose combination the higher is the likelihood of compromised quality, a finding similar to what other researchers reported from the global drug market (Bhutani, 2004; Singh, 2003). Previous studies have attributed the frequent occurrence of substandard rifampicin content in 4-drug and 3-drug FDCs to the presence of ethambutol in the formulations, which creates an environment that causes rifampicin to be degraded in the presence of isoniazid (Singh, 2001; Sankar, 2003). However, bad formulations due to poor manufacturing practice are more likely to be the reason for the poor quality products found in this study. This is supported by the findings that some 2-drug FDC and single formulation rifampicin products also failed the quality test. While the low rifampicin content in the FDC drugs pose risk of resistance development in patients and in the general population (Panchagnula, 2004; Long, 1979), it would however be most tragic if the single formulation of rifampicin is still being used for treatment of patients with tuberculosis in the private sector. This is because of lack of patient monitoring in the private sector exposing them to risks of inadequate treatment (Blomberg, 2001).

Conclusion and recommendations

In Ugandan drug market, unregistered and sub-standard R-FDC anti-TB drugs are commonly accessed from both the private sector and national TB treatment centers**.**

Acknowledgement

We acknowledge the support of the National Drug Quality Control Laboratory of Uganda for sharing the process of quality control. Mr. Ochana Godfrey and Mr. Owuori Sam, staff Quality Control laboratory of Kampala Pharmaceutical Industries, and the laboratory staff of the Department of Pharmacology and Therapeutics Makerere University for assistance during the analysis of the samples. Ethical clearance was obtained from the College of Health Sciences Research and Ethics Committee and permission to conduct the research was obtained from the Uganda National Council for Science and Technology.

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