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Quality Surveillance of Anti-Tuberculosis Medicines in Tanzania, 2012-2018

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Abstract

Background: The use of substandard and falsified (SF) anti-tuberculosis (ant-TB) medicines may lead to treatment failure and development of drug resistance. SF medicinal products are claimed to be more prevalent in developing countries with high burden of tuberculosis disease. National Medicines Regulatory Authorities therefore, should ensure that the quality of these life-saving medicines is systematically monitored. We conducted a post marketing surveillance study to determine the quality of anti-tuberculosis medicines circulating on the market in Tanzania Mainland.

Methods: This was a prospective cross sectional study conducted between 2012 and 2018. Purposive sampling technique was used in collecting a total of 777 samples of anti-tuberculosis medicines. Samples were collected from ports of entry, Medical Stores Department (MSD) and healthcare facilities in 16 regions of Tanzania Mainland. All collected samples were subjected to quality screening using Global Pharma Health Fund® (GPHF) Mini-Lab kits. Only samples collected from MSD and healthcare facilities were subjected to product information review. Samples collected from MSD and healthcare facilities that did not comply with GPHF protocol requirements or yielded doubtful results and ten percent (10%) of all those that complied were subjected to tier II confirmatory testing using full pharmacopoeia monographs at the Tanzania Medicines and Medical Device (TMDA) Quality Control Laboratory which is prequalified by the World Health Organization.

Results: All 777 collected samples complied with the requirements of both GPHF minilab protocol and respective compendial monographs when subjected to screening and confirmatory testing, respectively. Of the samples collected from medicine distribution outlets 71.3% (176/247) samples did not comply with product information requirements as per TMDA labelling requirements and approved product information.

Conclusion: These Results calls for continuously reinforcing and monitoring of Ant-TB medicines to ensure that only those of good quality and proper information are circulating on the Tanzanian mainland market.

Keywords: Post marketing surveillance; Medicines quality; Substandard; Falsified; TLC screening; Tuberculosis

Introduction

Tuberculosis (TB) is an airborne and contagious disease which is among the top ten causes of death worldwide [1]. In 2017, TB accounted for over 1.3 million deaths [1]. Africa is the most affected region contributing to over 85% of the highest incidence rates while half of all new cases are in Asia [2]. Tuberculosis is a third major cause of morbidity and mortality among adults in Tanzania after HIV/AIDS and Malaria [2]. Over 65,000 cases were reported in 2016 in Tanzania compared to 62,000 in the previous year an increase which drastically overstretch the already weakened existing health systems [3].

The use of medicines of acceptable quality and the provision of a standardized multi-drug regimen for the treatment of active TB patients under direct observation are two essential components of combating TB [4,5]. However, a worldwide increase in resistance to anti-TB drugs, threatens the success of this strategy [6,7]. Over 558,000 people worldwide developed TB which is resistant to rifampicin and the majority of these had multi-drug resistant TB (MDR-TB) [2]. Apart from use of substandard medicines, drug resistance may develop through various other factors including poor patient adherence to treatment and poor clinical or program management [4,6,8].

The extent of substandard anti-TB drugs has not been established because the countries with the greatest burden of TB are the same countries where quality assurance laboratory facilities are still at infant stage to effectively allow testing for substandard and falsified medicines (SF) [2,8,9]. SF medicinal products including anti-TB agents still constitute a worldwide problem in low and middle income countries as well as in the industrialized world [7,8,10,11].

In 2006, it was reported that up to 10% of medicines circulating in the Russian Federation market were falsified and 70% were manufactured domestically [6]. The most common

quality problems reported among anti-TB medicines were due to inadequate content of the active ingredient and poor bioavailability particularly for rifampicin both in mono-component products and fixed dose combinations (FDC) [5-7,11-15].

This study therefore reports the cumulative outcome of the implementation of a structured TMDA post marketing surveillance program of registered anti-TB medicines, for samples collected and tested between 2012 and 2018.

Methods

Sampling

Purposive sampling technique was used to collect samples from port of entries (POEs), Medical Stores Department (MSD) and healthcare facilities (health centers and hospitals) in 16 regions of Tanzania Mainland. The 16 regions were chosen because of either bordering other countries, being highly populated or having high burden of TB disease.

Sampling was conducted by trained and experienced drug inspectors. A sampling form was used to document the name of medicine, batch number, manufacturing and expiry date, date of collection and place, storage conditions and unit pack size for each sample collected. Each sample was specifically coded, separately packed in a designated bag, sealed and stored according to the manufacturers recommended storage conditions at TMDA zone offices before being transported to TMDA headquarters for quality evaluation.

Quality evaluation

Product information review: Prior to further laboratory analysis, all samples collected from health centers, hospitals and MSD were subjected to product information review (PIR). Each sample was examined on physical appearance, information on primary and secondary packaging and availability of package insert and information based on TMDA labeling requirements. The verified information included but not limited to product name, dosage form and strength of medicine, name and address of the manufacturer, batch or lot number, registration number, manufacturing and expiry date as well as language and information on patient information leaflet (PIL). Observations were documented in PIR results forms.

Screening by using GPHF Minilab Protocol kit: All collected samples were screened by using Global Pharma Health Fund (GPHF) Mini-Lab kit following a predetermined protocol. Evaluated parameters included visual inspection, simple disintegration and identification and semi-quantitative determination test by using Thin Layer Chromatography (TLC) method.

Visual inspection: The appearance of the dosage forms were examined for discoloration, breaking, leaking or excessive powder/tablets/capsules.

Simple disintegration test: This was carried out by using a 100 ml wide neck glass bottle filled with water heated to 37°C. A tablet was then introduced into the heated water, shaken occasionally for about 30 minutes. The procedure was repeated for other five tablets and those that required more than 30 minutes disintegrating were considered to have failed the test.

Thin layer chromatography: TLC method was used for qualitative determination of active ingredients, related substances and impurities present on the dosage forms. This method employed the principle of comparing spots test sample and reference solutions according to GPHF Minilab protocol. The principal spot obtained with the test sample was required to correspond with the chromatographic runs of the standard solution in terms of colour, shape, size, intensity and retardation factor (Rf) value. The test sample was considered failed if the Rf value of the test sample was different by more than 10% from that of the standard sample.

Confirmatory testing: All samples collected from the targeted supply chain that did not comply or their results were deemed doubtful and 10% of all that complied with the quality evaluation by using GPHF minilab kit were subjected to confirmatory testing against the respective pharmacopoeial monographs. Testing was done at the TMDA Quality Control Laboratory which has been prequalified by the World Health Organization (WHO). Parameters tested for solid dosage forms included appearance, identification, assay and related substances/impurities, dissolution and mass variation. For liquid dosage forms parameters tested were appearance, identification, microbial limit, pH and assay.

Results

Samples collected

A total of 777 anti-TB samples were collected from targeted sampling points between January 2012 and December 2018. A total of 31.8% (247/777) were sampled from distribution outlets such as Medical Stores Department (MSD) in Dar es Salaam and health centres and hospitals located in Iringa, Morogoro, Mtwara, Kagera, Singida, Rukwa, Geita, Kilimanjaro, Tanga, Coastal, Kigoma, Dar es Salaam, Mwanza, Simiyu, Manyara and Mbeya regions of Tanzania Mainland. Details on the number and specific medicinal products collected has been provided in **Table 1**. The remaining 68.2% (530/777) samples were collected from PoE as part of quality assurance programme as depicted in **Figure 1**.

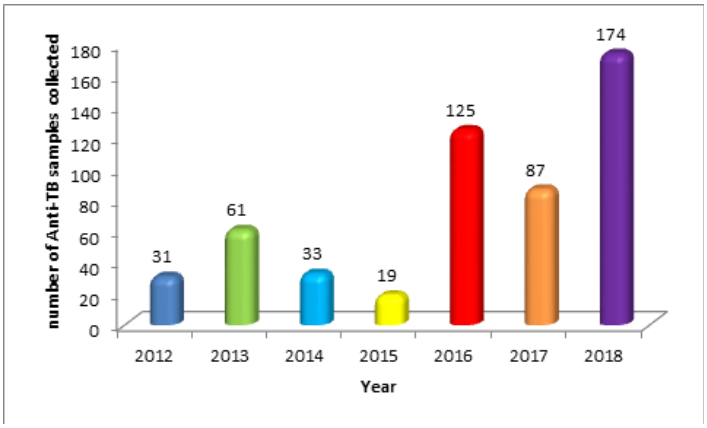

Figure 1: Samples of Anti-TB collected from port of entry between 2012 and 2018

Table 1: Anti-tuberculosis products collected from different distribution outlets in Tanzania Mainland (2012-2015)

Product	2012	2013	2014	2015	Total
Streptomycin Sulphate powder for injection	28	0	0	8	36
Isoniazid tablets	0	0	8	0	8
Rifampicin/Isoniazid tablets	56	0	14	13	83
Rifampicin/Ethambutol tablets	0	0	0	1	1
Rifampicin/Isoniazid/Pyrazinamide tablets	8	0	7	0	15
Rifampicin/Isoniazid/Ethambutol tablets	29	0	0	6	35
Rifampicin/isoniazid/Pyrazinamide/Ethambutol tablets	36	0	19	14	69
Total	157	0	48	42	247

Product information review

Samples collected from distribution outlets were evaluated for compliance with TMDA labelling requirements on the primary and secondary packaging material as well as respective packaging inserts [16,17]. On average, 71.3% (176/247) of the samples did not comply with labelling and packaging insert requirements as summarized in **Table 2** However, the high percentage of failure in the average was contributed by the very high failure in 2012. Main deficience observed during evaluation included lack of instructions on appropriate storage conditions, TMDA registration number, name and address of the manufacturer of the product on label. In some cases, there were no package insert in the product package (Table 2).

Table 2: Product information review evaluation for samples collected between 2012-2015 from medicine distribution outlets

Year	Evaluated	Complied	Not complied	% non-compliance
2012	157	6	151	96.2
2013	0	0	0	0
2014	48	35	13	27.1
2015	42	30	12	28.6
Total	247	57	176	71.3

Sample screening

All samples complied with evaluated parameters as per GPHF protocol requirements in terms of identification and semi quantitative determination by using TLC, physical inspection and simple disintegration test [7].

Confirmatory testing

All 46 samples selected for confirmatory testing based on criteria prescribed above, complied with the evaluated parameters as per the International Pharmacopoeia [18,19] requirements.

Discussion

The sampling was done according to sampling plan which prescribed the respective regions, sampling sites as well as the number of samples per brand. Other requirements such as the integrity of samples and handling after collection are prescribed in the post marketing surveillance (PMS) program standard operating procedure. Out of 293 samples planned to be collected from the distribution outlets, over the span of four (4) years of implementation, 247 (84%) were collected.

The overall performance in PIR as per TMDA regulations was not complying in 2012 whereby about 96% of all samples did not comply with TMDA requirement in this aspect. However, over the years the situation has improved significantly as shown in **Table 2**. The observed decrease in non-compliance could be ascribed to improvement brought about by regulatory actions that are taken after each post marketing surveillance as well as implementation of harmonized marketing authorization requirements in the region. These results are also consistent with PIR results for other medicine categories surveyed under TMDA PMS programmes [20-23]. The compliance of all 247 samples with the evaluated GPHF minilab protocol requirements is in-line with reported performance in the previous year reports in terms of identification and semi quantitative determination by using TLC, physical inspection and simple disintegration test [20].

Furthermore, the compliance of all 46 samples to the respective pharmacopeia monograph requirements was equally similar to PMS results for the period between 2009–2013 [19]. These results suggest that, the anti-tuberculosis agents were of acceptable quality and that the implemented TMDA quality assurance systems including marketing authorization and post marketing surveillance programs are effective.

Conclusion

These results suggest that the anti-TB medicines that were circulating on Tanzanian market for the period under study were of acceptable quality. However, the lack of adherence to TMDA labelling requirements highlighted in this study need to be addressed. Adequate and clear information need to be provided to users, patient as well as healthcare providers to ensure rational use of the respective medicinal products. Adherence to labeling requirements is equally important in the detection of substandard and falsified medical products. Overall, results emphasize the need for continuous monitoring of quality of products on the market.

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