

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 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 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].

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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 [7-11].

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) [5-7,10-15].

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 drug, 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 [16-19].

Quality evaluation

Product information review: Prior to further laboratory analysis, all samples collected from health centres, 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 100ml 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 (R_f) value. The test sample was considered failed if the R_f 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 have been detailed in Table 1.

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 n/ Ethambutol tablets	0	0	0	1	1
Rifampicin n/ Isoniazid / Pyrazinamide tablets	8	0	7	0	15
Rifampicin n/ Isoniazid / Ethambutol tablets	29	0	0	6	35
Rifampicin / Isoniazid / Pyrazinamide/ Ethambutol tablets	36	0	19	14	69
Total	157	0	48	42	247

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

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.

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 deficiencies 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.

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

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

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 requirements [8].

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 failed in this aspect. But progressively as years went by the situation 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 consistent with PIR results for other medicine categories in the implementation of PMS programmes [20-22].

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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 labeling 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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REFERENCES

1. Kato K, Sawada M, Nishimura Y. Bypassing stroke-damaged neural pathways via a neural interface induces targeted cortical adaptation. *Nat Commun.* 2019;10(1):4699.
2. Houwink A, Nijland RH, Geurts AC, Kwakkel G. Functional recovery of the paretic upper limb after stroke: who regains hand capacity? *Arch Phys Med Rehabil.* 2013;94(5):839-844.
3. Ethier C, Oby ER, Bauman MJ, Miller LE. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature.* 2012;485(7398):368-371.
4. Bouton CE, Shaikhouni A, Annetta NV, Bockbrader MA, Friedenberg DA, Nielson DM, et al. Restoring cortical control of functional movement in a human with quadriplegia. *Nature.* 2016;533(7602):247-250.
5. Nishimura Y, Perlmutter SI, Fetzi EE. Restoration of upper limb movement via artificial corticospinal and musculoskeletal connections in a monkey with spinal cord injury. *Front Neurol.* 2013;7:57.
6. Kato K, Nishihara Y, Nishimura Y. Stimulus outputs induced by subdural electrodes on the cervical spinal cord in monkeys. *J Neural Eng.* 2020;17(1):016044.
7. Kirin SC, Yanagisawa T, Oshino S, Edakawa K, Tanaka M, Kishima H, et al. Somatosensation Evoked by Cortical Surface Stimulation of the Human Primary Somatosensory Cortex. *Front Neurosci.* 2019;13:1019.
8. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin D. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *2010;127:2893-2917.*
9. Adebamowo CA, Ajayi O. Breast cancer in Nigeria. *West Afr J Med.* 2000;19:179-191.
10. Augustus M, Adeyinka A, Chinyelu O, Chidinma M. Breast self examination among non-health professionals in Nigeria. *Nig J Sur Sci.* 2005;15:74-77.
11. Adetifa F, Ojikutu R. Prevalence and trends in breast cancer in Lagos State, Nigeria. *Nigeria. Afr Res Rev.* 2009;3.
12. Asay TP, Lambert MJ. The empirical case for the common factors in therapy: Quantitative findings. 1999.
13. Lin Y. The framework for integrating common and specific factors in therapy: A resolution. *Int J Psychol Couns.* 2016;8:81-95.
14. Okobia MN, Bunker CH, Okonofua FE, Osime U. Knowledge, attitude and practice of Nigerian women towards breast cancer: a cross-sectional study. *World J Sur Onco.* 2006;4:11.
15. Janz NK, Wren PA, Copeland LA, Lowery JC, Goldfarb SL, Wilkins E. Patient-physician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision. *J Clin Onco.* 2004;22:3091-3098.
16. Ukwenya A, Yusufu L, Nmadu P, Garba E, Ahmed A. Delayed treatment of symptomatic breast cancer: the experience from Kaduna, Nigeria. *South African J Sur.* 2008;46.
17. Sharma K, Costas A, Shulman LN, Meara J. A systematic review of barriers to breast cancer care in developing countries resulting in delayed patient presentation. *J Onco.* 2012.
18. Adisa A, Arowolo O, Akinkuolie A, Titiloye N, Alatishe O, Lawal O, et al. Metastatic breast cancer in a Nigerian tertiary hospital. *African Health Sciences.* 2011;11.
19. Ogundiran TO, Ayandipo OO, Ademola AF, Adebamowo C. Mastectomy for management of breast cancer in Ibadan, Nigeria. *BMC surgery.* 2013;13:59.
20. Azubuike SO, Celestina U. Breast cancer: The perspective of Northern Nigerian women. *International J Prev Med.* 2015;6.

21. Akanbi O, Adeoti M, Habeeb O, Idris O, Abiodun A, Ajiboye O. The Acceptance and the Perception of Mastectomy by Males whose Spouses are Diagnosed with Breast Cancer in South Western, Nigeria: Are male spouses an obstacle? *Nigerian Hospital Practice. Nig Hos Prac.* 2016;18:33-39.
22. Gumus M, Ustaalioglu BO, Garip M, Kiziltan E, Bilici A, Sekerm M, et al. Factors that affect patients' decision-making about mastectomy or breast conserving surgery, and the psychological effect of this choice on breast cancer patients. *Breast Care.* 2010;5:164-168.