PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania from 2005–2015: a retrospective review of data from the regulatory authority
AUTHORS	Mori, Amani; Meena, Estella; Kaale, Eliangiringa

VERSION 1 – REVIEW

REVIEWER	Dr. Ronald Kiguba Makerere University College of Health Sciences, Kampala, Uganda
REVIEW RETURNED	08-Feb-2018

GENERAL COMMENTS	Thank you for giving me the opportunity to review the manuscript entitled "The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania from 2005-2015: Implications for medicines regulatory policy". General comments This is a timely study on the costs of substandard and counterfeit medicines from a sub-Saharan African (SSA) setting. The paper is generally well written. Abstract Lines 30-32 (page 2): The statement 'The economic cost increased from 89.8 US$ in 2005 to 6.8 million US$ in 2014' should be modified or deleted as it seems to suggest that there was a consistent smooth increase in costs over the entire course of 10-years. Methods Lines 50-54 (page 5): The authors stated that data from the regulatory authority were complemented with data from importers and distributors. It would be interesting to know the kind of data obtained from the importers/distributors which were/were not available from the regulatory authority and vice versa. This would inform and/or prime future cost studies from similar resource-limited settings. Lines 3-5 (page 6): Why were unregistered medicines excluded from this review? SSA has a weak drug regulatory environment compounded by porous borders. Thus, unregistered medicines could constitute an important proportion of medicines circulating on SSA markets. It would have been interesting to know the proportion of unregistered medicines that are substandard and/or falsified and their associated costs. The authors may have reasons for this exclusion which they ought to articulate in this paper. Lines 18-22 (page 6): What proportion of costs were reported without details of identity and quantities? Lines 27-38) (page 6): The authors should provide more clarity regarding how other costs (especially transportation, disposal, court cases e.t.c.) were applied in computations/estimations. Results

	Lines 17-43 (page 7): Extra columns could be added to Table 1 to show proportionate (percentage) contribution of substandard and/or falsified medicines/cosmetics. Lines 52-53 (page 7): Improve statement to read 'Substandard medicines contributed two-thirds or more of total economic cost .....' Lines 12-13 (page 8): Which dosage forms contributed the largest proportion of costs associated with substandard and falsified medicines? Lines 9-12 (page 9): 'This may imply.....' Transfer sentence to the discussion section. Discussion What events occurred around 2011-2012 that could have caused the big leap in costs from 627,411 to 3.9 million US$? (Table 1). This was highlighted in bullet 4 of the summary (Lines 26-30 - page 3) but was ommitted in the Discussion section. Did the regulatory authority acquire new surveillance equipment or step up other surveillance activities? Or did the volume of imports into the country increase suddenly? The authors could have attempted to find out from the qualitative structured interviews with the regulators. Figures legends are missing. The Figure on page 17 should provide numerator and denominator data for the reader to place more meaning to the results.

REVIEWER	Atholl Johnston Queen Mary University of London, United Kingdom
REVIEW RETURNED	15-Mar-2018

GENERAL COMMENTS	Thank you for revising this submission. The additional information provided makes for a better manuscript.

VERSION 1 – AUTHOR RESPONSE

REVIEWERS COMMENTS
Comment 1: Abstract
Lines 30-32 (page 2): The statement 'The economic cost increased from 89.8 US$ in 2005 to 6.8 million US$ in 2014' should be modified or deleted as it seems to suggest that there was a consistent smooth increase in costs over the entire course of 10-years.

Response: We agree with reviewer’s comments; the sentence in question has been deleted.

Comment 2: Methods
Lines 50-54 (page 5): The authors stated that data from the regulatory authority were complemented with data from importers and distributors. It would be interesting to know the kind of data obtained from the importers/distributors which were/were not available from the regulatory authority and vice versa. This would inform and/or prime future cost studies from similar resource-limited settings.

Response: As we described in the paper, the main source of data was the regulatory authority’s confiscation and inspection report forms that were filed in its zonal and headquarter offices. However, some data forms were missing at the regulatory authority but there were copies at the importers and distributors offices. We have improved the text and now it reads as follows:
“We also used confiscation report forms from the importers and distributors of pharmaceuticals to complement data from the regulatory authority. This means, in case the report forms were not filed at the regulatory authority, copies that were available at the importers and distributors offices were used. We were careful to avoid double counting..”

Comment 3
Lines 3-5 (page 6): Why were unregistered medicines excluded from this review? SSA has a weak drug regulatory environment compounded by porous borders. Thus, unregistered medicines could constitute an important proportion of medicines circulating on SSA markets. It would have been interesting to know the proportion of unregistered medicines that are substandard and/or falsified and their associated costs. The authors may have reasons for this exclusion which they ought to articulate in this paper.

Response: We thank the reviewer again for this comment. Unregistered medicines do not undergo evaluation and approval by the regulatory authority. Hence once a drug is categorized as unregistered, it is not common for it to be categorized as falsified or substandard. For this reason, we did not include them in the cost analysis. We have now provided some explanations in the paper, which reads as follows:
Unregistered medicines do not undergo evaluation and approval by the regulatory authority; hence, together with the expired human medicines were not included in the cost analysis.

Comment 4
Lines 18-22 (page 6): What proportion of costs were reported without details of identity and quantities?

Response: As we mentioned in the paper, details on identity and quantities were not available mainly for cosmetics. We don't see how this information will add value to the paper, hence we opted not to include it.

Comment 5
Lines 27-38) (page 6): The authors should provide more clarity regarding how other costs (especially transportation, disposal, court cases etc.) were applied in computations/estimations.

Response: We agree with the reviewer's suggestions. We have improved the text that describes the additional costs that was added to medicine values and now reads as follows:
Once the yearly value of falsified medicines, substandard medicines and cosmetics with banned ingredients were estimated, we added the "other costs" which included the storage costs, transportation costs, cost of disposal and cost charges for court cases to arrive to the total cost for that year.

Comment
Lines 17-43 (page 7): Extra columns could be added to Table 1 to show proportionate (percentage) contribution of substandard and/or falsified medicines/cosmetics.

Response: We agree with the reviewer's suggestions, we have added the columns to show the proportions of the total cost in each year.

Comment
Lines 52-53 (page 7): Improve statement to read 'Substandard medicines contributed two-thirds or more of total economic cost .....'

Response: We thank the reviewer for this suggestion. We have improved the sentence and now it reads as:
"From 2011, substandard medicines contributed two-thirds or more of the total cost."

Comment

Lines 12-13 (page 8): Which dosage forms contributed the largest proportion of costs associated with substandard and falsified medicines?

Response: We thank the reviewer for this comment. Majority of falsified and substandard medicines were tablets/capsules, but we have realized that this was not clearly explained in the manuscript. Unfortunately, we did not categorize our analysis based on dosage forms because we felt it was not important. But we see the reviewer's point. We have now improved the results section and we have include quantities for each dosage form. The revised text reads as follows:

Quantities
Between 2005 and 2015, there was a total of 519,889,388 and 1,216,630 substandard and falsified human medicines, respectively, that were recorded. Dosage forms were tablets/capsules, suspensions and injections (vials/ampoules). Among the group of substandard medicines, quantities of antibiotics were 222,236,052 (66%), which included 160,087,188 tablets/capsules; 61,957,667 bottles and 191,197 vials/ampoules. (Figure 3). Among the most commonly used antibiotics that were identified are penicillin (83%), which included phenoxymethylpenicillin: 80,812,600 tablets and 65 bottles; amoxicillin: 495,677 capsules and 61,582,700 bottles; cloxacillin: 42,137,592 capsules and 2,766 bottles; co-trimoxazole (Sulfamethoxazole-Trimethoprim): 28,825,400 tablets and 110 bottles (13%); erythromycin 7,185,954 tablets (3%) and ciprofloxacillin: 623,265 tablets and 372,000 bottles (0.4%).

Among substandard medicines, quantities of antimalarials were 33,124,501 (10%), which included 33,032,825 tablets/capsules; 90,046 bottles and 1,630 vials/ampoules (Figure 3). Quantities of quinine were: 29,057,100 tablets, 24 bottles and 1,630 ampoules which accounted for 88%; sulfadoxine-pyrimethamine: 3,392,103 tablets and 83 bottles (10%); amodiaquine: 268,543 tablets, 42,400 bottles; Sulfamethoxypyrazine-Pyrimethamine (SP): 216,450 tablets and 10,764 bottles; SP/artesunate: 87,990 tablets; artemether/lumefantrine: 8,640 tablets and 36,775 bottles and chloroquine 2,000 tablets. The group named "Other" which accounted for 24% of substandard human medicines consist of many items including aminophylline 37,374,000 tablets and 2,930 vials (47%), paracetamol 17,413,300 tablets and 50,905 bottles (22%), diazepam 9,141,500 tablets (11%) and prednisolone 7,101,000 tablets (9%) etc.
For the group of falsified medicines, there were 819,660 tablets (67%) of antiretrovirals, followed with antimalarials and antibiotics 302,609 (25%) and 94,200 (8%), respectively (Figure 3). Other groups accounted for negligible percentage. All falsified antiretrovirals were a combination of stavudine, lamivudine and nevirapine tablets. Among falsified antimalarials, quantities of quinine tablets were 171,900 (57%); praziquantel-amodiaquine tablets 117,000 (39%); sulfamethoxypyrazine-pyrimethamine 11,704 tablets (4%), sulfadoxine-pyrimethamine tablets 1,501 (0.5%) and artemether-lumefantrine 504 tablets (0.2%). Falsified antibiotics included doxycycline capsules 68,000 and cloxacillin capsules 26,200.

As for cosmetics, there were 250 metric tons, 833.20 kilograms, 646 cartons and 1,476 items that were just recorded as 'different types of cosmetics'.

Comment
Lines 9-12 (page 9): 'This may imply.....' Transfer sentence to the discussion section.

Response: We have moved the sentence to the discussion part

Comment: Discussion
What events occurred around 2011-2012 that could have caused the big leap in costs from 627,411 to 3.9 million US$? (Table 1). This was highlighted in bullet 4 of the summary (Lines 26-30 - page 3) but was omitted in the Discussion section. Did the regulatory authority acquire new surveillance

equipment or step up other surveillance activities? Or did the volume of imports into the country increase suddenly? The authors could have attempted to find out from the qualitative structured interviews with the regulators.

Response: We thank the reviewer for this comment. The observed sharp increase in total costs from 2011 was noted after we have completed the data collection. We have discussed this in the limitations by adding the following sentence:
"Thirdly, we were not able to determine the reasons behind the increasing quantities and costs. However, we believe this could be due to improvement in regulatory capacity and public awareness rather than an absolute increase in the amount of poor-quality medicines and banned cosmetics."

In the conclusion it was also written that:
"The increase in the quantities identified and the economic cost of these products over time could partly be due to improved regulatory capacity in terms of human resources, infrastructure, frequency of inspections, implementation of post-marketing surveillance, establishment of more zone offices, and strengthened quality control laboratory with WHO prequalification. These improvements in addition to efforts by the authority and the government to increase awareness among stakeholders….."

Comment
Figures legends are missing. The Figure on page 17 should provide numerator and denominator data for the reader to place more meaning to the results.

Response: Figure legends were placed in the last page of the main manuscript. As of figure 3, we reported absolute numbers and hence we feel there is no need to include numerator and denominators. There is sufficient description in the text under subsection titled "quantities".

ADDITIONAL CHANGES
• We have added an acknowledgement sub-section on page 13 that reads as follows:
Acknowledgements
We thank the University of Bergen for providing open access publication fund to ATM. We also thank the Tanzanian Food and Drugs Authority and the involved importers and distributors of pharmaceuticals for their support in conducting the study.

• We have improved the results section of the abstract by adding some poor-quality medicines that are of common use. It reads as follows:
"…..Some of the identified substandard and falsified human medicines include commonly used antibiotics such as phenoxymethylpenicillin, amoxicillin, cloxacillin and co-trimoxazole; antimalarials such quinine, sulfadoxine-pyrimethamine, sulfamethoxypyrazine-pyrimethamine and artemether-lumefantrine; antiretroviral drugs; antipyretics and vitamins among others."

VERSION 2 – REVIEW

REVIEWER	Dr. Ronald Kiguba Makerere University College of Health Sciences
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	Comments adequately addressed.