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The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania from 2005–2015: Implication for medicines regulatory policy

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ABSTRACT

Objective: To estimate the economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania from 2005–2015.

Design: A retrospective review of data.

Setting: Tanzania Food and Drugs Authority and premises dealing with importations and distributions of pharmaceuticals.

Eligibility criteria: Confiscation reports of substandard human medicines, falsified human medicines and cosmetics with banned ingredients.

Primary and secondary outcome measures: Quantities and costs of pharmaceutical products, costs of transportation, storage, court cases and disposal of products.

Results: The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients was estimated at 16.2 million US$ i.e. substandard 13.7 million US$, falsified 0.2 million US$, cosmetics with banned ingredients 1.3 million US$ and other costs 1.1 million US$. Substandard medicines alone accounted for 84.6% of the total cost. The economic cost increased from 89.8 US$ in 2005 to 6.8 million US$ in 2014. The identified substandard and falsified human medicines include commonly used antibiotics, antimalarials, antiretroviral drugs, antipyretics and vitamins among others.

Conclusion: The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients represent a relatively large loss of scarce resources for a poor country like Tanzania. 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 and frequency of inspections.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study from a low-income country to use national representative data to estimate the economic cost of poor-quality medicines and cosmetics with banned ingredients over a ten-year period.
- We were able to identify the manufactures of substandard medicines and purported manufacturers for falsified medicines, which enabled us to isolate those whose products were more frequently found in the market.
- Some data particularly for cosmetics, were poorly recorded, which made it difficult to apply the proper costing approach of identification, quantification and valuation.
- The sharp increase in quantities and cost could be due to increased availability of data because of improved regulatory capacity and public awareness, as opposed to an absolute increase in the problem of poor-quality medicines and cosmetics.
- We were not able to include patient and health system costs for morbidities and mortalities associated with the use of poor-quality medicines and cosmetics with banned ingredients; hence, the study underestimates the actual economic cost.

INTRODUCTION

In June 2012, customs officials in Luanda-Angola seized a cargo with about 1.4 million packets of fake Coartem® (artemether-lumefantrine) hidden in loudspeakers. The cargo originated from Guangzhou in southern China, and the amount of fake antimalarials was estimated to be enough to treat more than half of all annual malaria cases in Angola [1]. This example highlights the problem of substandard and falsified medicines (defined in **Box 1**) and its potential public health impact. Substandard and falsified medicines represent about 10% of all medicines sold in low- and middle-income countries [2]. Expenditure on these products in low- and middle-income countries is estimated at 30.5 billion US$ [2]. Falsified medicines represent one of the most lucrative criminal business and is estimated to be worth between 75–200 billion US$ [3].

The use of substandard and falsified medicines and cosmetics with banned ingredients can have a tremendous negative impact on patient's health, that can range from serious harm to treatment failure that can lead to severe illness and death. It is estimated that between 90,000–200,000 malaria deaths could be prevented if all antimalarials were genuine [4, 5]. Sub-therapeutic plasma levels due to poor-quality medicines are strongly associated with emergence of antimicrobial resistance [6, 7], hence increasing costs of treatment by switching from cheap first-line medicines to more expensive second-line medicines. The pharmaceutical industry is also a victim of falsified medicines, with annual losses estimated to be 45 million Euros, which consequently reduces investments in innovative research and development [8].

Box 1: Definitions of substandard medicines, falsified medicines

Substandard medicines: According to WHO, these are genuine medicines that are authorized by the national medicines authorities, but which fails to meet national or international quality standards or specifications.

Falsified medicines: According to WHO, these represent deliberately and fraudulently labeled medicines with respect to identity, composition and source and may include products with the correct or wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging [9].

Low-income countries are the prime targets of substandard and falsified medicines because regulatory agencies and law enforcement systems are relatively weak, accompanied by poorly regulated markets, and scarcity and/or erratic supply of basic medicines [10, 11]. Porous borders and complex supply chain system of pharmaceuticals also contributes to the problem. There is scarcity of national level data from low-income countries despite all evidences pointing towards an increasing problem of substandard and falsified medicines. Therefore, the objective of this study was to estimate the economic cost of substandard and falsified human medicines including cosmetics with banned ingredients in Tanzania from 2005–2015.

METHODS

This costing study used an ingredient approach to estimate the economic cost of substandard and falsified human medicines and cosmetics with banned ingredients between 2005–2015. This method involves identification, quantification and valuation of individual items. Costing was done from the perspective of the regulatory authority and the pharmaceutical distributors. We did not include patient and health system costs because of scarcity of data on morbidities and mortalities likely to be caused by the use of these products.

Sources of data

We used data from the regulatory authority and the major importers and distributors of pharmaceuticals from 2005–2015. The regulatory authority usually keeps all the confiscation reports for poor-quality medicines and cosmetics that are collected during routine inspections of premises and major operations. The report usually contains among other information, the name of the premise, generic and brand names of the product, strength, physical description of the package and products, batch number, manufacturing and expiry dates as well as the quantities and sometimes an estimated value. Premises usually remain with the signed copy of the confiscation report. In this study we retrieved all the confiscation data that was available at the regulatory authority's headquarter and from its zonal offices. This data was complemented with that from the importers and distributors of pharmaceuticals and we were careful to avoid double counting. We also conducted a series of structured interviews with officials at the regulatory authority, importers and distributors to estimate operational cost incurred in the process of

confiscation, withdraw of products from the market, storage, disposal and court cases. Unregistered and expired medicines were not included.

Cost estimates

The study used the median buyer prices from the International Drug Price Indicator Guide (IDPIG) as a primary source of medicines prices and when they were not available the Medical Stores Price Catalogue of 2015/16 was used. In the absence of median buyer prices, the median supplier prices were used, with an inflation factor of 10% as recommended in the costing studies [12]. Prices from the IDPIG were inflated further by 10% to account for local opportunity costs. Cost was calculated by multiplying the tallied quantities with unit prices for item. In some cases, only the estimated value of the items in the local currency were reported without information about the identity and quantities and this was common for cosmetics. In this case the total value in the local currency was first converted to US$ by using relevant exchange rate for that year before adjusting to the present value using relevant consumer price indices.

In addition, the study included storage costs, transportation costs, cost of disposal and cost charges for court cases. We measured the storage space (m^2) which was multiplied by 10 US$/$m^2$ which was the rate of rental charge used for warehouses by the Tanzania National Housing Corporation (NHC) and reported by most distributors of pharmaceuticals. Yearly storage costs were obtained by multiplying monthly rental charges by 12. Storage costs for the importers and distributors was considered only for the year when there was an incident of confiscation of substandard or falsified medicine or cosmetics with banned ingredients.

Ethical considerations

Ethical approval was obtained from the research and publication committee of the Muhimbili University of Health and Allied Sciences (MUHAS). The regulatory authority also granted research permission and issued an official letter to all local importers and distributors requesting them to make the relevant data available to the researchers and assuring them that the data requested will be used for research purpose only. A consent form was provided to all the interviewees and signed prior to interviews.

RESULTS

Economic cost

The estimated economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania from 2005–2015 was 16.20 million US$. Substandard medicines contributed 13.65 million US$, falsified medicines 149,369 US$ and cosmetics with banned ingredients 1.29 million US$. Other costs that include transportation, storage, court cases and disposal contributed 1.09 million US$ (Table 1).

Table 1: Costs of the products and other associated costs

Year	Cost (US$)				
	Falsified	**Substandard**	**Cosmetics**	**Other cost**	**Total**
2005	33.3	56.5	0.0	0.0	89.8
2006	49.9	0.0	0.0	0.0	49.9
2007	63.8	19,424.4	162,478.8	51,720.9	233,688.0
2008	96.7	0.0	42,979.2	138,929.7	182,005.6
2009	1,701.6	58,032.3	180,158.7	97,782.9	337,675.5
2010	17.6	57,299.5	52,983.1	117,907.7	228,207.9
2011	1,676.4	398,474.0	123,347.6	103,913.3	627,411.3
2012	141,493.3	3,530,672.6	91,968.4	180,557.0	3,944,691.2
2013	2,129.9	1,808,340.3	131,273.7	149,425.8	2,091,169.6
2014	1,724.2	6,453,613.0	240,335.9	112,258.6	6,807,931.8
2015	382.7	1,326,139.4	265,326.6	134,143.4	1,725,992.1
Total	**149,369.3**	**13,652,052.1**	**1,290,852.0**	**1,086,639.3**	**16,178,912.7**

Between 2005 and 2011, the estimated annual economic cost increased from about 90 US$ to 0.63 million US$, with some fluctuation in between. The annual cost increased sharply to 3.94 million US$ in 2012, then dropped to about 2.09 million in 2014. The annual total cost rose again to 6.8 million US$ the following year (Figure 1). Substandard medicines contributed the highest proportion of total economic cost in 2005 and from 2011 to mid-2015, which range

between 63 to 95%. In 2006 only falsified medicines were recorded, while cosmetics with banned ingredients contributed the highest cost in 2007 and 2009 (Figure 2).

Quantities

Between 2005 to 2015, there was a total of 519,889,388 and 1,216,630 substandard and falsified human medicines, respectively. Dosage forms include tablets, capsules, oral suspensions and vials/ampoules for injections. Among the group of substandard medicines, quantities of antibiotics and antimalarials were 222,236,052 (66%) and 133,124,501 (10%), respectively (Figure 3). The group named "Other" which accounted for 24% of substandard human medicines consist of many items including aminophylline 47%%, paracetamol 22%, diazepam 11% and prednisolone 9%. Among the commonly used antibiotics that were identified are penicillins, which included phenoxymethylpenicillin, amoxicillin and cloxacillin 83%, co-trimoxazole (Sulfamethoxazole/ Trimethoprim) 13%, erythromycin 3% and ciprofloxacillin 0.4%. Among antimalarials, quinine accounted for 88% and sulfadoxine-pyrimethamine 10%.

For the group of falsified medicines, there were 819,660 tablets (67%) of antiretrovirals containing Stavudine/Lamivudine and Nevirapine, followed with antimalarials and antibiotics 302,609 (25%) and 94,200 (8%), respectively (Figure 3). Among falsified antimalarials quinine and artemether-lumefantrine tablets were 171,900 (57%) and 504 (0.2%), respectively. Falsified antibiotics were only doxycycline capsules 68,000 and cloxacillin capsules 26,200.

Manufacturers of substandard and purported manufacturers of falsified medicines

Table 2 shows generic names of medicines and the coded names of manufactures of substandard medicines and purported manufacturers of falsified, which were repeatedly circulating in Tanzania between 2005–2015. Phenoxymethypenicillin, ciprofloxacillin, prednisolone, diazepam and salbutamol from manufacturer N were identified over several years implying consistent failure to meet Good Manufacturing Practice standards. The same was seen for manufacturer E, M and B for quinine, paracetamol and aminophylline, respectively.

The same observation was also made for falsified medicines, in that falsified products bearing the name of the same purported manufacturer were consistently found on the market over several years. Example quinine and Sulphamethoxypyrazine/Pyrimethamine from manufacturer C and H, respectively, were identified circulating in the market over 3 years. This may imply that the culprits were not caught and continued to release the product into the market for several years, the sanctions were not deterrent, or the inspection and confiscation were not effective.

Table 2: Manufacturers of commonly identified poor-quality medicines

Substandard medicines (Manufacturers)	**Year**							
	2005	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Phenoxymethylpenicillin				N	N	N		
Ciprofloxacillin				N	N			
Quinine					E		E	
Prednisolone			N	N	N	N		
Paracetamol					M			M
Diazepam				N	N	N		N
Aminophylline							B	B
Salbutamol				N	N	N		
Falsified medicines (Purported manufacturers	**Year**							
	2005	**2008**	**2009**	**2011**	**2012**	**2013**	**2014**	**2015**
Quinine tablets	B				C	B, C, D	C, D, E	B, C
Sulphamethoxypyrazine/Pyrimethamine			H	H, B		H, B		K
Sulfadoxine/Pyrimethamine					E, I, J	E	C, J	
Halofantrine Hydrochloride	A					A		
Artemether/Lumefantrine		F		F				
Dihydroartemisinin/Piperaquine		G	G					

* Letter code represents a name of manufacturer or purported manufacturer

DISCUSSION

It is difficult to estimate the actual economic cost of substandard and falsified medicines in any country not least in a low-income setting because data are usually not available [13]. However, using data from the regulatory authority, pharmaceutical importers and distributors we were able to estimate this burden in Tanzania. Our findings show that the estimated economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania between 2005–2015 was 16.20 million US$. Generally, the economic burden shows an increasing trend and the substandard medicines contribute the largest proportion of the total costs. The estimated economic cost represents 0.24% of the GDP, which is relatively large considering that Tanzania is one of the poorest countries in the world.

Based on the existing data, our analysis shows that there were large quantities of substandard and less falsified human medicines in Tanzania over the past ten years. This include commonly used inexpensive antibiotics such as phenoxymethypenicillin, amoxicillin, cloxacillin, erythromycin, sufamethoxazole/trimethoprim; antimalarials such as quinine, sufadoxine-pyrimethamine, sulphayrazime/pyrimetahmine and antiretrovirals among others. Use of poor-quality medicines is one of the main causes of antimicrobial resistance, which was recently declared by WHO as a major global public health threat as it causes treatment to be difficult and more expensive [2, 14]. Several studies have reported high levels of antibiotic resistance in Tanzania especially for commonly used and cheap antibiotics [15-18], which has prompted the government to develop a national action plan to curb antimicrobial resistance [19].

Policy implications

The quantities and the economic cost of substandard and falsified human medicines including cosmetics with banned ingredients in Tanzania over the past ten years is alarming. Policy-makers in Tanzania need to improve the existing post-marketing surveillance (PMS) and pharmacovigillance (PV) system for effective prevention, detection and response to poor-quality products, adverse effects and other medicines-related health and economic problems. An effective PMS and PV systems are essential components of any healthcare system. However, in low-income countries including Tanzania such systems are weak or non-existent, hence health

problems associated with the use of substandard and falsified medicines such as adverse reactions, ineffective treatment or even death often go undetected.

The government and policy makers need to provide more resources to the regulatory authorities in Tanzania to enhance supervision and inspection to ensure integrity of the supply chain of pharmaceuticals both in the public and the private sectors. Limited access to affordable essential medicines in the public health system has resulted in the opening of a large number of private retail pharmacies and small accredited drug dispensing outlets in the country, which have proved very difficult to control [20]. As a consequence, malpractices are common including selling medicines without prescriptions, stocking medicines from unofficial sources, poor documentation and hiring of people without the required qualifications, making them the prime target for the business of substandard and falsified medicines [13].

The fact that some substandard and falsified human medicines from certain manufacturers were confiscated over several years raise a more serious concern. This was observed for example for falsified quinine tablets purporting to be from manufacturer B and C, and sulphamethoxypyrazine/pyrimethamine tablets mimicking that of manufacturer H. There could be several reasons behind this; first it could indicate a sign of insufficient inspection or ineffective removal of the product from the market. Secondly, it could be that the products were easy to be falsified and smuggled into the country; thirdly, poor compliance with Good Manufacturing Practices and lastly it could also imply that the culprits were not identified, or if identified the sanctions were not deterrent, hence continued to supply the products.

Strengths and limitations

To the best of our knowledge, this is the first study to systematically combine data retrieved from the regulatory authority, importers and distributors of pharmaceuticals to estimate the economic cost of substandard and falsified medicines and cosmetics with banned ingredients in a low-income country. The data also facilitated the identification of the manufactures of substandard medicines and manufacturers whose products were falsified, which enabled us to isolate those whose products were repetitively found circulating in the market. However, this study has several limitations. Firstly, we did not have morbidity and mortality data to facilitate the inclusion of patient and health system costs associated with the use of poor-quality medicines

and cosmetics with banned ingredients. This means our study underestimates the actual economic cost of these products. Secondly, some data was poorly recorded, which made it difficult to follow the proper costing procedure of identification, quantification and valuation.

CONCLUSION

The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients represent a relatively large loss of scarce resources for a low-income country like Tanzania. 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 could have positive and sustainable impact in the longer term. However, proliferation of retail drug outlets that are difficult to regulate and ineffective control of many porous borders will continue to be a challenge to the regulatory authority. Policy-makers should make the fight against substandard and falsified medicines a national priority agenda, including development of national strategies and action plans.

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Competing interests

None

Contributors

ATM and EK conceived the idea of the study; ATM, EM and EK designed the study. EM collected the data. ATM and EM analyzed the data. ATM and EM wrote the first draft of the manuscript. All authors approved the final version of the manuscript.

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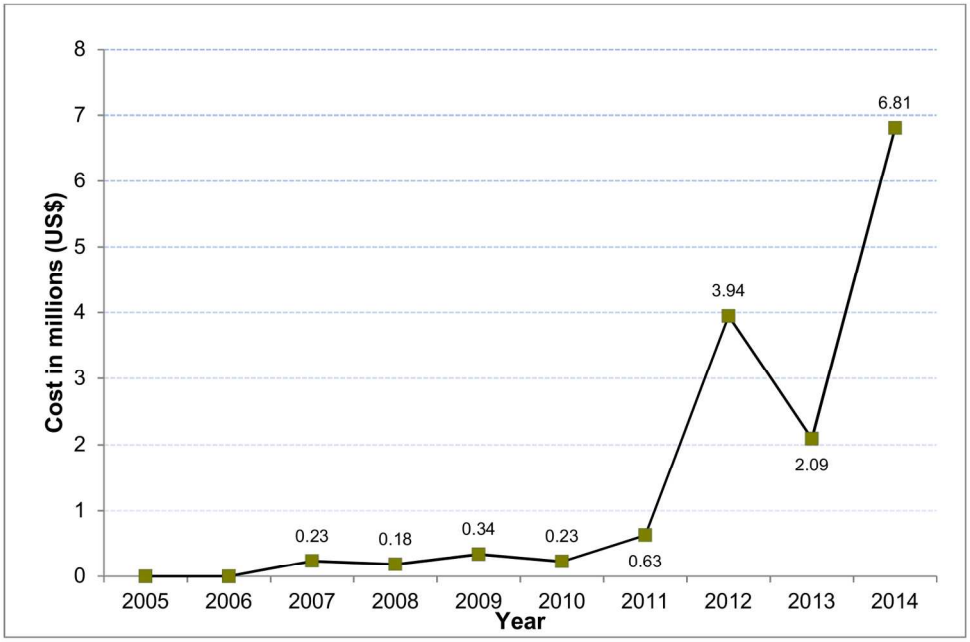
Figure 1: Estimated annual economic cost between 2005–2015

Figure 2: Relative contributions of the products to the total economic cost in Tanzania, 2005–2015

Figure 3: Quantities of poor-quality medicines in Tanzania, 2005-2015



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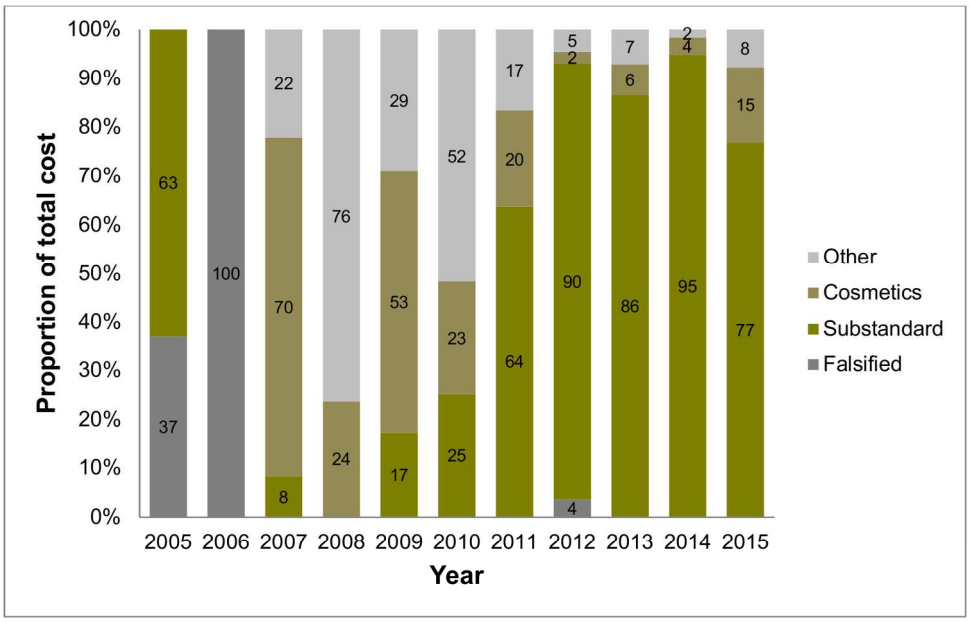

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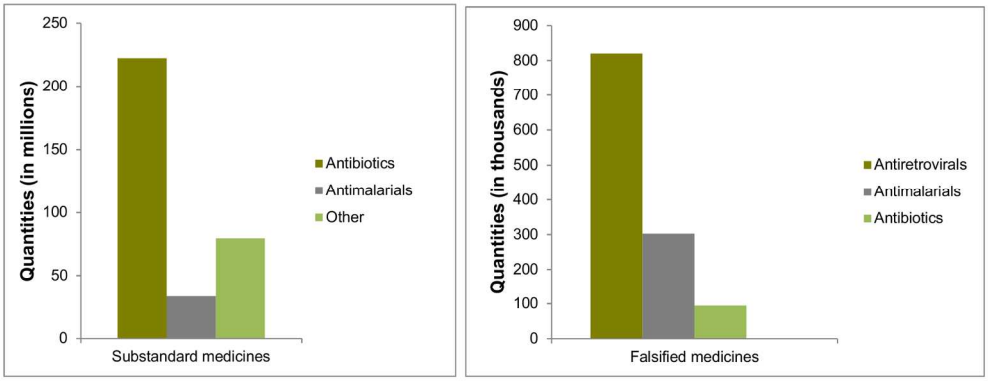

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Results: The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients was estimated at 16.2 million US$ i.e. value of substandard medicines 13.7 million US$ (84.4%), falsified medicines 0.1 million US$ (1%), cosmetics with banned ingredients 1.3 million US$ (8%) and other/operational costs 1.1 million US$ (6.6%). 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.

Conclusion: The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients represent a relatively large loss of scarce resources for a poor country like Tanzania. We believe that the observed increase in the quantities and the economic cost of these products over time could partly be due to the improvement in the regulatory capacity in terms of human resources, infrastructure and frequency of inspections.

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- Some data particularly for cosmetics, were poorly recorded, which made it difficult to apply the proper costing approach of identification, quantification and valuation.
- We could not determine the reasons for the increase in quantities and cost over time, but we believe this could be due to increased availability of data because of improved regulatory capacity and public awareness, as opposed to an absolute increase in the amount of poor-quality medicines and cosmetics.
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INTRODUCTION

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Substandard medicines: According to WHO, these are genuine medicines that are authorized by the national medicines authorities, but which fails to meet national or international quality standards or specifications.

Falsified medicines: According to WHO, these represent deliberately and fraudulently labeled medicines with respect to identity, composition and source and may include products with the correct or wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging [9].

Low-income countries are the prime targets of substandard and falsified medicines because regulatory agencies and law enforcement systems are relatively weak, accompanied by poorly regulated markets, and scarcity and/or erratic supply of basic medicines [10, 11]. Porous borders and complex supply chain system of pharmaceuticals also contributes to the problem. There is scarcity of national level data from low-income countries despite all evidences pointing towards an increasing problem of substandard and falsified medicines. Therefore, the objective of this study was to estimate the economic cost of substandard and falsified human medicines including cosmetics with banned ingredients in Tanzania from 2005–2015.

METHODS

This costing study used an ingredient approach to estimate the economic cost of substandard and falsified human medicines and cosmetics with banned ingredients between 2005–2015. This method involves identification, quantification and valuation of individual items. Costing was done from the perspective of the regulatory authority and the pharmaceutical distributors. We did not include patient and health system costs because of scarcity of data on morbidities and mortalities likely to be caused by the use of these products.

Sources of data

We used data from the regulatory authority and the major importers and distributors of pharmaceuticals from 2005–2015. The regulatory authority usually keeps all the confiscation reports for poor-quality medicines and banned cosmetics that are collected during routine inspections of premises and major operations. The report usually contains among other information, the name of the premise, generic and brand names of the product, strength, physical description of the package and products, batch number, manufacturing and expiry dates as well as the quantities and sometimes an estimated value. Premises usually remain with the signed copy of the confiscation report. In this study we retrieved all the confiscation data that was available at the regulatory authority's headquarter and from its zonal offices. 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. We also conducted a series of structured interviews with some officials at the regulatory authority and the importers and distributors of pharmaceuticals to estimate operational cost incurred in the process of confiscation, withdraw of products from the market, storage, disposal and proceedings of court cases. 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.

Cost estimations

The study used the median buyer prices from the International Drug Price Indicator Guide (IDPIG) as a primary source of medicines prices and when they were not available the Tanzanian Medical Stores Price Catalogue of 2015/16 was used. In the absence of median buyer prices, the median supplier prices were used, with an inflation factor of 10% as recommended in the costing studies [12]. Prices from the IDPIG were inflated further by 10% to account for local opportunity costs. Cost was calculated by multiplying the tallied quantities with unit prices for each item. In some cases, only the estimated value of the items in the local currency were reported without information about the identity and quantities and this was common for cosmetics. In this case the total value in the local currency was first converted to US$ by using relevant exchange rate for that year before adjusting to the present value using relevant consumer price indices.

Once the yearly value of falsified medicines, substandard medicines and cosmetics with banned ingredients were estimated, we added other/operational costs which included the storage costs, transportation costs, cost of disposal and cost charges for court cases to arrive to the annual total cost. We measured the storage area (m^2) which was multiplied by 10 US$/$m^2$ which was the rate of rental charge used for warehouses by the Tanzania National Housing Corporation (NHC) and reported by most distributors of pharmaceuticals. Yearly storage costs were obtained by multiplying monthly rental charges by 12. Storage costs for the importers and distributors was considered only for the year when there was an incident of confiscation of substandard or falsified medicine or cosmetics with banned ingredients.

Ethical considerations

Ethical approval was obtained from the research and publication committee of the Muhimbili University of Health and Allied Sciences (MUHAS). The regulatory authority also granted

research permission and issued an official letter to all local importers and distributors requesting them to make the relevant data available to the researchers and assuring them that the data requested will be used for research purpose only. A consent form was provided to all the interviewees and signed prior to interviews.

Patient and Public Involvement

Patients were not directly involved in the study. However, the research question and outcome measures were informed with concerns for safety and economic wellbeing of patients and the public. Poor-quality medicines and banned cosmetics not only contribute to increased morbidity and mortality but also can cause substantial economic loss to patients, families, health systems and everyone involved with the sale and manufacture of pharmaceuticals.

RESULTS

Economic cost

The estimated economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania from 2005–2015 was 16.20 million US$. Substandard medicines contributed 13.65 million US$, falsified medicines 149,369 US$ and cosmetics with banned ingredients 1.29 million US$. Other costs that include transportation, storage, court cases and disposal contributed 1.09 million US$ (Table 1).

Table 1: Costs of the products and other associated costs

Year	Cost (US$)							
	Falsified	%	Substandard	%	Cosmetics	%	Other cost	Total cost
2005	33.3	37.1	56.5	62.9	0	0.0	0	89.8
2006	49.9	100.0	0	0.0	0	0.0	0 0.0	49.9
2007	63.8	0.0	19,424.4	8.3	162,478.8	69.5	51,720.9	233,688.0
2008	96.7	0.1	0	0.0	42,979.2	23.6	138,929.7	182,005.6
2009	1,701.60	0.5	58,032.3	17.2	180,158.7	53.4	97,782.9	337,675.5
2010	17.6	0.0	57,299.5	25.1	52,983.1	23.2	117,907.7	228,207.9
2011	1,676.4	0.3	398,474.0	63.5	123,347.6	19.7	103,913.3	627,411.3
2012	141,493.3	3.6	3,530,672.6	89.5	91,968.4	2.3	180,557.0	3,944,691.2

2013	2,129.9	0.1	1,808,340.3	86.5	131,273.7	6.3	149,425.8	2,091,169.6
2014	1,724.2	0.0	6,453,613.0	94.8	240,335.9	3.5	112,258.6	6,807,931.8
2015	382.7	0.0	1,326,139.4	76.8	265,326.6	15.4	134,143.4	1,725,992.1
Total	**149,369.3**	0.9	**13,652,052.1**	84.4	**1,290,852.0**	8.0	**1,086,639.3**	**16,178,912.7**

Between 2005 and 2011, the estimated annual economic cost increased from about 90 US$ to 0.63 million US$, with some fluctuation in between. The annual cost increased sharply to 3.94 million US$ in 2012, then dropped to about 2.09 million in 2014. The annual total cost rose again to 6.8 million US$ the following year (Figure 1). From 2011, substandard medicines contributed two thirds or more of the total cost. In 2006 only falsified medicines were recorded, and in 2007 and 2009 cosmetics contributed more than half of the total cost (Figure 2).

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'.

Manufacturers of substandard and purported manufacturers of falsified medicines

Table 2 shows generic names of medicines and the anonymized names of manufactures of substandard medicines and purported manufacturers of falsified, which were repeatedly circulating in Tanzania between 2005–2015. Note that the letters used to denote manufacturers do not relate directly to their true names. Phenoxymethylpenicillin, ciprofloxacillin, prednisolone, diazepam and salbutamol from manufacturer N were identified over several years implying consistent failure to meet Good Manufacturing Practice standards. The same was seen for manufacturer E, M and B for quinine, paracetamol and aminophylline, respectively.

The same observation was also made for falsified medicines, in that falsified products bearing the name of the same purported manufacturer were consistently found on the market over several years. Example quinine and sulfamethoxypyrazine-pyrimethamine from manufacturer C and H, respectively, were identified circulating in the market over 3 years.

Table 2: Manufacturers of commonly identified poor-quality medicines

Substandard medicines (Manufacturers)	**Year**							
	2005	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Phenoxymethylpenicillin				N	N	N		
Ciprofloxacillin				N	N			
Quinine					E		E	
Prednisolone			N	N	N	N		
Paracetamol					M			M
Diazepam				N	N	N		N
Aminophylline							B	B
Salbutamol				N	N	N		
Falsified medicines (Purported manufacturers)	**Year**							
	2005	**2008**	**2009**	**2011**	**2012**	**2013**	**2014**	**2015**
Quinine tablets	B				C	B, C, D	C, D, E	B, C
Sulfamethoxypyrazine/Pyrimethamine			H	H, B		H, B		K
Sulfadoxine-Pyrimethamine					E, I, J	E	C, J	
Halofantrine Hydrochloride	A					A		
Artemether-Lumefantrine		F		F				
Dihydroartemisinin-Piperaquine		G	G					

* Letter codes represent anonymized names of manufacturer or purported manufacturers

DISCUSSION

It is difficult to estimate the actual economic cost of substandard and falsified medicines in any country not least in a low-income setting because data are usually not available [13]. However, using data from the regulatory authority, pharmaceutical importers and distributors we were able to estimate this burden in Tanzania. Our findings show that the estimated economic cost of substandard and falsified human medicines and cosmetics with banned ingredients in Tanzania between 2005–2015 was 16.20 million US$. Generally, the economic burden shows an increasing trend and the substandard medicines contribute the largest proportion of the total costs. The estimated economic cost represents 0.24% of the GDP, which is relatively large considering that Tanzania is one of the poorest countries in the world.

Based on the existing data, our analysis shows that there were large quantities of substandard and less falsified human medicines in Tanzania over the past ten years. This include commonly used inexpensive antibiotics such as phenoxymethylpenicillin, amoxicillin, cloxacillin, erythromycin, sulfamethoxazole-trimethoprim; antimalarials such as quinine, sulfadoxine-pyrimethamine, sulfamethoxypyrazime-pyrimetahmine and antiretrovirals among others. Use of poor-quality medicines is one of the main causes of antimicrobial resistance, which was recently declared by WHO as a major global public health threat as it causes treatment to be difficult and more expensive [2, 14]. Several studies have reported high levels of antibiotic resistance in Tanzania especially for commonly used and cheap antibiotics [15-18], which has prompted the government to develop a national action plan to curb antimicrobial resistance [19].

Policy implications

The quantities and the economic cost of substandard and falsified human medicines including cosmetics with banned ingredients in Tanzania over the past ten years is alarming. Policy-makers in Tanzania need to continue to improve the existing post-marketing surveillance (PMS) and pharmacovigillance (PV) system for effective prevention, detection and response to poor-quality products, adverse effects and other medicines-related health and economic problems. An effective PMS and PV systems are essential components of any healthcare system. However, in low-income countries including Tanzania such systems are weak or non-existent, hence health problems associated with the use of substandard and falsified medicines such as adverse reactions, ineffective treatment or even death often go undetected.

The government and policy makers need to provide more resources to the regulatory authorities in Tanzania to enhance supervision and inspection to ensure integrity of the supply chain of pharmaceuticals both in the public and the private sectors. Limited access to affordable essential medicines in the public health system has resulted in the opening of many private retail pharmacies and small accredited drug dispensing outlets in the country, which have proved very difficult to control [20]. As a consequence, malpractices are common including selling medicines without prescriptions, stocking medicines from unofficial sources, poor documentation and hiring of people without the required qualifications, making them the prime target for the business of substandard and falsified medicines [13].

The fact that some substandard and falsified human medicines from certain manufacturers were confiscated over several years raise a more serious concern. This was observed for example for falsified quinine tablets purporting to be from manufacturer B and C, and sulfamethoxypyrazine-pyrimethamine tablets mimicking that of manufacturer H. There could be several reasons behind this; first it could indicate a sign of insufficient inspection or ineffective removal of the product from the market. Secondly, it could be that the products were easy to be falsified and smuggled into the country; thirdly, poor compliance with Good Manufacturing Practices and lastly it could also imply that the culprits were not identified, or if identified the sanctions were not deterrent, hence continued to supply the products.

Strengths and limitations

To the best of our knowledge, this is the first study to systematically combine data retrieved from the regulatory authority, importers and distributors of pharmaceuticals to estimate the economic cost of substandard and falsified medicines and cosmetics with banned ingredients in a low-income country. The data also facilitated the identification of the manufactures of substandard medicines and manufacturers whose products were falsified, which enabled us to isolate those whose products were repetitively found circulating in the market. However, this study has several limitations. Firstly, we did not have morbidity and mortality data to facilitate the inclusion of patient and health system costs associated with the use of poor-quality medicines and cosmetics with banned ingredients. This means our study underestimates the actual economic cost of these products. Secondly, some data was poorly recorded, which made it difficult to follow the proper costing procedure of identification, quantification and valuation. 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.

CONCLUSION

The economic cost of substandard and falsified human medicines and cosmetics with banned ingredients represent a relatively large loss of scarce resources for a low-income country like

Tanzania. 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 could have positive and sustainable impact in the longer term. However, proliferation of retail drug outlets that are difficult to regulate and ineffective control of many porous borders will continue to be a challenge to the regulatory authority. Policy-makers should make the fight against substandard and falsified medicines a national priority agenda, including development of national strategies and action plans.

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Competing interests

None

Contributors

ATM and EK conceived the idea of the study; ATM, EM and EK designed the study. EM collected the data. ATM and EM analyzed the data. ATM and EM wrote the first draft of the manuscript. All authors approved the final version of the manuscript.

Data sharing

There is no unpublished data for this study

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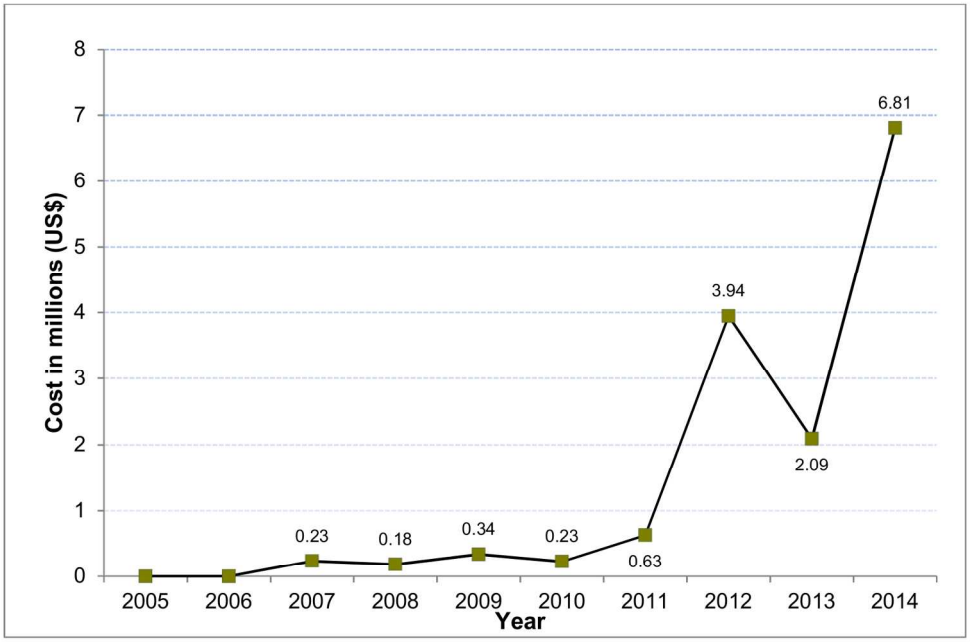
Figure 1: Estimated annual economic cost between 2005–2015

Figure 2: Relative contributions of the products to the total economic cost in Tanzania, 2005–2015

Figure 3: Quantities of poor-quality medicines in Tanzania, 2005-2015



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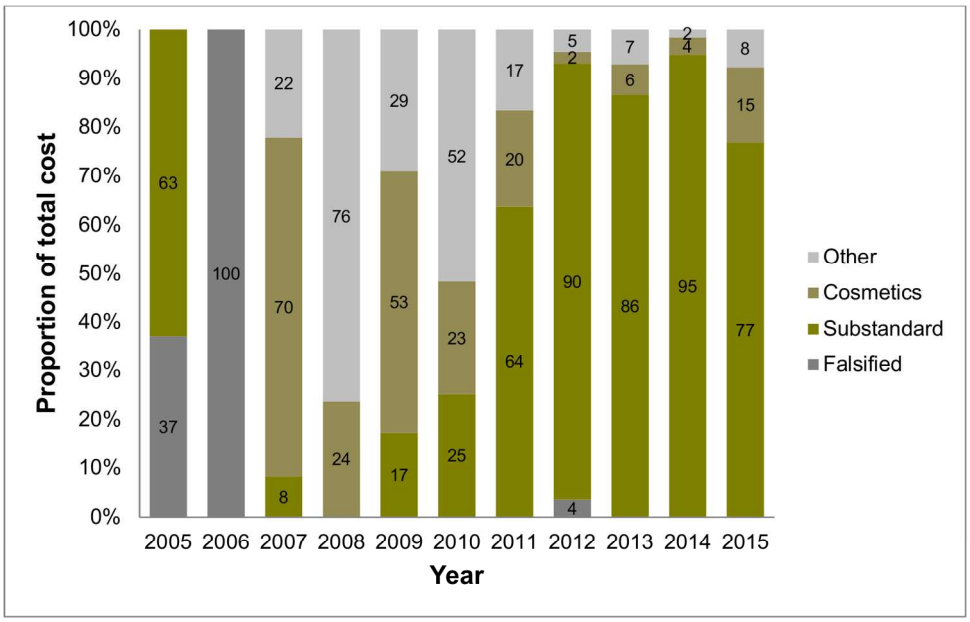

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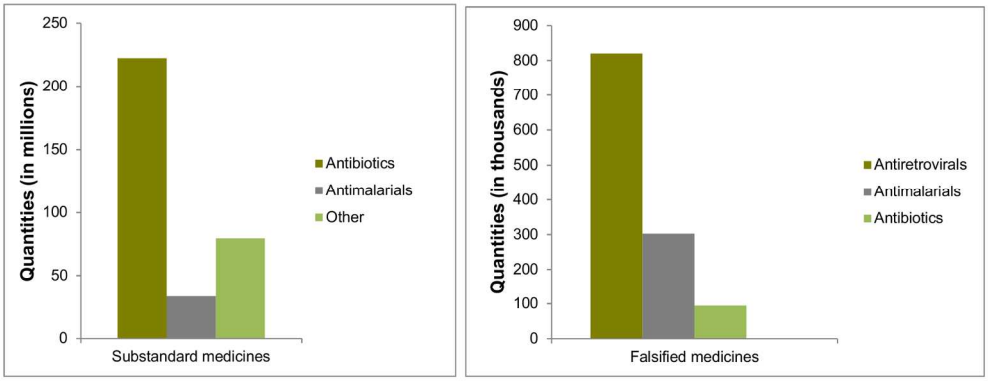

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Table

Table 1| **CHEERS checklist—Items to include when reporting economic evaluations of health interventions**

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1 line 4-6
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	4-5
		Present the study question and its relevance for health policy or practice decisions.	5 line 3-16
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	—
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5 line 36-40
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5 line 26-28
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	—
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5 line 24
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	—
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	—
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	—
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	—
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	—
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	—
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	—
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	6 line 16-31
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	—
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	—
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	—
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	—
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	—
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	—

(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	–
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	–
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	7e-12
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	13 line 9-10
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	13 line 15

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist