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National Antibiotics Utilization Trends for Human Use in Tanzania from 2010 to 2016 Inferred from Tanzania Medicines and Medical Devices Authority Importation Data

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Abstract: Antimicrobial use (AMU) is one of the major drivers of emerging antimicrobial resistance (AMR). Surveillance of AMU, a pillar of AMR stewardship (AMS), helps devise strategies to mitigate AMR. This descriptive, longitudinal retrospective study quantified the trends in human antibiotic utilization between 2010 and 2016 using data on all antibiotics imported for systemic human use into Tanzania's mainland. Regression and time series analyses were used to establish trends in antibiotics use. A total of 12,073 records for antibiotics were retrieved, totaling 154.51 Daily Defined Doses per 1,000 inhabitants per day (DID) with a mean (\pm standard deviation) of 22.07 (\pm 48.85) DID. The private sector contributed 93.76% of utilized antibiotics. The top-ranking antibiotics were amoxicillin, metronidazole, tetracycline, ciprofloxacin and cefalexin. The DDIs and percentage contribution of these antibiotics were 53.78 (34.81%), 23.86 (15.44), 20.53 (13.29), 9.27 (6.0) and 6.94 (4.49), respectively. The time series model predicted significant increase in utilization (p -value = 0.002). The model forecasted that by 2022, the total antibiotics consumed would reach 89.6 DDIs, corresponding to a 13-fold increase compared to 2010. Government intervention to curb inappropriate antibiotic utilization to mitigate the rising threat of antibiotic resistance should focus on implementing AMS programs in pharmacies and hospitals in Tanzania.

Keywords: antimicrobial; antimicrobial use; antimicrobial resistance; antibiotic utilization; Tanzania; defined daily dose, Anatomical Therapeutic and Chemical Classification

1. Introduction

Antimicrobial use (AMU) is one of the major drivers of the emergence of antibiotic-resistant microbes. Antimicrobial resistance (AMR) is also a natural evolutionary phenomenon [1–3]. In the past decade, AMU has continuously increased globally, contributed mainly by the dramatic increase in consumption rates in low-and-middle-income countries (LMICs). The increase in AMU has also been partly due to increased consumption of the "new and last resort" antibiotics, carbapenems, polymyxins, glycolcyclines, and oxazolidinones [4–6].

It is well established that AMU influences resistance [1]. Thus changes in AMU patterns may be a proxy reflecting the change in the AMR patterns, which then influences the antimicrobial prescribing of antibiotics. In LMICs and higher-income countries (HICs), there has been a generally increased utilization of broad-spectrum antibiotics, including broad-spectrum penicillins, carbapenems and polymyxins. However, consumption of some classes of antibiotics such as cephalosporins, fluoroquinolones, macrolides, and second-line oxazolidinones have increased in the LMICs but have decreased in the HICs [4,5]. The implication of the increase in consumption of some antibiotics, such as third-generation cephalosporins, is that they influence the emergence of extended-spectrum beta-lactamase-producing bacteria, which then confer resistance to other beta-lactam antibiotics [1,7]. Moreover, once present in the pool of bacteria, these resistant genes can hardly be removed and can be quickly passed to other bacteria through vertical transmission or through lateral transmission, which can even be passed to bacteria of different species [1,2,8].

The increase of antibiotic consumption, especially in the LMIC, is linked to economic growth as access to services and goods improves. However, economic growth is also linked with urbanization, facilitating infectious diseases such as enteric fevers, dengue, chikungunya, and viral diarrheal diseases. Also, there is an increase in respiratory illnesses due to declining air quality [5,9–11]. All these influence antibiotics use, especially in the communities in LMICs where access is poorly controlled. Furthermore, despite economic growth and access to antibiotics, the utilization is somewhat influenced by the social and cultural norms towards prescribing and using antibiotics [4,12–16].

Tanzania is one of the fastest-growing economies on the African continent, with an average growth of 7% since 2000. Moreover, as access to medicines has recently improved in Tanzania, measures such as training a cadre of dispensers to dispense various medicines in the outlets have been implemented. This was designed to increase accessibility to medicines as well as dispense appropriately [17]. However, studies in Tanzania indicate a high burden of inappropriate use of antibiotics in the communities, driven mainly by inadequate knowledge of individuals who pressure these dispensers and the need to make profits, which influence dispensers to abandon their knowledge and training rational dispensing. Similarly, inappropriate prescribing and use of antibiotics have been documented in hospital settings [10,12,18–21].

Consequently, resistance to the commonly available antibiotics has been rapidly and continuously increasing. Reports show the presence of up to 100% resistance of *E. coli* and *Klebsiella pneumoniae* to the commonly available penicillins and over 50% resistance to the third-generation cephalosporins [22,23]. Resistance to the "new and last resorts" such as meropenem has been documented in Tanzania to almost 10% and MRSA to about two-thirds of microbes [7,22,24].

These reports of inappropriate prescribing, dispensing and use, emanate from different areas, as we lack national surveillance on the use of antibiotics. Similarly, national antibiotic resistance surveillance is lacking. The reports on overall antibiotic consumption can serve as a baseline evaluation of antibiotic use for future efforts to control antibiotics use. It will further enable the trend analyses of antibiotic use and resistance over time and, thus, affirm the enforcement of policies to reduce antibiotic use in the country [5,25,26].

The standard method for estimating medicine utilization uses prescription data from hospitals and the sales estimates from community medicine outlets. However, this method is limited by a lack of or inaccuracy of records; and there is a paucity of such data

properly organized in our setting. Medicines regulatory authorities, such as the Tanzania Medicines and Medical Devices Authority (TMDA), are responsible for supervising the importation of medicines. Therefore, their medicine's importation data can be used as a tool to estimate medicine utilization.

The need for accurate and more detailed antibiotic consumption data has led to the development of the Anatomical Therapeutic Chemical (ATC) and Defined Daily Dose (DDD) classification systems which are used to measure medicine utilization based on the usual daily dose for a given drug, defined as the assumed average maintenance dose per day for a drug used for its main indication in adults [27,28]. We report the trend of antibiotic consumption in Tanzania based on human medicine importation data as a proxy for antibiotic utilization.

2. Results

A total of 14,301 records for antibiotics importation from 2010 to 2016 were retrieved. Of these, 12,073 were of antibiotics for systemic use in humans. A total of 2,228 records did not meet inclusion criteria either due to being antibiotics for topical use or outside the study range or antibiotics for veterinary use. A total of 154.51 DDD per 1000 inhabitants per day (DID) was utilized in Tanzania between 2010 and 2016 (Table 1) with a mean (standard deviation) of 22.07 (± 48.85) DID.

Table 1: Yearly distribution of DIDs and number of permits

Year	Number of permit	DID
2010	1154	6.78
2011	1578	13.26
2012	2008	9.78
2013	2000	14.65
2014	2136	29.86
2015	1551	31.98
2016	1646	48.19
Total	12073	154.51

The public and private sectors contributed 6.24 % and 93.76%, respectively, of all DIDs all antibiotics utilized.

The oral and parenteral dosage forms contributed 151.18 (97.85%) and 3.33 (2.15%) DIDs (%), respectively (Figure 1). On further sub-dividing the antibiotics into respective dosage forms, capsules comprised the major form of consumption of antibiotics (Supplementary Table A3).

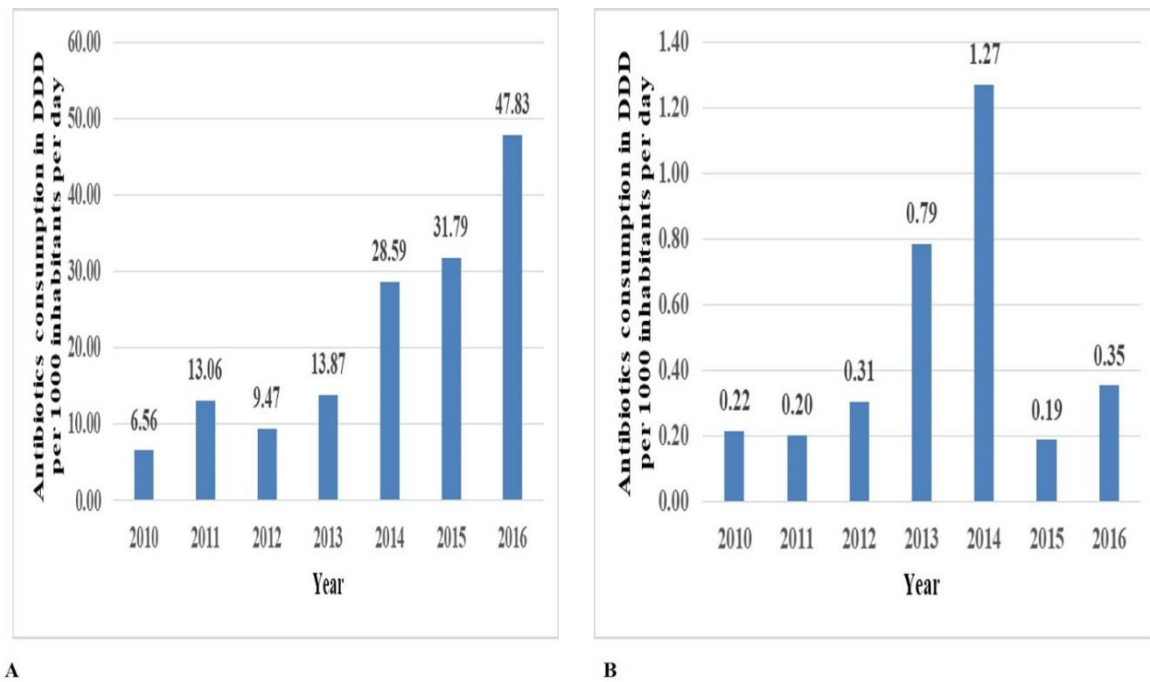


Figure 1: Contribution of oral A) and parenteral B) route of medicine administration for systemic antibiotics utilized over seven years.

According to ATC Level 3 groups (Figure 2), we found that utilization of the beta-lactam antibiotics, penicillins (J01C), followed by the top five, the other antibacterials (J01X), tetracyclines (J01A), quinolones (J01M) and other beta-lactam antibiotics (J01D) and macrolides lincosamides and streptogramins (J01F)(Figure 2). These top 5 classes contributed 97.55% of all consumption, with the beta-lactam antibiotics, penicillins (J01C) alone contributing 45.83% of all antibiotics utilized.

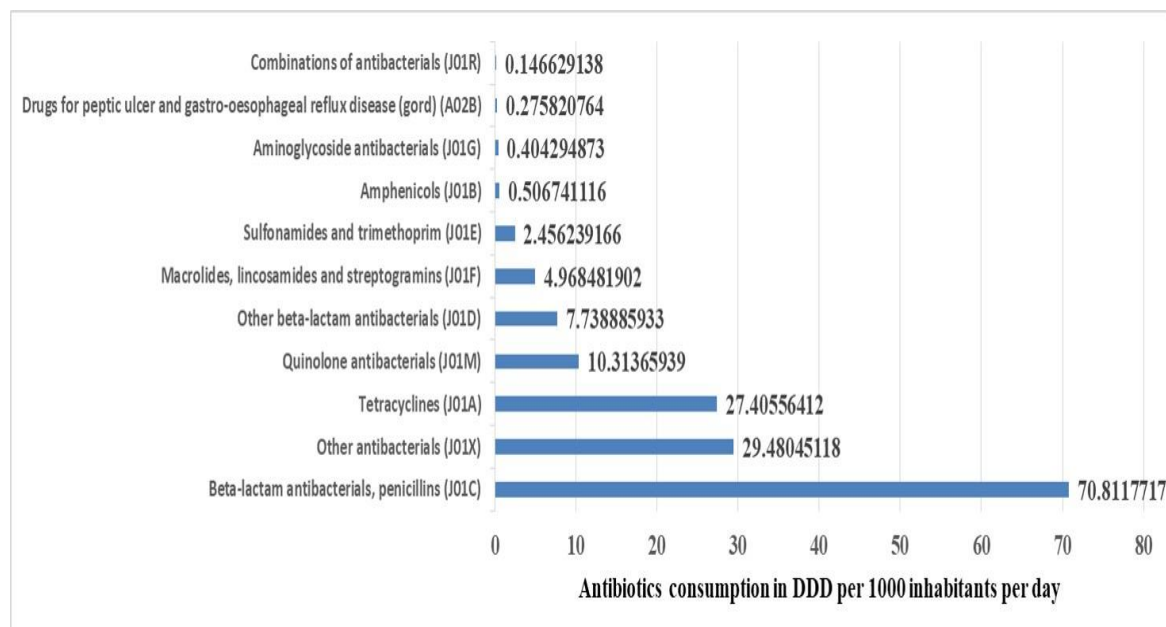


Figure 2: Contribution of each class (ATC level) antibiotics utilized over seven years. From 2010 to 2017 in Tanzania.

The beta-lactam antibiotics, penicillins (J01C) was the most important level 3 ATC class that contributed the most. The individual antibiotics that made up the volumes of this class include Amoxicillin (J01CA04) (Figure 3 A) and then followed by ampicillin,

ampicillin + cloxacillin, cloxacillin, phenoxymethyl penicillin, procaine benzylpenicillin, amoxicillin + clavulanate, benzathine penicillin, ampicillin + cloxacillin, benzyl penicillin, amoxicillin + flucloxacillin, flucloxacillin, sultamicillin, piperacillin + tazobactam, ampicillin combination and ampicillin + sulbactam in increasing order (Figure 3 B) and Supplementary Table A4.

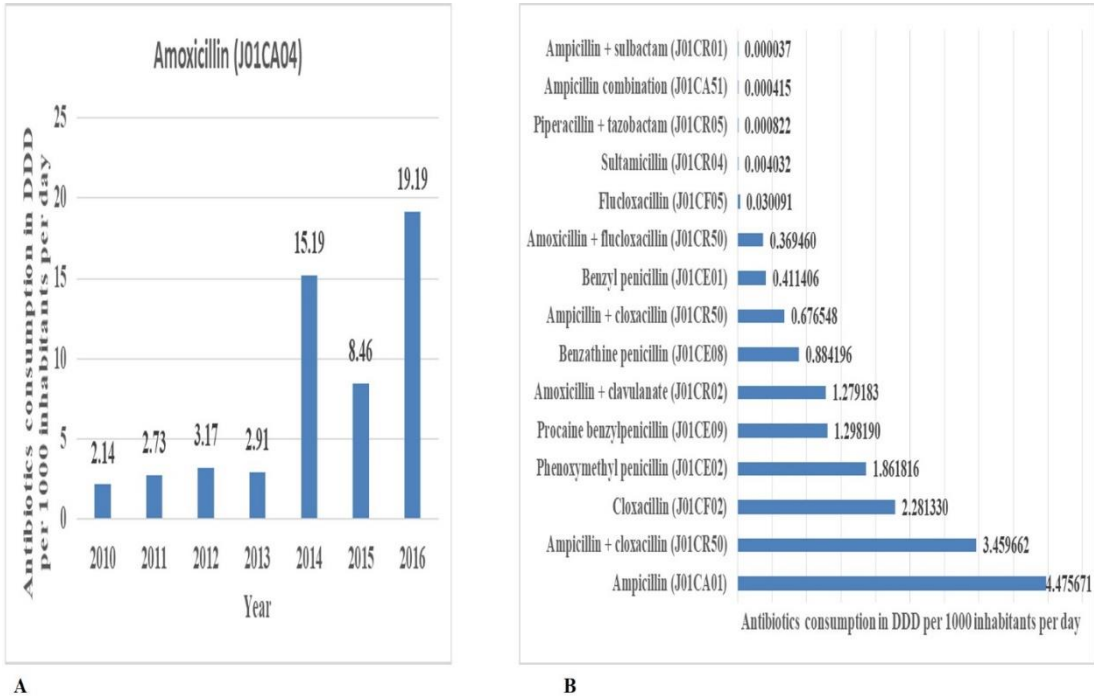


Figure 3: Contribution of each antibiotic in ATC class level J01C A) for amoxycillin per year and B) for the other antibiotics in class J01C utilized over seven years from 2010 to 2017 in Tanzania.

The other antibacterials (J01X), metronidazole, was the most important utilized antibiotic other antibiotics. The individual antibiotics that make up the volumes of this class include tinidazole, nitrofurantoin, ornidazole, linezolid and vancomycin (Figure 4) in increasing order of DIDs.

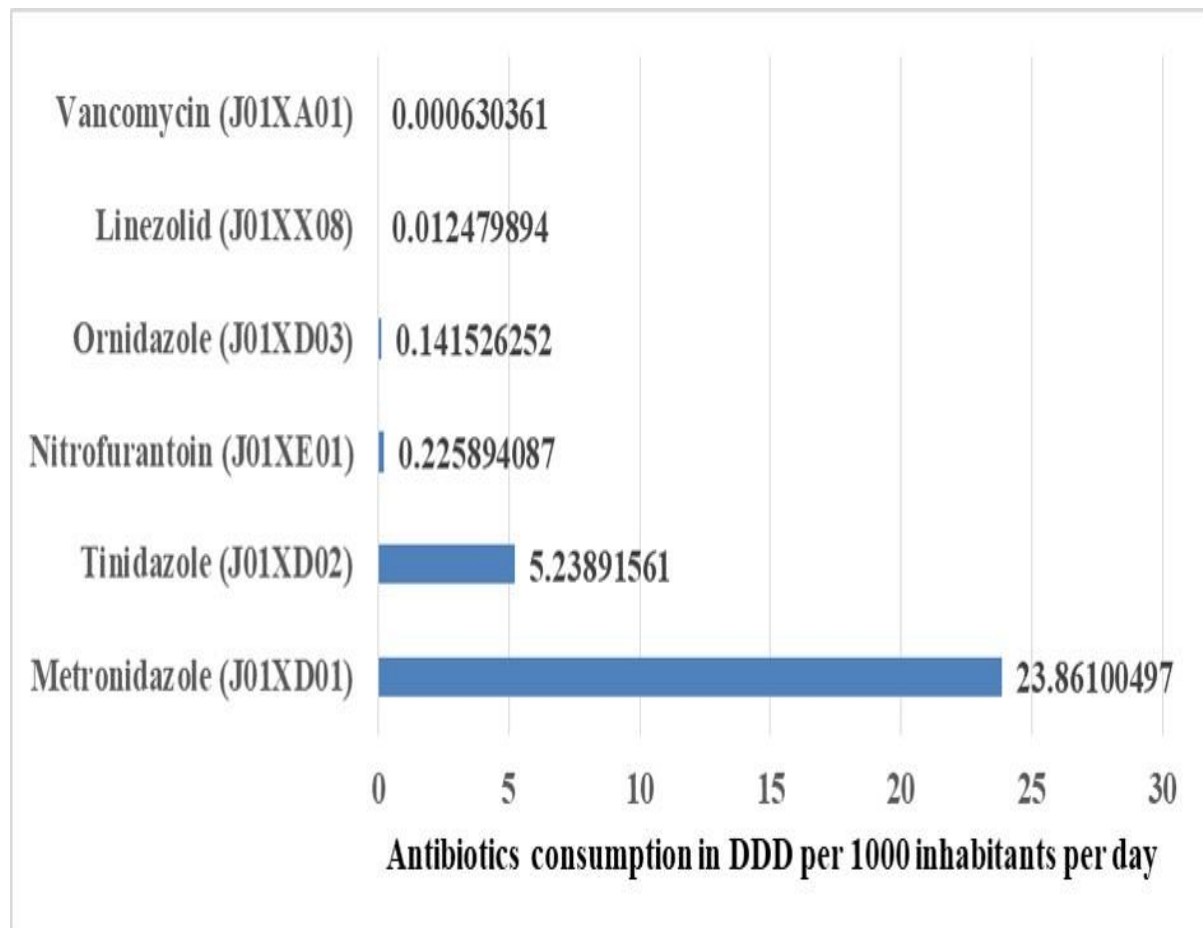


Figure 4: Contribution of each antibiotic in ATC class level J01X for the other antibiotics utilized over seven years from 2010 to 2017 in Tanzania.

For tetracyclines (J01A), the order of increasing order was tetracycline, doxycycline, oxytetracycline combinations and chlortetracycline. For quinolones (J01M), the order was ciprofloxacin, levofloxacin, ofloxacin, norfloxacin, perfloxacin, sparfloxacin, nalidixic acid and moxifloxacin (Supplementary Table A4) and for other beta-lactam antibiotics (J01D) was cefalexin, cefuroxime, cefadroxil, cefixime, cefpodoxime, ceftriaxone, ceftazidime, cefaclor, cefotaxime, cefprozil, meropenem, cefepime, ceftriaxone combinations, cefoperazone, combinations and cefazolin (Supplementary Table A4). For macrolides, lincosamides and streptogramins (J01F) were erythromycin, azithromycin, clarithromycin, clindamycin and roxithromycin (Supplementary Table A4). All DIDs of individual antibiotics are ranked in Supplementary Table A4 per year to show the annual trends.

According to the WHO AwaRe classification, the distribution of Access, Watch and Reserve groups was 83.1%, 10.1% and 0.008%, respectively (Table 2). There were combinations of antibiotics not recommended in the WHO AwaRe classification contributing to 6.8% of the antibiotics in Tanzania from 2010 to 2016.

Table 2: Distribution of Defined Daily Dose (DDD per 1000 inhabitants per day (DID) antibiotics per World Health organizations' AwaRe class for antibiotics utilized in Tanzania from 2010-2016

Defined Daily Dose (DDD per 1000 inhabitants per day (DID)								All year's total	% of class
AwaRe class	2010	2011	2012	2013	2014	2015	2016		
Access	5.060	11.238	6.307	10.049	25.382	28.879	41.456	128.371	83.083
Watch	1.253	1.454	2.445	2.000	2.655	2.020	3.729	15.554	10.067
Other	0.466	0.572	1.029	2.596	1.827	1.080	3.001	10.571	6.842
Reserve	0.0			0.010	0.002		0.001	0.012	0.008
Total	6.779	13.263	9.781	14.654	29.865	31.979	48.187	154.509	100.000

The model that included the data for the years 2010 to 2016 could significantly predict the future utilization of antibiotics (Figure 5). The ARIMA model could significantly (p -value = 0.002) predict the increase in utilization and forecast the trends of antibiotics up to the period 2022. The model estimated that by 2022, the total antibiotics consumed would reach 89.60 DDIs (Supplementary Table A5). This increase corresponds to about a 13-fold increase compared to the year 2010.

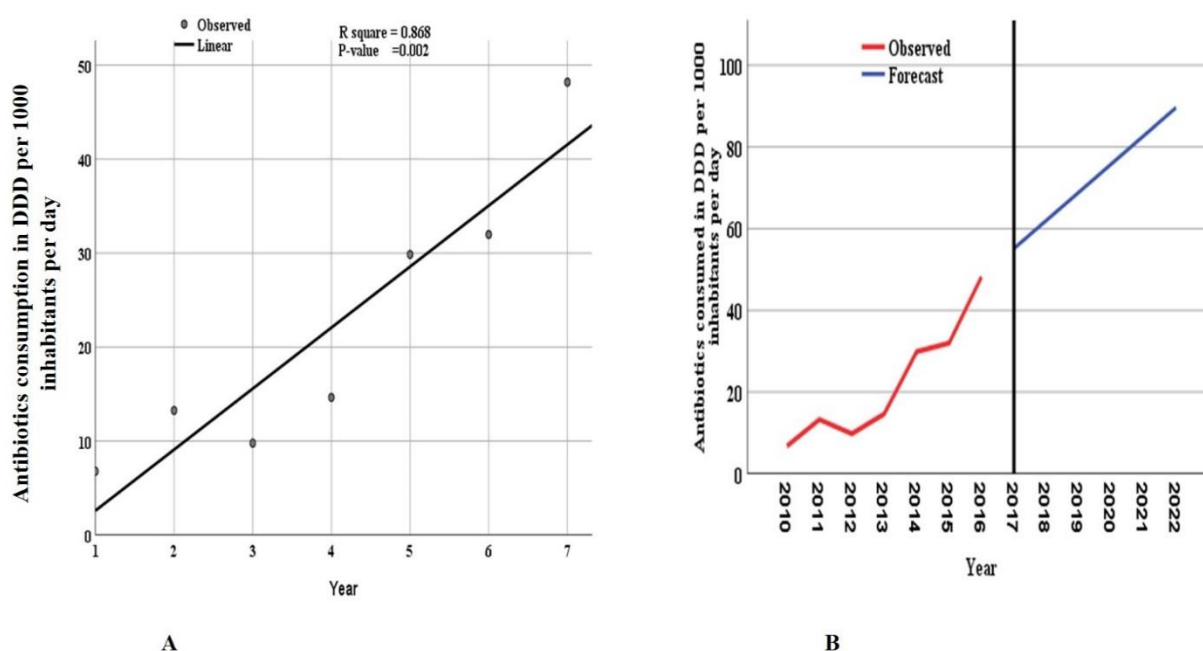


Figure 5: Trends of total consumed antibiotics over seven years from 2010 to 2016. Period 1 corresponds to 2010 and year 7 to 2016. The linear curve estimation for (A) overall consumption of antibiotics shows an increasing trend, (B) The autoregressive integrated moving average (ARIMA, 0, 1, 0) model forecasted the utilization between 2010 - 2022.

The top ten most important foreign antibiotics suppliers and local antibiotics importers are shown in Figures 7 and 8.

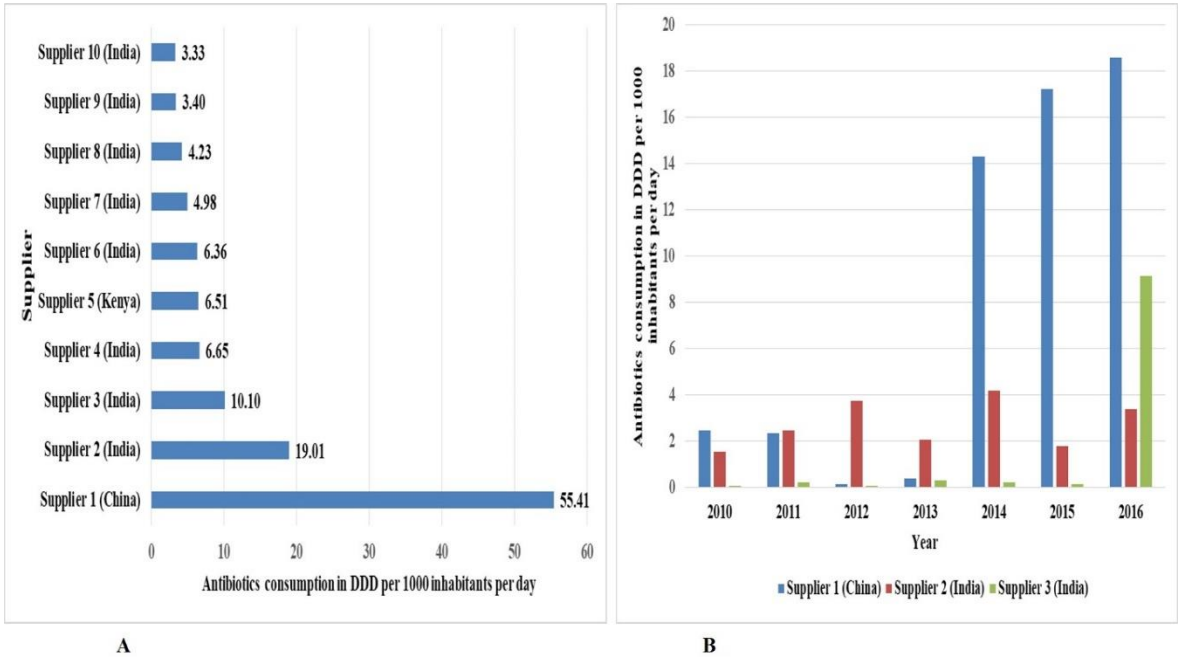


Figure 2: Top (local) importers of antibiotics utilized in Tanzania between 2010 and 2016. Panel A) shows the top 10 importers and B) annual distribution of the top 3 importers

The top supplier of antibiotics in the study period is from China. Eight of the top ten suppliers are from India and one company is from Kenya.

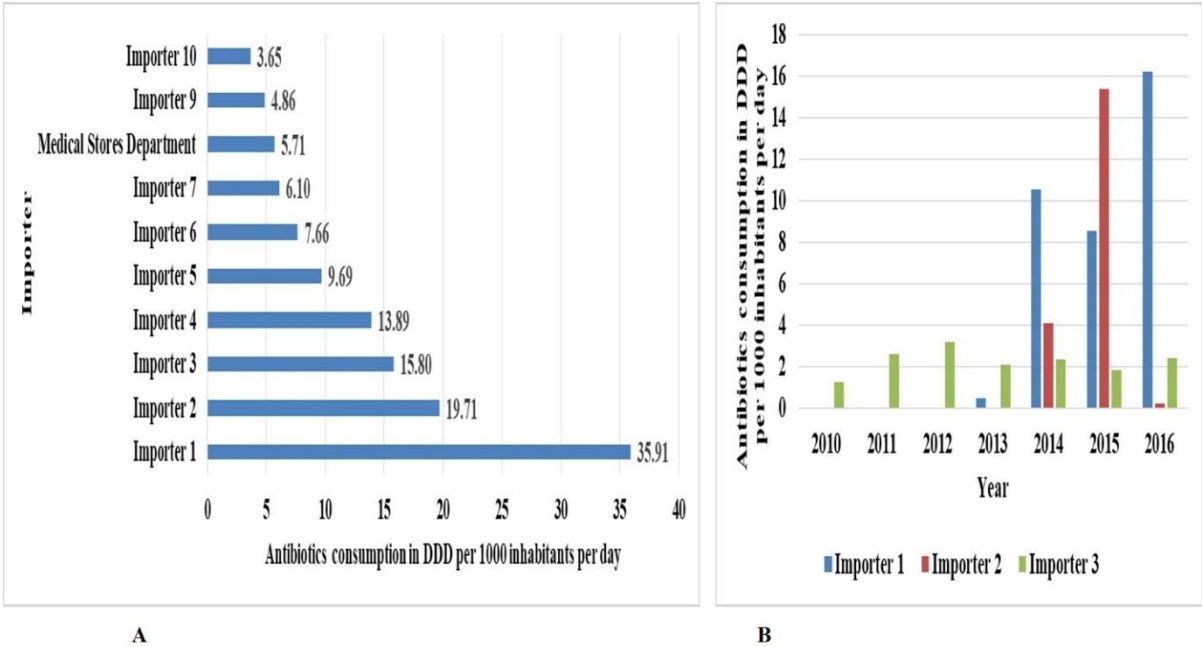


Figure 3: Top (foreign) suppliers of antibiotics utilized in Tanzania between 2010 and 2016. Panel A) shows the top 10 importers and B) annual distribution of the top 3 importers

Medical Stores Department is the eighth top importer of antibiotics in the study period.

3. Discussion

The Global Action Plan of antimicrobial resistance stipulates the surveillance of AMR and AMU to guide antimicrobial stewardship (AMS) in member countries [29]. In Tanzania, the implementation of AMS has just begun [26,30]. One of the critical elements of AMS is the monitoring of AMU in both animals and humans. Recently we conducted a study to report the trend of AMU on antibiotics for veterinary use, which showed that tetracycline, sulfonamides and trimethoprim, quinolones, aminoglycosides beta-lactams and antibacterial combinations were the frequently used antibiotics, with tetracycline on the top of the list in Tanzania. [31]. The current study complements the trends of AMU in humans to a recent report by Mbwasia and colleagues [31]. The linear curve estimation for overall antibiotic consumption and the Autoregressive Integrated Moving Average (ARIMA) model that forecasted antibiotic utilization between 2010- 2022 show an increasing trend.

This is one of the few studies in sub-Saharan Africa that attempt to estimate antibiotic utilization at the national level. Our data suggest an increase in the consumption of antibiotics, as reflected by a linear regression model. A total of 154.51 DIDs of antibiotics with a mean of 57.4 (± 48.85) DID (standard deviation) were utilized in Tanzania between 2010 and 2016. This average amount is slightly less than that reported for years 2017 to 2019 in Tanzania [32], in which the mean consumption of antibiotics was 80.8 DIDs over three years. This difference can be due to changing utilization patterns over the years and the latter had a shorter duration of observation. According to our data, there is an increase in utilization from 2010 to 2016. The utilizations seem to peak in 2017, according to the study by Mbwasia and colleagues [32], then decline in 2018 and 2019. The difference in the two reports is due to the fact that there is an increase in the trends of the utilization of antibiotics and the additional data used in the study by Mbwasia and colleagues [32].

A similar study performed in Kenya in 2004 showed a net decrease in antibiotic consumption [33]. Another similar study in Iran compared the utilization of antibiotics from 2000 to 2016 with the Organization for Economic Co-operation and Development (OECD) countries. In the Iranian study, antibiotic consumption ranged from 33.6 DID to 60 DID. The study noted a general increase in the consumption of antibiotics in certain classes of antibiotics such as sulfonamide and aminoglycosides decreased [34]. A study comparing antibiotic utilization among European Countries revealed an increase in antibiotic consumption by 36% from 2000 to 2010 [4]. In Sierra Leone, the total consumption of antimicrobials for the years 2017-2019 was 19 DDIs which is much lower than the rates found in our study [35].

We noted a significant annual increase in antibiotic utilization in Tanzania from 2010 to 2016. Using an autoregressive integrated moving average (ARIMA) model, we found a significant increase in antibiotic use in the study period in Tanzania. The model predicted that consumption of antimicrobials for 2017, 2018, 2019, 2020, 2021 and 2022 would be 55.09, 61.99, 68.90, 75.80, 82.70 and 89.60 DIDs, respectively. These predicted values are slightly more than those reported by the study of 2017-2019 [32] because the latter study noted a peak in 2017, followed by a decline in 2018 and 2019. Therefore validating the ARIMA prediction model would require a dataset of more than seven years. The current model predicts that by 2022, antibiotic utilization will reach 89.90 DIDs, which is a 13 fold increase in antibiotics utilization. This is an alarming excessive antibiotic consumption likely to escalate AMR. An urgent need to institute AMS in Tanzanian hospitals and pharmacies is warranted.

The current study shows that the public sector contributed 6.2% of all antibiotics in Tanzania between 2010 and 2016. These data were mainly contributed by the Medical Stores Department (MSD), the government authority for procuring medicines in Tanzania. This was less than the 35% public sector contribution in a previous study [32] in Tanzania. We found greater consumption of oral antibiotics (97.85%) compared to parenteral ones (2.15%) for antibiotics for systemic use. This may imply that there are successful campaigns by the Ministry of Health on the safe use of oral products compared to injections,

given that Tanzania has just begun implementing AMS [26,30]. This same reason may have applied to the decline of antibiotic utilization in 2018 and 2019 [32].

According to ATC Level 3 groups, we found that utilization of the beta-lactam antibiotics, penicillins (J01C), other antibacterials (J01X), tetracyclines (J01A), quinolones (J01M), other beta-lactam antibiotics (J01D), and macrolides lincosamides and streptogramins (J01F) were the top 5 classes that contributed 97.55% of all antibiotic utilization, with the beta-lactam antibiotics, penicillins (J01C) alone contributing 45.83% of all antibiotics utilized.

The five top-ranking individually utilized antibiotics in the study periods were amoxicillin (J01CA04), metronidazole (J01XD01), tetracycline (J01AA07), ciprofloxacin (J01MA02) and cefalexin (J01DB01). The DDIs and percentage contribution of these antibiotics were 53.78 (34.81%), 23.86 (15.44), 20.53 (13.29), 9.27 (6.0) and 6.94 (4.49), respectively.

These top five antibiotics are recommended for various conditions in Tanzania Mainland's Standard Treatment Guidelines (STG). Amoxicillin is recommended to treat acute respiratory infections [36], metronidazole is used in anaerobic bacterial infections. On the other hand, tetracycline has been replaced by doxycycline in treating cholera, pelvic inflammatory diseases, and sexually transmitted diseases. Ciprofloxacin is mainly used for the treatment of urinary tract infections. Cefalexin is used in regional referral hospitals to replace penicillins [36]. The resistance levels to these antibiotics in this setting have been noted to be increasing [24]. The extensive use of amoxicillin in Tanzania may be attributed to its use in accredited drug dispensing outlets (ADDO). The program provides training to dispensers, including the Integrated Management of Childhood Illness (IMCI), which includes managing acute respiratory tract infections (ARIs) and diarrhea in children. The program guides to when antibiotics are indicated for pneumonia and severe pneumonia only [18]. However, there are reports where antibiotic overuse and inappropriate antibiotic use have been observed [12,16–18] among ADDO dispensers. This may have driven the overuse of amoxicillin in Tanzania.

In the class beta-lactam antibiotics, penicillins, the other most consumed antibiotic were ampicillin and cloxacillin alone or in combination. In the class, other antibacterials were tinidazole and nitrofurantoin. In case quinolone antibacterial ciprofloxacin, levofloxacin and ofloxacin contributed to the most in the group. For the group, macrolides, lincosamides, streptogramins, erythromycin azithromycin, clindamycin, clarithromycin and roxithromycin were the only imported products.

We found a higher dominance of suppliers of antibiotics from India. In the top ten suppliers of antibiotics in Tanzania, this trend has also been shown in other studies [37], indicating a good trade between Tanzania and India in the sales of pharmaceuticals. However, the antibiotic quality determination was beyond the scope of this study.

Limitation of this analysis

It is assumed that almost most of the antibiotics imported are used, where the Medical Stores Department (MSD) imports 80% of all antibiotics. The proper inventory control means in medicine outlets also ensure that a few medicines end up expired. However, the contribution of public data from MSD was low in this dataset, exclusively from TMDA.

Nevertheless, this study provides baseline data on antimicrobial drug usage, and it helps interpret any current or future emergence of antibiotic resistance.

4. Materials and Methods

4.1 Study Design

This was a retrospective, longitudinal analytical study that assessed consumption trends of standard units of antibiotics for human systemic use from the importation data on human medicine from 1st January 2010 to 31st December 2016 in Tanzania mainland.

4.2 Study setting

This study was done in The United Republic of Tanzania. The country is located at a latitude of 6.3690° S. and longitude 34.8888° E, bordered by eight countries with the Indian Ocean along the eastern border. Uganda is to the north, Malawi and Mozambique are

found to the south. Zambia is on the southwest border and Kenya is northeast. The Democratic Republic of Congo, Rwanda, and Burundi are three countries on the western border. These borders are the entry points of imported medicines into the country through the sea harbor and airports. The ports of entries of medicines include Dar es Salaam airport and sea harbor (6.7924° S, 39.2083° E), Kilimanjaro airport (3.4245° S, 37.0651° E) National terrestrial border checkpoints at Sirari at 1.2512° S, 34.4763° E, Horohoro at 6.369° S and 34.8888° E, Namanga (Kenya border), Tunduma at 9.3096° S, 32.7689° E (Zambia border) and Mutukula at 1.0007° S, 31.4156° E (Uganda border).

4.3 Data sources

The study used data on all antibiotics imported for human systemic use into Tanzania's mainland obtained from the Tanzania Medicines and Medical Devices Authority (TMDA). The data included the port of entry identification at both air, sea and border checkpoints at Sirari, Horohoro, Namanga, Tunduma, Mutukula and the seaport in Dar es Salaam. Importation data can serve as a proxy to estimate the utilization of antibiotics as information on all medicines imported into the country are available. This method assumes that all medicines imported are utilized in Tanzania and that all medicines entering the country are through the normal legal pathway as regulated by TMDA. We also assume that there is no illegal importation of medicines that would go undocumented [27]. Another assumption is that proper inventory control measures are generally taken to minimize expiry and losses in the retail medicine stores. Almost all antibiotics imported are utilized for systemic use by humans.

The antibiotics used for systemic use were extracted, including those assigned the code J in the ATC system. Within this group, there are several subgroups. The defined daily dose is defined as the average dose required for maintenance.

Data were adjusted to the WHO/Anatomic Therapeutic Classification (ATC) classification system and expressed as a number of defined daily doses (DDD). DDD is a function of the total amount in grams of the antibiotics consumed and the DDD for a particular dosage form is shown by the equation following equation: [38]

$$\frac{((\text{No of packages} \times \text{No of tablets per package} \times \text{No of g. per package}))}{((\text{DDD of antimicrobial in grams}))}$$

ATC classification system as a tool for medicine utilization research was used. This is a gold standard for medicines utilization research worldwide. The defined daily doses of the antibiotics were calculated as shown in the formula.

$$((\text{Total amount consumed in grams})) / ((\text{DDD of antimicrobial in grams}))$$

Reference was made to the DDD list available at www.whocc.no for the DDD values assigned to different antibiotics. Then the amounts in defined daily doses/1000 inhabitants-day were determined for each antibiotic and the overall amount was determined using the function

$$\text{DDD}/1000 \text{ inhabitants-day} = (\text{Total DDDs in grams} \times 1000) / (\text{Population} \times 365)$$

Reference was made to population estimates from the National Bureau of Statistics for the covered years (Supplementary Table A1).

4.4 Exclusion criteria

All records, including topical products such as lotion, cream, ointment, pessaries and shampoos and ophthalmic solutions, were excluded from the analysis. In addition, records without permit numbers, reference numbers, or permit issue dates were also excluded because, for these, the importation year could be derived to be included in the analysis. In addition, records including dates out of the study range were also omitted.

4.5 Data collection

TMDA is a medical products regulatory authority regulating and approving the importation of medicines into the Tanzanian mainland market. TMDA outlined regulations and procedures that oblige importers to apply for an importation permit. After successfully evaluating the application, import permits are issued and archived using the TMDA's Management Information System (MIS). Records were retrieved from the TMDA database of imported medicines.

The importation data collected include the date, generic and brand name of medicine, strength, category, quantity, the ATC classification of the antibiotic, company (suppliers or importer), price, currency, product manufacturer and country of origin. Data were adjusted to the WHO Anatomical Therapeutic Classification (ATC) system and expressed as Defined Daily Dose (DDD) measurement units. Utilization was expressed in DDD per 1000 inhabitants per day (DID). Antiviral and antifungal substances were grouped according to their main indications.

We also classified antibiotics according to the AWARe classes. According to this classification, the Access group consists of antibiotics with activity against a wide range of commonly encountered susceptible bacteria with lower resistance potential than antibiotics in the other groups. The watch class consists of antibiotics with higher resistance potential and includes most of the highest priority agents among the critically important antimicrobials for human use. The reserve group includes antibiotics and antibiotic classes that should be reserved to treat confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options [39].

4.6 Data cleaning

Years were computed from dates, and where a date was missing, the reference number of the import permit that contains the year of approval was considered.

Data were reorganized to calculate milligrams (mg) and subsequent DDDs, as shown in the expression above. It involved rearranging pack size and strength to determine the total amount in mg for individual dosage units in different dosage forms.

Data were checked for accuracy, completeness and reliability before analysis. The total grams of the medicines utilized were quantified by grouping the total amounts of active ingredients across the various formulations, accounting for the differences in strengths, dosage forms, and pack sizes.

We calculated the DDD of each antibiotic using the formula [40,41], where the total amount consumed in grams was divided by the DDD of antimicrobial in grams. Reference was made to the DDD list available at www.whooc.no. The amounts in defined daily doses/1000 inhabitants-day were determined for each antibiotic, and the overall amount was determined using the equation;

$$\text{DDD/1000 inhabitants-day} = (\text{Total DDDs in grams} * 1000) / (\text{population} * 365)$$

Reference was made to population estimates from the Tanzania Bureau of Statistics (TBS) to adjust the antivirals and antifungals consumption trends to the country population (Supplementary Table A2).

According to the AwaRE classes of antibiotics, we re-categorized the data proposed by the WHO [39,42]. The system comprises three groups of antibiotics: Access, Watch and Reserve (AwaRe) antibiotics.

4.7 Data analysis

Data files were combined, pivoted and aggregated using Microsoft Excel 2013 (Microsoft Corporation, Redmond, Washington, USA). We converted the strength, pack size and the quantity of the antibiotic product into milligrams, grams and kilograms. Generic names were harmonized to match the names in the ATC mapping file. We assigned each product a corresponding ATC code by matching it with the imported product's generic name. This mapping allowed the matching of the ATC category and the pharmaceutical category. The amount in milligram and DDD of an antimicrobial agent's active ingredient

was calculated and aggregated for each class collected. Tables and graphs were plotted to depict the trends in antibiotic utilization. Annual utilization data, aggregated per year, were entered into the Statistical Package for the Social Sciences (SPSS) version 20 (IBM Corp., Armonk, NY, USA). Time series and regression analyses were performed to ascertain the annual trend of antibiotic utilization. An autoregressive integrated moving average (ARIMA) model was established to predict the trends of antibiotic use. A p-value of less than 0.05 was considered statistically significant.

5. Conclusions

Overall, our data indicate an increase in the actual and projected use of antibiotics. Beta-lactams antibiotics comprised 45.8% of all utilized antibiotics in Tanzania. Therefore, there is a need for a Government intervention to curb inappropriate antibiotic utilization to mitigate the rising threat of antibiotic resistance should be a focus of the National Action plan on AMR and AMR stewardship.

However, this study should be considered a baseline for further studies that account for the local manufacturers' and export records, as some imported medicines may be exported to other countries. In addition, a population-based prescription database for antibiotics may be developed for easy antibiotics prescription monitoring and gathering of information for medicine utilization studies in Tanzania and other sub-Saharan African countries.

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