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Antibiotic Utilisation Patterns in Tanzania: A Retrospective Longitudinal Study Comparing Pre-and Intra-COVID-19 Pandemic Era Using Tanzania Medicines and Medical Devices Authority Data

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Short title: Influence of COVID-19 on Antibiotic Utilization Patterns in Tanzania

Synopsis

Background: Antimicrobial resistance (AMR) is a growing public health concern globally, and misuse of antibiotics is a major contributor.

Objective: This study investigated antibiotic utilisation patterns before and during the COVID-19 pandemic in Tanzania using data from the Tanzania Medicines and Medical Devices Authority (TMDA).

Methods: This retrospective longitudinal study analysed secondary data. The study compared antibiotics consumption in defined daily doses (DDD) per 1000 inhabitants per day (DID) in two distinct eras: 2018-2019 as the pre-COVID-19 era and 2020-2021 as the intra-COVID-19 era. Samples t-test was conducted using Statistical Package for the Social Sciences (SPSS).

Results: The study analysed 10,614 records and found an overall increase in antibiotics consumption from 2018 to 2021. We found that the consumption was 61.24 DID in the intra-COVID-19 era and 50.32 DID in the pre-COVID-19 era. Levofloxacin had the highest percentage increase in use, with a 700% increase in DID during the intra-COVID-19 era. Azithromycin had a 163.79% increase, while cefotaxime had a 600% increase. In contrast, some antibiotics exhibited a decrease in usage during the intra-COVID-19 era, such as nalidixic acid, which had a 100% decrease, and cefpodoxime, which had a 66.67% decrease.

Conclusion: Increased antibiotic consumption during the COVID-19 pandemic highlights the importance of implementing effective antimicrobial stewardship strategies to prevent AMR, especially during pandemics.

Introduction

Antimicrobial resistance (AMR) poses a serious global health threat by hindering the treatment of bacterial infections.[1] In low- and middle-income countries (LMICs), including Tanzania, the misuse and overuse of antibiotics have resulted in high rates of AMR, making it challenging to treat bacterial infections[2,3].

The Global Action Plan for Antimicrobial Resistance aims to address the mounting challenge of increasing antimicrobial resistance (AMR) through surveillance of antimicrobial use (AMU) and the development of antimicrobial stewardship (AMS) programs. Consequently, in Tanzania, AMS was introduced through the NAP on AMR[4] in 2017 and the second version of NAP[5] 2023-2028 focuses on monitoring AMU in humans and animals. [6]

This study aimed to investigate the changes and trends in antibiotic utilisation patterns in Tanzania before and during the intra-COVID-19 eras using Tanzania Medicines and Medical Devices Authority (TMDA) data from 2018 to 2021.

Methods

Study design, setting and period

This was a retrospective and longitudinal study conducted in Tanzania Mainland. The importation data was collected from TMDA headquarters in Dodoma, Tanzania, from January 2018 to December 2021.

Data collection

TMDA has developed and issued regulations and procedures that compel importers to apply for importation permits archived in the Regulatory Information Management System (RIMS)[6]. The data retrieved included antibiotic descriptions, generic names, strengths, dosage forms, pack sizes, prices, quantities, unit prices and issue dates. Anatomical Therapeutic Chemical (ATC) classification system and the daily defined dose (DDD), importers, and WHO Access, Watch, Reserve (AWaRe) classification (2021) status of antibiotics were also included [7]. Utilisation was expressed in DDD per 1000 inhabitants per day (DID) in accordance with the ATC/DDD (2019) WHO collaborating Center for Statistics Methodology. [8]

Data analysis

The sample t-test was conducted using the Statistical Package for the Social Sciences (SPSS) version 26.0 to assess the impact of the pre-and intra-COVID-19 era on antibiotics consumption. A *p*-value of less than 0.05 was considered statistically significant.

Ethical considerations

Ethical approval (DA. 25/111/28/01/2021) was obtained from the Muhimbili University of Health and Allied Sciences Research Ethics Committee.

Results

In total, 9,610 records of antibiotics imported for systemic use by humans between 2018 and 2021 were retrieved.

A total of 117.02 DID were utilised in Tanzania between 2018 and 2021, with a mean (standard deviation) of 29.25 (±4.63) DIDs. The year 2021 had the highest DID at 33.1, 47.0% higher than 2019, with the lowest DID at 22.5 (Table S1).

Tanzania imports these antibiotics from across continents and Kenya, India, and China were the major sources of antibiotics in the pre-and intra-COVID-19 eras. Tanzania and South Africa were sources of antibiotics only during the intra-COVID-19 era (Figure 1).

The oral dosage form contributed 151.18 (96.93%) of the DIDs (Figure S1). The contribution of individual dosage forms indicated that capsules contributed the most (Figure S2) and (Table S2).

Overall, the Access group had the highest DID at 82.9, followed by Watch, other, and Reserve. The Access group accounted for 70.8% (Figure S3) of the DID. The annual increase in the Watch group of antibiotics parallels a general decline in the Access group (Figure S3) and (Figure S4).

Using a paired samples t-test, the mean (M) and standard deviation (S.D.) of antibiotics consumption in the pre-COVID-19 period (M = 1.018, SD = 3.311) was significantly different from the intra-COVID-19 period (M = 1.232, SD = 3.796), t (51= -2.513, p-value = 0.015 and paired sample correlation of 0.994 with effect size, as measured by Cohen's d, being 0.312.

Overall, there was a 21% increase in the utilisation of antibiotics intra-COVID-19. Azithromycin (J01FA10) increased by 163% during the intra-COVID-19 era (Table S3).

Using level 3 of the ATC classification, beta-lactam antibacterials and penicillins (J01C) registered a significant 28.32% increase in consumption. A 4.96 DID increase between post-covid and pre-covid was noted for the beta-lactam antibacterials (Figure 2) and (Table S4).

Aminoglycoside antibacterials (J01G) exhibited a remarkable 186.44% increase. In contrast, amphenicols (J01B) experienced a substantial decrease by 63.79%. The class of macrolides, lincosamides and streptogramins (J01F) flagged a remarkable increase of 110.53% in consumption (Table S4). In addition, annual trends of antibiotics at class 3 of the ATC classification were observed (Table S5), where sulfonamides and trimethoprim (J01E) comprised 20.62% of all DID utilised, with the highest totals in pre-and intra-COVID-19 eras. Similar trends were indicated when considering the level 4 ATC classification (Table S6).

Discussion

We observed an annual increase in the total consumption of antibiotics, reaching 117.02 DID over four years. The consumption was 64.09 DID in the intra-COVID-19 era and 52.93 DID in the pre-COVID-19 era. Nevertheless, the mean is 29.25 (±4.01) compared to the mean of 22.07 (±48.85) DID in 2010 to 2016 consumption data in Tanzania[6]. The 2019 value of utilisation is less than previously predicted,[6] reflecting the impact of AMS under the NAP implementation. [4]

A paired samples t-test indicated a statistically significant increase in antibiotics consumption during the intra-COVID-19 era. The effect size, as measured by Cohen's d, was 0.312, indicating a small but practically significant increase. The high correlation ($r = 0.994$) between the two eras reinforces the reliability that the COVID-19 pandemic had a notable impact on antibiotics consumption in Tanzania.

The combined use of all antibiotics increased by 21.1% from the pre-COVID-19 period to the intra-COVID-19 period. An increase was noted for gentamicin (J01GB03) at +204.3%, followed by azithromycin (J01FA10) at +163.3% and tetracycline (J01AA07) at +141.2%. A decrease was observed in chloramphenicol (J01BA01) (-64.6%), norfloxacin (J01MA06) (-37.4%), and nitrofurantoin (J01XE01) (-31.1%). A 150% increase in azithromycin use was noted in other studies in LMICS and HICs. [9] A study in Croatia showed that azithromycin distribution increased from 1.76 in 2017 to 2.01 Days of Therapy (DOTS) units/1000 inhabitant-days in 2017–2020, indicating azithromycin overuse.[10] Other reports during the pandemic showed that azithromycin consumption increased up to 3 times compared to pre-COVID-19.[9,10]

Interestingly, the popularity of azithromycin emerged from reports of its antiviral activity and early pandemic reports of screening indicating potential activity for SARS-CoV-2 alone or in combination with hydroxychloroquine.[11] Later, several randomised clinical trials (RCTs) suggested that azithromycin does not reduce hospital admissions, respiratory failure, or death when compared to conventional therapy, and therefore, azithromycin should no longer be used to treat COVID-19.[12–15]

Several studies have revealed a significant increase in resistance to azithromycin in some strains of *Neisseria gonorrhoeae, E. coli and Streptococcus pneumoniae* [11,16–18] Therefore, continued use of azithromycin should have been limited to infections for which azithromycin is recommended rather than COVID-19. [11]

Examining the consumption at level 3 of ATC classification, we noted a remarkable increase during the intra-COVID-19 era of beta-lactam antibacterials, which penicillins (J01C) and aminoglycoside antibacterials (J01G) exhibited. At the same time, amphenicols (J01B) experienced a substantial decrease of up to -63.79%. The use of macrolides, lincosamides and streptogramins (J01F) also increased remarkably by 110.53%. This finding underscores the specific impact of the pandemic on the consumption of these antibiotics. The major contributor to this increase was azithromycin.

The overall consumption of antibiotics increased from 52.935 DID (pre-COVID-19) to 64.088 DID (intra-COVID-19, with a total change of 21.07%.

Overall, the ATC level 3 class of sulfonamides and trimethoprim (J01E) ranked the top consumed group with only a 10.19% increase in consumption, suggesting continued reliance on this class of antibiotics during the pandemic. This could be due to their effectiveness against certain infections and their wide availability, especially for HIV/AIDS patients. This is usually indicated by the higher contribution of sulfamethoxazole + trimethoprim (J01EE01) used in the HIV program.

For tetracycline (level 3 class J01A), there was a moderate consumption increase from 0.145 DID (pre-COVID-19) to 0.251 DID (intra-COVID-19, a 72.96% increase, even though this class ranked lower compared to previous studies in Tanzania where the class was among the top contributors of consumed antibiotics.[6] It is important to note that the percentage change in usage should be taken with caution since it is calculated based on a relatively small difference in values, and the absolute values of DID for each antibiotic may vary significantly.

A recent study conducted in Cameroon during the COVID-19 pandemic revealed that antibiotics were highly overused and misused, leading to increased AMR.[19]

This study is one of the few conducted in sub-Saharan Africa to estimate antibiotics utilisation at the national level. The data indicate an increase in the consumption of antibiotics during the intra-COVID-19 era, with a mean of 29.25 DIDs utilised in Tanzania between 2018 and 2021. This average was less than that studied between 2010 and 2016 in Tanzania, where the mean was 57.4 DIDs over seven years. A study conducted in Tanzania from 2017 to 2019 also reported a slightly higher average compared to this study.[20]

These results highlight the importance of expanding the monitoring of AMU and implementing AMS programs to address the issue of AMR, especially during global health crises such as the COVID-19 pandemic. The observed changes in antibiotic consumption highlight the need for continued monitoring and the development of interventions to ensure the rational use of antibiotics since the increase in overall consumption may contribute to AMR. Antibiotic stewardship programs must be emphasised intra-COVID-19 in the healthcare landscape.

According to this AWaRe classification, the Access group consists of antibiotics that are active against many susceptible bacteria and have lower resistance potential than antibiotics in the other groups. In this study, the proportion of Access antibiotics was 82.9%, more than the 60% cutoff suggested by the WHO. The utilisation of Watch antibiotics with higher resistance potential is increasing annually. Nevertheless, utilisation of Reserve antibiotics for treating infections due to multi-drug-resistant organisms [7] is minimal.

Limitations of the study

Our study could not exclude some antibiotics, that may have expired or were re-exported to neighbouring countries and those produced locally. Moreover, regional variations in consumption are not accounted for, which is important for understanding local healthcare practices and the impact of AMS interventions.

Conclusion

This study highlights an increase in the consumption of antibiotics during the COVID-19 pandemic in Tanzania.

Recommendations

Monitoring AMU in countries via import permits may be a novel way to track this consumption in LMICs. Informative studies using data from community pharmacies and hospitals may provide accurate antibiotic consumption, continuous surveillance, and AMS interventions.

Availability of Data and Materials

All data are included in this article.

Acknowledgement

We thank the TMDA staff for providing the importation data.

Funding

This study was carried out as part of our routine work

Transparency declarations

None to declare

Supplementary data

Figures (S1-S4) and Tables (S1-S6) are available as Supplementary data at JAC-AMR Online.

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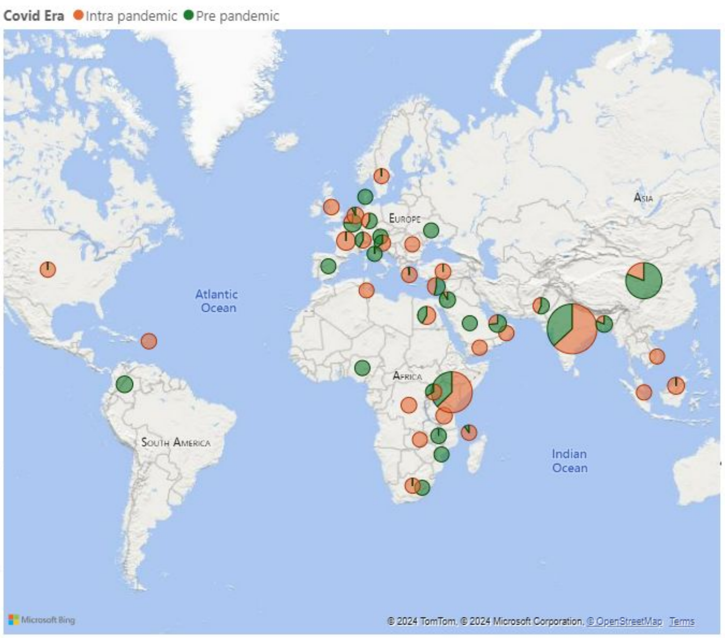
Figures



Supplier country	Intra pandemic	Pre pandemic	Total
India	37.409779	21.793166	**59.202945**
Kenya	20.477139	12.227278	**32.704417**
China	4.109403	17.567528	**21.676931**
France	0.668055	0.001317	**0.669372**
Egypt	0.245378	0.175342	**0.420721**
Belgium	0.091799	0.286489	**0.378288**
Cyprus	0.155306	0.179270	**0.334576**
United Arab Emirates	0.085874	0.238659	**0.324533**
Dubai	0.195148	0.066028	**0.261176**
Malaysia	0.165985	0.000026	**0.166010**
Netherlands	0.118351	0.009103	**0.127453**
Columbia		0.122548	**0.122548**
Tanzania	0.113635		**0.113635**
Bangladesh	0.020896	0.089552	**0.110448**
Slovenia	0.043744	0.025022	**0.068766**
Pakistan	0.029441	0.038719	**0.068160**
Jordan	0.005260	0.055877	**0.061138**
Uganda	0.028394	0.014415	**0.042809**
Switzerland	0.023149	0.016926	**0.040075**
Turkey	0.023767	0.000000	**0.023767**
Democratic Republic Of Congo	0.023045		**0.023045**
United Kingdom	0.016502		**0.016502**
Germany	0.006227	0.008540	**0.014767**
Malawi	0.000029	0.012790	**0.012820**
Greece	0.011969	0.000271	**0.012240**
Comoro	0.004922	0.000560	**0.005483**
Korea	0.002725	0.002665	**0.005390**
British Virgin Islands	0.003457		**0.003457**
Yemen	0.002820		**0.002820**
Singapore	0.002305		**0.002305**
Total	**64.087948**	**52.934562**	**117.022510**

Figure 1: Worldwide country frequency of importation of antibiotics in the pre-and intra-COVID-19 eras. The size of the bubble signifies the DIDs imported from the respective country.

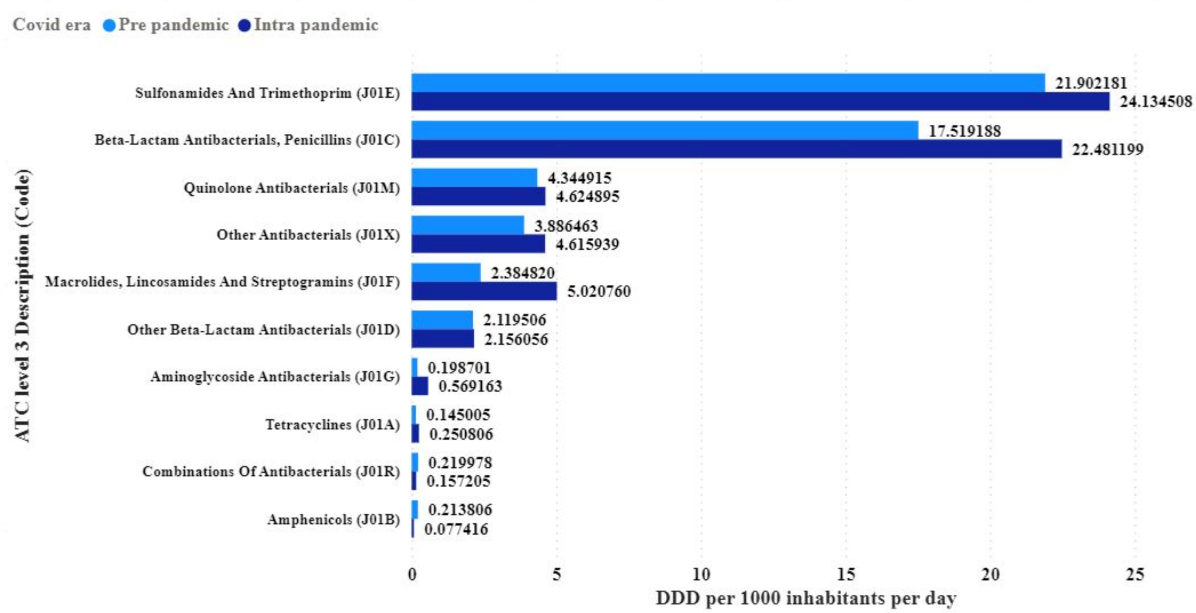


Figure 2: Contribution of each class (level 3 ATC classification) of antibiotics utilised in Tanzania from 2018 to 2021.

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The Global Action Plan for Antimicrobial Resistance aims to address the mounting challenge of increasing antimicrobial resistance (AMR) through ~~the~~ surveillance of antimicrobial use (AMU) and the development of antimicrobial stewardship (AMS) programs. Consequently, in Tanzania, AMS was introduced through the NAP on AMR[4] in 2017 and the second version of NAP[5] 2023-2028 focuses on monitoring AMU in humans and animals. [6]

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Methods

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Aminoglycoside antibacterials (J01G) exhibited a remarkable 186.44% increase. In contrast, amphenicols (J01B) experienced a substantial decrease by 63.79%. The class of macrolides, lincosamides and streptogramins (J01F) flagged a remarkable increase of 110.53% in consumption (Table S4). In addition, annual trends of antibiotics at class 3 of the ATC classification were observed (Table S5), where sulfonamides and trimethoprim (J01E) comprised 20.62% of all DID utilised, with the highest totals in pre-and intra-COVID-19 eras. Similar trends arewere indicated when considering the level 4 ATC classification (Table S6).

Discussion

We observed an annual increase in the total consumption of antibiotics, reaching 117.02 DID over four years. The consumption was 64.09 DID in the intra-COVID-19 era and 52.93 DID in the pre-COVID-19 era. Nevertheless, the mean is 29.25 (±4.01) compared to the mean of 22.07 (±48.85) DID in 2010 to 2016 consumption data in Tanzania[6]. The 2019 value of utilisation is less than previously predicted,[6] reflecting the impact of AMS under the NAP implementation. [4]

A paired samples t-test indicated a statistically significant increase in antibiotics consumption during the ~~pandemic.~~intra-COVID-19 era. The effect size, as measured by Cohen's d, was 0.312, indicating a small but practically significant increase. The high correlation (r = 0.994) between the two eras reinforces the reliability that the COVID-19 pandemic had a notable impact on antibiotics consumption in Tanzania.

The combined ~~usage~~use of all antibiotics increased by 21.1% from the pre-COVID-19 period to the intra-COVID-19 period. An increase was noted for gentamicin (J01GB03) at +204.3%, followed by azithromycin (J01FA10) at +163.3% and tetracycline (J01AA07) at +141.2%. A decrease was observed in chloramphenicol (J01BA01) (-64.6%), norfloxacin (J01MA06) (-37.4%), and nitrofurantoin (J01XE01) (-31.1%). A 150% increase in azithromycin use was noted in other studies in LMICS and HICs. [9] A study in Croatia showed that azithromycin distribution increased from 1.76 in 2017 to 2.01 Days of Therapy (DOTS) units/1000 inhabitant-days in 2017–2020, indicating azithromycin overuse.[10] Other reports during the pandemic showed that azithromycin consumption increased up to 3 times compared to pre-COVID-19.[9,10]

Interestingly, the popularity of azithromycin emerged from reports of its antiviral activity and early pandemic reports of screening indicating potential activity for SARS-CoV-2 alone or in combination with hydroxychloroquine.[11] Later, several randomised clinical trials (RCTs) suggested that azithromycin does not reduce hospital admissions, respiratory failure, or death when compared to conventional therapy, and therefore, azithromycin should no longer be used to treat COVID-19.[12–15]

Several studies have revealed a significant increase in resistance to azithromycin in some strains of *Neisseria gonorrhoeae, E. coli and Streptococcus pneumoniae* [11,16–18] Therefore, continued use of azithromycin should have been limited to infections for which azithromycin is recommended rather than COVID-19. [11]

Examining the consumption at level 3 of ATC classification, we noted a remarkable increase during the intra-COVID-19 era of beta-lactam antibacterials, which penicillins (J01C) and aminoglycoside antibacterials (J01G) exhibited. At the same time, amphenicols (J01B) experienced a substantial decrease of up to -63.79%. The use of macrolides, lincosamides and streptogramins (J01F) also increased remarkably by 110.53%. This finding underscores the specific impact of the pandemic on the consumption of these antibiotics; the. The major contributor to this increase was azithromycin.

The overall consumption of antibiotics increased from 52.935 DID (pre-COVID-19) to 64.088 DID (intra-COVID-19, with a total change of 21.07%.

Overall, the ATC level 3 class of sulfonamides and trimethoprim (J01E) ranked the top consumed group with only a 10.19% increase in consumption, suggesting continued reliance on this class of antibiotics during the pandemic. This could be due to their effectiveness against certain infections and their wide availability, especially for HIV/AIDS patients. This is usually indicated by the higher contribution of sulfamethoxazole + trimethoprim (J01EE01) used in the HIV program.

For tetracycline (level 3 class J01A), there was a moderate consumption increase from 0.145 DID (pre-COVID-19) to 0.251 DID (intra-COVID-19, a 72.96% increase, even though this class ranked lower compared to previous studies in Tanzania where the class was among the top contributors of consumed antibiotics.[6] It is important to note that the percentage change in usage should be taken with caution since it is calculated based on a relatively small difference in values, and the absolute values of DID for each antibiotic may vary significantly.

A recent study conducted in Cameroon during the COVID-19 pandemic revealed that antibiotics were highly overused and misused, leading to increased AMR.[19]

This study is one of the few conducted in sub-Saharan Africa to estimate antibiotics utilisation at the national level. The data indicate an increase in the consumption of antibiotics during the ~~pandemic~~intra-COVID-19 era, with a mean of 29.25 DIDs utilised in Tanzania between 2018 and 2021. This average was less than that studied between 2010 and 2016 in Tanzania, where the mean was 57.4 DIDs over seven years. ~~The~~A study conducted in Tanzania from 2017 to 2019 also reported a slightly higher average compared to this study.[20]

These results highlight the importance of expanding the monitoring of AMU and implementing AMS programs to address the issue of AMR, especially during global health crises such as the COVID-19 pandemic. The observed changes in antibiotic consumption highlight the need for continued monitoring and the development of interventions to ensure the rational use of antibiotics since the increase in overall consumption may contribute to AMR. Antibiotic stewardship programs must be emphasised intra-COVID-19 in the healthcare landscape.

According to this AWaRe classification, the Access group consists of antibiotics ~~with activity~~that are active against many susceptible bacteria and have lower resistance potential than antibiotics in the other groups. In this study, the proportion of Access antibiotics was 82.9%, more than the 60% cutoff suggested by the WHO. The utilisation of Watch antibiotics with higher resistance potential is increasing annually. Nevertheless, utilisation of Reserve antibiotics for treating infections due to multi-drug-resistant organisms [7] is minimal.

Limitations of the study

Our study could not exclude some antibiotics, that may have expired or were re-exported to neighbouring countries and those produced locally. Moreover, regional variations ~~of~~in consumption are not accounted for, which is important for understanding local healthcare practices and the impact of AMS interventions.

Conclusion

This study highlights an increase in the consumption of antibiotics during the COVID-19 pandemic in Tanzania.

Recommendations

Monitoring AMU in countries via import permits may be a novel way to track this consumption in LMICs. Informative studies using data from community pharmacies and hospitals may provide accurate antibiotic consumption, continuous surveillance, and AMS interventions.

Availability of Data and Materials

All data are included in this article.

Acknowledgement

We thank the TMDA staff for providing the importation data.

Funding

This study was carried out as part of our routine work

Transparency declarations

None to declare

Supplementary data

Figures (S1-S4) and Tables (S1-S6) are available as Supplementary data at JAC-AMR Online.

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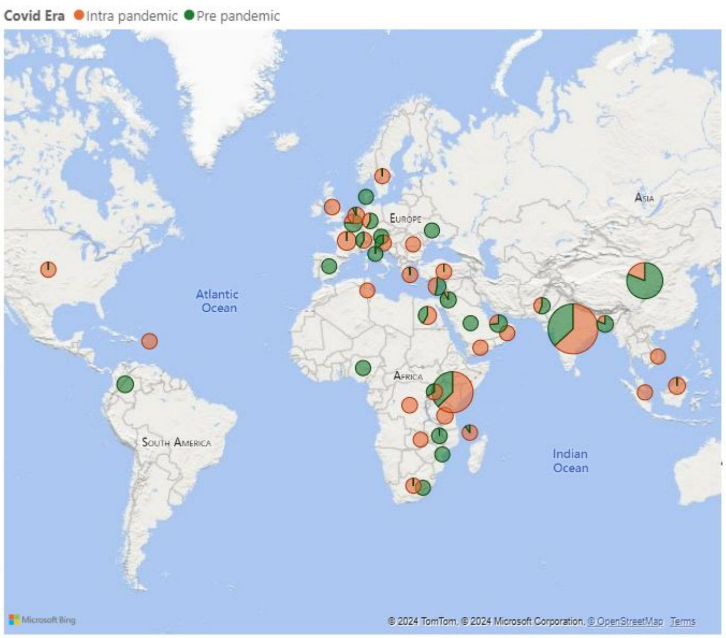
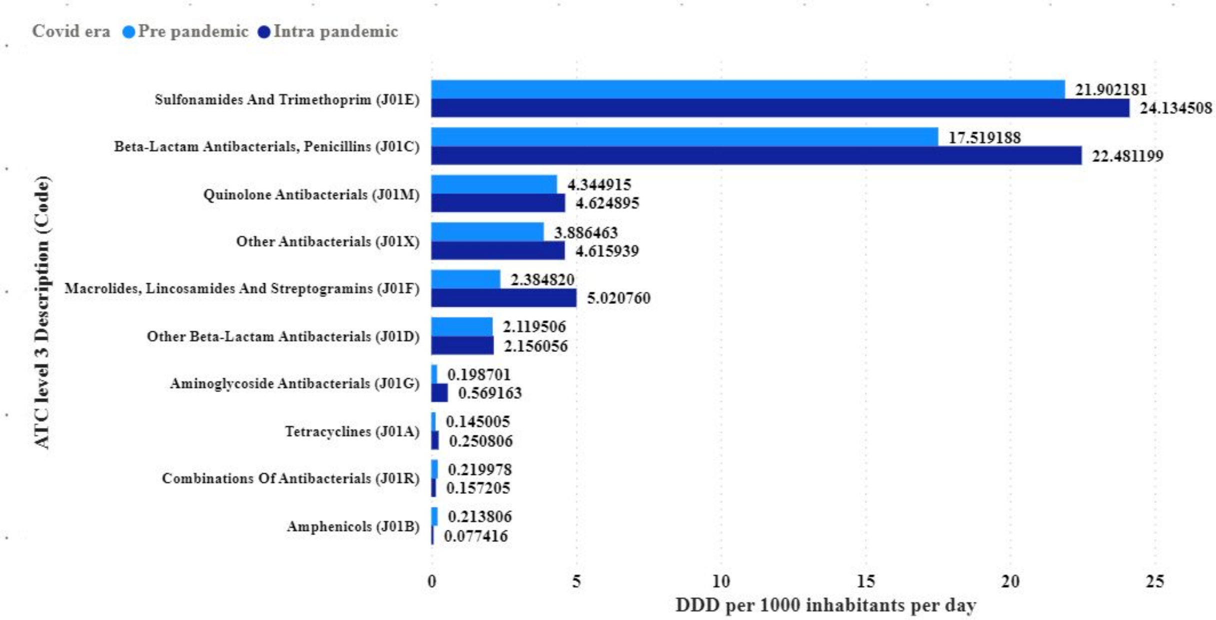
Figures



Supplier country	Intra pandemic	Pre pandemic	**Total**
India	37.409779	21.793166	**59.202945**
Kenya	20.477139	12.227278	**32.704417**
China	4.109403	17.567528	**21.676931**
France	0.668055	0.001317	**0.669372**
Egypt	0.245378	0.175342	**0.420721**
Belgium	0.091799	0.286489	**0.378288**
Cyprus	0.155306	0.179270	**0.334576**
United Arab Emirates	0.085874	0.238659	**0.324533**
Dubai	0.195148	0.066028	**0.261176**
Malaysia	0.165985	0.000026	**0.166010**
Netherlands	0.118351	0.009103	**0.127453**
Columbia		0.122548	**0.122548**
Tanzania	0.113635		**0.113635**
Bangladesh	0.020896	0.089552	**0.110448**
Slovenia	0.043744	0.025022	**0.068766**
Pakistan	0.029441	0.038719	**0.068160**
Jordan	0.005260	0.055877	**0.061138**
Uganda	0.028394	0.014415	**0.042809**
Switzerland	0.023149	0.016926	**0.040075**
Turkey	0.023767	0.000000	**0.023767**
Democratic Republic Of Congo	0.023045		**0.023045**
United Kingdom	0.016502		**0.016502**
Germany	0.006227	0.008540	**0.014767**
Malawi	0.000029	0.012790	**0.012820**
Greece	0.011969	0.000271	**0.012240**
Comoro	0.004922	0.000560	**0.005483**
Korea	0.002725	0.002665	**0.005390**
British Virgin Islands	0.003457		**0.003457**
Yemen	0.002820		**0.002820**
Singapore	0.002305		**0.002305**
Total	**64.087948**	**52.934562**	**117.022510**

Figure 1: Worldwide country frequency of ~~importations~~importation of antibiotics in the pre-and intra-COVID-19 ~~pandemic~~eras. The size of the bubble signifies the DIDs imported from the respective country.



266 **Figure 2: Contribution of each class (level 3 ATC classification) of antibiotics utilised in**
267 **Tanzania from 2018 to 2021.**

RESPONSE LETTER TO EDITOR AND REVIEWERS

Dear Dr. Priscilla Rupali, the Editor of JAC-Antimicrobial Resistance, Dear Reviewers,

This response concerns the Manuscript ID: JAC-AMR-2023-279-R1 titled " Antibiotic Utilisation Patterns in Tanzania: A Retrospective Longitudinal Study Comparing Pre-and Intra-COVID-19 Pandemic Era Using Tanzania Medicines and Medical Devices Authority Data" Submitted to the JAC-Antimicrobial Resistance for consideration to be published.

We respond point by point, following each comment raised by the Editor and the reviewers.

We attach the new manuscript and a document with track changes to indicate changes that were effected.

We are grateful for the time the Editor and reviewers have taken to review it and hope that the manuscript will be given due consideration for publication in JAC-Antimicrobial Resistance.

Kind regards

Raphael Z Sangeda, Corresponding Author

Comments by the Editor 1

The above manuscript has been reviewed and I have given it my consideration. The comments of the reviewer(s) are included at the foot of this letter.

Comments to the Author:
The article proposes to compare antibiotic utilisation during two time periods - pre COVID and during COVID pandemic.

1.However in the abstract it still talks about cefpodoxime and nalidixic acid use increasing after COVID.

Response to the Editor 1

We thank the Editor for the additional comment we addressed to improve the readability of the manuscript. The sentence now reads In contrast, some antibiotics exhibited a decrease in usage during the intra-COVID-19 era, such as nalidixic acid, which had a 100% decrease, and cefpodoxime, which had a 66.67% decrease.

We investigated all antibiotics consumed during this period without inclusion or exclusion criteria apart from the exclusion of antibiotics for topical use. Hence, the reporting of nalidixic acid and cefpodoxime.

Comment 2

2. Line 103 again after the pandemic rather than the intrapandemic period.

Response comment 2:

Thank you for this observation. We have changed all occurrences of the phrase "after pandemic" to "intra-COVID-19 era."

Comment 3

3.112 line - please delete redundant phrase "this study" ...

Response: This sentence has been corrected.

Comment 4
4. Line 318 please complete "A ....% increase in Azithromycin

Response 4:

We have changed the phrase, which now reads, "A 150% increase in azithromycin was noted …"

Supplementary Figures and Tables

Antibiotic Utilisation Patterns in Tanzania: A Retrospective Longitudinal Study Comparing Pre-and Intra-COVID-19 Pandemic Era Using Tanzania Medicines and Medical Devices Authority Data

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Short title: Influence of COVID-19 on Antibiotic Utilization Patterns in Tanzania

Table S1: Annual distribution of DIDs and number of permits of antibiotics imported in Tanzania between 2018 and 2021

Year	DID	Number of Permits
2018	30.39831	2,491
2019	22.53625	2,426
2020	30.96806	2,152
2021	33.11989	2,541
Total	**117.0225**	**9,610**

Key: DID: Daily Defined Dose per 1000 inhabitants per day

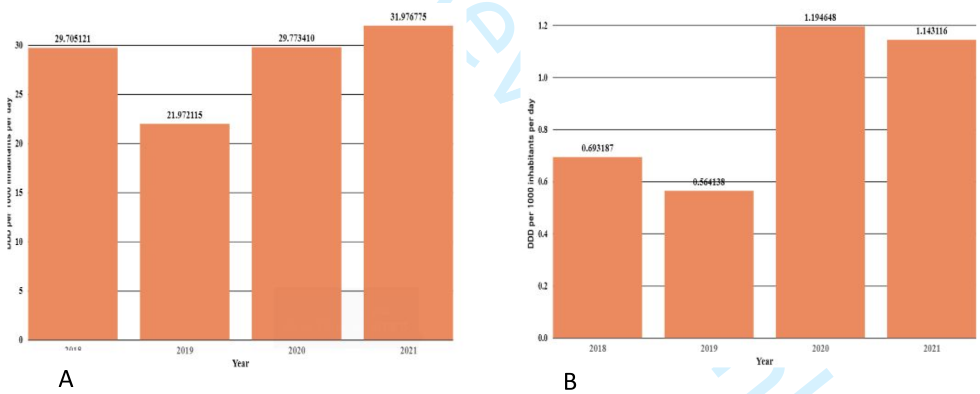

Figure S1: DID contribution for oral (Panel A) and parenteral (panel B) antibiotics

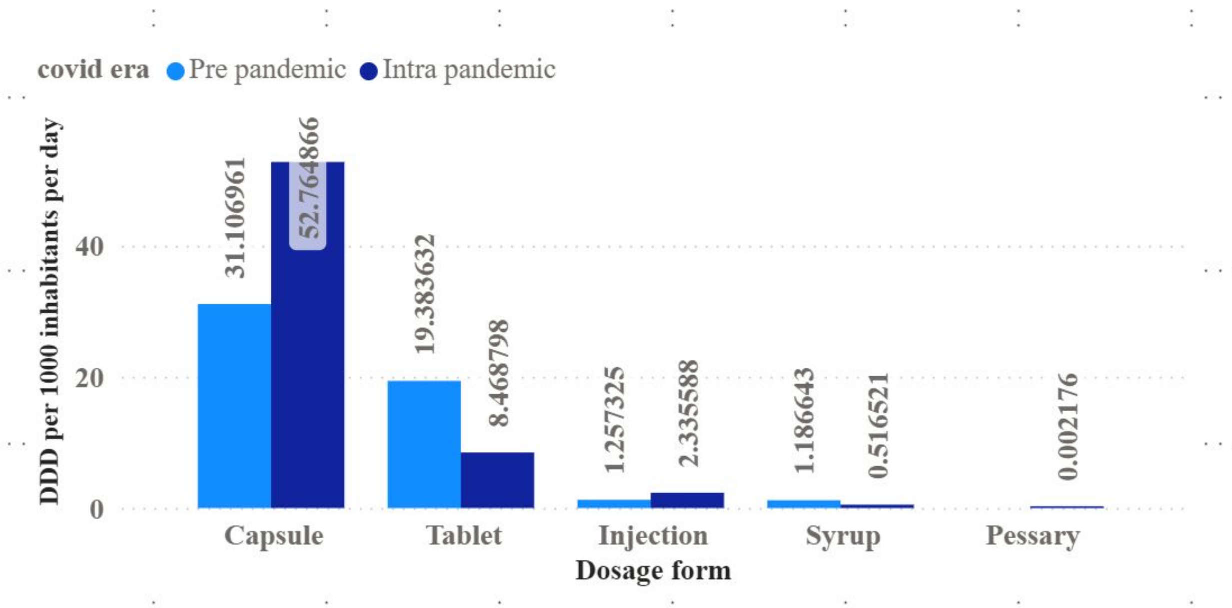

Figure S2: Contribution of antibiotics consumption per dosage and by COVID-19 era

Table S2: Annual contribution of consumption of antibiotics per dosage form

	Year	**% contribution**			
Dosage form	**2018**	**2019**	**2020**	**2021**	**All time**
Capsules	52.5	67.2	84.7	80.2	71.1
Injections	2.3	2.5	3.9	3.4	3.0
Pessaries				0.0	0.0
Syrup	2.7	1.6	0.7	0.9	1.5
Tablets	42.5	28.7	10.8	15.5	24.4
Total	**100.0**	**100.0**	**100.0**	**100.0**	100.0

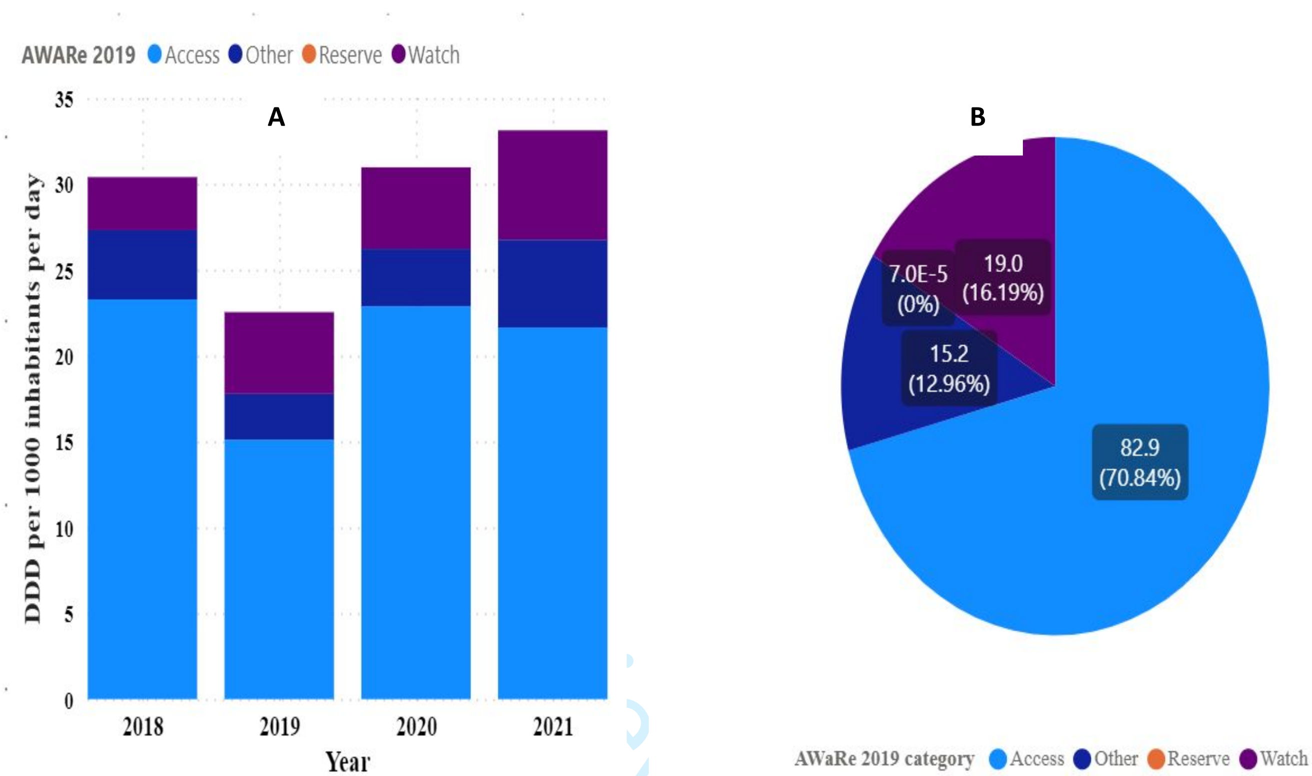

Figure S3: DID contribution per WHO AWaRe classification of antibiotics consumption from 2018-2021 (Panel) and overall for four years (panel b)

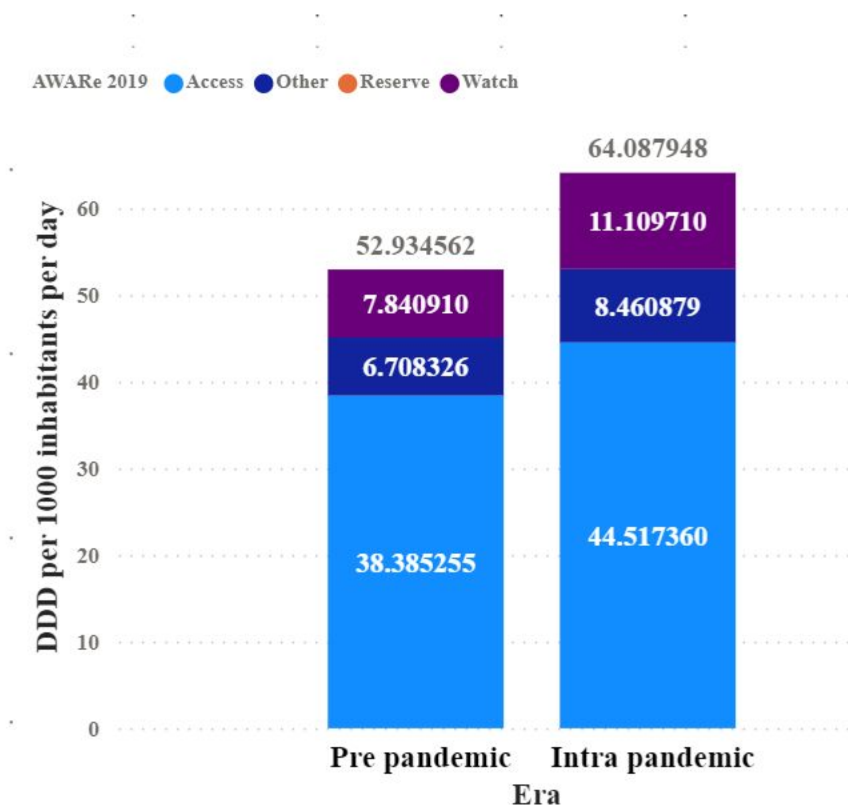

Figure S4: Distribution of Defined Daily Dose (DDD per 1000 inhabitants per day (DID)) of antibiotics per the World Health Organization's AWaRe class for antibiotics utilised in Tanzania from 2018 to 2020.

Table S3: Percentage changes in consumption during COVID-19 for top 20 consumed antibiotics aggregated per level 5 WHO ATC classification in DID

	DID			% Change
Antibiotic (ATC level 5 code)	**Pre COVID-19**	**Intra COVID-19**	**Total**	
Sulfamethoxazole + Trimethoprim (J01EE01)	21.90206	24.134214	46.036274	10.2
Amoxicillin (J01CA04)	8.958047	12.109729	21.067776	35.2
Ampicillin + Cloxacillin (J01CR50)	4.957764	6.056899	11.014663	22.2
Ciprofloxacin (J01MA02)	3.320329	3.875245	7.195574	16.7
Metronidazole (J01XD01)	2.550591	3.007772	5.558363	17.9
Azithromycin (J01FA10)	1.163502	3.063967	4.227469	163.3
Phenoxy methyl Penicillin (J01CE02)	1.839013	2.112984	3.951997	14.9
Erythromycin (J01FA01)	1.103971	1.837235	2.941206	66.4
Tinidazole (J01XD02)	0.988315	1.399698	2.388013	41.6
Amoxicillin + Clavulanate (J01CR02)	0.81814	1.280495	2.098635	56.5
Ceftriaxone (J01DD04)	0.912814	1.147269	2.060083	25.7
Cefalexin (J01DB01)	0.956694	0.637602	1.594296	-33.4
Norfloxacin (J01MA06)	0.929865	0.582542	1.512407	-37.4
Ampicillin (J01CA01)	0.737038	0.699213	1.436251	-5.1
Gentamicin (J01GB03)	0.184052	0.560144	0.744196	204.3
Amoxicillin + Flucloxacillin (J01CR50)	0.1963	0.216417	0.412717	10.2
Ciprofloxacin + Tinidazole (J01RA11)	0.219978	0.157204	0.377182	-28.5
Nitrofurantoin (J01XE01)	0.220675	0.152053	0.372728	-31.1
Tetracycline (J01AA07)	0.09207	0.222064	0.314134	141.2
Chloramphenicol (J01BA01)	0.210731	0.074664	0.285395	-64.6
Cefixime (J01DD08)	0.089679	0.18745	0.277129	109.0
Clarithromycin (J01FA09)	0.116368	0.116796	0.233164	0.4
Ornidazole (J01XD03)	0.124153	0.053845	0.177998	-56.6
Cefuroxime (J01DC02)	0.073682	0.04626	0.119942	-37.2
Ofloxacin (J01MA01)	0.052129	0.06318	0.115309	21.2
Cefadroxil (J01DB05)	0.041038	0.050992	0.09203	24.3
Levofloxacin (J01MA13)	0.008836	0.082444	0.09128	833.0
Doxycycline (J01AA02)	0.052935	0.028352	0.081287	-46.4
Cefotaxime (J01DD01)	0.005643	0.066155	0.071798	1072.3
Cefpodoxime (J01DD13)	0.02914	0.006786	0.035926	-76.7
Moxifloxacin (J01MA15)	0.015046	0.012868	0.027914	-14.5
Dexamethasone + Neomycin + Polymyxin B (J01GB05)	0.014225	0.008568	0.022793	-39.8
Lomefloxacin (J01MA07)	0.010553	0.008616	0.019169	-18.4
Meropenem (J01DH02)	0.00761	0.009849	0.017459	29.4

Ampicillin + enzyme inhibitor (J01CA51)	0.011029	0.004753	0.015782	-56.9
Nalidixic Acid (J01MB02)	0.008157		0.008157	-100.0
Lignocaine + Chloramphenicol + Beclomethasone Dipropiote + Clotrimazole (J01BA01)	0.003076	0.002752	0.005828	-10.5
Clindamycin (J01FF01)	0.00078	0.002762	0.003542	254.1
Spectinomycin (J01XX04)	0.001507	0.00086	0.002367	-42.9
Cefepime (J01DE01)	0.001017	0.000937	0.001954	-7.9
Flucloxacillin (J01CF05)	0.001857		0.001857	-100.0
Vancomycin (J01XA01)	0.000392	0.001189	0.001581	203.3
Cefoperazone + combinations (J01DD62)	0.000996	0.000461	0.001457	-53.7
Cefoperazone + Sulbactam (J01DD62)	0.000497	0.000615	0.001112	23.7
Bacitracin + Neomycin + Polymyxin B (J01XX10)	0.000561	0.000423	0.000984	-24.6
Cefpirome (J01DE02)		0.000867	0.000867	NA
Cilastatin + Imipenem (J01DH51)	0.0003	0.000487	0.000787	62.3
Cloxacillin (J01CF02)		0.000709	0.000709	NA
Amikacin (J01GB06)	0.00027	0.000181	0.000451	-33.0
Cefazolin (J01DB04)	0.000174	0.000275	0.000449	58.0
Tylosin Tartrate + Doxycycline Hyclate (J01AA02)		0.000389	0.000389	NA
PolyMyxin B (J01XB02)	0.000199	0.0001	0.000299	-49.7
Neomycin (J01GB05)		0.000267	0.000267	NA
Roxithromycin (J01FA06)	0.000199		0.000199	-100.0
Sulfadiazine + Trimethoprim (J01EE02)	0.000051	0.000136	0.000187	166.7
Kanamycin (J01GB04)	0.000153		0.000153	-100.0
Sulfadimidine (J01EB03)		0.000123	0.000123	NA
Trimethoprim (J01EA01)	0.00007	0.000035	0.000105	-50.0
Cefaclor (J01DC04)	0.000077	0.000027	0.000104	-64.9
Imipenem + enzyme inhibitor (J01DH56)	0.000089		0.000089	-100.0
Ceftazidime (J01DD02)	0.000056	0.000024	0.00008	-57.1
Linezolid (J01XX08)	0.00007		0.00007	-100.0
Tobramycin (J01GB01)	0.000001	0.000002	0.000003	100.0
Isoniazid + Pyridoxine + Sulfamethoxazole + Trimethoprim (J04AM08)		0.000001	0.000001	NA
Ampicillin + Sulbactam (J01CR01)	0		0	NA
Azithromycin + fluconazole + secnidazole (J01RA07)		0	0	NA
Erythromycin + combinations (J01FA01)		0	0	N.A.
Period Total	**52.934564**	**64.087946**	**117.02251**	21.1

Table S4: Consumption aggregated at ATC level 3 in the pre-COVID-19 and intra-COVID-19 era in Tanzania

ATC level 3 Description (Code)	Pre COVID-19	Intra COVID-19	Class Total	Change %
Sulfonamides And Trimethoprim (J01E)	21.902181	24.134508	46.036689	10.19226
Beta-Lactam Antibacterials, Penicillins (J01C)	17.519188	22.481199	40.000387	28.32329
Quinolone Antibacterials (J01M)	4.344915	4.624895	8.96981	6.443854
Other Antibacterials (J01X)	3.886463	4.615939	8.502402	18.76966
Macrolides, Lincosamides And Streptogramins (J01F)	2.38482	5.02076	7.40558	110.5299
Other Beta-Lactam Antibacterials (J01D)	2.119506	2.156056	4.275562	1.724458
Aminoglycoside Antibacterials (J01G)	0.198701	0.569163	0.767864	186.4419
Tetracyclines (J01A)	0.145005	0.250806	0.395811	72.96369
Combinations Of Antibacterials (J01R)	0.219978	0.157205	0.377183	-28.536
Amphenicols (J01B)	0.213806	0.077416	0.291222	-63.7915
Period Total	**52.934563**	**64.087947**	**117.02251**	**21.07014**

Table S5: Consumption aggregated at ATC level 3 from 2018 to 2021 in Tanzania

ATC Class level 3	2018	2019	2020	2021	Four Years Total
Sulfonamides And Trimethoprim (J01E)	14.617083	7.285097	12.50324	11.631268	46.036688
Beta-Lactam Antibacterials, Penicillins (J01C)	10.173568	7.34562	11.12656	11.35464	40.000388
Quinolone Antibacterials (J01M)	1.462383	2.882532	2.309063	2.315832	8.96981
Other Antibacterials (J01X)	1.784649	2.101814	1.960377	2.655562	8.502402
Macrolides, Lincosamides And Streptogramins (J01F)	1.064215	1.320605	1.65612	3.364641	7.405581
Other Beta-Lactam Antibacterials (J01D)	0.872695	1.24681	1.157145	0.998911	4.275561
Aminoglycoside Antibacterials (J01G)	0.155795	0.042906	0.07892	0.490243	0.767864
Tetracyclines (J01A)	0.042675	0.10233	0.10106	0.149746	0.395811
Combinations Of Antibacterials (J01R)	0.060057	0.159921	0.024369	0.132836	0.377183
Amphenicols (J01B)	0.165188	0.048619	0.051204	0.026212	0.291223
Drugs For Treatment Of Tuberculosis (J04A)				0.000001	0.000001
Year Total	**30.398308**	**22.536254**	**30.968058**	**33.119892**	**117.022512**

Table S6: Consumption aggregated at ATC level 4 from 2018 to 2021 in Tanzania.

ATC Class level 4	2018	2019	2020	2021	Four years Total
Amphenicols (J01BA)	0.165188	0.048619	0.051204	0.026212	0.291223
Beta-Lactamase Resistant Penicillins (J01CF)	0.000632	0.001225	0.000709		0.002566
Beta-Lactamase Sensitive Penicillins (J01CE)	0.97563	0.863383	1.066293	1.04669	3.951996
Carbapenems (J01DH)	0.006551	0.001447	0.00222	0.008116	0.018334
Combinations Of Antibacterials (J01RA)	0.060057	0.159921	0.024369	0.132836	0.377183
Combinations Of Drugs For Treatment Of Tuberculosis (J04AM)				0.000001	0.000001
Combinations Of Penicillins, Incl. Beta-Lactamase Inhibitors (J01CR)	3.626861	2.345343	3.431805	4.122006	13.526015
Combinations Of Sulphonamides And Trimethoprim Incl. Derivatives (J01EE)	14.617026	7.285085	12.503105	11.631245	46.036461
First Generation Cephalosporins (J01DB)	0.310298	0.687607	0.376731	0.312137	1.686773
Fluoroquinolones (J01MA)	1.454226	2.882532	2.309063	2.315832	8.961653
Fourth Generation Cephalosporins (J01DE)	0.000656	0.000361	0.00063	0.001174	0.002821
Glycopeptide Antibacterials (J01XA)	0.000293	0.000098	0.000166	0.001022	0.001579
Imidazole Derivatives (J01XD)	1.710669	1.952389	1.893326	2.567989	8.124373
Lincosamides (J01FF)	0.000276	0.000503	0.000896	0.001866	0.003541
Macrolides (J01FA)	1.063939	1.320101	1.655224	3.362775	7.402039
Other Aminoglycosides (J01GB)	0.155795	0.042906	0.07892	0.490243	0.767864
Other Antibacterials (J01XX)	0.001017	0.001122	0	0.001283	0.003422
Other Quinolones (J01MB)	0.008157				0.008157
Penicillins With Extended Spectrum (J01CA)	5.570445	4.135668	6.627752	6.185944	22.519809
Second Generation Cephalosporins (J01DC)	0.042137	0.031622	0.009737	0.03655	0.120046
Short-Acting Sulfonamides (J01EB)			0.000123		0.000123
Tetracyclines (J01AA)	0.042675	0.10233	0.10106	0.149746	0.395811
Third Generation Cephalosporins (J01DD)	0.513052	0.525773	0.767827	0.640932	2.447584
(Not classified)	0.072727	0.148216	0.066897	0.085291	0.373131
Year Total	**30.398307**	**22.536251**	**30.968057**	**33.11989**	**117.022505**