Knowledge of use of antibiotics among consumers in Tanzania

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Background: Studies assessing consumers' knowledge of the rational use of antibiotics are essential to understand the knowledge gap before intervention strategies are instituted.

Objectives: To assess the knowledge of rational use of antibiotics among consumers in Dar es Salaam, Tanzania.

Methods: A cross-sectional study assessing knowledge of rational use of antibiotics among 960 consumers was conducted in Dar es Salaam in March 2021. Participants were consecutively enrolled from outpatient pharmacies in selected public and private hospitals and marketplaces in Ilala Municipality. Data were collected using the WHO-validated questions on knowledge of consumers of antibiotic uses.

Results: Overall, 196 (20.4%) and 503 (52.4%) participants demonstrated good knowledge of rational antibiotic use and conditions that can be treated with antibiotics, respectively. However, 678 (70.6%) responded that they stopped using antibiotics after dose completion, 515 (53.6%) would request the same antibiotic if it had helped to treat a similar condition in the past and 406 (42.3%) are willing to use the same antibiotic if a friend or family member used the medication previously to treat similar signs and symptoms. Besides, the following conditions were mentioned as being treatable with antibiotics: influenza (50.7%), sore throat (61.4%) and urinary tract infection (60.5%).

Conclusions: The majority of the consumers had poor knowledge of the rational uses of antibiotics and a moderate proportion had good knowledge of the conditions that are treatable with antibiotics. Those with a high level of education and with health insurance had good knowledge of rational uses of antibiotics.

Introduction

Antibiotic resistance (AR) is a major global health challenge. It is defined as the ability of microbes such as bacteria or fungi to resist standard dose(s) of antibiotics that were previously effective. Inappropriate use of antibiotics in treating infectious diseases, animal keeping and agricultural activities are the major contributing factors towards the emergence and spread of AR. A recent update on antibiotic susceptibility profiles from Tanzania reported that most of the clinical bacterial isolates tested were resistant to most first- and second-line antibiotics. Another study from Tanzania on the susceptibility of reserved antibiotics demonstrated that 68% of the clinical isolates of Staphylococcus aureus tested were resistant to clindamycin, and 8.5% and 75.6% of the tested Klebsiella spp. were resistant to meropenem and cefepime, respectively. Similar trends of resistance of clinical bacterial isolates toward commonly used antibiotics have been reported in Kenya and Malawi, which are located in the same geographical location.

Antibiotics are misused in low- and middle-income countries. Shortage of healthcare services, dispensing of antibiotics as over-the-counter medication, profit inclination and weak regulatory authorities contribute to the observed misuse of antibiotics in developing countries. Also, lack of knowledge of antibiotic uses, potential side effects, correct dose and dosage, indication and drug–drug interaction have been associated with the observed poor patient management and occurrence of AR. Due to inadequate healthcare services in developing countries, most people rely on private community drug outlets, which embrace self-medication practice, as their primary level of care. Private drug outlets are claimed to be profit-oriented businesses, provide poor quality services and employ incompetent dispensers that...
significantly contribute to inappropriate use of medications. For instance, Minzi et al. (2013) observed a massive violation of antibiotic use in accredited drug dispensing outlet shops in Tanzania, where patients would be irrationally given antibiotics, including undergoing intramuscular injection of penicillins.

Shortage of guidelines on how to dispense and treat patients using antibiotics, lack of surveillance systems; lack of updated local treatment guidelines and continuing education to healthcare providers on uses of antibiotics; poor regulation on the use of human antibiotics in veterinary and agricultural activities; and misuses of antibiotics by livestock keepers (wrong dose, route of administration and antibiotic combination) have been suggested as the source of AR in developing countries. In addition, lack of knowledge of the consequences of inappropriate use and poor disposal of antibiotics among consumers contribute significantly to the emergence and spread of AR.

AR poses a burden and stress to the resource-scarce healthcare system already existing in developing countries through increasing treatment costs, increasing the risk of adverse drug reactions, long duration of hospital stays and increased mortality due to manageable conditions. Globally, it is estimated that by 2050, 10 million people will die of infectious diseases if new antibiotics are not discovered, or if the existing ones are not protected from resistance. Several measures have been proposed to fight AR, such as raising the level of knowledge of the community on the appropriate use of antibiotics and the consequences of using the drugs without medical consultation. However, understanding the knowledge gap among antibiotic consumers before intervention strategies are instituted is of paramount importance. Therefore, this study aimed to assess the knowledge of appropriate uses of antibiotics among consumers exiting public hospitals, private hospitals and market vendors as representative of antibiotic consumers who were not sick.

Methods

Study design and setting

This cross-sectional study was initiated in March 2021 in Dar es Salaam, Tanzania. Dar es Salaam is the largest city in Tanzania, and the 2012 census reported a population of 4.36 million within the region, accounting for 10% of the total Tanzania Mainland population. It is also Tanzania's major business city. Three different areas were used to recruit participants: patients who exited outpatient pharmacies in the selected public and private hospitals and people in marketplaces in Ilala Municipality. The permission for data collection was obtained in three regional referral public hospitals (Temekete, Mwananyamala and Amana), two private hospitals (Ekenywa and Mvungi) and the three most prominent markets in Ilala Municipality (Kariakoo, Karume and Buguruni).

Study population

Adult patients who purchased drugs from pharmacies in the private and public hospitals with at least one antibiotic in their prescription and market vendors who provided written informed consent were recruited.

Sample size and sampling

The sample size was calculated using the formula for cross-sectional study \[n = \frac{Z^2p(1-p)}{d^2}\]. Using a proportion (p) of 25% of the consumers with adequate knowledge of antibiotic uses obtained from a study by Mboya et al (2020), the confidence level of 95% (Z = 1.96) and precision (d) of 5%, a minimum sample size of 288 antibiotic consumers was obtained. Considering 10% to be non-respondents, a total of 320 antibiotic consumers was obtained. To get the most significant representation of the community, 320 consumers were assessed from public hospitals, 320 from private hospitals and 320 from the marketplaces to reach a target of 960 participants. In each setting, participants were recruited using a convenience sampling technique.

Data collection

A questionnaire comprised of two sections was used to collect data. Section A collected sociodemographic characteristics of the participants, including age, gender, marital status, residence, health insurance status, educational level, employment status and data collection setting. Section B contained two parts of the WHO-validated questions that assessed the consumers' knowledge of appropriate uses of antibiotics.

Part I consisted of three questions that were analysed individually. Respondents who answered correctly for all three questions were regarded as having good knowledge of the uses of antibiotics. Part II asked whether consumers knew if antibiotics can or cannot be used to treat the following infections: malaria, sore throat, influenza, diarrhoea, headache, body aches, fever, infected skin wounds and urinary tract infections (UTIs). A participant was regarded as having good knowledge of treatable conditions using antibiotics if he/she managed to answer a minimum of four conditions correctly.

Data analysis

Data were entered in an MS Excel sheet and transferred to SPSS version 25 (IBM SPSS Statistics for Windows, Version 25.0, released 2017; IBM Corp., Armonk, NY, USA) for data cleaning and analysis. Results were summarized using frequency and percentages. A binary logistic regression model was used to check for the determinants of the consumers' knowledge of antibiotic uses and conditions that can be treated with antibiotics. A P value of <0.05 was considered statistically significant.

Ethical considerations

Ethical clearance was granted by the director of research and publication ethics committee of Muhimbili University of Health and Allied Sciences (MUHAS). Permission to conduct the study was sought from the respective hospitals and markets administration before commencement of data collection. The purpose of the study was explained to every participant and informed written consent was obtained: i.e. an individual purchased an antibiotic, the drug dispenser informed the clients of the ongoing study (for hospital settings) and directed the patient to the room that was used for data collection within the pharmacy building. After obtaining informed consent, face-to-face interviews were conducted using a Swahili version of the questionnaire.

Data availability

The dataset generated and/or analysed during the current study is available from the corresponding author upon reasonable request.

Results

Out of 960 respondents, 494 (51.5%) were female and 559 (58.2%) were married. More than a third (344, 35%) of the participants had primary education, 457 (47.6%) were self-employed and the majority (568, 59.2%) were not covered by health insurance (Table 1).
Knowledge of the rational use of antibiotics

In total, 406 (42%) of the antibiotic consumers responded it is okay to use the same antibiotic if a friend or family member used it to treat the same symptom or disease before. More than half (515, 53.6%) of respondents said it is okay to request the same antibiotic if it helped you treat the same symptoms/disease previously. The majority (678, 70.6%) replied that they stop using antibiotics after finishing the dose indicated. Generally, 196 (20.4%) of the consumers had adequate knowledge of the uses of antibiotics (Table 2).

Consumers’ knowledge of conditions that can be managed using antibiotics

The participants responded that the following conditions could be treated using antibiotics: UTI 581 (60.5%), infected skin wound 462 (48.1%), fever 367 (38.2%), diarrhoea 568 (59.2%), influenza 487 (50.7%) and sore throat 589 (61.4%). In total, 592 (62%) and 511 (53.3%) of the respondents said antibiotics could not treat malaria and body aches, respectively. Overall, 503 (52.4%) of the respondents had good and 457 (47.6%) poor knowledge of the conditions treated with antibiotics (Figure 1).

**Table 1.** Demographic characteristics of the respondents and area of recruitment (n = 960)

| Variables          | n (%)   |
|--------------------|---------|
| Gender             |         |
| Male               | 466 (48.5) |
| Female             | 494 (51.5) |
| Age                |         |
| 18–35              | 539 (56.1) |
| 36–55              | 333 (34.7) |
| >55                | 88 (9.2)  |
| Marital status     |         |
| Married            | 559 (58.2) |
| Unmarried          | 401 (41.8) |
| Residence          |         |
| Urban              | 736 (76.7) |
| Semi-urban         | 224 (23.3) |
| Employment         |         |
| Self-employed      | 457 (47.6) |
| Employed           | 278 (29.0) |
| Unemployed         | 225 (23.4) |
| Education level    |         |
| Primary            | 344 (35.8) |
| Secondary          | 328 (34.2) |
| Tertiary           | 288 (30.0) |
| Health insurance status |      |
| Yes                | 392 (40.8) |
| No                 | 568 (59.2) |
| Place of recruitment |       |
| Community          | 320 (33.3) |
| Public hospitals   | 320 (33.3) |
| Private hospitals  | 320 (33.3) |

Knowledge of the rational use of antibiotics

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Consumers’ knowledge of conditions that can be managed using antibiotics

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**Table 2.** Consumers’ knowledge of the uses of antibiotics (n = 960)

| Variable                                                                 | n (%)   |
|--------------------------------------------------------------------------|---------|
| Do you think it is good to use the same antibiotic if a friend or family member used it to treat the same symptom or disease before? |         |
| Yes                                                                      | 406 (42.3) |
| No                                                                       | 517 (53.8) |
| I don’t know                                                             | 37 (3.9)  |
| Do you think it is good to ask/request the same antibiotic if it helped you treat the same symptoms/disease previously? |         |
| Yes                                                                      | 515 (53.6) |
| No                                                                       | 429 (44.7) |
| I don’t know                                                             | 16 (1.7)  |
| When do you think you should stop taking antibiotics once you have started treatment? |         |
| When I finish the dose as directed                                       | 678 (70.6) |
| When I feel better                                                       | 251 (26.2) |
| I don’t know                                                             | 31 (3.2)  |
| Overall knowledge                                                        |         |
| Good                                                                     | 196 (20.4) |
| Poor                                                                     | 764 (79.6) |

Determinants of consumers’ knowledge of the uses of antibiotics

Following binary logistic regression, participants with secondary education (aOR = 1.5, 95% CI = 1.01–2.38, P = 0.04), unemployed (aOR = 1.5, 95% CI = 1.03–2.33, P = 0.04) and those who attended public hospitals (aOR = 1.92, 95% CI = 1.21–3.04, P = 0.005) were more likely to have low knowledge of antibiotic uses, and the differences were statistically significant. Gender, age, marital status, health insurance status and residence showed no effect on the level of knowledge of antibiotic uses among the consumers following multivariate binary logistic regression analysis (Table 3).

Determinants of consumers’ knowledge of conditions that are treated with antibiotics

Following binary logistic regression analysis, gender, residence and marital status showed no association with the consumers’ knowledge of conditions that can be treated using antibiotics. Consumers with primary education were about two times more likely to have poor knowledge than those with tertiary education (aOR = 1.77, 95% CI = 1.19–2.61, P = 0.004). Respondents from the community markets and public hospitals were 1.67 and 1.46 times more likely to have poor knowledge of conditions that are treated with antibiotics compared with those who attended private hospitals (aOR = 1.67, 95% CI = 1.18–2.36, P = 0.004 and aOR = 1.46, 95% CI = 1.03–2.08, P = 0.03, respectively). Good knowledge of the conditions that are treatable with antibiotics was significantly associated with age and health insurance. Those aged between 26 and 35 years were 1.72 times more likely to have good knowledge compared with those <25 years (aOR = 1.72, 95% CI = 1.25–2.36, P = 0.001); individuals with health insurance...
Figure 1. Response of the respondents on conditions that are treatable using antibiotics (n = 960).

Table 3. Determinants of consumers’ knowledge of the uses of antibiotics (n = 960)

| Variables                        | cOR (95% CI) | P value | aOR (95% CI) | P value |
|----------------------------------|--------------|---------|--------------|---------|
| Gender                           |              |         |              |         |
| Male                             | 0.98 (0.72–1.33) | 0.89    | 1 (0.75–1.44) | 0.79    |
| Female                           | 1            |         | 1            |         |
| Age                              |              |         |              |         |
| 18–35                            | 0.5 (0.22–1.03) | 0.06    | 1.84 (0.81–4.16) | 0.14    |
| 36–55                            | 1.5 (1.06–2.13) | 0.02    | 1.2 (0.80–1.82) | 0.38    |
| >55                              | 1            |         | 1            |         |
| Marital status                   |              |         |              |         |
| Married                          | 1.2 (0.88–1.65) | 0.25    | 1.1 (0.77–1.58) | 0.58    |
| Unmarried                        | 1            |         | 1            |         |
| Residence                        |              |         |              |         |
| Urban                            | 1 (0.72–1.52) | 0.81    | 1.1 (0.93–1.59) | 0.72    |
| Semi-urban                       | 1            |         | 1            |         |
| Employment                       |              |         |              |         |
| Self employed                    | 1            |         | 1            |         |
| Employed                         | 1.2 (0.72–1.85) | 0.55    | 1.5 (0.93–2.50) | 0.1     |
| Unemployed                        | 1.6 (1.12–2.44) | 0.01    | 1.5 (1.03–2.33) | 0.04    |
| Education level                  |              |         |              |         |
| Primary                          | 1.09 (0.72–1.64) | 0.68    | 1.2 (0.76–2.04) | 0.4     |
| Secondary                        | 1.6 (1.08–2.33) | 0.02    | 1.5 (1.01–2.38) | 0.04    |
| Tertiary                         | 1            |         | 1            |         |
| Health insurance status          |              |         |              |         |
| Yes                              | 1.2 (0.90–1.70) | 0.19    | 0.9 (0.64–1.19) | 0.76    |
| No                               | 1            |         | 1            |         |
| Place of recruitment             |              |         |              |         |
| Community                        | 1.3 (0.92–1.90) | 0.14    | 1.7 (0.82–1.82) | 0.34    |
| Public hospitals                 | 2.12 (1.37–3.25) | 0.001   | 1.92 (1.21–3.04) | 0.005   |
| Private hospitals                | 1            |         | 1            |         |

cOR, crude OR; aOR, adjusted OR.
were 1.69 times more likely to have good knowledge compared with those with no insurance (aOR = 1.69, 95% CI = 1.24–2.32, \( P = 0.001 \)) (Table 4).

### Discussion

WHO highlighted several measures to fight AR worldwide, including raising the community level of knowledge of the rational use of antibiotics. To design and formulate interventions accordingly, understanding the baseline knowledge of the community is of importance. This study aimed to assess the level of knowledge and its determinants among consumers of the rational uses of antibiotics in Dar es Salaam, Tanzania.

Generally, the study found that the majority (79.6%) of respondents had inadequate knowledge of the uses of antibiotics. Specifically, 42.3% and 53.6% of the consumers responded that it is okay to use/request the same antibiotics if a friend or family member previously used them or it helped to treat the same symptom or disease, respectively. Also, 70.6% of the respondents said they stopped using antibiotics after finishing the dose as directed. Regarding the knowledge of conditions that are treatable using antibiotics, 52.4% demonstrated good knowledge. Most respondents said it is okay to use antibiotics to treat sore throat (61.4%) and influenza (50.7%) despite the conditions being viral diseases. However, a satisfactory (60.5%) number of consumers know that UTIs are treated using antibiotics and a good proportion agreed that body aches (53.3%) and malaria (60.5%) are not treatable using antibiotics. Respondents with tertiary education, with health insurance, who were employed and who attended private health facilities demonstrated good knowledge of the uses of antibiotics and conditions that can be treated using antibiotics.

Studies conducted in developing countries like Tanzania, Ethiopia, Nepal and Jordan on knowledge of antibiotic use among consumers reported similar findings. However, studies conducted in developed countries like Norway and Sweden reported that the majority of consumers have moderate to high knowledge. The observed inconsistency could be due to differences in respondents’ socioeconomic status. Low knowledge of antibiotic use observed in developing countries could be attributed to the lack of awareness campaigns and the fact that the majority have no formal education. Lack of formal education and having primary and secondary education levels have been associated with having poor knowledge of antibiotic uses among consumers in developing countries.

The current study demonstrated that a significant number of respondents reported that it is okay to use/request the same

| Variables                        | cOR (95% CI)   | \( P \) value | aOR (95% CI)   | \( P \) value |
|----------------------------------|----------------|---------------|----------------|---------------|
| Gender                           |                |               |                |               |
| Male                             | 0.88 (0.68–1.14) | 0.35          | 0.84 (0.64–1.09) | 0.19          |
| Female                           | 1              |               | 1              |               |
| Age                              |                |               |                |               |
| 18–35                            | 1.98 (1.23–3.19) | 0.01          | 1.57 (0.94–2.63) | 0.09          |
| 36–55                            | 1.69 (1.28–2.24) | 0.00          | 1.72 (1.25–2.36) | 0.001         |
| >55                              | 1              |               | 1              |               |
| Marital status                   |                |               |                |               |
| Married                          | 0.64 (0.49–0.83) | 0.001         | 0.75 (0.56–1.01) | 0.05          |
| Unmarried                        | 1              |               | 1              |               |
| Residence                        |                |               |                |               |
| Urban                            | 1.06 (0.78–1.43) | 0.72          | 1.05 (0.76–1.44) | 0.77          |
| Semi-urban                       | 1              |               | 1              |               |
| Employment                       |                |               |                |               |
| Employed                         | 1.64 (1.15–2.34) | 0.01          | 1.39 (0.95–2.04) | 0.09          |
| Unemployed                       | 1.17 (0.87–1.59) | 0.28          | 0.97 (0.70–1.35) | 0.88          |
| Self-employed                    | 1              |               | 1              |               |
| Education level                  |                |               |                |               |
| Primary                          | 2.01 (1.46–2.76) | 0.00          | 1.77 (1.19–2.61) | 0.004         |
| Secondary                        | 1.10 (0.79–1.52) | 0.55          | 0.93 (0.65–1.33) | 0.68          |
| Tertiary                         | 1              |               | 1              |               |
| Health insurance status          |                |               |                |               |
| Yes                              | 2.00 (1.54–2.61) | 0.00          | 1.69 (1.24–2.32) | 0.001         |
| No                               | 1              |               | 1              |               |
| Place of recruitment             |                |               |                |               |
| Community                        | 2.17 (1.58–2.98) | 0.00          | 1.67 (1.18–2.36) | 0.004         |
| Public hospitals                 | 1.65 (1.20–2.26) | 0.002         | 1.46 (1.03–2.08) | 0.03          |
| Private hospitals                | 1              |               | 1              |               |

cOR, crude OR; aOR, adjusted OR.
antibiotics if a friend or family member had used them or it helps him/her to treat the same symptom or disease as previously. Uses of antibiotics without medical consultation have been reported in many places and are among the contributors to AR.26,27 Unfortunately, most consumers believe that antibiotics are ‘wonder drugs’ that can cure any diseases.11 Studies around the region report a misunderstanding within the community, particularly with respiratory diseases. People believe that antibiotics help to accelerate healing from conditions like cough and sore throat, which primarily are due to viral infection.28–30

Although self-medication has its own advantages, the approach has been associated with the emergence and spread of AR.29,30 Due to weak regulatory systems, poor availability of medicine in healthcare facilities and the distance from residences to health facilities, the majority of people in developing countries depend on private drug outlets as the place for getting healthcare services.31,32 Unfortunately, studies show that private drug outlets embrace self-medication.33–35 In 2011 and 2013, studies conducted in Riyadh and Jeddah reported that 77.6% and 97.9% of the community pharmacies dispense antibiotics to consumers without a prescription.36,37 Most of the dispensers in private outlets have inadequate knowledge of the pharmacology of antibiotics, which is likely to contribute to irrational dispensing. In order to curb the emerging challenge of antibiotic overuse and misuse by the community in Tanzania, the regulatory authority introduced a guideline that each community outlet should have a prescription book to record the dispensed antibiotics. However, this approach has been ineffective due to weak supervision and inspection capacity of the authorities, hence the self-medication practice has not changed.

Besides, a satisfactory (60.5%) number of consumers know that UTI is treated using antibiotics. UTI is one of the infections that affect people living in low-income countries, especially women.38 Escherichia coli is the main bacteria causing UTI and is among the three bacterial agents listed by WHO as a threat to public health.3 The remaining common ones are Klebsiella pneumoniae and S. aureus.2 Studies conducted around the East African region show that most isolated clinical isolates of E. coli were resistant to the standard antibiotics used as a first- or second-line regimen.6,7 The high level of resistance demonstrated indicates that patients use antibiotics frequently to manage the condition, which could be the reason why most of the consumers are knowledgeable on the uses of antibiotics in the treatment of UTI.

The study also demonstrated that a good proportion of consumers agreed that antibiotics could not treat body aches (53.3%) and malaria (60.5%). These findings differ from what was reported in a study conducted in the Northern Zone, Tanzania, whereby 68.4% of the respondents agreed that antibiotics could be used to treat malaria.20 The difference in the study settings, sample size and prevalence of malaria between Dar es Salaam and Kilimanjaro could be reasons for the observed discrepancy. Several studies conducted in the malaria-endemic region to assess consumers’ behaviour towards the uses of antimalarial drugs reported that most patients visit community drug outlets to purchase the medication without medical consultation. The studies described further that because people living in the malaria-endemic region get malaria repeatedly, their level of awareness on drugs used to manage malaria is high.39 However, 39.5% still believe that antibiotics can be used to treat malaria, which signifies the importance of raising community awareness on the rational uses of antibiotics.

Again, the study demonstrated that respondents with a tertiary education level, having health insurance, who are employed and who attended private hospitals were more likely to have more knowledge of the uses of antibiotics and conditions that are treatable with antibiotics. Similar findings were reported in Tanzania in 2017 and 2020, in which those with tertiary education levels had good knowledge of antibiotic uses. Mbaya et al. (2020)20 reported that those with health insurance had good knowledge of antibiotic uses. Studies conducted in other developing countries (Trinidad and Tobago, Nepal) and a developed country (Norway) reported similar findings.21–23 Usually, education increases the level of understanding and changes the attitude and practice of most individuals. A study conducted in Portugal on the knowledge of students of antibiotics reported that a lack of formal education on the subject of interest can be a contributing factor.40 Nevertheless, in developing countries, most individuals with health insurance are employed and are also more likely to have high education. Besides, to avoid traffic in public hospitals, most individuals with health insurance opt to obtain health services from private health facilities.

The strength of the study is that it assessed a large number of antibiotic consumers from different catchment points (market vendors and antibiotic consumers in public and private hospitals). Also, the study adopted a validated WHO tool for assessing consumers’ knowledge of rational antibiotic uses. Lastly, filling out the questionnaire was supervised by an investigator for the purpose of offering clarification when it was needed.

Despite the strengths, because the study was cross-sectional it cannot establish any causal relationship between the variables. Since some of the respondents were exiting outpatients’ pharmacies in the hospitals with antibiotic prescriptions, this might have exaggerated the reported level of knowledge.

Conclusions
The majority of consumers had poor knowledge of the rational uses of antibiotics and a moderate proportion had good knowledge of conditions that are treatable with antibiotics. Those with a high level of education and health insurance demonstrated good knowledge of the rational uses of antibiotics. This study recommends that interventions are needed to raise the level of knowledge of the community of rational uses of antibiotics as a measure to fight AR.

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Transparency declarations
None to declare.

Author contributions
S.G. and M.K. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S.G., L.M., O. Mkusa, M.K., W.P.M., H.J.M., A.I.M. and R.F.M. Acquisition, analysis or interpretation of data: S.G., L.M., O. Minzi, R.F.M. and M.K. Drafting the manuscript: M.K. Critical revision of the manuscript for important intellectual content: all authors. All authors read and approved the final manuscript.

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