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Original Article

Assessment of the rational use of the most commonly prescribed antibiotics at the Department of Health of Ramallah in Palestine

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Abstract

Introduction: Appropriate antibiotic use requires using the right antibiotic, at the right dose, for the right duration, and at the right time. Drug-resistant diseases cause numerous deaths globally a year, and antibiotic stewardship is a cornerstone in fighting antibiotic resistance. This study focuses on tracking the antibiotic prescribing practices in Palestine and improving future antibiotic prescribing.

Methodology: Data from prescriptions of the most commonly prescribed antibiotics was collected from the Health Department of Ramallah and Al-Bireh clinics between January 1 to March 31, 2020. The prescriptions were divided into three categories according to the diagnosis status: unwritten, unspecific, and precise diagnosis. The precise prescriptions were further divided into two categories: appropriate or inappropriate indication. Only appropriate prescriptions were candidates for the assessment of dose and duration appropriateness.

Results: The percentages of the three categories of diagnosis precise, unspecific, and unwritten were 23.4%, 20.4%, and 56.2%, respectively. The percentage of appropriate prescriptions was 16.2%. Azithromycin was the most over-utilized antibiotic, followed by co-amoxiclav (amoxicillin/clavulanic acid). Amoxicillin and co-trimoxazole (trimethoprim/sulfamethoxazole) were under-prescribed. All the prescriptions indicated for urinary tract infections (UTIs) were inappropriate.

Conclusions: Most prescriptions were not candidates for analysis due to missing diagnosis. Amoxicillin, co-amoxiclav, cefuroxime, azithromycin, and ciprofloxacin were the most commonly prescribed antibiotics and were mostly indicated for pharyngitis. The duration of all sinusitis regimens was inappropriate. More rational antibiotic use in the Department of Health could be achieved by improving documentation, following updated guidelines, choosing cost-effective agents, and keeping track of local resistance patterns and antibiograms.

Key words: antibiotic; stewardship; resistance; infection; Palestine.

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Introduction

Antibiotics have transformed healthcare all over the world making once life-threatening diseases treatable and saving countless lives [1]. Resistance to antibiotics occurs when bacteria develop ways to evade drugs designed to kill them, hence taking the world back to times when simple infections were deadly [2-3]. Appropriate antibiotic use means using the right antibiotic, at the right dose, for the right duration, and at the right time [2]. Inappropriate antibiotic use in humans, animals, and plants is rapidly increasing the emergence and spread of bacterial resistance that threatens the healthcare, veterinary, and agriculture industries [4]. Drug-resistant diseases already cause at least 700,000 deaths globally a year and if no action is taken urgently, it is estimated that deaths could increase to 10 million globally per year by 2050 [4].

National and global campaigns are concerned with the rational use of available antibiotics because inappropriate use contributes to the emergence of multidrug-resistant bacteria, while there is a decline in the development of new antibiotics [5]. These drug-resistant pathogens include methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococci,* and resistant Gram-negative rod-shaped bacteria. Although empirical therapy using broad-spectrum antibiotics reduces mortality rates, prolonged and irrational antibiotic use is associated with drug interactions or diarrhea due to the spread of *Clostridium difficile*. The implementation of management programs for the available antibiotics aims to maintain their effectiveness by rational use and to limit the emergence of resistant strains [6-7].

Generally, the direct side effects of antibiotics like diarrhea, abdominal cramps, loss of appetite, nausea, photosensitivity, oral thrush, and rash are tolerated as the benefits of treatment can outweigh the side effects. However, the severe allergic reactions against some antibiotics, nephrotoxicity, and hepatotoxicity are exceptions. On the other hand, clinicians are less likely to consider another important side effect which is the overgrowth of resistant microorganisms that can precipitate secondary infections which are more difficult to treat. These resistant bacteria can spread to other patients and the environment. Acquired drug-resistance occurs when the organisms exposed to antibiotics undergo molecular changes that may enhance virulence and pathogenicity [8].

Resistance is increasing in many Gram-negative pathogens resulting in serious infections, due to extended-spectrum β-lactamases. A study on extended spectrum β-lactamase and carbapenem resistant Gram-negative bacilli in a Palestinian hospital found that over half of the patients had previous exposure to antibiotics [9]. The emergence of multidrug-resistant strains of these resistant Gram-negative bacteria is linked with longer hospital stays, higher healthcare costs, and increased mortality [10]. Another study on patients with resistant infections in two Palestinian intensive care units demonstrated high resistance patterns and increased use of the strongest antibiotics [11]. An additional factor that contributes to the increased rates of resistance in Palestine and other developing countries is the patient's self-medication with antibiotics [12-13].

Improving antibiotic use and antibiotic stewardship is a cornerstone in fighting antibiotic resistance. There are four strategies to combat antibiotic resistance that include preventing the spread of infections caused by resistant bacteria, monitoring and reporting antibiotic prescribing practices, improving antibiotic prescribing i.e. "stewardship" and developing new drugs and diagnostics [2]. Antibiotic stewardship interventions can reduce unnecessary antibiotic prescribing, prevent avoidable side effects, decrease *C. difficile* infections, and decrease antibiotic resistance and healthcare costs [2,14].

This study focuses on tracking the prescribing practices and improving future antibiotic prescribing. This can be achieved by using up-to-date antibiotic prescribing guidelines such as the National Institute for Health and Care Excellence (NICE) and the Infectious Diseases Society of America (IDSA) guidelines for managing common bacterial infections along with evaluating the general health status of patients and their other current medications.

Methodology

Data collection

A retrospective study design was used, data from 555 antibiotic prescriptions of the most commonly prescribed antibiotics was collected from the electronic health information system AviCenna, which is the official health information system adopted by the Palestinian Ministry of Health. Data was transferred to Microsoft Excel spreadsheets and qualitative analysis was conducted to examine the appropriateness of antibiotic prescribing. The study included all prescriptions for the commonly used antibiotics within the settings of the clinics of the Health Department of Ramallah and Al-Bireh, from January 1st to March 31st, 2020. The study population consisted of adults who were prescribed oral solid dosage forms of antibiotics.

Inclusion criteria

- Prescriptions for solid dosage forms of the most commonly prescribed antibiotics: amoxicillin, co-amoxiclav (amoxicillin/clavulanic acid), cefuroxime, azithromycin and ciprofloxacin, which were prescribed between January and March 2020, for the most common infections such as pharyngitis, bronchitis, urinary tract infections (UTIs), animal bites, sinusitis and otitis media, within the primary healthcare clinics of the Health Department of Ramallah and Al-Bireh settings.

Exclusion criteria

- Prescriptions for children.
- Prescriptions for forms other than oral dosage forms.

The collected data included the date of admission, clinic, antibiotic name, dose and regimen, output quantity, patient information including age, gender, pregnancy status, ICD-10 diagnosis, physician's note, past medical history, patient's drug list, malignancies, chronic viral infections, and allergy.

Data analysis

In order to assess the appropriateness of the prescriptions, they were divided into three categories according to the diagnosis status: unwritten diagnosis, unspecific diagnosis, and precise diagnosis. Unwritten prescriptions are the ones that do not include any description of a medical condition for diagnosis.

Unspecific prescriptions are those with diagnoses that are not mentioned in the guidelines or lack the site of infection. For example, prescriptions with acute pain, pain, and cough are considered unspecific prescriptions. Precise prescriptions are those with clearly mentioned diagnoses that can be found in the guidelines. Only precise prescriptions were candidates for the assessment of indications. The status of indication was also divided into two categories: appropriate and inappropriate according to IDSA and NICE antibiotics prescription guidelines [15]. Only appropriate prescriptions were candidates for the assessment of dose and duration appropriateness. Prescriptions with appropriate indication, dose, and duration were considered rational. The indication is central to the process of evaluation. The reason behind this approach is that the use of antibiotics that are not indicated for certain infections carries many negative consequences, including increased bacterial resistance, drug-related problems, and financial burden. Therefore, further analysis of the dose and duration for the prescriptions with inappropriate indications is unnecessary and meaningless.

Ethical considerations

Data was gathered after obtaining the approval of the research ethics committee at the College of Pharmacy at Birzeit University, approval number BZU-PNH-2003, the informed consent was waived by the College of Pharmacy research ethics committee as the data was collected from electronic medical records. The approval of the Palestinian Ministry of Health was also obtained prior to data collection. The privacy of the patients was maintained and their identities remained unknown. The study was conducted in accordance with the local legislation and Birzeit University institutional requirements which follow the ethical principles of the declaration of Helsinki.

Results

The 555 antibiotic prescriptions of the most commonly prescribed antibiotics examined in this study were collected from the Department of Health clinics of Ramallah and Al-Bireh between January and March 2020. These antibiotic prescriptions were analyzed according to the diagnosis status. They were divided into three categories: precise, unspecific, and unwritten with the following percentages, 23.4%, 20.4%, and 56.2%, respectively (Figure 1).

The antibiotic prescriptions with precise diagnosis were analyzed according to the indication status. They were divided into two categories: appropriate and inappropriate with the following percentages; 16.2%, and 83.8%, respectively (Figure 2).

The precise antibiotic prescriptions were distributed according to the diagnosis, appropriateness of indication, and the overall strength of the prescription. All the antibiotics that were prescribed for each precise diagnosis were recorded, counted, and evaluated in terms of their appropriateness of prescribing. The prescriptions containing antibiotics with appropriate indications were further analyzed and evaluated for dose and duration of treatment. The strength of each of these prescriptions evaluated for indication, dose, and

Figure 1. Percentages of the three categories of diagnosis for prescriptions (n=555): precise diagnosis, unspecific diagnosis, and unwritten diagnosis.

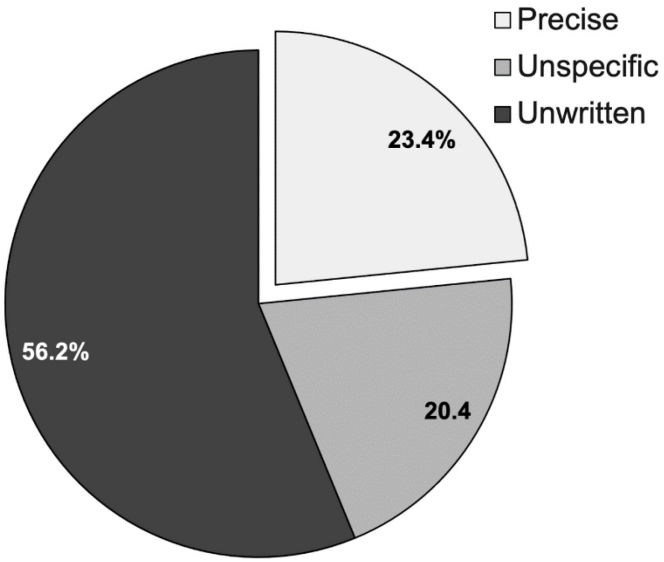
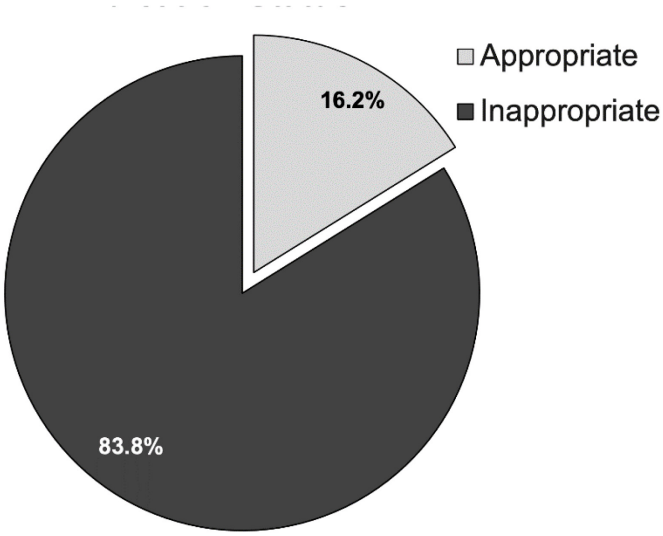


Figure 2. Percentages of the categories of indication for the precise antibiotic prescriptions (n=130) classified as appropriate or inappropriate indication.



duration was represented by the (+) symbol. Five out of 130 precise prescriptions were considered overall rational prescriptions that met all three criteria, having appropriate indication, dose, and duration. Eleven prescriptions out of the 130 precise prescriptions could have been rational if the durations were appropriate (Table 1).

The most common infections during the period of the study were pharyngitis, uncomplicated UTIs, and bronchitis. The greatest number of antibiotics was prescribed for these most common infections. For example, cefuroxime was overprescribed for UTIs and all of its prescriptions were inappropriately indicated. Only 2 out of the 30 azithromycin prescriptions for pharyngitis were appropriately indicated. Moreover, all co-amoxiclav prescribed for pharyngitis (n = 27) were inappropriately indicated and only 3 out of the 12 azithromycin prescriptions for bronchitis were appropriately indicated. It was remarkable that all co-amoxiclav prescribed for sinusitis were appropriately indicated (Table 1).

Discussion

The 555 antibiotic prescriptions of the most commonly prescribed antibiotics were collected from the Department of Health of Ramallah and Al-Bireh between January and March, 2020. These antibiotic prescriptions were analyzed according to the diagnosis status. They were divided into three categories: precise, unspecific, and unwritten with the following percentages; 23.4%, 20.4%, and 56.2%, respectively.

The presence of the health information system AviCenna in the Health Department of Ramallah and Al-Bireh is very important for documentation, as it allows for the easy registration and extraction of patient data. Information about the antibiotics prescribed was retrieved from the system. However, it can be utilized more effectively since only 23.4% of the prescriptions were precise. This was a major limitation as only 130 out of 555 prescriptions were candidates for analysis. The remaining 425 prescriptions had either no diagnoses or unspecific diagnoses. Therefore, further analysis for these prescriptions was not possible. Penicillin allergy is a crucial factor in selecting antibiotic therapy, especially when beta-lactams are considered as an option. In general, penicillin allergy was documented. However, the type of penicillin allergy for penicillin-allergic patients was not mentioned. The exact type of allergy contributes to the proper selection of the antibiotic [16]. For example, the narrow-spectrum cephalosporin cephalexin can be used for pharyngitis in patients who do not have anaphylactic reactions to penicillin. It is recommended to enhance the documentation of both the diagnosis of infection and the type of penicillin allergy for each patient.

As shown in Figure 2, the majority of the antibiotics prescribed were inappropriately indicated. Only 21 out of 130 prescriptions with precise diagnosis were considered appropriate in terms of indication. The most common infections during the period of the study were pharyngitis, uncomplicated UTIs and bronchitis. The greatest number of antibiotics was prescribed for these most common infections. The majority of azithromycin and co-amoxiclav prescriptions were indicated for pharyngitis cases, even though pharyngitis is a self-limiting infection and these antibiotics are broad-spectrum and more expensive than first-line agents such as amoxicillin [16]. Azithromycin is appropriately indicated for pharyngitis in patients with penicillin allergy, however, resistance of group A *Streptococcus* (GAS) to macrolides has become highly prevalent around the world and resulted in treatment failures [16]. On the other hand, GAS is the most common cause of bacterial pharyngitis and penicillin-resistant GAS has

Table 1. Distribution of Precise Antibiotic Prescriptions According to Diagnosis, Indication and Strength.

Diagnosis	ABx Indicated (no.)	No. of Appropriately Indicated Abx	Strength*
Pharyngitis	Azithromycin (30)	2	+++ ; ++
	Co-amoxiclav (27)	0	
	Amoxicillin (6)	4	2 (++) ; 2 (+)
	Cefuroxime (1)	0	
UTIs (Uncomplicated)	Cefuroxime (12), Ciprofloxacin (4), Co-amoxiclav (1), Azithromycin (1), Amoxicillin (1)	0	
Bronchitis	Azithromycin (12)	3	+++, ++, +
Animal Bites	Co-amoxiclav (2)	2	++, +
	Amoxicillin (4), Azithromycin (2)	0	
Sinusitis	Co-amoxiclav (8)	8	3 (+++), 5 (++)
Otitis Media	Co-amoxiclav (3)	0	
Others	Cefuroxime (5), Co-amoxiclav (4), Azithromycin (2)	0	
	Ciprofloxacin (5)	2	2 (++)

Abx: antibiotics; no.: number; UTI: urinary tract infection. (+) denotes that the indication of the antibiotic is appropriate; (++) either the indication and the dose or the indication and the duration are appropriate for the antibiotic prescribed; (+++) prescription is rational overall and meets all the three criteria, i.e, indication, dose and duration of therapy.

never been documented [16]. The use of co-amoxiclav for pharyngitis is not recommended and unnecessary in non-penicillin allergic patients. The wise use of antibiotics in the case of pharyngitis could be achieved simply if amoxicillin was prescribed instead of co-amoxiclav, and azithromycin was only indicated for penicillin-allergic patients.

A study examining the practices of antibiotic prescribing for upper respiratory tract infections within a hospital in Palestine showed that antibiotic prescribing was improper, but the prescription pattern was improved following certain interventions such as interviews, educational presentations, and the use of mobile applications, all of which can be implemented in other areas in Palestine to improve antibiotics prescribing [17].

There is a need for complete reform of the prescribing policies regarding UTIs cases. All of the antibiotics prescribed for uncomplicated UTIs were inappropriately indicated especially the 12 cefuroxime prescriptions. Co-trimoxazole (trimethoprim/sulfamethoxazole) was underutilized and was not one of the most commonly prescribed antibiotics in the Department of Health although it is considered one of the first-line agents for uncomplicated UTIs [18]. Only in one prescription co-trimoxazole was indicated for UTI.

The overprescription of cefuroxime for UTIs as an empiric treatment is not justified. Although cefuroxime is licensed to be given for uncomplicated UTIs, beta-lactams generally have inferior efficacy and more side effects than other antibiotics used for UTIs [18]. Moreover, according to the price list of medications of the Palestinian Ministry of Health, cefuroxime is much more expensive than most of the first-line agents recommended for uncomplicated UTIs. Co-trimoxazole was found to be the optimal first-line treatment of uncomplicated UTIs because of its low dosage frequency, and low treatment duration, also it is much more cost-effective and more suitable for non-pregnant patients compared to all other agents recommended for uncomplicated UTIs [18].

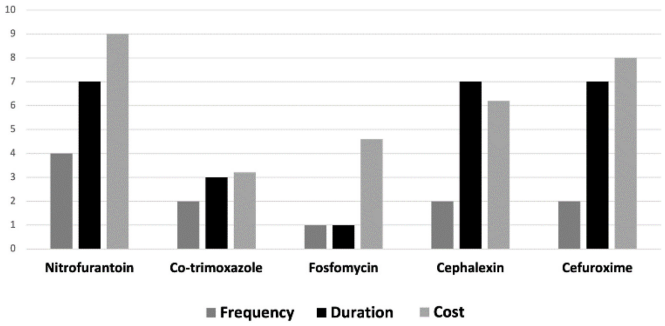
Nitrofurantoin is highly recommended as a first-line agent for uncomplicated UTIs because of its high efficacy and minimal resistance risk. However, in Palestine, nitrofurantoin is only available in the macrocrystals form that should be administered every 6 hours for at least one week, and it is relatively more expensive than most other recommended agents, also it has some restrictions for use in pregnant patients with uncomplicated UTIs. The use of nitrofurantoin may become preferable if the monohydrate/macrocrystals formulation is available and registered in Palestine because it is administered twice daily for a duration of 5 days and is more effective when compared to 3 days of co-trimoxazole [18].

Fosfomycin is one of the recommended first-line agents for uncomplicated UTIs due to its extremely low dosage frequency and duration because it is administered as a single-dose therapy. In addition, it has minimal resistance risk and is generally well-tolerated. On the other hand, it is important to notice that fosfomycin appears to have inferior efficacy compared to nitrofurantoin and co-trimoxazole. It is recommended to register fosfomycin in the essential drug list of the Palestinian Ministry of Health because it is considered safe in pregnancy, generally well-tolerated, could enhance patient adherence, and is of lower cost than all other available agents for uncomplicated UTIs except co-trimoxazole [18].

Although beta-lactams have inferior efficacy and more side effects than other antibiotics used for UTIs, they are an appropriate choice in case of uncomplicated UTIs in pregnant patients due to their safety. Cephalexin is a recommended beta-lactam because its spectrum of activity is narrower and it is of lower cost than other cephalosporins. Therefore, cephalexin turned out to be extremely underutilized at the Department of Health of Ramallah and Al-Bireh. The study recommendations can be relevant to other Ministry of Health Departments within the West Bank, because similar medications are supplied to the Department of Health clinics in different areas.

Figure 3 shows a comparison between different antibiotics prescribed for UTIs in terms of frequency and duration of dosage and cost. Since the choice of the appropriate antibiotic for uncomplicated UTIs depends on several factors such as drug allergy, tolerance, and pregnancy status, it is recommended to focus on the

Figure 3. Comparison between antibiotics prescribed for uncomplicated urinary tract infections (UTIs) in terms of frequency per day, duration (days), and average cost in Jordanian dinar (JOD).



documentation of sulfa drug allergy, G6PD deficiency, and pregnancy status.

As shown in Table 1, the second largest amount of azithromycin prescribed within the period of study was for acute bronchitis cases. It is critical to emphasize that acute bronchitis is almost exclusively viral in aetiology [19]. Therefore, only 3 out of the 12 azithromycin prescriptions were appropriately indicated. Antibiotics such as azithromycin may be considered for acute bronchitis cases in the following conditions: persistent high fever, purulent sputum or respiratory symptoms for more than 5 to 7 days. Moreover, they may also be considered for special populations such as elderly, immunocompromised and COPD patients [20]. Although the bacterial aetiology is extremely rare in the cases of acute bronchitis, the three most common pathogens responsible for bacterial acute bronchitis are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Bordetella pertussis* for which azithromycin is indicated [20]. It is recommended to encourage patients to use mist therapy (vaporizer/humidifier) and drink fluids to stay well-hydrated since hydration decreases respiratory secretions viscosity. In addition, mild analgesic-antipyretic therapy such as ibuprofen and paracetamol may be considered in cases of fever and malaise [20].

Similar to our study, a systematic review on the use of medicines in Arab countries found that antibiotic use was excessive and inappropriate [21]. A newly published study conducted in two government hospitals in Palestine also found that there was an inappropriate use of antibiotics [22]. All this improper use is associated with increased healthcare costs, high resistance patterns and increased use of the more powerful antibiotics as demonstrated in recent studies conducted in Palestine [9,11].

It was remarkable that all the eight antibiotic prescriptions for sinusitis were appropriately indicated since standard-dose co-amoxiclav is recommended as first-line therapy for acute bacterial rhinosinusitis in both children and adults, and 3 out of the 8 prescriptions were overall rational (Table 1). The remaining five prescriptions could have been rational if the durations were appropriate. The recommended duration of co-amoxiclav treatment for adults is 5-7 days [23]. However, the five prescriptions of co-amoxiclav were indicated for 10 or more days.

The ideal selection of empirical antibiotic therapy in the Department of Health of Ramallah and Al-Bireh could be achieved if local resistance rates are available since the guidelines link the use of certain antibiotics with their local resistance rates such as co-trimoxazole, macrolides and fluoroquinolones.

This study had some limitations. It was a retrospective study with data collected from electronic health records, where some crucial information was missing such as the precise diagnosis, which affected the analysis of many prescriptions. Also, the doses were missing for liquid antibiotic dosage forms and so pediatric patients were excluded from the study. Furthermore, the pregnancy status was not recorded and the appropriateness of antibiotics use in pregnancy could not be assessed. Additional missing data included current medications and the type of penicillin allergy. All this limited the data analysis. In addition, data collection was done during COVID lockdown which limited the access of researchers to the clinics where data was stored and increased the time needed for data collection.

Conclusions

Most antibiotic prescriptions in this study were not candidates for analysis due to inadequate diagnoses information. The antibiotics that were most commonly prescribed included amoxicillin, co-amoxiclav, cefuroxime, azithromycin and ciprofloxacin, with pharyngitis as the most common indication. More rational antibiotic use in the Department of Health could be achieved if the health information system was utilized more effectively in documenting precise diagnosis for each infection, types of drug allergies and pregnancy status. Antibiotics prescribing could be improved by following updated guidelines and choosing cost-effective agents. In addition, the availability of local resistance rates is the cornerstone towards ideal empirical antibiotic therapy. Further research could add to antibiotic stewardship such as studies that investigate the approaches the physicians utilize in diagnosis of infections and the development of local resistance rates of certain bacterial species to certain antibiotics.

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Authors' Contributions

All authors were involved in the planning and design of the study. OA CS FZ DA-H and DA-T performed the data acquisition. OA CS and FZ did the interpretation and analysis of data and wrote the first draft of the manuscript. LA did the

revising of the manuscript and supervised the research. All authors read and approved the final manuscript.

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