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Research Article

# OFF-LABEL USE OF ANTIBACTERIALS IN A CONTEXT OF ANTIMICROBIAL RESISTANCE THREAT

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**ABSTRACT**

**Objective:** The objective of the study was to describe the off-label use of antibacterial in prescriptions for hospitalized adult patients as per the Brazilian drug regulatory agency, namely, the National Health Surveillance Agency (ANVISA).

**Methods:** This is a cross-sectional study with prescriptions for inpatients in a teaching hospital. Data collection and analysis were based on the checklist of the Medicine Prescription, Use and Administration Protocol of the Ministry of Health, where the off-label use is classified as per information of ANVISA's Electronic Bulletin. Descriptive analyses were performed, and the method of logistic regression was used to evaluate the association between the off-label use of antibacterial and the explanatory variables age, gender, hospitalization clinic, and medical specialty.

**Results:** About one-third of the antibacterial was prescribed for off-label use, and the frequency of administration was the primary use outside standards established in the products' licenses (87.3%), and dose (7.4%) and the administration route was next. The third-generation cephalosporin was the most consumed class in this regimen (69.5%). In some cases, the off-label use was not supported by scientific evidence. The off-label use was positively associated with the variables gender (odds ratio [OR] = 2.48; confidence interval [CI] = 1.23–4.92) and the prescribing clinic (OR = 4.94; CI = 2.61–8.96).

**Conclusion:** Off-label use is a frequent practice in the studied environment, and in the face of a dramatic scenario of increased antibacterial resistance, it is imperative to adopt measures for the standardization of records and the rational use of this class of drugs.

**Keywords:** Drug prescriptions, Anti-infective agents, Drug use, Patient safety, Off-label use, Hospitals.

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## INTRODUCTION

One of the global challenges in the area of health is antimicrobial resistance, and it is urgent to rethink the use of antimicrobial drugs (AMD). The higher frequency of microbial resistance threatens the return of a time when infections were inevitably deadly or disabling, compromising treatments, and prevention in surgical and chemotherapy procedures. This raises the need to promote strategies to increase awareness and knowledge of the subject and foster safe and appropriate AMD use [1,2]. This is especially noticeable in hospitals where they are the second most used drug class and are responsible for the high drug costs [3].

The use of clinical and epidemiological methods to analyze the potential benefits and risks of drug therapy has become a requirement for the rational use of drugs. The knowledge of how drugs are being prescribed is necessary to suggest measures to improve prescribing habits, and the scientific evidence-based practice seeks to ensure drug safety, efficacy, and effectiveness [1-4]. The introduction of an antimicrobial stewardship program is required to improve the rational use of AMD, besides guidelines and an antimicrobial use monitoring process [4,5].

Off-label use is the term utilized for the use of a drug other than that recommended and listed in the product registration and package insert. It is associated with the freedom of evaluation and decision of the prescriber and is not illegal or necessarily incorrect [1]. Prescribing AMD is a common practice both in outpatient and inpatient care [6, 7]. High rates of off-label use of these drugs in adult (19% to 43%) and pediatric (1% to 94%) patients have been reported [8]. Decision-making for this type of use must be guided by safe and evidence-based criteria, ensuring adequate drug therapy. It involves, among other factors, indication, dose, administration route, frequency of administration, duration of treatment, lack of contraindications, and minimum likelihood of adverse reactions.

Further studies are required on this thematic to encourage the ethical use of off-label drugs. The checklist of the Brazilian Medication Prescription, Use and Administration Safety Protocol of the Ministry of Health is a document based on well-established scientific evidence and is a reliable source evaluating prescriptions in drug use studies [9]. Based on this instrument, we aimed to analyze the practice of prescriptions off-label AMDs in a public teaching hospital. The study bridges a gap in literature describing the off-label use of antibacterial in prescriptions for hospitalized adult patients as per the Brazilian drug regulatory agency, namely, the National Health Surveillance Agency (ANVISA).

## METHODS

### Study design and setting

This is a cross-sectional study carried out in a public hospital that provides care exclusively through the Unified Health System (SUS) and locates in the Northeast of Brazil. The hospital provides teaching, research, and related activities for undergraduate and graduate students. It is the reference hospital for the care of approximately 600,000 inhabitants in 26 cities of the South Regional Health Center, with a 180-bed urgency and emergency capacity, internal medicine, surgical and orthopedic clinic, pediatrics, psychiatry, neurology, and intensive

care unit (ICU). Antimicrobial stewardship was not implemented in the hospital. Clinical pathways published by the Hospital Infection Control Committee are not available frequently. Thus, AMDs are prescribed empirically and sometimes without microbial culture or gram. The hospital prescription is performed by a computerized physician order entry. The inpatient drug distribution system is individualized up to 24 h.

**Sample**

Individual prescriptions of patients of all ages with a hospital stay of more than 24 h in the period July 1–31, 2016, were included in this study. AMDs were chosen as markers because they were among the most prescribed drugs used in hospitals [4]. Prescriptions kept at the hospital pharmacy after drug dispensing was used as sample units, and the antimicrobials were the unit of analysis.

Inclusion criteria were individualized prescriptions of inpatients containing at least one drug on the hospital standardization list issued during the time of the survey as per the sampling process. Exclusion criteria were prescriptions of non-hospitalized patients attended in the emergency and outpatient services, and prescriptions without drug therapy. Prescriptions from Internal Medicine, surgical and orthopedic clinic, Neurology and the ICU were included. The other clinics were excluded because they did not issue individualized prescriptions (adopting a bulk ward stock), due to operational difficulties and technical access to medical records or because they did not have an inpatient service, respectively.

The sample was calculated using the StatCalc tool from Epi Info software 7.0, considering a 5% alpha error, a 10% beta error, and the mean prescriptions containing AMDs in the month before the start of the collection, resulting in 340 prescriptions. Hospital pharmacy prescriptions were sequentially numbered,and sampling was performed as per the traditionalsystematic sampling criteria, with a prospect of 15 daily prescriptions and a sampling interval of six. Considering thedecision to sample all the prescriptions issued in a given month, namely, July 2016, the process was continued even after reaching the calculated value, raising the sample to 352 prescriptions.

**Data collection, instrument, and variables**

For the collection, we used a form based on the checklist of the Medication Prescription, Use and Administration Safety Protocol [9].

The off-label use of AMDs was considered the outcome, characterized as any information discrepancy between the prescription and the product's package insert. We considered in this study the off-label use of "dose," "administration route," "administration frequency," and "age" (higher or lower than prescribed doses, administration frequency other than those recommended, administration routes that are in disagreement with those indicated and drugs prescribed for ages different from those recommended) [10]. The off-label use was classified as per the product license information contained in the professional's leaflet of ANVISA's Electronic Bulletin, the authority responsible for the regulation of medicines in Brazil [11]. The indication of use was not taken into consideration since all the prescriptions of AMD were administered immediately, timely, and empirically because the hospital did not have clinical protocols for AMD use, did not perform microbiological culture or gram. The independent variables were age (categorized from 0 to 18 years, from 19 to 59 years, and 60 years and over), gender, inpatient clinic, and medical specialty.

The patient's sociodemographic and clinical variations were collected from the medical records and the antimicrobials' data in the prescription.

The ATB were classified as per the first and fourth level of the Anatomical Therapeutic Chemical Classification (ATC) of the World Health Organization (WHO) in 15 pharmacological groups (fourth level). The evaluation of the off-label use of dose and frequency of administration (dose adjustment in geriatrics or patients with hepatic or renal function impairment) was performed by searching in laboratory tests (tests of creatinine, prothrombin time, albumin, and bilirubin) and clinical evaluation notes the diagnosis for renal or hepatic impairment. The Cockcroft-Gault formula was used to evaluate the need for renal adjustment.

**Data analysis**

A descriptive analysis was performed by estimating the absolute and relative frequencies of the selected variables. The continuous variables were shown through means and standard deviation. The Pearson's Chi-square test was used to compare proportions of categorical variables.

The association between the off-label use and the selected independent variables was performed through univariate and multivariate analyses using the binary logistic regression model. The magnitude of the association was calculated using odds ratios (ORs) with 95% confidence intervals (CI) and a significance level of 0.05. The independent effect of the variables on off-label use was verified in the multivariate analysis. The strategy of constructing the models was carried out by deleting variables until the final model was obtained, in which those with $p < 0.05$ remained. The Hosmer-Lemeshow test was used to verify the suitability of the final model. EpiData 3.1, 2008 (EpiData Association, Odense, Denmark) and SPSS 21.0, 2016 (IBM Corporation, Armonk, United States, USA) were used for tabulation and data analysis, respectively.

**Ethical considerations**

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (UFMG) under CAAE 1.325.634/2015.

## RESULTS

Of the 352 prescriptions, 59.0% (n = 211) contained AMDs. In total, 289 antimicrobial agents were prescribed containing 18 different drugs. Prescriptions had one (66.8%), two (29.4%) or three (3.8%) AMDs, but not all of them could be evaluated for off-label use, and 4.5% (13) did not contain information on dose, frequency, or administration route. Of the prescribed AMDs, 93 (33.6%) had discrepancies with the registry at ANVISA, and two prescriptions had two off-label types, totaling 95 (Table 1).

AMDs were classified according to the ATC classes, in which the five most prescribed classes were third-generation cephalosporins (28.1%), fluoroquinolones (23.6%), lincosamides (12.1%), fourth-generation

**Table 1: Demographic and pharmacotherapeutic characteristics of antimicrobial prescription of patients hospitalized in a public teaching hospital (n=211)**

| Characteristics | |
|---|---|
| Clinic, n (%) | |
| Internal medicine | 70 (33.2) |
| Surgical and orthopedic surgery | 83 (39.3) |
| Neurology | 22 (10.4) |
| ICU | 36 (17.1) |
| Gender, n (%) | |
| Male | 151 (71.6) |
| Female | 60 (28.4) |
| Age range (years), n (%) | |
| 0–18 | 13 (6.2) |
| 19–59 | 112 (53.1) |
| >60 | 85 (40.5) |
| Pharmacotherapy, n (%) | |
| Number of prescription | 352 |
| Number of antimicrobial prescription | 211 |
| Number of antimicrobial drugs | 289 |
| Number of antimicrobial prescriptions off-label as per ANVISA | 93 |
| Number of off-label prescribed | 95 |

ICU: Intensive care unit, ANVISA: National Health Surveillance Agency

cephalosporin (9%), carbapenems (7.6%), and others (19.6%). Table 2 shows the frequency of AMD used in the off-label regime, as per the ATC classification. The off-label use of "administration frequency" had the highest occurrence (87.3%), 95.2% toward increase and 4.8% toward decrease in the frequency. Third-generation cephalosporin ceftriaxone accounted for 78.4% of this discrepancy, all involving a two- to four-fold increase compared to the recommended frequency. Metronidazole, cefepime, and meropenem for parenteral use had up to four-fold daily increase in the frequency of administration, and ampicillin a six-fold daily increase.

Off-label use of "administration route" and "dose" appeared with frequencies of 5.3% and 7.4%, respectively. In the case of the "administration route," all involved the administration through a nasoenteral or gastric probe; while in the case of "dose," 57.1% was related to sub dose and 42.9%, overdose. The dose discrepancies involved vancomycin doses of 500 or 2000 mg every 12 h and levofloxacin 500 mg at 12-h intervals. No age use off-label was found.

The classes of AMDs prescribed in off-label regimen varied with the medical specialty and the hospitalization clinic, and the surgical and orthopedic clinic was the most frequent location of the event (63.4%). The general practitioner (university graduate) was the one that most prescribed AMDs for off-label use (38.5%) (Table 3).

The mean age of patients with off-label AMD prescriptions was 45.9 ± 22.6 years (13–91 years), and third-generation cephalosporin was the most used class in off-label regimen in all age groups. The age range of 19–59 years and males was the most involved in off-label use (57.0% and 72.0%, respectively). Eight prescriptions contained two classes of AMDs associated in an off-label regime (carbapenems and glycopeptides used in a higher frequency of association).

In the univariate analysis, the medical specialty and the prescribing clinic were associated with off-label use. On the other hand, the prescribing clinic was independently associated with off-label use (Table 4).

## DISCUSSION

Our findings confirm that despite all the problems involving antimicrobial agents, these are still prescribed off-label and allow us to show that this practice was adopted in about one-third of prescriptions containing AMD. These findings sensitize us about the higher risk of adverse events associated with this prescription profile, considering that off-label drug's efficacy/effectiveness and safety are not (generally) adequately assessed. The current scenario of AMD use worldwide has shown increasing levels of microbial resistance, and declining discovery of novel AMD drugs. Therefore, the off-label use of AMD is of great concern and should be further investigated [12,13].

The unit where the study was performed is a teaching hospital linked to the SUS, but until then, it had not implemented policies to control the prescribed drugs. There were no AMD use protocols and microbiological cultures were interrupted due to contractual and bidding problems with the outsourced provision of this service. This is very relevant if we consider the professional training process developed there and the consolidation of government policy to promote patient safety and the threat of bacterial resistance.

Most patients received a monotherapy treatment, in line with the main recommendations for the rational use of AMD [14]. The prevalence of males in the general and off-label consumption of AMD is a probable consequence of the higher number of hospitalizations due to accidents, mainly road traffic injuries, and other external causes prevalent in Brazil [15]. Since the Ministry of Health classifies it as medium-and high-complexity traumatology and orthopedics care unit, the hospital plays a key role as a referral to provide care to these cases in the region. Most of those involved in these accidents are middle-aged, which explains the higher consumption of AMD in the 19–59 years' age group.

While high, the frequency found by us underestimates the reality of this practice, since we did not evaluate the off-label use of AMD indication. The frequency was lower than that found in another university

**Table 2: Frequency distribution of the off-label use of antimicrobial drugs as per the anatomical therapeutic chemical classification (n=95)**

| ATC code | Class | Off-label use (%) | | |
|---|---|---|---|---|
| | | AF (n=83) | Dose (n=7) | Administration route (n=5) |
| J01DD | Third-generation cephalosporins (ceftriaxone) | 78.4 | - | - |
| J01DE | Fourth-generation cephalosporins (cefepime) | 6.0 | - | - |
| J01XA | Glycopeptide anti-bacterial (vancomycin) | - | 80.0 | - |
| J01MA | Fluoroquinolones (ciprofloxacin, levofloxacin) | 2.4 | 20.0 | 80.0 |
| J01DH | Carbapenems (meropenem) | 4.8 | - | - |
| S01AA | Eye antibiotics (tobramycin) | 4.8 | - | - |
| J01XD | Imidazole derivative (metronidazole) | 2.4 | - | 20.0 |
| J01CA | Penicillins, extended-spectrum (ampicillin sodium) | 1.2 | - | - |
| Total | | 100.0 | 100.0 | 100.0 |

ATC: Anatomical therapeutic chemical, AF: Administration frequency

**Table 3: Frequency distribution of the off-label use of antimicrobial prescription as per the prescribing clinic and medical specialty**

| | Off-label use | | p** |
|---|---|---|---|
| | Yes (%) | No (%) | |
| Clinic (n=93) | | | |
| Internal medicine (n=82) | 22.0 | 78.0 | <0.001 |
| Surgical and orthopedic surgery (n=111) | 53.2 | 46.8 | |
| Neurology (n=31) | 25.8 | 74.2 | |
| ICU (n=52) | 15.4 | 84.6 | |
| Medical specialty (n=91) | | | |
| Others* (n=85) | 29.4 | 70.6 | 0.003 |
| General surgeon (n=80) | 23.8 | 76.3 | |
| General practitioner (university graduate) (n=77) | 45.5 | 54.5 | |
| Orthopedist (n=23) | 52.2 | 47.8 | |

*Others: Neurologist, gastroenterologist, nephrologist, dermatologist, neurologist, maxillofacial, cardiologist, **Pearson's Chi-square test, p<0.05. ICU: Intensive care unit

**Table 4: Multiple logistic regression for off-label use with explanatory variables included in the model: Age, gender, medical specialty and prescribing clinic (n=95)**

| Explanatory variable | Off-label use (%) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | OR (CI) | p* | OR (CI) | p* |
| Age | | | | | |
| 0–59 years | 69.9 | 1.0 | 0.076 | | |
| 60 years and over | 30.1 | 1.62 (0.96–2.77) | | | |
| Gender | | | | | |
| Male | 72.0 | 1.39 (0.78–2.46) | 0.263 | | |
| Female | 28.0 | 1.0 | | | |
| Medical specialty | | | | | |
| Medical specialists** | 61.5 | 1.96 (1.14–3.39) | 0.016 | | |
| General practitioner (university graduate) | 38.5 | 1.0 | | | |
| Clinic | | | | | |
| ICU + internal medicine + neurology | 36.6 | 1.0 | <0.001 | 1.0 | <0.001 |
| Surgical and orthopedic | 63.4 | 4.37 (2.57–7.43) | | 4.20 (2.28–7.72) | |
| Hosmer–Lemeshow test | 0.962 | | | | |

*Binary logistic regression, statistically significant p value (<0.05), CI=95%, **Medical specialists: Neurologist, gastroenterologist, nephrologist, dermatologist, neurologist, maxillofacial, cardiologist, general surgeon, orthopedist. ICU: Intensive care unit, CI: Confidence interval, OR: Odds ratio

hospital [1], although similar to that found in the ICU [16]. Third-generation cephalosporins, the most prescribed antimicrobial agents, for off-label use as well, and the most consumed in all age groups, have low relative toxicity and extended spectrum [1-4]. This may be due to difficulties in determining the etiology of infection through the current hospital conditions, and by the lack of standardization in the decision-making for a prescription. These conditions lead to greater difficulties in acquiring knowledge about ADMs and the presence of multi-resistant strains [17]. Thus, the off-label use of this class of drugs is safer to the prescriber.

The practice of off-label use may be supported in situations where the drug has already shown to be useful in non-approved regimens, mainly if some scientific evidence includes at least one randomized controlled trial (RCT) [17], even without changes to the registry. Studies suggest that the prescription of a drug is not based only on what is recommended in the package insert, but one should take into account whether or not alternative treatments exist, the severity of the clinical condition and the lack of records due to market reasons [18]. We analyzed 13 different regimens prescribed in off-label use as per ANVISA, and when compared to the Food and Drug Administration (FDA) [19], we found ten off-label regimens, that is, the labels registered in regulatory agencies, sometimes by the same manufacturer, are different, thus reinforcing the need to consider such a reality in future drug registration decisions.

The most prevalent off-label use refers to changes in the frequency of administration. Such changes, when not performed safely and based on scientific evidence, may harm patient care [1,19]. For example, ceftriaxone powder for injectable solution, namely, the primary drug involved with this type of off-label use, was prescribed at 12-h intervals or even every 6 h instead of every 24 h, but the daily dose of 2 g was maintained. Ceftriaxone is among the time-dependent antibiotics due to its long half-life time and high plasma protein binding, assuring a serum concentration between 60% and 70% above the minimum inhibitory concentration between doses [20]. Although in this study we do not have the possibility of a clinical trial for use outside established standards, and while pharmacokinetics, in this case, favor a 24-h dosing schedule, there is scientific evidence that, for critically ill patients, ceftriaxone dose is indicated to be fractionated at 12-h intervals [21,22], which is a clinical prerogative for the prescriber's decision. The registration in the regulatory agencies of the U. S. and the European Union is permissive with the administration regimen at every 12 h, although with reservations (the European Medicines Agency records the dosage indication at the maximum dose of 4 g/day) [23,24]. These data suggest the outdated registration of ANVISA and reaffirm the need to update this document by manufacturers and review the product license at this regulatory agency. Thus, the Brazilian package insert could also be adapted and RCT could be conducted to compare ceftriaxone administration, the full dose administered once or full dose divided into two daily administrations.

Pharmacokinetic and pharmacodynamic parameters must be evaluated before any change in the frequency of administration or the dose of medicines. For example, for concentration-dependent AMDs, such as levofloxacin, as an injectable solution, a single dose per day is recommended, which achieves maximum concentrations at the site of infection, thus producing the maximum bactericidal effect [20]. However, we found in this study that it was prescribed twice a day, maintaining the usual dose of 500 mg, which disregards the pharmacokinetic and pharmacodynamic profile of the drug, impairing safety, and generating possible additional costs. It has been documented in literature that fluoroquinolones, including levofloxacin, are associated with increased risk of tendinitis, tendon rupture, cardiac arrhythmia, renal injury, and retinal detachment [7]. Thus, if there is no evidence to ensure the change in administration or dose intervals, the guidelines recommended in the package insert should be maintained. Therefore, our primary challenge is to maintain the effectiveness of the available AMDs, using them as per their individual pharmacokinetic and pharmacodynamic characteristics [14].

Regarding the off-label use of the "administration route," it was associated with a change in the administration of coated tablets through a nasogastric or nasoenteral tube. The recommendations in the package insert instructions are clear of not breaking, opening, or chewing such tablets. The prescription of this route can be considered a prescription error leading to a possible administration error. The preventable adverse events are a worldwide concern; one of the five leading causes of death [25] and nonoptimized drug therapy are responsible for costs of around 500 billion per year [26]. Another critical issue is that the manufacturer provides the pharmaceutical form of levofloxacin oral solution registered at the FDA [19], but not in Brazil, which is the most indicated pharmaceutical form for use in a probe.

Vancomycin was also involved in the off-label use of the dose. In this study, the dose of vancomycin was considered as off-label, since the package insert registered at ANVISA is incomplete, without the option of a dose per mg/kg of weight for adult or elderly patients with normal renal function. Another relevant measure would be the elaboration of clinical protocols by the hospital institution since the quality of drug therapy is not necessarily associated with the product registration status [10]. Vancomycin was also involved in the association with meropenem, both in an off-label regimen, and this association is the most recurrent. Patients who receive an overdose of vancomycin or in an off-label combination were at a higher risk of adverse reactions since vancomycin is among the main responsible for interactions and risks of nephrotoxicity [27].

In a prospective cohort [17], it has been found that adverse drug events are more frequent in situations where the use is not based on scientific evidence. Our data allow us to emphasize that use without this evidence is not uncommon, and AMD use control policies (antimicrobial stewardship program) must be formulated and conducted by specialists, including physicians, pharmacists, microbiologists, and nurses [4,5]. Pharmacists play a key role in drug use studies due to their expertise in the area of pharmaceutical care, such as minimizing toxicity and other adverse events, reducing the costs of health care for infections, limiting the selection of antimicrobial resistant strains and ensuring patient safety [4,28].

The off-label use was more frequently associated with males and the surgical and orthopedic clinic as a location of hospitalization. In Brazil, surgical site infections comprised 14%–16% of infections in hospitalized patients and are the second or third most frequent infection among all infections in health-care services [29,30], and the hospital is a reference in urgency and emergency and is accredited by the Ministry of Health for High Complexity Services in Traumatology and Orthopedics. Due to the experimental use, the prevalence of off-label prescription of extended-spectrum antimicrobials could be a reasonable indication for this association.

The cross-sectional design of our study prevented us from ascertaining the International Classification of Diseases (if available) related to AMDs prescription and, therefore, the off-label indication use of AMDs could not be analyzed. Furthermore, as a limitation is a fact that the study was performed in only one hospital. Notwithstanding this, we believe that the study contributed significantly by showing that off-label use is common practice (even) in a teaching hospital. In the face of a dramatic setting of increased antibacterial resistance associated with few novel AMD registries [3,4,12,17], there is the need to plan prescription monitoring actions, encompassing the implantation of a microbiology laboratory to support therapeutic decisions, inclusion of AMD prescription protocols, drug restriction, continuing education, and pharmacotherapeutic follow-up by specialized professional, pharmacists [4,5,31]. Considering that the studied hospital is an educational institution, this need is even more relevant because elaborating better quality prescriptions is an example of the training of new professionals, not only physicians but also the whole team. It is also worth noting that a permissive environment for lower risk errors will also be an environment in which the risk of serious errors can occur more easily. Finally, the pharmaceutical industry often proceeds against this rationality, registering package inserts that can be different dosing profiles for the AMDs. Since the package insert is a public document with up-to-date information on efficacy, effectiveness, safety, and also studies on pharmacoeconomics, the regulatory agencies should act more rigorously in the analysis of marketed products and their information.

## CONCLUSION

Off-label prescription is a reality in the hospital studied and is found in about one-third of prescriptions containing AMD. In several occasions, it occurred with no scientific evidence to support it. The creation of mechanisms that regulate the AMD use, especially in off-label regimen should be adopted in our hospitals, so that the use of these medicines is done rationally, providing the patient with the effectiveness and safety of drug therapy so as to contribute to the new strategic plan of the WHO – 13th General Program of Work – which will last 5 years.

## AUTHORS' CONTRIBUTIONS

Lemos GS and Mota IVR contributed to data collection, analysis, and interpretation. Lemos GSL, Rosa MB, Perini E, Padua CAM contributed substantially to the design and planning of the project; contributed significantly in drafting or critically reviewing content; participated in the approval of the final version of the manuscript.

## CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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