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Antibiotic consumption in Brazil: an overview of the COVID-19 pandemic era

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Abstract:	Background Although antimicrobial resistance (AMR) is a natural evolutionary process, the indiscriminate and irresponsible use of antibiotics has favored the selective pressure of multidrug resistance among microorganisms. This study aimed to assess the trend in antibiotic prescription in the Brazilian population from January 2018 to December 2021, particularly during the COVID-19 pandemic. Methods We compared hospital and community antimicrobial consumption from the National Health Surveillance Agency Database and correlated it to the microorganisms associated with healthcare-related infections. Results The post-pandemic period showed a 26% increase in the consumption of antimicrobials in the hospital environment. The main increase was observed in the consumption of polymyxin B (137%). In 2021, 244,266 hospital-acquired infections were reported in the country. The rate of resistance to polymyxin-B was higher in 2021, mainly in Pseudomonas aeruginosa (1,400%) and Klebsiella pneumoniae (514%). On the other hand, azithromycin was the most common community-consumed antibiotic in Brazil, contributing to 24% of the total antibiotic consumption. Correlation analysis indicated a moderate to strong correlation between the increased consumption of azithromycin and COVID-19 infection. Conclusion Our results indicate an increase in antimicrobial consumption in Brazil during the COVID-19 pandemic and reinforce the fact that the misuse of antimicrobials may lead to an increase in AMR.
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Cover letter

15 th March 2023

Patricia Stone

Editor-in-Chief

American Journal of Infection Control

Dear Editor,

This letter acts as a cover letter to accompany the manuscript being submitted to for journal **American Journal of Infection Control** consideration as an article. The manuscript is entitled: "**Antibiotic consumption in Brazil: an overview of the COVID-19 pandemic era**". The COVID-19 pandemic presented a high mortality rate worldwide, and this caused antibiotics to be used in excess. This excessive consumption has led to a concern about increasing antibiotic resistance and making them ineffective for previously treated diseases. In this study, we analyzed the consumption of antibiotics in the community and hospital environment and compared antimicrobial resistance before and after the pandemic. The result All the different analyses conducted revealed a strong relationship between the increase in antibiotic consumption and the increase in COVID-19 cases. In 2021, a 26% increase in antimicrobial consumption, especially that of POL B (137%), was observed compared to 2019. Our study showed a surprising increase in resistance to POL B in *P. aeruginosa* and *K. pneumoniae* (1,400% and 514%, respectively). In the community, AZM showed a 43% increase in consumption (18.392 units vs. 12.844 units) in 2021, whereas AMX and CIP showed a decrease. Before the pandemic, antimicrobial resistance was already a concern, the numbers found after the pandemic show that the world needs the warning to review their consumption of antibiotics and establish measures to slow down or we will have a new pandemic of antimicrobial resistance. We believe that our manuscript will be of interest to the readers of this prestigious journal, making it a widely publicized and cited article. Thank you for your time and consideration for a review.

Yours Sincerely,

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Antibiotic consumption in Brazil: an overview of the COVID-19 Pandemic era

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Conflicts of interest: The authors declare no conflict of interest.

Abstract

Background: Although antimicrobial resistance (AMR) is a natural evolutionary process, the indiscriminate and irresponsible use of antibiotics has favored the selective pressure of multidrug resistance among microorganisms. This study aimed to assess the trend in antibiotic prescription in the Brazilian population from January 2018 to December 2021, particularly during the COVID-19 pandemic. **Methods:** We compared hospital and community antimicrobial consumption from the National Health Surveillance Agency Database and correlated it to the microorganisms associated with healthcare-related infections. **Results:** The post-pandemic period showed a 26% increase in the consumption of antimicrobials in the hospital environment. The main increase was observed in the consumption of polymyxin B (137%). In 2021, 244,266 hospital-acquired infections were reported in the country. The rate of resistance to polymyxin-B was higher in 2021, mainly in Pseudomonas aeruginosa (1,400%) and Klebsiella pneumoniae (514%). On the other hand, azithromycin was the most common community-consumed antibiotic in Brazil, contributing to 24% of the total antibiotic consumption. Correlation analysis indicated a moderate to strong correlation between the increased consumption of azithromycin and COVID-19 infection. **Conclusion:** Our results indicate an increase in antimicrobial consumption in Brazil during the COVID-19 pandemic and reinforce the fact that the misuse of antimicrobials may lead to an increase in AMR.

Highlights

- The consumption of antibiotics during the COVID-19 pandemic increased mainly azithromycin (43%) and Polymyxin B (48%), in the community and hospital environment, respectively.
- After the pandemic, we saw an increase in antimicrobial resistance, mainly in using Polymyxin B and Oxacillin.
- From 2018 to 2021 primary bloodstream infections increased by 170%.
- In 2021, 244,266 healthcare-associated infections were reported, which refers to a hospital-acquired infection rate of 7.9%, higher than in previous years.

Antibiotic consumption in Brazil: an overview of the COVID-19 pandemic era

Abstract

Background: Although antimicrobial resistance (AMR) is a natural evolutionary process, the indiscriminate and irresponsible use of antibiotics has favored the selective pressure of multidrug resistance among microorganisms. This study aimed to assess the trend in antibiotic prescription in the Brazilian population from January 2018 to December 2021, particularly during the COVID-19 pandemic. **Methods:** We compared hospital and community antimicrobial consumption from the National Health Surveillance Agency Database and correlated it to the microorganisms associated with healthcare-related infections. **Results:** The post-pandemic period showed a 26% increase in the consumption of antimicrobials in the hospital environment. The main increase was observed in the consumption of polymyxin B (137%). In 2021, 244,266 hospital-acquired infections were reported in the country. The rate of resistance to polymyxin-B was higher in 2021, mainly in Pseudomonas aeruginosa (1,400%) and Klebsiella pneumoniae (514%). On the other hand, azithromycin was the most common community-consumed antibiotic in Brazil, contributing to 24% of the total antibiotic consumption. Correlation analysis indicated a moderate to strong correlation between the increased consumption of azithromycin and COVID-19 infection. **Conclusion:** Our results indicate an increase in antimicrobial consumption in Brazil during the COVID-19 pandemic and reinforce the fact that the misuse of antimicrobials may lead to an increase in AMR.

Keywords: COVID-19, Antimicrobial, Antimicrobial resistance.

Introduction:

Healthcare-related infections (HAIs) contribute to higher rates of morbidity and mortality, prolonged hospital stays, and high costs, and more importantly, introduce the constant threat of the spread of multidrug-resistant (MDR) bacteria and fungi[1]. Antimicrobial resistance (AMR) is a serious threat to human health in the 21st century globally[2]. Infections caused by MDR microorganisms are associated with increased morbidity and mortality rates, length of stay, and treatment costs[3]. In 2014, it was estimated that if there was no change in the global trend of antibiotic consumption, AMR could result in up to 10 million deaths by 2050 and cause a cumulative loss of at least 60 trillion USD in economic output[4]. Thus, the impact of AMR on public health and the economy in the short and medium term is enormous, particularly in developing countries such as Brazil[2,4].

Although antibiotics are ineffective in treating COVID-19, they were prescribed to patients with suspected or diagnosed COVID-19 for various reasons, including the difficulty in ruling out bacterial coinfection at presentation and the possibility of secondary bacterial infections during the disease[5]. The empirical use of antibiotics for patients with COVID-19 raises concerns about their overuse and the subsequent harm associated with AMR[5,6]. Azithromycin (AZM) was the second most prescribed drug in the treatment of COVID-19 globally by doctors participating in the Sermo survey,[20] a worldwide platform used by these professionals. An aggravating factor in Brazil was the availability of the Brazilian Covid Kit in primary care for early treatment, which contained AZM, among other medicines, to reduce the transmission of the virus and, therefore, the spread of infection[7]. The increase in the number of invasive procedures associated with the use of antibiotics, steroidal anti-inflammatory drugs, and other immunomodulatory drugs, as well as overcrowding in healthcare settings,[8] can contribute to the spread of AMR[5].

Although laws exist to restrict antibiotic use, their implementation has remained insufficient. Moreover, most antibiotic stewardship programs have only focused on hospitals where resistant infections are identified, whereas the vast majority of antibiotic consumption occurs in the community[9], representing up to 80% of the total consumption in several countries[10]. These antibiotics are either prescribed by healthcare professionals or purchased directly by consumers without a prescription[11]. Considering this worrying scenario, multidrug resistance and the limited therapeutic arsenal may be among the main causes of mortality in patients with infections caused by MDR microorganisms[12]. Several countries, including Argentina, Brazil, Uruguay, Ecuador, Guatemala, and Paraguay, have reported increased MDR infections due to the indiscriminate community use of antimicrobials during the pandemic[13]. This should serve as a warning to promote the rational use of antimicrobials, preventive measures, and multidisciplinary strategies for the prevention of HAIs[12,8].

In Brazil, the consumption of antibiotics and the increase in AMR during the COVID-19 pandemic are poorly understood and have been identified as an important knowledge gap that needs investigation and better understanding[12]. This study aimed to assess the trend in antibiotic prescription in the Brazilian population over time, particularly during the COVID-19 pandemic.

Material and Methods

2.1 Study design

We performed a cross-sectional observational and retrospective study of antibiotic consumption registered by the National Health Surveillance Agency (NHSA) from 2018 to December 2021 based on hospital and community consumption in Brazil. Brazil has 213.3 million inhabitants and is divided into 26 states, and federal districts with 5,570 municipalities in 2022[14]. The pharmacy data of all antimicrobials dispensed to in-patients were analyzed to provide an acquired representation of antibiotic consumption before and after the pandemic. As the data were openly sourced, approval from the research ethics committee was not necessary.

2.1.1 Hospital setting

According to the January 2021 data mapping based on the National Registry of Health Establishments by the DATASUS, NHSA, and the Brazilian Institute of Geography and Statistics, Brazil has 45,848 ICU beds, of which 22,844 are the party of the Unified Health System (SUS) and 23,004 are the party of the private system. NHSA recommends that hospitals in Brazil, through the Hospital Infection Control Commissions, collect and notify information about HAIs through FormSus version 3.0. However, this information is not mandatory, and the number of hospitals reporting this information varies every month[15]. The data are public and available on the NHSA website (https//app.powerbi.com/view). To maintain the completeness of the data, only the hospitals that reported HAIs for at least 10 to 12 months throughout the year were selected.

The percentage of registered ICUs that disclosed their data during each year of the study was 57%, 45%, 54%, and 74% in 2018, 2019, 2020, and 2021, respectively. Data on central line-associated bloodstream infections (CLABSI) and the phenotypic profiles of this infection from January 2018 to December 2021 in all hospitals with an Intensive Care Unit (UTI) (adult, pediatric, and neonatal) were analyzed.

2.1.2 Community setting

In Brazil, access to antibiotics for use in humans is restricted to people having a prescription by medical practitioners, dentists, and veterinarians, which is enforced based on reports on the sales of these controlled substances since 2010[16,17]. The Brazilian government maintains 517 public pharmacies in 440 municipalities and subsidized purchases can be made at one of 34,627 registered private drugstores, covering 4,467 municipalities[18,19]. Information on the strengths and dosages of prescription drugs was obtained from the NHSA. A box or an ampoule of the antimicrobial represents one unit.

2.2 Antibiotics

For hospital consumption, we selected the following antimicrobials 3rd or 4th generation cephalosporin (ceftriaxone, CRO cefepime, CEF), fluoroquinolones (ciprofloxacin, CIP), carbapenems (meropenem, MER), penicillin (piperacillin, PIP), polypeptides (polymyxin, POL B), and glycopeptides (vancomycin, VAN). Antimicrobials with the most differences in consumption during the pandemic period compared to the other years were selected. According to Intercontinental Medical Statistics Health Brazil (IMS Health Brazil), six classes and 10 substances accounted for 96% of Brazilian community sales. Based on this finding, we included the following six classes beta-lactams (amoxicillin, AMX cephalexin, LEX), pyridines (trimethoprim, TMP), sulfonamides (sulfamethoxazole, SMX), tetracycline (tetracycline, TET), macrolides (azithromycin, AZM clarithromycin, CLR erythromycin, ERY), and fluoroquinolones (ciprofloxacin, CIP levofloxacin, LVX).[18,20]

2.3 Data analysis

2.3.1 Defined Daly Dose - DDD

The data on antimicrobial consumption were retrieved from NHSA and expressed as the defined daily dose (DDD) according to the anatomical therapeutic chemical (ATC)/DDD index 2020[21]. For the hospital setting, the observed period was up to 90 days of hospitalization and a median was determined for the years 2018 to 2021. Drugs administered through any other route than parenteral, such as oral antibiotics, were excluded. The consumption of antimicrobials was verified in DDD/patient days, according to Eq 1.

DDD / 1000 beds/DAY= *(amount of drug consumed x 1000) / (DDD established for the drug x period observed in days x beds available in hospital units x occupancy rate of hospital beds in the period studied.*

To check whether antimicrobial consumption during the pandemic period was higher than that during the previous two years, the data retrieved from the open data survey of the NHSA system were analyzed using tables prepared by GraphPad Prisma version 7 and presented as graphs and descriptive statistics.

2.3.2 Community consumption of azithromycin compared to the occurrence of COVID-19

The consumption patterns of AZM, LEX, and CIP before and after the COVID-19 pandemic were compared. Thus, we correlated an increase in the monthly number of COVID-19 cases with the increase in antibiotic consumption. Data on AZM, CIP, and LEX consumption from 2018 to 2021 were adjusted for 100,000 inhabitants according to the population estimate reported by the Brazilian Institute of Geography and Statistics[22]. Correlation analyses were performed using antibiotic consumption data from January 2018 to December 2021 for COVID-19 cases. We assigned the number zero from January to February 2020, when cases began being reported in Brazil. To identify the seasonal peak of antibiotic consumption, we used two statistical analyses, which measured the degree of correlation of two variables (in this case, the number of COVID-19 cases was correlated with AZM consumption). Pearson's and Spearman's correlation were performed using the statistical software IBM SPSS, whereas, for non-normally distributed data, the natural log was used.

3. Results

3.1 – Antimicrobial consumption in hospitals

The average consumption of antimicrobials for hospital use, expressed in DDD/1000 beds-day, was 26% higher in 2020 than in 2019. The main contributors to this increase were POL B (104%), CRO (42%), PIP (24%), and MER (21%). The consumption of CIP was reduced by 17%. Although MER was the most consumed antibiotic in 2018 and 2019, the consumption of CRO increased in 2020, surpassing the consumption of MER. In 2021, this increase in consumption was practically maintained, but with a decrease in the consumption of CRO (-28%) and an increase in the consumption of MER (10%) and POL B (48%), while the rest remained unchanged (figure 1).

Figure 1: The average antibiotic consumption in the Brazilian hospital environment, expressed in DDD/1000 beds-day.

Analysis of the incidence of HAIs from 2018 to 2021 showed that CLABSI increased by 170%. In 2020 a total of 41,600 HAIs were reported by hospitals in Brazil, which refers to an HAI resistance rate of 1.34%. In 2021 this figure was 244,266 HAIs, which refers to an HAI rate of 7.9%. All pathogens identified over the 4 years of the study, with respective incidence rates and percentages of AMR among CLABSI, are presented in Figure 2. During this period, 110,217 strains were identified, and their resistance profiles were tested for the following antibiotics oxacillin and VAN for gram-positive and carbapenems, POL B, and 3rd and 4th generation cephalosporin for gram-negative bacteria. Our data showed that during the study period, *Klebsiella pneumoniae* (20%), *Pseudomonas aeruginosa* (7.5%), and *Acinetobacter* (9.6%) were the most common gram-negative bacteria. Among gram-positive bacteria, coagulase-negative *Staphylococcus* spp. (31%), *Staphylococcus aureus* (13.5%) and *Enterococcus faecalis* (5%) were the most common.

On the other hand, the resistance profile was not the same over the years. We observed an increase in resistance during 2020 and 2021 (the COVID-19 pandemic period), mainly in the use of oxacillin against coagulase-negative *Staphylococcus* spp., which showed 41% higher resistance after the start of the pandemic compared to the pre-pandemic period. Regarding gram-negative bacteria, the resistance to POL B was higher in 2021, for all strains tested mainly in adult patients admitted to the intensive care unit. The resistance rates of *P. aeruginosa* and *K. pneumoniae* increased by 1,400% and 514% in 2021, respectively (Figure 2). In 2020 and 2021, 4,190 fungal pathogens were isolated in cultures associated with CLABSI and urinary infections associated with urinary catheters, of which 1,769 were *Candida albicans,* and 2,421 were others, although the antibiograms were not performed. Full HAI data from adult, child and neonatal intensive care units for the period from 2018 to 2021 can be seen in the supplementary material.

Figure 2: Antimicrobial resistance profile of gram-positive (A) and gram-negative (B) bacteria in patients admitted to ICUs in Brazil, with primary bloodstream infections associated with the central venous catheter. The data described are from adults admitted to the intensive care unit and are expressed as a percentage, from 2018 to 2021.

3.3- Community consumption of azithromycin during the COVID-19 Pandemic

During the entire study period, the Brazilian community consumed 292,943,776 boxes of antibiotics. A total of 187,100,807 prescriptions issued by medical professionals, veterinarians, and dentists were analyzed, of which 23,336,647 (12%) were issued by veterinarians, 3,399,002 (0.2%) by dentists, and the rest by medical practitioners. The most consumed antibiotic was AZM, which contributed to 23.5% (68,846,570 boxes) of the total consumption, followed by AMX (20.7%) and LEX (20.6%). ERY (0.3%) and CLR (1.7%) were the least consumed antibiotics during the study period. The other antibiotics, namely, TET, TMP, SMX, LVX, and CIP, comprised the remaining 33% (53,364,135 boxes) of the total consumption.

The community consumption of AZM was analyzed and five consumption peaks were observed from January 2018 to December 2021. The first peak occurred in the post-pandemic period (June 2020), when 912.40 boxes/100,000 inhabitants were consumed. The second was in December 2020, when 1305 boxes/100,000 inhabitants were consumed; the third was in March 2021, when 1120.81 boxes/100,000 inhabitants were consumed. The fourth was in July 2021, when 1126.90 boxes/100,000 inhabitants were consumed, and the last and the largest was in September 2021, when 1614.61 boxes/100,000 inhabitants were consumed (Figure 3).

The average consumption of AZM before and after the onset of COVID-19 in Brazil changed. Before the onset of COVID-19, the mean consumption of AZM was 12.844 boxes/100,000 inhabitants, which increased to 18.392 boxes/100,000 inhabitants, representing a 43% increase. The COVID-19 cases were evaluated to see if there was any relationship with an increase in the consumption of AZM. In a non-empirical evaluation of the graphs of AZM consumption and COVID-19 cases, an alignment between the peaks and valleys of the two variables was observed, while the Pearson's [ρ=0.717 (95% CI: 0.543 – 0.831)] and Spearman's [s=0.720 (95% CI: 0.542 – 0.836)] indicating the moderate to strong correlation (Figure 3).

We compared the increase in the number of COVID-19 cases with the consumption of other antibiotics, such as CIP and LEX, and did not observe an association between them, as seen with AZM. On the other hand, the mean consumption of LEX and CIP decreased after the onset of COVID-19 (Figure 3). Furthermore, the correlation analysis did not indicate a correlation between the consumption of LEX or CIP and the onset of COVID-19 or between the consumption of the two antibiotics.

Figure 3: Relation between the community consumption of azithromycin and COVID-19 cases in 100,000 inhabitants in Brazil from January 2018 to December 2021. Azithromycin consumption average before and after the onset of COVID-19 cases in Brazil, and consumption forecast considering the period before the COVID-19 pandemic. The Redline means average consumption after COVID-19, the blue line means average consumption between 2018 and 2021, the orange line means average consumption before COVID-19, and the black line means expected consumption. LEX and CIP community consumption were also compared to COVID-19 cases /100,000. LEX and CIP average consumption before and after COVID-19 cases. The green line means CIP average consumption before and after the COVID-19 pandemic and the yellow line means LEX average consumption before and after the COVID-19 pandemic.

4. Discussion

Antimicrobial agents are overused in people with viral respiratory infections and several other self-limiting illnesses. Given that the indiscriminate use of antimicrobials contributes to increasing rates of AMR, restricting the use of antimicrobials by humans is imperative[23]. This retrospective study provides evidence of user behaviors of antimicrobial consumption, which can help design an AMR scenario. Our study sought to analyze antimicrobial consumption in Brazil before and during the COVID-19 pandemic and investigate the reasons for the possible increase in antimicrobial consumption. All the different analyses conducted revealed a strong relationship between the increase in antibiotic consumption and the increase in COVID-19 cases. In 2021, a 26% increase in antimicrobial consumption, especially that of POL B (137%), was observed compared to 2019. Our study showed a surprising increase in resistance to POL B in *P. aeruginosa* and *K. pneumoniae* (1,400% and 514%, respectively). In the community, AZM showed a 43% increase in consumption (18.392 units vs. 12.844 units) in 2021, whereas AMX and CIP showed a decrease.

A higher overall antimicrobial use has been reported in COVID-19 patients (74.6% and 72% of total COVID-19 patients)[24,25] from China [26]. In a smaller Brazilian cohort of 72 hospitalized patients, 84.7% had received antibiotic therapy[28]. The high percentage of antimicrobials contrasts with the low incidence of coinfections and secondary infections in COVID-19 patients reported in the literature. The overall rate of bacterial or fungal infections was approximately 7–8%[27,24].

Antibiotic consumption in Brazil is consistent with the published literature, in which treatment with cephalosporins, fluoroquinolones, macrolides, beta-lactams with beta-lactamase inhibitors, and carbapenems are most commonly described[24,25,28], except for POL B. In our study, the use of POL B increased by 137%, which becomes a major concern given the limited treatment options. Patients who had undergone surgical procedures or had previous carbapenem exposure were at 16.5- and 45.5-fold higher risk, respectively, of developing a polymyxin-resistant infection[29]. The occurrence of polymyxin resistance is associated with an increased risk of hospital mortality[30,31] and deserves attention. Carbapenems and broad-spectrum resistance among *Acinetobacter* sp. and *Klebsiella pneumoniae* were the most frequent in Italy, with resistance rates of 86% and 79% in ICU samples, respectively[32]. During the pandemic, the incidence of carbapenem-resistant enterobacterial colonization in Italy increased from 6.7% in 2019 to 50% in March 2020[32].

HAIs are invariably associated with an increased length of ICU stay[32]. Several reports have described an increase in MDR organisms during the COVID-19 pandemic[33,34,35]. In our study, 244,266 HAIs were reported during the second year of the pandemic, which were mainly primary bloodstream infections (36,241) in ICUs, representing a 170% increase in 2021 compared to 2018[36]. In the US, 1.7 million HAIs were reported per year, with a mortality rate of 100,000/year and the cost for the treatment of resistant infections reaching 9.8 billion USD[36]. In the United Kingdom, the mortality rate reached 33,000/year, and the costs of treatment were 774 million pounds per year[36]. In Brazil, mortality from ventilator-associated pneumonia was 33% and the estimated costs ranged from 7,906 to 89,966 dollars per episode of CLAUBSI[36]. In other previously experienced pandemics, such as influenza A, the emergence of resistant strains has also been reported. A multicenter cohort study conducted with strains of the influenza A virus (H1N1) showed resistance to oseltamivir in 23% of the patients, who also showed a higher rate of mortality[37].

Coagulase-negative *Staphylococcus* (31%), *K.* p*neumoniae* (20%), *S. aureus* (13.5%), *A. baumannii* (9.6%), and *P. aeruginosa* (7.5%) were the most commonly isolated strains in our study. These findings were in line with studies in Italian ICUs from 2015 to 2019,[38] where the predominance of gram-positive pathogens was documented[39,40]. Even before the pandemic, Brazil had a high rate of resistance to POL B (last-choice antibiotic) of 27.1%[9]. After the pandemic, these numbers increased, reaching 43% in the treatment of *K. pneumoniae* and 30% in *P. aeruginosa*. POL B is currently considered the last-line defense against problematic gram-negative superbugs, notably carbapenem-resistant Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii*, which have been classified as urgent or serious threats by the US Centers for Disease Control and Prevention (CDC)[41].

On the other hand, the results of community-consumed antibiotics in this study indicate that AZM, AMX, and LEX were the most consumed antibiotics, which corroborates with the pattern in the pre-COVID period from 2013 to 2016[42] and 2008 to 2012[20]. Moreover, these antibiotics were the most consumed by the community in the European Union from 1997 to 2017[23] and in rural pharmacies in Vietnam[43]. Brazil showed an increase in AZM consumption during the pandemic period, similar to the trend reported in 10 African countries Ghana, Kenya, Uganda, Nigeria, South Africa, Zimbabwe, Botswana, Liberia, Ethiopia, and Rwanda[44]. However, other countries such as Union European[45], Canada[46], United States[47,] and the UK[44] reported a decrease in community antibiotic consumption. During the COVID-19 pandemic, Canada showed a 26.5% decrease in antibiotic consumption by community retail pharmacies compared to 2019[48]. This decrease was 70% in children and 34% in the elderly[48].

Before the COVID-19 pandemic (2018 and 2019), our study showed that a pattern of antibiotic consumption was maintained, with AMX being the most consumed antibiotic, followed by LEX and AZM. However, in 2020 a change was observed in the patterns, and AZM became the most prescribed antibiotic, probably due to the onset of the COVID-19 pandemic on January 30, 2020[5]. This was confirmed by Pearson's (p 0.71) and Spearman's (s 0.72) correlation coefficients, both indicating a strong correlation between the increase in COVID-19 cases and the consumption of AZM. In contrast, LEX and CIP showed a low correlation. Both AMX and AZM have been widely used against respiratory infections, which occur more frequently during the coldest months of the year[49]. AZM and AMX, used as the first choice for respiratory infections, accounted for half of the antibiotics prescribed in the country[49].

WHO recommends the use of AZM in the treatment of moderate to severe COVID-19 with a risk of bacterial infection[5], which has probably encouraged the increase in community antimicrobial consumption, supposedly for mild cases[50,51]. Another reason for the increase in the community consumption of AZM is the availability of the Brazilian Covid Kit (consisting of various combinations including chloroquine/hydroxychloroquine, AZM, and ivermectin) for the initial symptoms of COVID-19. In Brazil, it was widely distributed to the general population in primary care[37,39]. It is estimated that one in four Brazilians have consumed drugs from the Covid Kit[7]. Besides, data from the DETECTCoV-19 study [52,7] showed that 77% of people with a previous diagnosis of COVID-19 used AZM[39,41]. This possible selective pressure imposed by the exacerbated use of AZM may favor microorganisms causing lower respiratory tract infections, such as bronchitis and pneumonia, and upper respiratory tract infections, such as sinusitis, pharyngitis, and otitis, besides sexually transmitted infections caused by chlamydia[53].

This high rate of consumption of antimicrobials in the treatment of COVID-19 may be related to the symptoms being similar to bacterial pneumonia, which would be indicative of the use of antimicrobials, the fear regarding the proportion that the pandemic took and the number of deaths, the uncertainty in the association of co-infections or secondary infections and finally the lack of effective treatments and protocols[54].

Although the major strength of this study is the completeness of the recorded data, the aggregated nature of the collected data is a limitation. The data only contained information on antibiotic consumption rates in the country. We did not segregate the findings by age (e.g., children or elderly) or sex. Besides, the aggregation of data fails to distinguish between high but appropriate and inappropriate antibiotic prescriptions, which is crucial to fighting the overconsumption of antibiotics. The potentially high use of antimicrobials in COVID-19 patients may also shift gains in short-term COVID-19 mortality to an increase in long-term mortality, AMR mortality, our biggest concern being the emergence of a new pandemic bacterial resistance[48]. Thus, managing the use of antimicrobials will continue to be an administrative challenge for Brazilian health services.

5. Conclusion

The results indicate that there was an increase in antimicrobial consumption during the COVID-19 pandemic in Brazil. The indiscriminate use of antibiotics has led to an increase in AMR, and we need to review the actions taken. Health authorities need to take measures to reduce the inappropriate prescription of antibiotics, resume control measures, and invest in accurate diagnoses to curb the spread of AMR or else prepare for the next possible silent pandemic, the AMR pandemic.

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Conflicts of interest: The authors declare no conflict of interest.

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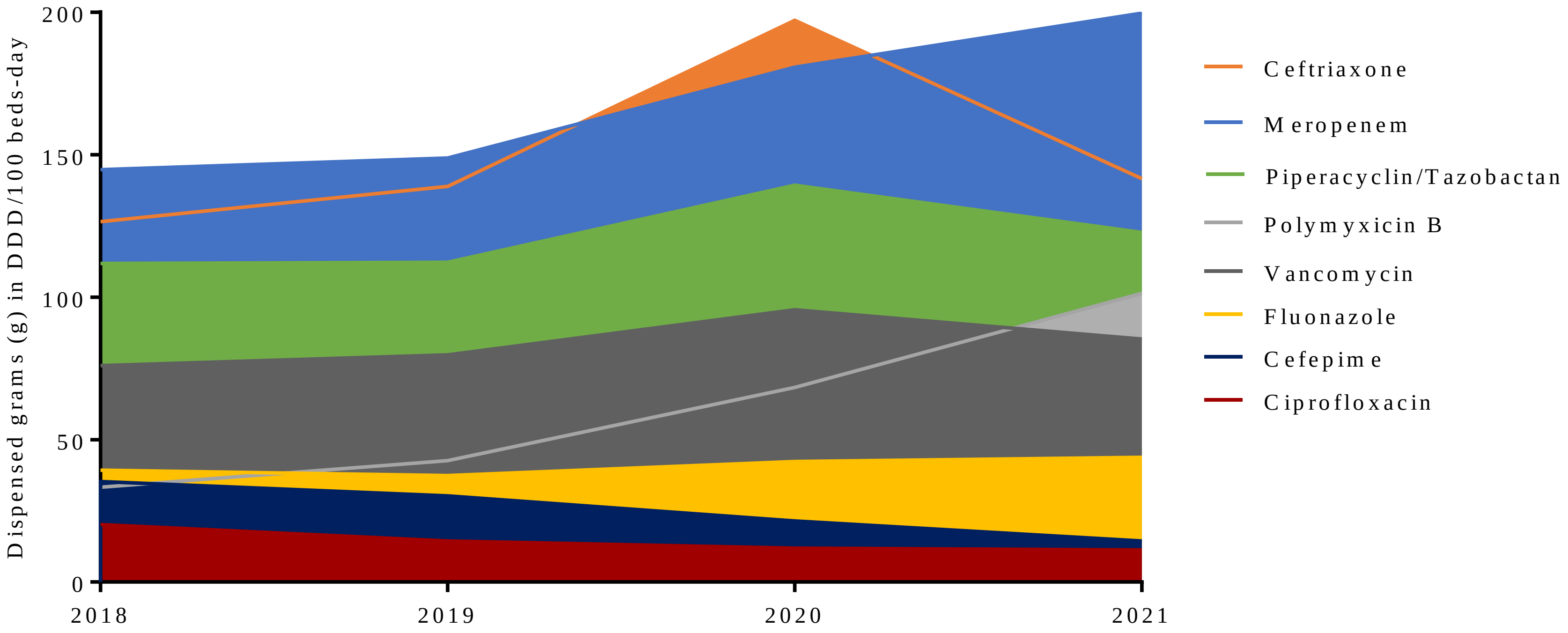
Tabela(s)

		Vancomycin (%)		**Oxacillin (%)**
Gram – Positive	*Enterococcus faecalis*	19%; 6,3%; 2% 14%; 3%; 6% 19%; 5%; 4%; 16%; 3%; 2%		----
	Enterococcus faecium	51%; 33%; 25% 55%; 11%; 15% 52%; 22%, 15%; 53%; 41%; 15%		----
	Enterococcus spp, exceto faecium e faecalis	25%; 10%; 9% 20%; 25%; 10% 20%; 6%, 2% 26%; 15%; 1,6%		----
	Staphylococcus aureus	7%; 3%; 5% 4%; 2%; 2% 4%; 2%, 2% 4%; 1%; 2%		50%, 42%; 37% 60%; 43%; 47% 59%; 41%, 43% 52%; 42%; 37%
	Staphylococcus coagulase negative	15%; 2%; 3% 3%; 4%; 3% 2,5%; 2%; 3% 5%; 3,7%; 3%		110%; 78%; 84% 81%; 77%; 81% 78%; 80%; 83% 71%; 71%; 75%
		Carbapenemics (%)	**Polymyxin B (%)**	**Cephalosporin (%)**
Gram-	*Acinetobacter baumannii-calcoaceticus*	82%; 35%, 34% 80%; 29%; 40% 80%; 23%, 40% 79%;44%; 28%	12%; 14%; 1% 6%; 6%; 4% 4,7; 5%; 2,6% 3,3%; 6%; 1%	----
	Burkholderia cepacia	-; -; - 19%; 18%; 6% 23%; 22%, 26%	----	----
	Enterobacter spp	31%; 12%; 10% 27%; 15%; 8% 25,4; 10%; 7% 21%; 6%; 6%	13%; 4%; 4% 4%; 0%; 0,5% 5,6; 1%; 1% 3,7%, 0; 1%	50%; 36%; 39% 47%; 32%; 35% 47,6; 34%; 33% 24%; 23%; 28%
	Escherichia coli	16%; 10%; 10% 15%; 6%; 6% 9%; 4%; 1,4% 9%; 8%; 7%	7%; 0%; 4% 5%; 5%; 2% 2%; 2%; 0,6% 0,5%; 0%; 1%	48%; 44%; 27% 48%; 31%; 22% 44,7; 34%; 18% 33%, 0%; 19%
	Klebsiella pneumoniae	67%; 25%; 45% 63%; 26%; 14% 52%; 22%, 12% 44%; 21%; 10%	43%; 7%; 3% 15%; 3%; 3% 12%; 4%, 2% 7%; 1%; 1%	71%; 48%; 49% 72%; 47%; 48% 68%; 49%; 47,5% 27%; 30%; 35%

	Outras Enterobactérias	-; -; - 34%; 13%; 12% 26,4; 16%; 9% 22%; 25%; 9%	----	-; -; - 55%; 43%; 35% 53,4; 34%; 34% 23%; 17%; 19%
	Pseudomonas aeruginosa	42%; 34%; 25% 40%; 35%; 24% 40%; 33%; 15%; 29%; 41%; 23%	30%; 6%; 5% 4%; 1%; 2% 2,3; 5%; 3% 2%; 3%; 2%	
	Serratia spp	50%; 23%; 18% 34%; 17%; 11% 43%; 26%; 7% 34%; 9%; 6%	----	59%; 118%; 40% 50%; 49%; 40% 53%; 38%; 48% 20%; 28%; 73%


Dispensed grams (g) in DDD/100 beds-day
200
150
100
50
0
2018
2019
2020
2021
Ceftriaxone
Meropenem
Piperacyclin/Tazobactan
Polymyxicin B
Vancomycin
Fluonazole
Cefepime
Ciprofloxacin

Figura(s)

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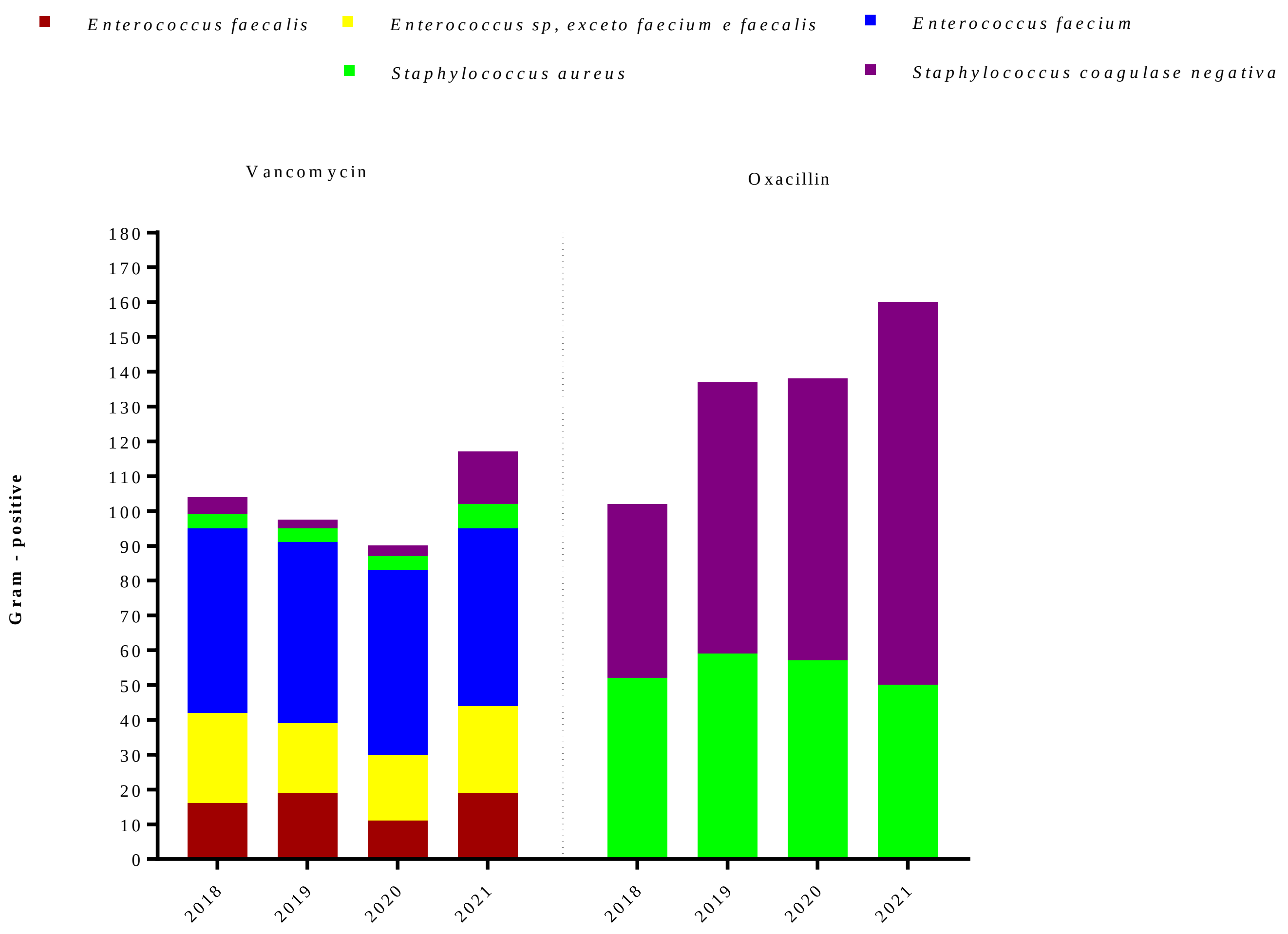
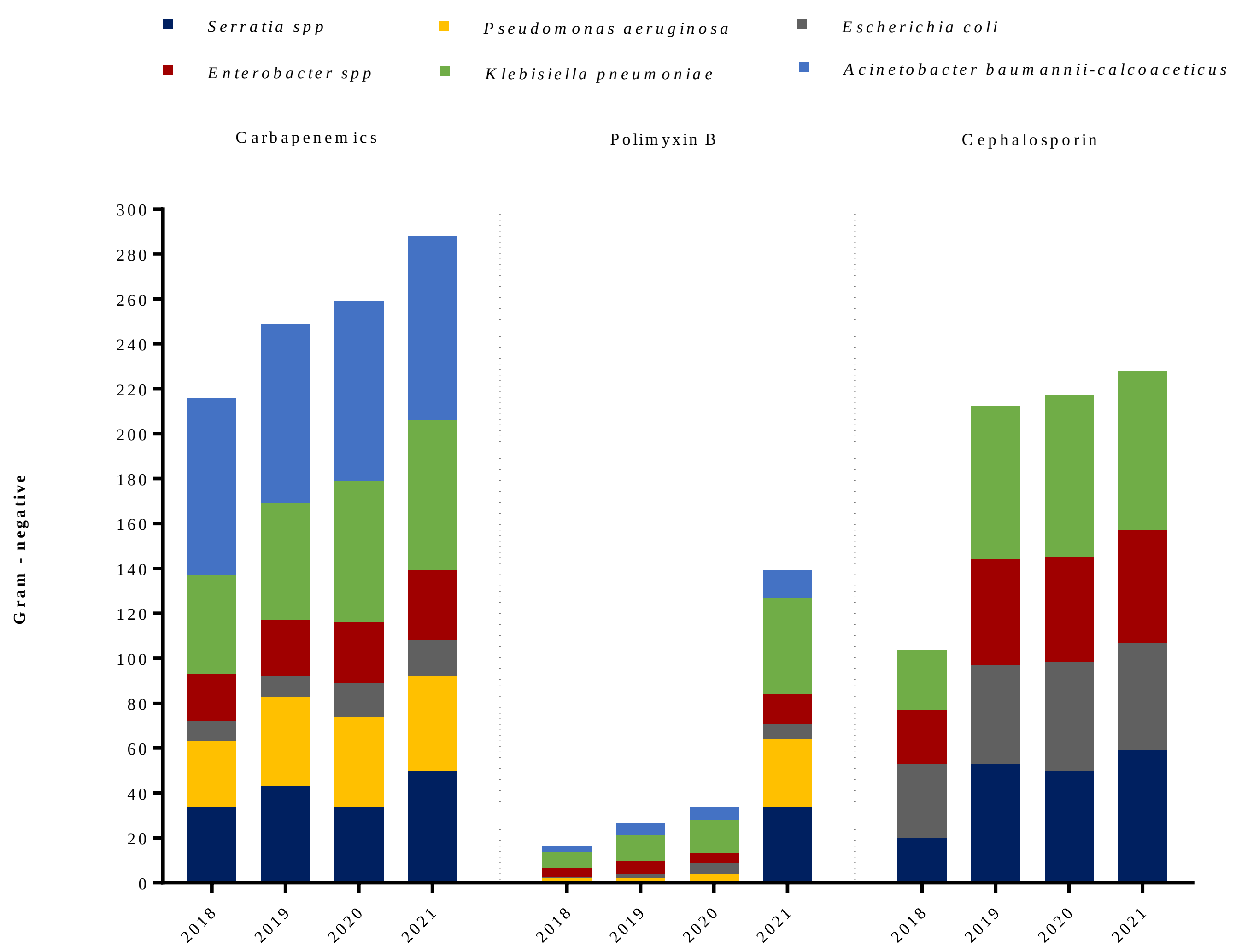
A)



B)



Serratia spp
Pseudomonas aeruginosa
Escherichia coli
Enterobacter spp
Klebisiella pneumoniae
Acinetobacter baumannii-calcoaceticus
Carbapenemics
Polimyxin B
Cephalosporin
Gram - negative
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
2018
2019
2020
2021
2018
2019
2020
2021
2018
2019
2020
2021

Figura(s)

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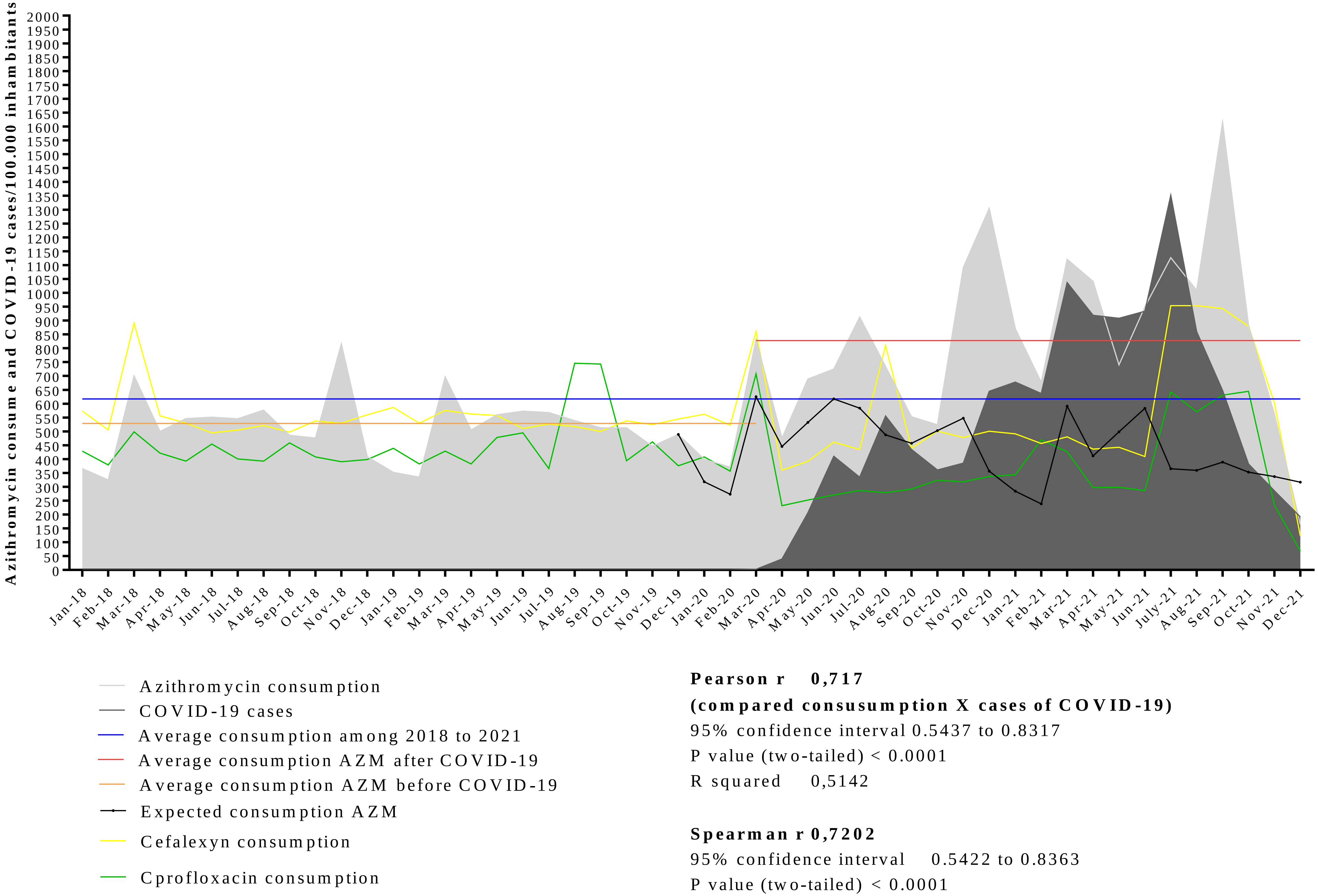

Pearson r 0,717
(compared consusumption X cases of COVID-19)
95% confidence interval 0.5437 to 0.8317
P value (two-tailed) < 0.0001
R squared 0,5142

Spearman r 0,7202
95% confidence interval 0.5422 to 0.8363
P value (two-tailed) < 0.0001

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