Infection Prevention in Practice 4 (2022) 100201

Available online at www.sciencedirect.com

Infection Prevention in Practice

journal homepage: www.elsevier.com/locate/ipip

Assessment of preauthorization and 24-hour expert consultation as a restrictive antimicrobial stewardship bundle in a Brazilian tertiary-care hospital: an interrupted time series analysis

Andréa Beltrami Doltrario [a], Gilberto Gambero Gaspar [a], Andrea Queiroz Ungari [b], Roberto Martinez [a], Antonio Pazin Filho [a], Benedito Carlos Maciel [a], Fernando Bellissimo-Rodrigues [c], Rodrigo de Carvalho Santana [a,*]

[a] Internal Medicine Department, Ribeirão Preto Medical School, University of São Paulo (USP), Ribeirão Preto, SP, Brazil
[b] Division of Pharmacy, Hospital das Clínicas. Ribeirão Preto Medical School, University of São Paulo (USP), Ribeirão Preto, SP, Brazil
[c] Social Medicine Department, Ribeirão Preto Medical School, University of São Paulo (USP), Ribeirão Preto, SP, Brazil

ARTICLE INFO

Article history:
Received 26 August 2021
Accepted 4 January 2022
Available online 12 January 2022

Keywords:
Antimicrobial stewardship
Preauthorization
Antibiotic restriction
Interrupted time series
Low- and middle-income countries

SUMMARY

Background: Worldwide, healthcare facilities face high and often inappropriate consumption of antimicrobials. However, there are limited antimicrobial stewardship (ASP) studies from low- and middle-income countries that include restrictive measures and their impacts on antimicrobial consumption.

Aim: This study aims to assess the impact of a restrictive bundle (preauthorization requirements and offering consultation with an infectious diseases physician 24 hours a day) on antimicrobial consumption, in a tertiary hospital in Brazil.

Methods: We conducted an interrupted time series analysis (ITS) with pharmacy-based data from January 2010 to December 2018 to evaluate changes of level and slope in antimicrobial consumption (expressed in DDD/1,000 patient-days) after the implementation of the restrictive bundle in September 2014. Fourteen restricted antimicrobials (amphotericin B deoxycholate, liposomal amphotericin B, micafungin, voriconazole, ganciclovir, amikacin, ampicillin/sulbactam, daptomycin, ertapenem, levofloxacin, linezolid, piperacillin/tazobactam, polymyxin B, and tigecycline) and eight unrestricted were analysed.

Findings: Among the 14 restricted antimicrobials, four presented a significant negative level change: micafungin (-2,14, p=.027), voriconazole (-14.72, p<.001), ertapenem (-1.89, p=.007) and amikacin (-13.98, p<.001). The only negative slope change was observed for the liposomal amphotericin B, -0.532 (p=.009). The restricted antibiotics group presented an increased consumption trend (1.068, p=.002) compared to the pre-intervention period, a similar change was observed for the unrestricted antibiotics group (1.360, p<.001).

* Corresponding author. Address: Departamento de Clínica Médica, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP), Ribeirão Preto, São Paulo, CEP: 14049-900, Brazil. Tel.: +55 16 3602 2719.
E-mail address: santanacrod@fmrp.usp.br (R. de C. Santana).

https://doi.org/10.1016/j.infpip.2022.100201

Conclusion: Preauthorization and 24 hour expert consultation were partially effective as a restrictive antimicrobial stewardship bundle in a Brazilian tertiary-care hospital. Increased consumption of unrestricted antimicrobials was observed as a side effect of the intervention.

Introduction

In healthcare facilities and outpatient settings worldwide, we face the high and often inappropriate consumption of antimicrobials. In a hospital environment, 30% of hospitalized patients will receive antibiotics [1], and at least one kind of inadequacy can be present in up to 50% of all antibiotic prescriptions [2]. Outside the intensive care unit, 30% of the prescribed antibiotics are estimated to be unnecessary [2].

The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guideline for antimicrobial stewardship program (ASP) implementation [3] assembles the current recommendations, suggesting interventions to improve and stimulate the rational use of antibiotics and promoting better therapeutic regimens regarding dosage, therapy duration and drug route of administration. The guide strongly recommends preauthorization and/or prospective audits and feedback interventions over using no intervention at all [3].

A systematic review from 2018 [4], after screening and assessment, included only 27 articles of ASP interventions for hospitalized patients from low- and middle-income countries, two of them from Brazil. This same review concluded that although developing countries are numerous, the results of ASP interventions for this group of countries, Brazil included, are still unclear. A Cochrane review [5] in 2017 analysed 221 articles on antibiotic medical prescription practices in hospital settings. Among them, 96 studies were from North America, 87 from Europe, and eight from South America, only four from Brazil.

The present study aimed to assess the impact of requiring preauthorization and offering expert consultation 24 hours a day as a restrictive ASP intervention implemented in a Brazilian tertiary-care university hospital.

Methods

Study design

In a quasi-experimental design, we conducted an interrupted time series analysis (ITS) to determine antimicrobial consumption level shift between pre-and post-intervention periods. This methodological design is a robust option to evaluate health interventions in non-randomized studies [6,7].

Settings

The study was conducted at the University Hospital of the Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP), located in the state of São Paulo, Brazil. The institution is a tertiary-care teaching hospital that attends to high complexity cases. It comprises two primary institutions, the Campus Unit with around 750 beds and the Emergency Unit with 180 beds. The hospital includes several units: surgical, medical, intensive care, immunocompromised, and emergency care, and is part of the comprehensive health care network of the public health care system of Brazil.

The Antimicrobial Use and Control Committee ("CUCA") and the Infection Prevention and Control Service ("CCIH") are responsible for implementing ASP strategies. The ASP team includes a clinical pharmacist, a microbiologist, nurses, and infectious disease (ID) specialists. They are responsible for promoting ASP interventions to enhance the control and prevention of healthcare-associated infections. The main ASP measures taken are antimicrobial consulting, prospective auditing and feedback, and ID specialist rounds in strategic units such as intensive care, haematology, bone marrow transplantation (BMT), and orthopaedics. Additionally, a written antimicrobial guide with institutional treatment protocols is available for consultation and educative measures. All the strategies mentioned above were implemented in the baseline period and remained active during the intervention period.

In September 2014, a restrictive ASP bundle was officially implemented and integrated into the other strategies. It comprised two interventions: (1) preauthorization requirement for specific antimicrobials and (2) additional availability of ID experts for consultation during non-business hours through telephone calls. Before this bundle implementation, ID physicians were already available for consultation during business hours, which included most clinical discussions. However, to enforce restrictions orders or allow exceptional changes in previous decisions, a 24/7 availability was implemented.

A high number of prescriptions of antifungals triggered the implementation of the restrictive measure. The consumption was related, at first, to a higher-than-expected number of fungal infections among haematological and BMT patients. However, an ASP team observation, at the time of the restrictive implementation, indicated an increment of antifungal prescription without ID consultation and for patients without proper indication for prophylaxis or treatment. In this scenario, the ASP team received formal support from the hospital administrators to implement the preauthorization requirement for some antifungals and other antimicrobials.

The ASP team stipulated a list of restricted antimicrobials. The pharmacy would only dispense the target antimicrobials after preapproval from the ASP team, based on the clinical case discussion between the assistant prescribing physician and the ID specialist.

Study outcomes and data collection

The present study assessed the impact of the implemented restrictive intervention on the monthly antimicrobial consumption of selected antimicrobials for adult hospitalized patients (≥18 years old). We worked with pharmacy-based

Table I
Observed changes in the level and the slope of antimicrobial consumption, globally and disaggregated, when comparing the pre-and post-intervention periods.

Drug/Groups	Level Change			Slope Change	
	Parameter Estimate [CI]	P value	%[a]	Parameter Estimate [CI]	P value
Amphotericin B-deoxycholate (AmB-D)	0.89 [-2.33, 4.11]	.587		-0.051 [-0.213, 0.110]	.537
Liposomal amphotericin B (L-AmB)	-3.82 [-16.62, 8.97]	.558		-0.532 [-0.931, -0.133]	.009
Micafungin	-2.14 [-4.04, -0.24]	.027		0.046 [-0.063, 0.155]	.409
Voriconazole	-14.72 [-20.57, -8.88]	<.001		0.011 [-0.317, 0.338]	.949
Restricted antifungals	-14.86 [-32.26, 2.55]	.094		0.002 [-0.553, 0.556]	.994
Restricted antivirals[b]	-4.47 [-9.28, 0.45]	.074		-0.005 [-0.154, 0.145]	.953
Amikacin[c]	-13.98 [-20.99, -6.97]	<.001		-0.028 [-0.441, 0.384]	.892
Ampicillin/Sulbactam	2.03 [-3.34, 7.40]	.458		0.007 [-0.152, 0.166]	.930
Daptomycin	-0.08 [-0.90, 0.74]	.840		0.021 [-0.003, 0.045]	.092
Ertapenem	-1.89 [-3.28, -0.51]	.007	-70.28%	0.053 [0.011, 0.094]	.013
Levofloxacin	-0.39 [-2,29, 1.51]	.688		0.019 [-0.038, 0.075]	.510
Linezolid	-1.29 [-2.79, 0,20]	.089		0.013 [-0.032, 0.057]	.575
Piperacillin/Tazobactam	5.91 [0.29, 11.52]	.039	+69.5%	0.068 [-0.085, 0.220]	.385
Polymyxin B	0.49 [-7.62, 8.59]	.906		0.180 [-0.067, 0.426]	.152
Tigecycline	-2.38 [-7.93, 3.18]	.401		0.197 [0.026, 0.368]	.023
Restricted antibiotics	-8.04 [-27.53, 11.46]	.418		1.068 [0.384, 1.751]	.002
Restricted antimicrobials	-17.43 [-49.48, 14.62]	.286		0.705 [-0.335, 1.744]	.184
Cefepime	-2.34 [-19.74, 15.05]	.791		0.173 [-0.592, 0.938]	.658
Ceftriaxone	0.73 [-7.42, 8.89]	.860		-0.520 [-0.791, -0.248]	<.001
Ciprofloxacin	-0.59 [-8.14, 6.97]	.879		-0.026 [-0.251, 0.198]	.819
Gentamicin	7.50 [2.24, 12.78]	.005	+104.02%	0.295 [0.138, 0.452]	<.001
Imipenem/Cilastatin	0.06 [-3.61, 3.73]	.973		-0.076 [-0.471, 0.319]	.707
Meropenem	4.26 [-9.52, 18.03]	.544		0.922 [0.461, 1.383]	<.001
Teicoplanin	-5.79 [-7.93, -3.66]	<.001	- 46.77%	0.006 [-0.056, 0.067]	.850
Vancomycin	9.51 [2.03, 17.01]	.012	+ 20.63%	0.190 [-0.035, 0.415]	.097
Unrestricted antibiotics	12.00 [-5.46, 29.47]	.177		1.360 [0.840, 1.879]	<.001

NOTE. Values are presented in DDD/1,000 patient-days.
CI: 95% confidence interval.
[a] Significant level change in percentage, for stationary ARIMA models.
[b] This class includes only ganciclovir.
[c] Its consumption was not accounted for in the analysis of the Restricted antibiotics and Restricted antimicrobials groups.

information containing dispensing data per drug, month and year of dispensation, and the hospital unit for which the drug was dispensed. This data and patient-days data were extracted from the databases of official systems of the institution.

We included fourteen restricted antimicrobials at the hospital: amphotericin B-deoxycholate (AmB-D), liposomal amphotericin B (L-AmB), micafungin (only echinocandin available in this hospital), voriconazole, ganciclovir, amikacin, ampicillin/sulbactam, daptomycin, ertapenem, levofloxacin, linezolid, piperacillin/tazobactam, polymyxin B and tigecycline. Infectious diseases physicians and the hospital administration considered, in general, the cost of the drugs to the hospital, the rate of consumption, and the antimicrobial spectrum to define the restrictions. Amphotericin B lipid complex (ABCL), although a restricted antifungal agent, was excluded from the interrupted time series analysis because its consumption started only post-intervention. We present only a graphic (Supplementary Figure A1) and brief descriptive analysis for this drug.

We also assessed the consumption of eight unrestricted antibiotics (cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem/cilastatin, meropenem, teicoplanin, and vancomycin), chosen due to at least one the following characteristics: clinical importance, high consumption, potential to promote resistance and a restricted spectrum of action.

We calculated drug consumption by the DDD/ATC (Defined Daily Dose/Anatomical Therapeutic Chemical Classification System) methodology suggested by the World Health Organization [8], based on DDD values from the DDD/ATC Index 2017. The final monthly consumption unit was expressed in DDD/1,000 patient-days.

We next generated a time-series of monthly observations for each drug individually, and drugs were grouped as restricted antifungals, restricted antivirals, restricted antibiotics, restricted antimicrobials, and unrestricted antibiotics. In our study, antibiotic and antimicrobial are not used as synonyms.

The pre-intervention period included 56 observations (from January 2010 to August 2014), and the post-intervention period, 52 observations (from September 2014 to December 2018). Except for the drug amikacin, which was restricted in April 2016. This drug was studied individually, with 75 observations for the pre-and 33 for the post-intervention period.

Statistical analysis

We performed an ITS analysis of the generated time series to test the hypothesis that implementing the restrictive measure caused immediate consumption level and slope change for the variables studied. We utilized autoregressive integrated

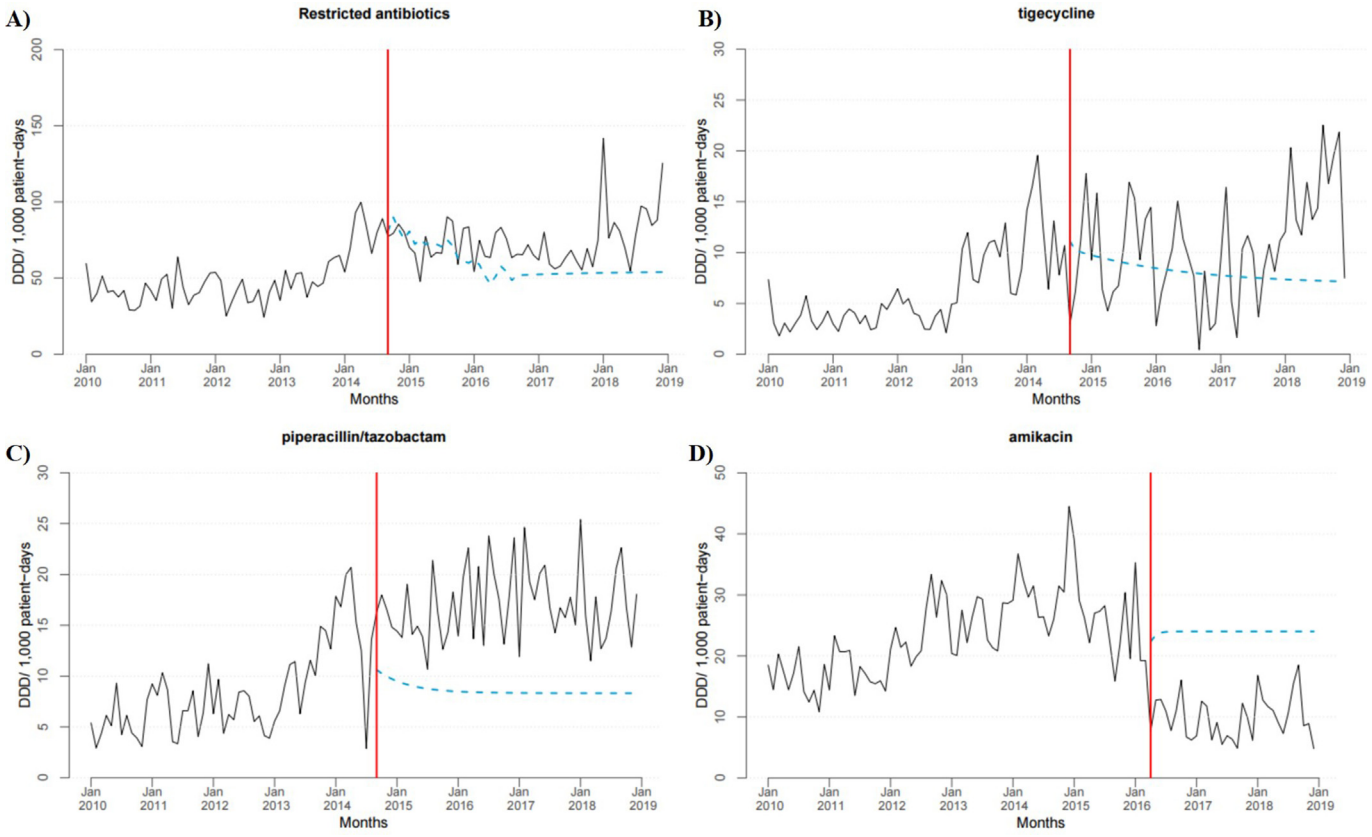

Figure 1. Consumption time series graphs for A) restricted antibiotics (slope change, p=.002), B) tigecycline (slope change, p=.023), C) piperacillin/tazobactam (level change, p<.039) and D) amikacin (level change, p<.001). The blue dashed line represents the consumption forecast for a scenario without intervention. The red segment indicates the start of the restrictive bundle in September 2014. The drug amikacin was restricted in April 2016.

moving average (ARIMA) models for the statistical approach. The analyses were performed using the *forecast* package [9] for R software (4.0.3) [10]. We used *auto.arima()* algorithm that returns the best ARIMA model for each variable, controlling for time-series seasonality and stationarity. We created two *dummy* variables to indicate the pre-and post-intervention period to assess the level and slope change in consumption. We performed the Ljung-Box $\chi 2$ test to check for residuals autocorrelation. We based the statistical approach on the suggestions of Schaffer *et al.* [7].

Irregular periods of national shortage for the drugs amikacin, voriconazole, and polymyxin B were corrected to avoid undesirable effects on the statistical model. The amikacin shortage was followed by an extra artificial increase of gentamicin use, which was corrected. These corrections were made by imputation, replacing these exceptional values with overall mean values [11].

The ARIMA model estimated the occurrence (or not) of changes in the level or slope of consumption. When present, the changes start immediately after the new strategy begins and are valid until the end of the analysed time series for each monthly observation. A level or slope change with *P* value <.05 was considered significant. For the variables with stationary time series, we indicated the significant level change in percentage.

ATC codes, estimated ARIMA model, intercept or drift and Ljung-Box $\chi 2$ test (*P* value) for each analysed variables can be found at Supplementary Table B.

Ethical considerations

The study protocol was approved by the Research Ethics Committee of HCFMRP-USP (CAAA 14596819.7.0000.5440, June 2019).

Results

When analysed as a group, the restricted antimicrobials (restricted antifungals, antivirals, and antibiotics) presented a non-significant consumption level change of -17.43 DDD/1,000 patient-days (95% CI -49.48, 14.62) and slope change of 0.705 DDD/1,000 patient-days (95% CI -0.335, 1.744). We also analysed the components of this group separately.

In the restricted antibiotics, there was a non-significant decrease in the level of consumption (-8.04, 95% CI -27.53, 11.46), as displayed in Table I. However, the statistical model found a significant increase slope for this category, meaning that the consumption presented an additional 1.068 DDD/1,000 patient-days (95% CI 0.384, 1.751) for each month on the post-intervention period, Figure 1(A). Among the antibiotics of this group, we found two that also presented a significant increase in the slope of consumption: tigecycline (0.197, 95% CI 0.026, 0.368), Figure 1(B), and ertapenem (0.053, 95% CI 0.011, 0.094). Although demonstrating a tendency of increased consumption, ertapenem use had a significant level decrease of

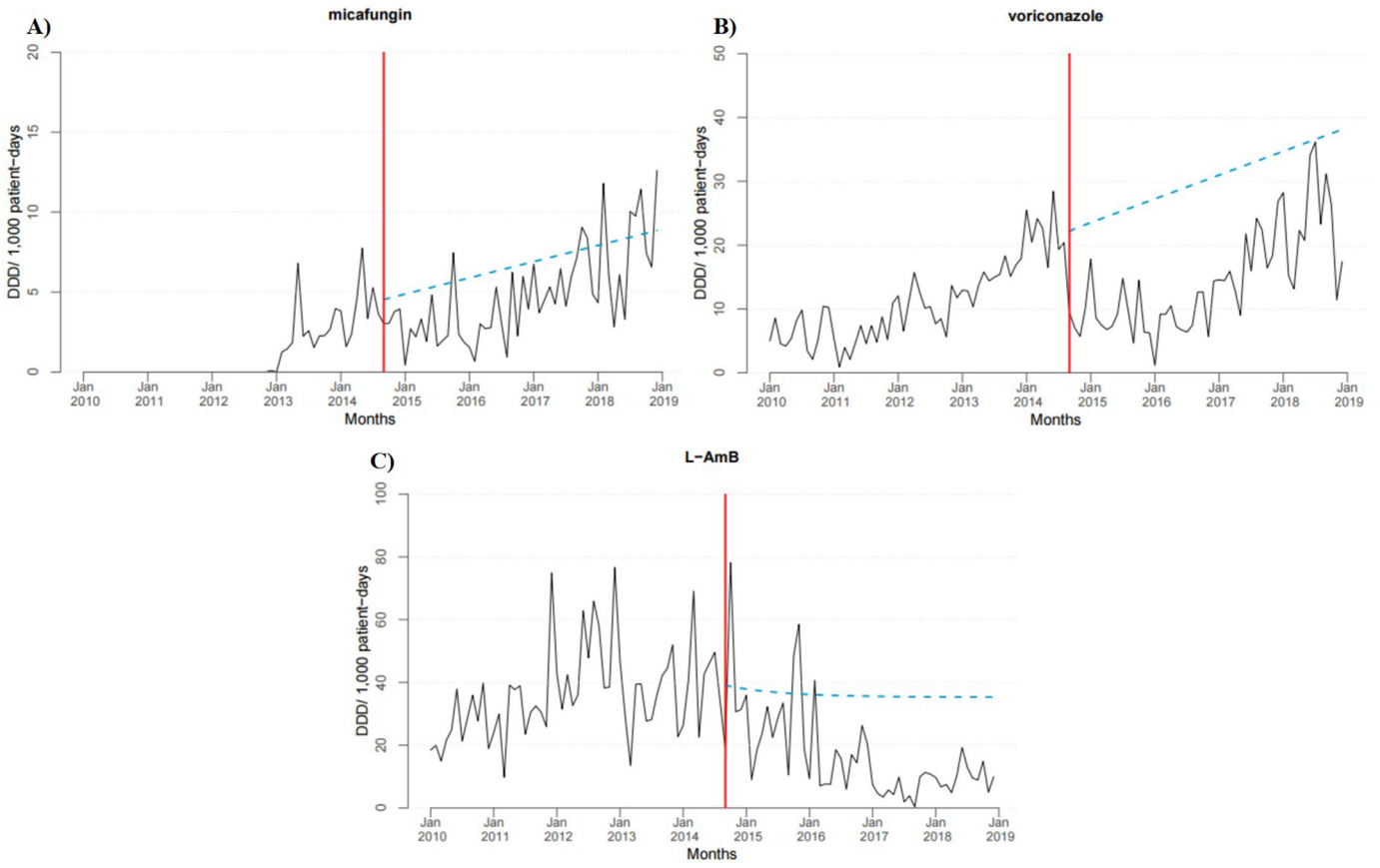

Figure 2. Consumption time series graphs for A) micafungin (level change, p=.027), B) voriconazole (level change, p<.001) and C) L-AmB, liposomal amphotericin B (slope change, p=.009). The blue dashed line represents the consumption forecast for a scenario without intervention. The red segment indicates the start of the restrictive intervention in September 2014.

-70.28% (-1.89, 95% CI -3.28, -0.51), associated with the new bundle incorporation.

We can observe (Table I) that two more restricted antibiotics presented a significant level change. Piperacillin/tazobactam had a 69.5% level increase (5.91 DDD/1,000 patient-days, 95% CI 0.29, 11.52), Figure 1(C). Amikacin had a significant level reduction. It was restricted in April 2016, and for each month in the post-intervention period, there was a mean of 13.98 DDD/1,000 patient-days less consumption than the expected counterfactual, as illustrated in Figure 1(D).

In Table I, it is possible to observe that the model found a non-significant decrease in the level and slope consumption for the restricted antivirals (ganciclovir) associated with the restrictive bundle implementation.

Although presenting individual changes for three drugs of the restricted antifungals group, the analyses of this group did not demonstrate significant changes in level and slope (Table I). The restrictive bundle was associated with a significant mean decrease of 2.14 DDD/1,000 patient-days (95% CI -4.04, -0.24) for micafungin, Figure 2(A), and 14.72 (95% CI -20.57, -8.88) for voriconazole, Figure 2(B). It is worth pointing out a slow increase factor (drift) estimated by the ARIMA model for these two drugs. This means that despite the decrease after the restriction, both maintained a monthly increment during the entire time series (Supplementary Table B).

As shown in Table I, L-AmB, restricted antifungal, had a non-significant reduction in the consumption level (-3.82, 95% CI -16.62, 8.97). The time-series graph of this amphotericin formulation can be seen in Figure 2(C). However, the model detected that the newly restrictive measures imposed a slope change for this drug. There was a significant monthly additional decrease of 0.532 DDD/1,000 patient-days, starting after the new ASP strategy.

The ARIMA model for unrestricted antibiotics estimated a non-significant level increase of 12 DDD/1,000 patient-days (95%CI -5.46, 29.47), Figure 3(A). However, the slope change reflected a significant monthly increase of consumption of the drugs in this group of 1.36 (95% CI 0.840, 1.879). Significant slope changes were found for the drugs: meropenem (0.922 DDD/1,000 patient-days), Figure 3(B); gentamicin (0.295 DDD/1,000 patient-days), Figure 3(C), and ceftriaxone, Figure 3(D), which presented slope decrease of 0.520 DDD/1,000 patient-days, as shown in Table I.

Among the drugs in the unrestricted antibiotics group, the restriction implementation affected the consumption levels of three drugs. There was an increase in consumption level for gentamicin of 104.02% (7.50 DDD/1,000 patient-days, 95% CI 2.24, 12.78) and for vancomycin an increase of 20.63% (9.51 DDD/1,000 patient-days, 95% CI 2.03, 17.01), Figure 3(E). The unrestricted drug teicoplanin had a significant decrease of 46.77% in its level of consumption.

Discussion

Implementing a restrictive measure is associated with a decreased use of the target antibiotics, and some studies

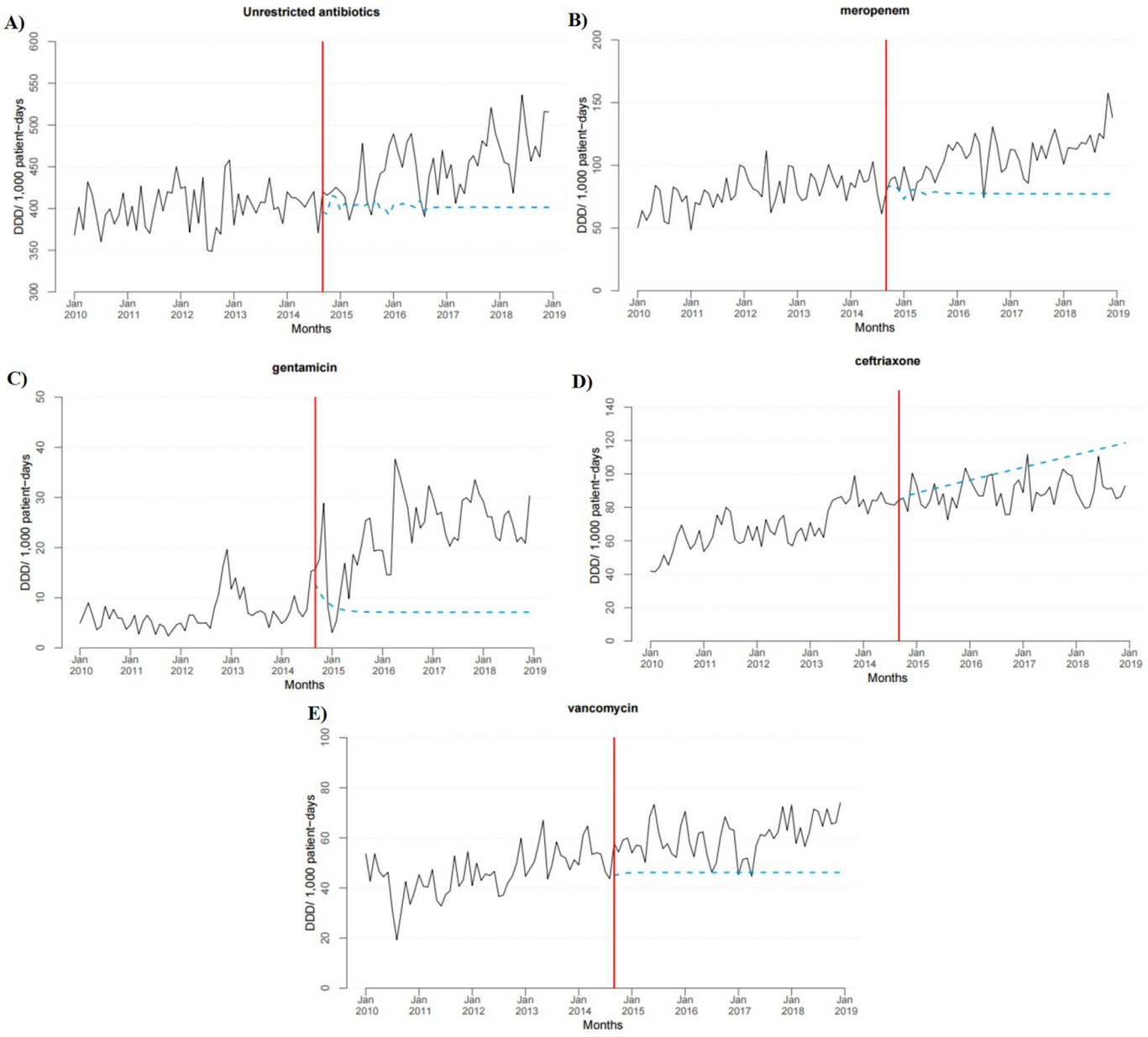

Figure 3. Consumption time series graphs for A) unrestricted antibiotics (slope change, p<.001), B) meropenem (slope change, p<.001, C) gentamicin (level change, p=.005 and slope change, p<.001), D) ceftriaxone (slope change, p<0.01) and E) vancomycin (level change, p=.012). The blue dashed line represents the consumption forecast for a scenario without intervention. The red segment indicates the start of the restrictive intervention in September 2014.

demonstrated a reduction in cost and antibiotic resistance [3]. This hospital implemented a restrictive ASP bundle in September 2014. The authors hypothesized that implementing the preauthorization requirement would encourage a change in the consumption level and trend of restricted antimicrobials, mainly for some antifungal agents.

We found that micafungin and voriconazole presented a level reduction that was not associated with a sustained change in the trend. Possible explanations for this observation include increasing purchase after the voriconazole patent litigation in 2016, associated with the ASP team indication of primary antifungal prophylaxis with voriconazole for specific haematological diagnostics due to antifungals infections surge, as of December 2017. Conceivably, micafungin consumption increased due to a change in the susceptibility profile to fluconazole in *Candida* species isolated from critical care patients.

We did not find significant change level for the drug L-AmB starting in September 2014. However, this agent was the only antifungal that presented a change in trend. This change started with the restriction bundle, but further investigation should be done to assess the influence of a shift in use between amphotericin formulations, mainly after 2016, as the ABLC presents a lower price and practically equivalent adverse effects as the L-AmB formulation [12]. The observation of the ABLC formulation time series demonstrates an

increased consumption over time, after the first purchases in 2015. The AmB-D formulation presents a limited use, mainly due to intolerable side effects, and the statistical model did not find any change in level and slope for this drug. Despite the changes in the individual drugs, the analysis of the restricted antifungal as a group did not demonstrate changes in level or slope.

Only two restricted antibiotics, ertapenem and amikacin, had a significant decrease of consumption level. One antibiotic, piperacillin/tazobactam, presented an increase in level. Its consumption approximately doubled. We suggest that this could be due to increased indication after ID specialist discussion and change in resistance patterns among gram-negative bacteria. Nevertheless, more studies are needed to evaluate the appropriateness of drug prescription. The restriction bundle did not produce a reduction of the consumption trend of any of the restricted antibiotics studied individually. Instead, this study found an increase in the consumption trend of the restricted antibiotics as a group, a trend also observed for the drugs Ertapenem and Tigecycline.

This work did not analyse a formal control group. However, we believe that the study of the selected unrestricted antibiotics (as a group and individually) can highlight the effects of a restrictive bundle on this type of drug. As another limitation, we did not evaluate all the unrestricted antimicrobials among the standardized drugs at the institution.

The selected unrestricted antibiotics group did not present a level change, but an increased trend. Two unrestricted antibiotics increased the level of use: gentamicin and vancomycin. Also, in this group, two antibiotics presented an increasing trend in the post-intervention period: gentamicin and meropenem.

Meropenem and vancomycin are restricted drugs in some antibiotic guides of international institutions [13]. In the guide for implementing ASP in low- and middle-income countries of the WHO, both drugs are in the "watch group" which includes target antibiotics with an elevated risk of resistance selection and therefore should be prioritized as the main targets of management and monitoring programs [14,15].

The consumption changes of the aminoglycosides (gentamicin and amikacin), as found in our study, deserve attention as they interfere with antibiotic resistance patterns, mainly among the drugs of this class [16,17]. This situation can be associated to the squeezing the balloon effect, which means restrictive measures could lead to a relevant reduction in the use of target antibiotics and a shift towards substitute agents with a similar change in evolutionary pressure [18]. It refers to the disadvantage of restriction, which can cause a deviation in consumption, leading to increased use and resistance to agents that are not restricted [13,15].

Although the chosen methodology for this present work cannot directly confirm the squeezing the balloon effect, as shifts in bacteria resistance patterns were not studied, it works as a benchmark for the institution, helping the decision-making process to improve the ASP interventions. Periodically assessment should be encouraged, as we observed that most of the antimicrobials that presented a level change did not present a slope change, maintaining the same consumption trend from the pre-intervention period.

The study presents some limitations associated with the analysis of pharmacy-based data. The data did not include patient level information that could be used to assess prescription appropriateness. The purpose of antimicrobials, for treatment or prophylaxis, was not discriminated and clinical outcomes (such as mortality, nosocomial infection rates, reduction of adverse effects caused by antimicrobials, rates of susceptibility to antibiotics, or changes in rates of infections by *C. difficile*) were not verified. This type of information is necessary to evaluate the quality of ASP interventions at the patient level [15]. The antifungal consumption described for haematology-BMT patients could benefit from a future, more in-depth study of prescription correctness.

The authors also acknowledge that a sub analysis of consumption by hospital units not conducted on this study could bring more information about the effects of the new ASP implementation, considering different patients' and medical teams' profiles.

Another limitation of the study was that the restrictive measure was not conducted alone, as other ASP interventions were performed during the entire studied period. A 2017 Cochrane review [5] discusses this scenario where few studies compare two interventions in isolation. However, the authors believe the assessment of the restriction impact was possible and trustworthy because, as explained in the methodology, other ASP activities continued throughout the nine years analysed.

Nevertheless, despite the limitations, to the best of our knowledge, this is the first Brazilian ITS study of ASP interventions that analyses a 9-year time series of antimicrobial consumption in a hospital setting.

Conclusions

Preauthorization and 24 hour expert consultation were partially effective as a restrictive antimicrobial stewardship bundle in a Brazilian tertiary-care hospital.

Increased consumption of unrestricted antimicrobials was observed as a side effect of the intervention. This study can indicate a red flag for the occurrence of the squeezing the balloon effect with the need for further investigation and attention.

Performing a detailed consumption analysis when evaluating the impacts of ASP interventions is of extreme importance to a periodic reassessment of the restrictive measure and the list of restricted antimicrobials considering the local particularities.

Acknowledgments

The authors want to thank the institution where the study took place for the technical support and all the professionals involved with the ASP activities.

Conflict of interest statement

All authors declare no conflicts of interest.

Funding

The authors declare that they did not receive any funding for the study.

Credit author statement

ABD: Conceptualization, Methodology, Formal Analysis, Writing — Original Draft. **GGG:** Conceptualization, Writing - Review & Editing. **AQU:** Data Curation, Writing - Review & Editing. **RM:** Writing - Review & Editing. **APF:** Methodology, Writing - Review & Editing. **BCM:** Writing - Review & Editing. **FBR:** Methodology, Writing - Review & Editing. **RCS:** Visualization, Writing - Review & Editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.infpip.2022.100201.

References

[1] ANTIMICROBIAL STEWARDSHIP A practical guide to implementation in hospitals. Available at: https://www.biomerieux.com/sites/corporate/files/antimicrobial-stewardship-educational-booklet-offered-by-biomerieux.pdf [Accessed 5 April 2021].

[2] Fridkin S, Baggs J, Fagan R, Magil S, Pollack LA, Malpiedi P, et al. Vital Signs: Improving Antibiotic Use Among Hospitalized Patients. Morb Mortal Wkly Rep 2014;63:194—200.

[3] Barlam TF, Cosgrove SE, Abbo LM, Macdougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:51—77. https://doi.org/10.1093/cid/ciw118.

[4] van Dijck C, Vlieghe E, Cox JA. Antibiotic stewardship interventions in hospitals in low-and middle-income countries: A systematic review. Bull World Health Organ 2018;96(4):266—80. https://doi.org/10.2471/FBLT.17.203448.

[5] Davey P, Marwick CA, Scott CL, Charani E, Mcneil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2017;2:2017. https://doi.org/10.1002/14651858.CD003543.pub4.

[6] Hategeka C, Ruton H, Karamouzian M, Lynd LD, Law MR. Use of interrupted time series methods in the evaluation of health system quality improvement interventions: a methodological systematic review. BMJ Glob Health. Oct 2020;5(10):e003567. https://doi.org/10.1136/bmjgh-2020-003567.

[7] Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. BMC Med Res Methodol 2021;21:58. https://doi.org/10.1186/s12874-021-01235-8.

[8] Guidelines for ATC classification and DDD assignment 2021. Available at: https://www.whocc.no/filearchive/publications/2021_guidelines_web.pdf [Accessed 5 April 2021].

[9] Hyndman RJ, Khandakar Y. Automatic time series forecasting: the forecast package for R. J Stat Software 2008;27:1—22.

[10] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. Available at: https://www.R-project.org. [Accessed 5 May 2020].

[11] Moritz S, Bartz-Beielstein, imputeTS T. Time Series Missing Value Imputation in R. R J. 2017;9:207.

[12] Hamill RJ. Amphotericin B formulations: a comparative review of efficacy and toxicity. Drugs 2013;73(9):919—34. https://doi.org/10.1007/s40265-013-0069-4.

[13] Ontario Agency for Health Protection and Promotion (Public Health Ontario). Antimicrobial stewardship strategy: formulary restriction with preauthorization. Toronto, ON: Queen's Printer for Ontario; 2016. Available at: https://www.publichealthontario.ca/apps/asp-strategies/data/pdf/ASP_Strategy_Formulary_Restriction_Preauthorization.pdf. [Accessed 5 April 2021].

[14] World Health Organization. Antimicrobial stewardship programmes in healthcare facilities in low- and middle-income countries: a WHO practical toolkit. 2019. Available at: https://apps.who.int/iris/handle/10665/329404. [Accessed 5 May 2020].

[15] Morris AM. Antimicrobial Stewardship Programs: Appropriate Measures and Metrics to Study their Impact. Curr Treat Options Infect Dis 2014;6(2):101—12. https://doi.org/10.1007/s40506-014-0015-3.

[16] Young EJ, Mack Sewell C, Koza MA, Clarridge JE. Antibiotic resistance patterns during aminoglycoside restriction. Am J Med Sci 1985;290(6):223—7. https://doi.org/10.1097/00000441-198512000-00001.

[17] Peterson LR. Squeezing the antibiotic balloon: The impact of antimicrobial classes on emerging resistance. Clin Microbiol Infect Suppl 2005;11(5):4—16. https://doi.org/10.1111/j.1469-0691.2005.01238.x.

[18] Chatzopoulou M, Reynolds L. Role of antimicrobial restrictions in bacterial resistance control: a systematic literature review. J Hosp Infect 2020;104(2):125—36. https://doi.org/10.1016/j.jhin.2019.09.011.