https://doi.org/10.31925/farmacia.2025.2.12 **ORIGINAL ARTICLE**

IMPLEMENTATION OF AN ANTIBIOTIC RESTRICTION FORMULARY AND THE IMPACT ON CONSUMPTION IN A ROMANIAN HOSPITAL: A THREE-YEAR RETROSPECTIVE STUDY

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Abstract

Antimicrobial resistance is a growing public health challenge exacerbated by excessive antibiotic use in hospitals. Antimicrobial stewardship programs (AMS) aim to optimise antibiotic prescribing to curb resistance. This study evaluates the impact of implementing a restriction formulary on antibiotic consumption in a Romanian hospital over three years. A retrospective analysis was conducted at Fundeni Clinical Institute in Bucharest from 2022 to 2024. Antibiotic consumption was quantified using the Defined Daily Dose (DDD) *per* 100 patient-days. The study compared antibiotic use before (2022) and after (2023 - 2024) the implementation of a restriction formulary in December 2022. Statistical analyses assessed trends in antibiotic consumption across different hospital wards. Following the formulary's implementation, overall consumption of reserve antibiotics, including carbapenems and glycopeptides, declined, while narrower-spectrum agents, such as ceftazidime-avibactam and ertapenem, increased. The intensive care unit and haematology wards had the highest antibiotic usage. Although the formulary reduced the prescription of last-line antibiotics, total antibiotic consumption remained stable ($p = 0.7$). The restriction formulary effectively optimised antimicrobial selection, reducing the overuse of broad-spectrum antibiotics while promoting targeted therapies. However, continued monitoring is necessary to prevent resistance in newly preferred antibiotics and ensure long-term efficacy.

Rezumat

Rezistența la medicamentele antimicrobiene reprezintă o provocare tot mai mare pentru sănătatea publică. Programele de *stewardship* antimicrobian (AMS) au ca obiectiv optimizarea prescrierii antibioticelor, în vederea limitării apariției rezistenței. Acest studiu a evaluat impactul implementării unui formular de restricție asupra consumului de antibiotice într-un spital din România, pe o perioadă de trei ani. Analiza retrospectivă a fost realizată în cadrul Institutului Clinic Fundeni din București, în intervalul 2022–2024. Consumul de antibiotice a fost cuantificat utilizând indicatorul *Defined Daily Dose* (DDD) raportat la 100 de zile de spitalizare. S-a analizat utilizarea antibioticelor înainte (2022) și după (2023–2024) introducerea formularului de restricție, implementat în decembrie 2022. Astfel, a fost observată o scădere a consumului global de antibiotice de rezervă, precum carbapenemele și glicopeptidele, concomitent cu o creștere a utilizării unor agenți cu spectru mai restrâns, precum ceftazidim-avibactamul și ertapenemul. Secțiile de terapie intensivă și hematologie au înregistrat cel mai ridicat consum de antibiotice. Deși formularul de restricție a redus prescrierea antibioticelor de rezervă, consumul total de antibiotice a rămas relativ constant ($p = 0,7$). Implementarea formularului de restricție s-a dovedit a fi o strategie eficientă pentru optimizarea selecției agenților antimicrobieni, contribuind la reducerea utilizării excesive a antibioticelor cu spectru larg și la promovarea terapiilor direcționate. Totuși, este necesară monitorizarea continuă pentru a preveni apariția rezistenței la antibioticele și pentru a menține eficacitatea tratamentelor pe termen lung.

Keywords: antibiotic resistance, antimicrobial stewardship, retrospective study, antibiotic consumption, restriction formulary

Introduction

Antibiotic resistance constitutes a significant public health issue in Europe. Currently, almost a century after the introduction of antibiotics, there is a rising discourse on the escalation of antibiotic resistance, which is responsible for an estimated 1.27 million fatalities globally attributed to multidrug-resistant bacteria. The resistance to antibiotics is the genetic capacity of a microbe to develop a mechanism that enables it to neutralise the beneficial effects of an antibiotic, even at elevated concentrations [1]. Antibiotic resistance mechanisms are categorised into four primary types: restriction of drug uptake, alteration of drug targets, drug inactivation, and active efflux of drugs. Differences in structure and other factors allow Gram-positive and Gram-negative bacteria to employ various resistance strategies. Gram-negative bacteria

utilise all four primary mechanisms, while Gram-positive bacteria less frequently employ the limitation of drug uptake due to the absence of an LPS outer membrane and lack of particular kinds of drug efflux mechanisms [2, 3].

The overreliance on antibiotics has led to the rise of antibiotic-resistant bacteria, referred to as superbugs, which present considerable challenges to treatment effectiveness and may result in serious infections. The insufficient advancement in the development of new antimicrobial agents intensifies the problem, as the speed of resistance emergence exceeds that of effective therapy identification [4-6]. Moreover, the widespread administration of antibiotics in hospitals creates selective pressure that facilitates the rapid development of multidrug-resistant bacteria [7]. Today, nosocomial infections can arise in many healthcare sectors and threaten patient safety. These can aggravate chronic diseases and increase mortality, morbidity, and healthcare costs. Therefore, novel combinations are being developed as therapy options, which mainly contain antibiotics and non-antibiotics or antibiotics used in conjunction with other antibiotics. In order to treat multidrug-resistant bacteria, drug-drug interactions may become more common, which could affect health-care expenditures and results [8].

Ongoing monitoring of antibiotic consumption and the promotion of rational use are necessary for mitigating the immediate risks associated with anti-microbial resistance. Initiatives designed to enhance awareness among healthcare professionals and the general public are indispensable for promoting responsible antibiotic use [9, 10]. The World Health Organisation (WHO) established a set of instruments for drug utilisation studies to facilitate the review and evaluation of prescribing, dispensing, and usage of prescription drugs [11]. For adults, DDD is the daily maintenance dose of a medicine used for its primary indication. The DDD is just a measuring unit and does not represent the suggested or prescribed daily dosage. Individual and group therapeutic dosages will deviate from the DDD due to pharmacokinetic factors, patient variables (*e.g.*, age, weight, ethnicity), disease type and severity, among other factors [12]. The DDD was developed to overcome challenges with dosage forms and is also a convenient way of following changes in use over time, especially when the mix of formulations changes or even when there are changes in pack sizes, which often occur in hospitals [11].

The purpose of antimicrobial stewardship programs (AMS) is to optimise the use of antimicrobial drugs in healthcare facilities such as hospitals, long-term care homes, and outpatient clinics. These initiatives aim to raise patient outcomes, control the spread of antibiotic resistance, and cut back on medical expenses [13]. Restricted antimicrobials comply with hospital restriction policies aimed at limiting their use as part of antimicrobial stewardship, as defined by the DTC in collaboration with the AMS committee. Restricted antimicrobials necessitate strict monitoring and compliance with the hospital's antimicrobial prescribing policy. Prescription may be limited to consultations involving an infectious diseases specialist, clinical microbiologist, or the antimicrobial stewardship team [14]. The hospital pharmacy role is essential in controlling antibiotic consumption, the prescription approval and respecting the recommendation of AMS committee.

Therefore, the main objectives of the present study were to monitor antibiotic consumption in a hospital in Bucharest, to compare antibiotic use before and after the introduction of a restriction formulary as part of the antimicrobial stewardship program, and to analyse consumption trends and the effects of the antimicrobial stewardship program on the use of broad-spectrum antibiotics.

Materials and Methods

Study design

The present study was a retrospective investigation conducted at the Fundeni Clinical Institute in Bucharest with the primary objective of assessing antibiotic consumption through the defined daily dose (DDD) method. This internationally recognised indicator allows standardisation of antibiotic consumption and its comparison over time between different health units [15, 16]. The study covers a three-year period (2022 - 2024), allowing the analysis of consumption trends and the impact of regulatory measures such as the introduction of a restriction formulary for certain antibiotics.

The particularities of each year were taken into account in the analysis. In December 2022, a restriction formulary was implemented as part of an antimicrobial stewardship program with the aim to optimise antibiotic use and reduce anti-microbial resistance selection. The years 2023 and 2024 were analysed to assess the impact of this intervention on antibiotic consumption. It should be noted that December 2024 was not included in the analysis, as an updated version of the restriction formulary was implemented during this period.

Restriction formulary description

As of December 2022, an antibiotic restriction form has been implemented at the Fundeni Clinical Institute as part of the antimicrobial stewardship strategy. This form has been introduced to control the prescription of certain broad-spectrum antibiotics, reduce unwarranted use, and consequently, reduce the risk of developing antimicrobial resistance.

The restriction formulary is an official internal hospital document that must be completed by the prescribing physician prior to the administration of antibiotics included in the restricted antimicrobial category. It encourages therapeutic decisions to be made in multi-

disciplinary and scientifically based teams with medical specialists. The formulary broadly comprises four sections. The first one refers to general data about the patient (patient's name and surname, hospitalisation ward, observation sheet number, date of completion of the form). The second section is dedicated to restricted antibiotics, including carbapenems (meropenem, imipenem-cilastatin), polymyxins (colistin), tigecycline, linezolid, vancomycin, daptomycin, intravenous fosfomycin and 4th generation cephalosporins (cefepime, ceftazidime-avibactam) and the justification for their use.

For each antibiotic requested, the prescribing physician must justify its use, indicating the patient's clinical diagnosis, the type of infection (nosocomial infection, community infection, infection in an immunosuppressed patient, *etc*.), the microorganism involved (if known) and its susceptibility to antibiotics based on the anti-biogram, the reason why first-line antibiotics are not appropriate and the estimated duration of treatment.

The formulary states that a mandatory validation by an on-call physician, ward manager or infectious disease specialist from the antibiotic stewardship team is required before the antibiotic is administered. It is also specified whether treatment is initiated empirically (in the absence of an antibiogram) or targeted (based on microbiological results). In the case of empiric treatment, it is mentioned whether the patient has risk factors for multidrug-resistant infections, such as recent ICU admission, prolonged antibiotic use, severe comorbidities and last available biological changes (creatinine, CRP, leukocytes).

The formulary also includes a section for reassessment, whether microbiologic confirmation of the diagnosis has been obtained, whether improvement in the patient's condition has been observed and whether the initial treatment should be continued, adjusted, or discontinued.

In the final step, the hospital pharmacist or a clinical pharmacist requires the restriction formulary for delivering antibiotic prescriptions on the wards. Thus, there is strict control over the antibiotic prescribing and delivery network in the hospital, strengthening local antibiotic consumption.

Data collection and analysis

Data on antibiotic consumption were collected from all wards of the Fundeni Clinical Institute, using internal records on drug consumption. For each antibiotic analysed, the DDD was calculated according to the methodology established by the WHO, using the standard formula:

$$\text{Defined Daily Dose (DDD)} = \frac{\text{Total amount of antibiotic used (mg)}}{\text{DDD defined by WHO for that antibiotic (mg)}}.$$

The DDD is a measuring unit and does not necessarily align with the recommended or prescribed daily dose. Therapeutic dosages for certain patients and patient populations frequently diverge from the DDD due to individual factors, including age, weight, ethnic variations, disease kind and severity, and pharmaco-kinetic concerns. Drug utilisation data expressed in DDDs provides an approximate assessment of intake rather than an accurate representation of actual usage. DDD offer a standardised measuring unit that is unaffected by price, currency, packaging, or potency, allowing researchers to evaluate medication utilisation patterns and conduct comparisons among different demographic groups [17].

Antibiotic usage was standardised *per* 100 bed-days by dividing the DDD by the number of daily occupied beds and multiplying the result by 100. This method allows for a standardised estimate of consumption *per* 100 patient-days. In this way, antibiotic consumption is comparable between different periods and hospital wards, irrespective of fluctuations in the number of hospitalised patients. Moreover, this study included adult patients (aged 15 years or older) in order to reduce the disadvantages of applying DDD [18]. For the analysis of consumption trends, data were stratified by year and ward, and for antibiotics included in the restriction formulary, a comparison was made between pre- and post-implementation of the restrictions. Consumption trends were analysed both overall and by antibiotic class, with a focus on antibiotics with a high risk of resistance selection.

Statistical analysis

The statistical analysis was conducted using the open-source software R (version 4.1.3) [19]. Antibiotic consumption was quantified using the DDD and analysed as a dependent variable in relation to the primary independent variables: department (11 categories), year of administration (3 categories) and month of administration (12 categories). Since the data did not meet the normality assumption, the nonparametric Kruskal-Wallis test was applied to assess differences in the distribution of DDD values concerning each of the considered factors. The graphical representation of the results was performed using boxplot diagrams, highlighting the quartiles of the analysed samples in relation to one or two of the aforementioned factors. The results were considered significant for a significance level of 0.05.

Results and Discussion

General characteristics of antibiotic consumption and impact of restrictive measures

Table I presents a descriptive analysis of antibiotic consumption in Fundeni Clinical Institute from 2022 to 2024.

Table I

General overview of antibiotic consumption by years and antibiotic classes

Variables	N	Year			p-value[2]
		2022 N = 2,940[1]	2023 N = 1,556[1]	2024 N = 1,610[1]	
Antibiotic	6,106				
Aztreonamum 1000 mg		0 (0%)	0 (0%)	30 (1.9%)	
Cefiderocolum 1 g		0 (0%)	0 (0%)	12 (0.7%)	
Ceftarolinum 600 mg		6 (0.2%)	4 (0.3%)	0 (0%)	
Ceftazidimum+Avibactamum 2 g/0.5 g		176 (6.0%)	113 (7.3%)	132 (8.2%)	
Ceftolozanum+Tazobactamum 1 g/0.5 g		4 (0.1%)	1 (<0.1%)	4 (0.2%)	
Colistinum 1000000 UI		376 (13%)	225 (14%)	227 (14%)	
Dalbavancinum 500 mg		0 (0%)	0 (0%)	1 (<0.1%)	
Ertapenemum 1 g		224 (7.6%)	133 (8.5%)	139 (8.6%)	
Fidaxomicinum 200 mg		12 (0.4%)	17 (1.1%)	15 (0.9%)	
Imipenemum+Cilastatinum 500 mg		172 (5.9%)	81 (5.2%)	87 (5.4%)	
Imipenemum+Cilastatinum+Relebactamum 500 mg/500 mg/250 mg		10 (0.3%)	3 (0.2%)	1 (<0.1%)	
Linezolidum 600 mg		526 (18%)	260 (17%)	257 (16%)	
Meropenemum 1 g		596 (20%)	289 (19%)	273 (17%)	
Teicoplaninum 400 mg		60 (2.0%)	20 (1.3%)	24 (1.5%)	
Tigecyclinum 50 mg		186 (6.3%)	125 (8.0%)	131 (8.1%)	
Vancomycinum 1 g		592 (20%)	285 (18%)	277 (17%)	
DDD	6,102	2.3 (0.9, 5.9)	2.2 (0.9, 5.3)	2.3 (0.9, 5.5)	0.7

[1]n (%); Median (Q1, Q3); [2]Kruskal-Wallis rank sum test

In 2022, the most used antibiotic was meropenem, with 596 uses (20%), followed by vancomycin, with 592 uses (20%), and linezolid, with 526 uses (18%). Colistin was also used 376 times (13%) and ceftazidime-avibactam had 176 uses (6%). Therefore, it was observed a high reliance on back-up antibiotics, such as carbapenems, glycopeptides and oxazolidinones, which are commonly used in severe infections but are at high risk of developing antimicrobial resistance [20]. In this context, the high use of meropenem and vancomycin suggests a pattern of intensive empiric treatment, probably justified by a high incidence of nosocomial infections with resistant germs.

In 2023, there was a decline in the consumption of certain antibiotics compared to 2022. Meropenem was utilised 289 times (19%), while vancomycin was used 285 times (18%), with both demonstrating a reduction. Linezolid was utilised 260 times (17%), while colistin 225 times (14%), showing minimal variation compared to the preceding year. The decline in consumption can be directly associated with the implementation of the restriction formulary in December 2022, which established more stringent criteria for the prescription of reserve antibiotics. Consequently, physicians were compelled to justify their usage and evaluate less aggressive alternatives, resulting in a gradual decrease in the consumption of meropenem, vancomycin, and linezolid.

Moreover, in 2024, the prescription of meropenem and vancomycin declined further, with 273 (17%) and 277 (17%) administrations. However, the prescription of ceftazidime-avibactam rose to 132 uses (8.2%), while tigecycline 50mg reached 131 uses (8.1%), maintaining a comparable level to the previous year. This suggests that physicians increasingly opted for more selective alternatives, such as β-lactamase inhibitors (*e.g.*, ceftazidime-avibactam) and antibiotics with a more controlled spectrum (*e.g.*, tigecycline, ertapenem), rather than relying on carbapenems and glycopeptides, which might illustrate the beneficial outcomes of restrictions, by promoting judicious antibiotic prescribing and decreasing exposure to treatments that significantly influence the selection of resistant bacteria.

However, certain antibiotics were underutilised throughout the analysed period. Dalbavancin and imipenem-cilastatin-relebactam were administered once (< 0.1%) in 2024, which indicates that these antibiotics are utilised solely in exceptional circumstances, likely due to high costs, restricted availability, or very specific indications. Interestingly, in an investigation, Yang *et al*. suggested the elevated drug cost of acquisition for imipenem-relebactam was counterbalanced by reduced hospital length of stay and diminished adverse event-related expenses, which might be a different perspective that needs further investigation [21].

Total antibiotic consumption, measured in DDD/100 days of hospitalisation, was 2.3 in 2022, decreased to 2.2 in 2023, and returned to 2.3 in 2024. The Kruskal-Wallis test yielded a p-value of 0.7, indicating no statistically significant difference among the analysed years. This finding suggests that despite significant changes in the types of antibiotics administered, there was no significant decrease in overall consumption. The restrictive measures did not reduce the total antibiotic administration but instead redistributed consumption. The stability of the DDD indicates that

the strategy to minimise the use of back-up antibiotics has been effectively executed; however, this has not resulted in a decrease in overall consumption. Therefore, complementary strategies are necessary, such as the optimisation of treatment duration and the promotion of rapid microbiological testing, to avert unnecessary antibiotic use across all classes [22].

In the same direction, a longitudinal study conducted in 74 French hospitals found that antibiotic stewardship programs resulted in stable antibiotic use, with variations observed across different hospital groups and antibiotic classes. In hospitals implementing a greater number of antibiotic stewardship program measures, overall antibiotic use and fluoroquinolone use generally exhibited stability or a decline [23].

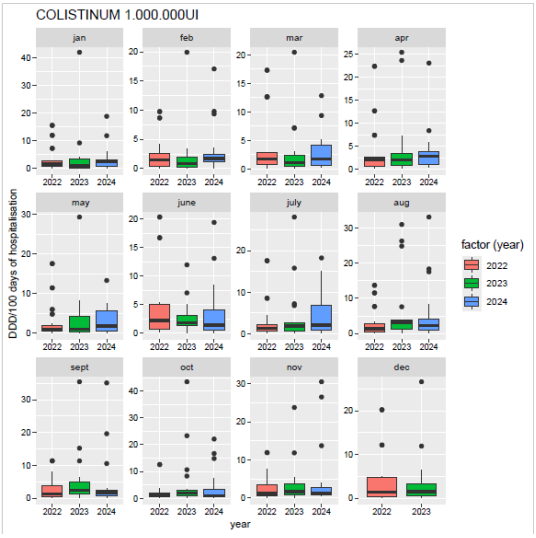
A separate study investigated the effects of the antibiotic restriction policy implemented by the Saudi Ministry of Health in April 2018 on antibiotic usage, focusing on changes and seasonal variations post-enforcement. The findings indicated a significant reduction in both total and oral antibiotic use, with mean reductions of -96.9 DDD and -98 DDD in a quarter, respectively. Conversely, a notable rise in parenteral antibiotic consumption was recorded, with a mean increase of 1.4 DDD in a quarter [24].

In addition, following the implementation of restrictive prescribing stewardship, a study that examined the impact on antibiotic consumption in primary care in China discovered that overall antibiotic consumption decreased significantly. The use of the penicillins, cephalosporins and macrolides, lincosamides and streptogramins exhibited declining trends following the intervention. Following the intervention, there was a significant rise in the prescription of third and fourth-generation cephalosporins, along with a rising trend in the prescription of fluoroquinolones. The stewardship resulted in an immediate rise in the ratio of broad- to narrow-spectrum antibiotic use, despite both exhibiting a significant downward trend [25].

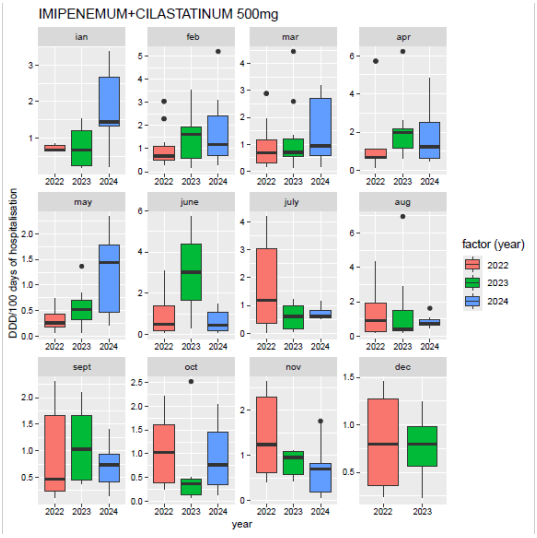
A multi-site qualitative study identified the primary barriers to the implementation of antimicrobial stewardship programs in three tertiary care settings within low- and middle-income countries. Factors preventing the improvement of antimicrobial prescribing encompass high costs of antimicrobials, restricted availability, resistance to altering existing prescribing practices and inadequate diagnostic capabilities. Limited drug availability was the most common barrier observed across all three locations. A significant number of physicians across all three locations were unfamiliar with antimicrobial stewardship programs. Rolfe R *et al*. emphasised that strengthening drug availability, enhancing the accessibility and trust in microbiologic data, developing local guidelines and educating physicians on antimicrobial prescribing are important measures that should be undertaken [26].

Analysis of antibiotic consumption by classes and types of antibiotics

Figure 1 shows the decrease in consumption of the main reserve antibiotics after implementation of the restriction formulary, expressed in DDD/100 days of hospitalisation and compared for the years 2022, 2023 and 2024.



a.



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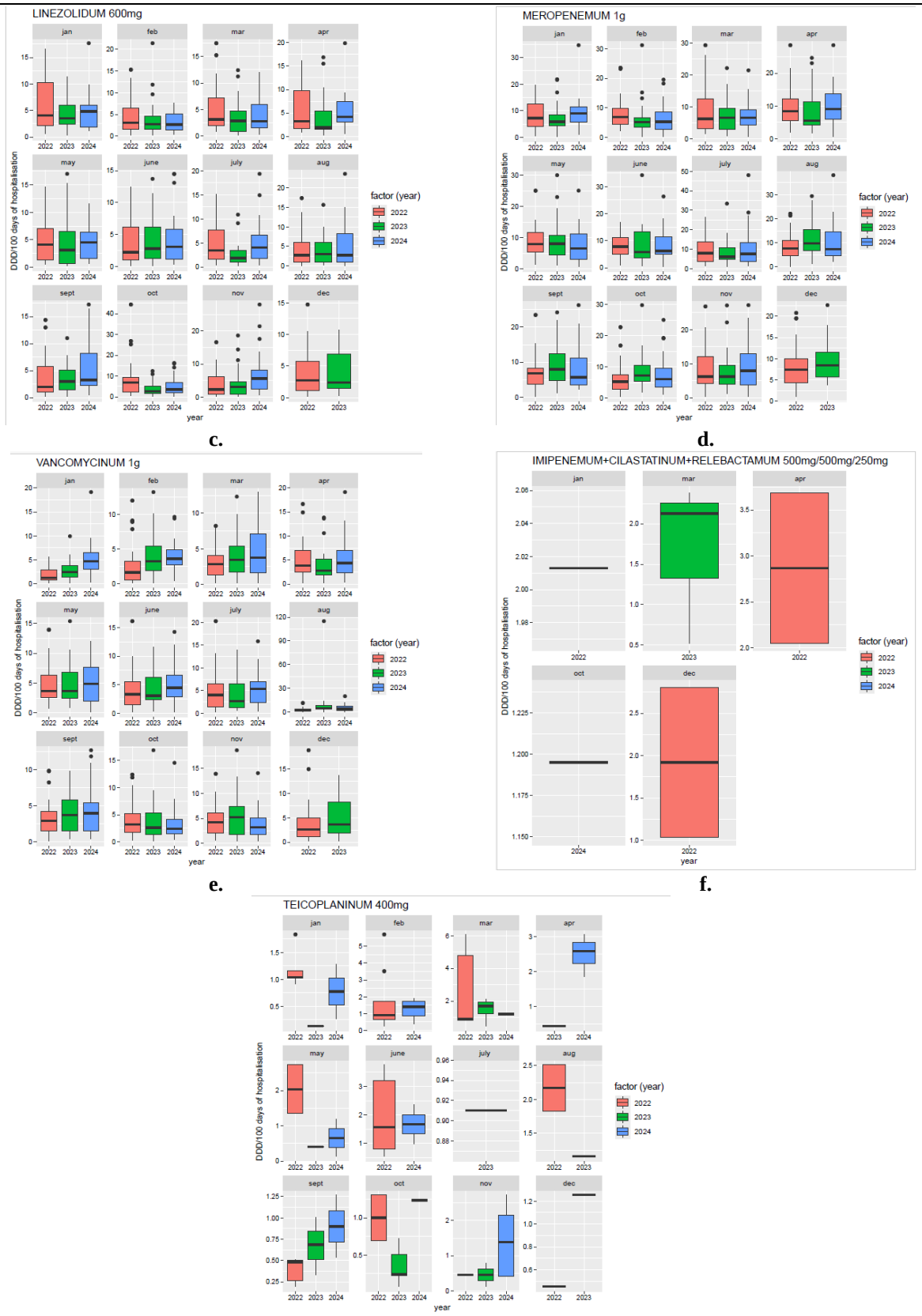

c. **d.**

e. **f.**

g.

Figure 1.

Decreased consumption of the main antibiotics after implementation of the restriction formulary: a. Colistinum, b. Imipenemum + Cilastatinum, c. Linezolidum, d. Meropenemum, e. Vancomycinum, f. Imipenemum+Cilastatinum+Relebactamum, g. Teicoplaninum

Colistin, or polymyxin E, is an antibiotic utilised as a last-resort option for treating multidrug-resistant Gram-negative infections [27]. The risk of nephrotoxicity of polymyxins significantly restricts their clinical application, with incidence rates ranging from 40% to 60%. Moreover, given the narrow therapeutic window of polymyxins, which closely coincides with nephrotoxicity concentrations, along with significant variation between individuals, especially in critically ill patients, therapeutic drug monitoring for polymyxins is recommended [28]. In the present study, colistin consumption exceeded 20 DDD *per* 100 days of hospitalisation in 2022, with peak values in the summer months (June - August). In 2023, consumption started to decrease (5 - 15 DDD), while in 2024, its use decreased statistically significantly (10 DDD in most months). This decrease in colistin consumption reflects the impact of the restriction formulary, which limited its prescription to severe cases. Since polymyxin-based combination therapy demonstrates high efficacy in treating multidrug-resistant Gram-negative infections, these antibiotics should be reserved for instances where other antibiotic regimens have proven ineffective [28].

Carbapenems are potent agents demonstrating a wide range of antimicrobial efficacy, accompanied by an increased likelihood of resistance development. Imipenem/cilastatin and meropenem are the predominant carbapenems utilised for critically ill patients in the intensive care unit. The elevated usage rates and insufficient drug exposure, particularly in critically ill patients, contribute to the emergence of carbapenem-resistant bacteria. Consequently, in order to extend their clinical lifespan by inhibiting the development of resistance, it is mandatory to optimise the usage of these pharmaceuticals in addition to ensuring optimal clinical outcomes [29]. In the present study, in 2022, imipenem+cilastatin consumption peaked in March - April, reaching almost 6 DDD/100 hospitalisation days. In 2023, the values decreased, ranging between 1 and 4 DDD. In 2024, consumption continued to decrease, remaining below 2 DDD in most months. Moreover, consumption of meropenem was extremely elevated in 2022, frequently exceeding 30 DDD/100 days of hospitalisation. In 2023, its use stayed in the range of 10 - 20 DDD. In 2024, consumption stabilised below 15 DDD, with a clear decrease in the winter months. In the same direction, in 2022, consumption of imipenem+cilastatin+relebactam was relatively constant, ranging between 1.5 and 3.5 DDD, while, in 2023, its use decreased slightly, falling below 2.5 DDD. Importantly, in 2024, consumption was almost non-existent, with values below 1.5 DDD.

It is important to note that of the various β-lactams, only carbapenems have shown a post-antibiotic action on Gram-negative bacteria. The post-antibiotic effect refers to the sustained inhibition of bacterial growth following the exposure of the microbe to an antibiotic. The post-antibiotic effect may result from the prolonged or permanent acylation of penicillin-binding proteins in conjunction with β-lactam antibiotics [30]. This might be one explanation for clinicians' preference for prescribing carbapenems before the introduction of the restriction formulary. However, the progressive decrease in the consumption of imipenem+cilastatin and meropenem has, as a direct clinical consequence, a reduction in the selective pressure on Gram-negative bacteria, which may slow down the selection of carbapenem-resistant strains [31]. These antibiotics have an increased affinity for penicillin-binding proteins, inhibiting bacterial wall synthesis, but their excessive use leads to the selection of carbapenemase-producing bacteria (KPC, NDM, OXA-48), reducing their efficacy over time [32]. Additionally, imipenem+cilastatin+relebactam was almost eliminated from clinical use in 2024, suggesting either clinicians understood the need to use therapeutic alternatives or disruptions in antibiotic supply. Relebactam, a class A and C β-lactamase inhibitor, restores the activity of imipenem against Ampicillin C and *Klebsiella pneumoniae* carbapenemase β-lactamase-producing *Enterobacteriaceae*, but has no effect on metallo-β-lactamases (New Delhi metallo-β-lactamase, Verona integron-encoded metallo-β-lactamase) [33]. Its decrease could suggest that the predominant infections were caused by metallo-β-lactamase-producing bacteria, where this antibiotic is not effective.

In 2022, linezolid consumption was extremely elevated, with values of 15 - 20 DDD in several months. In 2023, its use gradually declined, remaining between 5 - 15 DDD, while in 2024, consumption continued to decline, falling below 10 DDD in almost all months analysed. A recent meta-analysis demonstrated that linezolid exhibits significant therapeutic efficacy against various nosocomial infections. The clinical efficacy of linezolid therapy ranged from 84.4% to 94%. Consequently, prescribing this medication serves as a significant strategy in global initiatives to combat multi-drug-resistant infections [34]. To mitigate the risk of resistance development and maintain its efficacy, the administration of linezolid should be limited to patients with infections that present high morbidity and mortality rates, such as those with resistant Gram-positive germs [35]. A multicentre study identified linezolid as the most commonly contraindicated drug in all cases of drug-drug interactions. Clinicians frequently lack awareness of the potential risks linked to this drug and commonly prescribe it [36], as seen in our analysis before the implementation of the restriction formulary. Its progressive decline might suggest a reduction in empiric use and a shift towards safer alternatives, avoiding prolonged exposure.

In 2022, vancomycin exceeded 100 DDD in some months. In stark contrast, in 2023, its use was drastically reduced (10 - 20 DDD), while in 2024, consumption dropped even further, reaching below 10 DDD in several months. In clinical settings,

vancomycin is utilised extensively for the treatment of Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* and resistant *Enterococcus* sp. [37]. Although widely used in clinics, vancomycin has survived *Staphylococcus aureus* resistance evolution. Only 16 instances of vancomycin-resistant *S. aureus* (VRSA) were reported in 2024 in the USA. VRSA's reluctance to propagate may be related to the vanA operon's fitness cost, which is the only known high-level resistance. VRSA can potentially be able to compensate for vanA-mediated resistance's fitness deficit, which could threaten vancomycin's clinical durability. To prevent adaptations, Samuel E Blechman and Erik S Wright advised discontinuing vancomycin medication promptly when VRSA is diagnosed [38]. The drastic drop in consumption reflects the effectiveness of restrictions, reducing empiric use and promoting better-targeted alternatives.

In 2022, utilisation of teicoplanin ranged between 1 and 2 DDD. In 2023, utilisation remained constant, with no large variations, while in 2024, utilisation was almost insignificant, remaining below 1 DDD. Teicoplanin demonstrates comparable efficacy to vancomycin in the majority of indications, is non-toxic, simple to administer, and serves as an important medication in the treatment of Gram-positive infections [39]. Its decrease indicates a preference for other antibiotic classes due to the treatment cost and shortages over these years.

After the implementation of the restriction formulary, a progressive increase in the consumption of certain alternative antibiotics was observed. Among these, ceftazidime-avibactam, ceftolozan-tazobactam, ertapenem and tigecycline were the most affected by the change in prescribing practices, as illustrated in Figure 2.

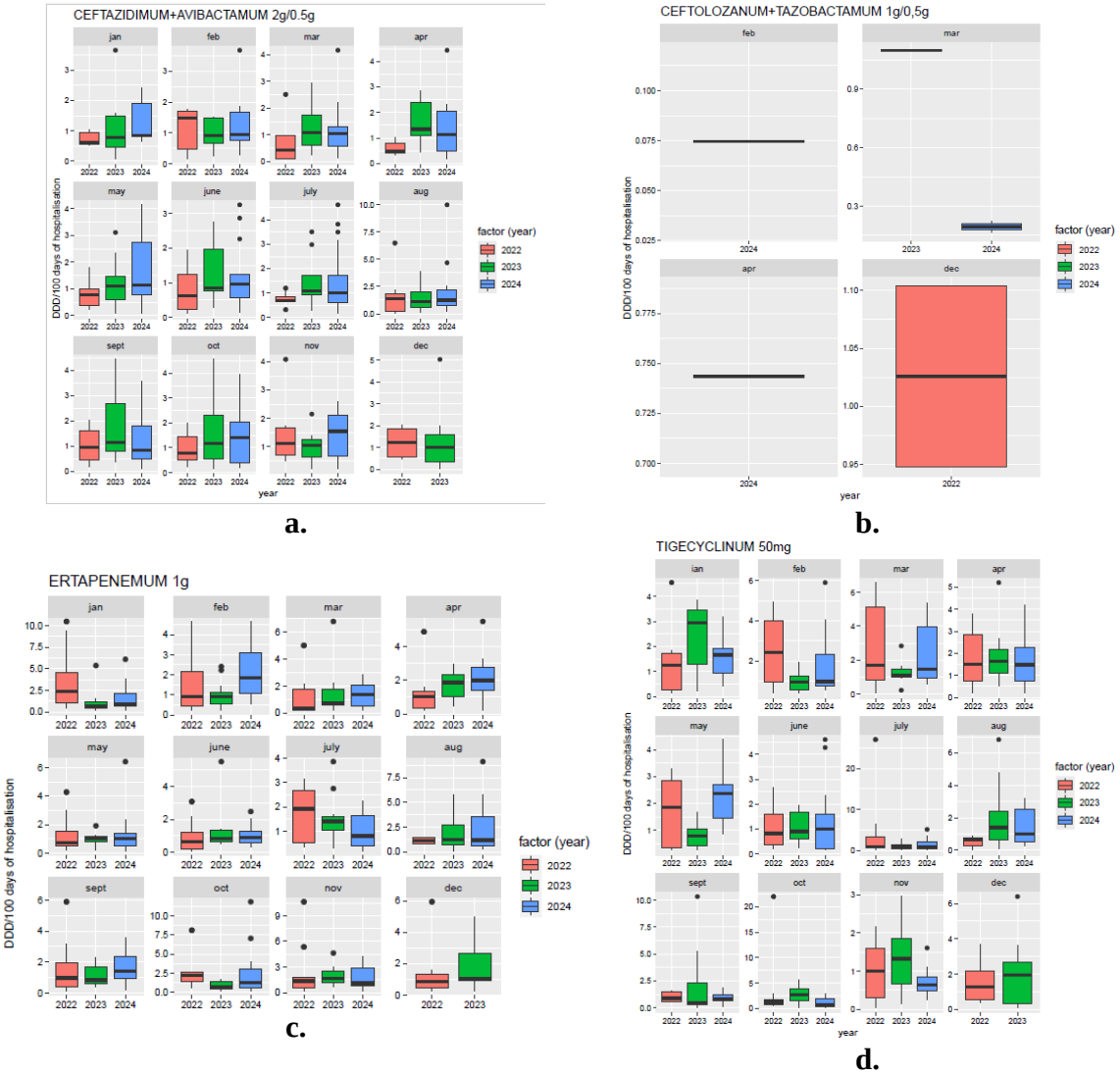

Figure 2.

Antibiotics with an increase in consumption after implementation of the restriction formulary:
a. Ceftazidimum+Avibactamum; b. Ceftolozanum+Tazobactamum; c. Ertapenemum; d. Tigecyclinum

Ceftazidime-avibactam has experienced an upward trend in usage, being an alternative for patients with severe nosocomial infections. This antibiotic is preferred for infections caused by carbapenemase-producing *Enterobacteriaceae* and multidrug-resistant *Pseudomonas aeruginosa*, having an efficacy profile similar to that of carbapenems [40, 41]. The increase in utilisation indicates a shift in therapeutic strategies, with clinicians transitioning from meropenem and imipenem to more selective alternatives. The implementation of the restriction formulary has perhaps influenced this transition, leading to clinicians providing justification for the use of carbapenems and resulting in the selection of ceftazidime-avibactam as a treatment for infections caused by organisms resistant to standard β-lactams. This strategy is consistent with the findings of Guptha *et al*., who discovered an improved clinical and microbiological cure rate, along with a more favourable tolerability profile, for ceftazidime-avibactam in cases of carbapenem-resistant *Klebsiella pneumoniae* nosocomial pneumonia and ventilator-associated pneumonia. Nosocomial pneumonia incidence in intensive care units in India ranges from 9% to 58%, with an associated mortality rate of 30 - 70%. Ceftazidime-avibactam demonstrates efficacy against OXA-48-like carbapenem-resistant *Enterobacterales* and presents a more favourable adverse effect profile relative to the nephrotoxic agent colistin [42].

Ceftolozan-tazobactam was more commonly used after 2022, with an increase in prescribing in the second half of each year. This antibiotic is one of the most effective options against multidrug-resistant *Pseudomonas aeruginosa* [43]. Nosocomial pneumonia can be treated with the intravenous combination of ceftolozane and tazobactam, which was approved for this indication. The recommended dosage is 3 g every 8 hours for 8 - 14 days. In addition, other infections can be treated with ceftolozane-tazobactam, albeit at half the dosage regimen needed for nosocomial pneumonia, such as difficult intra-abdominal infections and urinary tract infections [44]. The increase in consumption can be explained by doctors having had to limit the use of colistin and carbapenems. Compared to these, ceftolozan-tazobactam offers high efficacy and a favourable safety profile, reducing the risk of nephrotoxicity and complications associated with polymyxin therapy. Despite its therapeutic benefits, the high cost of the drug remains a significant barrier to its use and acquisition in hospital settings.

Ertapenem was used steadily from 2022 to 2024 but saw a slight increase in 2024. Unlike meropenem and imipenem, ertapenem does not act on *Pseudomonas* and *Acinetobacter*, making it a safer option in terms of selective pressure on antimicrobial resistance [45]. Its consumption was highest in the fall-winter months when complicated infections were more common. The application of restrictions on the other carbapenems might have led to a shift in consumption towards ertapenem, which was used where its narrow spectrum was sufficient. This is a beneficial trend, as the use of carbapenems must be limited to prevent the development of highly resistant strains. Moreover, it is noteworthy that the half-life of most carbapenems is roughly 1 hour, with the exception of ertapenem, which has a half-life of 3.8 hours. The extended half-life of ertapenem allows for once-daily administration [45].

Tigecycline was used steadily between 2022 and 2024, peaking at the end of each year. This antibiotic has a broad spectrum, being effective against Gram-positive, Gram-negative and anaerobic bacteria, but does not act on *Pseudomonas* [46]. The increase in use could be explained by its role as a backup option, typically prescribed only in cases of multidrug-resistant strains, or especially in severe polymicrobial infections where alternative treatments are limited. However, its particular pharmacokinetics, with low blood concentrations, limit its use in severe systemic infections [47]. Increased consumption could be a direct consequence of the restriction of carbapenems and colistin, but prescribing only in appropriate indications should be emphasised, given the risk of resistance development.

Figure 3 illustrates the impact of the application of the restriction formulary on the use of less common antibiotics, such as aztreonam, cefiderocol, ceftarolline, dalbavancin and fidaxomicin, was variably affected. These antibiotics have specific indications and have been included in the restrictions either because of high cost or because of narrow spectrum or restricted use in multidrug-resistant germ infections. Their availability for acquisition is not predictable; some were available by donations or recently received marketing authorisation in Romania (*e.g.* aztreonam).

Aztreonam consumption was low and fluctuating in 2024, remaining below 5 DDD/100 hospitalization days in most months analysed. Aztreonam is a monobactam with a spectrum limited exclusively to aerobic Gram-negative bacteria, having the advantage of tolerability in β-lactam allergic patients [48]. The formulary did not restrict aztreonam, as this active substance received authorisation for Romania in August 2024.

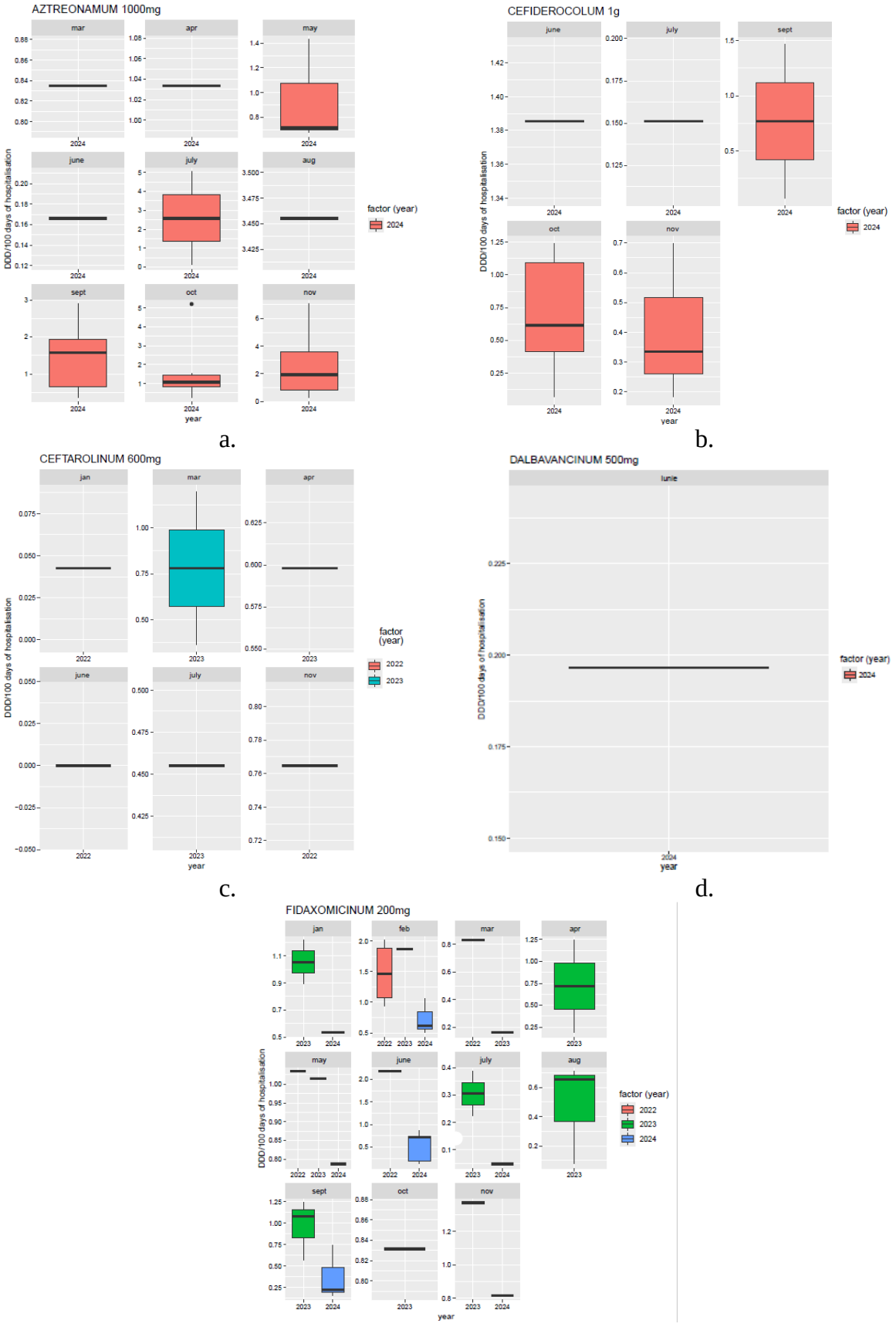

Figure 3.

The impact of the application of the restriction formulary on the use of less common antibiotics: a. Aztreonam; b. Cefiderocolum; c. Ceftarolinum; d. Dalbavancinum; e. Fidaxomicinum

In 2024, the consumption of cefiderocol was minimal, with values below 1.5 DDD/100 hospitalisation days. Given the high costs and restricted indications, the fact that its use was reported in only a few months suggests a selective prescribing pattern and a strict control of use. Cefiderocol is a cephalosporin that is effective against carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. It is a therapeutic option for infections caused by resistant bacteria. Cefiderocol should be reserved exclusively for situations in which there are no other viable alternatives [49]. Interestingly, cefiderocol enhances antibacterial activity by facilitating improved bacterial membrane penetration. By employing iron transport systems, cefiderocol is capable of more effectively targeting and eliminating resistant bacteria as a result of its distinctive structure. Cefiderocol bypasses conventional resistance pathways and promotes bacterial cell disintegration by inhibiting peptidoglycan biosynthesis through binding to penicillin-binding proteins [50].

Ceftaroline consumption was low, with values below 0.8 DDD/100 hospital days in 2022 and 2023. Use was limited to a few months *per* year, with no statistically significant upward trend. Ceftaroline is a cephalosporin antibiotic characterised by its extensive efficacy against both Gram-positive and Gram-negative bacteria. This includes notable resistant gram-positive strains, such as methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *Streptococcus pneumoniae* and penicillin-resistant *S. pneumoniae*, and is indicated in nosocomial pneumonia and complicated skin and soft tissue infections [51]. The low consumption suggests that it has not been used extensively, probably due to the preference for glycopeptides and oxazolidinones in the treatment of MRSA. Also, shortages and costs were probably among the limiting factors. Although the formulary did not restrict Ceftaroline, the low prescribing indicates a preference for better-studied alternatives, such as vancomycin and linezolid.

Dalbavancin consumption was almost non-existent, with use reported only in June 2024 and values below 0.2 DDD/100 hospital days. Dalbavancin is a glycopeptide with a long half-life, which allows weekly administration in MRSA and enterococcal infections [52]. However, its high cost [53] and lack of extensive clinical experience have limited its use in practice. Its limited use indicates that it has not been favoured over more affordable alternatives, such as vancomycin and teicoplanin.

Between 2022 and 2024, fidaxomicin use fluctuated between 0.5 and 2.0 DDD/100 hospital days, with higher consumption in 2023 and 2024 compared to 2022. Considered the gold standard in the treatment of *Clostridioides difficile* infection [54], fidaxomicin has a low effect on the intestinal microbiota and a lower risk of recurrence compared to vancomycin [55]. The increase in consumption in the last two years of the analysis may indicate a prescription in accordance with therapeutic guidelines, which recommend fidaxomicin as the first option for severe or recurrent infections.

Comparison of antibiotic consumption between wards

In a retrospective study (2017 - 2019), Liu and Qin found that *Pseudomonas aeruginosa* constituted the most significant microorganism in the central intensive care unit and the respiratory intensive care unit, whereas *Acinetobacter baumannii* was the predominant pathogen in the emergency intensive care unit. The distribution of harmful microorganisms across several departments in the hospital and sample sources exhibited significant variation. Consequently, the focused prevention and management of significant pathogenic bacteria across several hospital departments is necessary, and comprehending both drug resistance and multidrug resistance of primary pathogenic bacteria may inform the judicious application of antibiotics in clinical settings [56]. Therefore, the distribution of antibiotic consumption in different departments indicates the aetiology of prevalent infections and the therapeutic strategies used according to the severity of cases and the presence of multidrug-resistant bacteria. The implementation of the restriction formulary led to a statistically significant decrease in the use of certain antibiotics, while narrow-spectrum alternatives were preferred to increase the efficacy of antimicrobial treatment. Table III analyses the antibiotic consumption between departments.

The intensive care unit (ICU) showed a high use of reserve antibiotics, with meropenem (16%), vancomycin (16%), linezolid (15%) and colistin (15%) being the most commonly prescribed antimicrobial agents. Patients in intensive care units are at elevated risk for health-care-associated infections due to the frequent use of invasive therapies and devices, induced immune suppression, comorbidities, vulnerability and advanced age [57]. When it comes to the management of infections caused by Gram-negative bacteria that are resistant to multiple drugs, carbapenems are considered to be the antibiotics of last resort. At this time, there are relatively few antibiotic choices available for the therapeutic management of carbapenem-resistant *Enterobacteriaceae* [58]. The most common antibiotics used for treatment include polymyxins, tigecycline, fosfomycin and aminoglycosides. Currently, colistin is a treatment that is frequently employed to treat multidrug-resistant *Acinetobacter baumannii* and carbapenem-resistant *Klebsiella pneumoniae*, acting as the final line of defence. Nevertheless, the imperative necessity of the development of alternative medications and restrictive measures to combat these severe pathogens has been underscored by the emergence of colistin-resistant strains of *A. baumannii* [59]. The implementation of the restriction formulary resulted in a decrease in carbapenem use and a 6.8% increase in ceftazidime-avibactam prescriptions, indicating a

shift toward narrower-spectrum antibiotics aimed at minimising the selective pressure that causes antibiotic resistance. Our findings align with a study conducted in a tertiary hospital in India, which demonstrated extensive use of Meropenem in the ICU. Colistin and Vancomycin were the most frequently prescribed antibiotics [60]. An analysis conducted in intensive care departments of a Referral Teaching Hospital in Iran identified meropenem (15.9%), metronidazole (15.9%) and vancomycin (11.5%) as the most commonly prescribed antibiotics in ICU environments [61]. A comprehensive study involving 43 ICUs throughout Latin America revealed that carbapenems (imipenem/meropenem) were the most commonly prescribed antibiotics, accounting for 22% of prescriptions, followed by vancomycin at 15% and piperacillin-tazobactam at 12.5% [62].

Table III

Distribution of antibiotic consumption within the wards of Fundeni Clinical Institute

Variables	**N**	**ICU** N = 907[1]	**GS** N = 990[1]	**G** N = 673[1]	**H** N = 674[1]	**IM** N = 582[1]	**NPH** N = 283[1]	**N** N = 394[1]	**P** N = 459[1]	**MT** N = 211[1]	**RT** N = 112[1]	**U** N = 821[1]	**p-value**[2]
Antibiotic	6106												
Aztreonamum 1000 mg		9 (1.0%)	3 (0.3%)	0 (0%)	6 (0.9%)	0 (0%)	3 (1.1%)	0 (0%)	5 (1.1%)	1 (0.5%)	1 (0.9%)	2 (0.2%)	
Cefiderocolum 1 g		5 (0.6%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	3 (0.7%)	0 (0%)	1 (0.9%)	0 (0%)	
Ceftarolinum 600 mg		2 (0.2%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	7 (1.5%)	0 (0%)	0 (0%)	0 (0%)	
Ceftazidimum+ Avibactamum 2 g/0.5 g		62 (6.8%)	63 (6.4%)	24 (3.6%)	46 (6.8%)	69 (12%)	26 (9.2%)	28 (7.1%)	49 (11%)	1 (0.5%)	6 (5.4%)	47 (5.7%)	
Ceftolozanum+ Tazobactamum 1 g/0.5 g		4 (0.4%)	2 (0.2%)	0 (0%)	2 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	
Colistinum 1000000 UI		138 (15%)	122 (12%)	72 (11%)	87 (13%)	53 (9.1%)	36 (13%)	72 (18%)	73 (16%)	33 (16%)	11 (9.8%)	131 (16%)	
Dalbavancinum 500 mg		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	
Ertapenemum 1 g		93 (10%)	100 (10%)	53 (7.9%)	19 (2.8%)	65 (11%)	28 (9.9%)	19 (4.8%)	3 (0.7%)	17 (8.1%)	12 (11%)	87 (11%)	
Fidaxomicinum 200 mg		4 (0.4%)	7 (0.7%)	2 (0.3%)	3 (0.4%)	5 (0.9%)	2 (0.7%)	5 (1.3%)	10 (2.2%)	6 (2.8%)	0 (0%)	0 (0%)	
Imipenemum+ Cilastatinum 500 mg		50 (5.5%)	51 (5.2%)	70 (10%)	24 (3.6%)	54 (9.3%)	15 (5.3%)	5 (1.3%)	7 (1.5%)	5 (2.4%)	12 (11%)	47 (5.7%)	
Imipenemum+ Cilastatinum+ Relebactamum 500 mg/500 mg/ 250 mg		14 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Linezolidum 600 mg		138 (15%)	175 (18%)	124 (18%)	135 (20%)	83 (14%)	47 (17%)	69 (18%)	75 (16%)	40 (19%)	16 (14%)	141 (17%)	
Meropenemum 1 g		141 (16%)	184 (19%)	139 (21%)	141 (21%)	91 (16%)	46 (16%)	83 (21%)	90 (20%)	39 (18%)	22 (20%)	182 (22%)	
Teicoplaninum 400 mg		19 (2.1%)	9 (0.9%)	4 (0.6%)	4 (0.6%)	20 (3.4%)	9 (3.2%)	2 (0.5%)	23 (5.0%)	10 (4.7%)	2 (1.8%)	2 (0.2%)	
Tigecyclinum 50 mg		84 (9.3%)	90 (9.1%)	45 (6.7%)	67 (9.9%)	56 (9.6%)	21 (7.4%)	23 (5.8%)	25 (5.4%)	12 (5.7%)	1 (0.9%)	18 (2.2%)	
Vancomycinum 1 g		144 (16%)	182 (18%)	140 (21%)	139 (21%)	86 (15%)	49 (17%)	88 (22%)	89 (19%)	46 (22%)	28 (25%)	163 (20%)	
DDD	6102	5.9 (1.7, 12.6)	2.8 (1.1, 6.1)	1.6 (0.6, 3.7)	3.6 (1.3, 8.4)	1.6 (0.7, 3.4)	1.7 (0.6, 5.3)	1.9 (0.7, 3.1)	2.5 (1.0, 5.4)	2.0 (0.9, 4.2)	1.5 (0.4, 3.7)	1.4 (0.7, 3.5)	< 0.001

ICU: intensive care unit; GS: general surgery; G: gastroenterology; H: haematology; IM: internal medicine; NPH: nephrology; N: neurology; P: paediatrics; MT: bone marrow transplantation; RT: renal transplantation; U: urology; [1]n (%); Median (Q1, Q3); [2]Kruskal-Wallis rank sum test

In General Surgery departments, antibiotics are generally used for the management of postoperative infections. In our study, the most commonly prescribed were meropenem (19%), vancomycin (18%) and linezolid (18%). The high frequencies of vancomycin and linezolid might suggest a high incidence of MRSA infections. This is consistent with the findings of Akhi *et al.*, who discovered a significant prevalence of MRSA in surgical site infections. Given the increased MIC of vancomycin, they recommend the use of alternative effective agents for the treatment of surgical site infections [63]. Moreover, the use of

meropenem and colistin might indicate the presence of multiresistant Gram-negative bacteria. The restriction of carbapenems has led to an increase in the use of ertapenem (10%), a narrower spectrum carbapenem preferred in complicated intra-abdominal due to its lower impact on antimicrobial resistance [64].

In Haematology and Bone Marrow Transplant wards, where patients are severely immunosuppressed and at risk of serious opportunistic infections [65], the most commonly used antibiotics were meropenem (21%), vancomycin (21%) and linezolid (20%). These antibiotics are frequently prescribed for the treatment of systemic bacterial infections, including severe bacteraemia caused by MRSA and the resistant enterococci [66].

The highest DDD was recorded in ICU, with a median of 5.9 (1.7, 12.6), followed by Haematology, 3.6 (1.3, 8.4) and General Surgery, 2.8 (1.1, 6.1). The lowest DDD was observed in Urology, with a median of 1.4 (0.7, 3.5). Statistical analysis by the Kruskal-Wallis test showed significant differences between wards, with a p-value < 0.001.

In the ICU, the highest DDD might suggest intensive use of broad-spectrum antibiotics, which is justified by the severity of infections encountered in critically ill patients. These patients often present with multiple organ dysfunction, critical illness-induced immunosuppression and prolonged exposure to invasive devices (mechanical ventilation, central catheters), which favours colonisation and infection with multidrug-resistant pathogens [67, 68]. In this context, the antibiotic pharmacokinetics may be significantly altered. Increased volume of distribution due to interstitial oedema and altered renal clearance (through hyperfiltration syndrome or acute renal failure) require dose adjustment and, in many cases, continuous infusion to maintain efficacy.

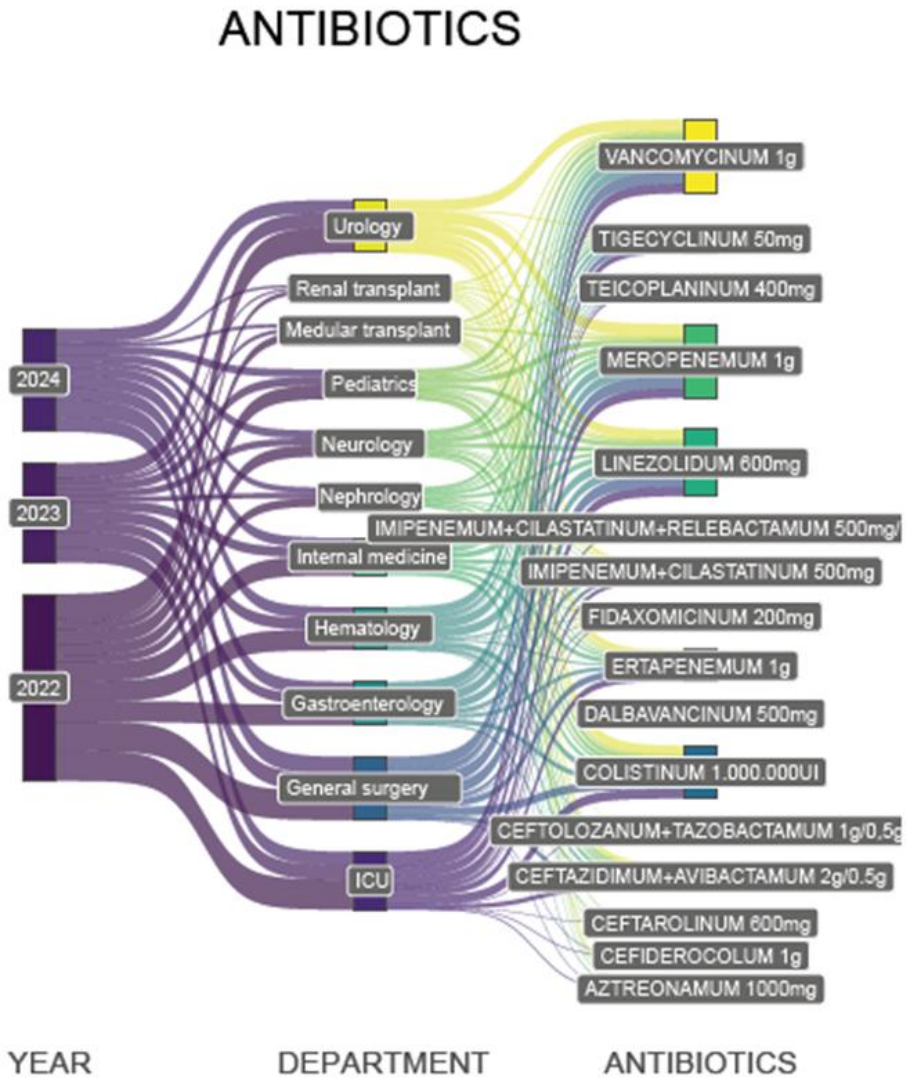

Figure 4.
Sankey illustrating antibiotic consumption between 2022, 2023 and 2024 among different wards within the Fundeni Clinical Institute

In the Haematology department, DDD could be explained by the increased incidence of severe infections in patients with neutropenia induced by chemotherapy or bone marrow transplantation. Severe neutropenia (< 500/mm³) compromises the innate immune response and might increase the incidence of infections with multidrug-resistant Gram-negative bacteria and opportunistic fungi [69]. This might be a possible explanation for the frequent use of carbapenems, colistin and glycopeptides.

In General Surgery, the DDD of 2.8 is relatively high, which may indicate frequent use of perioperative antibiotics. Prophylactic antibiotic therapy is standard in surgery to prevent wound infections, and in cases with postoperative infectious complications (peritonitis, intra-abdominal abscesses), the use of carbapenems, vancomycin and piperacillin-tazobactam is frequent [70, 71].

The lowest DDD was recorded in the Urology ward, which might suggest a more selective use of antibiotics, most likely for complicated urinary tract infections. Most of the antibiotics used are excreted predominantly renally, reaching high concentrations in the urine, which influences the therapeutic decision, since antibiotics with broad spectrum and systemic distribution (*e.g.*, carbapenems) are less utilised than those with optimal urinary penetration [72]. However, in our study, we observed relatively high utilisation of meropenem (22%) and ertapenem (11%). This could imply either an increased prevalence of complicated UTIs with multidrug-resistant germs or a noncompliant empiric prescribing practice. Careful monitoring of local bacterial resistance and implementation of effective antimicrobial stewardship strategies are needed to optimise the use of carbapenems and prevent further selection of resistant bacteria.

A decrease in the use of carbapenems and glycopeptides was observed, in parallel with an increase in the prescription of ceftazidime-avibactam inhibitors and the narrower-spectrum carbapenem, ertapenem. Administration of colistin was limited, while tigecycline and linezolid were increasingly used in wards with immunosuppressed patients. These changes might suggest a transition towards antibiotics with a narrower spectrum of action and presenting fewer adverse reactions. Thus, there may be a reduction in excessive empiric prescribing and better alignment with current therapeutic guidelines.

Conclusions

In the present retrospective study, a reduction in the use of broad-spectrum reserve antibiotics was observed as a result of optimisation of antibiotic prescribing patterns in the hospital by implementing a restriction formulary. In particular, prescriptions for reserve, broad-spectrum antibiotics have decreased, while narrower-spectrum alternatives have become more popular. Despite these changes, overall antibiotic consumption remained constant, which may suggest the existence of a redistribution rather than an absolute decline in use. These results underline the need for continued initiatives to optimise antibiotic prescribing to prevent the development of resistance and to increase the clinical lifetime of these drugs. To ensure sustainable long-term benefits, future efforts should focus on improving diagnostic capabilities and further refining prescribing guidelines.

Conflict of interest

The authors declare no conflict of interest.

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