JURNAL ILMIAH MEDICAMENTO

Vol.11 No.2 (September 2025)
page 120-130
https://doi.org/10.36733/medicamento.v11i2.11156
e-ISSN: 2356-4814

Original Article

Antibiotic Consumption and Its Influence on *Escherichia coli* and *Klebsiella pneumoniae* Resistance: A Five-Year Ecological Study in a Regional Hospital

Penggunaan Antibiotik dan Resistensi *Escherichia coli and Klebsiella pneumoniae*: Studi Ekologikal Lima Tahun di Sebuah Rumah Sakit Umum Daerah

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Submitted : 28-02-2025
Reviewed : 07-07-2025
Accepted : 11-09-2025

Keywords: cross-resistance, DDD/100 bed-days, *Escherichia coli*, *Klebsiella pneumoniae*, meropenem.

Abstract

Antibiotic resistance is a growing global health threat, partly driven by high antibiotic consumption. The World Health Organization (WHO) has identified critical-priority bacteria, including *Escherichia coli* and *Klebsiella pneumoniae*, due to their increasing resistance to multiple antibiotics. This study aimed to evaluate the correlation between antibiotic consumption and resistance rates in *Escherichia coli* and *Klebsiella pneumoniae*. This ecological study was conducted at a Regional Hospital in Indonesia based on retrospective inpatient data from January 2019 to December 2023. The population in this study is all data on systemic antibiotic consumption based on the J01 category of the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system and antibiogram from inpatient databases. Pearson and Spearman's rank correlation analyses were performed to examine the associations between systemic antibiotic consumption levels and the percentage of *Escherichia coli* and *Klebsiella pneumoniae* resistance to other antibiotics. The most frequently used antibiotics were cefixime (305.664 DDD/100 bed-days), levofloxacin (139.552 DDD/100 bed-days), and ceftriaxone (109.805 DDD/100 bed-days). A strong and statistically significant correlation was observed between doxycycline consumption and *Escherichia coli* resistance to meropenem (r=0.894; p=0.041). Moreover, consumption levels of cefazolin, ceftazidime, cefepime, and ciprofloxacin were correlated with *Escherichia coli* resistance to ceftriaxone ($p<0.05$), while cefoperazone use demonstrated a very strong and statistically significant correlation with *Escherichia coli* resistance to ampicillin-sulbactam (r=0.952; p=0.012). Conversely, no significant correlation was found between antibiotic consumption and resistance in *Klebsiella pneumoniae*, suggesting that alternative factors such as intrinsic resistance mechanisms, mobile genetic elements, and environmental reservoirs may influence resistance development.

Kata Kunci: DDD/100 bed-days, *Escherichia coli*, *Klebsiella pneumoniae* meropenem, resistensi silang.

Abstrak

Resistensi bakteri merupakan ancaman kesehatan global yang semakin meningkat, yang sebagian disebabkan oleh tingginya tingkat penggunaan antibiotik. Organisasi Kesehatan Dunia (WHO) telah mengidentifikasi *critical-priority bacteria*, termasuk *Escherichia coli* dan *Klebsiella pneumoniae*, karena meningkatnya resistensi mereka terhadap berbagai jenis antibiotik. Penelitian ini bertujuan mengetahui korelasi antara tingkat penggunaan antibiotik dan tingkat resistensi pada *Escherichia coli* dan *Klebsiella pneumoniae*. Studi ekologikal ini dilakukan di sebuah Rumah Sakit Umum Daerah di Indonesia berdasarkan data retrospektif pasien rawat inap dari Januari 2019 hingga Desember 2023. Populasi dalam studi ini mencakup seluruh data penggunaan antibiotik sistemik berdasarkan kategori J01 dari sistem klasifikasi *Anatomical Therapeutic Chemical/Defined Daily Dose* (ATC/DDD), serta antibiogram dari basis data pasien rawat inap. Analisis korelasi Pearson dan Spearman dilakukan untuk menilai hubungan antara tingkat penggunaan antibiotik sistemik dan persentase resistensi *Escherichia coli* dan *Klebsiella pneumoniae* terhadap antibiotik lain. Antibiotik yang sering digunakan adalah sefiksim (305,664 DDD/100 hari rawat inap), levoflokasasin (139,552 DDD/100 hari rawat inap), dan seftriakson (109,805 DDD/100 hari rawat inap). Terdapat korelasi yang kuat dan signifikan secara statistik antara penggunaan doksisiklin dan resistensi *Escherichia coli* terhadap meropenem (r=0,894; p=0,041). Selain itu, penggunaan sefazolin, seftazidim, sefepim, dan siprofloksasin berkorelasi dengan resistensi *Escherichia coli* terhadap seftriakson ($p<0,05$), sementara penggunaan sefoperazon menunjukkan korelasi sangat kuat dan signifikan secara statistik dengan resistensi *Escherichia coli* terhadap ampisilin-sulbaktam

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(r=0,952; p=0,012). Sebaliknya, tidak ditemukan korelasi yang signifikan antara penggunaan antibiotik dan resistensi pada *Klebsiella pneumoniae*, yang mengindikasikan bahwa faktor lain seperti mekanisme resistensi intrinsik, elemen genetik mobil, dan reservoir lingkungan mungkin lebih berperan dalam perkembangan resistensi.

How to cite: (citation style AMA 11th Ed.)
Sanjaya DA, Meriyani H, Juanita RA, Siada NB, Mahaputra Y, Kamalia MGA. Antibiotic Consumption and Its Influence on *Escherichia coli* and *Klebsiella pneumoniae* Resistance: A Five-Year Ecological Study in a Regional Hospital. *J. Ilm. Medicam.*, 2025:11(2), 120-130, DOI: 10.36733/medicamento.v11i2.11156

INTRODUCTION

Global antibiotic consumption increased significantly by approximately 65% between 2000 and 2015.[1] In Indonesia, antibiotic consumption remains relatively high, with prevalence estimates ranging from 40% to 60%.[2] This upward trend has contributed to the accelerating problem of bacterial resistance, which now poses a major threat to achieving the Sustainable Development Goals (SDGs) by 2030. The emergence of antibiotic-resistant bacteria has led to increased rates of treatment failure, healthcare-associated infections (HAIs), and morbidity and mortality.[3,4] Furthermore, resistance amplifies healthcare costs, placing additional financial burdens on patients.[5–8]

The World Health Organization (WHO) has identified a group of critical-priority bacteria that pose an urgent threat to global public health due to their escalating resistance to multiple antibiotics. Infections caused by these bacteria are difficult to prevent because of their high transmissibility and the presence of global resistance mechanisms. Many of them have developed multidrug-resistant (MDR) strains, especially in specific populations or geographic regions. This multidrug resistance (MDR) severely limits available treatment options, complicating patient management and outcomes. Among the most concerning are *Escherichia coli* and *Klebsiella pneumoniae*, both of which are frequently implicated in life-threatening infections such as sepsis and pneumonia. Their widespread resistance patterns not only hinder therapeutic efficacy but also represent a formidable barrier to infection control efforts worldwide.[9–11]

A significant factor contributing to the development of resistance in various bacteria is the high level of antibiotic consumption. Several studies have shown a correlation between increased antibiotic consumption and and the development of resistance in *Escherichia coli* and *Klebsiella pneumoniae*, including the phenomenon of cross-resistance.[12,13] A study conducted at a hospital in Peru showed that using ceftazidime can enhance the resistance of *Enterobacter spp*. to piperacillin/tazobactam and ciprofloxacin.[12] Furthermore, research at a Malaysian hospital revealed that increased use of polymyxin antibiotics may lead to the development of carbapenem resistance in Enterobacteriaceae.[13] Klebsiella pneumoniae has developed resistance to four major classes of antibiotics, such as third-generation cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems.[11,14] The development of carbapenem resistance in *Escherichia coli* and *Klebsiella pneumoniae* due to the influence of other antibiotics would significantly complicate and limit treatment options. This is particularly concerning because carbapenem antibiotics, such as meropenem, are considered last-line therapy for multidrug-resistant Gram-negative bacteria, including *Escherichia coli* and *Klebsiella pneumoniae*.[15]

Given the regional variations in antibiotic consumption and resistance patterns, understanding these dynamics in local healthcare contexts is critical. The use of one antibiotic may not only induce resistance to itself but also promote resistance to other unrelated agents through cross-resistance.[9,15–17] Despite these global findings, there is a scarcity of studies in Indonesia that link specific antibiotic consumption to resistance trends in critical-priority bacteria, particularly *Escherichia coli* and *Klebsiella pneumoniae*. According to the 2023 report from Indonesia's national antimicrobial resistance surveillance network, Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*, exhibit notably high resistance rates, especially against advanced-generation beta-lactam antibiotics. Resistance in *Klebsiella pneumoniae* remains a significant concern, with more than 65% of isolates exhibiting decreased sensitivity to third-generation cephalosporins, including ceftriaxone. Resistance to carbapenems, such as meropenem, has exceeded 20%, underscoring the increasing

presence of Carbapenem-Resistant Enterobacteriaceae (CRE) in clinical settings. Ampicillin resistance is widespread, with reported rates consistently surpassing 90% across clinical isolates. *Escherichia coli* also demonstrates an alarming resistance profile with more than 50% of isolates resistant to third generation cephalosporins and above 60% resistance rates to fluoroquinolones, including ciprofloxacin. The national surveillance system primarily collects and analyzes antimicrobial resistance data from hospitals across Indonesia to provide an overview of current conditions and resistance trends. However, it does not include correlation analysis with local or regional patterns of antibiotic consumption.[18] Understanding local resistance patterns is essential for guiding appropriate antibiotic selection. Therefore, this study aims to determine the extent of antibiotic consumption and investigate the correlation between specific antibiotics and the emergence of resistance, including potential cross-resistance pattern in critical-priority bacteria. It emphasizes the need for localized evidence to optimize antibiotic stewardship policies and improve patient outcomes.

RESEARCH METHOD

Study Design

This ecological study was conducted at a regional general hospital in Indonesia using retrospective inpatient data collected from January 2019 to December 2023. The hospital is a tertiary care facility with a capacity of 300 beds and reported bed occupancy rates (BOR) of 59%, 72%, 44%, 53%, and 59% annually from 2019 to 2023. Ethical approval for this study was granted by the hospital's ethics committee in May 2024 under approval number 070/18054/RSU.

Secondary data were used in this study, including records on antibiotic consumption, antibiograms, bed occupancy rates, and bed capacity. The independent variable was systemic antibiotic consumption, expressed in DDD per 100 bed-days. The dependent variable was the percentage of *Escherichia coli* and *Klebsiella pneumoniae* resistance. This study examines both the level of antibiotic consumption and the correlation between the use of specific antibiotics and the development of *Escherichia coli* and *Klebsiella pneumoniae* resistance to other antibiotics.

Population and Sample

The study population comprised inpatient antibiotic consumption data obtained from electronic pharmacy records and the corresponding percentages of *Escherichia coli* and *Klebsiella pneumoniae* resistance. All bacterial isolates collected between 2019 and 2023 were included, totaling 258 *E. coli* isolates and 129 *K. pneumoniae* isolates. Antibiotics analyzed were systemic agents classified under the J01 category according to the World Health Organization's Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system. Data were excluded if information on antibiotic consumption or resistance percentages was unavailable for any given timeframe within the study period.

The Level of Systemic Antibiotic Consumption

The level of antibiotic consumption was expressed as defined daily doses (DDD) per 100 bed-days. It was calculated using the following formula.[19]

$$\text{DDD/100 bed-days} = \frac{\text{Number of units administered in a given period (milligram)} \times 100}{\text{DDD (milligram)} \times \text{number of beds} \times \text{BOR} \times 365}$$

Percentage of *Escherichia coli* and *Klebsiella pneumoniae* Resistance

Antibiotic susceptibility data for *Escherichia coli* and *Klebsiella pneumoniae* were obtained from antibiogram records. The antibiogram were sourced from the Antimicrobial Resistance Control Program at the hospital where the study was conducted and included data on the percentage of *Escherichia coli* and *Klebsiella pneumoniae* susceptibility. *Escherichia coli* and *Klebsiella pneumoniae* isolates were collected from blood, sputum, and urine specimens. Susceptibility testing within the antibiograms followed the Clinical and

Laboratory Standards Institute (CLSI) guidelines, utilizing the disk diffusion method. The percentage of *Escherichia coli* and *Klebsiella pneumoniae* resistance was calculated by subtracting the susceptibility percentage from 100 percent.

Data Analysis

Data normality was assessed using the Shapiro–Wilk test. Variables conforming to the normality assumption were analyzed with Pearson's correlation, whereas those violating this assumption were analyzed with Spearman's rank correlation. Correlation analysis quantified the association between systemic antibiotic consumption and the percentage of *Escherichia coli* and *Klebsiella pneumoniae* isolates resistant to other antibiotics. Results are reported as correlation coefficients (r) with corresponding p-values.

The correlation coefficient (r) was used to assess the strength and direction of the relationship between variables, with values ranging from −1 (perfect negative correlation) to +1 (perfect positive correlation). Correlation strength was interpreted as follows: 0.90–1.00, very strong; 0.70–0.89, strong; 0.40–0.69, moderate; 0.10–0.39, weak; and 0.00–0.10, negligible. Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).[20]

RESULT AND DISCUSSION

Antibiotic Consumption

Table 1 presents data on systemic antibiotic consumption at a Regional Hospital in Indonesia from 2019 to 2023. Over this five-year period, the most frequently used antibiotics were cefixime (305.664 DDD/100 bed-days), levofloxacin (139.552 DDD/100 bed-days), and ceftriaxone (109.805 DDD/100 bed-days). The findings of this study align with previous research conducted in inpatient departments of hospitals in China between 2013 and 2021, which identified third-generation cephalosporins as the most frequently used antibiotics.[21] Another study, covering hospital inpatient facilities in China from 2012 to 2022, indicated that third-generation cephalosporins, second-generation cephalosporins, and fluoroquinolones consistently ranked as the top three classes of antibiotics throughout the study period.[22] Similarly, a study at M. Natsir Hospital in Solok City in 2020 identified cefixime as the most widely used antibiotic, with a DDD/100 bed-days value of 67.791.[23] Third-generation cephalosporins are broad-spectrum antibiotics with a good pharmacokinetic profile, a low incidence of side effects, and relatively affordable prices. They show stronger activity against gram-negative bacteria.[24]

A recent cross-sectional study at Kiruddu National Referral Hospital in Uganda analyzed medicine delivery records for antibiotic consumption and utilization from 2021-2022, found third-generation cephalosporins and fluoroquinolones among the most consumed.[25] A study conducted in the inpatient ward of internal medicine at a hospital in Bandung in 2020 stated that the highest-consumed antibiotic was levofloxacin.[26] In addition to cefixime, levofloxacin also exhibited high total consumption between 2019 and 2023. Levofloxacin, a member of the fluoroquinolone class, provides broad-spectrum activity against both Gram-positive and Gram-negative bacteria. Moreover, it is a concentration-dependent antibiotic—higher concentrations enhance its bactericidal efficacy.[27]

Given their pharmacological advantages and broad-spectrum capabilities, both third-generation cephalosporins and fluoroquinolones are classified by the World Health Organization (WHO) under the Watch category in the AWaRe (Access, Watch, Reserve) framework. This classification indicates their elevated potential for resistance development and highlights the need for cautious and selective use. The inclusion of cefixime, ceftriaxone, and levofloxacin—commonly used antibiotics in this study—within the Watch group underscores the importance of reserving these agents for targeted therapy rather than empirical treatment. WHO recommends that Watch antibiotics be used only when Access group alternatives are ineffective due to clinical severity or microbial resistance.[28]

Table 1. The Level of Systemic Antibiotic Consumption at a Regional Hospital in Indonesia from 2019 to 2023

ATC Code	Antibiotic	Antibiotic Consumption (DDD/100 Bed-Days)					
		2019	2020	2021	2022	2023	Total 2019-2023
J01DD08	Cefixime	50.676	50.816	49.659	77.116	77.397	305.664
J01MA12	Levofloxacin	24.323	31.419	39.751	21.940	22.119	139.552
J01DD04	Ceftriaxone	15.968	16.242	20.024	29.694	27.877	109.805
J01FA10	Azithromycin	15.648	19.558	11.078	21.827	24.192	92.303
J01CA04	Amoxicillin	19.886	13.564	19.537	26.123	0.704	79.814
J01MA02	Ciprofloxacin	11.107	9.695	12.564	13.121	12.345	58.832
J01DB05	Cefadroxil	13.209	9.112	20.445	8.694	6.898	58.358
J01DD01	Cefotaxime	6.591	5.238	4.699	5.024	4.280	25.832
J01AA02	Doxycycline	5.241	3.425	5.063	3.610	2.914	20.252
J01MA14	Moxifloxacin	3.020	3.709	4.252	1.403	1.927	14.311
J01CR02	Amoxicillin and Clavulanic Acid	3.508	1.771	1.139	0.953	3.285	10.656
J01DB04	Cefazoline	1.525	0.938	2.053	2.511	1.833	8.860
J01DE01	Cefepime	1.156	2.253	0.637	0.442	0.765	5.253
J01DH02	Meropenem	0.369	0.800	1.916	1.285	0.796	5.166
J01DD12	Cefoperazone	0.611	0.385	1.775	0.637	1.011	4.418
J01DD02	Ceftazidime	0.500	0.090	0.446	1.251	0.719	3.006
J01CR01	Ampicillin and Sulbactam	1.766	0.670	0.041	0.129	0.212	2.818
J01CA01	Ampicillin	0.322	0.146	0.055	0.087	0.164	0.775
J01CE08	Benzylpenicillin	0.009	0.001	0.035	0.096	0.199	0.340
	Total	**175.433**	**169.831**	**195.170**	**215.944**	**189.637**	**946.016**

Resistance Profile of *Escherichia coli* and *Klebsiella pneumoniae*

Table 2 shows the percentage of resistance in *Escherichia coli* and *Klebsiella pneumoniae* from 2019 to 2022. Based on the 2021 resistance pattern shown in **Table 2**, *Escherichia coli* demonstrated multi-drug resistance (MDR), becoming resistant to three or more antibiotics, such as ampicillin-sulbactam, ceftriaxone, and ciprofloxacin. Meanwhile, *Klebsiella pneumoniae* exhibited resistance to ampicillin throughout the study period.

Table 2. Percentage of *Escherichia coli* and *Klebsiella pneumoniae* Resistance at a Regional Hospital in Indonesia from 2019 to 2023

Antibiotic	Percentage of Resistance (%)				
	2019	2020	2021	2022	2023
Escherichia coli					
Number of Isolate (n)	**19**	**17**	**54**	**65**	**103**
Ampicillin and Sulbactam	57.90	47.10	77.00*	50.00	57.30
Piperacillin and Tazobactam	15.80	0.00	13.00	6.30	10.80
Ceftriaxone	52.60	41.20	65.00*	74.60*	65.70*
Ceftazidime	47.40	18.70	43.00	31.20	52.90
Cefepime	0.00	11.90	43.00	20.30	29.40
Amikacin	0.00	0.00	0.00	0.00	3.90
Meropenem	5.30	0.00	2.00	0.00	0.00
Ciprofloxacin	84.20*	47.10	78.00*	68.70*	78.60*
Klebsiella pneumoniae					
Number of Isolate (n)	**10**	**7**	**28**	**34**	**50**
Ampicillin	100.00*	85.70*	100.00*	100.00*	100.00*
Ceftriaxone	50.00	28.60	43.00	50.00	36.00
Ceftazidime	50.00	14.30	39.00	41.20	35.40
Amikacin	0.00	0.00	0.00	0.00	0.00
Meropenem	0.00	10.00	0.00	2.90	0.00
Ciprofloxacin	80.00*	33.30	54.00	61.80*	54.00

*Highly resistance (more than 60%)

A study conducted in Thailand from 2017 to 2018 found that 41.3% of *Escherichia coli* isolates were classified as MDR.[29] Similarly, a 10-year retrospective study from a tertiary hospital in China, which analyzed antimicrobial resistance patterns in *Escherichia coli* isolates collected from various clinical samples and across different patient age groups, showed findings consistent with the present study. This study revealed a high prevalence of MDR *Escherichia coli*, with notable resistance to commonly used antibiotics, including ampicillin, ceftriaxone, and ciprofloxacin.[30] Comparable resistance patterns have also been reported in *Klebsiella pneumoniae*. A study conducted in Duhok City, located in the Kurdistan Region of Iraq between 2017 and 2019, documented a very high level of resistance of *Klebsiella pneumoniae* to ampicillin.[31] Likewise, a study conducted in Vietnam found that *Klebsiella pneumoniae* exhibited the highest resistance rates to ampicillin among all antibiotics tested.[32]

In gram-negative bacteria such as *Escherichia coli*, resistance to β-lactam antibiotics such as penicillins, cephalosporins, carbapenems, and monobactams occurs primarily through three mechanisms: the production of β-lactamases that hydrolyze antibiotics, increased expression of efflux pumps that expel antibiotics from the bacterial cel, and decreased expression or loss of porins, which limits antibiotic penetration into the cell[33]. Fluoroquinolone resistance in *Escherichia coli* involves several mechanisms, including chromosomal mutations that alter target enzymes such as the GyrA subunit of DNA gyrase and the ParC subunit of topoisomerase IV. Additionally, decreased intracellular drug concentrations may result from overexpression of efflux pumps and downregulation of porins. The emergence of plasmid-mediated quinolone resistance (PMQR) genes also contributes, involving qnr (protects target enzymes), *aac(6')-Ib-cr* (modifies quinolones), and *qepA* and *oqxAB* (enhance drug efflux).[34]

In *Klebsiella pneumoniae*, resistance to ampicillin is primarily mediated by the production of TEM-1 and SHV-1 β-lactamases, which are encoded chromosomally and efficiently hydrolyze penicillins.[35,36] Mutations in these genes can give rise to extended-spectrum β-lactamases (ESBLs), capable of hydrolyzing a broader range of β-lactams, including third-generation cephalosporins and monobactams. ESBLs are frequently plasmid-borne, facilitating horizontal gene transfer. Additionally, loss or modification of outer membrane porins (e.g., OmpK35, OmpK36) reduces antibiotic influx, further enhancing resistance when combined with β-lactamase activity. *K. pneumoniae* also employs efflux systems, such as AcrAB-TolC, to actively expel antibiotics like ampicillin. Moreover, biofilm formation contributes to resistance by creating a physical barrier that limits antibiotic penetration; ampicillin, in particular, exhibits poor diffusion through biofilms.[36]

Correlation between antibiotic consumption and the percentage of resistance to other antibiotics in *Escherichia coli* and *Klebsiella pneumoniae*

Table 3 shows a correlation coefficient between antibiotic consumption and the percentage of resistance to other antibiotics in *Escherichia coli*. A strong and statistically significant correlation was observed between the level of doxycycline consumption and *Escherichia coli* resistance to meropenem ($r=0.894$ and $p<0.05$). Doxycycline, a tetracycline-class antibiotic, induces the tet(A) gene in *Escherichia coli* isolates, which encodes efflux pumps that confer resistance to all tetracycline-class antibiotics.[37,38] Resistance genes such as tet(A) are found in multi-resistance plasmids such as the 225 kb IncHI2/IncP plasmid, which also carries the blaCTX, blaTEM-1, blaNDM-5, sul1, sul2, dfrA1, and aadA1 genes. The 90-120 kb IncI1 plasmid carries resistance genes such as tet(A) along with blaSHV-12, blaNDM-5, blaKPC-2, blaOXA-48, aadA1, cmlA1, and aadA2 genes. The 250 kb IncFIB/IncHI2 plasmid carries the tet(B) gene and the blaCTX-M-2, blaNDM-5, sul1, aadA29, strA, and strB genes. The IncFIC plasmid carries the tet(A) gene along with the blaCMY-2, blaNDM-5, blaKPC-2, blaOXA-48, cmlA, floR, strA, strB, sul1, sul3, and aadA7 genes. The 40 kb IncFIB/IncN plasmid carries the tet(A) gene and the blaNDM-5, sul1, dfrA16, and dfrA29 genes. These multi-resistance plasmids may subsequently be transferred horizontally by conjugation to other *Escherichia coli* bacteria. Thus, the use of doxycycline can accelerate the spread of resistance genes that cause cross-resistance to meropenem.[39–41]

Table 3. The Correlation Coefficient between Antibiotic Consumption and The Percentage of Resistance to Other Antibiotics in *Escherichia coli* at a Regional Hospital in Indonesia from 2019 to 2023

Antibiotic Resistance	Antibiotic Consumption					
	Doxycycline	Cefazolin	Ceftazidime	Cefoperazone	Cefepime	Ciprofloxacin
Ciprofloxacin Resistance	0.495	0.505	0.367	0.503	-0.735	0.593
Ceftazidime Resistance	0.253	0.343	0.233	0.504	-0.617	0.494
Meropenem Resistance	0.894*	-0.112	-0.224	0.112	0.112	-0.112
Amikacin Resistance	-0.707	0.001	0.354	0.354	0.001	0.001
Ampicillin and Sulbactam Resistance	0.624	0.310	-0.133	0.952*	-0.473	0.415
Cefepime Resistance	-0.281	0.492	0.141	0.868	-0.513	0.603
Piperacillin and Tazobactam Resistance	0.657	0.347	0.165	0.524	-0.595	0.466
Ceftriaxone Resistance	-0.090	0.980*	0.886*	0.456	0.957*	0.991*

*Significant (p<0,05)

Very strong correlation
Strong correlation
Moderate correlation
Weak-negligible correlation

In addition to doxycycline, other antibiotic classes such as cephalosporins also show significant associations with *Escherichia coli* resistance patterns. The consumption of antibiotics such as cefepime, ceftazidime, and cefazolin is correlated with *Escherichia coli* resistance to ceftriaxone ($p<0.05$), which is a third-generation cephalosporin antibiotic. In addition, the consumption of cefoperazone antibiotics is correlated with *Escherichia coli* resistance to ampicillin sulbactam ($r=0.952$ and $p=0.012$). Cephalosporin antibiotics induce resistance genes such as TEM, SHV, blaCTX-M, and OXA. These genes encode Extended-Spectrum Beta-Lactamase (ESBL) enzymes that confer resistance to the penicillin and cephalosporin groups (generations I, II, and III) and aztreonam[42]. In a study in Indonesia, the most common gene causing *Escherichia coli* resistance to third-generation cephalosporin antibiotics is the blaCTX-M gene, and globally, the most dominant gene causing resistance is blaCTX-M-15 and blaCTX-M-14, which contributes to a phenomenon known as "The CTX-M β-lactamase pandemic".[43,44]

This study also showed that the use of ciprofloxacin increased the percentage of *Escherichia coli* resistance to ceftriaxone ($r=0.991$ and $p<0.05$). Ciprofloxacin will induce the qnr gene, which protects DNA gyrase and topoisomerase IV from fluoroquinolone inhibition. This gene can be found on IncF, IncA/C2, and IncHI2 plasmids, which also carry resistance genes for ceftriaxone, namely blaCTX-M and blaCMY-2. The IncF, IncA/C2, and IncHI2 plasmids containing the qnr, aac(6')-Ib-cr, blaCTX-M, and blaCMY-2 genes can be transferred from one bacteria to another either horizontally or vertically.[45]

Table 4 shows that there is no significant correlation between antibiotic consumption and the percentage of resistance to other antibiotics in *Klebsiella pneumoniae*. However, antibiotics should not be administered without careful consideration. *Klebsiella pneumoniae* possesses intrinsic resistance mechanisms, such as reduced outer membrane permeability (e.g., porin loss), active efflux pumps, and chromosomally encoded β-lactamases. Moreover, resistance genes in *Klebsiella pneumoniae* are frequently located on mobile genetic elements, including plasmids, integrons, and transposons, which facilitate their rapid dissemination through horizontal gene transfer. Moreover, the persistence of resistance may be influenced by environmental contamination in hospital settings, including surfaces, medical equipment, and wastewater systems, as reservoirs for resistant strains of *Klebsiella pneumoniae*.[36]

In addition, there may be several inherent and ecological factors contributing to this lack of a statistically significant association of *Klebsiella pneumoniae* resistance with antibiotic consumption. *Klebsiella pneumoniae* has a more dynamic resistance profile and has more complex mechanisms that are less associated to only the level of antibiotics applied. A major contributing factor is the ability of the organism to form biofilms, which protect against environmental stresses and impede antibiotic penetration. Biofilm-associated cells exhibit altered metabolic states and reduced susceptibility, rendering them less responsive to antimicrobial pressure in a manner not directly reflected by antibiotic consumption. Furthermore, *Klebsiella pneumoniae* is characterized by innate resistance mechanisms and has the ability to acquire resistance genes

through horizontal gene transfer, primarily through plasmids encoding carbapenemases or extended-spectrum β-lactamases (ESBLs). These genetic traits may be disseminated regardless of the local use of antimicrobials, particularly in overcrowded healthcare-facilities and poor infection control environments.[46,47]

Table 4. The Correlation Coefficient between Antibiotic Consumption and The Percentage of Resistance to Other Antibiotics in *Klebsiella pneumoniae* at a Regional Hospital in Indonesia from 2019 to 2023

Antibiotic Resistance	Antibiotic Consumption					
	Doxycycline	Benzylpenicillin	Cefazolin	Ceftazidime	Cefoperazone	Ciprofloxacin
Ampicillin Resistance	0.354	0.707	0.707	0.707	0.707	0.707
Ceftriaxone Resistance	0.577	-0.056	0.689	0.655	0.131	0.603
Ceftazidime Resistance	0.575	0.137	0.618	0.552	0.287	0.616
Meropenem Resistance	0.667	-0.447	-0.224	-0.224	-0.671	-0.224
Ciprofloxacin Resistance	0.579	0.013	0.420	0.453	0.036	0.393

Strong correlation
Moderate correlation
Weak-negligible correlation

Despite these findings, the ecological design of this study imposes inherent limitations. This design only allows data analysis at the population level, preventing the identification of individual-level antibiotic exposure durations within the studied population. The duration of such exposure may significantly influence the percentage of antibiotic resistance in *Escherichia coli* and *Klebsiella pneumoniae*. Certain classes of antibiotics, such as beta-lactams, exhibit time-dependent pharmacodynamics, where their efficacy relies on the duration of time the drug concentration remains above the minimum inhibitory concentration (MIC).[48] Inappropriate use of time-dependent antibiotics—such as insufficient dosing or extended intervals between doses—can facilitate the emergence of resistance by exposing bacteria to suboptimal drug concentrations for prolonged periods, thereby allowing them to develop adaptive mechanisms against these agents.[49]

This analysis used Defined Daily Dose (DDD) calculation with Bed Occupancy Rate (BOR) as part of standard methodology to estimate antibiotic use.[50] It did not however, explicitly consider variations of BOR during the COVID-19 pandemic period (2020–2021) during which the general pattern of hospital admissions and occupancy rates was heavily influenced by public health measures and by changing clinical priorities. It is accepted that the changes in BOR during pandemic could have affected DDDs and estimated consumptions in both 2019 and 2020. However, these variations were not considered as a factor in this study. It is suggested that future research should consider more detailed hospital-level data to better control for such contextual variables and offer a more robust interpretation of consumption measures in times of disruption.

Although the study has certain methodological limitations, the results still offer meaningful insights that can support the development of antibiotic stewardship strategies. The findings of this study highlight the importance of improving antibacterial stewardship through monitoring antibiotic consumption and the integration of resistance data into prescribing practices. As such, clear institutional policies and focused education for the health care provider are critical to maintaining responsible use of antibiotics and prevent the development of antibiotic resistance. Therefore, developing clear institutional protocols and delivering focused educational initiatives for healthcare professionals represent fundamental measures in promoting responsible antibiotic consumption and slowing the advancement of antibiotic resistance.

CONCLUSION

This study identified significant correlations between antibiotic consumption and resistance in *Escherichia coli*, particularly for doxycycline, cephalosporins, and ciprofloxacin, whereas no significant

association was observed for *Klebsiella pneumoniae*. These findings underscore the multifactorial nature of antimicrobial resistance and highlight the need for comprehensive stewardship strategies that integrate optimized prescribing, robust infection prevention, environmental controls, and genomic surveillance. Targeted interventions should prioritize third-generation cephalosporins and fluoroquinolones, given their strong association with resistance. Furthermore, antibiotic use policies should be locally adapted and guided by resistance profiles to promote prudent prescribing and mitigate the emergence and dissemination of resistant strains.

ACKNOWLEDGEMENT

This study was supported by Universitas Mahasaraswati Denpasar (Grant number: K.171/B.01.01/LPPM-Unmas/IV/2024).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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