Correlation between antibiotic use and resistance of gram-negative bacteria at a university hospital in Japan from 2013 to 2021: A study using the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system

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Abstract

Objectives: The Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system aggregates information related to antimicrobial resistance (AMR) measures. We aimed to investigate the correlation between antibiotic use and antibiotic resistance at a university hospital from 2013 to 2021 in a time series analysis using this system. We also studied this correlation in each ward (inter-ward analysis).

Methods: Data on antibiotic use and resistance rates were collected from J-SIPHE system, except for the resistance rate in each ward, which was calculated from the source data prepared for this system.

Results: Piperacillin/tazobactam use was positively correlated with piperacillin/tazobactam

resistance in *Escherichia coli* and *Klebsiella pneumoniae* in the inter-ward analysis, and in *Pseudomonas aeruginosa* in both analyses. Carbapenem use was positively correlated with meropenem resistance in *Enterobacter cloacae* in the time series analysis and in *P. aeruginosa* in both analyses, and imipenem/cilastatin resistance in *P. aeruginosa* in inter-ward analysis. Quinolone use was positively correlated with levofloxacin resistance in *E. coli* in both analyses, and in *K. pneumoniae* in inter-ward analysis.

Conclusions: This is the first study to investigate the correlation between antibiotic use and antibiotic resistance at a single hospital in time series and inter-ward analyses using the J-SIPHE system and data prepared for this system, suggesting that this system may be useful for promoting AMR measures.

Keywords: J-SIPHE; surveillance; antibiotic use; antibiotic resistance; carbapenems

What is already known on this topic

Although the relationship between the antibiotic use and resistance has been investigated in several studies, these results are controversial. Therefore, further studies are needed to clarify this correlation.

What this study adds

Using The Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system, we demonstrated several correlations between the antibiotic use and resistance in a university hospital.

How this study might affect research, practice or policy

This study could contribute to promoting the use of the J-SIPHE system in other hospitals and aid in the implementation of antimicrobial resistance (AMR) measures such as antimicrobial stewardship programs.

Introduction

Recently, antimicrobial resistance (AMR) has become a global issue because it threatens public health [1-3]. The emergence of resistant bacteria makes it difficult to treat infections, thereby extending hospital stays, increasing medical costs, and increasing the mortality rate [1-3]. Several factors are thought to be involved in the increased AMR, and one of the factors is thought to be the increase in antibiotic use. However, results regarding the correlation between antibiotic use and antibiotic resistance are controversial [4-8]. Therefore, further studies are required to clarify this correlation.

The Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system [9] is a national surveillance system for AMR measures. It was developed by the National Center for Global Health and Medicine and the AMR Clinical Reference Center, commissioned by the Japanese government in 2019, in response to the adoption of the Global Action Plan on AMR issued by the World Health Organization (WHO) [10,11]. The J-SIPHE system can aggregate information related to AMR measures, including the status of antibiotic use and the emergence of major bacteria and antimicrobial-resistant bacteria in medical institutions nationwide. Registered information can be visualized as a graph on the website and downloaded at any time.

A previous study investigated the correlation between antibiotic use and antibiotic resistance in a single-year multicenter study using the J-SIPHE system, revealing several correlations between antibiotic use and antibiotic resistance [12]. In the present study, we aimed to investigate this correlation in a single institution for further analysis. We evaluated the correlation between antibiotic use and antibiotic resistance via time series analysis using the J-SIPHE system. Furthermore, we conducted additional analysis to compare these correlations among wards, as this has rarely been addressed in previous studies. We evaluated the correlation between broad-spectrum antibiotic use and resistance of gram-negative bacteria, which have been of concern due to their increasing resistance rates and are targeted in the AMR countermeasure plan of the Japanese government [11].

Methods

Study design

This study was conducted at a university hospital, a 939-bed tertiary care medical center, in Japan. The amount of antibiotics used and the resistance rates of bacteria were automatically calculated on the website of the J-SIPHE system. In this study, data from January 2013 to December 2021 were obtained from the J-SIPHE system and analyzed. All the data included in the time series analysis were obtained from this system. To compare between wards, data of antibiotic use were retrieved from the J-SIPHE system and the resistance rates of bacteria were calculated from the source data prepared for this system. In this inter-ward analysis, data from May 2018 to December 2021 were used because ward reorganization was conducted at the beginning of May 2018.

The requirement for ethics committee approval and informed consent was waived because this study analyzed surveillance data that did not include individual patient information.

Antibiotic use

The amount of antibiotics used was obtained from the J-SIPHE system for all time series and inter-ward analyses. We evaluated the use of broad-spectrum antibiotics (piperacillin/tazobactam, third-generation cephalosporins, fourth-generation cephalosporins, carbapenems, aminoglycosides, and quinolones), including both intravenous and oral

antibiotics. Antibiotic use was evaluated based on both the antibiotic use density (AUD) and days of therapy (DOT), which were automatically calculated on the J-SIPHE system website. AUD was defined as antibiotic use (in grams)/defined daily dose (DDD) per 100 patient-days. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, as indicated by the World Health Organization (WHO) [13]. DOT was defined as DOTs per 100 patient-days.

Antibiotic resistance

Susceptibility testing was performed based on the broth microdilution method with the turbidity standard technique using a MicroScan WalkAway plus System (Beckman Coulter, Tokyo, Japan). Susceptibility was determined according to the Clinical Laboratory Standards Institute (CLSI) guidelines [14].

Bacterial resistance rates were calculated as a percentage of resistant isolates, including those showing intermediate resistance, in all isolates. For the time series analysis, resistance rates were retrieved from the J-SIPHE system; however, for the inter-ward analysis, resistance rates were calculated from the source data prepared for this system. The gram-negative bacteria investigated were *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.

Correlations between antibiotic use and antibiotic resistance

We analyzed the correlation between the amount of antibiotics used and resistance rates using two different modalities: time series and inter-ward analyses. In the time series analysis, annual antibiotic use and resistance rates at the hospital were investigated. In the inter-ward analysis, the mean value of antibiotic use and the resistance rate in each ward during the survey period were evaluated.

Mapping of wards with correlations between antibiotic use and antibiotic resistance

For combinations of antibiotic use and resistance rates that showed a significant correlation in inter-ward analysis, each ward was divided and mapped to high and low based on their median values of antibiotic use and resistance rates. If the value of each ward was equal to the median (for example, both values were zero), it was mapped to low.

Statistical analysis

Trends and correlations between antibiotic use and resistance rates were analyzed using the Spearman's rank correlation coefficient. For all comparisons, P values < 0.05 were considered statistically significant. All calculations were performed using the JMP Pro version 14 (SAS Institute Inc., Tokyo, Japan).

Results

Antibiotic use

The trends in broad-spectrum antibiotic use are shown in Supplementary Table 1. According to the AUD, quinolones were used most often during the entire study period, followed by third-generation cephalosporins, carbapenems, piperacillin/tazobactam, fourth-generation cephalosporins, and aminoglycosides. In addition, a significant increase in the AUD was observed for piperacillin/tazobactam (Spearman's $\rho = 0.962$; $P < 0.001$) and fourth-generation cephalosporins (Spearman's $\rho = 0.683$; $P = 0.042$). In contrast, a significant decrease in antibiotic use was observed for third-generation cephalosporins (Spearman's $\rho = -0.733$; $P = 0.025$) and aminoglycosides (Spearman's $\rho = -0.817$; $P = 0.007$). Regarding carbapenem use, the AUD was highest in 2017 and declined thereafter (from 3.11 in 2017 to 2.17 in 2021). In DOT, the trends of broad-spectrum antibiotic use were similar to those in AUD.

Antibiotic resistance

Trends in the resistance rates of bacteria are shown in Supplementary Table 2. During the study period, a significant increase in resistance rates was observed in ceftazidime-resistant *K. pneumoniae* (Spearman's $\rho = 0.733$; $P = 0.025$), cefepime-resistant *K. pneumoniae* (Spearman's $\rho = 0.717$; $P = 0.03$), and imipenem/cilastatin-resistant *E. cloacae* (Spearman's ρ

= 0.817; P = 0.007). In contrast, a significant decrease was observed in piperacillin/tazobactam-resistant *S. marcescens* (Spearman's ρ = -0.819; P = 0.007), ceftazidime-resistant *S. marcescens* (Spearman's ρ = -0.745; P = 0.021), cefepime-resistant *E. cloacae* (Spearman's ρ = -0.867; P = 0.003), and meropenem-resistant *A. baumannii* (Spearman's ρ = -0.772; P = 0.015).

Correlation between antibiotic use and bacterial resistance in time series analysis

The correlation between the annual amount of antibiotics used and rates of bacterial resistance is shown in Figure 1 and Supplementary Table 3. The AUD of piperacillin/tazobactam was significantly positively correlated with the rate of piperacillin/tazobactam resistance in *P. aeruginosa* (Spearman's ρ = 0.711; P = 0.032) but was significantly negatively correlated with the rate of piperacillin/tazobactam resistance in *S. marcescens* (Spearman's ρ = -0.759; P = 0.018). Furthermore, the AUD of third-generation cephalosporins was significantly negatively correlated with the rate of ceftazidime resistance in *K. pneumoniae* (Spearman's ρ = -0.867; P = 0.003). In contrast, the AUD of carbapenems was significantly positively correlated with the rates of meropenem resistance in *E. cloacae* (Spearman's ρ = 0.712; P = 0.031) and *P. aeruginosa* (Spearman's ρ = 0.767; P = 0.016). The DOT of quinolones was significantly positively correlated with the rate of levofloxacin resistance in *E. coli* (Spearman's ρ = 0.7; P = 0.036).

Correlation between antibiotic use and bacterial resistance in inter-ward analysis

The correlation between the amount of antibiotics used and rates of bacterial resistance among wards is shown in Figure 2 and Supplementary Table 4. A total of 22 wards were analyzed, which included medical, surgical, mixed medical and surgical, and intensive care wards (8, 7, 4, and 3 wards, respectively). The intensive care wards comprised the neonatal intensive care unit/growing care unit (NICU/GCU), intensive care unit (ICU), and emergency ward. The AUD of piperacillin/tazobactam was significantly positively correlated with the rates of piperacillin/tazobactam resistance in *E. coli* (Spearman's $\rho = 0.544$; $P = 0.009$), *K. pneumoniae* (Spearman's $\rho = 0.498$; $P = 0.018$), and *P. aeruginosa* (Spearman's $\rho = 0.728$; $P < 0.001$). The DOT of third-generation cephalosporins was significantly positively correlated with the rates of *S. marcescens* resistance to ceftriaxone (Spearman's $\rho = 0.463$; $P = 0.046$) and ceftazidime (Spearman's $\rho = 0.546$; $P = 0.011$). Furthermore, the AUD of fourth-generation cephalosporins was significantly positively correlated with the rate of cefepime resistance in *K. pneumoniae* (Spearman's $\rho = 0.602$; $P = 0.003$). Similarly, the AUD of carbapenems was significantly positively correlated with the rates of *P. aeruginosa* resistance to meropenem (Spearman's $\rho = 0.678$; $P < 0.001$) and imipenem/cilastatin (Spearman's $\rho = 0.688$; $P < 0.001$). The AUD of quinolones was significantly positively

correlated with the rates of levofloxacin resistance in *E. coli* (Spearman's $\rho = 0.476$; $P = 0.025$) and *K. pneumoniae* (Spearman's $\rho = 0.594$; $P = 0.004$).

Mapping of wards with correlations between antibiotic use and bacterial resistance

The mapping of wards with significant correlations between the antibiotics used and bacterial resistance derived from inter-ward analysis was shown in Figure 3. Each ward was divided and mapped to high and low based on the median values of antibiotic use and resistance rates. The total number mapped to high and/or low was shown in Table 1. Ward numbers 1, 14, 16, and 21 had higher than median antibiotic use and resistance rates in 8 or 9 of the 10 combinations that were significantly correlated. In contrast, ward numbers 5, 7, 9, and 20 had lower than or equal to median antibiotic use and resistance rate in 8 or 9 of the 10 combinations that were significantly correlated.

Discussion

A previous study has demonstrated that the J-SIPHE system could easily be used to evaluate the correlation between antibiotic use and antibiotic resistance in a single-year multicenter study [12]. In the current study, we demonstrated that this system could also be easily used to evaluate this correlation in a time series analysis for a single hospital and also in an inter-ward analysis using the source data prepared for this system. The spread and emergence

of AMR are multifaceted and are not only affected by antibiotic use [15-17]. However, monitoring antibiotic use and resistant bacteria constitutes an essential part of antimicrobial stewardship programs [18], and recognizing this correlation is considered a useful tool for developing antimicrobial stewardship policies [15]. Thus, we believe that our study could contribute to promoting the use of the J-SIPHE system in other hospitals and aid in the implementation of AMR measures such as antimicrobial stewardship programs.

Most studies investigating the correlation between antibiotic use and resistant bacteria have evaluated antibiotic use as AUD. Although it is difficult to calculate DOT in many institutions [19], we also evaluated antibiotic use as DOT in addition to AUD (Supplementary Table 1) because these indexes are easily obtained from the J-SIPHE system. AUD measurements are useful for benchmarking; however, it may not fully correlate with AMR due to intrinsic biases, such as in the case of low-dose administration in pediatric patients or individuals with renal dysfunction [20]. In contrast to AUD, DOT does not introduce these biases. Thus, the Infectious Diseases Society of America (IDSA) recommends DOT as an index of antibiotic use [18]. Upon evaluating both AUD and DOT, these parameters showed similar trends during the study period.

Notably, in terms of antibiotic use, carbapenem use showed a decreasing trend starting from 2018, after the highest in 2017 (Supplementary Table 1). In our hospital, monitoring and feedback for carbapenems has been conducted more frequency since 2018 [21]. This might

explain the decreasing trend of carbapenem use since 2018. In contrast to carbapenems, piperacillin/tazobactam use showed an increasing trend during the study period. This trend is consistent with previous studies [6,8,15]. As in previous studies [6], an increasing trend in the use of fourth-generation cephalosporins was also observed. The use of piperacillin/tazobactam and fourth-generation cephalosporins as alternatives to carbapenems might explain this increase. Aminoglycoside use showed a decreasing trend, which is consistent with previous studies [4,7,8].

The rates of *K. pneumoniae* resistance to ceftazidime or cefepime were significantly increased (Supplementary Table 2), which is consistent with previous studies [6,8]. The resistance rate of piperacillin/tazobactam in *E. coli* showed a numerically increasing trend, as in previous studies [8], although without statistical significance (Spearman's $\rho = 0.667$; $P = 0.05$). In previous studies, increasing trends in the rates of *P. aeruginosa* resistance to meropenem or imipenem/cilastatin were observed [5,6,22]. In our study, resistance to these carbapenems in *P. aeruginosa* showed increasing trends until 2016, followed by a decreasing trends.

Regarding the correlation between antibiotic use and bacterial resistance, some previous studies demonstrated that there was no correlation between piperacillin/tazobactam use and the rates of resistance to piperacillin/tazobactam in *E. coli*, *K. pneumoniae*, and *P. aeruginosa* [6,15]. In contrast to these studies, we found a positive correlation in *E. coli* and *K.*

pneumoniae in the inter-ward analysis and in *P. aeruginosa* in the time series and inter-ward analyses (Figures 1 and 2 and Supplementary Tables 3 and 4). These findings are consistent with previous reports that found a correlation between piperacillin/tazobactam use and the rates of resistance to piperacillin/tazobactam in *E. coli* [7], *K. pneumoniae*, and *P. aeruginosa* [8].

Few studies have investigated the effect of carbapenem use on the prevalence of carbapenem-resistant *E. cloacae*. In the current study, we investigated this effect and found a positive correlation between them in a time series analysis. Some reports demonstrated a positive correlation between carbapenem use and the rate of resistance to carbapenems in *P. aeruginosa* [22,23] but some did not [4-7]. In the current study, a significant positive correlation between them was observed, which supports the results of previous studies showing this correlation.

Previous studies have demonstrated a positive correlation between quinolone use and the rates of resistance to quinolones in *E. coli* [6,24] and *K. pneumoniae* [8,24], although these correlations were not found in other previous studies on *E. coli* [4,7] and *K. pneumoniae* [4,6,7]. In the current study, we found a positive correlation between quinolone use and quinolone resistance rates in *E. coli* (time series and inter-ward analyses) and *K. pneumoniae* (inter-ward analysis).

Most previous studies investigating the correlation between antibiotic use and antibiotic

resistance evaluated only time series correlations and did not evaluate inter-ward correlations. However, as each ward has different characteristics, antibiotic use in each ward also differs. Thus, it is important to investigate whether differences in antibiotic use affect the resistance rates of bacteria in each ward to promote the proper use of antibiotics in hospitals. Similar to the time series analysis, several correlations between antibiotic use and antibiotic resistance were observed in the inter-ward analysis (Figure 2 and Supplementary Table 4). Notably, wards with less antibiotic use often showed resistance rates of 0% in various bacteria. These results highlight the importance of recognizing the correlation between antibiotic use and bacterial resistance in each ward and promoting the implementation of AMR measures, such as antimicrobial stewardship programs, in each ward.

To investigate which wards are more involved in antibiotic resistance, each ward was divided and mapped to high and low based on the median values of antibiotic use and resistance rates in the combinations that were significantly correlated (Figure 3 and Table 1). Here, ward numbers 1, 14, 16, and 21 had higher than median values for antibiotic use and resistance rates in many combinations with marked correlations and were considered to have been more involved in antibiotic resistance. Notably, these wards did not have lower antibiotic use and resistance rates in any combination. Ward number 1 included hematology wards, which were considered to have been involved in more uses of broad-spectrum antibiotics for febrile neutropenia than other wards. It was assumed that this led to increases

in antibiotic resistance here. Ward numbers 14 and 16 included the gastroenterological surgery wards and ward number 21 included the ICU. It was possible that more antibiotic agents were used to treat postoperative infections and/or infections in critically ill patients in these wards, which might have led to increases in antibiotic resistance here. In contrast, ward numbers 5, 7, 9, and 20 had lower than or equal to median antibiotic use and resistance rates in many combinations with marked correlations; these wards included the psychiatry and neurology ward, radiation oncology ward, ophthalmology ward, and NICU/GCU, respectively. In these wards, a lower use of antibiotics may have led to lower resistant rates. Notably, these wards rarely had higher antibiotic use and resistance rates in many combinations. These results suggest that the implications with resistant bacteria vary greatly among wards.

In this study, significant positive correlations between the use of piperacillin/tazobactam or carbapenems and the rates of resistance to related antibiotics in *P. aeruginosa* and the use of quinolones and levofloxacin resistance in *E. coli* were observed in both analyses, whereas the results of other correlations were different in each analysis (Figures 1 and 2 and Supplementary Tables 3 and 4). The reason why the results differed in each analysis in this study is unknown. However, considering that more various correlations between antibiotic use and antibiotic resistance were observed in the inter-ward analysis than in the time series analysis, longer-term usage habits in each ward might have more influence than yearly

changes at an entire hospital.

Despite the importance of this study, it has several limitations. First, this retrospective study did not consider potential confounders such as patient parameters, infection control strategies, antimicrobial stewardship interventions, clonal spread of strains, and the occurrence of outbreaks due to resistant organisms. AMR is considered to be related not only to antibiotic use but also to these multiple factors [15-17]. Second, this study investigated the correlation between antibiotic use and antibiotic resistance in each year in a time series analysis and did not take into account the time lag in the changes in bacterial resistance rates. Third, AUD and DOT measurements are useful for benchmarking, but cannot reflect individual exposure to antibiotics. Due to the nature of the surveillance data, the correlation between antibiotic use and antibiotic resistance could not be investigated at the individual level. Finally, this study was conducted at a single university hospital. Therefore, our results may not be generalizable to other hospitals. These limitations should be considered when interpreting the results of this study.

In conclusion, this study is the first to investigate the correlation between annual antibiotic use and antibiotic resistance at a single hospital in a time series analysis based on the J-SIPHE system data [9]. Additionally, we evaluated this correlation in different wards by combining the J-SIPHE system and the source data prepared for this system. Although several studies have investigated this correlation, the results are controversial [4-8]. In addition, few studies

have compared this correlation among wards. We showed several correlations between antibiotic use and resistant bacteria in the time series and inter-ward analyses. Further studies using the J-SIPHE system are needed to more accurately elucidate the correlation between antibiotic use and antibiotic resistance.

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Competing interests

None declared.

Ethics approval statement

The requirement for ethics committee approval and informed consent was waived because this study analyzed surveillance data that did not include individual patient information.

Contributorship Statement

KK and NI conceived and designed the study. KK, SI, KT, TF, KH, RO, TW corrected data. KK performed statistical analyses. KK prepared the initial draft of the manuscript, and NI, SN, YN, MS, YT revised it. All authors have read and approved the final manuscript.

References

[1] Cao H, Phe K, Laine GA, et al. An institutional review of antimicrobial stewardship interventions. J Glob Antimicrob Resist 2016;6:75–77. https://doi.org/10.1016/j.jgar.2016.03.006.

[2] Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis 2006;42;Supplement 2:S82–89. https://doi.org/10.1086/499406.

[3] Roberts RR, Hota B, Ahmad I, et al. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin Infect Dis 2009;49:1175–1184. https://doi.org/10.1086/605630.

[4] Guo W, He Q, Wang Z, et al. Influence of antimicrobial consumption on gram-negative bacteria in inpatients receiving antimicrobial resistance therapy from 2008–2013 at a tertiary hospital in Shanghai, China. Am J Infect Control 2015;43:358–364. https://doi.org/10.1016/j.ajic.2014.12.010.

[5] Hao Y, Chen S, Chang H, et al. Temporal association between carbapenems usage and antimicrobial resistance in gram-negative bacteria at a tertiary hospital in Nanjing, China. Diagn Microbiol Infect Dis 2020;98:115083. https://doi.org/10.1016/j.diagmicrobio.2020.115083.

[6] Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial

resistance in Gram-negative bacteria causing nosocomial infections from 1991–2003 at a university hospital in Taiwan. Int J Antimicrob Agents 2005;26:463–472. https://doi.org/10.1016/j.ijantimicag.2005.08.016.

[7] Lai CC, Wang CY, Chu CC, et al. Correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. J Antimicrob Chemother 2011;66:1374–1382. https://doi.org/10.1093/jac/dkr103.

[8] Lee HS, Loh YX, Lee JJ, et al. Antimicrobial consumption and resistance in five Gram-negative bacterial species in a hospital from 2003 to 2011. J Microbiol Immunol Infect 2015;48:647–654. https://doi.org/10.1016/j.jmii.2014.04.009.

[9] National Center for Global Health and Medicine, AMR Clinical Reference Center. Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) annual report 2019. https://j-siphe.ncgm.go.jp/files/JSIPHE_AnnualReport_2019en.pdf (Accessed 1 March 2023).

[10] World Health Organization (WHO). Global action plan on antimicrobial resistance. http://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf (Accessed 1 March 2023).

[11] The Government of Japan. National action plan on antimicrobial resistance (AMR); 2016–2020.

https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf (Accessed 1 March 2023).

[12] Kagami K, Ishiguro N, Iwasaki S, et al. Correlation between antibiotic use and antibiotic resistance: a multicenter study using the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system in Hokkaido, Japan. Am J Infect Control 2023;51:163–171. https://doi.org/10.1016/j.ajic.2022.05.025.

[13] WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignments. 2020. https://www.whocc.no/atc_ddd_index/ (Accessed 1 March 2023).

[14] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twenty-first informational supplement M100-S21. Wayne, PA: CLSI; 2011.

[15] Mascarello M, Simonetti O, Knezevich A, et al. Correlation between antibiotic consumption and resistance of bloodstream bacteria in a University Hospital in North Eastern Italy, 2008–2014. Infection 2017;45:459–467. https://doi.org/10.1007/s15010-017-0998-z.

[16] Sedláková MH, Urbánek K, Vojtová V, et al. Antibiotic consumption and its influence on the resistance in *Enterobacteriaceae*. BMC Res Notes 2014;7:454. https://doi.org/10.1186/1756-0500-7-454.

[17] Meyer E, Schwab F, Schroeren-Boersch B, et al. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care 2010;14:R113. https://doi.org/10.1186/cc9062.

[18] Barlam TF, Cosgrove SE, Abbo LM, 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:e51–77. https://doi.org/10.1093/cid/ciw118.

[19] Ibrahim OM, Polk RE. Antimicrobial use metrics and benchmarking to improve stewardship outcomes: methodology, opportunities, and challenges. Infect Dis Clin North Am 2014;28:195–214. https://doi.org/10.1016/j.idc.2014.01.006

[20] Morris AM. Antimicrobial stewardship programs: appropriate measures and metrics to study their impact. Curr Treat Options Infect Dis 2014;6:101–12. https://doi.org/10.1007/s40506-014-0015-3.

[21] Kagami K, Ishiguro N, Yamada T, et al. Clinical outcomes of intervention for carbapenems and anti-methicillin-resistant Staphylococcus aureus antibiotics by an antimicrobial stewardship team. Am J Infect Control. 2021;49:1493–1498. https://doi.org/10.1016/j.ajic.2021.08.011.

[22] Mladenovic-Antic S, Kocic B, Velickovic-Radovanovic R, et al. Correlation between

antimicrobial consumption and antimicrobial resistance of Pseudomonas aeruginosa in a hospital setting: a 10-year study. J Clin Pharm Ther 2016;41:532–537. https://doi.org/10.1111/jcpt.12432.

[23] Yang P, Chen Y, Jiang S, et al. Association between antibiotic consumption and the rate of carbapenem-resistant Gram-negative bacteria from China based on 153 tertiary hospitals data in 2014. Antimicrob Resist Infect Control 2018;7:137. https://doi.org/10.1186/s13756-018-0430-1.

[24] Yang P, Chen Y, Jiang S, et al. Association between the rate of fluoroquinolones-resistant gram-negative bacteria and antibiotic consumption from China based on 145 tertiary hospitals data in 2014. BMC Infect Dis 2020;20:269. https://doi.org/10.1186/s12879-020-04981-0.

Figure legends

Figure 1

Correlation between the annual amount of antibiotics used and rates of bacterial resistance in time series analysis; (a), (b) piperacillin/tazobactam and piperacillin/tazobactam-resistant *Pseudomonas aeruginosa*; (c), (d) carbapenems and meropenem-resistant *Enterobacter cloacae*; (e), (f) carbapenems and meropenem-resistant *P. aeruginosa*; (g), (h) quinolones and levofloxacin-resistant *Escherichia coli*.

Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses; DOT, days of therapy.

ρ indicates Spearman's correlation coefficient.

Figure 2. Correlation between the amount of antibiotics used and bacterial resistance among wards. Mean values in each ward from May 2018 to December 2021 were analyzed.

Dashed lines represent the median of each plot.

(a)–(c) Piperacillin/tazobactam; (d), (e) third-generation cephalosporin; (f) fourth-generation cephalosporin; (g), (h) carbapenems; (i), (j) quinolones.

Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses; DOT, days of therapy.

ρ indicates Spearman's correlation coefficient.

Figure 3. Mapping of wards with correlations between the amount of antibiotics used and bacterial resistance.

Each ward was divided and mapped to high and low based on the median values of antibiotic use and resistance rate. If the value of each ward was equal to the median (for example, both values were zero), it was mapped to low.

Blue, medical wards (ward nos. 1–8); red, surgical wards (ward nos. 9–15); green, medical and surgical wards (ward nos. 16–19); purple, intensive care wards (ward nos. 20–22).

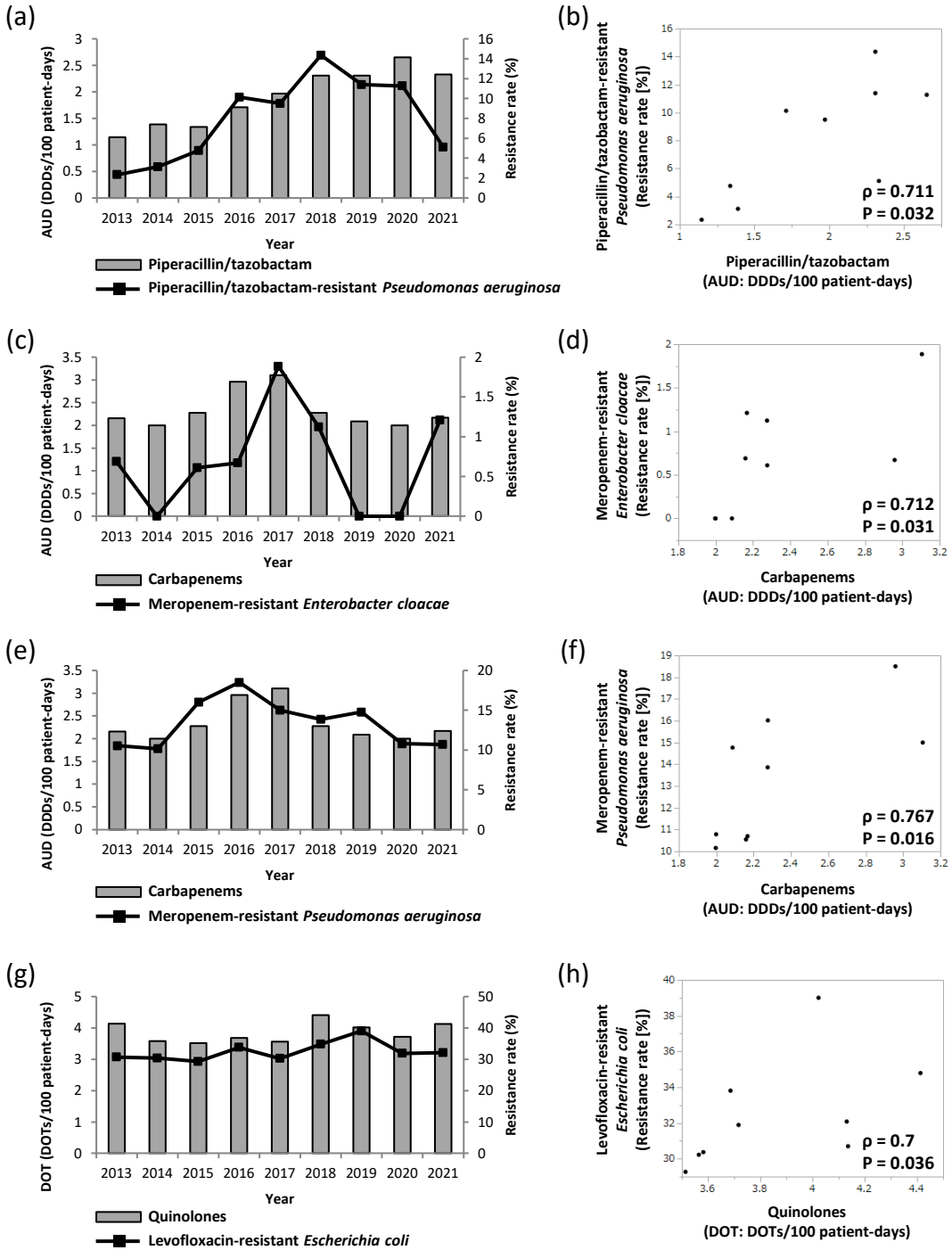
(a)–(c) Piperacillin/tazobactam; (d), (e) third-generation cephalosporin; (f) fourth-generation cephalosporin; (g), (h) carbapenems; (i), (j) quinolones.

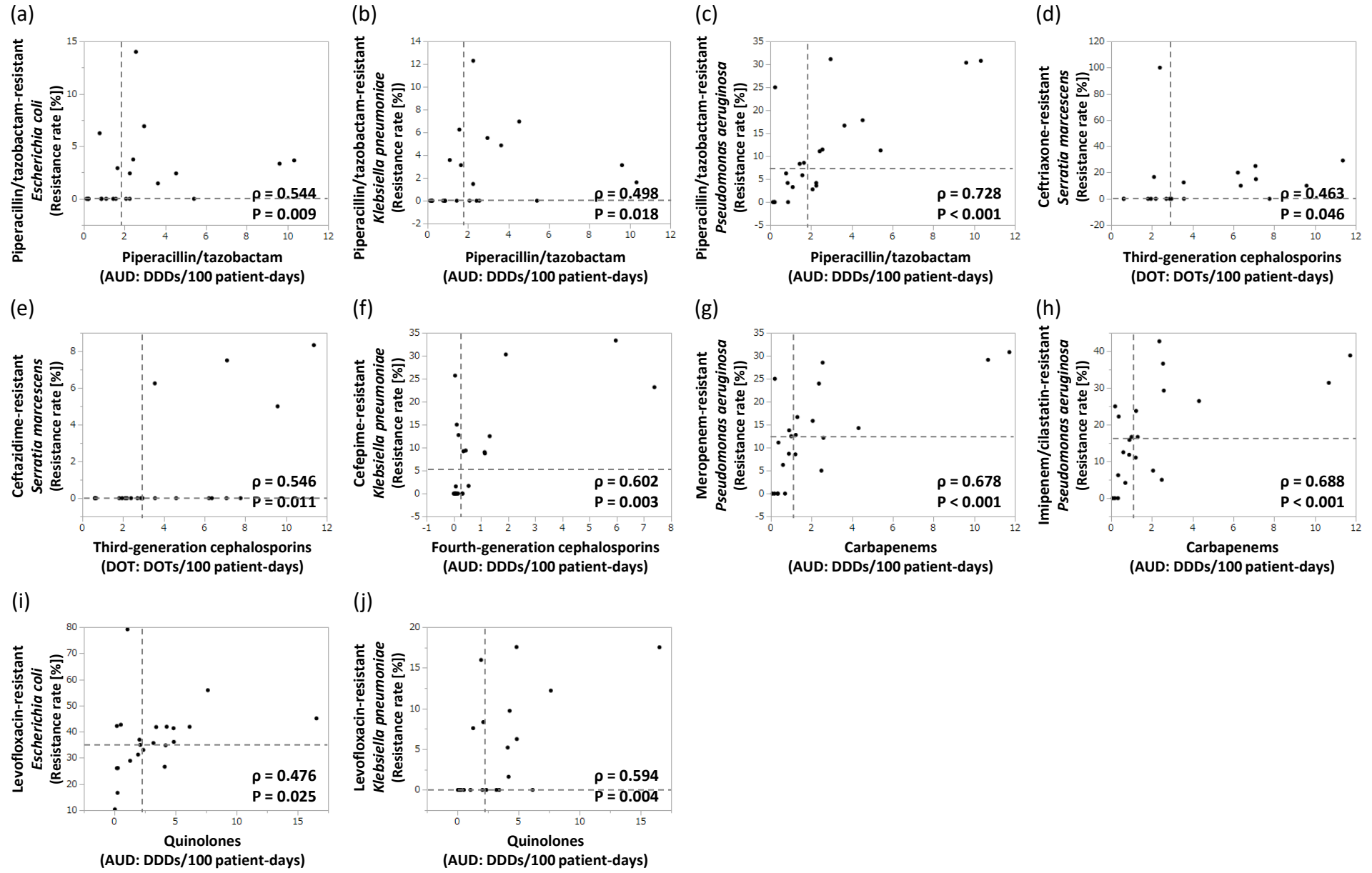
Abbreviation: DOT, days of therapy.

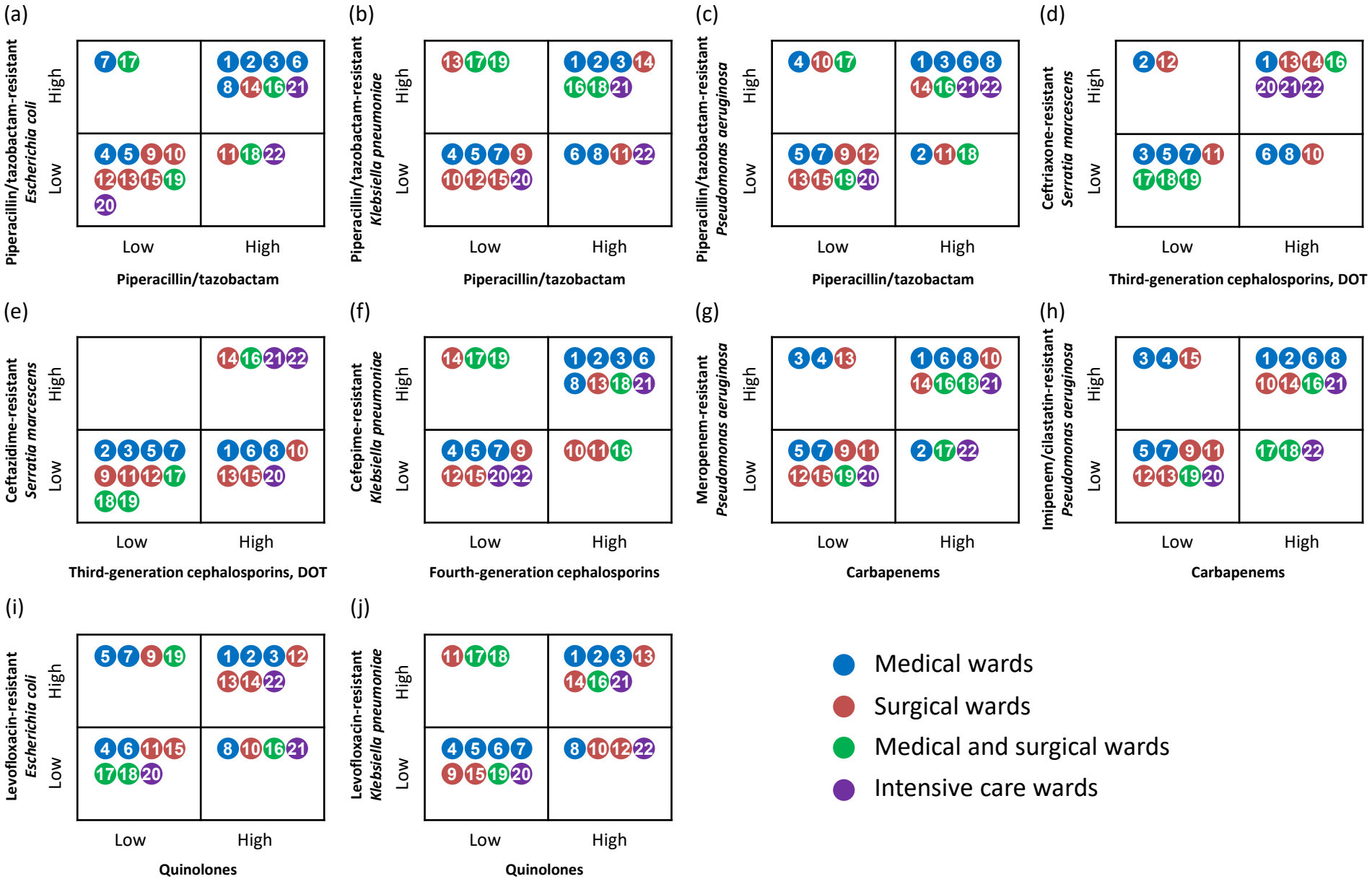
Table 1 Total number mapped to each high and/or low square represented in Figure 3

Ward classification	Ward no.	Total number mapped to high and/or low (Antibiotic use/resistant rate)			
		High/High	High/Low	Low/High	Low/Low
Medical wards	1	9	1	0	0
	2	6	2	1	1
	3	6	0	2	2
	4	0	0	3	5
	5	0	0	1	9
	6	5	3	0	2
	7	0	0	2	8
	8	5	5	0	0
Surgical wards	9	0	0	1	8
	10	2	5	1	2
	11	0	4	1	5
	12	1	1	1	7
	13	4	1	2	3
	14	9	0	1	0
	15	0	1	1	7
Medical and surgical wards	16	8	2	0	0
	17	0	2	5	3
	18	3	3	1	3
	19	0	0	3	7
Intensive care wards*	20	1	1	0	8
	21	9	1	0	0
	22	4	5	0	1

*Intensive care wards (ward nos. 20–22) included neonatal intensive care unit/growing care unit (NICU/GCU), intensive care unit (ICU), and emergency ward, respectively.


(a)
AUD (DDDs/100 patient-days)
Resistance rate (%)
Year
Piperacillin/tazobactam
Piperacillin/tazobactam-resistant Pseudomonas aeruginosa
(b)
Piperacillin/tazobactam-resistant Pseudomonas aeruginosa (Resistance rate [%])
ρ = 0.711
P = 0.032
Piperacillin/tazobactam (AUD: DDDs/100 patient-days)
(c)
AUD (DDDs/100 patient-days)
Resistance rate (%)
Year
Carbapenems
Meropenem-resistant Enterobacter cloacae
(d)
Meropenem-resistant Enterobacter cloacae (Resistance rate [%])
ρ = 0.712
P = 0.031
Carbapenems (AUD: DDDs/100 patient-days)
(e)
AUD (DDDs/100 patient-days)
Resistance rate (%)
Year
Carbapenems
Meropenem-resistant Pseudomonas aeruginosa
(f)
Meropenem-resistant Pseudomonas aeruginosa (Resistance rate [%])
ρ = 0.767
P = 0.016
Carbapenems (AUD: DDDs/100 patient-days)
(g)
DOT (DOTs/100 patient-days)
Resistance rate (%)
Year
Quinolones
Levofloxacin-resistant Escherichia coli
(h)
Levofloxacin-resistant Escherichia coli (Resistance rate [%])
ρ = 0.7
P = 0.036
Quinolones (DOT: DOTs/100 patient-days)


(a)
Piperacillin/tazobactam-resistant *Escherichia coli* (Resistance rate [%])
ρ = 0.544
P = 0.009
Piperacillin/tazobactam (AUD: DDDs/100 patient-days)
(b)
Piperacillin/tazobactam-resistant *Klebsiella pneumoniae* (Resistance rate [%])
ρ = 0.498
P = 0.018
Piperacillin/tazobactam (AUD: DDDs/100 patient-days)
(c)
Piperacillin/tazobactam-resistant *Pseudomonas aeruginosa* (Resistance rate [%])
ρ = 0.728
P < 0.001
Piperacillin/tazobactam (AUD: DDDs/100 patient-days)
(d)
Ceftriaxone-resistant *Serratia marcescens* (Resistance rate [%])
ρ = 0.463
P = 0.046
Third-generation cephalosporins (DOT: DOTs/100 patient-days)
(e)
Ceftazidime-resistant *Serratia marcescens* (Resistance rate [%])
ρ = 0.546
P = 0.011
Third-generation cephalosporins (DOT: DOTs/100 patient-days)
(f)
Cefepime-resistant *Klebsiella pneumoniae* (Resistance rate [%])
ρ = 0.602
P = 0.003
Fourth-generation cephalosporins (AUD: DDDs/100 patient-days)
(g)
Meropenem-resistant *Pseudomonas aeruginosa* (Resistance rate [%])
ρ = 0.678
P < 0.001
Carbapenems (AUD: DDDs/100 patient-days)
(h)
Imipenem/cilastatin-resistant *Pseudomonas aeruginosa* (Resistance rate [%])
ρ = 0.688
P < 0.001
Carbapenems (AUD: DDDs/100 patient-days)
(i)
Levofloxacin-resistant *Escherichia coli* (Resistance rate [%])
ρ = 0.476
P = 0.025
Quinolones (AUD: DDDs/100 patient-days)
(j)
Levofloxacin-resistant *Klebsiella pneumoniae* (Resistance rate [%])
ρ = 0.594
P = 0.004
Quinolones (AUD: DDDs/100 patient-days)


(a)
Piperacillin/tazobactam-resistant Escherichia coli
High
Low
7 17
1 2 3 6 8 14 16 21
4 5 9 10 12 13 15 19 20
11 18 22
Low
High
Piperacillin/tazobactam
(b)
Piperacillin/tazobactam-resistant Klebsiella pneumoniae
13 17 19
1 2 3 14 16 18 21
4 5 7 9 10 12 15 20
6 8 11 22
Piperacillin/tazobactam
(c)
Piperacillin/tazobactam-resistant Pseudomonas aeruginosa
4 10 17
1 3 6 8 14 16 21 22
5 7 9 12 13 15 19 20
2 11 18
Piperacillin/tazobactam
(d)
Ceftriaxone-resistant Serratia marcescens
2 12
1 13 14 16 20 21 22
3 5 7 11 17 18 19
6 8 10
Third-generation cephalosporins, DOT
(e)
Ceftazidime-resistant Serratia marcescens
14 16 21 22
2 3 5 7 9 11 12 17 18 19
1 6 8 10 13 15 20
Third-generation cephalosporins, DOT
(f)
Cefepime-resistant Klebsiella pneumoniae
14 17 19
1 2 3 6 8 13 18 21
4 5 7 9 12 15 20 22
10 11 16
Fourth-generation cephalosporins
(g)
Meropenem-resistant Pseudomonas aeruginosa
3 4 13
1 6 8 10 14 16 18 21
5 7 9 11 12 15 19 20
2 17 22
Carbapenems
(h)
Imipenem/cilastatin-resistant Pseudomonas aeruginosa
3 4 15
1 2 6 8 10 14 16 21
5 7 9 11 12 13 19 20
17 18 22
Carbapenems
(i)
Levofloxacin-resistant Escherichia coli
5 7 9 19
1 2 3 12 13 14 22
4 6 11 15 17 18 20
8 10 16 21
Quinolones
(j)
Levofloxacin-resistant Klebsiella pneumoniae
11 17 18
1 2 3 13 14 16 21
4 5 6 7 9 15 19 20
8 10 12 22
Quinolones
Medical wards
Surgical wards
Medical and surgical wards
Intensive care wards