PHARMACY PRACTICE AND DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

THE REPORT ON ANTIBIOTIC UTILISATION IN MALAYSIAN HOSPITALS

2008-2017

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Table of Contents

1. Acknowledgements……ii

2. Abbreviations……..iii

3. Executive Summary..……iv

4. Introduction……..……....1

5. Methods…..……..2

6. Results……..……..3

7. Discussions……...15

8. Conclusions……...17

9. References……..……..18

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Abbreviations

AMS	Antimicrobial stewardship
DDD	Defined Daily Dose
ICU	Intensive Care Unit
IQR	Interquartile range
MDR	Multidrug-resistant
MOD	Ministry of Defence
MOH	Ministry of Health
MOHE	Ministry of Higher Education
NSAU	National Surveillance on Antibiotic Utilisation

Executive Summary

Periodic surveillance of antibiotic consumption in healthcare facilities is one of the key approaches in controlling the emergence of resistant organisms, particularly the highly virulent nosocomial pathogens. National surveillance of antibiotic utilisation across Malaysian hospitals has been conducted more than a decade ago. The aim of this surveillance is to evaluate the magnitude and trend of antibiotic utilisation across hospitals of different settings in Malaysia and the potential relationships contributed to particular antibiotic utilisation. At hospital level, these data have been assisting local healthcare practitioners in their clinical practice, especially in the implementation of antimicrobial stewardship.

Annual data of antibiotic utilisation from 2008 to 2017 were retrieved from the National Surveillance on Antibiotic Utilisation coordinated by Pharmacy Practice and Development Division, Ministry of Health, Malaysia. Antibiotics were grouped according to their main classes. Antibiotic use was expressed in defined daily doses per 1000 patient days (DDD/1000 patient days). The relationship between antibiotic use and number of hospital beds, as well as the relationships across different classes of antibiotics were evaluated to determine possible factors contributed to antibiotic utilisation for the year 2016 to 2017.

University hospitals showed the highest total antibiotic utilisation overall and in ICU wards with median (interquartile range, IQR) of total DDD/1000 patient days of 324.14 (267.96-327.80) and 938.72 (727.13-1067.64), respectively, between 2008 and 2017. Cephalosporin was the antibiotic class with the highest utilisation in “All Wards” and ICUs over the 10-year period with median percentage of utilisation of 68.39 (IQR: 63.79-68.72) and 43.21 (IQR: 43.18-45.30), respectively, from total antibiotic utilisation. Significant low to moderate positive correlations are observed between the utilisation of carbapenems, fluoroquinolones, glycopeptides, polypeptides and piperacillin-tazobactams and the number of hospital beds. Additionally, moderate to strong correlations are observed between the utilisation of glycopeptides and piperacillin-tazobactams and the utilisation of carbapenems, r=0.65 and r=0.58, respectively ($p<0.0001$), and significantly positive moderate relationships are

observed between the usage of cephalosporins and carbapenems ($r=0.51$, $p<0.0001$), and between the usage of polypeptides and carbapenems ($r=0.51$, $p<0.0001$).

Utilisation of antibiotics had increased from the year 2008 to 2017. Significant relationships existed between the utilisation of broad-spectrum antibiotics such as carbapenems, glycopeptides and penicillin-beta lactamase inhibitors. Further study is needed to understand the implications of these relationships. Rational use of these agents must be evaluated to prevent unnecessary usage that could lead to the rise of resistant pathogens.

Introduction

Since the discovery of penicillin in 1928, antibiotics have saved many lives. Ironically, since then the emergence of antibiotic resistance has posed a serious global challenge, particularly limits the development of new class of antibiotic. Resistance to antibiotic occurs when bacteria adapt and continue growing in the presence of antibiotics. This can be provoked by the frequency of antibiotic use, misuse and/or overuse and/or inadequate administration of antibiotic when treatment is required. Up to 50% of antimicrobial agents used in acute care hospitals and more than 50% in outpatient settings are considered instances of misuse or overuse [1, 2].

Monitoring antibiotic use is one of the main components of antimicrobial stewardship programmes [3, 4]. Thorough understanding and monitoring of the antibiotic consumption enable to provide targeted information that could help in improving the quality of antibiotic use. In 2011, the European Surveillance of Antimicrobial Consumption (ESAC) project funded by the European Centre for Disease Prevention and Control (ECDC) published a data on outpatient quinolone use from 33 European countries, where they are able to describe in detail the trend, specific agent and location of quinolone usage [5]. Based on the findings, strategy that suits local practice could be identified to ensure appropriate use of quinolones in order to prevent quinolone-resistance. More antibiotic surveillance data have been published recently in other regions that could similarly help to identify areas particularly in prescribing practice that can be modified to control antibiotic use in this era of emergence of resistant pathogens [6-14].

This report analyses a 10-year trend of national antibiotic utilisation, from 2008 to 2017, in all wards, as well as in Intensive Care Unit (ICU) settings of selected Malaysian hospitals, with the aim to assess utilisation patterns and describe potential factors which had contributed to antibiotic utilisation. These might be the factors which could be modified to ensure appropriate antibiotic prescribing practice in Malaysia.

Methods

Data source

National antibiotic usage pattern data from 2008 to 2017 were obtained from the National Surveillance on Antibiotic Utilisation (NSAU) coordinated by the Pharmacy Practice and Development Division, Ministry of Health (MOH), Malaysia.

NSAU collected data annually for the period of 12 months; January to December. Data were contributed by selected hospitals across Malaysia, which included MOH, university, military and private hospitals. Participation from private hospitals only involved those with more than 100 beds.

Standard forms were used for data collection where a user manual was provided as guidance for contributors in completing and submitting the data collection forms. Data collected include:

a) total amount of selected injectable antibiotics (in grams) dispensed from the in-patient pharmacy to adult patients in wards; and
b) the number of days adult patients were admitted in the hospital for the reporting year.

NSAU only monitors systemic antibiotics administered via the parenteral route. Paediatric data are excluded. The number of antibiotics being monitored varies from year to year. The antibiotics currently included in the surveillance are cephalosporins (cefuroxime, ceftriaxone, cefotaxime, ceftazidime, cefoperazone, cefepime and cefoperazone/sulbactam), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), carbapenems (imipenem/cilastatin, meropenem, ertapenem, doripenem), vancomycin, polypeptides (polymyxin B, polymyxin E) and piperacillin/tazobactam.

Data were verified manually before analysis was performed.

Data analysis

Antibiotic usage was converted into defined daily dose (DDD) according to the Anatomical Therapeutic Chemical (ATC) classification system developed by the World

Health Organization (WHO) Collaboration Centre for Drug Statistics Methodology. For combination antibiotics, the quantity of active substances was converted into DDD [6]. DDD represents the average adult daily maintenance dose of a specific drug for its primary indication. The quantity of each antibiotic dispensed by the pharmacy to patients in wards during yearly periods was transformed into number of DDD and divided by the number of patient-days in that particular year. This value was then multiplied by 1,000 so that the final figure represented the level of utilisation of an antibiotic per 1,000 patient-days.

Data are divided into two main categories: “All Wards” and ICU usage data. Previously, “All Wards” consisted of all types of wards in the hospitals including ICU. Since 2016, ICU data have been excluded from “All Wards” data except for certain hospitals where separation of ICU data is not feasible.

Data were analysed using GraphPad Prism® version 8.0.1 and presented as median (interquartile range, IQR) and percentage where appropriate. The relationship between antibiotic use and number of hospital beds, as well as the relationships across different classes of antibiotics were evaluated for the year 2016 to 2017. Correlations were tested using Spearman correlation and p value of <0.05 was considered as statistically significant.

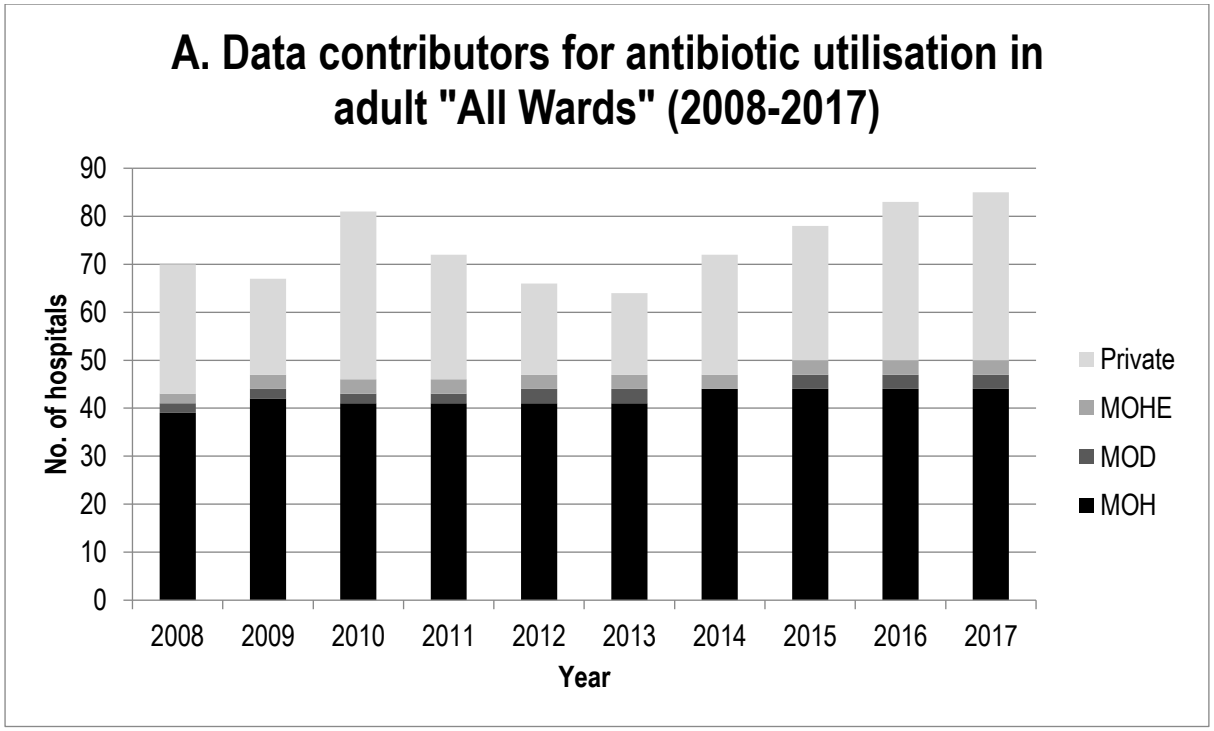
Results

In 2017, the public hospitals (44 hospitals) under the MOH Malaysia were the biggest contributors to the surveillance data, followed by the private hospitals (more than 30 hospitals). Overall, the number of hospitals contributing antibiotic utilisation data for “All Wards” had increased in the past 10 years, particularly the private hospitals, n=27 (2008) versus n=35 (2017). For ICU, data were mainly contributed by the public hospitals since 2009 and starting from the year 2012, other hospitals (university, military and private hospitals) had added to the data **(Figure 1)**.

University hospitals showed the highest total antibiotic consumption for “All Wards” and ICU wards with median (IQR) of total defined daily dose per 1000 patient days (DDD/1000 patient days) of 324.14 (267.96-327.80) and 938.72 (727.13-1067.64), respectively, between 2008 and 2017 **(Figure 2)**. Cephalosporin was the class of antibiotic with the highest utilisation for “All Wards” over the 10-year period with median percentage of utilisation of 68.39 (IQR: 63.79-68.72) from total antibiotic utilisation **(Figure 3)**. Ceftriaxone was the most utilised cephalosporin during that period [median (IQR) = 274.45 (256.50)]. Cephalosporins were also the most utilised antibiotic in ICU settings with median percentage of utilisation of 43.21 (IQR: 43.18-45.30) from total antibiotic utilisation **(Figure 3)**.

Significant low to moderate positive correlations between quantity of antibiotics used and number of hospital beds were revealed with carbapenem, fluoroquinolone, glycopeptide, polypeptide and piperacillin-tazobactam **(Table 1)**.

Various positive relationships were observed when utilisation of different classes of antibiotics was tested, with Spearman correlation (r) ranged from 0.10 to 0.70 **(Figure 4-Figure 9)**. Moderate to strong correlations were observed between the utilisation of glycopeptides and piperacillin-tazobactam with carbapenems, r=0.65 and r=0.58, respectively ($p<0.0001$). Significantly positive moderate relationships were observed between the usage of cephalosporins and carbapenems ($r=0.51$, $p<0.0001$) and poplypeptides with carbapenems ($r=0.51$, $p<0.0001$).



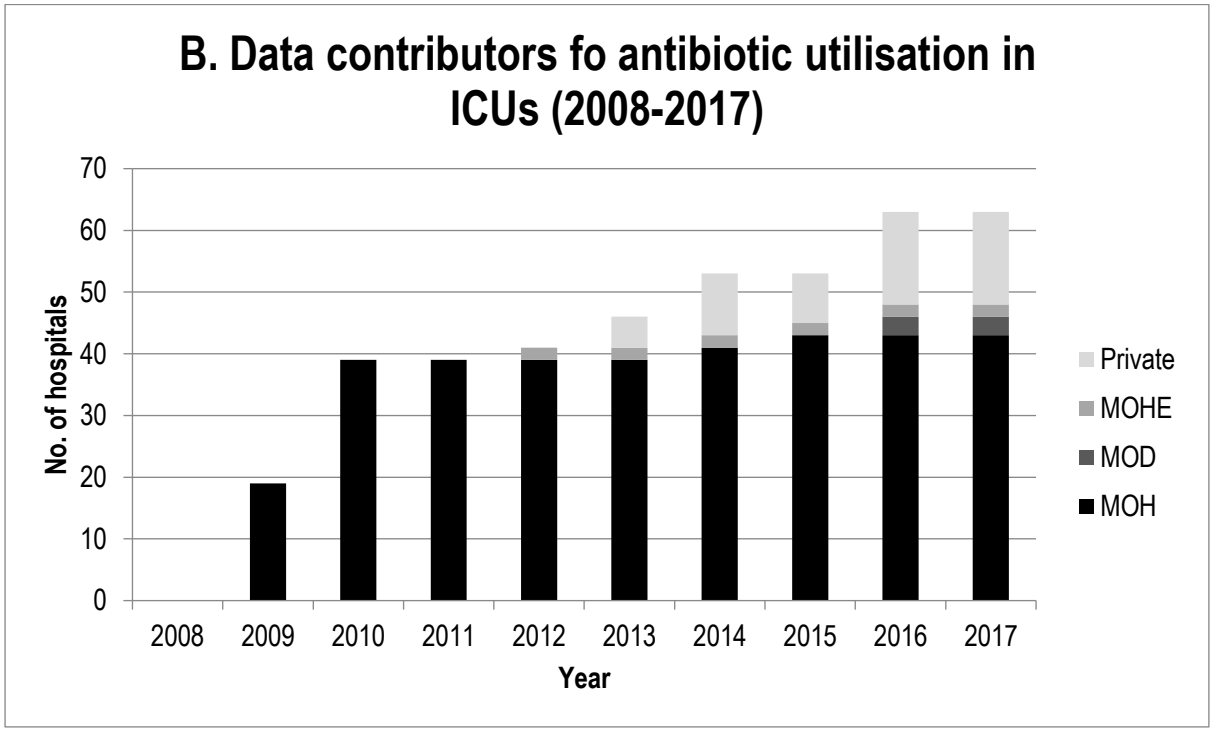


Figure 1: Number of hospitals participated in the National Surveillance on Antibiotic Utilisation (NSAU) from 2008-2017.

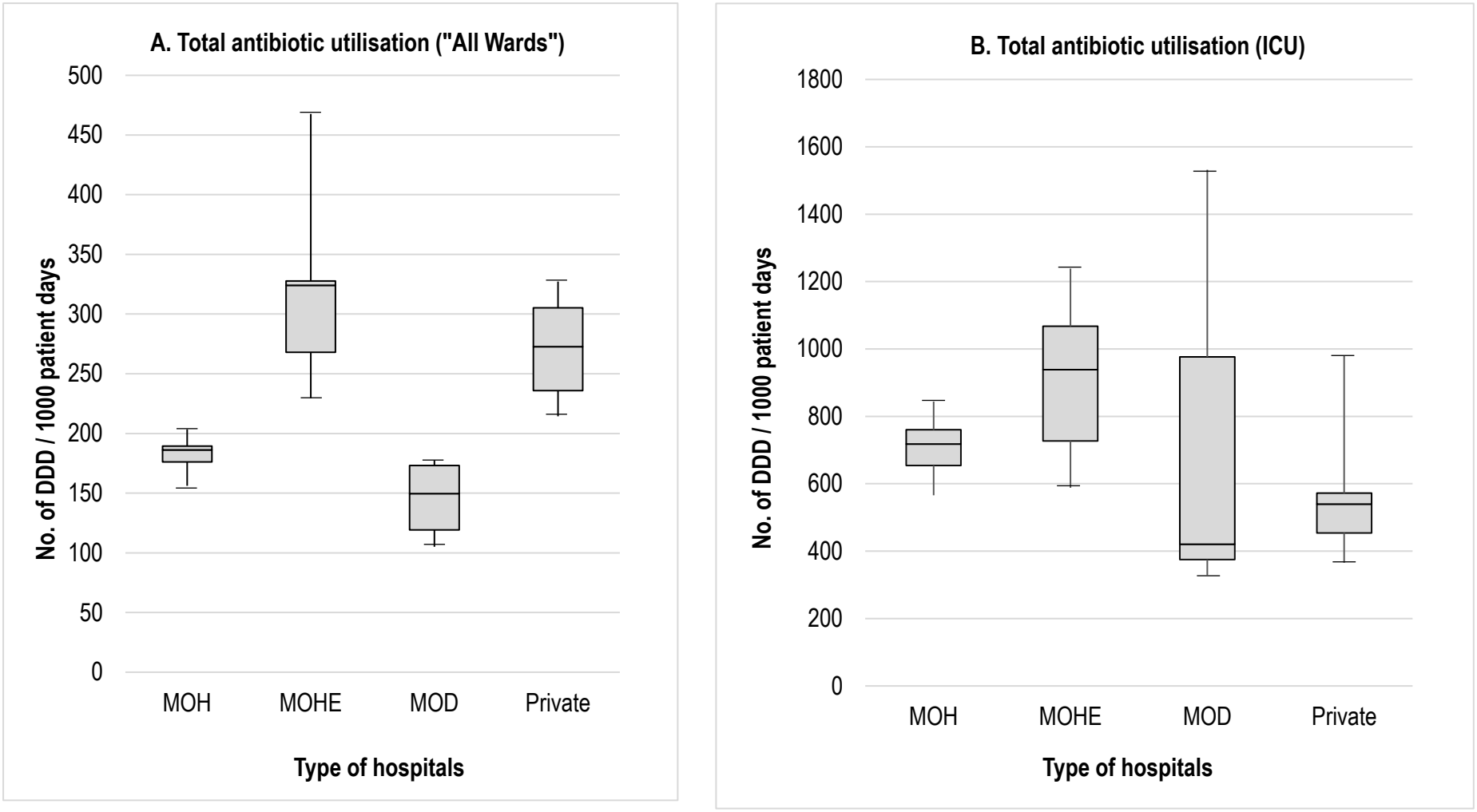
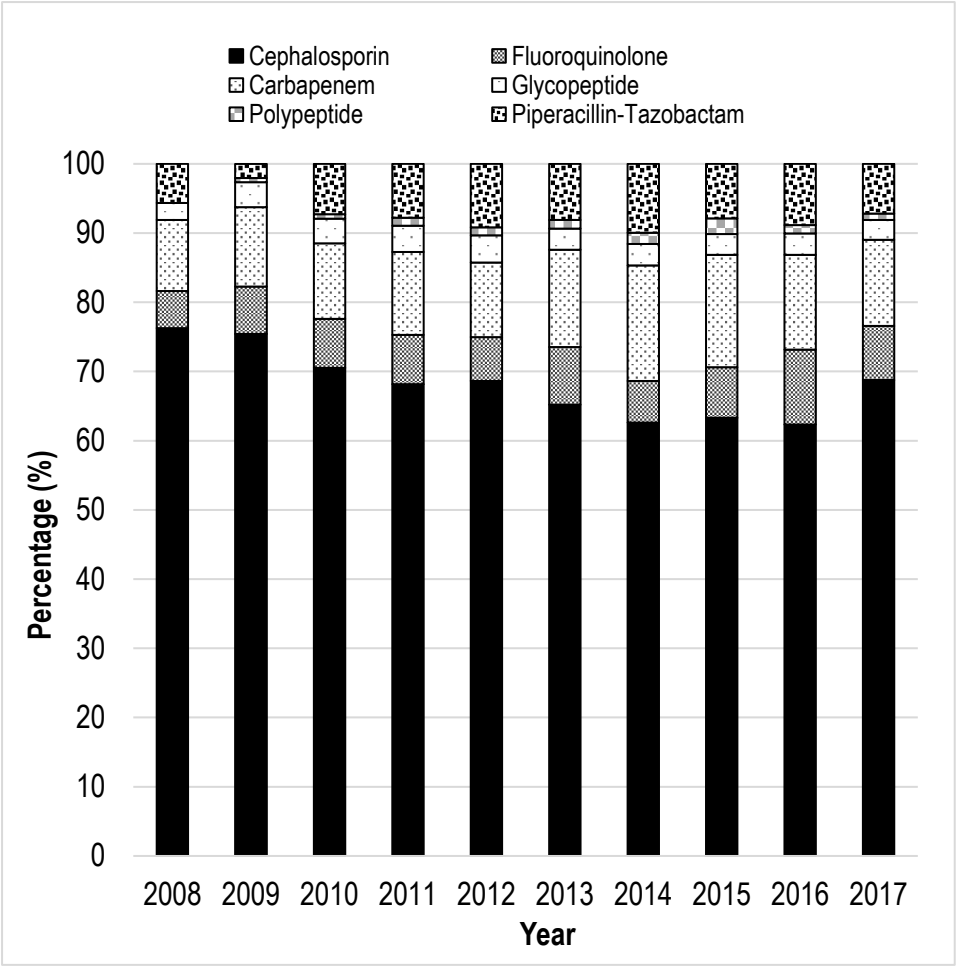
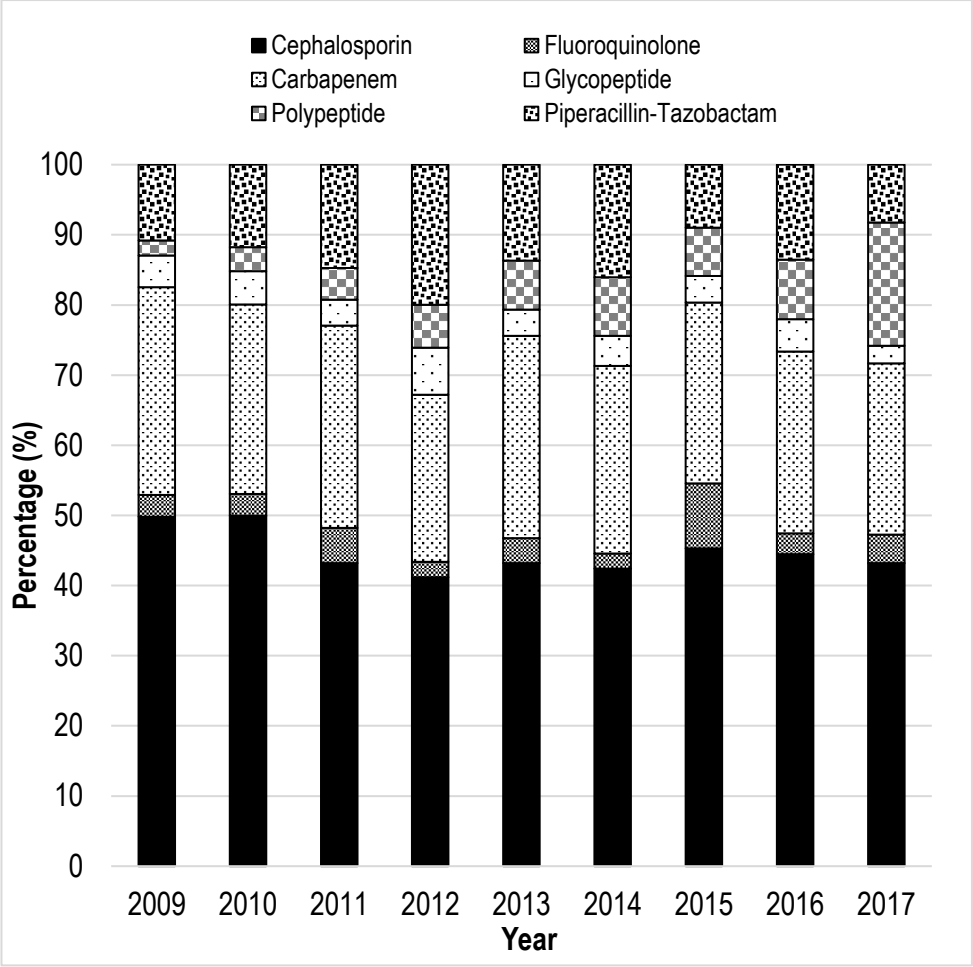


Figure 2: Total antibiotic utilisation for "All Wards" (A) and Intensive Care Unit (ICU) (B) settings across Malaysian hospitals, from 2008 to 2017.



a. Antibiotic utilisation in “All Wards”



b. Antibiotic utilisation in ICUs

Figure 3: Percentage of antibiotic utilisation according to antibiotic classes; a. “All Wards” and b. ICUs; from 2008 to 2017.

Table 1: Relationships between number of hospital beds and utilisation of different classes of antibiotics

Antibiotic (s)	n	Spearman correlation (ρ)	P value
Carbapenem	88	0.375	0.0003
Cephalosporin	88	0.000	0.9992
Fluoroquinolone	88	0.365	0.0005
Glycopeptide	88	0.408	<0.0001
Polypeptide	88	0.554	<0.0001
Piperacillin-tazobactam	88	0.351	0.0008

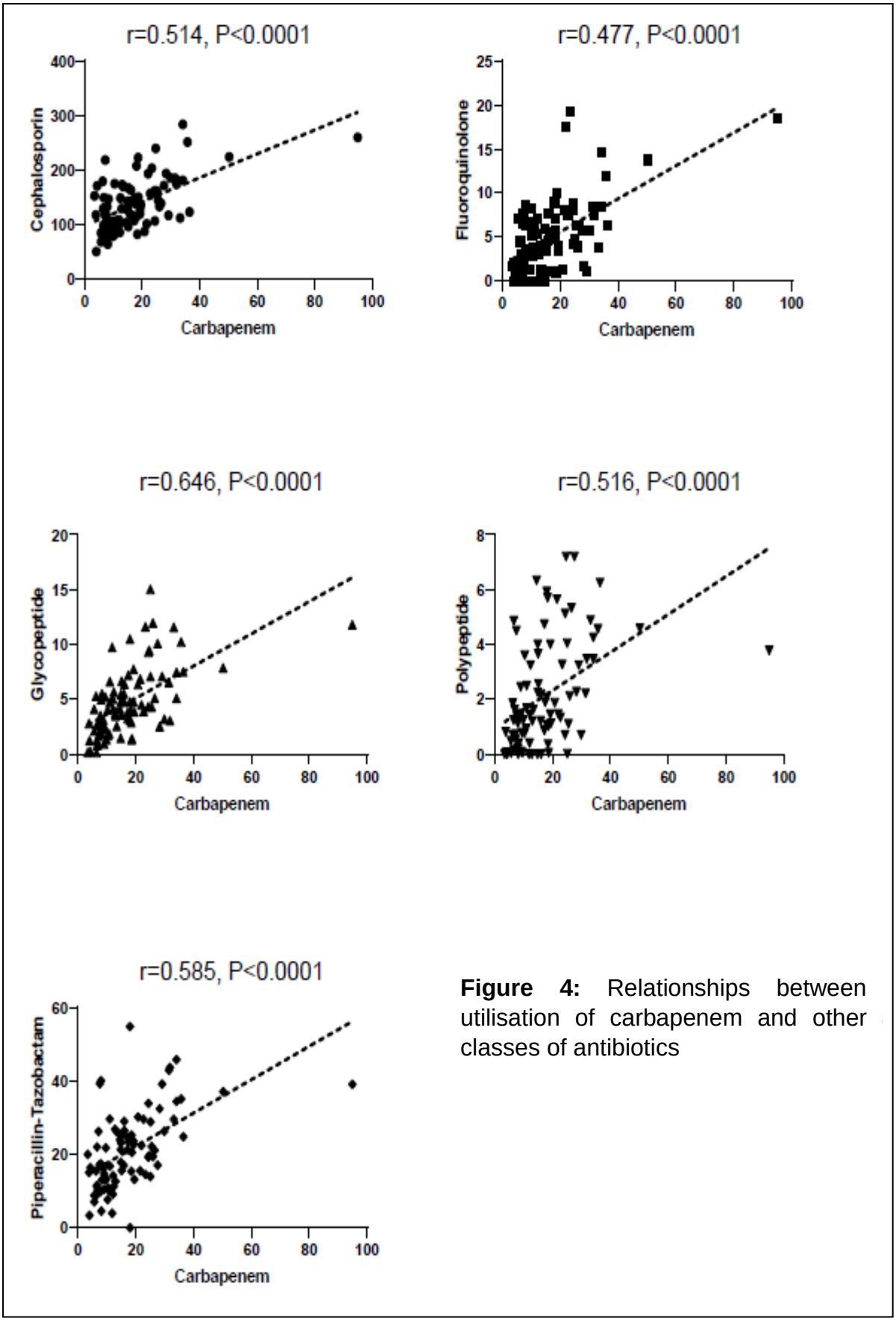


Figure 4: Relationships between utilisation of carbapenem and other classes of antibiotics

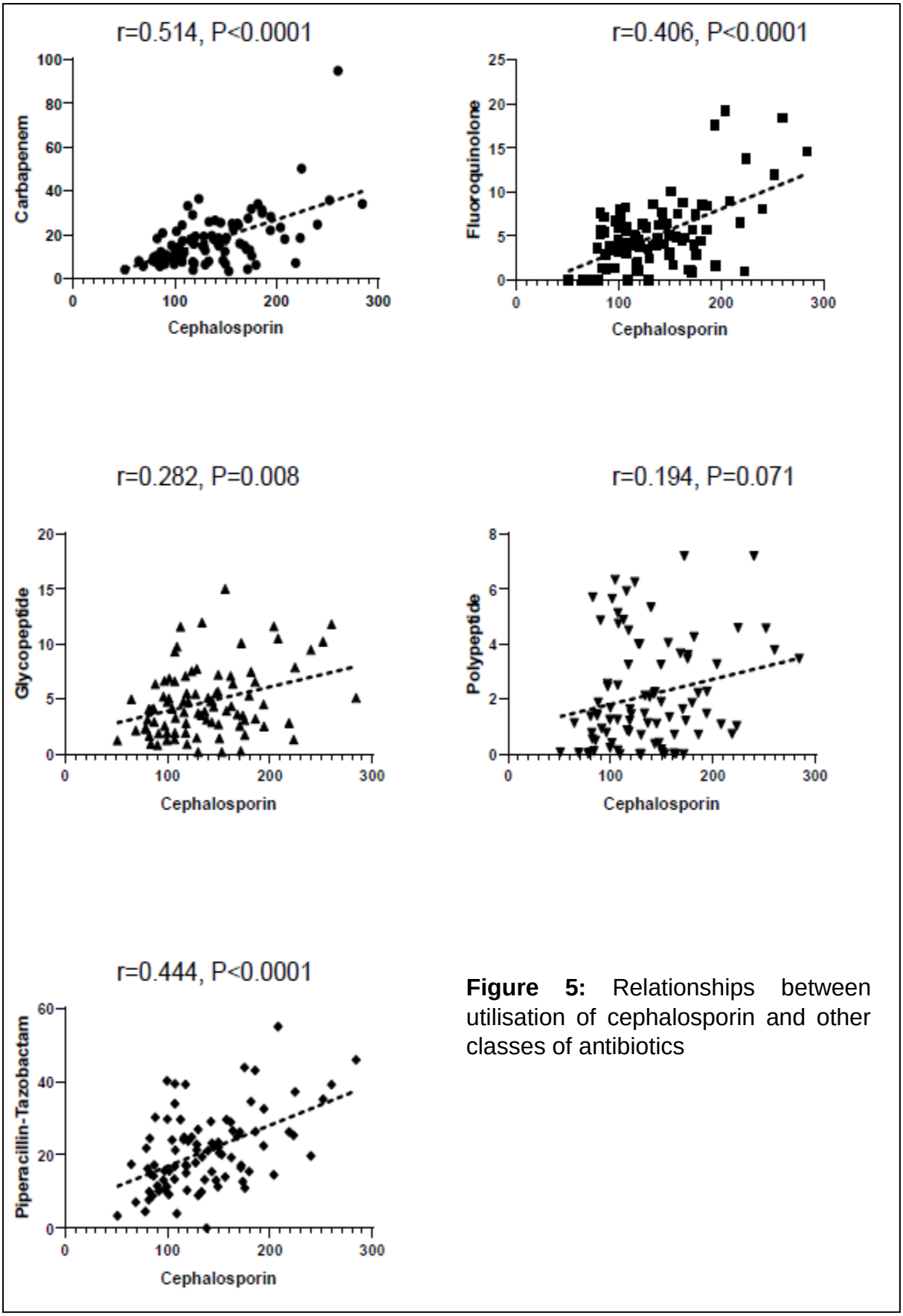


Figure 5: Relationships between utilisation of cephalosporin and other classes of antibiotics

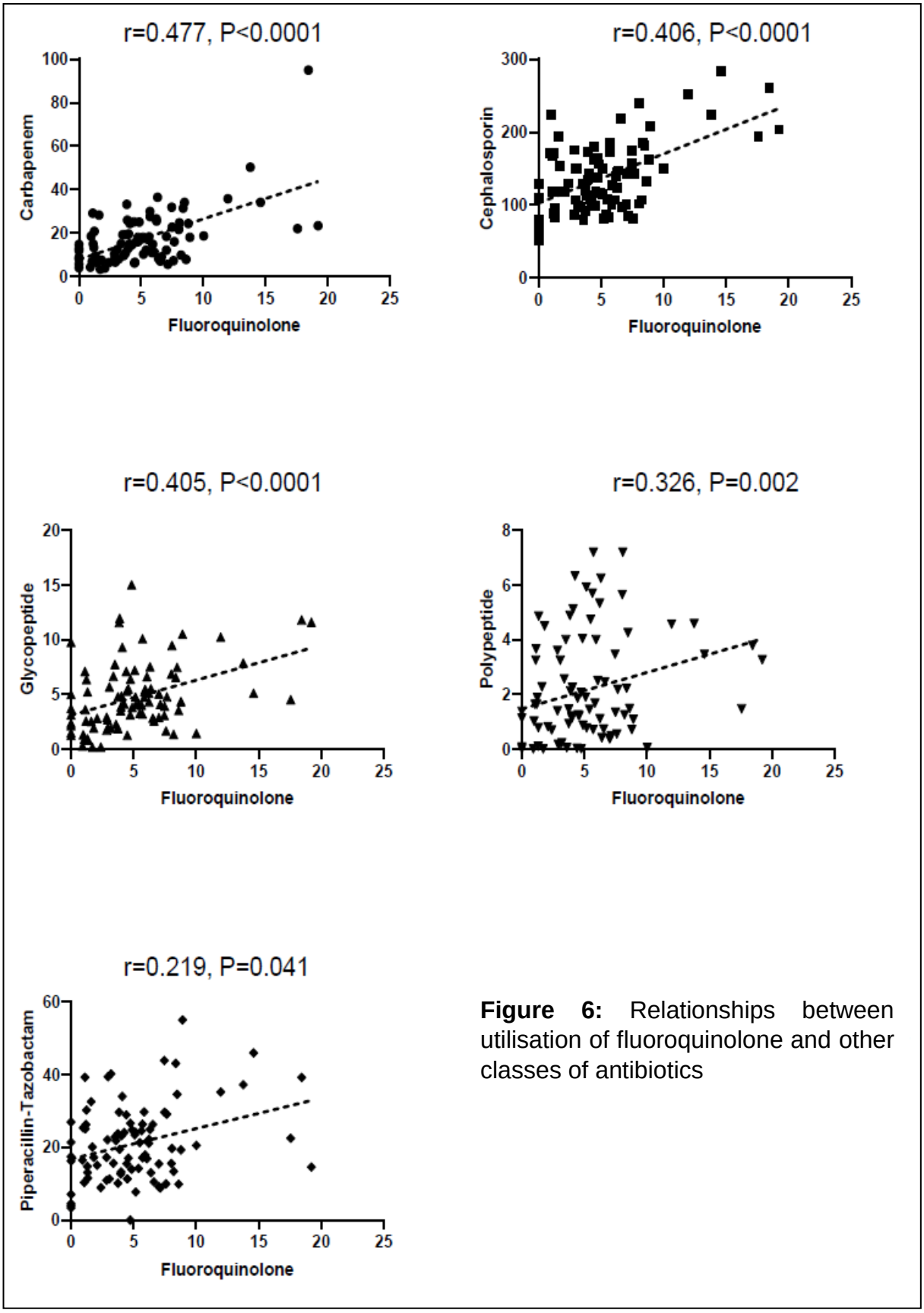


Figure 6: Relationships between utilisation of fluoroquinolone and other classes of antibiotics

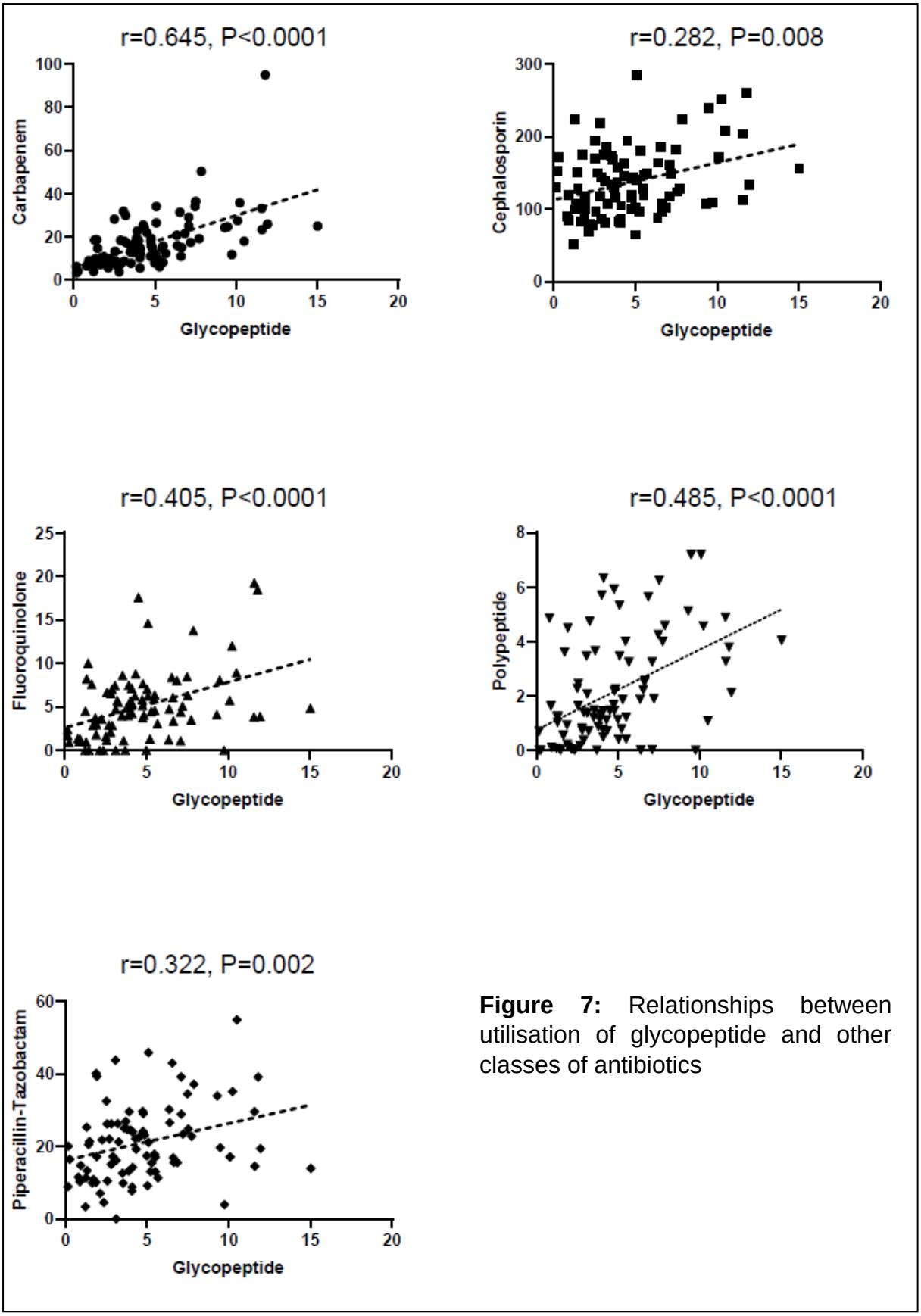


Figure 7: Relationships between utilisation of glycopeptide and other classes of antibiotics

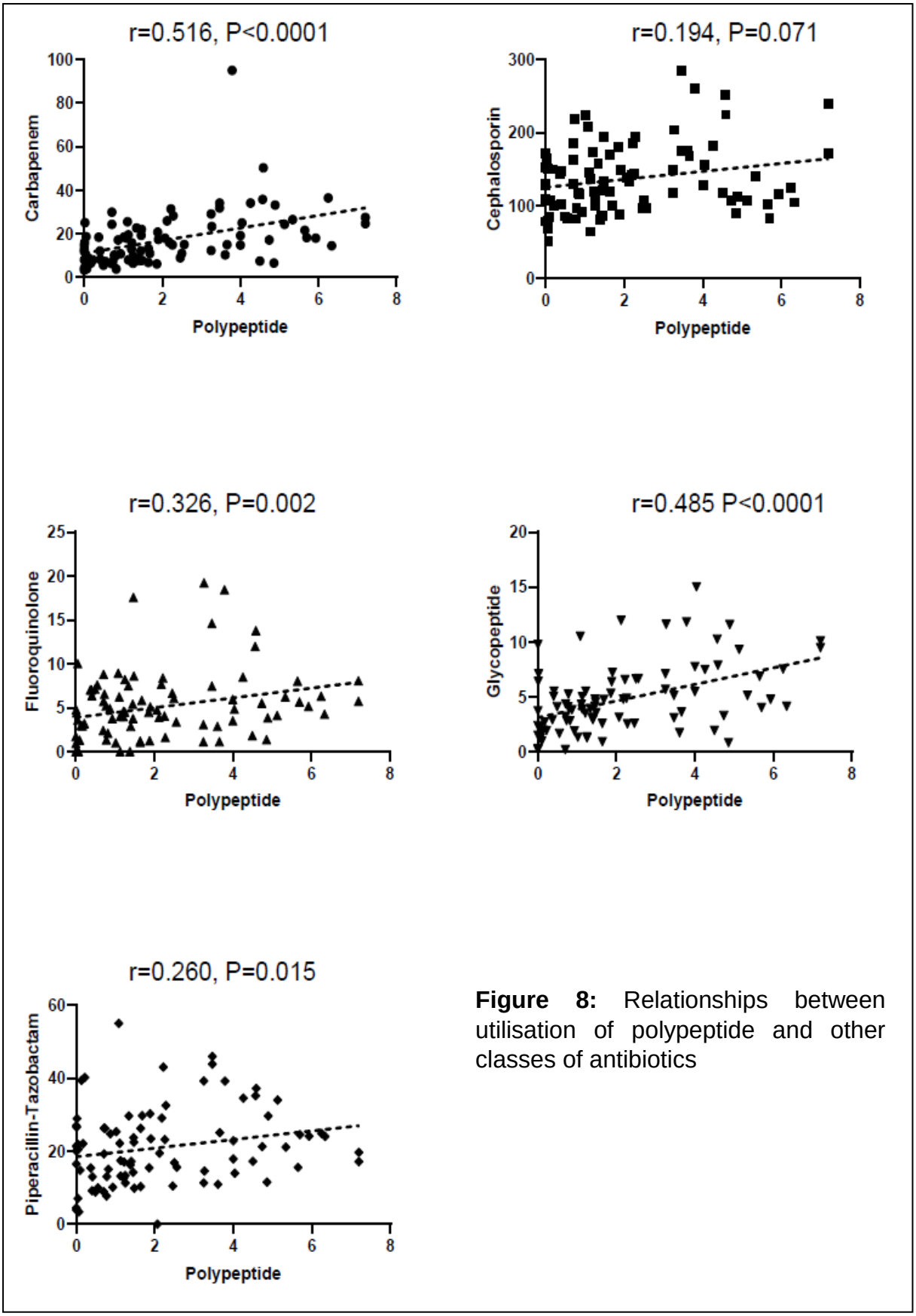


Figure 8: Relationships between utilisation of polypeptide and other classes of antibiotics

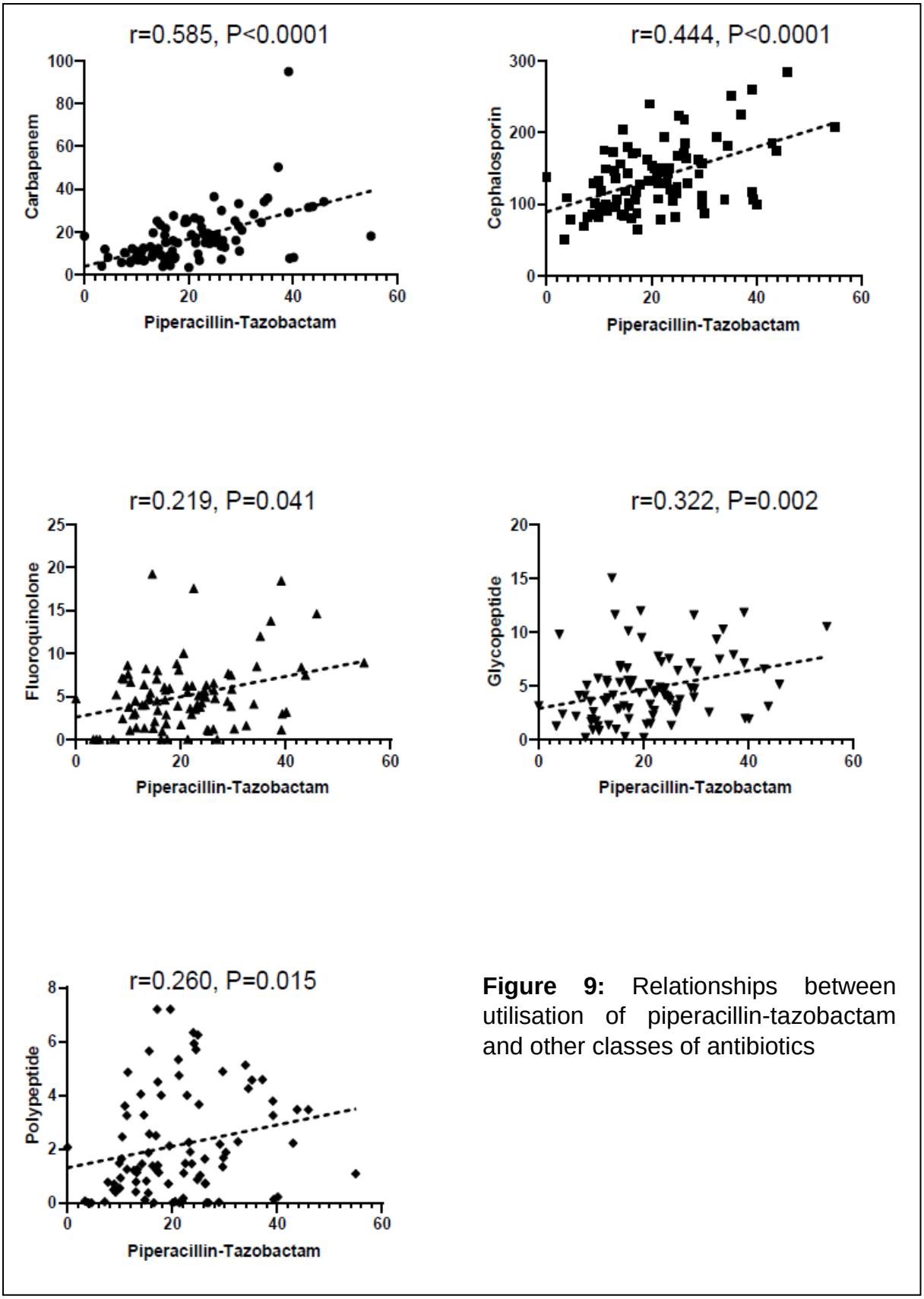


Figure 9: Relationships between utilisation of piperacillin-tazobactam and other classes of antibiotics

Discussions

This is the first report on antimicrobial surveillance from various hospitals across Malaysia over 10 years.

In 2015, the Global Point Prevalence Survey consisted of adult data from 303 hospitals across 53 countries showed that the top three antibiotics prescribed worldwide were penicillins with beta-lactamase inhibitors, third-generation cephalosporins and fluoroquinolones, while carbapenems were most frequently prescribed in the west and central Asian hospitals [15]. In another retrospective national surveillance, from 153 tertiary hospitals in China, cephalosporins were the most commonly used antibiotics in the region, followed by quinolones, penicillins and carbapenems [16]. Meanwhile, a surveillance study across 108 ICUs in Poland showed that among the three commonest antibiotics consumed in the ICU settings were carbapenems, quinolones and cephaloporins [17]. In relation to the above reported data, the usage of antibiotics in hospitals across Malaysia is consistent with those observed from other regions, either in “All Wards” or ICU settings.

Statistically significant moderate to high positive relationships among the utilisation of the broad-spectrum antibiotics (i.e. glycopeptide, piperacillin-tazobactam, carbapenem and polypeptide) in Malaysian hospitals suggest that utilisation of certain broad-spectrum antibiotics may induce usage of other broad-spectrum antibiotics. Further evaluation is required on this finding.

A multicenter retrospective study of French antibiotic and multidrug-resistant (MDR) bacteria surveillance networks in healthcare facilities revealed that beside clinical settings, other factor that independently associated with a lower probability of reducing carbapenem use was higher initial third-generation cephalosporin consumption, thus led to a recommendation that decreasing the third-generation cephalosporin consumption would allow reduction of carbapenem use [18] (Muller et al 2018). In the Malaysian surveillance data, significant moderate positive relationships between number of hospital beds and utilisation of broad-spectrum antibiotics including piperacillin-tazobactam, fluroquinolones, carbapenems, glycopeptides and

polypeptides were observed. As cephalosporin is the most utilised class of antibiotic either in “All Wards” or ICU settings, an attempt to reduce cephalosporin utilisation, particularly the third-generation, in larger hospitals such as the tertiary hospitals, should be beneficial in controlling the utilisation of carbapenems in Malaysian hospitals.

The increase in antibiotic resistance rate with increased consumption of broad-spectrum antibiotics, particularly those involving MDR pathogens were reported in many recent studies, which is worrying and becomes a major concern. A single-centre study at a tertiary care hospital evaluating the association between antibiotic use and resistance in *Klebsiella pneumoniae*, showed that consumption of beta-lactam and beta-lactamase inhibitor antibiotics significantly correlated to the resistance rates of *K. pneumoniae* to piperacillin/tazobactam, ceftazidime and levofloxacin [19]. In addition to the finding, significant correlations were also observed between the third-generation cephalosporins with the rates of resistance to ceftazidime and levofloxacin while consumption of fluoroquinolones was correlated with the resistance rate to ceftazidime [19]. Significant relationships between the consumption of carbapenem and rates of carbapenem-resistance in Gram-negative bacilli organisms such as *Escherichia coli*, *K. pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*, were also observed from a national surveillance data in China [16]. Correlation between antibiotic usage and resistance pattern has also been reported in Korea, where data from hospitalised patients at university hospitals showed that consumption of carbapenems and fluoroquinolones significantly correlated with the resistance rate of *E. coli* or *K. pneumoniae* to the third-generation cephalosporins and ciprofloxacin [20]. The same study also observes increasing resistance of *A. baumannii* to ciprofloxacin which is significantly correlated with the increase in consumption of fluoroquinolones, while increasing resistance to imipenem was associated with the increased consumption of carbapenem [20]. Other data from a single-centre retrospective study at a university hospital in Thailand revealed significant correlations between the prevalence of carbapenem-resistant *K. pneumoniae* and consumption of carbapenem ($r=0.55$, $P=0.04$) and levofloxacin ($r=0.65$, $P=0.01$) [21]. In agreement with this finding, a three-year surveillance data from a tertiary hospital in China demonstrated significant correlations between the prevalence of carbapenem-resistant *K. pneumoniae* with the usage of meropenem and imipenem [22]. Therefore, in light of

many recent evidences on emerging resistant pathogens due to excessive use of antibiotics, the Malaysian surveillance data should be considered highly important, and thus, relevant action should be implemented locally in order to improve quality of antibiotic use.

Further local study to identify factors which might contribute to the observed relationships between utilisation of various antibiotics is required, to further explain and establish proper action that needs to be taken to prevent any unwanted implications due to possible inappropriate antibiotic usage. Current data have observed a few potential areas that can be improved or implemented by the local practitioners and relevant policy makers in preventing overuse or misuse of antibiotics in Malaysia such as establishment of clinical pathways which not only suit the hospitals under MOH but also applicable to other hospitals such as the university, military and private hospitals. More stringent policy on the prescribing of broad-spectrum antibiotics should also be applied in all Malaysian healthcare facilities across sectors through nationwide implementation of antimicrobial stewardship programme.

Conclusions

In conclusion, similar trend of antibiotic usage was observed in Malaysia from 2008 to 2017 to those from other regions, with cephalosporin being the most used antibiotic class. Although the majority of data contributors were MOH hospitals, the university hospitals had showed the highest overall antibiotic utilisation, which warrants a closer antibiotic usage monitoring in these hospitals. Implementation of clinical pathways and establishment of proper AMS programme may be helpful in ensuring that antibiotics are not overused and/or misused and adequately administered when required for treatment in local practice.

References

1. Schuts EC, Hulscher M, Mouton JW, Verduin CM, Stuart J, Overdiek H, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016; 16:847-856

2. Drekonja DM, Filice GA, Greer N, Olson A, MacDonald R, Rutks I, et al. Antimicrobial stewardship in outpatient settings: a systematic review. Infect Control Hosp Epidemiol 2015; 36:142-152

3. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016; 62:e51-77

4. Dellit TH, Owens RC, McGowan JE, Jr., Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007; 44:159-177

5. Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G, Faes C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient quinolone use in Europe (1997-2009). J Antimicrob Chemother 2011; 66 Suppl 6:vi47-56

6. Tsutsui A, Yahara K, Shibayama K. Trends and patterns of national antimicrobial consumption in Japan from 2004 to 2016. J Infect Chemother 2018; 24:414-421

7. Kim YA, Park YS, Youk T, Lee H, Lee K. Changes in Antimicrobial Usage Patterns in Korea: 12-Year Analysis Based on Database of the National Health Insurance Service-National Sample Cohort. Sci Rep 2018; 8:12210

8. Chen J, Min R, Wang H, Zhao S, Li H, Fang P. Trends and Drivers of Inpatient Antibiotic Consumption among 89 China Tertiary General Hospitals from 2011Q1 to 2015Q4. Biomed Res Int 2018; 2018:5968653

9. Muraki Y, Yagi T, Tsuji Y, Nishimura N, Tanabe M, Niwa T, et al. Japanese antimicrobial consumption surveillance: First report on oral and parenteral antimicrobial consumption in Japan (2009-2013). J Glob Antimicrob Resist 2016; 7:19-23

10. Muraki Y, Kitamura M, Maeda Y, Kitahara T, Mori T, Ikeue H, et al. Nationwide surveillance of antimicrobial consumption and resistance to Pseudomonas aeruginosa isolates at 203 Japanese hospitals in 2010. Infection 2013; 41:415-423

11. Holloway K, Mathai E, Gray A, Community-Based Surveillance of Antimicrobial U, Resistance in Resource-Constrained Settings Project G. Surveillance of

community antimicrobial use in resource-constrained settings--experience from five pilot projects. Trop Med Int Health 2011; 16:152-161

12. Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G, Faes C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient macrolide, lincosamide and streptogramin (MLS) use in Europe (1997-2009). J Antimicrob Chemother 2011; 66 Suppl 6:vi37-45

13. Adriaenssens N, Coenen S, Kroes AC, Versporten A, Vankerckhoven V, Muller A, et al. European Surveillance of Antimicrobial Consumption (ESAC): systemic antiviral use in Europe. J Antimicrob Chemother 2011; 66:1897-1905

14. Shalit I, Low M, Levy E, Chowers M, Zimhony O, Riesenberg K, et al. Antibiotic use in 26 departments of internal medicine in 6 general hospitals in Israel: variability and contributing factors. J Antimicrob Chemother 2008; 62:196-204

15. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health 2018; 6:e619-e629

16. Yang P, Chen Y, Jiang S, Shen P, Lu X, Xiao Y. 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

17. Trejnowska E, Deptula A, Tarczynska-Slomian M, Knapik P, Jankowski M, Misiewska-Kaczur A, et al. Surveillance of Antibiotic Prescribing in Intensive Care Units in Poland. Can J Infect Dis Med Microbiol 2018; 2018:5670238

18. Muller A, Bertrand X, Rogues AM, Pefau M, Alfandari S, Gauzit R, et al. Higher third-generation cephalosporin prescription proportion is associated with lower probability of reducing carbapenem use: a nationwide retrospective study. Antimicrob Resist Infect Control 2018; 7:11

19. Ryu S, Klein EY, Chun BC. Temporal association between antibiotic use and resistance in Klebsiella pneumoniae at a tertiary care hospital. Antimicrob Resist Infect Control 2018; 7:83

20. Kim B, Kim Y, Hwang H, Kim J, Kim SW, Bae IG, et al. Trends and correlation between antibiotic usage and resistance pattern among hospitalized patients at university hospitals in Korea, 2004 to 2012: A nationwide multicenter study. Medicine (Baltimore) 2018; 97:e13719

21. Prakobsrikul N, Malathum K, Santanirand P, Chumnumwat S, Piebpien P, Montakantikul P. Correlation between antimicrobial consumption and the prevalence of carbapenem-resistant Escherichia coli and carbapenem-resistant Klebsiella pneumoniae at a university hospital in Thailand. J Clin Pharm Ther 2019; 44:292-299

22. Zhang D, Hu S, Sun J, Zhang L, Dong H, Feng W, et al. Antibiotic consumption versus the prevalence of carbapenem-resistant Gram-negative bacteria at a tertiary hospital in China from 2011 to 2017. J Infect Public Health 2019; 12:195-199

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