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IMPACT OF ANTIMICROBIAL STEWARDSHIP PROGRAMME ON ANTIMICROBIAL UTILISATION, COST AND BACTERIAL RESISTANCE IN A MALAYSIAN PUBLIC TERTIARY HOSPITAL

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ABSTRACT

Antimicrobial stewardship programme (ASP) was introduced as one of the strategies to curb the rise of multi-drug resistant (MDR) organism. The findings on the programme establishment are important in strengthening ASP measures. This study aimed to assess the impact of ASP implementation on the antimicrobial utilisation, antimicrobial cost and the MDR bacterial resistant rate before and after the programme initiation. A retrospective cohort study involving adult inpatient in a public tertiary hospital was conducted between pre-ASP implementation in year 2015 and post-ASP implementation from year 2016 to 2019. The statistical analysis of Student t-test or Mann-Whitney U test was used depending on the data distribution. The mean defined daily dose (DDD) per 1,000 patient days for ASP targeted antibiotics was significantly decreased by 17% from 161.52 DDD per 1,000 patient days in pre-ASP period to 134.49 DDD per 1,000 patient days in post-ASP period mainly from the usage of third generation cephalosporin, carbapenem and colistin. The annual expenditure for ASP targeted antibiotics had significant monetary reduction from RM30,580.50 in pre-ASP period to RM20,590.60 during post-ASP period. Significant reduction in the mean MDR bacterial resistant rate were notable for extended spectrum beta-lactamase E. coli (27.48%–17.85%), methicillin-resistant Staphylococcus aureus (22.25%–15.73%) and MDR Acinetobacter spp. (71.46%–49.34%). The implementation of ASP leads to significant reduction on the ASP targeted antibiotics utilisation, antimicrobial cost and MDR bacterial resistance rate. These outcomes are beneficial in justification and expansion of ASP activities in Malaysia.

Keywords: Antimicrobial stewardship, Antibiotic use, Antibiotic cost, Resistance

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INTRODUCTION

The emergence of antimicrobial resistance had become an alarming major public threat worldwide. The spreading of antimicrobial resistance was driven from the misuse or antimicrobial overuse either in human or animal industry. According to recent report from World Health Organization (WHO), antimicrobial resistance had been identified as one of the top ten global public health issues (WHO 2020). The issues pertaining antimicrobial resistance had significant impact on clinical and economic outcome. Patients who infected with multi-drug resistant (MDR) organism required more expensive alternative treatment or antibiotics and these patients will have longer hospitalisation thus exposed to higher risk of mortality and morbidity (Eliopoulos, Cosgrove and Carmeli 2003; MacGowan, 2008). In Malaysia, the National Antibiotic Resistance Surveillance Report (2019) shown an increase in resistance rate for the majority of antibiotics tested for *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Institute for Medical Research and National Institutes of Health Malaysia 2019). The association between antimicrobial usage and the development of bacterial resistance had been revealed in a systematic review by Bell *et al.* (2014) which revealed increment of antimicrobial consumption cause higher production of bacterial resistance.

In response to the challenge of antimicrobial resistant, antimicrobial stewardship programme (ASP) had been developed with the main goal of promoting judicious use of antimicrobial in delivering an effective and safe treatment to the patient, by implementing various strategies that suits to the practice facilities. Although ASP had been implemented in various countries worldwide, there were no clear consensus to evaluate the impact of the interventions from the programme (Davey *et al*. 2017; Morris 2014). Each of the countries or healthcare facilities had developed their own guidelines and all the intervention been executed were specified to their institution antimicrobial use issues (Schuts *et al*. 2016). Therefore, the different approaches taken by each facility will result in variation of outcomes. Most of the studies from a systematic review by Schuts *et al.* (2016) were directed on evaluating patients' clinical outcome, antimicrobial resistance rate and cost in assessing the impact of the ASP approaches. All the efforts for the measures taken in conducting the ASP had significant beneficial outcomes on the key impact measurement (Schuts *et al*. 2016). For instance, a retrospective quasi-experimental study evaluating the impact of ASP implementation showed a reduction of antibiotics utilisation with significant decrement of total antibiotic expenditure after ASP implementation (Timbrook, Hurst and Bosso 2016).

Currently, the evaluation of impact on ASP intervention in healthcare facilities are still scarce despite the establishment of ASP since 2014 in Malaysia. The previous studies in Malaysia were mostly focused on the antimicrobial utilisation, cost and appropriateness of measure from specific approaches of antimicrobial stewardship such as persuasive and restrictive approaches, restriction on the specific antibiotic use and promoting conversion of intravenous preparation to oral (Arulappen *et al*. 2021; Sze and Kong 2018; Yap *et al*. 2016). The antimicrobial utilisation become the most widely use key measurement of ASP evaluation and the impact on the bacterial resistance rate was sometimes disregard. This might be due to the fact that longer period is required to assess the changes in the drug resistance pattern (Dik *et al*. 2016). The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America had recommended to use selected bacterial resistance rate as one of the key measurements in evaluating the impact of ASP intervention (Barlam *et al.* 2016). Thus, there is a need to include all the importance key measurements in evaluating the impact of ASP implementation such as antimicrobial utilisation, the cost of the antimicrobial use throughout the programme and bacterial resistance rate. Furthermore, as the ASP in Hospital Kulim had been implemented since the end of 2015, a comparison of the recent years' outcomes with the year 2015 is important to measure the overall impact of the programme establishment. This study, therefore aimed to assess the impact of ASP implementation on the antimicrobial utilisation, antimicrobial cost and the MDR bacterial resistant rate before and after the programme initiation. The findings of the study are important in strengthening ASP measures taken in promoting judicious use of antimicrobial and to curb the emergence of resistant bacteria in future.

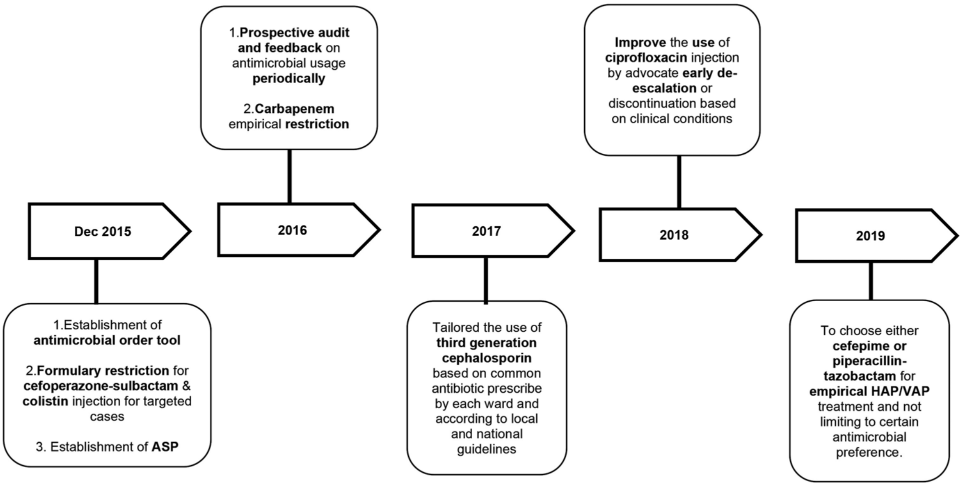
METHODS

Setting and Study Population

This was a retrospective cohort study conducted in Hospital Kulim, a major government specialist hospital in Kedah state, Malaysia. The ethics approval for this study was obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia (Ethics approval number: NMRR -20-2661-56936). Hospital Kulim served adults and pediatrics patients which equipped with 320 beds and 19 specialties. Its average annual admission is around 32,000 admissions per year. The ASP committee was fully established at the end of year 2015 in the Hospital Kulim. Despite of the unavailability of resident of infectious disease (ID) physician or ID-trained pharmacist, the appropriate measures had been planned to strengthen the programme with the guidance from ID physician of Hospital Sultanah Bahiyah, Alor Star, Kedah. The Hospital Kulim ASP team comprised of medical physician as a team leader, supported with a few other physicians, dedicated pharmacists, clinical microbiologist and infection control nurses. The ASP team was placed under Hospital Infection and Antibiotic Control Committee (HIACC) and chaired by the Director of Hospital Kulim. Prior to the establishment of ASP team, there was no coordinated surveillance or prospective review on the antimicrobial prescribing in the hospital in addition of unavailability of ID physician or ID-trained pharmacist to facilitate the programme. After the initiation of ASP, a few initiatives and activities were carried out and focused on improving the antimicrobial use in adult inpatient population as described in Table 1. All the measures were designed based on current issue on antimicrobial usage, emergence of bacterial resistance or infection control issues at that point of time.

The study period for this study was from year 2015 to 2019 which involved comparison of pre- and post-ASP implementation. The inclusion criteria was adult's patients admitted to the wards throughout the study period. This study excluded all the pediatric patients. As the Hospital Kulim ASP was initiated at year 2016, the pre-ASP period is defined as all the data collected in the year of 2015. Whereas, the data for post-ASP period analysis was collected from the year of 2016 to 2019. All the data collected was compared between pre-ASP and post ASP period.

Table 1: Examples of initiatives and ASP activities conducted in Hospital Kulim, Kedah.



DATA COLLECTION AND ANALYSIS

Data Collection for Antimicrobial Utilisation

The outcomes for analysis included antimicrobial utilisation, total antimicrobial expenditure and MDR bacterial resistance rate among adult inpatient population. Antimicrobial utilisation was measured as defined daily dose (DDD) and focused on the injectable ASP targeted antibiotics which were meropenem, imipenem-cilastatin, ertapenem, ceftriaxone, cefotaxime, cefoperazone-sulbactam, ceftazidime, cefoperazone, ciprofloxacin, vancomycin, piperacillin-tazobactam, cefepime and colistin. These antibiotics were routinely monitored by the ASP team for the appropriateness and optimisation of the use through policies, formulary restriction, protocols and education in ASP activities. The usage of other antibiotics such as aminoglycosides group, ampicillin-sulbactam, amoxicillin-clavulanic acid and cefuroxime were excluded as most ASP interventions were not involving these antibiotics. Other than that, antiviral and antifungal drugs also were excluded from the utilisation and expenditure evaluation.

The quantity of ASP targeted antibiotics in gram was captured from prescriptions received in In-Patient Pharmacy Unit of Hospital Kulim. Meanwhile, the total patient days for both analysis periods were gathered from Record and Admission Office of Hospital Kulim. These data were transferred to a standard Microsoft Excel spreadsheet and the final antimicrobial usage data was expressed as DDD per 1,000 patient days of ASP targeted antibiotics for both pre-ASP and post-ASP period.

Data Collection for Antimicrobial Expenditure

The evaluation for ASP targeted antibiotics expenditure in Ringgit Malaysia (RM) currency were done by using the total prescription received from In-Patient Pharmacy Unit of Hospital Kulim for both analysis period of time with the average price for ASP targeted antibiotics was gathered from Pharmacy Store Unit of Hospital Kulim annually.

Data Collection for Bacterial Resistance

Meanwhile, the MDR bacterial resistance rate evaluation was focused on extended spectrum beta-lactamase (ESBL) *E. coli*, ESBL *Klebsiella*, MDR *Acinetobacter*, MDR *Pseudomonas*, MRSA and carbapenem-resistant *Enterobacteriaceae* (CRE). The emergence of these MDR bacterial resistance rate were routinely monitored by the ASP team at hospital, state and national level. The selected MDR bacterial resistance rate was collected from Microbiology Unit of Hospital Kulim which isolated from adult inpatient clinical sample for both period of analysis (pre-ASP and post-ASP period). The prevalence for resistance rate of selected MDR organism were represent as the percentage of MDR cases from the sample tested which calculated using the following equation of:

$$\text{Resistant rate of bacteria} = \frac{\text{Total of bacteria resistant cases} \times 100}{\text{Total of both bacteria resistant and sensitive cases}}$$

Statistical Analysis

The analysis for all measured outcomes were carried out by using The IBM Statistical Product and Service Solutions (SPSS) software version 27.0. The difference between pre-ASP and post-ASP period for all the variables were compared by using Student's *t*-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). A *p*-value of 0.05 or less was considered to demonstrate statistical significance.

RESULTS

A total of 12,251 prescriptions of ASP targeted antibiotics had been reviewed from the Inpatient Pharmacy Unit for both the analysis period. For all ASP targeted antibiotics, the mean DDD per 1,000 patients days for pre-ASP period was 161.52 ± 30.91 and the usage significantly reduced to 134.49 ± 11.79 during the post-ASP period (Table 2). The ASP targeted antibiotics group which showed significant usage reduction after ASP implementation were all the third generation cephalosporin, carbapenem and colistin. The mean reduction of the usage between both analysis periods for all the third-generation cephalosporin were 83.89 ± 21.10 to 68.50 ± 8.29. Meanwhile, the carbapenem and colistin showed a reduction of 30.64 ± 11.08 to18.58 ± 2.31 and 5.33 ± 2.33 to 1.13 ± 0.82, respectively.

The type of antibiotics under the third-generation cephalosporin group which showed significant reduction of usage after the ASP implementation were cefotaxime and cefoperazone/sulbactam with mean reduction in DDD per 1,000 patients days of 2.59 ± 1.14 to 1.35 ± 0.68 and 2.86 ± 1.94 to 0.21 ± 0.23, respectively. Meanwhile, for antibiotic under carbapenem group, only imipenem/cilastatin showed significant reduction on the usage with the mean reduction of 9.79 ± 4.44 to 2.09 ± 1.18. Conversely, ertapenem showed significant increment in the usage after ASP implementation with median of 0.00 (IQR = 0.00–4.28) in pre-ASP to 1.54 (IQR = 0.22–3.10) during post-ASP period.

Other notable result was non-carbapenem antipseudomonal beta-lactam group which showed significant increment of the utilisation with mean DDD per 1,000 patients days of 29.43 ± 7.89 in pre-ASP and 36.80 ± 3.75 during the post-ASP period. Piperacillin/tazobactam was the antibiotic which showed significant increment in usage after ASP

Table 2: Antibiotic utilisation in DDD per 1,000 patient days between pre-ASP and post-ASP period.

Antibiotic group	No. of prescription (year 2015)	Pre-ASP		No. of prescription (years 2016–2019)	Post-ASP		Statistical analysis (critical value and *p*-value)	Significant changed in antibiotic usage[d]
		Mean	SD		Mean	SD		
All antibiotic groups	2,581	161.52	30.91	9,670	134.49	11.79	$t = 2.83$, $p = 0.013$	−16.7%
All third generation Cephalosporin	1,418	83.89	21.10	4,653	68.50	8.29	$t = 2.36$, $p = 0.034$	−18.3%
Ceftriaxone	640	53.67	17.39	2,030	43.64	6.59	$t = 1.87$, $p = 0.08$	–
Cefotaxime	81	2.59	1.14	168	1.35	0.68	$t = 3.25$, $p = 0.004$	−47.9%
Ceftazidime	265	16.93	8.88	952	15.41	3.23	$t = 0.56$, $p = 0.582$	–
Cefoperazone	370	7.84	2.71	1,472	7.90	1.65	$t = -0.06$, $p = 0.952$	–
Cefoperazone/sulbactam	62	2.86	1.94	31	0.21	0.23	$t = 4.7$, $p = 0.001$	−92.7%
All carbapenem	427	30.64	11.08	1,197	18.58	2.31	$t = 3.69$, $p = 0.003$	−39.4%
Imipenem/cilastatin	169	9.79	4.44	150	2.09	1.18	$t = 5.81$, $p < 0.001$	−78.7%
Meropenem	241	19.89	11.50	963	14.94	2.38	$t = 1.46$, $p = 0.17$	–
Ertapenem[a]	17	0.00[b]	0.00 – 4.28[c]	84	1.54[b]	0.22 – 3.10[c]	$Z = -2.12$, $p = 0.03$	+154.0%
All non-carbapenem anti-pseudomonal beta-lactams	510	29.43	7.89	2922	36.80	3.75	$t = -2.92$, $p = 0.008$	+25.0%
Cefepime	244	18.56	10.38	1063	18.38	3.51	$t = 0.06$, $p = 0.954$	–
Piperacillin/tazobactam	266	10.87	9.96	1859	18.42	2.45	$t = -2.55$, $p = 0.025$	+69.5%
Fluoroquinolone								
Ciprofloxacin	20	6.45	3.47	231	4.74	1.53	$t = 1.56$, $p = 0.139$	–
Glycopeptide								
Vancomycin	173	5.79	3.17	638	4.74	0.88	$t = 1.11$, $p = 0.287$	–
Other								
Colistin	33	5.33	2.33	29	1.13	0.82	$t = 5.88$, $p < 0.001$	−78.8%

Notes: [a]The Student's *t*-test were used for all variables in the statistical analysis except for ertapenem which used Mann-Whitney U test; [b]Median value; [c]Interquartile range; [d]Positive value = increment in usage, negative value = reduction in usage.

establishment with DDD per 1,000 patients days of 10.87 ± 9.96 in pre-ASP to 18.42 ± 2.45 during post-ASP period. Other results on the utilisation of ASP targeted antibiotics that captured in DDD per 1,000 patients days are illustrated in Table 2.

Considering the financial impact of the ASP, the annual expenditure for all ASP targeted antibiotics showed significant monetary reduction. The median total expenditure during pre-ASP was RM30,580.50 and it significantly declined to RM20,590.60 in post-ASP period (Table 3). The trend of the annual expenditure for total ASP targeted antibiotics is illustrated in Figure 1.

Table 3: Annual ASP targeted antibiotics expenditure in RM between pre-ASP and post-ASP period.

	Annual antibiotic cost		**Statistical analysis (critical value and *p*-value)[a]**	**Significant changed in annual cost[b]**
	Median (RM)	**IQR (RM)**		
Pre-ASP	30,580.50	19,737.20 – 32 949.10	$Z = -3.41$, $p = 0.001$	−32.70%
Post-ASP	20,590.60	16,991.30 – 22 148.50		

Notes: [a]Statistical analysis by using Mann-Whitney U test; [b]Negative value = reduction in annual cost.

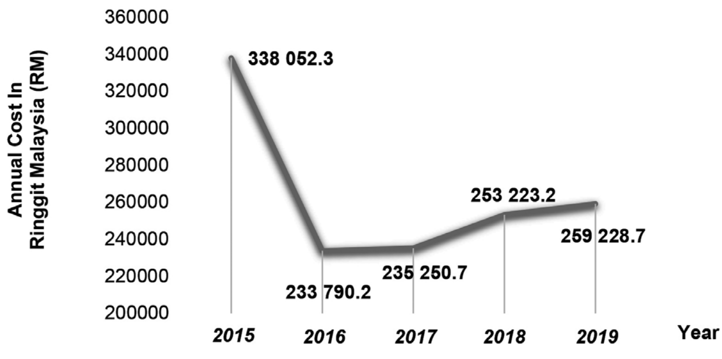


Figure 1: Annual expenditure trend of ASP targeted antibiotics

The changes of MDR resistance percentage were captured to measure the impact of ASP interventions and activities that have been carried out throughout the programme on the bacterial resistance effect. There were significant changes in the bacterial resistances rate for ESBL *E. coli*, MRSA, MDR *Acinetobacter* spp. and CRE (Table 4). For ESBL *E. coli*, there was a significant declined in the resistance percentage with mean 27.48 ± 7.74% in pre-ASP and 17.85 ± 5.20% in post-ASP period. Besides, the MDR resistance rate for MRSA was decreased from 22.25 ± 6.42% to 15.73 ± 2.88% while MDR *Acinetobacter sp.* showed a decrement of 71.46 ± 9.49% to 49.34 ± 13.23%. However, the bacterial resistance percentage of CRE was increased significantly after ASP implementation. The median bacterial resistance rate for pre-ASP and post-ASP were 0.00% (IQR = 0.00%–2.35%) and 1.86% (IQR = 0.94%–3.93%) respectively. Nevertheless, further subgroup analysis on bacterial resistance percentage of CRE during the years in post-ASP time periods showed significant difference of the resistance rate (Table 5). The resistance rate for CRE showed reducing trend from median of 1.22% in the first year of ASP implementation in 2016 to 0.73% in 2019. However, there was a sudden surged of resistance rate (2.90%) in year 2018.

Table 4: Multidrug resistance bacteria rate between pre-ASP and post-ASP Implementation period.

Type of Multidrug Resistance Bacteria	Pre-ASP			Post-ASP			Statistical analysis (critical value and *p*-value)	Significant changed in resistance rate[d]
	Number of isolates (year 2015)	Mean (%)	SD (%)	Number of isolates (year 2016–2019)	Mean (%)	SD (%)		
ESBL *E.coli*	87	27.48	7.74	193	17.85	5.2	$t = 3.58$, $p = 0.002$	−35.0%
ESBL *Klebsiella* spp.	133	28.03	6.68	468	31.79	3.3	$t = -1.75$, $p = 0.094$	–
MRSA	98	22.25	6.42	303	15.73	2.88	$t = 3.21$, $p = 0.006$	−29.3%
MDR *Acinetobacter* spp.	168	71.46	9.49	180	49.34	13.23	$t = 4.71$, $p < 0.001$	−31.0%
MDR *Pseudomonas aeruginosa*	24	11.39	6.23	67	9.35	4.42	$t = 0.93$, $p = 0.363$	–
CRE[a]	4	0.00[b]	0.00 − 2.35[c]	54	1.86[b]	0.94 − 3.93[c]	$Z = -3.29$, $p = 0.001$	+186.0%

Note: ESBL: Extended spectrum beta-lactamase; MRSA: Methicillin resistant *Staphylococcus aureus*; MDR: Multidrug resistant; CRE: Carbapenem resistant *Enterobacteriaceae*.

[a]The Student *t*-test were used for all variables for statistical analysis except for CRE which used Mann Whitney U-test; [b]Median value; [c]Interquartile range; [d]Positive value: increment in usage; negative value: reduction in usage

Table 5: Subgroup analysis of CRE resistance rate for year 2016 to 2019 (post-ASP period).

Year	Number of isolates	Median (%)	IQR (%)	Kruskal-Wallis test results (critical value & *p*-value)
2016	10	1.22	0.00 – 2.53	H = 10.28, *p* = 0.016
2017	8	0.00	0.00 – 4.05	
2018	23	2.90	0.00 – 4.55	
2019	13	0.73	0.00 – 8.77	

DISCUSSION

A multidisciplinary ASP was successfully implemented in Hospital Kulim and the judicious use of antimicrobial display as a major role in limiting the rise of antimicrobial resistance. This study was aimed to describe the changes in antimicrobial utilisation, the expenditure of antimicrobial use and effect on the MDR organisms resistant rate following ASP establishment. Following the ASP introduction, the marked changes was observed in ASP targeted antibiotics consumption with mean reduction of 17% in overall usage. This finding was consistent with a meta-analysis which shown a 16.0% to 35.9% reduction of antimicrobial consumption in DDD per 1,000 patient days after ASP interventions (Karanika *et al.* 2016).

The present study revealed that the changes of antimicrobial consumption may be related with the interventions incorporated throughout the ASP establishment. The reduction of 18% of all third generation cephalosporin usage may be due to the formulary restriction of cefoperazone/sulbactam use and tailored management of third generation cephalosporin prescribing according to local and national guidelines. The utilisation of carbapenem also showed tremendous reduction as 39% decrement following ASP interventions. This might be contributed by empowerment on indication of carbapenem as empirical use and periodical ASP rounds in evaluating the appropriateness of carbapenem therapy among the hospitalised patients. Conversely, the increment in the usage of ertapenem may be related to the introduction of ertapenem as one of the carbapenem de-escalation strategies in improving the judicious use of carbapenem therapy in Hospital Kulim. Ertapenem was added into Hospital Kulim formulary in July 2015 (pre-ASP) and the enforcement of carbapenem use in the following years contribute to this effect. Indeed, de-escalation to ertapenem in ESBL producing *Enterobacteriaceae* infection showed significantly lower defined daily dose of carbapenem use with lower mortality rate and non-inferiority to the superimposed infection rate in a study conducted by Rattanaumpawan *et al*. (2017).

The increment of piperacillin/tazobactam usage in the present study may be linked to the encouragement from ASP team to the prescribers. The piperacillin/tazobactam has been promoted by the ASP team as one of the antimicrobial choices before carbapenem in treating hospital acquired infection (HAI). The suggestion of using antipseudomonal beta-lactams antibiotics, piperacillin-tazobactam and cefepime had been proposed in the meeting with the head of all discipline department of Hospital Kulim and incorporated in ASP ward round interventions as one of the strategies to curb the increment of carbapanem usage. This is because the increased in usage of carbapenem will contribute to the emergence of MDR organisms. These interventions were concordance with Hospital Kulim's local commonest organism isolated data which showed that gram negative organism including *Pseudomonas aeruginosa*, *E.coli* and *Klebsiella* spp. were the most common isolated gram negative organisms being cultured. These antimicrobial agents were the preferable options of empirical therapy for hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) without risk factors of MDR organism (American Thoracic Society and Infectious Diseases Society of America 2005). A systematic review and meta-analysis by Sfeir, Askin and Christos (2018) showed that piperacillin-tazobactam can be considered as an alternative to carbapenem in treating ESBL-producing *Enterobacteriaceae* bloodstream infections as no significant difference in 30-day mortality was found between piperacillin-tazobactam and carbapenem when piperacillin-tazobactam was given as empirical or definitive therapy. However, the preference uses by the prescribers towards piperacillin/tazobactam as compared to cefepime may explained the difference in usage between both agents in the present study.

This study indirectly had identified several ASP interventions which were beneficial in improving antimicrobial prescribing practices. The ASP interventions such as pre-authorisation, prospective audit, feedback and review, restrictive technique and consultation with recommendations were proven to bring benefit either in antimicrobial utilisation or patients' clinical outcome (Davey *et al*. 2017; Lee *et al*. 2018). The findings on the effectiveness of these strategies were useful in determining future ASP targeted interventions as each institution would apply various strategies that suit to their practice. A sufficient duration was required in assessing the impact of ASP effectiveness considering on adaption on behavioral and policies changes. A recent study by Shafat *et al.* (2021) had revealed that the maximal effect of an ASP intervention can be seen after 1.5 years for a successful outcome measurement. This can be explained by the significant reduction of cefoperazone-sulbactam and carbapenem usage after the implementation of the usage restriction in the end of 2015 followed by the focused of ASP ward round team on the carbapenem therapy among the patients admitted to Hospital Kulim. These initiatives might contribute to the reduction of MDR *Acinetobacter* sp. and ESBL *E. coli* resistance prevalence rate in this study. All the significant effects were seen after the implementation of the above-mentioned strategies in 2016 to 2019.

The assessment for economic impact of a successful ASP introduction is essential. The present study focused on the antimicrobial expenditure which depends on the antimicrobial prescriptions received by the pharmacy department. This measurement for antibiotics expenditure is consistent with the Infectious Diseases Society of America (IDSA) recommendation in assessing the impact of ASP on antibiotic cost (Barlam *et al.* 2016). A reduction of 33% in annual ASP targeted antimicrobial expenditure had been captured in our study and this was comparable with other study which showed a significant reduction in antimicrobial expenditures following ASP introduction and interventions (Timbrook, Hurst and Bosso 2016). From a systematic review by Nathwani *et al.* (2019) on the economic outcomes of ASP implementation, there were 80 studies shown decrement in antimicrobial cost ranging from 0.06% to 80%. This systematic review also includes other key measurement in assessing the economic impact of ASP such as operational cost, patients' length of stay cost and overall cost saving. These key measurements may be beneficial in quantify and justify the continuity of ASP and assessing the overall effectiveness of antimicrobial activities economically.

The prevalence of MDR organism have risen alarming globally. The inappropriate use of antimicrobial was associated with the emergence of these MDR organism (Carrara *et al*. 2018). Antimicrobial stewardship activities or interventions were conducted to limit this unintended consequence by improving the use of antimicrobial judiciously. In our study, the antimicrobial stewardship interventions had showed beneficial impact on the reduction in the prevalence of MDR organism such as ESBL *E. coli*, MRSA and MDR *Acinetobacter spp*. A systematic review and meta-analysis in Asia Pacific region by Honda *et al.* (2017) found a reduction of overall trend in the incidence and resistant rate of MDR organism such as MRSA, ESBL-producing Enterobacteriacea, MDR *Acinetobacter spp.* and MDR *Pseudomonas spp.* after the implementation of ASP. Another systematic review and meta-analysis by Karanika *et al.* (2016) revealed that the ASP implementation had significant reduction on the prevalence of resistant strains such as MRSA, imipenem-resistant *Pseudomonas aeruginosa* and ESBL *Klebsiella* sp. but was unable to observe any significant reduction in the ESBL *E. coli* prevalence rate. The variation of these findings might be due to dissimilarity in the ASP interventions, and antimicrobial targeted in the ASP throughout these institutions. Limiting the emergence of MDR organism can be achieved by promoting the judicious use of antibiotics through the ASP, as the inappropriate use of antibiotics were one of the risk factors for MDR bacterial infection (Picot-Guéraud *et al.* 2015; Tacconelli *et al.* 2009). The overuse of carbapenem and third generation cephalosporin were linked with the MDR *Acinetobacter spp.* and ESBL acquisition, while the overuse of fluoroquinolone, glycopeptide and cephalosporin were associated with the risk of MRSA infection development (Falagas and Kopterides 2006; Tacconelli *et al*. 2008; Wang *et al*. 2019). The significant reduction on carbapenem and third generation cephalosporin usage might contribute to the decreased of those MDR bacteria resistant rate observed in this study.

Despite the reduction in resistance rate for most of the MDR bacteria, CRE resistant rate was increased after the ASP implementation. The small sample size of the CRE isolates between both the pre- and post-ASP implementation time period might have contributed to this finding. Thus, a subgroup analysis to assess the difference of CRE resistant rate during the year of ASP implementation was carried out to get an insight on the changes in CRE resistance rate. The subgroup analysis found an overall reducing trend of the resistant rate from year 2017 onwards as compared to the first year of ASP implementation in 2016. However, there are factors other than prior antibiotics exposure such as the use of medical devices and invasive procedures to the patients, and longer Intensive Care Unit (ICU) or hospital stay which may contribute to the resistance rate of the antibiotic (Snyder *et al*. 2019; van Loon, Voor In ‘T Holt and Vos 2018). Other than that, a study by Perez and Van Duin (2013) found systematic infection-prevention measures had an important impact on the prevalence and incidence rates of MDR organism infections including CRE. Besides, the control of CRE transmission by infection prevention strategies was important especially during CRE outbreak. These were the factors which may contribute to the difference on the findings of CRE resistance rate in the present study. Nevertheless, all the above mentioned factors were not assessed in this study.

Limitations of Study

The assessment on the patients’ clinical outcome and safety of the antimicrobial treatment cannot be done due to the unavailability of the data. Hence, there is a lack of overview on the overall clinical effectiveness of the ASP. Considering the antimicrobial cost analysis, we cannot hinder the antimicrobial price inflation throughout the analysis years. The changes of the antimicrobial brand to the generics product further affects the expenditures analysis. Other than that, the changes on the infection control measures and shortage of antimicrobial may had potential impact on the antimicrobial utilisation and the resistance rate of MDR organism isolates evaluation.

CONCLUSION

Initiation and establishment of antimicrobial stewardship activities in healthcare setting had significant reduction on antimicrobial utilisation, decrease antimicrobial expenditure and curb the emergence of MDR organism. These outcomes were consistent with the main goal of ASP initiation in improving the judicious use of antimicrobial and subsequently limit the development of resistance bacteria. The findings of this study can be utilised to improve preexisting strategies and organise future antimicrobial stewardship activities for the empowerment in improving the use of antimicrobial. The justification for the programme continuity and the expansion of the antimicrobial activities can be supported with these study findings. Furthermore, the method of assessment in this study can be set as an example for other institutions which conduct similar stewardship activities in evaluating the effect of ASP activities. It can also be used as supportive evidence and rationalise the ASP initiation at others healthcare facilities throughout Malaysia.

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