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EVALUATING AND COMPARING THE IMPACT OF AN ENHANCED ANTIMICROBIAL STEWARDSHIP PROGRAMME IN A DISTRICT SPECIALIST HOSPITAL: A TWO-YEAR RETROSPECTIVE STUDY

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ABSTRACT

Antimicrobial stewardship (AMS) programme is established to optimise use of antibiotics and to contain antibiotic resistance. This single centre, cross sectional retrospective study aimed to evaluate and compare the impact of an enhanced AMS programme in 2019 with data obtained in 2018 before its implementation. Types of interventions made by the AMS team, acceptance rate of AMS recommendations, antibiotic usage (DDD/1000 patients-days) and expenditure (antibiotic usage cost, RM) of 14 antibiotics under national surveillance were reviewed. Our study demonstrated non-significant reduction in total antibiotic usage (mean 188.25 versus 183.94; p = 0.523). Nonetheless, significant decline in prescribing of cefoperazone either alone or in combination with sulbactam, ciprofloxacin and meropenem was observed. There was a significant reduction in total usage cost (mean RM80,070.39 versus RM70,858.81; 95% confidence interval (CI):1519.48, 16903.69; p = 0.022) contributed in part by decreased third generation cephalosporins, meropenem and ciprofloxacin prescriptions. During enhanced AMS period, total AMS cases (45 versus 358), frequency of rounds (12 versus 37) and ward pharmacist-initiated AMS interventions were increased. The most common intervention and recommendation encountered were inappropriate choice and de-escalation of antibiotic, respectively. There was an improvement in overall acceptance rate in 2019 (67% versus 78%; p = 0.081). In conclusion, the enhanced

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programme resulted in decreased overall antibiotic prescription and expenditure, besides greater acceptance of AMS recommendations.

Keywords: Antimicrobial stewardship programme, Antibiotic usage, Antibiotic cost, Acceptance rate

INTRODUCTION

Antimicrobial stewardship (AMS) programme is an intervention designed to optimise use of antibiotics and is one of the key actions of the World Health Organization (WHO) Global Action Plan to contain antibiotic resistance (WHO 2012). The programme acts through 'coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobials regimen including dosing, duration of therapy, and route of administration' (Society for Healthcare Epidemiology of America, Infectious Diseases Society of America and Pediatric Infectious Diseases Society 2012).

Stewardship interventions are typically classified as structural (such as the introduction of new diagnostic tests to guide antibiotic treatment), enabling (such as guidelines or education on antibiotic use, expert audit of prescriptions and feedback advice to prescribers) or restrictive (such as prior authorisation, formulary restriction and automatic stop orders) (Davey *et al.* 2017). Often, different interventions are combined in antibiotic stewardship bundles. Several systematic reviews showed that these combined interventions increased compliance with local antibiotic policies and improved clinical patient outcomes (Schuts *et al.* 2016; Davey *et al.* 2017).

The AMS programme has already been in existence since 2014 in Hospital Taiping in line with the WHO's Global Action Plan. Routine AMS activities are outlined in the Protocol on Antimicrobial Stewardship Programme in Healthcare Facilities which was launched in 2014 (Ministry of Health Malaysia, 2014). Since Hospital Taiping was one of the top users of many antibiotics among major specialist hospitals in the year 2017 and 2018, an enhanced AMS programme was introduced in 2019 to urgently address this issue. Details of enhanced AMS initiatives are summarised in Figure 1.

Period	Activities
January–December 2018	Vancomycin retrospective audit and feedback[a]
April–June 2018	Carbapenem prospective audit and feedback[b]
August 2018	Updated antimicrobial order tool (e.g. antibiotic control form) to include ciprofloxacin injection
	Pre-authorisation for ciprofloxacin injection
October 2018	Ciprofloxacin injection retrospective audit and feedback[a]
November 2018	Antibiotic Awareness Week

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Figure 1: Enhanced AMS activities implemented in Hospital Taiping. Most initiatives were carried out in 2019.

Period	Activities
January–December 2019	Ward pharmacist-initiated daily AMS ward rounds in their respective wards. The ward pharmacist will take on the role of a non-ID trained AMS pharmacist to identify each patient on antimicrobial therapy, and review the indication for treatment, the prescribed regimen of therapy, the day of therapy, as well as relevant laboratory values and clinical assessment and any recommendations for improvement.
January–April 2019	Vancomycin retrospective audit and feedback[a]
January 2019	Hospital Taiping Antibiotics Dilution and Administration Protocol
April 2019	Cefoperazone prospective audit and feedback[b]
July–December 2019	Weekly AMS rounds with visiting infectious disease (ID) physician where complicated cases requiring ID assessment were referred to the AMS team for discussions and recommendations. Besides the ID physician, other AMS team members are two physicians, 15 ward pharmacists, two clinical microbiologists and infection control nurses.
July–August 2019	Removal of Cefoperazone injection from Maternity, Gynaecology and Labour room as imprest stock and replaced with Cefuroxime injection
May, August and November 2019	Email/Letter to Head of Departments regarding antibiotic usage in each discipline, outlier trends and suggestions for improvement
September 2019	Implementation of 72 h Antibiotic Automatic Stop Order
November 2019	Formulated clinical pathway on antibiotic selection in extended spectrum beta-lactamase (ESBL) microorganism treatment and protocol on management of *Staphylococcus aureus* bacteremia
	Updated antimicrobial order tool based on National Antimicrobial Guidelines 2019 recommendations on preferred indications for piperacillin-tazobactam, cefepime, meropenem and imipenem
	Antibiotic Awareness Week
December 2019	National Antimicrobial Quick Guide for Adult Medical Wards

Notes: [a]**Retrospective audit and feedback:** Antibiotic prescriptions over a specified period were retrospectively reviewed for several criteria such as guideline-adherence. Audit findings and suggestions were provided to primary physicians via presentation in hospital level infection control or department meetings and memo.
[b]**Prospective audit and feedback:** This was carried out by ward pharmacists who directly audited targeted antibiotics and provide feedback for change or discontinuation through written forms, memos or direct verbal communication to the primary physicians during clinical rounds.

Figure 1: (*continued*)

Besides, there emerges a necessity to evaluate the effect of AMS on process measures, particularly quantitative measures, after 5 years of its implementation. Thus, this study aims to evaluate and compare the impact of an enhanced AMS programme implemented in 2019 with pre-implementation period (2018) highlighting types of interventions, acceptance rate of AMS recommendations as well as antimicrobial usage and expenditure.

METHODS

Study Design

This was a single centre, cross-sectional, retrospective study, comparing two study periods 2018 with 2019. Universal sampling was used for collection of relevant data. Antimicrobial usage (DDD/1,000 patients-days and) and expenditure (antibiotic usage cost, RM) of 14 antibiotics listed under national surveillance, and monthly summaries of AMS cases in 2018 and 2019 (types of interventions and recommendations by the AMS team, acceptance rates) were extracted and recorded in the pre-designed data collection form. The study protocol was registered with the National Medical Research Register (NMRR) and ethical approval was obtained from the Medical Research & Ethics Committee (MREC). Due to its retrospective design, the need for informed consent was waived.

Data Analysis

Statistical analyses were performed using the Statistical Package for Social Science Software (SPSS) version 24. Data on AMS acceptance rates, types of intervention, antibiotic usage and expenditure were analysed descriptively either in percentages, mean ± standard deviation (SD) or median (interquartile range [IQR]). All continuous variables were tested for normality using Shapiro-Wilks statistic in view of sample size of less than 100. Normally distributed data was analysed using independent *t*-test, while Mann-Whitney U test was used for non-parametric data. For categorical variables, data were expressed as number and percentage and were analysed by the Pearson's chi-squared test. For all statistical tests performed, the significance level was set a priori at $p < 0.05$.

RESULTS

Overall, we reported reduction in total antimicrobial usage (DDD/1,000 patients-days) from 202.75 to 183.27 (Table 1) which was not statistically significant when their average values were compared. For third generation cephalosporins, the mean usage was lower in 2019 attributed in part to decreased in cefoperazone usage either alone or in combination with sulbactam. Cefuroxime was the only cephalosporin antibiotic which demonstrated increase in mean usage from 33.96 to 40.02 DDD/1,000 patient-days in 2018 and 2019, respectively. Total carbapenems recorded a non-significant 14.2% reduction in mean DDD/1,000 patient-days which was due to decline in meropenem prescribing. Mean ertapenem usage increased by 26.5% although the value was not statistically significant. Cefepime, vancomycin and ciprofloxacin recorded decline in usage trends, with the latter being a significant decrease. Of note, the prescribing of piperacillin-tazobactam was significantly increased by 16.8% during the enhanced AMS phase.

Table 1: Comparisons of antimicrobial usage (DDD/1,000 patients-days) between 2018 (before) and 2019 (during enhanced AMS programme).

	2018	**2019**	**95% CI**	***p*-value**
Total DDD/1,000 patient-days	202.75	183.27	-	-
mean (SD)	188.25 (18.80)	183.94 (13.22)	−9.46, 18.06	0.523 (t = −0.648[b])
Cefepime (median, IQR)	11.29 (6.64–27.00)	9.86 (7.76–14.64)	–	0.729 (Z = −0.346[a])
Piperacillin-tazobactam (median, IQR)	29.54 (0.98–34.18)	34.51 (32.03–42.53)	–	0.024 (Z = −2.254[a])
Vancomycin mean (SD)	4.35 (1.40)	4.14 (1.15)	−0.87, 1.30	0.685 (t = 0.411[b])
Ciprofloxacin mean (SD)	5.36 (1.59)	2.60 (1.31)	1.52, 3.99	0.000 (t = 4.632[b])
Polymixin E (median, IQR)	1.08 (0.56–2.04)	1.08 (0.56–1.69)	–	0.862 (Z = −0.173[a])
Cefuroxime mean (SD)	33.96 (5.66)	40.02 (12.62)	−14.55, 2.44	0.150 (t = −1.517[b])
3rd Generation Cephalosporins mean (SD)	77.76 (11.41)	63.93 (7.84)	5.54, 22.712	0.002 (t = 3.459[b])
Ceftriaxone mean (SD)	40.78 (9.98)	37.40 (5.02)	−3.45, 10.21	0.310 (t = 1.048[b])
Ceftazidimemean (SD)	19.48 (8.13)	15.58 (3.44)	−1.54, 9.34	0.147 (t = 1.530[b])
Cefoperazone mean (SD)	14.27 (2.74)	9.11 (3.54)	2.48, 7.84	0.001 (t = 3.997[b])
Cefotaxime mean (SD)	1.75 (1.28)	1.32 (0.68)	−0.44, 1.30	0.317 (t = 1.024[b])
Cefoperazone-Sulbactam (median, IQR)	1.27 (0.64–1.59)	0.23 (0.07–0.93)	–	0.007 (Z = −2.714[a])
Carbapenems mean (SD)	27.37 (7.68)	23.49 (4.31)	−1.39, 9.16	0.141 (t = 1.526[b])
Imipenem-Cilastatin mean (SD)	2.24 (1.67)	1.66 (1.04)	−0.60, 1.76	0.321 (t = 1.016[b])
Meropenem (median, IQR)	17.58 (15.57–22.71)	14.48 (12.90–18.43)	–	0.028 (Z = −2.194[a])
Ertapenem mean (SD)	5.13 (2.35)	6.49 (2.84)	−3.57, 0.85	0.216 (t = −1.273[b])

Notes: [a]Mann-Whitney U test; [b]Independent *t*-test.

The decline in total antibiotic usage in 2019 was accompanied by a cost saving of RM110,538.98 (Table 2) as a result of significantly lower antibiotic expenditure particularly for ciprofloxacin, third generation cephalosporins (ceftriaxone, cefoperazone, cefoperazone-sulbactam) and meropenem. During the enhanced AMS period, cefepime, vancomycin and polymixin E also reduced consumption costs by 21.0%, 14.6% and 11.9%, respectively. Nevertheless, the increased costs of piperacillin-tazobactam and ertapenem were in line with usage increment.

Table 2: Comparisons of antimicrobial expenditure between 2018 (before) and 2019 (during enhanced AMS programme).

	2018	**2019**	**95% CI**	***p*-value**
Total cost (RM)	960,844.71	850,305.73	–	–
mean (SD)	80,070.39 (11,730.68)	70,858.81 (3,946.97)	1,519.48, 16,903.69	0.022 (t = 2.578[b])
Cefepime (median, IQR)	2,597.80 (1,528.30–5,664.88)	2,051.01 (1,576.49–2,996.90)	–	0.453 (Z = −0.751[a])
Piperacillin-tazobactam (median, IQR)	9,328.83 (305.97–10,674.77)	9,927.75 (8,739.68–11,176.04)	–	0.326 (Z = −0.982[a])
Vancomycin mean (SD)	2,545.77 (854.99)	2,172.91 (575.56)	−244.18, 989.90	0.223 (t = 1.253[b])
Ciprofloxacin mean (SD)	1,815.98 (567.10)	787.50 (388.73)	616.86, 1440.09	0.000 (t = 5.182[b])
Polymixin E (median, IQR)	4,523.48 (2,313.94–8,768.59)	3,984.14 (2,322.63–6,506.85)	–	0.564 (Z = −0.577[a])
Cefuroxime mean (SD)	11,215.72 (2,246.19)	12,923.49 (3,770.59)	−3,370.30, 1,954.74	0.583 (t = −0.559[b])
3rd generation Cephalosporins mean (SD)	26,421.64 (4,720.35)	19,171.79 (2,627.16)	4,015.66, 10,484.04	0.000 (t = 4.649[b])
Ceftriaxone mean (SD)	11,296.45 (2,794.20)	9,397.34 (1,464.75)	10.39, 3,787.84	0.049 (t = 2.085[b])
Ceftazidime (median, IQR)	7,716.13 (5,756.53–9,755.29)	6,109.00 (5,858.26–6,977.59)	–	0.057 (Z = −1.905[a])
Cefoperazone mean (SD)	4,094.15 (788.20)	2,383.41 (979.65)	957.98, 2,463.49	0.000 (t = 4.713[b])
Cefotaxime (median, IQR)	620.22 (334.57–1,166.67)	643.72 (289.98–743.24)	–	0.453 (Z = −0.751[a])
Cefoperazone-Sulbactam (median, IQR)	2015.50 (975.13–2,443.25)	304.50 (97.88–1,261.50)	–	0.004 (Z = −2.888[a])

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Table 2: (*continued*)

	2018	2019	95% CI	*p*-value
Carbapenems mean (SD)	21,220.46 (5,644.48)	18,329.63 (3,724.68)	−1,157.79, 6,939.47	0.153 (t = 1.481[b])
Imipenem-Cilastatin mean (SD)	1,176.77 (804.58)	816.31 (514.91)	−211.42, 932.34	0.205 (t = 1.307[b])
Meropenem (median, IQR)	10,703.48 (9,699.79–14,119.88)	8,335.28 (7,425.83–9,538.09)	–	0.001 (Z = −3.175[a])
Ertapenem mean (SD)	7,862.33 (3,683.57)	8,940.54 (3,696.53)	−4,202.42, 2,045.00	0.482 (t = −0.716[b])

Notes: [a]Mann-Whitney U test; [b]Independent *t*-test

A total of 403 cases were reviewed by the AMS team with a sum of 447 interventions during the two-year study period (Table 3). Forty-five cases with antimicrobial issues were identified in 2018. However, total cases were increased to 358 in 2019 with the involvement of infectious-disease (ID) physician, greater frequency of AMS rounds (37 versus 12) and ward pharmacist-initiated AMS intervention (262 pharmacist rounds which reviewed 264 cases).

In view of changes in the AMS Review Form format from July 2019 onwards to capture more types of interventions and the accompanying recommendations in greater detail, information obtained from 2018 to June 2019 is discussed separately in Table 3. Common types of interventions from 1st January 2018 until June 2019 were inappropriate choice of antibiotic (n = 45; 33.1%), followed by others which comprised issues with dose/frequency, therapeutic drug monitoring, and obtaining culture and sensitivity (n = 31; 22.8%); therapy de-escalation (n = 23; 16.9%), improper duration of therapy (n = 18; 13.2%) and inappropriate combination therapy (n = 15; 11.0%). Only four interventions were related to clarification of microbiology results (2.9%).

A total of 311 AMS interventions were identified after June 2019 from 291 cases reviewed. Among the reasons for intervention were usage of too broad spectrum antibiotic (n = 90; 28.9%), inappropriate dose/frequency/duration (n = 75; 24.1%), inappropriate choice (n = 69; 22.2%), other reasons (infection control measures, further lab and culture investigation, and source control) (n = 28; 9.0%), indication does not require antibiotic (n = 24; 7.7%) and intravenous (IV) to oral conversion (n = 17; 5.5%). A small percentage of cases were related with overlapping antibiotic spectrum (n = 6; 1.9%) or narrow spectrum of activity (n = 2; 0.6%).

Table 4 compares the acceptance rates of AMS recommendations before and during enhanced AMS programme. In 2018, 30 out of 45 cases intervened by the AMS team had their suggestions accepted by the primary team, which corresponded to 67%. This was further increased to 78% in 2019 when AMS recommendations were acknowledged in 279 out of 358 cases reviewed. However, the increment was not statistically significant. Acceptance rates recorded between July and December 2019 showed that prescribers were more receptive to ward pharmacists' recommendations (84.7%) as compared to 65.2% attained during AMS rounds with ID physician.

Table 3: Summaries of AMS interventions in 2018 (before) and 2019 (during enhanced AMS programme).

	2018	**2019**
AMS cases	45	358[c]
AMS + ID physician ward rounds	12	37
Cases reviewed	45	94
AMS pharmacists rounds	0	262
Cases reviewed	0	264
Types of interventions (*n*, %) [a]	55	81
Choice of antibiotic	14 (25.5%)	31 (38.3%)
Duration of therapy	9 (16.4%)	9 (11.1%)
Combination therapy	11 (20.0%)	4 (4.9%)
De-escalation therapy	10 (18.2%)	13 (16.0%)
Microbiology results	2 (3.6%)	2 (2.5%)
Others (e.g. dose/frequency, TDM monitoring, culture and sensitivity)	9 (16.4%)	22 (27.2%)
Reason for intervention (*n*, %) [b]		311
Indication does not require antibiotic	–	24 (7.7%)
Inappropriate choice	–	69 (22.2%)
Inappropriate dose/frequency/duration	–	75 (24.1%)
Antibiotic spectrum too broad	–	90 (28.9%)
Antibiotic spectrum too narrow	–	2 (0.6%)
Antibiotic spectrum overlapping	–	6 (1.9%)
Fulfill IV to oral switch criteria	–	17 (5.5%)
Others	–	28 (9.0%)
AMS recommendation (*n*, %) [b]		325
Continue same regime	–	10 (3.1%)
Deescalate	–	83 (25.5%)
Escalate	–	8 (2.5%)
Switch to a new regime	–	46 (14.2%)
Stop current antibiotic	–	70 (21.5%)
Optimise dosage of antibiotic	–	50 (15.4%)
IV to oral switch	–	17 (5.2%)
Others (e.g. Infection control measures, further lab and culture investigation, remove line/catheter/drain collection)	–	41 (12.6%)

Notes: [a] For cases reviewed in 2018 and from January till June 2019 using previous version of AMS review form; [b] For cases reviewed from July till December 2019 using new version of AMS review form; [c] 67 and 291 cases were reviewed in January to June 2019, and July to December 2019, respectively.

Increased total antibiotic cost by RM128.62 following AMS recommendation acceptance was observed in 2019 (Table 4). On the contrary, a cost saving of RM1,290.96 was reported in 2018, thus bringing a nett cost saving of RM1,162.34 in the last 2 years. No statistically significant difference in terms of median cost saving was reported between 2018 and 2019.

Table 4: Comparisons of acceptance rate and cost-saving between 2018 (before) and 2019 (during enhanced AMS programme).

	2018	**2019**	**χ^2 statistics[a] (df)**	***p*-value**
Acceptance rate (%)	67	78	3.03 (1)	0.081
Total cases with intervention acceptance/total cases reviewed	30/45	279/358	–	–
Total cost saved with recommendation acceptance (RM)	1,290.96	−128.62	–	–
Median, IQR	105.94 (21.47−171.61)	−451.26 (−1453.64−1202.78)	–	0.326 (Z = −0.981[b])

Notes: [a] Chi-square test; [b] Mann-Whitney U test

Table 5: Most common redundant antibiotic combinations, defined as those in which the antimicrobial spectrum of one drug is largely or wholly subsumed within that of the other, in 2018 and 2019.

Antibiotic combination	**No. of redundant regimen prescribed, *n* = 19 (%)**
β-lactam/β-lactamase inhibitor + metronidazole	3 (15.8)
Carbapenem + metronidazole	3 (15.8)
Carbapenem + 1st generation cephalosporin	2 (10.5)
Carbapenem + anti-staphylococcal penicillin	1 (5.3)
β-lactam/β-lactamase inhibitor + aminopenicillin	1 (5.3)
β-lactam/β-lactamase inhibitor + anti-staphylococcal penicillin	4 (21.1)
Anti-staphylococcal penicillin + 1st generation cephalosporin/ 4th generation cephalosporin	2 (10.5)
β-lactam/β-lactamase inhibitor + vancomycin	1 (5.3)
Fluoroquinolone + carbapenem	1 (5.3)
Fluoroquinolone + 3rd generation cephalosporin	1 (5.3)

Table 5 showed various antibiotic combinations with overlapping spectrum of activities prescribed in 2018 and 2019. The AMS team intervened four cases (21.1%) prescribed with β-lactam/β-lactamase inhibitor plus anti-staphylococcal penicillin, three cases (15.8%) each for β-lactam/β-lactamase inhibitor + metronidazole and carbapenem + metronidazole; two cases (10.5%) each for carbapenem + first generation of cephalosporin and anti-staphylococcal penicillin + first generation of cephalosporin/ fourth generation of cephalosporin; while the remaining (1 each, 5.3%) were combinations involving carbapenem + anti-staphylococcal penicillin, β-lactam/β-lactamase inhibitor + aminopenicillin, β-lactam/β-lactamase inhibitor + vancomycin, fluoroquinolone + carbapenem, and fluoroquinolone + third generation of cephalosporin.

DISCUSSION

On the whole, several positive impacts were observed with our enhanced AMS programme. First, the improvement in third generation cephalosporins prescribing pattern and usage cost. Findings from a cefoperazone prospective audit and feedback conducted in 2019 have influenced switch of cefoperazone to cefuroxime injection as surgical prophylaxis in the Obstetrics & Gynaecology (O&G) department and substitution of cefoperazone with cefuroxime in medical wards imprest stock. As a result, cefuroxime was the only antibiotic among the cephalosporin group which showed an increment in 2019. Evidence has proven that excessive prescribing of cephalosporins, particularly third generation, can induce and select for extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (Sanders and Sanders 1988; Superti, Augusti and Zavascki 2009; Skrlin *et al.* 2011). Improvement in prescribing practice may have decreased the rate of ESBL in 2019 to 19.8% from 21.2% the year before.

Secondly, the reduction in group 2 carbapenems (meropenem and imipenem-cilastatin) usage was accompanied by an increase in ertapenem (group 1 carbapenem) in 2019 compared to 2018. This can be explained by the preferential use of ertapenem over group 2 carbapenems in ESBL-producing microorganism, which does not result in decreased *Pseudomonas* susceptibility to antipseudomonal carbapenems (Falagas *et al.* 2013; Zequinão *et al.* 2020). The strategy to use piperacillin-tazobactam in the treatment of ESBL infection in non-sterile sites e.g. urinary source, further reduced overall carbapenem usage and antibiotic expenditure. This approach to treat urinary tract infection was supported by limited data in two observational studies which reported no differences in mortality, resolution of clinical symptoms and microbiological eradication failure (Yoon *et al.* 2017; Sharara *et al.* 2020). However, care should be taken as overexposure to piperacillin-tazobactam was associated with high rates of piperacillin-tazobactam-resistant *Pseudomonas aeruginosa* (Allegranzi *et al.* 2002; Harris *et al.* 2002). Furthermore, the MERINO trial results do not support the use of piperacillin-tazobactam as a carbapenem-sparing treatment option for ESBL-producing Enterobacteriaceae bloodstream infections due to greater 30-day mortality (12.3% versus 3.7% for meropenem), hence pharmacists should encourage the use of a carbapenem in such cases (Harris *et al.* 2018).

Thirdly, the implementation of ciprofloxacin restriction and pre-authorisation, and retrospective audit and feedback in 2018 significantly decreased overall prescribing and usage cost in 2019. Additionally, the AMS team tend to recommend the use of piperacillin-tazobactam over ciprofloxacin in *Pseudomonas* infections as the latter will increase risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in a colonised patient (Weber *et al.* 2003; Knight *et al.* 2012). Isolated MRSA strains were lower in 2019 (15.7% versus 16.3%) corresponding with a slight decrease in vancomycin prescribing.

On the other hand, administration of piperacillin-tazobactam as a carbapenem-sparing agent, and as empirical or definitive treatment for *Pseudomonas* infections, caused significant increment in usage.

Our AMS programme is generally acknowledged by various clinical departments based on the acceptance rates, though it was considered modest compare with another published Malaysian study which achieved 83.3% during their first year of AMS implementation (Sing *et al.* 2016). In general, quasi-experimental, retrospective and non-controlled randomised studies in different patient populations and settings of care found figures within the range of 54%–93% (Liew *et al.* 2012; Nowak *et al.* 2012; Teo *et al.* 2012; Tsukamoto *et al.* 2014; Lew *et al.* 2015; Güerri-Fernández *et al.* 2016; Sing *et al.* 2016; El-Lababidi *et al.* 2017; Singh *et al.* 2019). Acceptance rates were also modest in Singaporean tertiary hospitals, ranging from 68%–77.8% after establishment of AMS in 2008 and 2009 (Liew *et al.* 2012; Teo *et al.* 2012; Lew *et al.* 2015). Although in many studies the rates were collective values involving multiple specialist disciplines, an overwhelming figure exceeding 90% was attained in a surgical inpatient tertiary care setting in Spain, thus reflecting a general approval towards the AMS programme (Güerri-Fernández *et al.* 2016).

The presence of non-ID trained AMS pharmacists, especially in the medical wards, to review antibiotic use and provide recommendations to the prescriber will encourage AMS principles by enabling the interdisciplinary team, thus helping to improve the quality of antibiotic decision making when ID physicians are not present in wards. This approach leverages the in-depth knowledge pharmacists possess about their patients as well as the trust gained with the prescriber through ongoing daily interactions (Glowacki *et al.* 2003; Langford *et al.* 2019). Thus, this may explain the high acceptance rate attained during pharmacist-initiated AMS rounds. In a study evaluating the impact of ward-based pharmacists in antibiotic stewardship of patients with community-acquired pneumonia, no differences were found in terms of acceptance rates, length of hospitalisation and mean reduction in total days of antibiotic therapy when compared with ID-trained pharmacist and physician (DiDiodato and McAthur 2017).

A systematic review found that AMS interventions did promote sustained effects on judicious antimicrobial use without compromising patients' clinical outcomes through combination of enabling and restrictive interventions. These were associated with increased compliance to policies or guidelines, reduced length of hospitalisation, increased appropriate use of antibiotic and shortened duration of antibiotic treatment without increasing the risk of mortality in inpatients (Davey *et al.* 2017). Our multimodal approaches such as antibiotic audit and feedback, pharmacist-led AMS rounds, AMS multidisciplinary rounds with infectious diseases specialist, implementation of 72 h automatic stop order and formulation of clinical pathways on antibiotic selection for ESBL microorganism treatment have contributed to the success of an evolving AMS programme.

The tremendous increase in antimicrobial cases which required intervention in 2019 was a result of ID physician involvement, greater frequency of AMS multidisciplinary and pharmacist-led AMS rounds, in addition to increased case referrals for AMS input, a sign of clinicians' confidence in AMS recommendations. Our rounds served as a platform to provide patient-specific educational session through proper advice on dosing, frequency of administration, choice of antibiotic and even duration of treatment as reflected by the high number of such interventions during the period of study. Using a concept called 'handshake stewardship', Hurst *et al*. (2016) focused on in-person, rounds-based audit and feedback led by a pharmacist-physician team in a paediatric hospital. As a direct effect of collegial communication during rounds and the indirect effect of improved antibiotic prescribing due to the educational nature of rounds, an overall reduction in antibiotic

usage was observed (Hurst *et al.* 2016). This was also acknowledged by Langford and colleagues, with the added advantage of ID physician's presence and twice-weekly AMS multidisciplinary rounds compared to once weekly AMS pharmacist rounds, there was an improved uptake of AMS recommendations through direct peer-to-peer communication, thereby reducing antibiotic prescribing without compromising patient outcomes (Langford *et al.* 2019).

A high proportion of AMS cases involving broad spectrum antibiotic prescribing may be attributed to concern that inappropriate empiric antibiotic was associated with higher mortality and delay in escalation therapy may not attenuate the risk of death (Zilberberg *et al.* 2008; Andersson *et al.* 2019). Additionally, redundant antibiotic combinations with overlapping anaerobic (31.6%) and Gram-positive (57.9%) spectrum of coverage were observed in this study. Glowacki *et al*. (2003) reported that 56% of inappropriate combinations was due to unintentional (multiple antibiotic orders from numerous clinical disciplines, incomplete knowledge of antibiotic spectrum) or intentional prescribing errors by physicians (antibiotic combinations lacking proven clinical benefits prescribed with intended overlap) (Glowacki *et al.* 2003). Therefore, AMS rounds were ideal to educate clinicians regarding de-escalation and indications for combination therapy.

We observed that suggestion for intravenous conversion to oral antibiotic therapy was well accepted by the treating physician (93.8%). This may be attributed to increased awareness on the benefit of an early switch of IV to oral therapy in terms of reduction in length of hospitalisation and lower healthcare-associated cost (Fischer *et al.* 2003; Cyriac and James 2014; Gasparetto *et al.* 2019). On the other hand, several cases had no microbiological cultures during antibiotic initiation or no repeated cultures at the change of antimicrobial therapy or for exclusion of antimicrobial failure. The underutilisation of microbiological tests is alarming as treatment duration and streamlining of antibiotic are based on culture results, thus directly influencing appropriateness of antibiotic prescribing, selection pressure for antimicrobial resistance and, possibly, antimicrobial-related adverse events, all of which contributed to elevated healthcare costs (Glowacki *et al.* 2003; Perez *et al.* 2013). Possible explanations included prescribers' perception of inability to make full use of microbiological tests due to prolonged turnaround times (TATs) (Skodvin *et al.* 2015) or failure to adhere to guideline-directed management. This highlighted the need to reduce TATs and ensure rapid delivery of culture results at an earlier stage of treatment (Skodvin *et al.* 2019).

The cost savings following AMS recommendation acceptance between 2018 and 2019 were negligible despite the increase in acceptance rates among clinicians. To begin, this was attributed to preferential use of ertapenem in patients with ESBL-producing Enterobacteriaceae infections in 2019 over group 2 carbapenems (meropenem and imipenem-cilastatin) in our hospital. Ertapenem is costlier (average price per vial was 7 to 11 times more than meropenem and imipenem-cilastatin) but with less collateral damage due to its limited activity against *Pseudomonas aeruginosa* (Falagas *et al.* 2013; Zequinão *et al.* 2020) and allowed preservation of *Acinetobacter baumannii* susceptibility to carbapenems. Moreover, the AMS team recommended initiation of polymixin E in cases of multidrug-resistant (MDR) *Acinetobacter baumannii* and carbapenem-resistant Enterobacteriaceae (CRE) sepsis, thus leading to extra cost incurred. Finally, a substantial number of AMS interventions caused increased antibiotic treatment cost, e.g prescribing high dosage of ampicillin-sulbactam in MDR *Acinetobacter baumannii* infections and prolonging the duration of vancomycin in complicated MRSA infections.

Contrary to our expectations, the overall prescribing of antibiotic did not decrease significantly after implementation of enhanced AMS programme with the exception of total antibiotic cost, possibly due to the relative short duration of study. Besides, most of the strategies were implemented in the second half of 2019. Langford *et al*. (2019) reported that greater reduction in antibiotic usage was observed in the second year after implementation of high-intensity prospective audit and feedback, thus results obtained beyond one year may yield more accurate findings. The study was also limited by its retrospective design with presence of probable confounding factors contributing to changes in antibiotic use over time.

There was a possibility of Hawthorne effect implicating antimicrobial prescribing especially in medical wards and intensive care units with pharmacists, whereby prescribers' awareness of being monitored could have led to a change in behaviour (Sikkens *et al.* 2017). However, we have attempted to minimise this influence through regular antibiotic audits and monthly surveillance of antibiotic usage, and subsequently provided feedback to prescribers from all clinical disciplines.

According to Davey *et al.* (2017), further studies evaluating AMS interventions are unlikely to alter the conclusion that AMS interventions are effective, hence additional work to evaluate and compare different AMS interventions to one other will be attempted in upcoming evaluation studies in our hospital. We may endeavour to integrate assessment of clinical outcomes such as mortality, *Clostridium difficile* infections and length of hospitalisation into future studies by employing quasi-experimental approaches such as interrupted time-series (ITS) as the ideal study design.

CONCLUSION

In conclusion, the enhanced AMS programme had enlisted a multidimensional approach to encourage prudent use of antibiotics resulting in decreased overall prescribing and drug costs, with improved recommendation acceptance rates due to increased recognition of AMS team and presence of non-ID trained AMS cum ward pharmacists in delivering AMS interventions and recommendations.

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