Post-Prescription Review and Feedback: A Major Specialist Hospital Experience

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Abstract

Introduction: One of the key Antimicrobial stewardship (AMS) interventions is post-prescription review and feedback (PPRF), which allows clinicians to initiate empirical antibiotic regimens based on clinical judgment while facilitating the AMS team review to guide therapy adjustments.

Objective: This study aimed to describe the implementation of an intensified PPRF in a major specialist hospital and compare the antibiotic consumption before and after the intervention.

Methods: An observational study was conducted at a major specialist hospital in Sabah, Malaysia, from July to December 2019. Data on patient demographic information, the type and indication of antibiotics prescribed, and the interventions made by the AMS team were collected. Data on the antibiotic consumption was extracted from the hospital's in-house electronic database. Antibiotic usage data from the pre-intervention period (July to December 2018) was compared with the post-intervention period (July to December 2019), during which an intensified PPRF approach was applied.

Results: A total of 538 patients who received antibiotics were included in the study, and 847 PPRF reviews were conducted during the six-month post-intervention period. On average, the AMS team performed reviews on an average of 2.5 ± 2.3 days after the primary team initiated antibiotic therapy. The overall antibiotic consumption decreased significantly by 56.31% (316.23 to 138.15 DDD/1,000 patient days) after the intervention ($p<0.001$).

Conclusion: The intensified PPRF strategy, supported by a dedicated AMS team and alongside other AMS strategies, may help to reduce antibiotic usage. Further studies are warranted to explore the effects of PPRF on patient outcomes and antimicrobial resistance patterns.

Keywords: Antimicrobial stewardship, prescription review, hospital, antibiotic, feedback

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Introduction

In recent years, antimicrobial resistance (AMR) has emerged as a significant global health concern, posing threats to individual health and imposing escalating costs on healthcare systems worldwide (1–4). Effective and urgent measures to control AMR are crucial to mitigating this growing crisis. In Malaysia, rising resistance rates against pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), carbapenem-resistant Acinetobacter baumannii (CRAB), and extended-spectrum beta-lactamase (ESBL)-producing Klebsiella pneumoniae have been reported (5). Overutilisation of antimicrobials is a major driver of AMR, contributing to the increasing prevalence of resistant organisms (6–8).

Antimicrobial Stewardship Programme (AMS) was introduced to promote prudent antimicrobial use in healthcare settings. The programme had demonstrated positive impacts on lowering antibiotic utilisation, improving patient outcomes, and reducing adverse effects such as *Clostridium difficile* infections and subsequently reducing the development of antibiotic resistance (10–13). The second edition of the "Protocol on AMS Programme in Healthcare Facilities," published by the Ministry of Health Malaysia's Pharmaceutical Services Program in 2022, listed prospective audit and feedback (PAF) as one of the core strategies for the implementation of AMS in hospitals, alongside other strategies such as antimicrobial consumption

surveillance and feedback mechanism, formulary restriction, pre-authorisation, antimicrobial order tools, de-escalation, and antimicrobial rounds by AMS team (14). The 2016 guidelines by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommended PAF as one of the key AMS strategies (15). Post-prescription review and feedback (PPRF) is a type of PAF that allows clinicians to initiate empirical antibiotic regimens based on clinical judgment while enabling the AMS team to review and provide recommendations for continuing, adjusting, or discontinuing therapy based on patient-specific factors (16). During patient reviews, the AMS team also communicate with the primary team on the antibiotic appropriateness, with the goal of improving future antibiotic utilisation.

In 2018, the National Surveillance on Antibiotic Utilisation (NSAU) identified Hospital Queen Elizabeth II (HQE II) as one of the top three users of broad-spectrum antibiotics, including cephalosporins, carbapenems, and piperacillin-tazobactam, among major specialist hospitals in Malaysia (9). This concerning findings spurred efforts to intensify the strategies aimed at reducing antimicrobial consumption. At HQE II, the AMS programme was established in 2017 with weekly AMS rounds held on Thursdays, focusing on patients receiving broad-spectrum antibiotics such as carbapenems, piperacillin-tazobactam, ceftazidime, cefepime, vancomycin, and polymyxin E, and providing feedback to guide the continuation, modification, or discontinuation of antibiotic therapy based on patient-specific factors and evolving clinical data. The AMS team comprises an infectious disease specialist, rotational doctors from the general medical and microbiology departments, and two clinical pharmacists. Despite these efforts, HQE II continued to report high antibiotic usage, particularly for cefuroxime and ceftriaxone, which surpassed the national upper limit. Both cefuroxime and ceftriaxone were not initially included in the PPRF reviews. Although cefuroxime and ceftriaxone are classified as narrow-spectrum antibiotics, their overuse is associated with the induction of ESBL production, and this is a serious concern in the context of AMR (17). To address this, a more intensified PPRF strategy was introduced in the year of 2019, increasing the frequency of AMS rounds to twice weekly and expanding the PPRF review to include cefuroxime and ceftriaxone.

The efficacy of PAF and PPRF strategies has been extensively documented in the literature (16, 18, 19) but most studies were conducted in the Western countries. There was limited data on the impact of these AMS strategies on antibiotic consumption and AMR in the local setting. Therefore, this study aimed to describe the implementation of PPRF at HQE II and to compare the antibiotic usage during the pre-intervention period (July to December 2018) with the post-intervention period (July to December 2019). The findings from this study were intended to highlight the potential impact of PPRF and encourage more policies that help to optimise antibiotic use and combat antibiotic resistance.

Method

This observational study was conducted at Hospital Queen Elizabeth II (HQE II), Sabah, Malaysia, from July 2019 to December 2019. HQE II is a major specialist hospital with 300 beds and seven clinical departments. This study was registered with the National Medical Research Registry (NMRR-20-676-54434) and received approval from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia.

All patients prescribed with the targeted antibiotics reviewed by the AMS team during July 2019 to December 2019 were included in the study. Exclusion criteria for the study included patients under 18 years of age, those receiving care in the emergency department during the review day, and patients receiving antibiotics not listed in the study or administered via non-parenteral routes. A standardised data collection form was used to extract relevant information, including patient demographics, the type and indication of antibiotic use, and the interventions recommended by the AMS team. In this study, the in-house electronic database (Pharmacy Information System, PhIS) was used to identify patients who received broad spectrum antibiotics as well as to retrieve data on antibiotic consumption. Information on patient demographics, antibiotic indication and AMS intervention were captured from the AMS registry (in the form of google sheet). Antibiotic consumption data were collected for both the post-intervention period (the study period) and the pre-intervention period in 2018 (July to December 2018).

Post-prescription Review and Feedback (PPRF) Workflow and Intervention

The PPRF process was outlined in Figure 1. The study included all adult patients admitted to the wards (medical, surgical, orthopaedic and intensive care) who were prescribed with the targeted intravenous antibiotics by the primary treatment team. The AMS pharmacist identified eligible patients using the hospital's in-house electronic database on the day before every AMS round. The targeted intravenous

antibiotics included second-generation cephalosporins and above (cefuroxime, ceftriaxone, ceftazidime, cefotaxime, cefoperazone-sulbactam, cefepime, ceftaroline), fluoroquinolones (ciprofloxacin), carbapenems (meropenem, imipenem, ertapenem), glycopeptides (vancomycin), oxazolidinones (linezolid), broad-spectrum beta-lactam/beta-lactamase inhibitors (piperacillin-tazobactam), and polymyxin-based antibiotics (colistin).

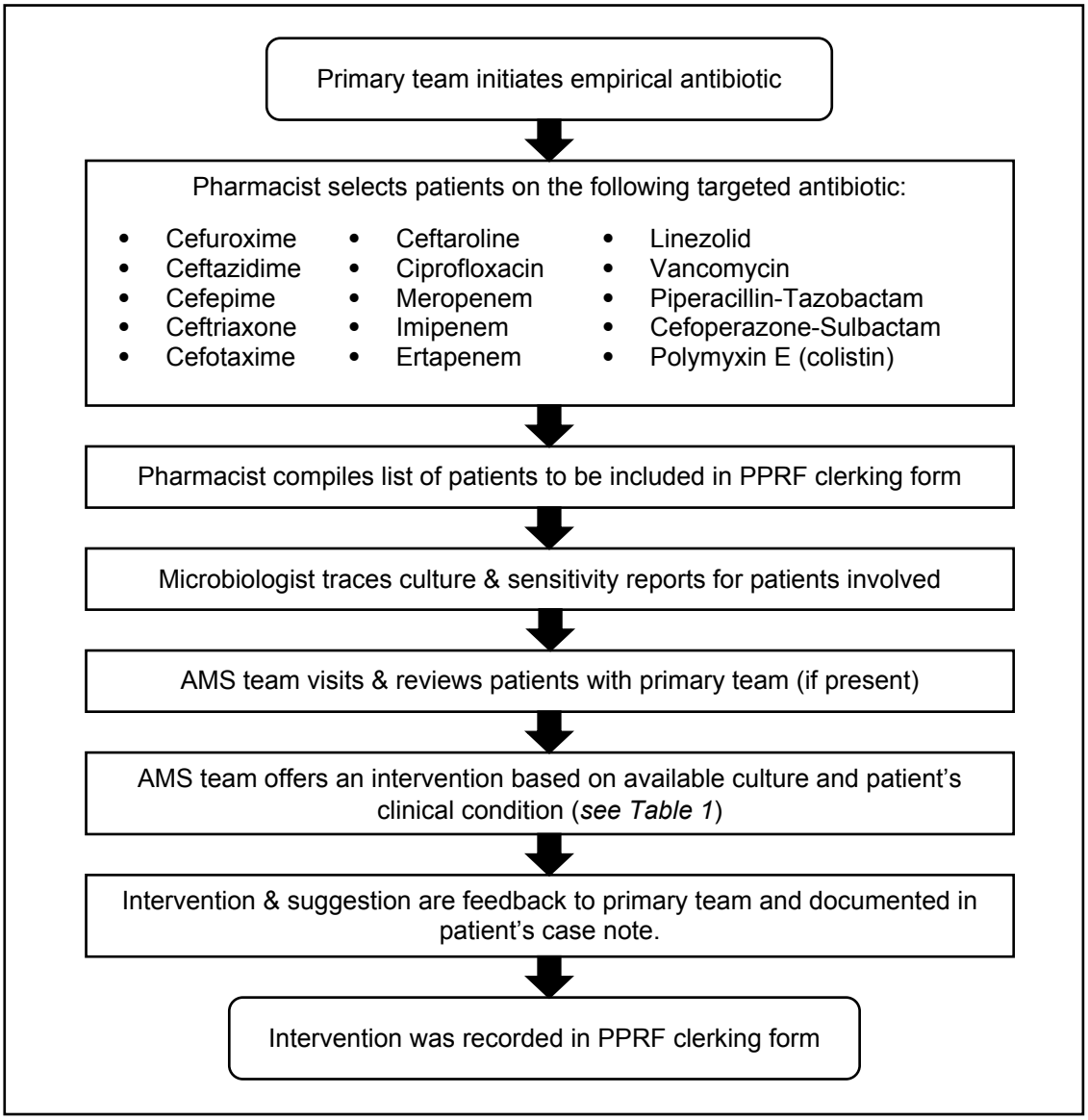

Figure 1: Post-prescription Review and Feedback (PPRF) workflow

During PPRF, the AMS team reviews the prescriptions, and provides feedback to guide the continuation, modification, or discontinuation of antibiotic therapy based on patient-specific factors and evolving clinical data. During the AMS rounds, the AMS team visits the identified patients, and reviews the prescriptions, microbiological culture results and patients' clinical condition. The AMS team may discuss among themselves to determine the appropriate interventions. Whenever possible, the discussions were conducted with the primary team responsible for the patients. . Feedback to guide the continuation, modification, or discontinuation of antibiotic therapy was communicated directly to the primary team and documented in the patients' case notes. The PPRF interventions were further defined in Table 1.

Table 1: Definition of interventions provided by the AMS team during PPRF

Intervention	Definition
Continue Empirically	To continue the current antibiotic regime as prescribed by the primary team while awaiting results for microbiological culture. The current antibiotic regime may change depending on the results of microbiological culture or clinical condition.
Continue Definitively	To continue the current antibiotic regime as prescribed by the primary team when it is definitively indicated. A planned duration may also be suggested by the AMS team.
De-escalate	The current antibiotic regime is changed from a broad-spectrum antibiotic to a narrower spectrum antibiotic or an antibiotic that induces less resistance.
IV to PO	An intravenous antibiotic is changed to an oral antibiotic of acceptable bioavailability.
Stop	The current antibiotic regime is stopped by the AMS team.
Escalate	The current antibiotic regime is changed to a broader spectrum antibiotic due to patient's deteriorating clinical condition or lack of response to current regimen.

Antibiotic Consumption

In this study, antibiotic consumption before and after the implementation of intensified PPRF intervention were compared. The total amount of intravenous antibiotics prescribed, measured in grams, was converted into defined daily doses (DDD) using the 2019 Anatomical Therapeutic Chemical Classification and Defined Daily Dose (ATC/DDD) index by the World Health Organization (WHO) (20). The DDD represents the assumed average daily maintenance dose of a drug when used for its main indication in adults. Antibiotic consumption, expressed as DDD per 1,000 patient days, during the pre-intervention period (July to December 2018) was compared to the post-intervention period (July to December 2019). 1,000The formula for DDD per 1,000 patient days was as below:

$$\frac{\text{Total antibiotic usage (grams) for adult per study period}}{\text{DDD (from WHO)}} = \text{Number of DDD per study period}$$

For 1,000 patient days:

$$\frac{\text{Number of DDD per study period}}{\text{Total number of patient days}} \times 1{,}000 = \text{Number of DDD per 1,000 patient days}$$

Statistical Analysis

The data was analysed using IBM SPSS Statistics version 22. Descriptive statistics were employed. Categorical variables were presented as numbers (n) and percentages (%), while continuous variables were expressed as means with standard deviations (SD) or medians with interquartile range (IQR), depending on the normality of the data. Independent t-test was used to compare the antibiotic consumption between the pre- and post-intervention periods. Statistical significance was set at $p < 0.05$.

Results

A total of 538 patients receiving the targeted antibiotics during the post-intervention period were included in the study, with 61% being men and a median age of 57 years (range: 41–68 years). During the 6-month post intervention period from July to December 2019, a total of 847 PPRF reviews were conducted. The average time from antibiotic initiation by the primary team to the AMS team review was 2.5 days (SD 2.3 days).

The characteristics of the reviews conducted during the PPRF process were summarised in Table 2. The majority of reviews were carried out in medical-based wards (46.3%) and surgical-based wards (26.8%). Respiratory tract infections were the most reviewed diagnosis (28.7%), followed by bone and joint infections (12.4%) and chemoprophylaxis (10.4%). The most frequently reviewed class of antibiotics were third-generation cephalosporins (32.2%), with ceftazidime (16.5%) and ceftriaxone (15%) being the most common. Ceftazidime was primarily indicated for tropical infections (5%, n=42 reviews), specifically for the empirical and definitive treatment of melioidosis, which is prevalent in Sabah. Ceftriaxone, on the other hand, was the preferred antibiotic for central nervous system infections (4.1%, n=35 reviews).

Table 2: Characteristics of PPRF reviews (n=847)

Characteristics	n (%)
Wards visited during PPRF	
Medical	393 (46.3)
Surgical	224 (26.8)
Intensive Care	115 (13.5)
Orthopaedic	112 (13.2)
Five most common diagnoses encountered	
Respiratory tract infection	243 (28.7)
Bone and joint infection	105 (12.4)
Chemoprophylaxis	88 (10.4)
Tropical infection	71 (8.4)
Central nervous system infection	48 (5.7)
Five most reviewed antibiotic groups prompting PPRF	
3rd generation cephalosporin	**273 (32.2)**
Ceftazidime	140 (16.5)
Ceftriaxone	127 (15.0)
Cefotaxime	5 (0.6)
Cefoprazone-Sulbactam	1 (0.1)
Penicillin/beta-lactamase combination	**228 (26.9)**
Piperacillin-Tazobactam	228 (26.9)
2nd generation cephalosporin	**123 (14.5)**
Cefuroxime	123 (14.5)
Carbapenems	**119 (14.0)**
Meropenem	116 (13.7)
Imipenenem	3 (0.4)
Ertapenem	0 (0.0)
4th generation cephalasoporin	**64 (7.5)**
Cefepime	64 (7.5)

The interventions made during the PPRF reviews are detailed in Figure 2. Among the 847 reviews, antibiotic de-escalation occurred in 264 cases (31.2%), antibiotics were continued definitively in 184 cases (21.7%), and therapy was stopped in 126 cases (14.9%). Respiratory tract infections accounted for the highest number of de-escalations, with 52 reviews (6.1%) leading to this intervention. Piperacillin-tazobactam was the most frequently de-escalated antibiotic, with 75 reviews (8.9%), followed by cefuroxime with 74 reviews (8.7%), and ceftriaxone with 51 reviews (6%).

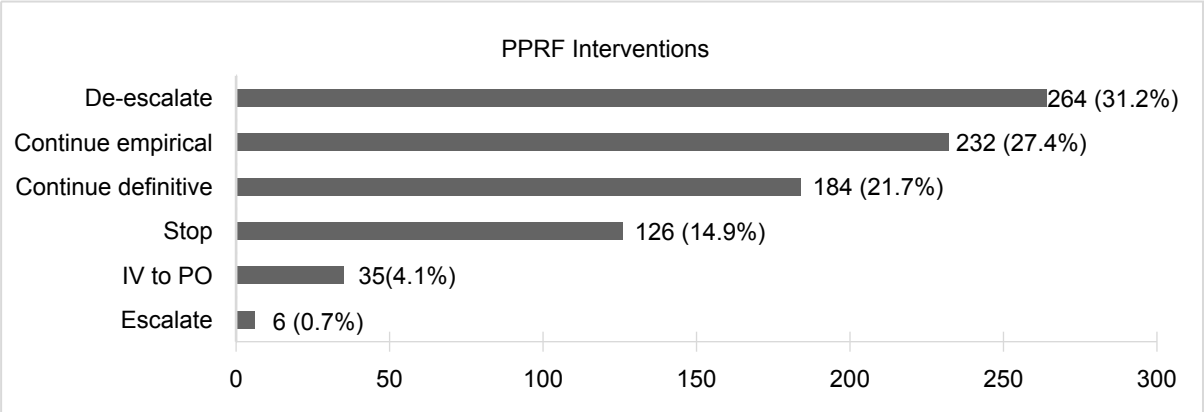

Figure 2: Interventions made by the AMS team during PPRF review

Antibiotics were continued either empirically or definitively in nearly half of the cases (49.1%). Among the third-generation cephalosporins, ceftazidime was the most frequently reviewed antibiotic, and it was also the most often continued (40 reviews, 4.7%) and stopped (39 reviews, 4.6%). Ceftazidime was

frequently continued empirically in respiratory infections (96 reviews, 11.3%) and definitively in tropical diseases, such as melioidosis (52 reviews, 6.1%).

Table 3 compares antibiotic utilisation before and after the implementation of the intensified PPRF intervention. The overall consumption of antibiotics, measured in DDD per 1,000 patient days, was significantly reduced by 56.3% (316.23 vs. 138.15 DDD per 1,000 patient days) during the post-intervention period from July to December 2019, compared to the pre-intervention period in July to December 2018 (p<0.001). Significant reductions were observed in the use of broad-spectrum antibiotics, including a 69.3% decrease in carbapenem consumption (p<0.001), a 44.8% reduction in piperacillin-tazobactam (p<0.001), and a 70.7% reduction in polymyxin E (p=0.009). Additionally, the utilisations of newly included cephalosporins in the intensified PPRF review, such as cefuroxime and ceftriaxone, were decreased by 77.4% (p=0.001) and 66.2% (p<0.001), respectively.

Table 3: Comparison of antibiotic utilisation during the pre- and post-implementation period of intensified PPRF, in DDD per 1,000 patient days

Antibiotic	Pre-PPRF [a]	Post-PPRF [a]	% change	p value [b]
2nd generation Cephalosporin				
Cefuroxime	88.57	20.06	-77.35	0.001
3rd generation Cephalosporin	118.84	66.47	-43.84	0.007
Ceftriaxone	77.26	26.12	-66.19	<0.001
Cefotaxime	0.74	0.92	24.32	0.65
Ceftazidime	40.59	39.27	-3.25	0.91
Cefoperazone-Sulbactam	0.26	0.11	-57.69	0.32
4th generation Cephalosporin				
Cefepime	14.16	9.31	-34.25	0.12
Carbapenems	31.67	9.72	-69.30	<0.001
Imipenem-Cilastin	1.27	0.15	-88.19	0.005
Meropenem	29.05	9.26	-68.12	<0.001
Ertapenem	1.37	0.31	-77.37	0.30
Anti-MRSA	7.75	3.97	-48.77	0.22
Vancomycin	6.6	3.62	-45.16	0.28
Linezolid	1.15	0.36	-68.70	0.18
Penicillin/Beta-lactam combination				
Piperacillin-Tazobactam	51.16	28.24	-44.80	<0.001
Others				
Polymyxin E (Colistin)	1.16	0.34	-70.69	0.009
Ciprofloxacin	2.89	0.08	-97.23	0.020
Total	316.23	138.15	-56.31	<0.001

[a] Pre-PPRF: July to December 2018; Post-PPRF: July to December 2019.
[b] Independent t-test
Abbreviation: DDD = Defined Daily Doses, PPRF = Post -Prescription Review and Feedback

Discussion

Our paper described the implementation of an intensified PPRF in a Malaysian specialist hospital and compare the antibiotic consumption before and after the intervention. PPRF has been shown to be an effective AMS strategy for reducing antibiotic consumption in many studies. In a 5-year descriptive study by Jover-Sáenz et al., conducted in a tertiary hospital, the implementation of an AMS program was associated with a 5.7% reduction in overall antibacterial consumption (21). Similarly, a systematic review by Kaki et al. reported that AMS interventions in critical care settings reduced antibiotic use by 11% to 38% in DDD per 1,000 patient-days (13). Our study demonstrated that by increasing the intensity of PPRF interventions, involving changing the once-weekly to twice-weekly reviews by a specialised AMS team, was associated

with a reduction in antibiotic consumption. This higher reduction may be attributable to the inclusion of antibiotic usage data from all general wards, not limited to intensive care units. Additionally, the high rate of antibiotic de-escalation recommended during PPRF rounds might have contributed to these findings.

A study conducted in Japan, using a similar PPRF intervention with a comparable AMS team composition but at a once-weekly frequency, also reported a reduction in antibiotic consumption (19). However, their PPRF focused solely on carbapenems and piperacillin-tazobactam, leading to an increased use of cefepime. In contrast, our study targeted a broader range of broad-spectrum antibiotics and involved twice-weekly reviews, resulting in reductions across various antibiotic classes, including carbapenems, piperacillin-tazobactam, cefepime, and polymyxin E (colistin). A high-intensity PAF strategy, like ours, was implemented in Canada with twice-weekly interdisciplinary rounds reviewing all internal medicine patients receiving any antimicrobial agent. This approach led to a 41.6% reduction in the overall antibiotic usage (22). These findings suggested that shifting from a lower-intensity strategy, which targets fewer antibiotics and is conducted less frequently, to a more frequent and comprehensive approach may result in a greater overall reduction in antibiotic consumption.

National data from 2008-2017 indicated that cephalosporins represented the highest-utilised class of antibiotics in Malaysia (5). Evidence suggested that cephalosporins contribute to the development of multidrug-resistant organisms, including extended-spectrum beta-lactamase (ESBL)-producing bacteria, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia (23)*. In our setting, cephalosporins comprised more than half of the antibiotics covered in the PPRF, with third-generation cephalosporins, specifically ceftazidime and ceftriaxone, being the most frequently reviewed antibiotics. We observed a notable reduction in the consumption of cefuroxime and ceftriaxone. A likely explanation for this reduction is the AMS team's active engagement with the primary team, who were mainly orthopaedic and general surgery departments, on the substitution of cefuroxime, which is commonly used for chemoprophylaxis with penicillin-based antibiotics or cefazolin. Similarly, ceftriaxone, often prescribed empirically for respiratory infections, was also switched to amoxicillin/clavulanate as the preferred option. This shift aligns with recommendations from the National Antimicrobial Guidelines 2019 (24) and is further reinforced by our local AMS policy. Supporting these findings, a study by Lester et al. in an urban hospital in Malawi demonstrated that an antimicrobial stewardship approach reduced third-generation cephalosporin prescriptions from 80.1% to 53.6% (25). Additionally, a Malaysian study showed that the appropriate use of third-generation cephalosporins increased significantly, from 77.1% to 95.8%, following AMS intervention (26). These findings highlighted the importance of targeted stewardship efforts in reducing the unnecessary use of cephalosporins, ultimately minimising antibiotic resistance pressure.

Choe and colleagues reported a 14.6% reduction in overall vancomycin use (37.6 DDD per 1,000 patient days vs. 32.1 DDD per 1,000 patient days) following intervention by the AMS team (27). In contrast, our study did not demonstrate a significant reduction in the use of anti-methicillin resistant staphylococcus aureus (MRSA) agents, particularly vancomycin. This outcome may be attributed to the relatively low prevalence of MRSA in Sabah, with an incidence rate of 0.12 per 100 admissions at HQE II, which is below the national target of less than 0.3 per 100 admissions (28). Consequently, empirical MRSA coverage is not routinely implemented. In our context, the initiation of anti-MRSA therapy is typically reserved for cases with positive cultures, and treatment is continued based on definitive microbiological evidence.

Similarly, we did not observe a significant decrease in ceftazidime usage between the pre- and post-intervention periods (40.59 DDD per 1,000 patient days vs. 39.27 DDD per 1,000 patient days). The primary indication for ceftazidime in our setting is for the empirical and definitive treatment of melioidosis, a condition with an incidence rate of 2.57 per 100,000 populations in Sabah (29) and an associated mortality rate of 25.6%. Given the high mortality rate, local health authorities advocate for the early initiation of ceftazidime in patients with known risk factors, such as diabetes mellitus, chronic lung disease (including old pulmonary tuberculosis), chronic renal failure, chronic alcoholism, thalassemia, patients who are on long term immunosuppressants (such as steroids or chemotherapy) and those with occupational exposure such as farmers, when they presented with pneumonia or sepsis symptoms (30). Additionally, when used for definitive treatment, the recommended high dose of 2g every six hours administered over an extended duration of 2 to 8 weeks contributed to the sustained elevated use of ceftazidime.

Our study acknowledged several limitations. Firstly, as a single-centre observational study, the findings cannot be generalisable to other settings with distinct patient populations, epidemiological profiles, and antibiotic prescribing practices. However, it is important to note that AMS interventions, as quality improvement initiatives, must be tailored to specific contexts. Our study provided some insights on the

potential efficacy of PPRF within the framework of our own setting. Secondly, the study was limited to a six-month duration. A longer follow-up period may yield more robust data regarding the sustainability of the PPRF programme and its long-term impact on antibiotic consumption. Furthermore, while interventions such as de-escalation were primarily guided by microbiological results, delays in obtaining these results might have impeded the timely treatment modifications, leading to prolonged antibiotic use. In our setting, it was not uncommon that certain cases of negative culture necessitated the outsourcing of the samples to another larger facility for further identification, with the results typically returning after a few weeks.

Although a reduced antibiotic consumption was observed after the implementation of intensified PPRF and AMS rounds, causality cannot be established. The study did not explore the potential confounding factors, including patient characteristics and concurrent AMS interventions that may have resulted in more restrictive antibiotic prescribing measures. This included formulary restrictions and pre-authorisation protocols, which may have also contributed to the observed reduction in antibiotic use. A controlled interrupted time-series analysis conducted in a vascular ward in Portugal found that a persuasive strategy, which was similar to our PPRF rounds, when implemented alongside existing restrictive interventions, contributed to a decrease in carbapenem consumption (31). Additionally, simultaneous infection prevention and control strategies aimed at preventing outbreaks of multi-drug-resistant organisms may have influenced the outcome data (32).

Moreover, the study's outcomes were limited to antibiotic consumption without assessing key patient-centred outcomes, such as clinical improvement or the economic impacts of the interventions. The study also did not investigate potential changes in antimicrobial resistance patterns over time. Nonetheless, previous research has demonstrated that reducing antibiotic consumption can improve clinical and economic outcomes, while also mitigating antimicrobial resistance (11, 33-34). Further research is warranted to evaluate the broader impact of PPRF, and the sustainability of implementing such a labour-intensive intervention. Future studies should also assess its long-term effects on mortality, infection rates, and antimicrobial resistance.

Conclusion

This study outlined the implementation of an intensified PPRF strategy within the hospital's AMS program. The combination of a more frequent review process and a dedicated AMS team could help to reduce antibiotic consumption, suggesting that a higher intensity approach may enhance AMS efforts. However, further research is needed to investigate the broader effects of PPRF, including its impact on patient clinical outcomes, local antimicrobial resistance patterns, and potential economic savings.

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Conflict of Interest

The authors declare that they have no conflicts of interest and they did not receive any financial support or funding that is relevant to this study.

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