TOWARDS REDUCING THE HEAVY USAGE OF CONTROLLED ANTIBIOTICS IN SEBERANG JAYA HOSPITAL

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Abstract

Seberang Jaya Hospital (HSJ) has been listed as Penang's highest controlled antibiotic user since 2018. It has led to the prevalence of resistant microorganisms and increased antibiotic expenditures. Therefore, reducing the usage of controlled antibiotics was an attempt done to reduce the defined daily dose (DDD)/1000 patient-days (PD) and improvise on the antibiogram and cost. The study aimed to reduce the DDD/1000 PD by over 30% from the baseline upper limit (UL) in 2019 for HSJ. A quality improvement study involving four cycles was conducted from July 2019 to June 2022. The sampling was done utilising a controlled antibiotic order form, an antimicrobial stewardship database and knowledge assessment questionnaires. During the verification study, the DDD/1000 PD was above the UL (4.5%), which was 25.5% below the standard. The contributing factors were the incomplete review of antibiotics after 72 hours (84%), inappropriate selection of antibiotics during the initial therapy (61%) and after review (88%), pending relevant culture results (36%) and unclear Standard Operating Procedure (SOP) in supplying the antibiotics (49%). Strategies developed were continuous education for healthcare professionals, formulation of new antibiotic guidelines and formulary restrictions, and development of an electronic antibiotic application. The Achievable Benefit Not Achieved (ABNA) was reduced from 25.5% to -6.7%. Improvement in the Model of Good Care (MOGC) was shown to affect the appropriate selection of antibiotics during the initial therapy from 39% to 99% and after review from 12% to 87%; active tracing of relevant results from 64% to 100%; active review of antibiotics from 16% to 100%; and proper supply of antibiotics based on the SOP from 51% to 90%. Approximately RM 165,000.00 (USD 36,600.00) of cost savings were accomplished. Improvement was seen in the antibiogram. Several strategies were implemented at the other hospitals, such as the electronic antibiotic application.

KEYWORDS: Controlled antibiotics, Defined daily dose (DDD), Antimicrobial resistance

Problem

Seberang Jaya Hospital (HSJ), one of the district hospitals with specialists in the Penang state, with 393-bed occupancy, serves a population of approximately 900,000 patients in Seberang Jaya. The hospital provides various specialist services, including Medical, Paediatric, Surgical, Orthopaedic, Anaesthetic, Obstetrics and Gynaecology, Dental, Emergency and Trauma, as well as Ear, Nose, and Throat. As one of the leading hospitals in the region, numerous diseases, including life-threatening infections, are treated in the wards daily. The common types of bacterial infections encountered among hospitalised patients from July to December 2020 are pneumonia (including community-acquired pneumonia [n=37], hospital-acquired pneumonia [n=51], and ventilator- associated pneumonia [n= 34]), urinary tract infection (including catheter- associated [n=36], non-catheter-associated [n=13]), bloodstream infections (including central line bloodstream infection [n=42], occult bacteremia [n=21]), skin and soft tissue infection (n=42), intra- abdominal infection (n=36), and surgical site infection (n=43). Due to the various infections of different severity, HSJ has been listed as one of the high users of several antibiotics, especially controlled antibiotics, since 2018 by the Ministry of Health (MOH), Malaysia (1).

Heavy usage of controlled antibiotics can lead to longer hospital stays, an increase in the cost of medications and other relevant accessories, a rise in the prevalence of resistant microorganisms, and an increased mortality rate (2-4). Antibiotic usage is monitored closely by the National Surveillance on Antibiotic Utilisation, MOH, in terms of the defined daily dose (DDD)/1000 patient-days (PD) across 91 hospitals nationwide. These include 44 government and 41 private hospitals, as well as three hospitals under the Ministry of Education and three more under the Ministry of Defense (5). An upper limit (UL) will be calculated based on the yearly usage data submitted by the hospitals listed above. A hospital will be labelled as an outlier if its antibiotic usage exceeds the UL of the yearly national antibiotic use. HSJ has been an outlier since 2016 (1), with a total cost increment estimated at approximately MYR 38,000.00 (USD 8,500.00) solely for antibiotic usage within a year. The number of estimated carbapenem-resistant Enterobacteriaceae (CRE) in this facility had also increased by 7 folds from 2018 (n=7) to 2019 (n=49).

In HSJ, the controlled antibiotics are meropenem, imipenem, ertapenem, vancomycin, ciprofloxacin, cefepime and piperacillin-tazobactam. It has become a serious problem as there is no restriction in the prescribing policy of controlled antibiotics. Antibiotics given empirically can be prescribed for a prolonged duration in this facility. A recent point prevalence survey (PPS) conducted at HSJ revealed that approximately 85% of antibiotics prescribed for various infections did not follow the local hospital guidelines. Therefore, the aim of this study was to reduce DDD/1000 PD by 30% from the baseline UL in 2019 within two years.

Background

Antimicrobial resistance is a global threat that refers to the resistance of a microorganism to the antimicrobials that were initially efficacious in eradicating the infections (4). Injudicious use is regarded as prescribed antibiotics that are not as per the established guidelines' recommendation such as the use of a broad-spectrum antibiotic for a bacterial strain that has specific sensitivities. This may also lead to worsening antibiogram which is a way to observe the susceptibility rates and monitor resistance trends within an institution itself (4).

Many studies have shown that injudicious use of antibiotics has led to untoward consequences (6-8). A multicenter study in China has pointed out the correlation between increased carbapenem use and increased CRE, and it is highly endemic, suggesting an urgent need to enhance infection control (9). In recent years, the rate of CRE has steadily increased up to 40% globally (1,6). There has been conflicting evidence about the relationship between antibiotic

treatment and antibiotic resistance. While treating certain infections, proving that antibiotic treatment creates a risk for the individual to acquire resistant organisms has been difficult (10,11). Nonetheless, the cumulative effect of using these antibiotics has been proven to increase the prevalence of resistant microorganisms in the population (10,12).

The emergence of antimicrobial resistance may cause resistance to the first-line antimicrobials, which then requires the usage of second or third-line antimicrobials, which are possibly less effective, more toxic, and more costly (2). The pace of antimicrobial development has decreased over the past few decades, and it is alarming that as more resistance is acquired, there will be limited options of available antimicrobials (2-3). Antimicrobial resistance negatively impacts patient outcomes, poses a major threat to patient safety, increases health expenditure, and consequently leads to no treatment options, even for common infections (2-4).

Several factors can contribute to the heavy usage of antibiotics in healthcare settings, and one of the most common is the inappropriate selection of antibiotics during the initial treatment and upon review after 72 hours. These contributing factors were mainly attributed to work culture and intense pressure from senior colleagues or peer practice (13-15). Therefore, prescribing a broader spectrum antibiotic initially and extending its use for one to two weeks has been the norm. Besides that, the lack of resources, such as the culture incubation facility and doctors' perception of the unnecessary antibiotic review, also contributed to the rise in antibiotic usage (16-19). This will subsequently result in pending culture and sensitivity results and thus an incomplete review of antibiotics after 72 hours.

Globally, the heavy use of antibiotics is directly linked to antibiotic resistance (24). This led to the establishment of antimicrobial stewardship (AMS) programs in healthcare settings, which generally involved multidisciplinary players on the ground. These players include microbiologists, pharmacists and infectious diseases specialists (10,20,21). AMS program by MOH was developed to improve and promote the judicious use of antimicrobials through optimal antimicrobial selection. This includes the right choice of antimicrobial, the right route of administration, the right dose, the right time and the right duration to minimise harm to the patients. Enforcement of AMS programs has significantly impacted the healthcare system, including cost savings, improvisation of antibiograms and reduced prevalence of resistant organisms (11,22). The AMS program consists of various activities or initiatives, such as antimicrobial streamlining. One of the principles of streamlining is the de-escalation of therapy. A broader spectrum of antimicrobials is switched to a narrow spectrum antimicrobial as empirical usage of broad-spectrum antimicrobials may exacerbate the risk of antimicrobial resistance. The de-escalation strategy can potentially improve patient outcomes without compromising patient safety and reduce mortality (23, 24).

Monitoring antibiotic usage is another recommended component of the AMS program, which provides information about the patterns and usage trends at intra-facility and inter-facility levels (1). Consequently, these data would provide evidence of injudicious use and reflect the necessity to perform constructive interventions to overcome this problem. It has been proven that implementing local guidelines and compliance with them, frequent audits on antibiotic use and good collaboration among healthcare professionals such as doctors, pharmacists and microbiologists have successfully improved the judicious use of antibiotics (25).

Measurement

This quality improvement study was conducted by an AMS team of two pharmacists, one infectious diseases consultant, one infectious disease/medical specialist, two microbiologists and an anaesthetist. The study was conducted from July 2019 to June 2022 using a convenience sampling method. It involved

two medical wards and one intensive care unit in the first two cycles and expanded to all wards in HSJ from the third cycle onwards once all the strategies were well established. Based on our inclusion and exclusion criteria, the study samples were recruited for one month only for each cycle. The inclusion criteria were all patients 15 years old and above who started on any of the seven types of controlled antibiotics: piperacillin-tazobactam, cefepime, meropenem, imipenem, ertapenem, vancomycin, and ciprofloxacin. On the other hand, the exclusion criteria were untraceable patients.

The study indicator used for this study was the percentage reduction of DDD/1000 PD from the calculated 2019 baseline UL, and the standard was set to be more than 30%. The percentage was computed using the formula below:

$$\text{Percentage reduction of DDD/1000PD from 2019 baseline UL} = \frac{\text{(Baseline average UL in DDD/1000PD) – (current UL in DDD/1000PD)}}{\text{Baseline average UL in DDD/1000PD}} \times 100\%$$

The 2019 baseline UL was obtained by determining the average percentage difference of the DDD/1000 PD from three different state hospitals, namely Pulau Pinang Hospital (11.1%), Kuala Lumpur Hospital (14.6%), and Raja Permaisuri Bainun Hospital (16.1%), which was approximately 15% upon average (1). It was further doubled to 30% in line with the vision of quality assurance and quality improvement concept to achieve the optimum achievable standard. This was also agreed upon through consensus by the AMS team.

The antibiotics consumption was measured as DDD/1000 PD based on the formula from the National Surveillance on Antibiotic Utilization (1) as shown below:

$$\text{No. of DDD per year} = \frac{\text{Antibiotics usage in grams for adult patients in a year}}{\text{DDD for respective antibiotics given by WHO}}$$

$$\text{DDD/ 1000 PD} = \frac{\text{No. of DDD per year}}{\text{Total no. of days adult patients warded for that particular year}} \times 100\%$$

Three data collection tools were utilised to collect the data on indicator and contributing factors concurrently. Firstly, a controlled antibiotic order form was used to briefly summarise the infection treated and previous antibiotic history. It was a crucial tool in tackling the antibiotic review and appropriate antibiotic selection afterwards. The second tool was the antimicrobial stewardship database to facilitate statistical analysis of the antibiotic usage trend, i.e., DDD and DDD/ 1000 PD. It also contained the culture and sensitivity test results of the treated patients. The results were accessible to all doctors and pharmacists, whereas the antibiotic usage trend was only accessible to the AMS team members. The last tool was two sets of self-administered questionnaires targeting doctors and pharmacists. The questionnaire for the doctor was used to assess their knowledge of antibiotic selection, while the other questionnaire for the pharmacist was used to assess their understanding of the SOP in supplying controlled antibiotics. Each questionnaire was distributed to 50 doctors and pharmacists during the first two cycles. All doctors and pharmacists were included during the subsequent cycles. All data collection tools were developed by the Pharmacy Department, Seberang Jaya Hospital and the questionnaires were reviewed and agreed upon by the infectious diseases consultant and senior ward pharmacists.

During the verification study phase, which was done in November 2019, the percentage reduction of DDD/1000 PD was only 4.5% for all the controlled antibiotics. The Achievable Benefit Not Achieved (ABNA) was 25.5%.

Initial Assessment of the Problem

The process of care, as depicted in Figure 1, was reviewed at the beginning to identify the critical steps leading to the heavy usage of controlled antibiotics.

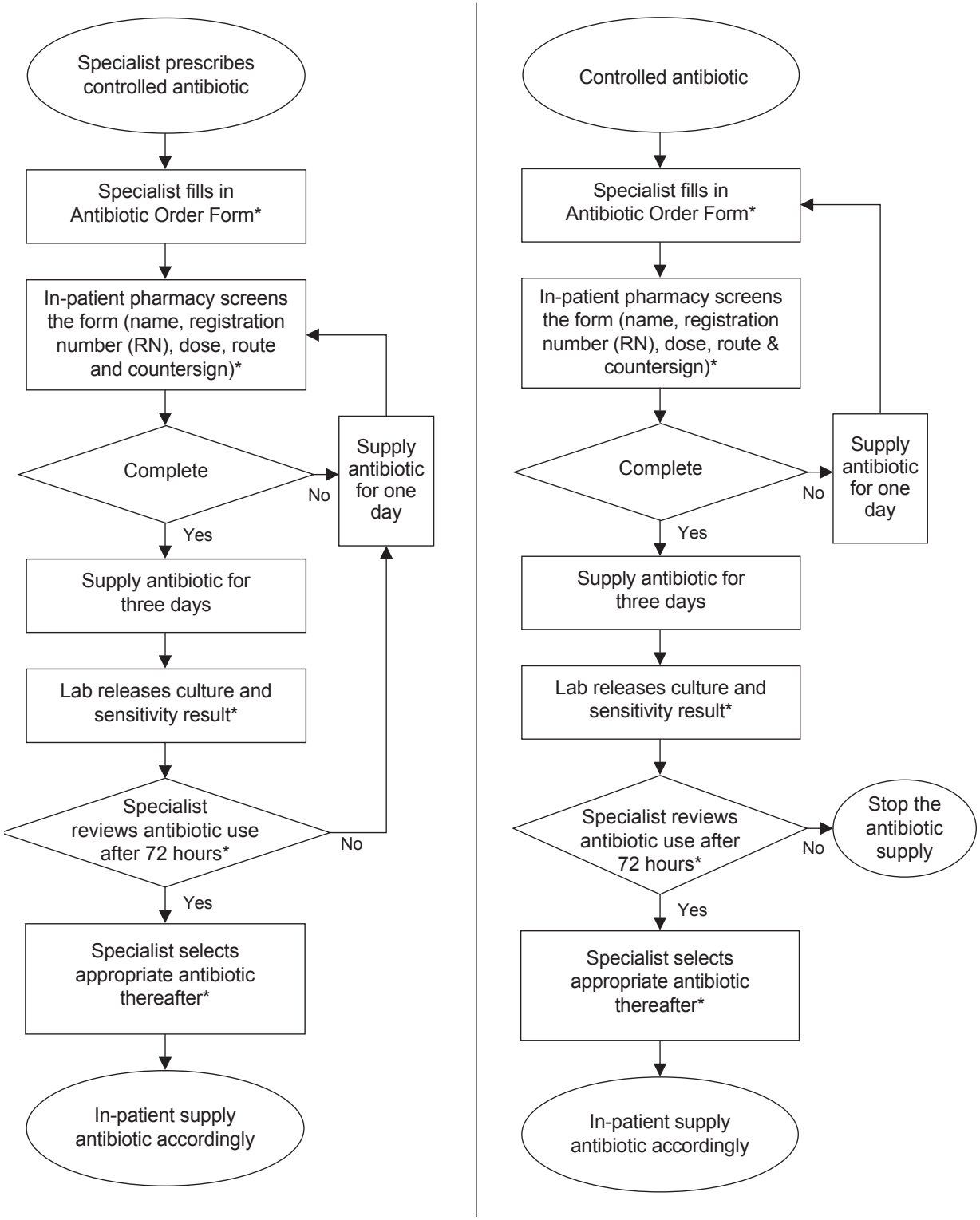


Figure 1: The initial (left) and revised (right) process of care for prescribing and supplying of controlled antibiotics in HSJ (* indicates critical step)

When there is a need to indent a controlled antibiotic, the specialist has to prescribe the in-patient prescription and fill in the antibiotic order form. In-patient pharmacy would screen the form (patient name, RN, dose, route and countersign) and supply it according to the agreed Standard Operating Procedure (SOP). If the specialist countersigns the antibiotic order form, the in-patient pharmacy will supply the antibiotic for three days consecutively, whereas only one day supply is given if the form is yet to be countersigned. The unsigned antibiotic order form will be passed to the specialist for countersign. After three days (72 hours), the relevant

cultures sent prior to initiating antibiotic therapy should be released. The respective specialist must review the antibiotic used and provide feedback. The review is based on the relevant culture results and the patient's condition. Various factors are considered during the decision-making process, such as temperature, white blood cell count, C-reactive protein, procalcitonin, ventilator settings and dependency on any inotropic support. However, the in-patient pharmacy would still supply the antibiotic, although the review process is still pending. Most of the time, the antibiotic prescribed will be continued for 7-14 days empirically. Hence, an audit using the controlled antibiotic order form and the antimicrobial stewardship database was conducted on 65 cases for a month involving the seven types of controlled antibiotics. This was mainly to identify the contributing factors that resulted in heavy usage of antibiotics, as illustrated in Figure 2. The contributing factors identified were the incomplete review of antibiotics after 72 hours (84%), inappropriate selection of antibiotics during the initial therapy (61%) and after review (88%), pending relevant culture results (36%) and unclear SOP in supplying the controlled antibiotics (49%). Each strategy developed was aimed to tackle at least two or more of the contributing factors identified.

Strategy

Remedial measures were implemented in three four-month cycles (Cycle 1: January to April 2020; Cycle

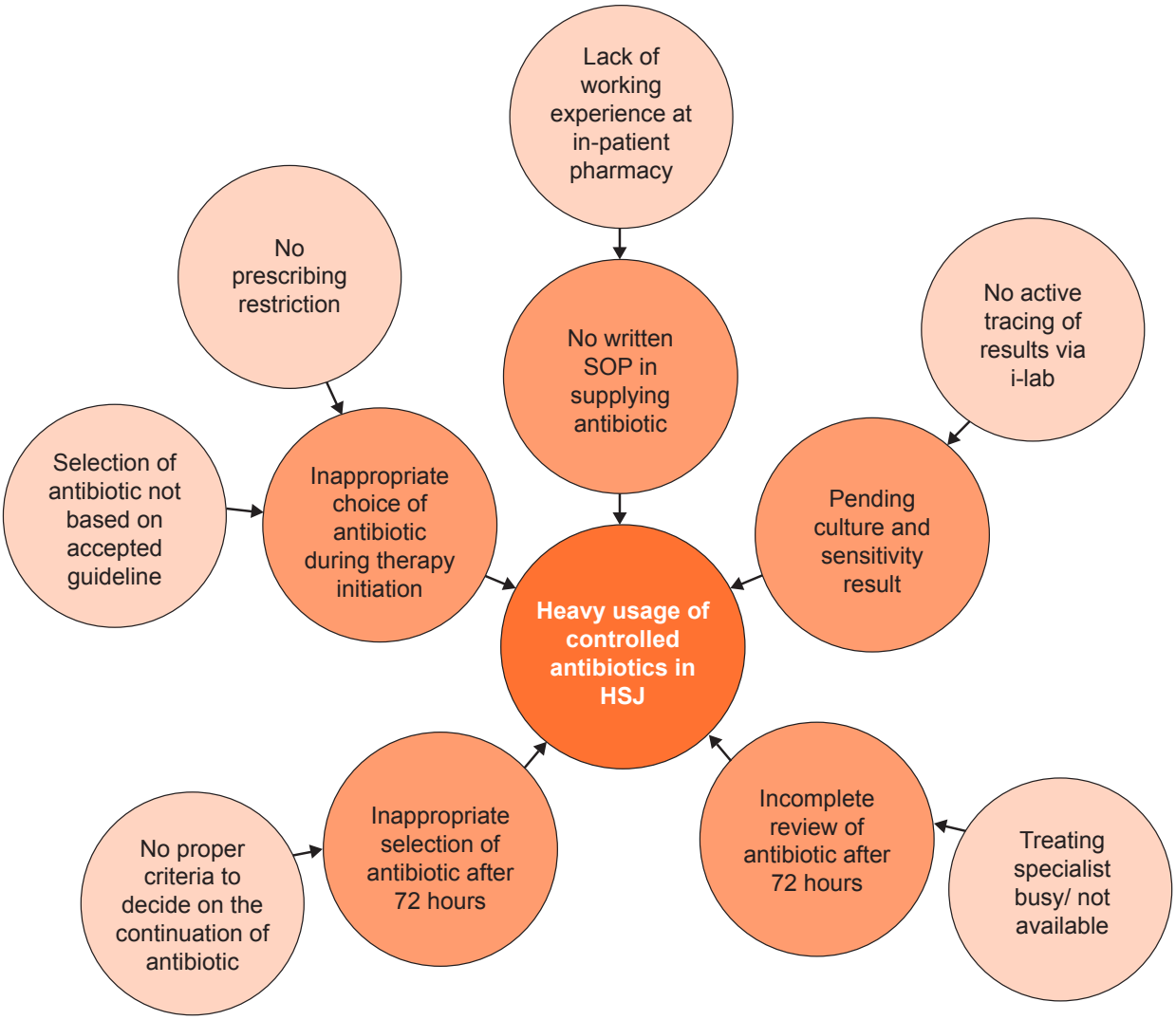


Figure 2: Problem Analysis Chart (PAC) of heavy usage of controlled antibiotics in HSJ

2: August to November 2020; Cycle 3: August to November 2021). The fourth cycle was conducted in June 2022 with no implementation of new remedial measures but to ensure the sustainability of this project. Seven strategies for change were formulated based on the contributing factors identified. All the strategies designed were the collective efforts of the AMS team members.

Three strategies were implemented during cycle 1. The first strategy was implemented to tackle the inappropriate choice of antibiotic selection. A simplified In-patient Empirical Antibiotic Guide was formulated by the pharmacists, microbiologists, and an infectious diseases consultant to facilitate the appropriate initial selection of antibiotics based on various indications and upon the review process after 72 hours. This guide was available on every patient's medication chart, which served as a quick reference for the doctors. Indirectly, this strategy prevented doctors from prescribing broad-spectrum antibiotics as the initial empirical therapy and facilitated the appropriate choice of antibiotic upon review, especially when there were no positive cultures. It was initially challenging for the doctors to adhere to the new guide, and the ward pharmacists emphasised the importance of adherence to the guide.

Besides that, as there were no prescribing restrictions that enabled the use of controlled antibiotics injudiciously, the development of a second strategy through a formulary restriction list between the Pharmacy Department and the Infection Disease Unit was done. This list comprises all antibiotics in HSJ based on the spectrum and their implications if used injudiciously (e.g., over-usage of third- generation cephalosporins leads to extended-spectrum beta-lactamase (ESBL) strains). Therefore, the initial prescribing of controlled antibiotics by the specialists was restricted to three days, whereas only infectious disease consultants can prescribe those restricted antibiotics as listed in the formulary restriction. This strategy could tackle most of the contributing factors, such as inappropriate initial selection of antibiotics, incomplete review after 72 hours, pending culture and sensitivity results and unclear SOP in supplying controlled antibiotics.

Apart from the two strategies above, frequent pending culture and sensitivity results were another significant contributing factor identified. Thus, the third strategy was to ensure consistent updates on the culture by the Microbiology Unit via an electronic database, namely the i-lab system, to aid in completing the review after 72 hours. The Microbiology Unit had requested all doctors and pharmacists to create an account in the i-lab system to facilitate an active culture tracing process. Each ward was equipped with at least two computers in common areas for easy accessibility. In ensuring the success of this strategy, one lab assistant was assigned to update the cultures daily and assist the doctors with the culture updates through phone calls if there were technical glitches. Henceforth, the doctors can trace the culture and sensitivity results conveniently and review the antibiotics used.

Although the three strategies in cycle 1 showed improvement in overcoming the contributing factors, the ABNA achieved in cycle 1 was 13.4%. Despite the helpful quick guide as verbally reported by the users, apparently, the spectrum of diseases covered was limited. Therefore, the fourth strategy during cycle 2 involved the establishment of a more comprehensive guideline based on the local antibiogram, including antibiotic choices for more infections and dosage adjustments in patients with acute or chronic kidney diseases. Both manual and electronic versions of the guidelines were distributed among the healthcare practitioners and existing wards in HSJ to ease the accessibility of the guidelines in a timely manner. This initiative was a group effort of pharmacists, microbiologists, and infectious diseases consultants to facilitate the selection of antibiotics based on various indications, especially when it was not culture-driven. The antibiotics were recommended as the primary choice,

and respective heads of the departments agreed on the alternative options. This strategy had constructively tackled all five contributing factors identified. The ABNA after cycle 2 was 0.2%, with a percentage reduction of 36.7%.

After cycle 2, 100% review of post 72 hours antibiotic prescribed remained the greatest challenge. The fifth strategy involved the development of a technology-driven measure called electronic antibiotic application to ensure a complete review of antibiotic forms and to monitor antibiotic usage based on several prescribing patterns. It is an electronic way to create, approve, and review antibiotic use via the online web-based system, which was also accessible through smartphones. This innovative strategy undoubtedly made a huge impact on the review process. The advantage of this application is that any injudicious use detected through the application is subjected to immediate intervention by the AMS team. This application has indirectly and directly tackled all five contributing factors. User satisfaction feedback was obtained through an electronic survey form, which was distributed to all users. More than 60% voted that this electronic antibiotic application eases their daily work process, is readily accessible to all staff and is user-friendly.

In order to sustain and improvise the technology-driven strategy, further steps were undertaken. The sixth strategy, a detailed flowchart on the supply of controlled antibiotics, was formulated. This provided a quick reference for the in-patient pharmacy and encouraged adherence to the SOP of supplying controlled antibiotics. This flowchart tackled two main contributing factors, including unclear SOP in supplying antibiotics and incomplete review after 72 hours. An improvised version of the process of care was developed, as shown in Figure 1. The seventh strategy was continuous medical education (CME) on antibiotic electronic application use (e-form manual) to facilitate understanding among the application users and ensure smooth flow throughout the prescribing process. This strategy tackled the pending culture and sensitivity result factor compared to the earlier flow chart strategy. It also provided an opportunity to raise issues and overcome the application flaws raised by the users.

Results

The heavy usage of controlled antibiotics gradually improved through the interventions done within two years. The ABNA eventually reduced from 25.5% to -6.7%. The DDD/1000 PD reduced from 126.7 (baseline UL in 2019) to 121 in the pre-remedial phase. Subsequent reductions of DDD/1000 PD were 105.7, 88.9, 80.7 and 80.2 from cycles 1 to 4, respectively, accounting for approximately 36.7% reduction from the baseline UL by the year 2021. A detailed ABNA and conformance to MOGC for every cycle are tabulated in Figure 3 and Table 1, respectively.

An approximate of MYR 165,000.00 (USD 36,500.00) of cost savings (usage of antibiotics) were accomplished through this study; from baseline in 2019 worth MYR 389,265.00 (USD 85,939.00) to MYR 224,265 (USD 49,439.00) during cycle 4. The reported CRE cases also reduced from 49 (2019) to 21 (2021). The antibiogram had shown improvement as well.

Lessons and Limitations

This study has demonstrated that reduced antibiotic usage led to reduced antibiotic expenditures and prevalence of resistant microorganisms (e.g., CRE) and subsequently improved the local antibiogram, which was in line with other literature (8,10,21,25). From the study, it was apparent that persistent continuous education on the judicious use of antibiotics among the doctors by the AMS team had impacted the antibiotic prescribing pattern as per recommendations (2). Secondly, a strong collaboration between the AMS team and staff from numerous departments helped to overcome the alarming antimicrobial resistance rate and high antibiotic usage. Feedback verbally received on the implementation of

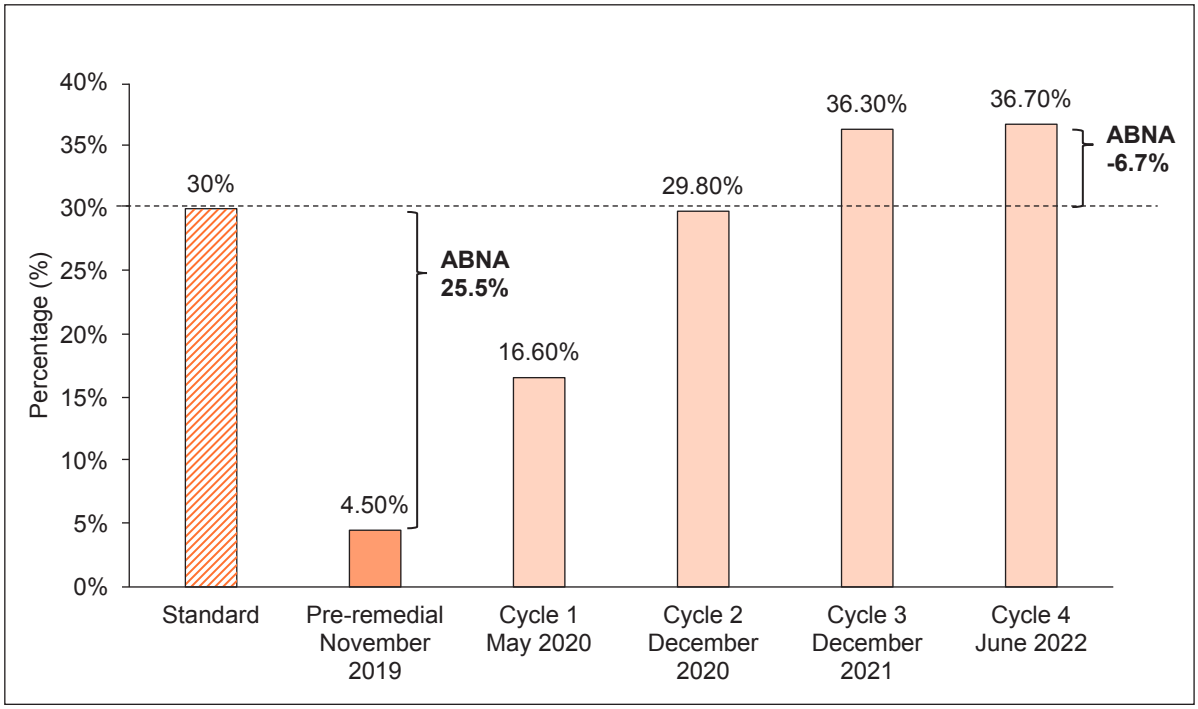


Figure 3: The percentage reduction trend of DDD/ 1000 PD with the identified ABNA. Cycle 1 and 2 involved two medical wards and one intensive care unit whereas Cycle 3 and 4 involved all wards in HSJ.

strategies showed good acceptance with a positive attitude without any significant complaints. Referring to the MOGC in Table 1, it was found that the standard for the three processes was not 100% until cycle 4. The two processes, namely the doctor filling in the antibiotic order form and the in-patient pharmacy screening the antibiotic forms, did not achieve the 100% target, probably due to the high turnover rate of new staff and fair consideration given to certain life- threatening emergency cases where immediate antibiotic doses will be released first, as evidence shows that antibiotics given within an hour of diagnosis reduce mortality rates (26). Therefore, in treating these cases, only prescriptions will be screened, and antibiotics will be released first before receiving the antibiotic order form. The process involving the specialist selection of appropriate antibiotics after 72 hours only attained up to 87%. Many specialists expressed the superiority of their personal experiences over the literature evidence. For instance, vancomycin is still used as surgical prophylaxis for a patient scheduled for implant surgery, although the patient was a non-MRSA carrier (nasal swab negative for MRSA). A separate internal audit on local data is planned to determine the correlation between the antibiotic used as surgical prophylaxis and incidences of surgical site infections (SSI). With this data, it is hoped that practices can be changed to be more evidence-based.

The detailed strategies developed have demonstrated an effect in combating the heavy usage of controlled antibiotics and can be adapted by other facilities. Among the strategies that were adapted by others were the electronic antibiotic application in different hospitals within Penang (e.g., Bukit Mertajam Hospital) and also outside Penang (e.g., Sultanah Bahiyah Hospital in Alor Setar, Kedah) by the visiting specialists. Besides that, our antimicrobial guideline was used as a reference for the development of local guidelines at other respective cluster hospitals and the renal dosing part was published with permission in another separate general renal dosing guideline. With all the efforts put in place, it was more meaningful as the team won the National Quality Assurance Convention in 2022.

There are several limitations in this study. The focus of the study was on controlled antibiotics only as we could not

Table 1: Model of Good Care (MOGC) to reduce the heavy usage of controlled antibiotics in HSJ.

Processes	Criteria	Standard	Pre-remedial Nov 2019 (n=65)	Cycle 1 May 2020 (n=59)	Cycle 2 Dec 2020 (n=71)	Cycle 3 Dec 2021 (n=68)	Cycle 4 June 2022 (n=62)
Specialist fills in Antibiotic Order Form	Specialist fills in antibiotic dose, frequency and duration	100%	39%	70%	75%	99%	99%
In-patient pharmacy screens the antibiotic form	The pharmacist screens for the patient's name, RN, dose, route, and signature by the prescribing specialist, and justification for the antibiotic	100%	51%	78%	86%	87%	90%
Lab releases culture and sensitivity result	Lab technician reports the name(s) of micro-organism(s) in the sample(s) sent, culture and sensitivity patterns, and minimum inhibitory concentration, where applicable	100%	64%	87%	94%	100%	100%
Specialist reviews antibiotic use after 72 hours	Review of antibiotic at 72 hours	100%	16%	59%	55%	100%	100%
Specialist selects appropriate antibiotic, thereafter	Specialist decides the choice of antibiotic, route, dose, and duration based on the culture and sensitivity results and septic parameters	100%	12%	68%	65%	82%	87%

include all the antibiotics, such as third-generation cephalosporins, which could also lead to antimicrobial resistance. Besides that, more time was spent on continuous education and guidance to sustain the outcomes because of the high turnover rate of new staff. The team is still seeking the most suitable and sustainable measures to overcome these limitations.

Conclusion and the Next Steps

Many studies have proven that judicious use of antibiotics prevents the unnecessary prevalence of resistant microorganisms. However, the process involved was not clearly defined and remained ambiguous. This quality assurance study has had multiple positive impacts towards achieving the study endpoints and gained attention in Penang. The project details, from problem analysis to strategies implementation and assessment, are clearly defined for convenience of adaptation by others and the ABNA was achieved (-6.7%). Nevertheless, frequent audits should be conducted at acceptable intervals to evaluate and ensure the outcomes' sustainability.

Our next step will be to extrapolate the electronic application to other drugs such as human albumin, sodium valproate injection and other drugs. Eventually, the usage could be monitored closely to avoid unnecessary wastage and for prescribers to follow its approved indication as in the Ministry of Health Malaysia Drug Formulary.

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Conflict of Interest

The authors declare that there was no conflict of interest.

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