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REVIEW ARTICLE

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A systematic review of the hospitals' antimicrobial stewardship programs implemented to improve antibiotics' utilization, cost and resistance patterns

Ovais Ullah Shirazi[1], Norny Syafinaz Ab Rahman[1,2,*], Che Suraya Zin[1,2]

ABSTRACT

Introduction: The high reliance of the physicians and surgeons on the antibiotics since their discovery has led to an irrational antibiotic utilization which not only has raised the incidence of antimicrobial resistance (AMR) but also increased the cost of treatment with antibiotics as high use of antibiotics has been found related to the occurrence of certain nosocomial infections which need extra antibiotic courses to be cured. In order to overcome these antibiotic utilization related problems an antimicrobial stewardship (AMS) program being the set of various persuasive, restrictive and structural interventions is considered an effective tool to rationalize the in-patient antimicrobial utilization worldwide.

Method: The focus of this review is on the interventions that are being implemented during the in-patient AMS programs and have been described effective in controlling the antibiotic utilization, their cost of treatment and an overall infection control. The literature containing the information about various AMS interventions effecting the utilization and cost patterns along with the impact on AMR was searched in various databases such as PubMed, Google Scholar, Science Direct, Ovid (Medline) and Scopus. The categorical sorting of the published data is based on various AMS interventions such as the guideline development, formulary restriction (pre-authorization), educative interventions, clinical pathway development and prospective (post prescription) audit. Considering the objectives of the study such as the goal to curb overutilization of antibiotics, control of their cost of treatment for in-patients and infection control the sorted literature is presented in three different tables describing the AMS impact on the said outcomes.

Results: The post AMS changes in utilization patterns are described as fall of antibiotics defined daily doses (DDD) and days of therapy (DOT) which resulted in the reduction of the cost of treatment with antibiotics. The reduction of the cost of treatment with antibiotics also resulted due to the AMS impact on the control of various nosocomial and multi-drug resistant (MDR) infections.

Conclusion: It has been concluded that the AMS program if implemented under the supervision of an expert AMS team mainly comprising of an infectious disease (ID) physician, clinical pharmacists and microbiologists with considerable support by the hospital authorities could be a highly efficient tool of the pharmacovigilance for rationalizing the in-patient antimicrobial practice.

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***Corresponding author:**

Email address: norny@iium.edu.my

Authors' Affiliation:

[1] *Department of Pharmacy Practice, Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.*

[2] *Department of Pharmacy Practice, Big Data Research in Drug Utilization Research Group Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.*

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Introduction

The antibiotics after their discovery have become an important shield against the deadly infections but a rapid development of the antimicrobial resistance (AMR) or a decreased susceptibility of bacteria to the antibiotics has invited the researchers to address this serious healthcare problem (Suwantarat & Carroll, 2016). The most common bacteria resistant to the broad spectrum antibiotics such as third generation cephalosporins and fluoroquinolones are Escherichia coli and Klebsiella pneumoniae (Phoon et al., 2018). Staphylococcus aureus are the important bacteria that are resistant to the Methicillin and are known as Methicillin resistant Staphylococcus aureus (MRSA) (Mendem et al., 2016). Over the past decades Streptococcus pneumoniae have exhibited marked reduction in their susceptibility against various penicillins and this fact is elaborated in the published reports of World Health Organization (WHO) (Cottagnoud et al., 2013). Vancomycin resistant Enterococci (VRE), carbapenem resistant Enterobacteriaceae (CRE) and Pseudomonas aeruginosa contain an effective gene modification capacity and plasmid equipped resistance that enabled them to challenge the efficacy of certain broad spectrum antibiotics namely vancomycin, carbapenems, ceftazidime and gentamicin etc. (O'Driscoll & Crank, 2015).

The contemporary literature reveals that the overutilization of the antibiotics within the hospital wards is one of the major causes of increased AMR. There have been published studies that positively correlate the high consumption of antibiotics to that of the increased AMR (Miliani et al., 2011). The high incidence of AMR further increases the antibiotic consumption as the multi-drug resistant (MDR) microbes are the basic cause of the healthcare associated infections (HAI) or the nosocomial infections that not only renders the patients to the toxicological impact of the antibiotics but also elevates the overall cost of treatment (Khan et al., 2017). The statistics of the antimicrobial consumption within the hospital wards worldwide highlight the trend that 30% to 50% antibiotic prescriptions do not match with antimicrobial spectrum of the antibiotics (Livermore et al., 2013). The overuse of antibiotics within the hospital wards increase the total cost of treatment which is a matter of concern for both the patients and the healthcare providers (Chandy et al., 2014). In order to overcome the overutilization of the antibiotics and to minimize the cost of antimicrobial treatment for the in-patients various hospitals worldwide have adopted a strategy which is the set of interventions commonly known as antimicrobial stewardship (AMS) program (Knox & Wiemiller, 2017).

The improvement of the prescribing patterns of the antibiotics is one of the most important goals of the AMS program so as to ensure a rational use of antibiotics (Chen et al., 2014). The AMS interventions being implemented during an in-patient AMS program are classified as persuasive, restrictive and structural interventions (Teixeira Rodrigues et al., 2019). The persuasive AMS interventions are comprised of education of the prescribers, development of the AMS guidelines along with the modification of the clinical pathways (Neo et al., 2020). The formulary restriction (pre-authorization) of the prescriptions mainly from an infectious disease (ID) physician, microbiologist or clinical pharmacist, stop order (de-escalation) practice for some highly consumed antibiotics along with the practice of antibiotic cycling or switch over between various antibiotic groups are some of the restrictive interventions being implemented as part of the hospitals' AMS programs (Dutcher et al., 2020). The structural interventions for the AMS are mainly the prospective (post-prescription) audit and the introduction of the computerized decision support system (CDSS) that automatically guides the prescribers regarding the AMS guidelines for a particular antibiotic (Huh et al., 2016). Introduction of the computerized prescribing and recording of the patient data within the electronic software of a hospital for traceability is an important structural intervention practiced worldwide so as to implement the AMS efficiently (Kauppinen et al., 2017).

The effective and successful implementation of an AMS program requires a team of multi-disciplinary healthcare professionals holding the responsibility to ensure a prudent antimicrobial practice within the hospital wards dealing with the antibiotics (Apisarnthanarak et al., 2018). The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) in the policy guidelines pertaining to the AMS describe the structure of the AMS team and the responsibilities of its members regarding the enforcement and implementation of the AMS policy (Barlam et al., 2016). According to the AMS policy guidelines an AMS team should contain an ID physician and a clinical pharmacist (with a specialised training regarding the infectious diseases) being the core members (Waters, 2015). Additionally, the inclusion of a clinical microbiologist, an information technology (IT) technician and a hospital epidemiologist is highly recommended for the efficient performance of the AMS team (Murri et al., 2018). Additional to the above-mentioned members of the AMS team in the healthcare settings of England a physician expert for acute care, a surgeon, a member from the pharmacy department team of management, a paediatrician, a senior nurse and an anaesthetist is also included as core members of the AMS team (Ashiru-Oredope et al., 2016). Considering the assessment of the AMS impact on the targeted outcomes various study designs are followed that categorically describe and evaluate the impact of the AMS interventions on the study population. The most commonly implied study designs for the said purpose are controlled before after (CBA), randomized controlled trial (RCT), controlled clinical trial (CCT) and interrupted time series (ITS).

Methodology

In order to collect the data pertaining to the impact of AMS programs within the in-patient settings worldwide the databases such as PubMed, Google Scholar, Science Direct, Ovid (Medline) and Scopus were searched systematically. The searching terms used for data exploration were antimicrobial stewardship programs, impact of antimicrobial stewardship program on antibiotic utilization, cost and resistance for in-patients etc. The studies published in English and covering the scope of the hospitals' AMS programs for the in-patients describing at least one AMS intervention with the resultant impact on the reduction of the antibiotic utilization, cost of treatment along with the control of healthcare associated infections (HAI) and AMR were included.

The studies which were focused on the AMS programs of the primary care settings and pediatric care wards and did not clearly described the AMS interventions and their impact on the antibiotic utilization, cost and resistance patterns for the in-patients were excluded for this review.

Results

The primary search of the relevant articles for this review from the said databases consisted of 2767 articles from 2014 - 2021 out of which 130 articles were short listed. Finally, 49 studies were included in this review and evaluation of these articles was performed to describe the impact of the AMS interventions on antibiotic utilization, cost and resistance patterns of the antibiotics used for the hospitalized patients. 24 of the sorted studies (Table 1) primarily reported the AMS impact on antibiotic utilization whereas 12 studies (Table 2) focused on the economic impact of the AMS. 13 studies elaborating the AMS impact on the infection control and the control of the AMR are presented in Table 3. Out of 49 studies included for this review 20 studies used CBA study design to assess the impact of hospitals' AMS programs, 7 studies followed the RCT study design, 6 studies used the CCT study design whereas 16 studies used ITS study design to assess the impact of the AMS interventions on antibiotics utilization, cost and resistance patterns for the in-patients.

Studies describing the AMS impact on antibiotic utilization patterns

The Table 1. describes the impact of AMS on the antibiotic utilization patterns. Most of the studies reported the defined daily doses (DDD) and days of therapy (DOT) of the antibiotics in order to describe the impact of the AMS interventions on utilization patterns. 4 studies described the educative interventions that were implied by the AMS team, ID physicians or by the clinical pharmacists to enhance the awareness of the prescribers and antibiotic handlers. 11 studies described that the prospective audit of the antibiotic prescription orders by the AMS team and ID specialists as an intervention to control the over utilization of certain antibiotics within the hospitalized patients. 2 studies described that the over utilization of the AMS included antibiotics was controlled by improving the clinical pathways. 5 studies mentioned that the formulary restrictive (pre-authorization) interventions were implemented to control the irrational use of antibiotics within the in-patient settings. 2 included studies elaborated the guideline development and the steps taken by the AMS team to ensure the adherence to such AMS guidelines as an AMS intervention to ensure a judicious use of antibiotics.

Studies describing the AMS impact on cost patterns

The Table 2. describes the impact of AMS on the antibiotics cost patterns. 4 studies described the educative interventions being implemented to elucidate the prescribers about the importance of AMS to control the overall cost of treatment with the antibiotics. 3 studies described the prospective audit done by the AMS team, ID physician or the clinical pharmacists as an intervention to improve the cost patterns of the antimicrobial treatment. 1 study performed in the hospital of USA described that to control the cost of treatment with antibiotics the improvement of the clinical pathways was done as an AMS intervention. A study performed in a German hospital mentioned the formulary restrictive intervention as a tool to control the high cost of treatment with 3rd generation cephalosporins. 1 study conducted in the in-patient setting of Spain elaborated that adherence to the AMS guidelines resulted in the control of the cost of treatment with meropenem. A study of a Malawian hospital claimed that the CDSS based AMS interventions were found an effective tool to control the antibiotics cost of treatment for the in-patients.

Studies describing the AMS impact on resistance patterns

The Table 3. describes the impact of AMS on the infection control and AMR patterns. 6 studies described the formulary restrictive interventions that were implemented within the hospital wards helped to control the AMR. The improvement of the clinical pathway during the AMS program of a Taiwanese hospital helped in infection control for the in-patients. 3 studies described that a decline of the incidence of the AMR and certain nosocomial infections namely Clostridium difficile infection (CDI) was observed as a result of continuous medical education (CME) of the hospital staff.

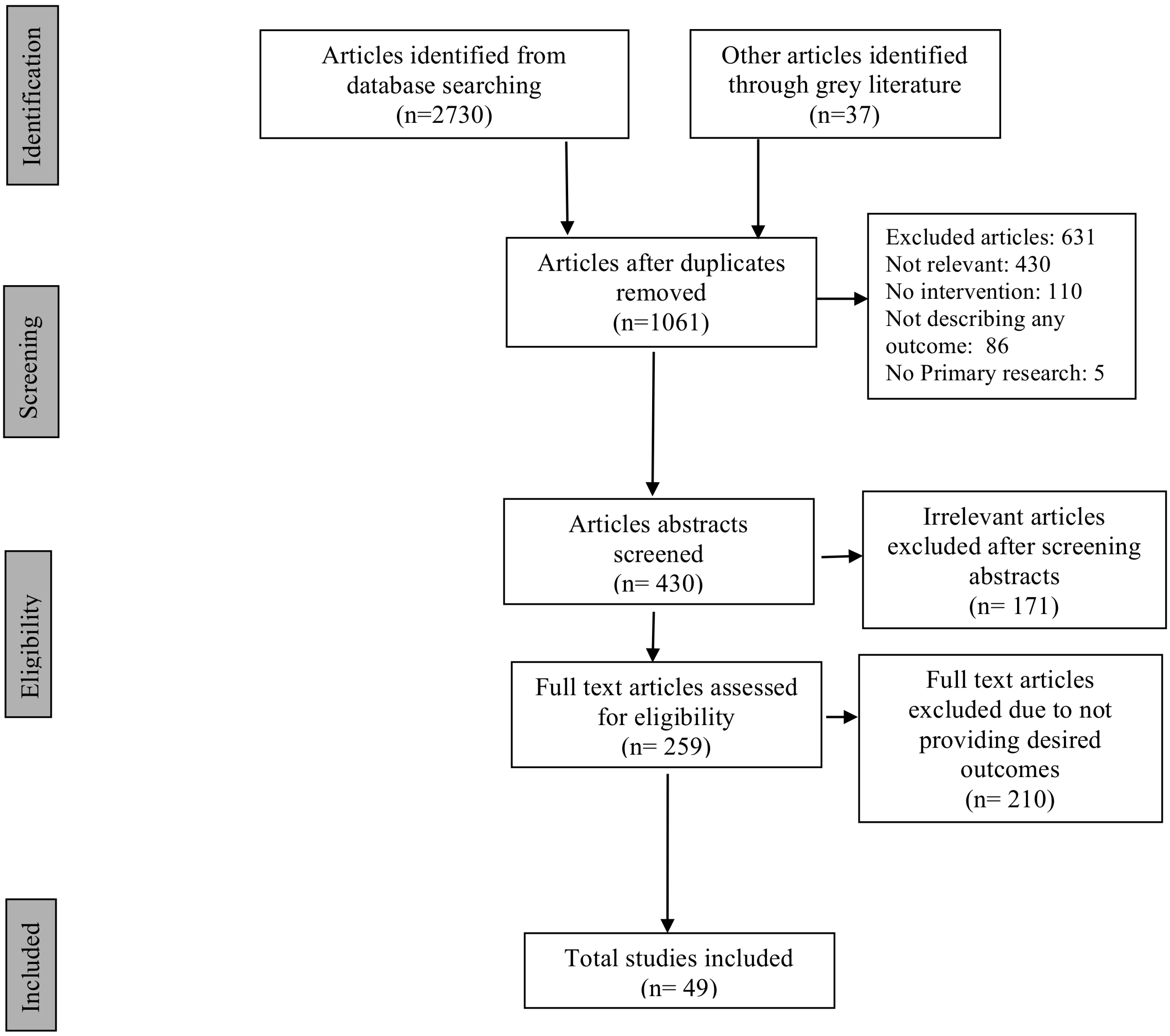

Figure 1: Study selection flowchart according to PRISMA checklist

Table 1: Studies describing the outcomes AMS impact on utilization

Author/Country/ Reference	Study Design	Intervention/Activity	AMS Intervention category	Results
(Garcell et al., 2017), Qatar	RCT	Education of the prescribers for judicious prescribing of antibiotics after appendectomies.	Educative	Post-AMS fall of the antibiotics defined daily dosses (DDD) by 18.9%
(Okumura et al., 2015), Brazil	CCT	Pharmacist led bundled AMS program	Educative	Post-AMS fall of antibiotic use by 140.2 DDD/1000 bed days (BD)
(Murri et al., 2018), Italy	CCT	Enhanced involvement of microbiologists to onset definitive therapy quickly	Clinical pathway development	Significant (P<0.002) fall of the number of days of therapy (DOT)
(Ruiz et al., 2018), Spain	RCT	Regular review of the prescriptions by AMS team and relevant feedback for prescribers	Prospective audit	Significant (P<0.015) fall of the number of DDD/100 stays
(Pitiriga et al., 2018), Greece	CCT	Mandatory order form introduced for broad-spectrum antibiotics prescribing	Formulary restriction	Significant (P<0.05) fall of the number of DDD
(Tang et al., 2018), United States of America (USA)	CBA	Continuous medical education of ward staff by clinical pharmacist by twice weekly ward rounds	Educative	Significant (P=0.01) fall of the number of DOT
(Palmay et al., 2014), Canada	RCT	Audit & feedback-based review of the prescriptions in ICU by the AMS staff.	Prospective audit	Significant (P=0.004) post-AMS fall of the number of DDD by 21%
(Didiodato et al., 2016), Canada	ITS	Prescription review by AMS staff for the patients with community acquired pneumonia (CAP)	Prospective audit	Post-AMS decline of the DOT by 29%.
(Khdour et al., 2018), Palestine	CBA	Regular prescription review by the AMS team for the intensive care unit (ICU) patients	Prospective audit	Significant (P<0.001) post-AMS fall of the use by 21.2 DDD/100 BD
(Lesprit et al., 2015), France	RCT	Regular post prescription review by the infectious disease (ID) physician	Prospective audit	Significant (p=0.003) post-AMS fall of DOT by 3 days
(Nilholm et al., 2015), Sweden	CBA	ID specialist led twice weekly audit of antibiotic prescriptions	Prospective audit	Significant (p<0.001) post-AMS fall of the number of DOT
(Boyles et al., 2017), South Africa	CBA	Review of antibiotic prescriptions during ward rounds by AMS team and feedback	Prospective audit	Post-AMS fall of antibiotic use by 178 DDD/1000 BD
(Trupka et al., 2017), USA	CCT	De-escalation of antibiotics for non-responsive ventilator patients	Formulary restriction	Fall of the number of DDD (non-significant)
(Seah et al., 2017), Singapore	CCT	Dose optimization of carbapenems after prescription review by AMS team	Formulary restriction	Significant (p<0.001) post-AMS fall of the number of DDD/1000 BD of carbapenems
(Tartof et al., 2020), USA	CBA	Targeted de-escalation of AMS included antibiotics implemented by the AMS team	Formulary restriction	Post-AMS fall of DDD by 6.1% & DOT by 4.3%
(García-Rodríguez et al., 2021), Spain	CBA	Post prescription audit of carbapenem prescriptions	Prospective audit	Significant (P<0.05) fall of the number of DDD of carbapenems

Table 1 (cont.): Studies describing the outcomes AMS impact on utilization

Author/Country/ Reference	Study Design	Intervention/Activity	AMS Intervention category	Results
(Dutcher et al., 2020), USA	CBA	Pharmacist led education for prescribers to encourage implementation of AMS prescribing guidelines for antibiotics	Educative	Significant ($P<0.001$) fall of the number of DDD of co-trimoxazole
(Surat et al., 2021), Germany	CBA	Introduction of AMS guidelines for postoperative treatment with antibiotics	Guideline development	Significant ($P<0.035$) fall of the number of DDD/100 BD
(Paulson et al., 2020), USA	CBA	Introduction of time out alerts for antibiotics used for 72 hours for the ICU patients	Formulary restriction	Significant ($P<0.014$) decline of the number of DOT
(Shively et al., 2020), USA	ITS	Post prescription review of antibiotic prescriptions by ID physician	Prospective audit	Significant ($P<0.001$) fall of DOT by 24.4%
(Du et al., 2020), China	ITS	Pharmacist led antibiotics prescription audit	Prospective audit	Significant ($P<0.01$) decline of DDD
(Pineda et al., 2020), USA	ITS	MRSA screening AMS introduction for rapid onset of definitive therapy	Clinical pathway development	Decline of use by 2.1 DOT/1000 BD
(Faraone et al., 2020), Italy	ITS	Adherence to the multimodal AMS guidelines for carbapenem use	Guideline development	Fall of carbapenem use by 3.6 DDD/100 BD
(Knight et al., 2020), USA	CBA	Post prescription review of broad-spectrum antibiotics by ID physician	Prospective audit	Post-AMS fall of the DOT/1000 BD by 4.6%

Table 2: Studies describing the AMS impact on cost of treatment with antibiotics

Author/Country/ Reference	Study Design	Intervention/Activity	AMS Intervention category	Results
(Lee et al., 2014), Canada	CBA	Introduction of electronic check list for antibiotics to perform twice weekly audit	Prospective audit	Fall of cost of treatment with antibiotics by \$69424
(Box et al., 2015), USA	ITS	Rapid diagnosis of Gram +ve bacteremia	Clinical pathway development	Fall of cost of treatment with antibiotics by \$7240
(Cisneros et al., 2014), Spain	RCT	Counselling sessions for prescribers by AMS team	Educative	Fall of post-AMS antibiotics treatment cost by 42%
(So et al., 2018), Canada	CCT	Academic detailing to treat leukemia patients in oncology unit	Educative	Significant (P=0.03) decline of cost of treatment with antibiotics
(Chandrasekhar & PokkaVayalil, 2019), India	CBA	Continuous medical education (CME) courses by AMS personnel	Educative	Significant (P<0.05) fall of cost of treatment with antibiotics by 19.5%
(Libertin et al., 2017), USA	CBA	Counselling sessions for prescribers by AMS team as part of continuous medical education (CME)	Educative	Decline of antibiotics treatment cost by 50% with savings of \$280000/year
(García-Rodríguez et al., 2019), Spain	CBA	Formal guidelines issued to meropenem prescribing physicians by the ID physician	Guideline development	Significant (P<0.05) reduction of post-AMS cost of treatment with meropenem
(Seah et al., 2014), Singapore	ITS	Post prescription review by AMS team	Prospective audit	Significant (P=0.01) post-AMS fall of antibiotics treatment cost by \$149/patient
(Cisneros et al., 2014), Spain	RCT	Counselling sessions for prescribers by AMS team	Educative	Post-AMS fall of antibiotics cost by 42%
(Borde et al., 2014), Germany	ITS	Replacement of 3rd generation cephalosporins with penicillins and fluoroquinolones	Formulary restriction	Significant (P<0.05) reduction of treatment cost with 3rd generation cephalosporins
(Day et al., 2015), USA	RCT	Hiring of an ID physician to check accurate susceptibility of microbes with the prescribed antibiotics	Prospective audit	Fall of cost of treatment with antibiotics by 42%
(Lester et al., 2020), Malawi	CBA	Introduction of software for the selection of empiric therapy of antibiotics to reduce high 3rd generation cephalosporin consumption	CDSS	Post-AMS savings by \$15000 for antibiotics treatment cost

Table 3: Impact of the AMS on resistance patterns

Author/Country/ Reference	Study Design	Intervention/Activity	AMS Intervention category	Results
(Wenisch et al., 2014), Austria	CBA	Preauthorization declared compulsory for moxifloxacin supply to patients	Formulary restriction	Significant (P<0.005) decline of the incidence of *Clostridium difficile* infection (CDI) by 46%
(Wang et al., 2014), Taiwan	ITS	Rapid onset of blood culture guided definitive therapy	Clinical pathway development	Gradual post-AMS decline of infections
(Libertin et al., 2017), USA	CBA	CME for prescribers by AMS team	Educative	Decline of the occurrence of CDI from 3.35 to 1.35 cases/1000 BD
(Percival et al., 2015), USA	CBA	CME done for prescribers dealing with the urinary tract infections (UTI)	Educative	Significant (P<0.05) decline of the occurrence of AMR by 5% after AMS
(Hecker et al., 2019), USA	ITS	Syndrome specific use for fluoroquinolones	Formulary restriction	Significant (P<0.05) control of *Pseudomonas aeruginosa* infection
(Tedeschi et al., 2017), Italy	ITS	Protocol revision for prophylactic therapy with antibiotics	Formulary restriction	Significant (P<0.001) fall of *Pseudomonas aeruginosa* infections
(Horikoshi et al., 2017), Japan	ITS	Investigation of gram-negative bacteria (GNB) resistance against carbapenems	Prospective audit	Significant (P<0.01) fall of *Pseudomonas aeruginosa* resistance for carbapenems
(Lawes et al., 2015), United Kingdom	ITS	Health screening termed mandatory for the penicillin, cephalosporins and fluoroquinolone use	Formulary restriction	Significant (P=0.006) fall of the occurrence of methicillin resistant *Staphylococcus aureus* (MRSA) by 50%
(Peragine et al., 2020), Canada	ITS	Regular ward rounds by AMS team for audit and feedback of antibiotic prescriptions	Prospective audit	Post-AMS decline of antibiotic resistant organisms by 9%
(Yusef et al., 2021), Jordan	CBA	Preauthorization policy introduced for carbapenems	Formulary restriction	Significant (P<0.024) fall of carbapenem resistant *Acinetobacter baumannii* infections
(Mardani et al., 2020), Iran	ITS	Regular audit and feedback of antibiotic prescriptions by AMS team	Prospective audit	Significant (P<0.05) reduction of the incidence of CDI
(Strazzulla et al., 2020), France	CBA	Training of prescribers and nurses by AMS team in urological ward	Educative	Significant (P<0.004) post-AMS fall of ofloxacin resistance by 16%
(Al-Omari et al., 2020), Saudi Arabia	ITS	Restrictive antibiotic usage policy for carbapenems and fluoroquinolones	Formulary restriction	Significant (P<0.024) fall of CDI & significant (P=0.001) fall of ventilator associated pneumonia (VAP)

Discussion

This review mainly focused on the impact of the AMS programs implemented within the hospital wards that resulted in the control of the overuse of antibiotics, the reduction of the antimicrobial cost of treatment and the control of the AMR.

Impact of AMS programs on antibiotic use

The AMS programs that primarily aimed to rationalize the antimicrobial use indirectly contribute to minimize various healthcare associated infections (HAI) (Deptuła et al., 2015). The occurrence of nosocomial infections within the in-patient populations contribute to the extra usage of broad-spectrum antibiotics which not only impart the adverse effects on patients' health but also increase the cost of treatment (So et al., 2018). The reviewed studies describing an AMS impact on the antibiotic utilization showed that DDD and DOT were the main matrices that were recorded to determine the AMS impact on antibiotic utilization. Impact of AMS on DDD was estimated in 14 studies while 10 studies described the AMS impact of DOT of the antibiotics. The implementation of prospective audit intervention to reduce the antibiotic utilization was the major AMS intervention being implemented during the AMS programs. Formulary restrictive and educative interventions were the other AMS interventions mainly used to curb the unjustified antibiotic utilization. It is suggested that an estimation of the impact of AMS on prescribed daily doses (PDD) other than DDD and DOT could outline the prescribing frequency of the antibiotics. But it is a common trend that most of the studies that focus on antibiotic utilization mainly use DDD and DOT as the PDD is a more efficient matrix to evaluate the drug (antibiotic) utilization for a particular clinical condition or infection (Gagliotti, et al., 2014). Among the antibiotic groups carbapenems were the antibiotics that were targeted by the AMS interventions in order to minimize their unjustified utilization within the hospital wards. Since carbapenems are the broad-spectrum antibiotics and must be protected by the AMS interventions as they have the ability to cure various deadly infections. Due to this reason most of the AMS programs have aimed to minimize carbapenem use for empiric therapy.

Impact of AMS programs on antibiotic cost

The high antimicrobial treatment cost is the matter of concern both for the patients and the healthcare providers (Chandrasekhar & PokkaVayalil, 2019). Due to such concerns the health governing bodies of USA such as the CDC and SHEA since 2014, have recommended a mandatory AMS program for every in-patient setting that deals with the antibiotics and infectious diseases (Lee et al., 2014). Out of the 12 studies in which the post-AMS reduction of the cost of treatment with antibiotics was observed 5 studies were found to report a significant ($P<0.05$) fall of the cost of treatment. The educative interventions being implemented during the AMS programs were found highly effective to minimize the antimicrobial cost of treatment. Similar to the educative interventions the prospective audit proved an efficient intervention in controlling the cost of treatment with the antibiotics where the post-prescription audit by the ID specialist and the AMS team effectively improved the un-justified inclusion of the antibiotics which indirectly minimized the antimicrobial treatment cost. It is suggested that the implementation of antibiotic rotation or antibiotic cycling (replacement of broad-spectrum expensive antibiotics with cost-effective antibiotics) interventions in the hospitals could be highly lucrative pertaining to the reduction of the in-patients' cost of treatment with antibiotics (Bruno-Murthaet al.,2005).

Impact of AMS programs on antimicrobial resistance

The AMS interventions performed for the in-patients targeting the control of various nosocomial infections mainly depicted a fall in the incidence rate of Clostridium difficile, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacteriaceae and MRSA infections which due to their multi-drug resistant capacity contribute to high utilization of the broad-spectrum antibiotics and sequentially a higher cost of antimicrobial treatment (Thampi et al., 2019). Out of the 13 studies describing the AMS interventions on the control of the AMR, 10 studies described a significant ($P<0.05$) fall of the AMR and certain nosocomial infections. Formulary restriction was found the most common intervention being implemented during the AMS programs that retarded the incidence of AMR and the nosocomial infections. The control of CDI was the main outcome being observed in majority of the AMS programs designed to control the AMR and nosocomial infection outbreaks. It is suggested that the hospitals that primarily deal with the infectious diseases and wide range of antimicrobials must hire an ID specialist physician to monitor the AMS activities targeting the infection control. As in developing countries the financial constraints hinder the availability of infectious disease physicians thus, to overcome such constraints the training of the physicians and pharmacists in the perspective of infection control could be a highly effective AMS intervention aimed to minimize AMR and nosocomial infections' outbreaks. Such moves would not only help the developing countries but also globally minimize the spread of AMR along with the preservation of the existing antibiotics' efficacies against various infections as the spread of antibiotic resistant microbes from one part of the world to other is much easier nowadays due to high tourism and efficient transportation (Dancer, 2013).

An AMS program is the set of interventions that requires a coordinated support from the health governing bodies to enforce the AMS guidelines and sequentially, the adherence of the prescribers (physicians and surgeons) to such policy guidelines is of utmost importance for the success of the AMS (Barlam et al., 2016). The ID physicians, clinical pharmacists and microbiologists are the leading healthcare personnel responsible to implement the AMS interventions and to monitor the degree of adherence of the antibiotic prescribers to the hospital's AMS policy (Waters, 2015). Most of the studies are performed over a limited period of time with brief follow up pertaining to the impact of AMS programs. The successful implementation of the AMS programs is highly dependent on the coordination of the various services and units of the hospital under the supervision of an AMS team led by the ID specialist (Garcell et al., 2017). The availability of the AMS experts and the monetary support ensured by the hospital directors is of prime importance as it has been observed that in low- and middle-income countries (LMIC) as compared to the developed countries the commitment of hospital management in terms of fund allocation for the AMS is much lower (Boyles et al., 2017). Therefore, a more systematic formative evaluation of the hospital's antibiotic related problems is of prime importance before finalizing the hospital's AMS policy as the intensity of the infection and antibiotic related problems vary country wise and region wise (Knight et al., 2020). Such formative evaluation prior to the onset of an AMS program must include the identification of the infections related problem, designing of a suitable intervention for the identified problem needing the AMS, successful implementation of the AMS intervention by ID specialists and finally the evaluation the outcomes of the AMS program is considered highly important (Adhikari et al., 2018). The coordination of pharmacy department, medical wards, medical record department, information technology department (ITD), microbiology department under the supervision of the ID specialists being the members of the hospital's AMS team is mandatory for a successful AMS program (Tartof et al., 2020). The AMS related data of the individual hospitals could be compiled into national database which enables the health policy makers to evaluate the AMS progress in national perspective (Aldeyab et al., 2012). Ultimately, a data sharing among various countries could contribute to the achievement of the United Nation's goal number 3 being designed for the global healthcare that also addresses the common threat of the onset of a post antibiotic era worldwide (Sadiq et al., 2018).

Conclusion

The AMS programs outlined in this review mainly implemented the prospective audit, formulary restrictive, educative, clinical pathway development and guideline development related interventions that controlled the misuse of antibiotics with the aim of the reduction of the antibiotic use related resistance and ultimately the higher cost of treatment. Most of the included studies focused the in-patient settings in relation to the AMS impact on antibiotic utilization, cost and infection control which invites the researchers to further explore the regionwide AMS related data so as to adopt a common global AMS policy that will also guide the LMIC lacking the strategy and resources for the AMS implementation. The findings of this study elucidate the effectiveness of AMS programs in controlling the irrational use of antibiotics within the in-patient clinical settings that is considered the first step towards the infection control and to minimize the cost of treatment with antibiotics.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

Adhikari, S., Piza, M., Taylor, P., Deshpande, K., Lam, D., & Konecny, P. (2018). Sustained multimodal antimicrobial stewardship in an Australian tertiary intensive care unit from 2008–2015: an interrupted time-series analysis. *International Journal of Antimicrobial Agents*, *51*(4), 620–628.

Al-Omari, A., Al Mutair, A., Alhumaid, S., Salih, S., Alanazi, A., Albarsan, H., Abourayan, M., & Al Subaie, M. (2020). The impact of antimicrobial stewardship program implementation at four tertiary private hospitals: results of a five-years pre-post analysis. *Antimicrobial Resistance & Infection Control*, *9*(1), 95.

Aldeyab, M. A., Harbarth, S., Vernaz, N., Kearney, M. P., Scott, M. G., Darwish Elhajji, F. W., Aldiab, M. A., & McElnay, J. C. (2012). The impact of antibiotic use on the incidence and resistance pattern of extended-spectrum beta-lactamase-producing bacteria in primary and secondary healthcare settings. *British Journal of Clinical Pharmacology*, *74*(1), 171–179.

Apisarnthanarak, A., Kwa, A. L.-H., Chiu, C.-H., Kumar, S., Thu, L. T. A., Tan, B. H., Zong, Z., Chuang, Y. C., Karuniawati, A., Tayzon, M. F., So, T.

M.-K., & Peterson, L. R. (2018). Antimicrobial stewardship for acute-care hospitals: An Asian perspective. *Infection Control & Hospital Epidemiology*, *39*(10), 1237–1245.

Ashiru-Oredope, D., Budd, E. L., Bhattacharya, A., Din, N., McNulty, C. A. M., Micallef, C., Ladenheim, D., Beech, E., Murdan, S., & Hopkins, S. (2016). Implementation of antimicrobial stewardship interventions recommended by national toolkits in primary and secondary healthcare sectors in England: TARGET and Start Smart Then Focus. *Journal of Antimicrobial Chemotherapy*, *71*(5), 1408–1414.

Barlam, T. F., Cosgrove, S. E., Abbo, L. M., Macdougall, C., Schuetz, A. N., Septimus, E. J., Srinivasan, A., Dellit, T. H., Falck-Ytter, Y. T., Fishman, N. O., Hamilton, C. W., Jenkins, T. C., Lipsett, P. A., Malani, P. N., May, L. S., Moran, G. J., Neuhauser, M. M., Newland, J. G., Ohl, C. A., Trivedi, K. K. (2016). Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. In *Clinical Infectious Diseases*, 62 (10), 51-77..

Borde, J. P., Kaier, K., Steib-Bauert, M., Vach, W., Geibel-Zehender, A., Busch, H., Bertz, H., Hug, M., de With, K., & Kern, W. V. (2014). Feasibility and impact of an intensified antibiotic stewardship programme targeting cephalosporin and fluoroquinolone use in a tertiary care university medical center. *BMC Infectious Diseases*, *14*(1).

Box, M. J., Sullivan, E. L., Ortwine, K. N., Parmenter, M. A., Quigley, M. M., Aguilar-Higgins, L. M., Macintosh, C. L., Goerke, K. F., & Lim, R. A. (2015). Outcomes of rapid identification for gram-positive bacteremia in combination with antibiotic stewardship at a community-based hospital system. *Pharmacotherapy*, *35*(3), 269–276.

Boyles, T. H., Naicker, V., Rawoot, N., Raubenheimer, P. J., Eick, B., & Mendelson, M. (2017). Sustained reduction in antibiotic consumption in a South African public sector hospital; Four year outcomes from the Groote Schuur Hospital antibiotic stewardship program. *South African Medical Journal*, *107*(2), 115.

Bruno-Murtha, L. A., Brusch, J., Bor, D., Li, W., & Zucker, D. (2005). A pilot study of antibiotic cycling in the community hospital setting. *Infection Control & Hospital Epidemiology*, *26*(1), 81-87.

Chandrasekhar, D., & PokkaVayalil, V. (2019). Cost minimization analysis on IV to oral conversion of antimicrobial agent by the clinical pharmacist intervention. *Clinical Epidemiology and Global Health*, *7*(1), 60–65.

Chandy, S. J., Naik, G. S., Balaji, V., Jeyaseelan, V., Thomas, K., & Lundborg, C. S. (2014). High cost burden and health consequences of antibiotic resistance: the price to pay. *The Journal of Infection in Developing Countries*, *8*(09), 1096–1102.

Chen, C., Dong, W., Shen, J. J., Cochran, C., Wang, Y., & Hao, M. (2014). Is the prescribing behavior of Chinese physicians driven by financial incentives? *Social Science and Medicine*, *120*, 40–48.

Cisneros, J. M., Neth, O., Gil-Navarro, M. V., Lepe, J. A., Jiménez-Parrilla, F., Cordero, E., Rodríguez-Hernández, M. J., Amaya-Villar, R., Cano, J., Gutiérrez-Pizarraya, A., García-Cabrera, E., & Molina, J. (2014). Global impact of an educational antimicrobial stewardship programme on prescribing practice in a tertiary hospital centre. *Clinical Microbiology and Infection*, *20*(1), 82–88.

Cottagnoud, P., Cottagnoud, M., Acosta, F., & Stucki, A. (2013). Efficacy of Ceftaroline Fosamil against Penicillin-Sensitive and -Resistant Streptococcus pneumoniae in an Experimental Rabbit Meningitis Model. *Antimicrobial Agents and Chemotherapy*, *57*(10), 4653–4655.

Dancer, S. J. (2013). Infection control in the post-antibiotic era. *Healthcare infection*, *18*(2), 51-60.

Day, S. R., Smith, D., Harris, K., Cox, H. L., & Mathers, A. J. (2015). An Infectious diseases physician-led antimicrobial stewardship program at a small community hospital associated with improved susceptibility patterns and cost-savings after the first year. *Open Forum Infectious Diseases*, *2*(2).

Deptuła, A., Trejnowska, E., Ozorowski, T., & Hryniewicz, W. (2015). Risk factors for healthcare-associated infection in light of two years of experience with the ECDC point prevalence survey of healthcare-associated infection and antimicrobial use in Poland. *Journal of Hospital Infection*, *90*(4), 310–315.

Didiodato, G., McArthur, L., Beyene, J., Smieja, M., & Thabane, L. (2016). Evaluating the impact of an antimicrobial stewardship program on the length of stay of immune-competent adult patients admitted to a hospital ward with a diagnosis of community-acquired pneumonia: A quasi-experimental study. *American Journal of Infection Control*, *44*(5), 73-79.

Du, Y., Li, J., Wang, X., Peng, X., Wang, X., He, W., Li, Y., Wang, X., Yang, Q., & Zhang, X. (2020). Impact of a Multifaceted Pharmacist-Led Intervention on Antimicrobial Stewardship in a Gastroenterology Ward: A Segmented Regression Analysis. *Frontiers in Pharmacology*, *11*.

Dutcher, L., Yeager, A., Gitelman, Y., Morgan, S., Laude, J. D., Binkley, S., Binkley, A., Cimino, C., McDonnell, L., Saw, S., Cluzet, V., Lautenbach, E., & Hamilton, K. W. (2020). Assessing an intervention to improve the safety of automatic stop orders for inpatient antimicrobials. *Infection Prevention in Practice*, *2*(2).

Faraone, A., Poggi, A., Cappugi, C., Tofani, L., Riccobono, E., Giani, T., & Fortini, A. (2020). Inappropriate use of carbapenems in an internal medicine ward: Impact of a carbapenem-focused antimicrobial stewardship program. *European Journal of Internal Medicine*, *78*, 50–57..

Gagliotti, C., Ricchizzi, E., Buttazzi, R., Tumietto, F., Resi, D., & Moro, M. L. (2014). Hospital statistics for antibiotics: defined versus prescribed daily dose. *Infection*, *42*(5), 869-873.

Garcell, H. G., Arias, A. V., Sandoval, C. P., Valle Gamboa, M. E., Sado, A. B., & Alfonso Serrano, R. N. (2017). Impact of a focused antimicrobial stewardship program in adherence to antibiotic prophylaxis and antimicrobial consumption in appendectomies. *Journal of Infection and Public Health*, *10*(4), 415–420.

García-Rodríguez, J. F., Bardán-García, B., Peña-Rodríguez, M. F., Álvarez-Díaz, H., & Mariño-Callejo, A. (2019). Meropenem antimicrobial stewardship program: clinical, economic, and antibiotic resistance impact. *European Journal of Clinical Microbiology and Infectious Diseases*, *38*(1), 161–170.

García-Rodríguez, José Francisco, Bardán-García, B., Juiz-González, P. M., Vilariño-Maneiro, L., Álvarez-Díaz, H., & Mariño-Callejo, A. (2021). Long-Term Carbapenems Antimicrobial Stewardship Program. *Antibiotics*, *10*(1), 15.

Hecker, M. T., Son, A. H., Murphy, N. N., Sethi, A. K., Wilson, B. M., Watkins, R. R., & Donskey, C. J. (2019). Impact of syndrome-specific antimicrobial stewardship interventions on use of and resistance to fluoroquinolones: An interrupted time series analysis. *American Journal of Infection Control*.

Horikoshi, Y., Suwa, J., Higuchi, H., Kaneko, T., Furuichi, M., Aizawa, Y., Fukuoka, K., Okazaki, K., Ito, K., & Shoji, T. (2017). Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. *International Journal of Infectious Diseases*, *64*, 69–73.

Huh, K., Chung, D. R., Park, H. J., Kim, M. J., Lee, N. Y., Ha, Y. E., Kang, C. I., Peck, K. R., & Song, J. H. (2016). Impact of monitoring surgical prophylactic antibiotics and a computerized decision support system on antimicrobial use and antimicrobial resistance. *American Journal of Infection Control*, *44*(9), 145-152.

Kauppinen, H., Ahonen, R., & Timonen, J. (2017). The impact of electronic prescriptions on medication safety in Finnish community pharmacies: A survey of pharmacists. *International Journal of Medical Informatics*, *100*, 56–62.

Khan, H. A., Baig, F. K., & Mehboob, R. (2017). Nosocomial infections: Epidemiology, prevention, control and surveillance. *Asian Pacific Journal of Tropical Biomedicine*, *7*(5), 478–482.

Khdour, M. R., Hallak, H. O., Aldeyab, M. A., Nasif, M. A., Khalili, A. M., Dallashi, A. A., Khofash, M. B., & Scott, M. G. (2018). Impact of antimicrobial stewardship programme on hospitalized patients at the intensive care unit: a prospective audit and feedback study. *British Journal of Clinical Pharmacology*, *84*(4), 708–715.

Knight, J., Michal, J., Milliken, S., & Swindler, J. (2020). Effects of a Remote Antimicrobial Stewardship Program on Antimicrobial Use in a Regional Hospital System. *Pharmacy*, *8*(1), 41.

Knox, J. F., & Wiemiller, M. J. P. (2017). Antibiotic Stewardship Choosing Wisely. In *Physician Assistant Clinics*, 2(3), 489–501

Lanbeck, P., Ragnarson Tennvall, G., & Resman, F. (2016). A cost analysis of introducing an infectious disease specialist-guided antimicrobial stewardship in an area with relatively low prevalence of antimicrobial resistance. *BMC Health Services Research*, *16*(1).

Lawes, T., Lopez-Lozano, J. M., Nebot, C. A., Macartney, G., Subbarao-Sharma, R., Dare, C. R. J., Wares, K. D., & Gould, I. M. (2015). Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: A non-linear time-series study. *The Lancet Infectious Diseases*, *15*(12), 1438–1449.

Lee, T. C., Frenette, C., Jayaraman, D., Green, L., & Pilote, L. (2014). Antibiotic self-stewardship: Trainee-led structured antibiotic time-outs to improve antimicrobial use. *Annals of Internal Medicine*, *161*, 53-58.

Lesprit, P., de Pontfarcy, A., Esposito-Farese, M., Ferrand, H., Mainardi, J. L., Lafaurie, M., Parize, P., Rioux, C., Tubach, F., & Lucet, J. C. (2015). Postprescription review improves in-hospital antibiotic use: A multicenter randomized controlled trial. *Clinical Microbiology and Infection*, *21*(2), 180-187.

Lester, R., Haigh, K., Wood, A., MacPherson, E. E., Maheswaran, H., Bogue, P., Hanger, S., Kalizang'oma, A., Srirathan, V., Kulapani, D., Mallewa, J., Nyirenda, M., Jewell, C. P., Heyderman, R., Gordon, M., Lalloo, D. G., Tolhurst, R., & Feasey, N. A. (2020). Sustained Reduction in Third-generation Cephalosporin Usage in Adult Inpatients Following Introduction of an Antimicrobial Stewardship Program in a Large, Urban Hospital in Malawi. *Clinical Infectious Diseases*.

Libertin, C. R., Watson, S. H., Tillett, W. L., & Peterson, J. H. (2017). Dramatic effects of a new antimicrobial stewardship program in a rural community hospital. *American Journal of Infection Control*, *45*(9), 979–982.

Livermore, D. M., Hope, R., Reynolds, R., Blackburn, R., Johnson, A. P., & Woodford, N. (2013). Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? *Journal of Antimicrobial Chemotherapy*, *68*(11), 2667–2674.

Mardani, M., Abolghasemi, S., & Shabani, S. (2020). Impact of an antimicrobial stewardship program in the antimicrobial-resistant and prevalence of clostridioides difficile infection and amount of antimicrobial consumed in cancer patients. *BMC Research Notes*, *13*(1), 246.

Mendem, S. K., Alasthimannahalli Gangadhara, T., Shivannavar, C. T., & Gaddad, S. M. (2016). Antibiotic resistance patterns of Staphylococcus aureus: A multi center study from India. *Microbial Pathogenesis*, *98*, 167–170.

Miliani, K., L'Hériteau, F., Lacavé, L., Carbonne, A., & Astagneau, P. (2011). Imipenem and ciprofloxacin consumption as factors associated with high incidence rates of resistant Pseudomonas aeruginosa in hospitals in northern France. *Journal of Hospital Infection*, *77*(4), 343–347.

Murri, R., Taccari, F., Spanu, T., D'Inzeo, T., Mastrorosa, I., Giovannenze, F., Scoppettuolo, G., Ventura, G., Palazzolo, C., Camici, M., Lardo, S., Fiori, B., Sanguinetti, M., Cauda, R., & Fantoni, M. (2018). A 72-h intervention for improvement of the rate of optimal antibiotic therapy in patients with bloodstream infections. *European Journal of Clinical Microbiology and Infectious Diseases*, *37*(1), 167–173.

Neo, J. R. J., Niederdeppe, J., Vielemeyer, O., Lau, B., Demetres, M., & Sadatsafavi, H. (2020). Evidence-Based Strategies in Using Persuasive Interventions to Optimize Antimicrobial Use in Healthcare: a Narrative Review. *Journal of Medical Systems*, *44*(3), 64.

Nilholm, H., Holmstrand, L., Ahl, J., Månsson, F., Odenholt, I., Tham, J., Melander, E., & Resman, F. (2015). An audit-based, infectious disease specialist-guided antimicrobial stewardship program profoundly reduced antibiotic use without negatively affecting patient outcomes. *Open Forum Infectious Diseases*, *2*(2).

O'Driscoll, T., & Crank, C. W. (2015). Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management. *Infection and Drug Resistance*, *8*, 217–230.

Okumura, L. M., da Silva, M. M. G., & Veroneze, I. (2015). Effects of a bundled Antimicrobial Stewardship Program on mortality: A cohort study. *Brazilian Journal of Infectious Diseases*, *19*(3), 246–252.

Palmay, L., Elligsen, M., Walker, S. A. N., Pinto, R., Walker, S., Einarson, T., Simor, A., Rachlis, A., Mubareka, S., & Daneman, N. (2014). Hospital-wide rollout of antimicrobial stewardship: A stepped-wedge randomized trial. *Clinical Infectious Diseases*, *59*(6), 867–874.

Pardo, J., Klinker, K. P., Borgert, S. J., Butler, B. M., Giglio, P. G., & Rand, K. H. (2016). Clinical and economic impact of antimicrobial stewardship interventions with the FilmArray blood culture identification panel. *Diagnostic Microbiology and Infectious Disease*, *84*(2), 159–164.

Paulson, C. M., Handley, J. F., Dilworth, T. J., Persells, D., Prusi, R. Y., Brummitt, C. F., Torres, K. M., & Skrupky, L. P. (2020). Impact of a Systematic Pharmacist-Initiated Antibiotic Time-Out Intervention for Hospitalized Adults. *Journal of Pharmacy Practice*.

Peragine, C., Walker, S. A. N., Simor, A., Walker, S. E., Kiss, A., & Leis, J. A. (2020). Impact of a Comprehensive Antimicrobial Stewardship Program on Institutional Burden of Antimicrobial Resistance: A 14-Year Controlled Interrupted Time-series Study. *Clinical Infectious Diseases*, *71*(11), 2897–2904.

Percival, K. M., Valenti, K. M., Schmittling, S. E., Strader, B. D., Lopez, R. R., & Bergman, S. J. (2015). Impact of an antimicrobial stewardship intervention on urinary tract infection treatment in the ED. *American Journal of Emergency Medicine*, *33*(9), 1129–1133.

Phoon, H. Y. P., Hussin, H., Hussain, B. M., Lim, S. Y., Woon, J. J., Er, Y. X., & Thong, K. L. (2018). Distribution, genetic diversity and antimicrobial resistance of clinically important bacteria from the environment of a tertiary hospital in Malaysia. *Journal of Global Antimicrobial Resistance*, *14*, 132–140.

Pineda, R., Kanatani, M., & Deville, J. (2020). 102. Effects of an Antimicrobial Stewardship-guided MRSA Nasal Screening Review on Vancomycin Utilization for Respiratory Infections: A Quasi-Experimental Study. *Open Forum Infectious Diseases*, *7*(1), 65.

Pitiriga, V., Kanellopoulos, P., Kampos, E., Panagiotakopoulos, G., Tsakris, A., & Saroglou, G. (2018). Antimicrobial stewardship program in a Greek hospital: Implementing a mandatory prescription form and prospective audits. *Future Microbiology*, *13*(8), 889–896.

Ruiz, J., Salavert, M., Ramirez, P., Montero, M., Castro, I., Gonzalez, E., Roma, E., & Poveda, J. L. (2018). [Antimicrobial stewardship programme implementation in a medical ward]. *Revista Espanola de Quimioterapia : Publicacion Oficial de La Sociedad Espanola de Quimioterapia*, *31*(5), 419–426.

Sadiq, M. B., Syed-Hussain, S. S., Ramanoon, S. Z., Saharee, A. A., Ahmad, N. I., Noraziah, M. Z., Khalid, S. F., Naseeha, D. S., Syahirah, A. A., & Mansor, R. (2018). Knowledge, attitude and perception regarding antimicrobial resistance and usage among ruminant farmers in Selangor, Malaysia. *Preventive Veterinary Medicine*, *156*, 76–83.

Seah, V. X. F., Ong, R. Y. L., Lim, A. S. Y., Chong, C. Y., Tan, N. W. H., & Thoon, K. C. (2017). Impact of a Carbapenem Antimicrobial Stewardship Program on Patient Outcomes. *Antimicrobial Agents and Chemotherapy*, *61*(9).

Seah, X. F. V., Ong, Y. L. R., Tan, S. W., Krishnaswamy, G., Chong, C. Y., Tan, N. W. H., & Thoon, K. C. (2014). Impact of an antimicrobial stewardship program on the use of carbapenems in a tertiary Women's and Children's Hospital, Singapore. *Pharmacotherapy*, *34*(11), 1141–1150.

Shively, N. R., Moffa, M. A., Paul, K. T., Wodusky, E. J., Schipani, B. A., Cuccaro, S. L., Harmanos, M. S., Cratty, M. S., Chamovitz, B. N., & Walsh, T. L. (2020). Impact of a Telehealth-Based Antimicrobial Stewardship Program in a Community Hospital Health System. *Clinical Infectious Diseases*, *71*(3), 539–545.

So, M., Mamdani, M. M., Morris, A. M., Lau, T. T. Y., Broady, R., Deotare, U., Grant, J., Kim, D., Schimmer, A. D., Schuh, A. C., Shajari, S., Steinberg, M., Bell, C. M., & Husain, S. (2018). Effect of an antimicrobial stewardship programme on antimicrobial utilisation and costs in patients with leukaemia: a retrospective controlled study. *Clinical Microbiology and Infection*, *24*(8), 882–888.

Strazzulla, A., Bokobza, S., Ombandza, E., Kherallah, K., Hommel, S., Draidi, R., Bonutto, C., Zamponi, D. B., Gauzit, R., & Diamantis, S. (2020). Impact of an Antimicrobial Stewardship Program on Resistance to Fluoroquinolones of Urinary Enterobacteriaceae Isolated From Nursing Home Residents: A Retrospective Cohort Study. *Journal of the American Medical Directors Association*, *21*(9), 1322–1326.

Surat, G., Vogel, U., Wiegering, A., Germer, C.-T., & Lock, J. F. (2021). Defining the Scope of Antimicrobial Stewardship Interventions on the Prescription Quality of Antibiotics for Surgical Intra-Abdominal Infections. *Antibiotics*, *10*(1), 73.

Suwantarat, N., & Carroll, K. C. (2016). Epidemiology and molecular characterization of multidrug-resistant Gram-negative bacteria in Southeast Asia. *Antimicrobial Resistance and Infection Control*, *5*(1).

Tang, S. J., Gupta, R., Lee, J. I., Majid, A. M., Patel, P., Efird, L., Loo, A., Mazur, S., Calfee, D. P., Archambault, A., Jannat-Khah, D., Dargar, S. K., & Simon, M. S. (2018). Impact of Hospitalist-Led Interdisciplinary Antimicrobial Stewardship Interventions at an Academic Medical Center. *Joint Commission Journal on Quality and Patient Safety*.

Tartof, S. Y., Chen, L. H., Tian, Y., Wei, R., Im, T., Yu, K., Rieg, G., Bider-Canfield, Z., Wong, F., Takhar, H. S., & Qian, L. (2020). Do Inpatient Antimicrobial Stewardship Programs help us in the Battle against Antimicrobial Resistance? *Clinical Infectious Diseases*.

Tedeschi, S., Trapani, F., Giannella, M., Cristini, F., Tumietto, F., Bartoletti, M., Liverani, A., Pignanelli, S., Toni, L., Pederzini, R., Cavina, A., & Viale, P. (2017). An Antimicrobial Stewardship Program Based on Systematic Infectious Disease Consultation in a Rehabilitation Facility. *Infection Control and Hospital Epidemiology*, *38*(1), 76–82.

Teixeira Rodrigues, A., Roque, F., Piñeiro-Lamas, M., Falcão, A., Figueiras, A., & Herdeiro, M. T. (2019). Effectiveness of an intervention to improve antibiotic-prescribing behaviour in primary care: a controlled, interrupted time-series study. *Journal of Antimicrobial Chemotherapy*, *74*(9), 2788–2796.

Thampi, N., Shah, P. S., Nelson, S., Agarwal, A., Steinberg, M., Diambomba, Y., & Morris, A. M. (2019). Prospective audit and feedback on antibiotic use in neonatal intensive care: a retrospective cohort study. *BMC Pediatrics*, *19*(1), 105.

Trupka, T., Fisher, K., Micek, S. T., Juang, P., & Kollef, M. H. (2017). Enhanced antimicrobial de-escalation for pneumonia in mechanically ventilated patients: A cross-over study. *Critical Care*, *21*(1).

Wang, H. Y., Chiu, C. H., Huang, C. T., Cheng, C. W., Lin, Y. J., Hsu, Y. J., Chen, C. H., Deng, S. T., & Leu, H. S. (2014). Blood culture-guided de-escalation of empirical antimicrobial regimen for critical patients in an online antimicrobial stewardship programme. *International Journal of Antimicrobial Agents*, *44*(6), 520–527.

Waters, C. D. (2015). Pharmacist-driven antimicrobial stewardship program in an institution without infectious diseases physician support. *American Journal of Health-System Pharmacy*, *72*(6), 466–468.

Wenisch, J. M., Equiluz-Bruck, S., Fudel, M., Reiter, I., Schmid, A., Singer, E., & Chott, A. (2014). Decreasing Clostridium difficile Infections by an Antimicrobial Stewardship Program That Reduces Moxifloxacin Use. *Antimicrobial Agents and Chemotherapy*, *58*(9), 5079–5083.

Yusef, D., Hayajneh, W. A., Bani Issa, A., Haddad, R., Al-Azzam, S., Lattyak, E. A., Lattyak, W. J., Gould, I., Conway, B. R., Bond, S., Conlon-Bingham, G., & Aldeyab, M. A. (2021). Impact of an antimicrobial stewardship programme on reducing broad-spectrum antibiotic use and its effect on carbapenem-resistant Acinetobacter baumannii (CRAb) in hospitals in Jordan. *Journal of Antimicrobial Chemotherapy*, *76*(2), 516–523.