A Narrative Review of Antimicrobial Stewardship Interventions within In-patient Settings and Resultant Patient Outcomes

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The overuse of antibiotics has led to various healthcare problems such as the emergence of resistance in infectious microbes and mortality due to antibiotic resistant healthcare associated infections (HAIs). An antimicrobial stewardship (AMS) program is the set of interventions used worldwide to enhance the rational use of antibiotics especially for the hospitalized patients. This review aimed to describe the characteristics of the implemented AMS programs in various hospitals of the world mainly focusing on the interventions and patients outcomes. The literature about AMS program was searched through various databases such as PubMed, Google Scholar, Science Direct, Cochran Library, Ovid (Medline), Web of Science and Scopus. In this review the literature pertaining to the AMS programs for hospitalized patients is sorted on the basis of various interventions that are categorized as formulary restriction (pre-authorization), guideline development, clinical pathway development, educative interventions and prospective audit. Moreover a clear emphasis is laid on the patient outcomes obtained as a result of these interventions namely the infection control, drop in readmission rate, mortality control, resistance control and the control of an overall cost of antibiotic treatment obtained mainly by curbing the overuse of antibiotics within the hospital wards. AMS program is an efficient strategy of pharmacovigilance to rationalize the antimicrobial practice for hospitalized patients as it prevents the misuse of antibiotics, which ultimately retards the health threatening effects of various antibiotics.

Keywords: Antimicrobial stewardship (AMS) program, interventions, patient outcomes, study designs

INTRODUCTION

The importance of antibiotics in controlling certain deadly infections is undeniable but due to this repute the antibiotics are used in high amounts that have led to certain health-related problems.[1] The high systemic use of antibiotics in the hospitals has given rise to various antibiotic-related adverse drug reactions (ADR) challenging the healthcare professionals.[2] The antibiotic-resistant organisms sequentially cause various superinfections which are hard to treat even with certain broad-spectrum antibiotics.[3] In recent years, a high incidence of hospital-acquired antibiotic resistance, the association of antibiotic use with Clostridium difficile infections (CDI) within the in-patients of clinical settings and an escalation of healthcare cost due to overuse of antibiotics are the problems needing special strategies to be controlled.[4]
In the 1950s, the establishment of the concept that an inappropriate use of antimicrobials is the cause of antimicrobial resistance (AMR); thus, to address this problem various hospitals in 1970s initiated localized antibiotic restriction programs to educate the prescribers which showed only a limited success.\[^3\] This initial restriction policy for antibiotics later on led to a more modified approach in the form of a set of interventions termed as an antimicrobial stewardship (AMS) program.\[^5\] The targeted patient outcomes of an AMS program are mainly to control the antibiotic-related adverse effects, antibiotic resistance, the incidence of superinfections, and a reduction in the total cost of treatment.\[^6\] These coordinated AMS efforts emphasize the selection of antibiotics based on culture sensitivity test (CST), optimal duration of therapy, and a selection of oral route rather than a parenteral route of antibiotic administration.\[^7-9\] There are certain interventions that can be categorized into restrictive, persuasive and structural being implemented during an AMS program targeting certain patient-related outcomes (primary or secondary) either in the form of a reduction in days of antibiotic therapy, a fall in microbiological resistance or as a cost reduction of antibiotic treatment.\[^10-12\]

The purpose of this review was to present summarized evidence of the effectiveness of AMS programs within the in-patient clinical settings in the perspective of clinical outcomes pertaining to the improvement in antibiotic prescribing trends, controlling the microbiological resistance, fall in the occurrence antibiotic-resistant infections, and the reduction of the cost of antibiotic treatment and to describe the recent studies elaborating various restrictive, persuasive, and structural interventions for AMS.

**Materials and Methods**

**Search strategy**

For the collection of the published data and findings of the AMS programs in the in-patient clinical settings, the most important databases such as PubMed, Google Scholar, Science Direct, Cochran Library, Ovid (Medline), Web of Science, and Scopus were searched. The reference lists of the reviewed articles were also searched to cover the pertinent studies describing the observations of healthcare researchers in the context of AMS.

**Study selection**

All the relevant titles, abstract, and articles were reviewed and the study populations and in-patient settings which were not relevant to Malaysia were excluded. In other words, the studies focusing on those infections which are not usually observed in the Malaysian population were excluded. Secondly, those studies in which the intervention was not made at all or the intervention was not relevant to the in-patient AMS program were excluded. Similarly, the studies where the impact of the in-patient AMS program was not assessed and was performed merely to increase awareness regardless of resultant outcomes were excluded in this review. Based on patient outcomes all the studies reporting at least one of the patient outcomes such as days of therapy (DOT) of antibiotics, the impact of intervention on the occurrence of ADR, microbial resistance, and the fall in the expenditure of antibiotic treatment were included. Studies focusing on the surgical and medical prophylaxis only were also excluded. Community-based studies performed other than the hospitals are not included in this review. Those studies focusing on the interventions targeting the antivirals, antifungals, and the topical use of antibiotics are excluded as well. In short, the main focus of this review was on the studies in which the set of interventions under the AMS programs being implemented for the hospitalized populations using various study designs namely interrupted time series (ITS), case-control trials (CCT), randomized controlled trials (RCT) and control before and after (CBA) to assess these programs. The Centre of Disease Control and Prevention (CDC) in its policy statement in the year 2014 recommended for all the acute care hospitals of the USA to implement an AMS program to rationalize the antimicrobial practice.\[^12\] Following the CDC policy statement regarding AMS program implementation in hospitals, all the published articles from 2014 till 2019 fulfilling the selection criteria mentioned above are included in this review. The study selection strategy for the reviewed literature is described in the Figure 1.

**Data abstraction**

The data were extracted for AMS efforts targeting the primary patient outcomes, prescribing outcomes, and the microbial resistance outcomes. The primary patient outcomes found were the impact of AMS program on mortality, duration of stay in hospital, further admissions in hospital after being treated for primary infection, and a fall in the occurrence of adverse drug reactions. The main prescribing outcomes being focused were the selection of antibiotics, dose of the antibiotic, route of administration, and the number of days of antibiotic therapy. Microbiological outcomes included the frequency of the emergence of AMR particularly that of CDI, *Acinetobacter baumannii* infections, and multidrug resistant *Staphylococcus aureus* (MRSA) infections. The criteria described above about the study
Data structure
The data information collected after the review of the literature covering the scope of the AMS programs within the in-patient clinical settings was structured based on the type of intervention being adopted to achieve various goals in the form of patient outcomes regarding the antibiotic use, cost, infection control, resistance, length of stay, and the control of overall mortality. The interventions found in included studies were classified as restriction (preauthorization), clinical pathway development, guidelined development, prospective audit, and the educative interventions. The studies following a particular study design to assess the outcomes of the AMS programs were mainly focused. The main study designs found in the included studies were RCTs, CCT, CBA, and ITS.

Results
The number of abstracts and titles that were found for this review were 5875 of which 48 studies were found relevant to the aforementioned criteria and were included based on their relevance. Most of the studies included have described the interventions under the scope of the AMS program being categorized as the formulary restriction (preauthorization), prospective audit, educative, clinical pathway development, and guideline development. The outcomes being obtained generally were the use of antibiotics, control of AMR, control of mortality, control of the antimicrobial cost of treatment, an overall impact on the length of patients’ stay in the hospital wards, and readmission rate.

Interventions and outcomes of antimicrobial stewardship programs for hospitalized patients

Formulary restriction
Of the 48 studies found relevant for this review, 11 (23%) have used formulary restrictions (preauthorization) as an intervention to rationalize the antimicrobial practice. One study performed in the Malaysian tertiary hospital used de-escalation policy for broad-spectrum antibiotics to control the ventilator-associated pneumonia (VAP) in intensive care unit (ICU) patients with the targeted outcome of mortality control and length of stay of patients. In a similar study, the use of broad-spectrum cephalosporins and fluoroquinolones was discouraged in a 300-bed hospital to control the overall cost of treatment. The infections within the hospital in patients, three studies were found to use formulary restriction as an intervention. The infections that were controlled in these studies were *A. baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA), healthcare-associated pneumonia, and CDI infections. Five studies use formulary restriction as an intervention to control the antimicrobial use within the hospital wards where the use of mandatory order form, revision of protocols of empiric antibiotic therapy, review of antibiotic prescriptions by AMS team for approval and discontinuation of antibiotics for the patients not having any bacterial infection were described as the major tools to implement this intervention. No effect of preauthorization was seen on mortality, length of stay, and readmission rate.

Prospective audit
The review of studies using AMS program as a tool to draw various clinical outcomes for the in-patients 16 studies (33%) used prospective audit solely as the main intervention during the implementation of AMS program and in most of the studies the AMS team, an infectious disease (ID) physician or a clinical pharmacist performed the prospective audits. Nine studies in which the prospective audit was used as an intervention described a fall in the overall usage of antibiotics. Three studies using the prospective audit as an intervention of the AMS program achieved the clinical outcome in the form of fall of overall length of stay of the patients. In two studies, prospective audit is used as an intervention to control the antimicrobial cost of treatment. A study being performed in the Tokyo Metropolitan Hospital in Japan using prospective audit intervention to control the resistant Gram-negative bacilli (GNB) infection found a significant ($P < 0.01$) fall of carbapenem resistance in *Pseudomonas aeruginosa*. In an ID physician-led community hospital AMS program where the ID physician closely monitored the susceptibility and cost patterns of antimicrobial practice showed a remarkable improvement in controlling the AMR and cost within the hospital.

Education
The review of AMS program-related published literature revealed that of 48 studies selected, 7 (14.6%) used continuous medical education (CME) and other educative methods for the healthcare staff of hospitals to obtains various clinical outcomes. Four studies used educative interventions to curb the overuse of antibiotics within the hospital wards. In a recent study, the general medicine department carried out a formal set of CME programs for the hospital staff to convert intravenous (IV) to oral route for antimicrobial practice and obtained the targeted cost-effectiveness as an outcome. To obtain the reduction in overall
mortality rate in the ID patients a study used an educative intervention-based AMS program in which a pharmacist did schedule discussions with the physicians and microbiologists to enhance their coordination for minimizing antimicrobial usage and resistance within the hospital.\cite{45} Another study using the educative intervention describes that a systematic counselling of prescribers by the AMS team resulted the faster cure of patients with urinary tract infections (UTI).\cite{56}

Two studies (4.2%) used the mixed prospective audit and educative interventions-based AMS programs to rationalize antimicrobial practice in hospital wards.\cite{47,48} A study in the rural hospital of Georgia the AMS team organized regular lectures for the prescribers of antibiotics followed by a regular feedback and audit to eradicate the CDI.\cite{47} In the second study using mixed educative and prospective audit interventions patient counseling and feedback audit was used to obtain the outcome of reduced antibiotic usage without influencing the mortality rate.\cite{48}

Clinical pathway development

During the review of literature, eight studies (16.6%) described the AMS programs in which certain constructive changes in the clinical pathways resulted in various clinical outcomes within the hospitalized patients. Three studies described an improvement in the overall length of stay of the in-patients where the AMS program focused on the development of an efficient clinical pathway to obtain various clinical outcomes.\cite{49,51,52} All these three studies focused on the improvement in clinical pathway by involving various diagnostic techniques for infections so as to shift rapidly from empiric to definitive therapy that highly influenced the patients' length of stay and the quality of treatment. The diagnostic procedures that were mainly introduced for rapid identification of infectious organisms were matrix-assisted laser desorption and implication of mass spectroscopy due to which a more focused antibiotic therapy was adopted that remarkably improved the course of treatment and clinical outcomes. In a study, the blood culture-guided de-escalation intervention was practiced during the AMS program where the ID physician had to review the regimen that remarkably benefited the cost control of antimicrobial therapy.\cite{52} In another study, the introduction of film array blood culture panel for diagnosis of bacteremia significantly ($P < 0.001$) helped to control the resistant MRSA that also decreased the overall cost of treatment.\cite{53} In three studies, the efficient coordination of microbiologist with the prescribers, the introduction of polymerase chain reaction (PCR) channels, and the use of matrix-assisted desorption targeted diagnosis of various blood stream infections (BSIs) including the identification of resistant genes that greatly helped to curb the overuse of antibiotics for a wide range of in-patients.\cite{54,56}

Guideline development

In a recent study focusing on AMS program in which the formal guidelines by an ID physician were given to the prescribers to control the Meropenem-related multi-drug resistant strains in patients with BSI. This intervention significantly ($P < 0.001$) decreased the use of Meropenem within the hospital and ultimately produced beneficial effects on cost and mortality due to multidrug-resistant infections.\cite{57} In another study, a bundled AMS program was adopted and the adherence to standard care guidelines during the treatment of bacteremia patients with antibiotics was strictly monitored by the AMS team that significantly ($P < 0.001$) reduced the mortality among the in-patients of a tertiary hospital.\cite{58} Another study performed in the pediatric ward of a hospital in Warsaw described that a committed adherence to the guidelines designed for the rational use of antibiotics as mentioned in the Hospital's Antibiotic Policy (HAP) decreased the overuse of various antibiotics estimated as defined daily dose DDD/100 admissions.\cite{59} The findings of the reviewed literature are summarized in the Table 1 as follows whereas the framework of interventions being implemented in the AMS programs and resultant outcomes is described in Figure 2.

Discussion

The findings of this review depict that the AMS program could be an effective set of interventions to improve the antimicrobial practice within the hospital wards whether it could be by the improvements in the prescribing patterns or by the control of microbiological resistance without a considerable adverse impact on overall course of treatment.\cite{60,61,62} Despite the fact that AMS program improves the overall use of antibiotics that ultimately reduce the cost of treatment, a lack of evidence has been found in terms of a clear relationship between the fall of antibiotic use and patients' outcomes such as infection control, mortality, readmission rate and length of stay.\cite{62}

The general concept found in most of the studies is that the overuse of antibiotics contributes to the emergence of antimicrobial-resistant strains, increase in the treatment cost, and various other deleterious health impacts. It is an obvious expectation that after implementation of AMS programs within the healthcare settings a clear impact could be seen in the form of declined occurrence of AMR, but in fact this outcome is quite hard to be tested and even harder to prove that the fall in AMR is an impact of AMS program.\cite{63}
Table 1: Description of included studies

| References | Study design | Intervention | Type of intervention | Purpose | Outcomes |
|------------|-------------|--------------|----------------------|---------|----------|
| [13]       | CBA         | Restriction of moxifloxacin use | Formulary restriction | Reduction in no. of CDI cases in hospital wards | Infection control (CDI), use (DDD) |
| [25]       | ITS         | Twice weekly time out audits using structured electronic check list | Prospective audit | Optimization of antibiotic use | Use (DDD), cost, infection control (CDI) |
| [49]       | ITS         | Rapid identification of gram positive bacteremia. | Clinical pathway development | Reduction in the length of patient stay in the hospital | Length of stay (LOS), use (DOT), cost |
| [52]       | ITS         | Blood culture guided definitive antibiotic therapy | Clinical pathway development | Shifting of empiric therapy to definitive therapy | Cost, use, infection control |
| [60]       | RCT         | Counselling sessions for prescribers within a tertiary hospital. | Educative | Improvement in prescribing patterns | Use (DDD), dose |
| [41]       | CCT         | Academic detailing in the leukemia units of the hospital. | Educative | Reduction in antimicrobial overuse in leukemia in-patients | Use (DDD), cost |
| [44]       | CBA         | Continuous medical education programs | Educative | Conversion of IV to oral consumption of antibiotics to control cost of treatment | Cost, use (DDD) |
| [45]       | CCT         | Bundled AMS program with scheduled discussions of clinical pharmacist with physicians and microbiologists. | Educative | Control the antimicrobial use to control mortality due to antimicrobial resistance. | Mortality, use (DDD) |
| [47]       | CBA         | Lectures for prescribers to achieve antimicrobial stewardship followed by regular audit. | Educative/ prospective audit | Control of CDI. | Infection control (C. difficile), cost, use |
| [46]       | CBA         | Educate the prescribers about the impact of resistance on over all treatment of urinary tract infections (UTI). | Educative | To achieve a faster cure of UTIs by controlling resistant microbes. | Resistance |
| [50]       | CBA         | Rapid identification of *Acinetobacter baumannii* infection by mass spectroscopy. | Clinical pathway development | To control the length of patient stay and cost of treatment. | Length of stay |
| [42]       | RCT         | Education of staff to use antibiotics carefully for the prophylaxis of infections after appendectomies | Educative | Control of prophylactic use of antibiotics. | Use (DDD) |
| [48]       | RCT         | Patient counseling on regular basis, audit and feedback in coordination with pharmacy and microbiological laboratory. | Educative/prospective audit | Reduction of antimicrobial days of therapy. | Use (DOT) |
| [37]       | CBA         | Formal recommendations of infectious disease physicians to Meropenem prescribing physicians. | Guideline development | Control of Meropenem overuse and resistance | Use (DOT), cost |
| [51]       | CBA         | Use of mass spectroscopy for rapid diagnosis of blood stream infections. | Clinical pathway development | Control of resistance in gram negative bacteria | Length of stay, mortality |
| [54]       | CCT         | Efficient coordination with microbiologists for a definitive therapy. | Clinical pathway development | De-escalation of antibiotic use for empiric therapy. | Use (DOT), length of stay |
| [14]       | ITS         | Sequential syndrome specific antimicrobial stewardship to control Fluoroquinolone use. | Formulary restriction | Control of healthcare-associated pneumonia | Use (DOT), resistance (P. aeruginosa) |
| [26]       | CBA         | AMS program based on ward rounds, | Prospective audit | Control of antimicrobial over usage in pediatric wards. | Use (DOT), length of stay |
| [13]       | ITS         | Revision of the protocols of prophylactic antibiotic therapy. | Formulary restriction | Control of antimicrobial usage. | Use (DDD), infection control (CDI, P. aeruginosa) |
| References | Study design | Intervention | Type of intervention | Purpose | Outcomes |
|------------|--------------|--------------|----------------------|---------|----------|
| [55] CCT   | Introduction of PCR based diagnostic panel for definitive therapy for 19 bacterial, 5 candida strains and 4 resistant genes. | Clinical pathway development | Control of usage and cost of use, cost antibiotic treatment. | Use (DDD) |
| [31] RCT   | Regular periodic review of antibiotic prescriptions of medical ward and recommendations for prescribers to control antibiotic usage. | Prospective audit | Control of antibiotic usage and cost effectiveness. | Use (DDD) |
| [16] CBA   | Introduction of mandatory order form for five broad-spectrum alert antibiotics. | Formulary restriction | Control of usage of certain broad-spectrum antibiotics | Use (DDD) |
| [24] ITS   | Review of antibiotic prescriptions by the AMS team prospectively. | Prospective audit | Control of overuse of Carbapenems. | Use (DDD, DOT), cost |
| [58] CBA   | Adoption of Antimicrobial Stewardship bundle in hospital. | Guideline development | Control of deaths due to Staphylococcus aureus bacteremia. | Mortality |
| [43] CBA   | Twice weekly rounds by the clinical pharmacist into the hospital wards as a part of continuous medical education for staff. | Educative | To enhance the appropriate use of antibiotics and prevent the misuse. | Use (DOT), length of stay |
| [38] ITS   | Evaluation of gram GNB resistance to Carbapenems | Prospective audit | Control of GNB resistance to Carbapenems. | Resistance (P. aeruginosa), use (DOT), length of stay, mortality, Cost |
| [39] ITS   | A regular audit of the prescribed antibiotics to the urology patients by the hospital antimicrobial stewardship team following a cost minimization model. | Prospective audit | Control of the antibiotic cost of treatment in the urology ward of the academic hospital | Cost |
| [32] RCT   | An audit and feedback based review of antibiotic prescription orders in ICUs. | Prospective audit | Control the over use of certain broad-spectrum antibiotics within the hospital ICU. | Use |
| [34] ITS   | An audit of community acquired pneumonia (CAP) adult in-patients using antibiotics and recommendations on review of prescriptions. | Prospective audit | Control the length of stay and duration of antibiotic therapy. | Length of stay, use (DOT) |
| [17] CCT   | The antibiotic use for patients with no bacterial infection was discontinued within 24 hours of the onset of treatment. | Formulary restriction | Control of misuse of antibiotics. | Use (DOT), length of stay, infection control and mortality control. |
| [27] CBA   | Regular review and feedback of antibiotic prescriptions of ICU by the AMS team. | Prospective audit | De-escalation of antibiotic empiric therapy and promotion of prescriptions based on culture sensitivity test (CST). | Use (DDD and DOT), length of stay. |
| [35] ITS   | Restriction of the use of Cephalosporins, Penicillins and Fluoroquinolones without health screening in primary care hospitals. | Formulary restriction | Control of the prevalence of healthcare-associated MRSA infections. | Infection control (MRSA), use (DDD) Use (DOT) |
| [32] RCT   | A regular post prescription review of antibiotic prescriptions by the infectious disease physician (IDP) performed. | Prospective audit | To enhance the appropriateness of antimicrobial prescriptions. | Use (DOT) |
| [20] CBA   | Infectious disease specialist guided twice weekly audit of antibiotic prescriptions. | Prospective audit | Reduction in the number of patients using antibiotics along with the reduction in duration of antibiotic therapy. | Use, mortality, readmission rate, length of stay |
**Table 1: Continued**

| References | Study design | Intervention | Type of intervention | Purpose | Outcomes |
|------------|--------------|--------------|----------------------|---------|----------|
| [37]       | CBA          | An audit of the antibiotic prescriptions for determining the cost of therapy. | Prospective audit | Control the cost of antibiotic therapy. | Cost |
| [34]       | ITS          | Case audits by AMS team by automatic e-mail alerts after 48 hours of antibiotic therapy. | Prospective audit | Control of length of patient stay. | Length of stay, use, cost |
| [59]       | CBA          | Implementation of a multidimensional HAP in pediatric ward. | Guideline development | Control of the misuse of antibiotics in pediatric ward. | Use |
| [56]       | CCT          | Targeted identification of pathogens by the use of matrix assisted desorption diagnosis. | Clinical pathway development | Control of overuse of antibiotics by minimizing multi-drug resistant infection rate, length of stay outbreaks. | Use, mortality, readmission rate, length of stay |
| [33]       | CBA          | Infectious disease pharmacist (IDP) had to perform an audit of antimicrobial prescriptions of the patients with community acquired pneumonia (CAP) on daily basis. | Prospective audit | Reduction in an average length of stay in the hospital wards of the patients with CAP. | Length of stay (not significant) |
| [22]       | ITS          | Restrictive policy for the use of third generation Cephalosporins and Fluoroquinolones and encouraged use of Penicillins as replacement therapy. | Formulary restriction | An effort to control the use and cost of treatment with third generation Cephalosporins and Fluoroquinolones. | Cost, use |
| [23]       | CCT          | Antibiotic de-escalation policy for ICU patients with ventilator-associated pneumonia (VAP). | Formulary restriction | To control the mortality and length of patient stay by conserving the effectiveness of broad-spectrum antibiotics. | Length of stay, mortality (both nonsignificant) |
| [39]       | RCT          | Infectious disease physician being hired to monitor the prescription and susceptibility patterns of antibiotics in the hospital. | Prospective audit | Control the antimicrobial treatment cost and emergence of resistant strains. | Cost, resistance |
| [53]       | CBA          | Film array blood culture diagnostic panel was introduced to achieve a definitive antibiotic therapy. | Clinical pathway development | Control of cost and antimicrobial resistance caused by MRSA. | Cost, resistance |
| [19]       | CCT          | Regular review of antimicrobial orders by the AMS team to de-escalate empiric therapy in un-responsive ventilator patients of ICU. | Formulary restriction | Control of in-appropriate antimicrobial therapy in mechanical ventilation patients with pneumonia. | Use (not significant) |
| [29]       | CBA          | Weekly dedicated ward rounds to review the antimicrobial patient record and necessary recommendations by AMS team. | Prospective audit | Control of an overall consumption of antibiotics within the hospital in-patient wards. | Use |
| [20]       | CCT          | Discontinuation of Carbapenems, dose optimization and transfer to narrower spectrum antibiotics by review of prescription by the AMS team. | Formulary restriction | Control the over use of Carbapenems within the in-patients. | Use, length of stay, cost |
| [21]       | CBA          | Strict restriction policy to reduce Carbapenem use within the ICU of tertiary care center. | Formulary restriction | Control of endemic of the multi-drug resistant *A. baumannii* outbreak in the ICU of a tertiary care center. | Infection control, use |

AMS is the field of research that requires systematic and coordinated efforts by the researchers in the form of updated reviews in the light of contemporary data assessment and information that will help the policymakers and health-governing bodies to design the guidelines to achieve the desired clinical outcomes. Most of the studies included here are performed within a particular healthcare setting and describe the role of ID physicians, clinical pharmacists, and microbiologists in stewardship efforts particularly by
effective ward rounds.\cite{26,28,39,45,54} Most of the studies are performed over a limited period of time with brief follow-up pertaining to the impact of AMS programs. The studies highlighting the interventions performed for infection, resistance, and mortality due to infections mostly aimed to control the outbreak of various healthcare-associated infections (HAIs) such as CDI, VAP, community-acquired pneumonia (CAP), MRSA infections, an outbreak of \textit{A. baumannii}, and the control of GNB resistance.\cite{13,14,18,21,33,38,47} Introduction of rapid coordination between the physicians and microbiologist, rapid diagnosis by the use of PCR, mass spectroscopy, matrix-assisted laser desorption-based diagnosis, and the use of film array diagnostic panel for hospitalized bacteremia patients are the most common interventions to improve the clinical pathway of treatment with antibiotics that helped to achieve the outcomes such as fall in length of stay of in-patients, resistance against antibiotics, and the treatment cost.\cite{49-56}

The healthcare settings particularly the hospitals consist of various units that work in coordination to achieve the desired goals regarding the AMS.\cite{64} To coordinate the AMS efforts, a formal support by the hospital directors and administrators is highly important along with the health professionals actually practicing the antibiotics.\cite{65} Though an AMS program has certain common basic features, it is highly beneficial to focus on formative evaluation of the program as different healthcare settings situated in different regions differ in the need of interventions being implemented during an AMS program.\cite{66} For the success of an AMS program formative evaluation of the program comprising of the analysis of the antimicrobial-associated problem, designing and development of an intervention to address the problem, implementation of intervention systematically and then the evaluation of the significant or nonsignificant outcomes of intervention is very important.\cite{67} The role of clinical pharmacists, ID physicians, and microbiologists is of great importance for the success of an AMS program as the lack of ID experts within the hospitals in one of the key factors that limit the effectiveness of AMS efforts.\cite{3} In general, an AMS team of the hospital coordinating all the relevant hospital units plays the most important role in the successful implementation of the AMS program in a particular healthcare setting.\cite{68} Moreover, the planning steps involve a comprehensive data collection regarding antibiotic use to find out the units of the hospital needing interventions for a proper and rational antimicrobial practice.\cite{69} The collected data should provide the information about the use of antibiotics exceeding the permitted maximum limits and the relevant information about the in-patient population.\cite{6}
that are designed by the government of a country in the light of national healthcare scenario and requirements.\[70\] The formative evaluation of an AMS program helps the responsible authorities of a hospital to decide the further continuation of an intervention if the desired impact is observed or to allocate the fiscal and human resources for another intervention more mandatory than the previous one.\[71\] In the modern era with the rapid discovery of new antimicrobials, there is always a chance of change of antimicrobial practice as the sensitivity level of microbes and resistance patterns change frequently and to adapt to all these patterns an AMS program could be an effective tool to ensure a rational antimicrobial practice within a particular healthcare setting.\[72\] In this era of big data where most of the data could be retrieved through the computerized hospital database by the use of which the impact of AMS interventions to control the use and cost of certain antibiotics being used in specific hospital units could be monitored periodically and the hospital units or services needing a stewardship intervention could be easily identified.\[18,73\] However, the comparison of the data of individual hospitals with those hospitals having more established AMS programs and then the contribution of the stewardship data to the national data could effectively contribute to design the national and sequentially a global AMS policy.\[74-76\]

**Recommendations and Conclusion**

The literature reviewed for this review paper reveals that various interventions such as clinical pathway development, guideline development, prospective audit, educative interventions, and formulary restriction paved the way to various in-patient outcomes regarding the control of readmission rate, certain infections, resistance, mortality and an overall fall in use and cost of antimicrobial treatment. However, there is a need of further description of the duration and the exact strength of the impact of various interventions that could be highly beneficial for the improvement of the future AMS programs. Furthermore, most of the studies reviewed for this paper were limited to a single setting focusing on small ward populations which invites the future researchers to establish a multicenter study design that covers and compares the hospital in-patient populations of various hospitals on a large scale. However, from this review it could be concluded that the AMS program is an effective tool for obtaining some of the basic in-patient outcomes.
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Conflicts of interest
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