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Antimicrobial Stewardship — Do we need it in Pakistan?

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Abstract

In order to identify the literature and research available on development and implementation of Antimicrobial Stewardship Programme (ASP) in Pakistan, a systematic search of various electronic databases such as PubMed, Cochrane, CINAHL and PakMedinet from January 1, 2008 till November 2018 was conducted. Studies were included if they were focused around the development and implementation of the ASP within Pakistan. The search revealed that a significant knowledge gap exists regarding antimicrobial/antibiotic stewardship within Pakistan and not much is known about the current status of the development and implementation of antimicrobial stewardship programme. Only two research studies were found to be significant. Antimicrobial Stewardship Programme's development and implementation is highly essential and important. Currently, there exists a huge knowledge and systematic gap regarding ASP implementation at healthcare institutions.

Keyword: Antimicrobial Stewardship Programme; Antimicrobial resistance

Introduction

Antimicrobial Resistance (AMR) is one of the biggest threats to global health system, that leaves no choices for the healthcare professionals against deadly

super-pathogens.[1] Although, it is not among the Sustainable Developmental Goals, this endangers them as interventions against most of the pandemic infectious diseases, such as HIV, malaria and tuberculosis can jeopardise the achievement Sustainable Developmental Goals.[2, 3] WHO describes Antimicrobial Resistance as: "When microorganisms (such as bacteria, fungi, viruses, and parasites) change on exposure to antimicrobial drugs (such as antibiotics, antifungals, antivirals, anti-malarial, and anthelmintic)". Therefore, the standard treatment no longer works, the medicines become ineffective and infection persists in the body, increasing the danger of transmission to other patients and health-care professionals; illness and hospital stays are prolonged which require more extensive care in multidrug resistant (MDR) pathogens.[4, 5] However, nowadays healthcare practitioners are encountering the widespread challenge of MDROs such as S*taphylococcus aureus*, *Klebsiella pneumoniae, Acinetobacter baumanii, Enterobacter species and Pseudomonas Aeruginosa. Kebsiella pneumoniae* is the major cause of the hospital-acquired infections which encompasses blood infections and pneumonia. In most of the countries around the world, more than half of the patients are resistant to Carbapenem antibiotics. Moreover, in several parts of the world *E.coli* has become so resistant that fluoroquinolone antibiotics for treating urinary tract infections are no longer effective. On the other hand, *Enterobacteriaceae* which are the important nosocomial pathogens have become resistant to Carbapenem.[6]

The term "Antimicrobial Stewardship" is defined as an "Approach that embodies an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness."[7] The Antimicrobial Stewardship Programme (ASP) is designed to provide assistance for innocuous and cost-effective use of antimicrobials based on patient's characteristic, the microorganisms involved, and the source of infection along with the pharmacokinetics and pharmacodynamics at all healthcare facilities. ASP necessitates the right drug, the right amount, the right

indication, the right time and the right duration. The primary goal of the ASP is to improve clinical outcomes while curtailing unintended consequences related to antimicrobial usage, such as toxicities or the emergence of resistance.[3] ASP is a multi-disciplinary team-based approach involving the pharmacy, microbiology, infectious diseases physician and information technology. ASP comprises a certain set of interventions recommended by the Society of Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America **(**IDSA), and includes formulary restrictions, drug pre-authorisation, prospective audit and feedbacks, clinical guideline, clinical decision support system, patient's and prescriber's education, and microbiology laboratory susceptibility reports.[8] Moreover, ASP comes up with regulatory domain, measurement of antimicrobial prescribing, appropriateness and effectiveness of stewardship programme, which is critical to assess the need and impact of stewardship activities at the hospitals. Quality measures, such as antibiotic de-escalation, IV to PO conversion, length of therapy, defined daily doses/1,000 patient days, mortality, length of stay in hospital, readmission rates, drug cost, hospitalisation cost, etc. These measurements are important for improving healthcare delivery which is the vital indicators for antimicrobial stewardship programme.[9]

To overcome AMR, the global example of Antimicrobial Stewardship Green Light Committee (GLC) Initiative undertook to fight against the growing epidemics of MDR-TB, through the "Get Smart: know when antibiotics work" programme by the Centre of Disease Control. In addition, Antimicrobial Stewardship Programme has shown 22-36% reduction in irrational antimicrobial prescriptions.[10] It has been associated with improvement in patient's clinical and microbiological outcomes and reduction in length of hospital stay (LOS)), drug cost, mortalities, multi-drug resistant pathogens and adverse drug events.[11] According to a study conducted at 448 hospitals in the United States, there is an inverse relationship between the existence of ASP and local antimicrobial

resistance rates. The study showed that the increased implementations of recommended guidelines practices were associated with the lower prevalence of resistant microorganisms.[12] Furthermore, in one pilot study, it was concluded that 330,000 €/year could be saved with the reduction in the use of broad spectrum antimicrobials.[13] However, the evidence for effective execution of ASP in lower middle income countries LMICs is limited.

In Pakistan, there is a huge burden of MDR bacteria leading towards mortalities and morbidities together with restraining treatment modalities for infectious diseases.[14-17] The irrational use of antibiotics ranges between 9 to 64%.[18] In Pakistan, the highest number of drugs being prescribed is > 3 drugs/patient.[19] However, 70% of the patients are being prescribed antibiotics.[20] The abuse and overuse of antimicrobials are commonest among the general practitioners and public hospitals specifically for third generation Cephalosporins and other costly antimicrobials.[21] One study aimed at unnecessary use of antibiotic, conducted at a tertiary care hospital, revealed that 30% prescribed antibiotics were unnecessary. On top was third generation Cephalosporin (14%) and Quinolone (5%). However, 88% of prescriptions contained antibiotics without checking bacteriological culture.[18] Additionally, in Pakistan ≈50,000 unnecessary drug products are registered.[22] The most common and prevalent resistants found are with Extended Spectrum Beta-Lactamase (EBSL), Methicillin-resistant Staphylococcus aureus **(**MRSA), Carbapenem and MDR-TB.[23] There is no surveillance system that identify the over or underutilisation of antibiotic prescription in Pakistan. Antibiotics are used as over-the-counter medicine in majority of pharmacy stores across the country. In 2016, Pakistan Global Antibiotic Resistance Partnership (GARP) was formed for antimicrobial resistance curtailment. A series of work has been done by GARP-Pakistan, which mainly includes the launch of "National Framework for containment of Antimicrobial Resistance" and coordination at "National Consultative meeting for finalisation of Pakistan's Five-Year National Action Plan in December 2016.

In early 2018, Situational Analysis Report on Antimicrobial Resistance in Pakistan was published. The report mainly consists of the most current data on different aspects of AMR in various fields in Pakistan. Additionally, it will help policy-makers in decision-making for National Action Plan on AMR together with its implementation.[4] Within this document, antimicrobial resistance and antimicrobial stewardship programme at national level is not thoroughly addressed. With the aim of reducing the development and outspread of resistant bacteria, and for delivering healthier outcomes in patients, numerous hospitals have implemented measures to ensure optimum practice for antibiotics. Implementation of Antimicrobial Stewardship Programme helped hospitals to reach the purpose of providing patients needing antibiotic treatment with the correct antibiotics, at the right time, in appropriate dosage, and for the rightly defined duration. This short commentary is aimed to identify the literature and researches available on ASP development and implementation in Pakistan.

Search Strategy and Results

An exploratory search was tracked with identified databases, such as PUBMED/MEDLINE (Ovid), Google Scholar, CINAHL- Cumulative Index of Nursing and Allied Health Literature and PakMedinet, for the literature and researches regarding Antimicrobial Stewardship Programme in Pakistan. The search was restricted from January 1, 2008 till November 2018, with enrolment of human subjects only and in English language. The search includes terms for antimicrobial-agents (e.g., anti-bacterial agents), programme interventions, infection types and context (Pakistan) while the non-context specific and non-ASP related searches were excluded.

Moreover, all the titles and abstracts of possibly appropriate studies were initially evaluated in the review based on eligibility criteria. Abstracts that were not compatible with the eligibility criteria were excluded. After the screening, filter

was applied to all selected research articles for retrieving full-text review. Complete search strategy is documented in Table 1.

Our search yielded a total of nine titles from which four articles were shortlisted for review according to the objective. After applying inclusion and exclusion criteria at abstract-level, two references were included and others were excluded. (*Table 2- Consort of the Study*). The search revealed that a significant knowledge gap exists regarding antimicrobial/antibiotic stewardship within Pakistan and not much is known about antimicrobial stewardship programme development and implementation. Only two research studies were found to be significant. One of the studies has assessed the impact of pharmacist-led antibiotic stewardship programme in a PICU of low/middle income country. The study has shown significant reduction in antibiotic use.[24] Another study is about rationalising the use of Linezolid through Antibiotic Stewardship programme in a tertiary care teaching hospital in Pakistan. The study had revealed good compliance for antibiotic restriction that is 94% to Linezolid according to the institutional criteria.[25]

Discussion

There is a serious dearth of publications on AMR stewardship in Pakistan. An attempt was made to assemble evidence on ASP in Pakistan by conducting the review of published and grey literature on the extent of development and implementation of the programme in Pakistan.

Despite a well-established and proven efficacy of ASP globally, such initiatives are not being taken in the countrywide healthcare institutions. Pakistan is one of the signatories of the global initiative, that is "Global Action Plan to tackle AMR" adopted in the 68th session of World Health Assembly which took place in Geneva, in May 2015.[26] To fulfil government of Pakistan's commitment to the resolution on AMR, Pakistan has successfully developed the National Action Plan (NAP) in May 2017. The objective- 4 of NAP, deals with optimising the use

of antimicrobial medicines in human and animal health. Though the strategic activities for curtailing antimicrobial resistance are being planned and placed according to the interventions, execution at the provincial and federal level is inadequate. Despite the advocacy events conducted country-wide for all the stakeholders of tertiary care hospitals regarding ASP and its instituting, according to one study conducted at a tertiary care hospital in Karachi, in which 257 healthcare providers participated, more than half of healthcare providers have no knowledge of ASP.[27] However, there is an urgent need to sensitise healthcare professionals regarding ASP and structuration of ASP at all the tiers of health-care and other sectors such as poultry, veterinary and agriculture across Pakistan to address antimicrobial resistance and its subsequent outrageous effects. A major contributing factor is non-judicial use of antibiotics in the healthcare system; i.e., persistent use of antibiotics when they are not required, constant use of broad-spectrum antibiotic needlessly after the sensitivity results have been done, wrong antibiotic usage or recommending the incorrect dosage, or practicing the use of prophylactic antibiotic when it is not suggested.[28, 29] There is a lack of healthcare surveillance system that can detect this un-necessary use of antimicrobials.[7] Additionally, without valuable antimicrobials, prevention and cure of infections in inpatient and intensive care units is not possible.[1] The emergence of drug resistance requires tracking dispensation of antimicrobial to humans and animal husbandry, prohibiting over-the-counter sale of antibiotics, countrywide national action plan, awareness campaigns targeting general public and healthcare settings, increasing awareness regarding infection control and prevention, improving microbiology lab facilities and capabilities, efforts for research and development of novel antimicrobials and initiation and support for ASP at all healthcare facilities.[4, 28] The further multifarious aspects of antimicrobial stewardship in Pakistan which are under-addressed despite being the dire obligation for effective ASP activities are presented in Figure-1.

There is a dire need of implementation of ASP across the country. Provincial health departments should establish AS leadership/governance in health departments. A surveillance system should be in place which caters national and provincial antimicrobial resistance patterns and trends, develop antibiograms, and helps outbreak of antimicrobial-resistant infections. Moreover, development and provision of educational tools on prescribing appropriate antimicrobial drugs should be made mandatory for all healthcare facilities/institutes and healthcare professionals. Research is needed to develop a standardised definition of both appropriate and inappropriate antimicrobial use and the risk factors that promote the unnecessary overuse and abuse of antimicrobial therapy, thereby developing standardised tool for data collection, facilitating in measuring and interpreting antimicrobial use within and amongst healthcare institutions and thus creating the benchmark. However, it would delineate the fostering of redundant antimicrobial therapies. Patient-centred research is required to determine the most effective and cost-efficient utilisation of stewardship interventions in health facilities. It should suggest which ASP intervention is more suitable for the remarkable decrease in antimicrobial resistance level together with the enhanced patient clinical outcomes. These researches should consider robust study designs, such as multicentre randomised cluster designs, that are capable of comparing impact of ASP interventions within and amongst the healthcare institutions. Last but not the least, there is a dire need to implement ASP strategies at the community level specifically for general practitioners, which includes antimicrobial restriction policy, patient and prescriber education, adherence to locally available clinical pathways or antimicrobial prescribing guidelines and carrying out self-audits for their prescriptions for commonly encountered diseases.

Way Forward:

Informal Sector:

Regulatory bodies such as Pakistan Medical and Dental Council (PMDC), Pakistan Medical Association (PMA) and the government (both provincial and

federal) should evolve a mechanism to oversee, monitor and regularise the practice of all informal healthcare providers together with the initiation of formalised educational training and capacity-building exercises on the multidimensional aspects of delivering quality healthcare services, drugs and it's rational use. This sector should be motivated for intrinsic aptitude and attitude for self-auditing their prescribing practices. Self-auditing practices could be achieved via development of standardised norms, rules and criteria by the governing bodies together with potent enforcement. Moreover, timely monitoring of their practices should be carried out by regulatory bodies.

Formal Sector (Public and Private):

The uniform implementation of strategies for rationalising drug prescriptions and implementation of ASP should be carried out for the healthcare providers in the formal sector (public and private). It is recommended that the healthcare institutions should conduct audits for the identification of institution and department specific antimicrobial utilisation and antimicrobial resistance rates. The federal government should structure standardised KPIs (Key Performing Indicators) for all healthcare institutes and make it mandatory to report it quarterly and annually. Prescriber's education on AMR and promotion of good prescribing behaviour should be adapted with separate training modules for undergraduates, postgraduates, practitioners and other professionals, together with creating awareness among formal sector administrators and health team on AMR and ASP.

Conclusion

Our search identified that ASP is new in Pakistan. There is a significant knowledge gap in development and implementation of ASP at health facilities. Steward-based antibiotic stewardship programme is the key to decrease resistance and improve patient's clinical outcomes.

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Table 1: Search Strategy

Databases Searched	Search Strategy	Search Terms
PubMed	("antimicrobial stewardship" OR "antibiotic stewardship") AND Pakistan	Antimicrobial stewardship, anti-bacterial agents, antibiotics, broad spectrum antibiotics, tertiary care centres, tertiary referral centres, tertiary care hospital, Community –acquired pneumonia, Urinary tract infection, Empiric treatment for MRSA, Non-C. Difficile Infections
Cochrane	Antimicrobial stewardship AND tertiary care hospital* AND Pakistan	
CINAHL (Cumulative Index of Nursing and Allied Health Literature)	Antimicrobial stewardship* AND prospective audits OR formulary restriction OR preauthorization AND tertiary care hospital* AND Pakistan	
PakMedinet	Antimicrobial stewardship AND Pakistan	

Table 2: Consort of Study.

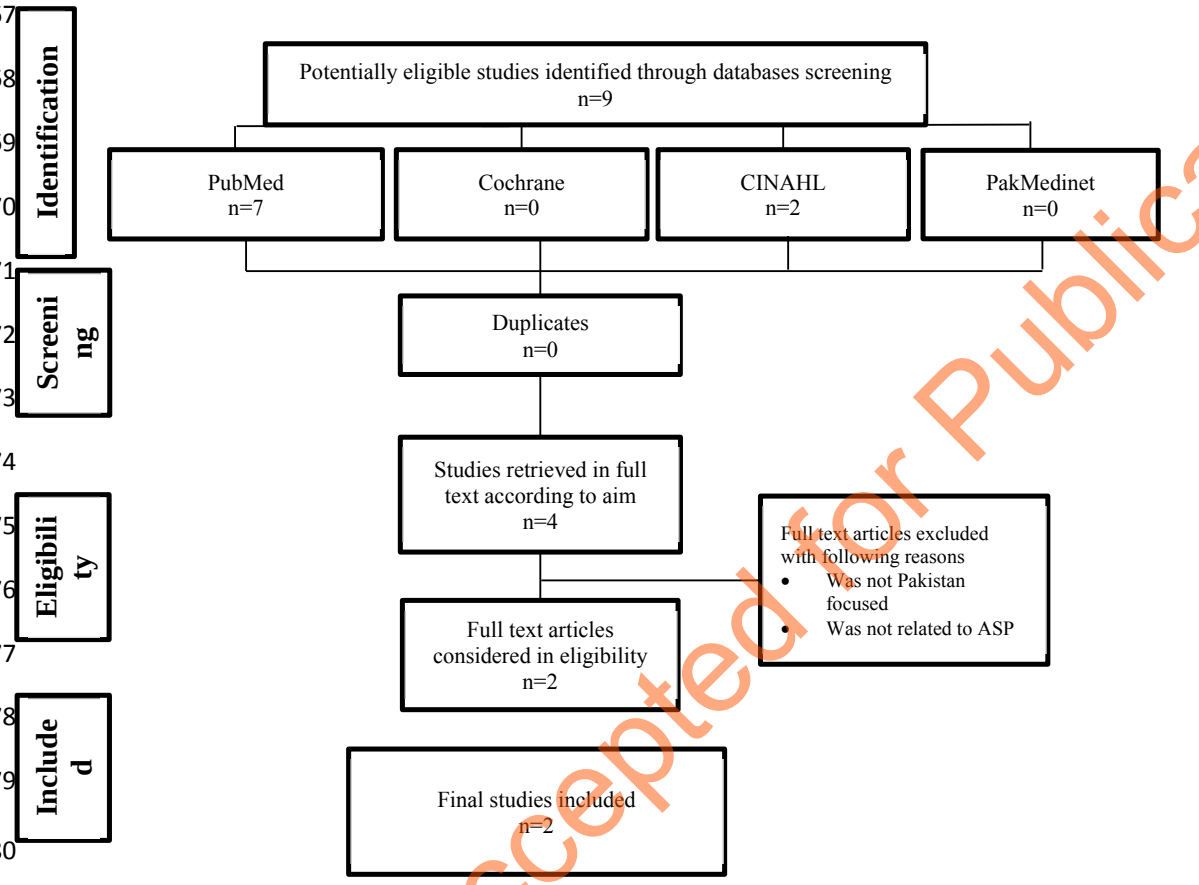

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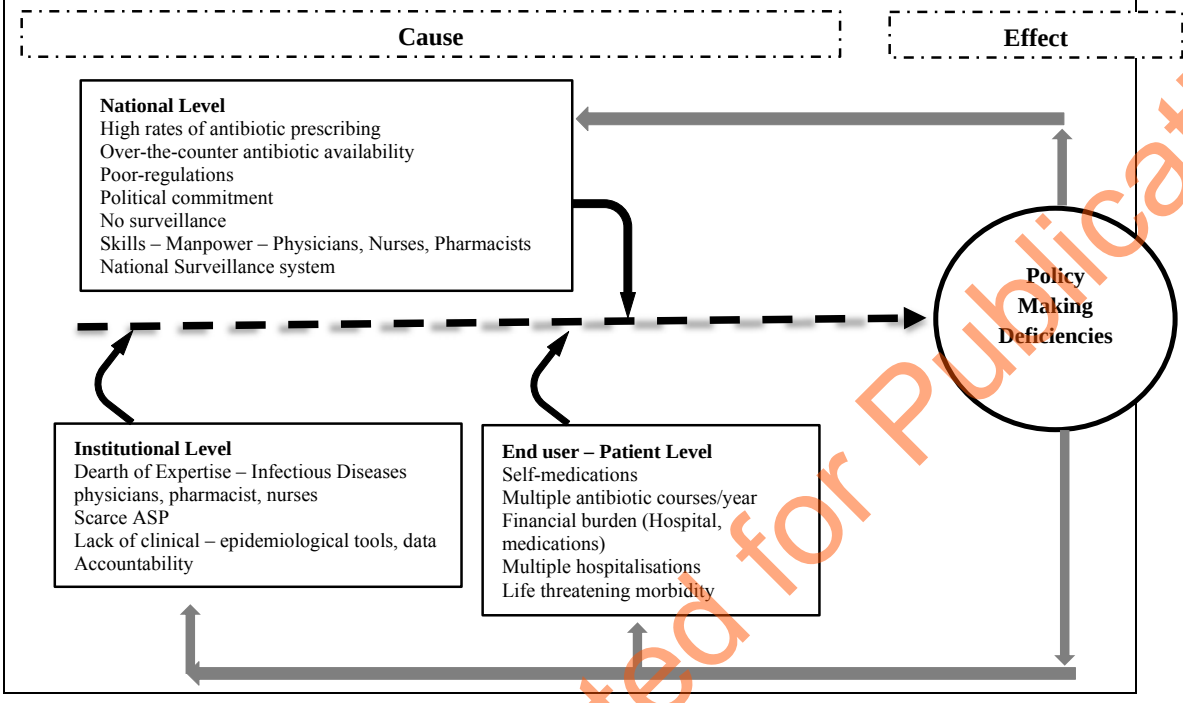
Figure 1: Fish Bone diagram to understand the complexity of AS, Pakistan



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