POINT PREVALENCE SURVEY OF ANTIMICROBIAL USE AND DETERMINANTS OF ANTIMICROBIAL RESISTANCE IN SELECTED HEALTHCARE SETTINGS IN PUNJAB, PAKISTAN

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by

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LIST OF ABBREVIATIONS

AC	Academic Council
ACF	Acute Care Facilities
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
ARPEC	Antibiotic Resistance and Prescribing in European Children
ASIP	Antibiotic Stewardship Initiative in Pakistan
ASP	Antibiotic Stewardship Programs
AST	Antimicrobial Susceptibility Testing
ATC	Anatomical Therapeutic Chemical
BJ	Bone & Joint
CAI	Community Acquired Infections
CCU	Critical Care Units
CDC	Centre of Disease Control and Prevention
CLSI	Clinical &Laboratory Standards Institute
CME	Continuing Medical Education
CNS	Central Nervous System
CSSD	Central Sterile Services Department
DDD	Defined Daily Dose
DRAP	Drug Regulatory Authority of Pakistan
DTL	Drug Testing Laboratory
ECDC	European Centre of Disease Prevention and Control
EQA	External Quality Assessment

ESBLs	Extended Spectrum Beta-Lactamases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GAAT	Glasgow Antimicrobial Audit Tool
GARP	Global Antibiotic Resistance Partnership
GAP	Global Action Plan
GDP	Gross Domestic Product
GHSA	Global Health Security Agenda
GIT	Gastro-Intestinal Tract
GLASS	Global Antimicrobial Resistance Surveillance System
HAIs	Healthcare-associated infections
HBHC	Home Based Hospital Care
HCWs	Healthcare Workers
HEC	Higher Education Council
HIC	High Income Countries
HVAC	Heating, Ventilation, and Air Conditioning
ICC	Intrasectoral Core Committee
ID	Infectious Disease
IDSA	Infectious Disease Society of America
IHR	International Health Regulations
IPC	Infection Prevention and Control
IV	Intravenous
JCI	Joint Commission International
JEE	Joint External Evaluation
LMICs	Low and Middle Income Countries

LRTI	Lower Respiratory Tract Infection
LTCFs	Long Term Care Facilities
LQMS	Laboratory Quality Management System
MDR	Multidrug Resistant Organisms
MeSH	Medical Subject Heading
MMIDSP	Medical Microbiology and Infectious Diseases Society of Pakistan
MP	Medical Prophylaxis
MRSA	Methicillin Resistant Staphylococcus Aureus
NA	Not Applicable
NAP	National Action Plan
NGO	Non-Governmental Organizations
NIH	National Institute of Health
NSI	Needle Stick Injury
OTC	Over the Counter
PARN	Pakistan Antimicrobial Resistance Network
PDR	Pan-Drug Resistance
PMDC	Pakistan Medical and Dental Council
PNC	Pakistan Nursing Council
POCT	Point of Care Testing
PPC	Pakistan Pharmacy Council
PPE	Personal Protective Equipment
PPS	Point Prevalence Surveys
PRISMA	Preferred Reporting Item for Systematic Review and Meta-analysis
P & TC	Pharmacy and Therapeutic Committees

PVMC	Pakistan Veterinary Medicine Council
RMP	Registered Medical Practitioners
SDGs	Sustainable Development Goals
SHEA	Society of Healthcare Epidemiology of America
SOPs	Standard Operating Procedures
STG	Standard Treatment Guidelines
SST	Skin and Soft Tissues
TCA	Thematic content analysis
TB	Tuberculosis
UN	United Nation
URTIs	Upper Respiratory Tract Infections
VRE	Vancomycin Resistance Enterococcus
WASH	Water, Sanitation and Hygiene
WHA	World Health Assembly
WHO	World Health Organization
XDR	Extreme Drug Resistance

TINJAUAN PREVALEN TITIK PENGGUNAAN ANTIMIKROB DAN PENENTU RINTANGAN ANTIMIKROB DALAM PENJAGAAN KESIHATAN TERPILIH DI PUNJAB, PAKISTAN

ABSTRAK

Ancaman kerintangan antimikrob (AMR) telah muncul sebagai krisis kesihatan global. Pertubuhan Kesihatan Sedunia (WHO) telah melancarkan Pelan Tindakan Global (GAP) untuk menangani AMR, yang telah disahkan oleh semua negara, termasuk Pakistan. Walaupun dengan Pelan Tindakan Negara (NAP) mengenai AMR, tiada pendekatan yang signifikant telah diambil setakat ini di Pakistan. Oleh itu, kajian ini bertujuan menilai pola preskripsi dan kerentanan antimikrob, kadar jangkitan berkaitan penjagaan kesihatan (HAI), tahap pencapaian program pengawasan antimikrob (ASP), faktor penentu AMR dan pola penetapandan dispensi antimikrob dalam kalangan pengamal perubatanserta ahli farmasi di daerah Punjab, Pakistan. Selaras dengan NAP baru-baru ini berkenaan AMR, kajian komprehensif ini adalah yang kali pertama telah dijalankan di Pakistan yakni negara keenam yang paling ramai penduduknya. Kaedah penyelidikan campuran telah digunakan, termasuk tinjauan titik prevalen (PPS) dan temu bual secara bersemuka. Daripada 1954 pesakit yang dianalisis melalui PPS, sebanyak 1516 (77.6%) telah dirawat dengan antimikrob, dengan ceftriaxone (35.0%) sebagai antimikrob yang paling biasa diberi. Kaedah yang sering dilaporkan adalah profilaksis dalam obstetrik atau ginekologi (16.5%). Untuk profilaksis pembedahan, 97.4% antimikrob telah diberikan selama lebih daripada satu hari. Dalam kajian PPS

yang diulang, didapati pengurangan yang signifikan dalam penggunaan meropenem, susulan daripada intervansi ahli farmasi klinikal. Dalam kajian lain, sebanyak 2,523 laporan kultur telah dikaji dan didapati Staphylococcus aureus adalah bakteria yang paling kerap dipencilkan (866, 34.3%) diikuti E.Coli, (814, 32.2%) yang kebanyakkannya dipencilkan daripada nanah (1464, 58.0%). Antimikrobial yang paling sensitif adalah polymyxin-B (274/298, 91.9%), tigecycline (208/236, 88.1%), fosfomycin (339/395, 85.8%), minocycline (345/431, 80.0%), imipenem (703 / 891, 78.9%) dan colistin (503/642, 78.3%). Daripada 1553 pesakit hospital yang dianalisis melalui PPS yang lain, 130 (8.4%) pesakit mempunyaisimptom HAI dengan jangkitan dari tempat pembedahan (40.0%), iaitu gejala HAI yang paling biasa. Lazimnya, simptom HAI ini didapati lebih tinggi di hospital swasta (25.0%), di kalangan bayi (23.8%) dan pesakit ICU (33.3%). Keseluruhan aktiviti pengawasan antimikrob didapati kurang baik di hospital yang dikaji tetapi fasa kualitatif kajian telah memberikan sedikit petunjuk. Amalan pengamal perubatan dan ahli farmasi didapati kurang memuaskan mengenai program ketahananan antimikrob, penggunaan dan pengawasannya. Walau bagaimanapun, kesedaran dan pandangan didapati positif serta menunjukkan kesediaan terhadap pelaksanaan NAP sekiranya kerajaan merumuskan dasar sedemikian untuk melaksanakan NAP di dalam negara. Kajian ini menyimpulkan bahawa pilihan antimikrob adalah minimum kerana kemunculan AMR. Pelbagai aktiviti melalui pendekatan pelbagai disiplin perlu dilaksanakan untuk meningkatkan penggunaan antimikrob di Pakistan sebagai sebahagian daripada NAP kepada AMR.

POINT PREVALENCE SURVEY OF ANTIMICROBIAL USE AND DETERMINANTS OF ANTIMICROBIAL RESISTANCE IN SELECTED HEALTHCARE SETTINGS IN PUNJAB, PAKISTAN

ABSTRACT

The threat of antimicrobial resistance (AMR) has appeared as a global health crisis. World Health Organization (WHO) has launched a Global Action Plan (GAP) to tackle AMR, which was endorsed by all countries, including Pakistan. Despite the National Action Plan (NAP) on AMR, no significant measures have been taken so far in Pakistan. Thus, this study aims to address this by assessing patterns of antimicrobial prescribing and susceptibility, healthcare-associated infection (HAI) rates, extent of antimicrobial stewardship programs (ASPs), determinants of AMR and patterns of antimicrobial prescribing and dispensing among physicians and pharmacists. In line with the recent NAP on AMR, the first time such a comprehensive study has been undertaken in Pakistan. Mixed methods research was used, including point prevalence surveys (PPS) and extensive face-to-face interviews. Out of 1954 patients analyzed in PPS, 1516 (77.6%, range 50.9%-100%) were treated with antimicrobials, with the most commonly prescribed antimicrobial was ceftriaxone (35.0%). The most commonly reported indication was prophylaxis for obstetrics or gynecological indications (16.5%). For surgical prophylaxis, 97.4% of antimicrobials were given for more than one day. In repeated PPS, there was a significant reduction in the use of meropenem following clinical pharmacists' interventions (10% in 2017; 4.9% in 2018). Retrospective data of 2,523 cultural reports were studied with the most frequently isolated pathogens being

Staphylococcus aureus (866, 34.3%) and *E.Coli*, (814, 32.2%), with most of the pathogens isolated from pus (1464, 58.0%). The most sensitive antimicrobials were polymyxin-B (274/298, 91.9%), tigecycline (208/236, 88.1%), fosfomycin (339/395, 85.8%), minocycline (345/431, 80.0%), imipenem (703/891, 78.9%) and colistin (503/642, 78.3%). Out of 1553 hospitalized patients analyzed in another PPS, 130 (8.4%) patients had symptoms of HAIs with surgical site infections (40.0%) the most common HAI. The prevalence of HAI was higher in private sector hospitals (25.0%, $p<0.001$), among neonates (23.8%, $p<0.001$) and ICU patients (33.3%, $p<0.001$). Overall antimicrobial stewardship activities were found to be poor in the selected hospitals. The use clinical guidelines to guide their prescribing (68.7%) and DTCs to approve antimicrobial use (65.5%) were the most common ASP activities. The qualitative phase of the study yielded that knowledge, and the practices of physicians and pharmacists were poor regarding antimicrobial resistance, utilization and stewardship programs, nevertheless, attitude towards the aforementioned was found to be positive and was found prepared if the government formulate such policies to implement the NAP in the country. The study concluded that antimicrobial options are minimal because of the emergence of AMR. There is a need to implement a range of activities through a multidisciplinary approach in order to improve antimicrobial utilization in Pakistan as part of the National Action Plan on AMR.

CHAPTER 1

INTRODUCTION

1.1 Background

The rising threat of antimicrobial resistance (AMR) has appeared as a global health crisis. Due to a lack of surveillance systems, it is difficult to develop policies and strategies for controlling AMR at regional as well as national levels or to assess the economic impact of AMR on the healthcare system in Pakistan. However, challenges to strictly monitor the dynamics of AMR have not yet been appropriately addressed at a national level. It is estimated that if the AMR is not properly controlled, it will cost 100 trillion USD on the world economy, by 2050 (J O'Neill, Davies, Rex, White, & Murray, 2016). Increased antibiotic consumption is directly associated with higher rates of resistance (JoSeph, Bhanupriya, ShewaDe, & Harish, 2015).

1.2 Antimicrobial use/consumption:

Even though many infectious diseases can be prevented with immunization, improved personal hygiene, and environmental sanitation, still antimicrobial agents are frequently used for the treatment of many infections worldwide (Yadesa, Gudina, & Angamo, 2015). Antimicrobial consumption is higher in primary care settings, and respiratory tract infections are the most common indications for use (Goossens, Ferech, Vander Stichele, Elseviers, & Group, 2005). Macrolides are often prescribed for the treatment of respiratory tract infections caused by gram-positive pathogens. The consumption of antimicrobial agents, especially broad-spectrum, may reflect physicians' concern and the need for an effective treatment for critically ill patients (Hanan H. Balkhy et al., 2018). The irrational use of antimicrobials is widespread not only in developing countries but also in developed countries, and the number of untrained physicians is the main contributor to antimicrobial misuse and overuse (Yadesa et al., 2015). Studies reported that up to 50% of antimicrobials are used unnecessarily in hospitals, and no policies regarding antimicrobial use and its resistance have been developed in the past 30 years (Burke, 2001; Martin, Goff, Karam, Dombrowski, & DeChant, 2011).

1.3 Antimicrobial resistance:

AMR is the ability of a microbe to resist the effects of a drug that once could effectively treat the microbe. AMR is a growing global threat to the healthcare system, causing serious negative impacts on humans, animals, and the environment. Many commensal and pathogenic organisms have developed resistance to antimicrobials (Lipsitch & Samore, 2002). The misuse and overuse of antimicrobials and the emergence of AMR have not only increased the mortality and morbidity rates but also increased healthcare costs annually (C Lee Ventola, 2015). World Health Organization (WHO) has realized the importance of studying the emergence of AMR and its determinants and the need for strategies to rationalise the use of antimicrobials (Bronzwaer et al., 2002; Lipsitch & Samore, 2002; Price & Sleigh, 1970).

1.4 Types of resistance

1.4.1 Pan-drug resistance

The prefix “pan” is derived from the Greek language, meaning “all” or “whole”. The term pan-drug resistance (PDR) means “resistance to all antimicrobial agents” (Karageorgopoulos & Falagas, 2008). For particular pathogens and bacterial isolates of that pathogens to be denoted as PDR, it must be examined and found to be resistant to all approved and useful antimicrobial agents. Other PDR definitions include “resistance to almost all commercially available drugs” and “resistance to all antibiotics class for empiric therapy” (Magiorakos et al., 2012). Pan-drug resistant *A. baumanni* isolates are resistant to all antimicrobial agents which are routinely tested including ampicillin-sulbactum, ceftazidime, piperacillin-tazobactum, aztreonam, imipenem and meropenem (Kuo, Teng, Yu, Ho, & Hsueh, 2004).

1.4.2 Multi-drug resistance

Another term “multidrug resistance” (MDR) has been observed in the medical literature. This term is preferably used to indicate the resistance of Gram-negative bacteria against different classes of antimicrobial agents (Falagas & Bliziotis, 2007). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (Magiorakos et al., 2012). However, the standardized definition has not yet been agreed upon by the medical community. Many definitions of MDR are being applied to identify the different patterns of gram-negative and gram-positive pathogens. Due to the lack of standardized definition for MDR in study protocols, it is difficult to compare the clinical data. The definition which is commonly applied for gram-negative and gram-positive pathogens is "resistance to three or more antimicrobial agents" (Magiorakos et al., 2012).

1.4.3 Extensively drug resistance

The term "extensively drug resistance" (XDR) was first applied in the oncology/hematology field to characterize tumor cell colonies that exhibited resistance to studied chemotherapeutic drugs (Kern & Weisenthal, 1990). Extensively drug-resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two antimicrobial categories) (Magiorakos et al., 2012). For example, XDR TB is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Whereas, MDR TB is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs.

1.5 Correlation between antimicrobial use and AMR:

Several ecological studies reported that increased antimicrobial consumption has led to the development of resistance worldwide (Hanan H. Balkhy et al., 2018; Goossens, Ferech, Coenen, Stephens, & Group, 2007; Malhotra-Kumar, Lammens, Coenen, Van Herck, & Goossens, 2007). Many surveillance programs have reported a positive correlation between antimicrobial use and AMR. High consumption of antimicrobials is the main driver of the emergence of resistant pathogens (Tangcharoensathien et al., 2017). Other factors that promote the emergence and spread of resistance include prolonged use of antimicrobials, frequent use of broad-spectrum antimicrobials, invasive devices and procedures and large numbers of critically ill patients who required prolonged hospitalization (H Goossens, 2009; Vlahović-Palčevski et al., 2007). In Europe, countries with high antimicrobial consumption rates have higher rates of AMR than the countries having low antimicrobial consumption rates (H Goossens, 2009). Antimicrobial consumption is considered as the major cause of the emergence and spread of AMR. Combined international efforts are required to counteract the global issue of AMR, as geographical differences exist in AMR rates to different classes of antimicrobials (Goossens et al., 2005). Differential selection pressure of antimicrobials could be responsible for these geographical differences (Bronzwaer et al., 2002). Hence, it is important to find out the spatial and temporal trends and relations between antimicrobial use and AMR, as such data would promote the targeted intervention programs (Wushouer et al., 2018).

1.6 Global action plan on antimicrobial resistance

In view of AMR threat, the World Health Organization (WHO) instituted a Global Action Plan (GAP) in the 68th World Health Assembly (WHA) in 2015 (Organization WH, 2015a). WHO also directed all the member countries to develop National Action Plans. It was estimated that the continued increase in AMR would lead to 10 million deaths every year by 2050 (Jim O'Neill, 2014). In addition, during the United Nation (UN) General Assembly on 21st September 2016, a political declaration was made on AMR by the Heads of State, reinforcing the GAP (Assembly, 2016).

1.7 National Action Plan of Pakistan on Antimicrobial Resistance

The rising threat of AMR has also increasingly emerged as a significant public health challenge for Pakistan, resulting in the increasing burden of infections due to resistant pathogens, while limiting the choice of antimicrobial agents for the treatment of such infections. The GAP to tackle AMR was endorsed by all countries, including Pakistan, which is the world's 6th most populous country and is expected to rise to 4th place by 2050 (Statistics, 2017). The first follow-up action was the development of the 'National Strategic Framework for Containment of Antimicrobial Resistance' which was translated into the National Action Plan (NAP) of Pakistan on AMR (NHSRC, 2017). The five strategic and operational work plan components were aligned with the objectives of the GAP (Figure 1.1). An Intra-sectoral Core Committee (ICC) on AMR was notified by the Government of Pakistan with the mandate to identify key stakeholders and experts in policymaking, assess the existing status of AMR, prepare a policy document and provide recommendations (NHSRC, 2017). Pakistan also completed the process of Joint External Evaluation (JEE) of International Health Regulations (IHR) and Global Health Security Agenda (GHSA) for assessment of priority areas for action on AMR (Tribune, 2018). The National Institute of Health (NIH) of Pakistan in collaboration with different partners has decided to be the custodian of AMR surveillance in Pakistan through participation in Global Antimicrobial Surveillance System (GLASS) (NIH, 2018).

Previously, few other organizations were already working at micro-level including Antibiotic Stewardship Initiative in Pakistan (ASIP) and Pakistan Antimicrobial Resistance Network (PARN) under the umbrella of Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) (MMIDSP, 1993; PARN, 2007). However, prioritization of activities are not carried out because there are no domestic resources allocated so far for AMR and the funding from the health department, and donors may not be sufficient. Therefore, the mission report of WHO had alerted that Pakistan is not completely prepared to detect, prevent, and respond to internal or external health threats which may threaten the country's population. The report said that this situation has the potential to jeopardize the travel and trade because Pakistan is a cosigner to the IHR, but it is yet to meet the essential core capacities in spite of several extensions (Tribune, 2018).

In April 2018, Pakistan Global Antibiotic Resistance Partnership (GARP-Pakistan) launched the Situation Analysis Report on Antimicrobial Resistance in Pakistan (CDDEP, 2018). The major challenges and issues identified in the report include unnecessary large number of registered products, unjustified or misleading advertisements, polypharmacy, quacks, irrational prescribing by physicians, availability of over the counter (OTC) without prescription antibiotics, bias towards costly broad spectrum antibiotics, lack of surveillance system and experts and widespread use of in poultry animals and agriculture (CDDEP, 2018). Pakistan also not responded to a recent WHO survey on monitoring global progress on addressing AMR (Organization WH, 2018a). Nonetheless, there is optimism as some existing infrastructure can be used for AMR surveillance through up-gradation of the existing facilities, with the existing national programs serving as a model for replication.

1.8 Antimicrobial Consumption in Pakistan

Antimicrobial consumption has been documented in a few studies and surveys performed in Pakistan (CDDEP, 2018). Due to the lack of regional and national data on antibiotic consumption, annual sales trends of conventional antibiotics result in higher consumption rates. National pharmaceutical sales data for the antibiotics which are used to treat resistant Gram-negative and Gram-positive infections include carbapenems, vancomycin, beta-lactams, beta-lactamases inhibitors, and the relatively new antibiotic, tigecyclines show increasing trends. However, the annual sale of carbapenems decreased from 2015 to 2016. Macrolides, which are commonly used for respiratory tract infections show increased sales trends, thus suggesting a rise in consumption. Various factors, including; over the counter sales, poor prescribing behavior by physicians and uncontrolled use due to the ease of access, contribute to the imprudent use of antibiotics. Increased sales trends of next-generation antibiotics may result in the inefficacy of the previous generation of antibiotics.

1.9 Antimicrobial Resistance in Pakistan

The average resistance rates of pathogens were estimated from antibiotic resistance data collected by the Pakistan Antimicrobial Resistance Network (PARN). AMR of selected pathogens and antimicrobial agents for these pathogens, suggested by the World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS) was commonly observed. The pathogens of interest, as recommended by GLASS, include *K. pneumonia, E. coli, A. baumanni, S. aureus, Salmonella species, S. pneumonia and N. gonorrhoeae* (Organization WH, 2016). Increased antimicrobial resistance among Gram-negative bacteria is a major concern around the globe (Falagas & Bliziotis, 2007). The high prevalence rate of multi-drug resistance (MDR) has been reported worldwide amongst Gram-negative bacteria including, *Acinetobacter species, P. aeruginosa, E. coli, K. pneumoniae* and Enterobacter species (Kanj & Kanafani, 2011). A study reported that MDR isolates of Acinetobacter species and *P. aeruginosa* were highly prevalent (M. Khan et al., 2009). However, another study reported 45% metallo-betalactamase resistance rates in *K. pneumonia*, 35% in E. coli, and 34% among P. aeruginosa isolates (Nahid, Khan, Rehman, & Zahra, 2013). Resistance to third-generation cephalosporins was reported 87% for cefotaxime, 85% for ceftazidime, and 85% for ceftriaxone, respectively (Irfan et al., 2008; Zahid, 2009).

Resistant gram-negative pathogens with extended-spectrum beta-lactamases (ESBLs) pose a greater risk to public health (Karthikeyan K. Kumarasamy et al., 2010). A study conducted during 2001- 2006 reported high resistance in *K. pneumonia* against carbapenems. Another survey on the bloodstream infections conducted in Lahore reported an increase in resistance in Enterobacteriaceae against third-generation cephalosporins (93.7%). Pandrug resistant Acinetobacter associated infections are also now resulting in high mortality rates among patients in different healthcare settings across Pakistan. Several studies conducted from 2004-2013 also revealed an alarming increase in resistance of E. coli to third-generation cephalosporins varying from 12.6--94% among clinical isolates ("Antimicrobial Resistance, National Action Plan, Pakistan," 2017). Studies conducted from 2001-2006 reported that *Acinetobacter baumani* is resistant to amikacin (52%) and imipenem (65-75%). However, from 2010-2011, resistance to carbapenems was high at 96% while resistance against amikacin was

33-77%. The immediate emergence of E. coli strains, resistant to fluoroquinolones and third-generation cephalosporins is a major concern, in both community and healthcare settings (Collignon, 2009). Data obtained from laboratories in Karachi, from 2013-2015 show a decline in resistance to carbapenems and a marginal increase in resistance to co-trimoxazole. Resistance to ampicillin, ciprofloxacin, and ceftriaxone remained high throughout this period. *K. pneumoniae* is commonly associated with resistance to a wide range of antibiotics. From 2013-2015, low resistance to imipenem amongst *K. pneumoniae* strains and moderately high resistance rates against co-trimoxazole, ceftriaxone, and ciprofloxacin have been reported (Akhtar, 2010; Podschun & Ullmann, 1998). Fluoroquinolones showed resistance amongst N. gonnorrheae (Jabeen et al., 2016). However, no resistance was reported against ceftriaxone, azithromycin, and spectinomycin. Typhoid remains a significant health threat across Pakistan owing to resistance of drug and subsequent treatment failure. Approximately 21 million cases of typhoid fever worldwide with 220,000 deaths have been documented annually. Another study reported high rates of MDR among *S. Typhi* isolates (34.2-48.5%).

Emerging and evolving AMR in Gram-positive pathogens have critical outcomes on the healthcare system (Rivera & Boucher, 2011). These include longer duration of hospital stay, increased mortality rate, and a higher probability of treatment failure. An increase in resistance has also been observed against aminoglycosides, glycopeptides, and penicillins in these organisms. MRSA usually associated with blood-stream infections, joint, bone, soft tissue, and skin infections, and hospital-acquired infections have reported high rates of resistance. From 2004-2005, a study reported the incidence of MRSA to be 43%.

Moreover, resistance against clindamycin was reported to be 90% amongst MRSA and 6% amongst MSSA. However, resistance against clindamycin was found to be 79% amongst S. aureus during 2005-2007, and no or little resistance to linezolid and vancomycin has been reported (Idrees, 2009; Saeed M et al, 2015). Resistance rates in enterococci species were reported at 13% to vancomycin and 74% to ampicillin during 2001-2006. However, data from Karachi laboratories showed a slight decrease in resistance rates from 39% to 27% while resistance against vancomycin varied between 8-15% during this time interval. *S. pneumoniae* exhibit resistance to penicillins, co-trimoxazole, and macrolides promoting towards increasing pneumococcal disease burden (Kim et al., 2012). Resistance rates for *S. pneumoniae* isolates for penicillins were 9-10%. Co-trimoxazole resistance rates decreased from 80% to 75% during 2013-2015.

To detect and control outbreaks of infections, identify populations who are at risks, design, and evaluate the intervention strategies, surveillance and monitoring of antibiotic-resistant pathogens are essential. Moreover, quality assured microbiology laboratory services are required to monitor AMR. But, unfortunately, these services have not yet been recognized by the Government of Pakistan since last few decades. Currently, clinical microbiology laboratories in many tertiary and secondary care hospitals have limited basic facilities, which result in compromised reporting. Differences between knowledge, implementations, and adherence to standardized susceptibility testing were observed (Ghanchi et al., 2014). Although 85% of respondents were aware of CLSI AST (Antimicrobial Susceptibility Testing) guidelines. Additionally, 50% of the laboratory workers were aware of non-standardized AST practices that were being followed in Pakistan. Similarly, 21% of laboratories do not maintain standard operating procedures (SOPs). Furthermore, rates of awareness concerning the role of waste disposal, hand-washing, and disinfection in minimizing the spread of AMR are reported at 75%, 81%, and 42%, respectively. A study which investigated the biosafety practices in microbiology laboratories in Karachi and Lahore reported several barriers; including a shortage of staff members to change or improve the guidelines, time to read and understand the biosafety guidelines and no career benefits for implementation of optimal practices (Shakoor et al., 2016). Change in resistance trends with time is hard to determine. Therefore, in order to generate reliable and accurate data for AMR surveillance in Pakistan, laboratory capacity needs to be strengthened and standardized.

The emergence of antimicrobial resistance in pathogens is an inescapable repercussion of conventional antibiotic use (French, 2010). However, there is a need of National Action Plan (NAP) on the growing burden of AMR within Pakistan as a commitment to the World Health Assembly Resolution (WHAR) to control AMR through “One Health” Approach ("Antimicrobial Resistance, National Action Plan, Pakistan," 2017). Pakistan Antimicrobial Resistance Network (PARN) in association with the Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) stands out as a highly effective resource for measuring AMR trends, using antibiograms data shared by participating clinical laboratories.

1.10 Threat of AMR in Pakistan and travel warning

The first deadly outbreak of a novel *S. Typhi* H58 clone harboring resistance to three first-line drugs (ampicillin, chloramphenicol, and co-trimoxazole) as well as the blaCTX-M-15 extended-spectrum β-lactamase and qnrS fluoroquinolone resistance gene was classified as extensively drug-resistant (XDR) in Sindh, Pakistan (Guardian, 2018; Klemm et al., 2018). There was no information available from authorities on case numbers or deaths, but media reports claim around one thousand cases of XDR typhoid were noticed in Hyderabad alone over ten months between 2016 and 2017 (Guardian, 2018). Some other published and unpublished data also highlighted high mortality among patients with infections associated with XDR typhoid (CDDEP, 2018). In 2018, a level-two alert was triggered as XDR Typhi cases have been reported in the United States and the United Kingdom among travelers returning from Pakistan. Consequently, the Centre of Disease Control and Prevention (CDC) issued a health warning that all travelers to Pakistan are at risk of getting XDR typhoid fever (CDC, 2018). CDC urged all travelers to Pakistan to take extra care with water and food and get other typhoid prevention measures. The US Agency for International Development has funded a vaccination initiative by donating 250 thousand syringes for a campaign to immunize children in two towns in Latifabad, Hyderabad, and Qasimabad in Sindh (Guardian, 2018). In the US, public health officers have also increased efforts to quickly interview and test samples from patients with suspected typhoid fever (Dawn, 2018). CDC also recommended that XDR strain from Pakistan remained susceptible to azithromycin and carbapenems. However, carbapenems should be prescribed for patients with complicated or severe typhoid fever who have traveled to Pakistan (CDC, 2018).

1.11 Five strategic and operational National Action Plans of Pakistan on AMR

In Pakistan, nationwide surveillance to capture data on antimicrobial resistance (AMR) or any action plan to address the growing threat of AMR is not in place. There is also a lack of relevant experts on AMR, Infection Prevention Control (IPC), and Antibiotic Stewardship Programs (ASP). The implementation and enactment of policy legislation are some of the additional challenges. Nevertheless, available specific expertise already existing in the health sector can be garnered to institute national bodies for the implementation of AMR activities using the One Health Approach. Furthermore, many professional national and international organizations should work together and support the Government of Pakistan to galvanize national efforts to deal comprehensively and successfully with the critical issue of addressing and containing AMR in Pakistan through implementing the National Action Plan on AMR (NHSRC, 2017). The five strategic and operational work plan components are described below.

1.11.1 Strategic Plan 1: To improve awareness and understanding of AMR

- Preparation of customized training material and awareness-raising tools on the rational use of antibiotics, infection prevention and control (IPC), antimicrobial stewardship programs (ASP), and AMR.
- Change the behavior and social norms of all key stockholders, including administrative heads, policymakers, manufacturers, consumers, prescribers, pharmacists, nurses, and other healthcare practitioners of both human and veterinary healthcare system.

- Expertise available at certain levels including academia, research institutions, electronic media, non-government organization (NGO), community-based organizations, international agencies, donors, vertical programs like TB control program can be involved for the educational and advisory purpose of the antibiotic awareness campaign
- Involvement of Provincial and Federal Governments for lawmaking and execution of policies including national public health agenda, drug sale rules, minimum service delivery standards of health care commission, etc.
- Include AMR, ASP, IPC in school/college curricula and core component of professional training and educational programs for healthcare practitioners and veterinary medicine by Higher Education Commission (HEC), Pakistan Medical and Dental Council (PMDC), Pakistan Nursing Council (PNC), Pakistan Veterinary and Medical Council (PVMC), Pakistan Pharmacy Council (PPC), Academic Council (AC), etc.

1.11.2 Strategic Plan 2: Strengthen the surveillance and research

- Development and up-gradation of National & Provincial/Regional Reference Laboratories in Human, Veterinary & Agriculture sectors
- Implementation of laboratory quality management system (LQMS), external quality assessment (EQA) and other standards along with the capacity building of the technical staff at various tiers
- Development of integrated common dashboard (National Focal Point) for data sharing in coordination and collaboration of public and private sector healthcare

settings, academic research units and other stakeholders from National, Provincial and District level

- Implementation of the standard operating procedures (SOPs) for surveillance of antimicrobial use, HAI and AMR
- Resource mapping on AMR surveillance for each sector (human and veterinary health)
- Based on local data, develop and review priority antimicrobials and pathogens list for each sector

1.11.3 Strategic Plan 3: Reduce the incidence of infection

- Formation of the infection prevention and control team and antibiotic stewardship programs in every hospital
- Development and dissemination of IPC guidelines and implementation of certified courses, training modules, and CMEs to educate healthcare and veterinary workers
- Addition of personal hygiene in the curriculum of primary and secondary education and water, sanitation and hygiene (WASH) improvement programs in the national development plan
- Availability of clean drinking water and handwashing facilities in hospitals and clean water for technical/clinical purposes (e.g., sterilization, renal dialysis, dental units, etc.)
- Monitoring of compliance and access to using personal protective equipment (PPE)

- Ensuring the availability of effective vaccination/immunizations and review of existing vaccines and vaccination strategies in human and livestock
- Availability of isolation facilities, central sterile services department (CSSD), storage area of sterile supplies, extraction fans, heating, ventilation and air conditioning (HVAC) units, autoclave, and other sterilization and disinfection supplies
- For health care facilities, implementation of IPC building codes
- Implementation of waste management according to environment protection act (EPA)
- Monitoring of compliance to vaccination, occupational safety of healthcare workers, body fluid exposures and needle stick injury (NSI)
- Strengthening capability for point of care testing (POCT) and diagnostics stewardship
- Revision of policies regarding slaughterhouses, promotion of hygienic slaughtering practices and adapting the existing standards of sustainable animal husbandry practices
- For food storage godowns, establish and monitor hygienic standards
- Establishment of disease detection, response and containment guidelines for zoonotic and foodborne

1.11.4 Strategic Plan 4: Optimize the antimicrobial use in human and animal health

- Ensure affordable and equitable access to existing and new quality-assured antimicrobials along with vaccines, alternatives and diagnostics, and their prudent and responsible use by licensed, competent professionals across animal, human and plant health

- Ensure availability of infectious disease (ID) physicians, infection control (IC) nurses, microbiologists, epidemiologists, and clinical pharmacists
- Implementation of ASP and standard treatment guidelines (STG)
- Implementation of DRAP Act 2012 and Drugs Act, 1976 regarding ethical marketing code, regulation and quality management for identification and reporting of falsified and substandard antibacterial medicines
- Sale of antibiotics only on standardized prescription by a registered medical practitioner (RMP) by upgrading of community pharmacies
- Control of antimicrobials usage as prophylaxis in the veterinary sector and growth promoters etc
- Strengthening human resource, infrastructures, equipment, and supplies of drug testing laboratories (DTLs)
- Establishment of the One Health network/forum on the Provisional and National level within the context of the sustainable development goals(SDGs)
- Certification of antibiotic-free milk and meat products
- Rationalise antimicrobial consumptions in humans, animals, and plants

1.11.5 Strategic Plan 5: Develop the economic case for sustainable investment

- Increase investment in the latest diagnostic kits, medicines, vaccines and other interventions
- Availability of infrastructure and facilities for vaccine production

- Availability of funds through various programs (e.g., through HEC, public-private partnership, pharmaceutical industries, etc.) and development of strong regional and international linkages for AMR research system
- Analysis of published data on AMR from Pakistan in order to evaluate the economic impact and identification of gaps in clinical practices through research in medical and veterinary fields.

1.12 Impact of implementing National Action Plans of Pakistan on AMR

These action plans were identified from overlapping themes on AMR. Each policy domain focuses on specific components and objectives of an effective national AMR response, starting from awareness and education regarding AMR to surveillance and monitoring AMR and AMU. These recommendations emphasize the importance of building and sustaining effective and tailored national responses to address antimicrobial resistance through increased political commitment and more coordinated multisectoral efforts across the One Health spectrum, while also leveraging gains across the SDGs. It sets out the key actions that the various actors involved should take, using an incremental approach over the next 5-10 years to combat antimicrobial resistance.

1.13 Point Prevalence survey

One of the strategies to achieve these goals is to conduct regular surveillance of antimicrobial use through point prevalence surveys (PPS) (Ann Versporten et al., 2016). Point prevalence is the number of individuals with a condition divided by total number of all the individuals in that population in a time interval (Woodward, 2013). Point prevalence surveys (PPS) of antimicrobial use are conducted to observe our progression with the treatment of infections (Aldeyab et al., 2011; Massele, Burger, et al., 2017; Xie et al., 2015; P Zarb et al., 2012). Similarly, surveillance of HAIs is an integral component of any comprehensive infection prevention and control (IPC) program, which provides information that is necessary to highlight and address challenging areas (Haley et al., 1985; Morton, 2006; Reilly et al., 2009; Talaat et al., 2016). Point-prevalence surveys (PPS) have been used for the surveillance of HAI for many years (Zingg, Huttner, Sax, & Pittet, 2014).

1.14 Burden and determinants of antimicrobial use and resistance

The studies found considerable regional variation in antimicrobial prescribing among hospitalized patients. The domination of third-generation cephalosporin and fluoroquinolones use across all regions suggests substantial use of broad-spectrum antimicrobials across countries. This may reflect high AMR or emergence of multidrug-resistant microbes (Gould, 2009; Jean & Hsueh, 2011; Tim Jinks et al., 2016; Ann Versporten et al., 2016); however, needs further investigation before definitive statements can be made. Extensive broad-spectrum antimicrobial prescribing could be explained by regionally high rates of carbapenem-resistant, or Gram-negative extended-spectrum beta-lactamase-producing organisms (Hawkey, 2015; Li & Cosgrove, 2017; Elda Righi et al., 2016). Among Latin American nations, surveillance programs have established an escalation in carbapenem-resistant Klebsiella species and resistance to extended-spectrum cephalosporins, with a high prevalence of Klebsiella spp and ESBL-producing Escherichia coli (Bartoloni et al., 2013b; Jones et al., 2013). Likewise, in

Asia, AMR rates are currently extremely high (Jean & Hsueh, 2011). Nevertheless, excessive empirical broad-spectrum antimicrobial prescribing may in part be inappropriate (De Waele et al., 2010; Levy, Swami, Dubois, Wendt, & Banerjee, 2012).

The review of literature exposed that the fact that most PPS of antimicrobial use are currently confined to European countries. Despite considerable research papers documenting the trend of antimicrobial use and potential adverse events, PPS studies from Asian countries are scarce. Published papers have been heterogeneous with respect to number of patients and hospitals. There have also been only a limited number of PPS studies in Africa despite the high burden of infectious diseases; however, this is beginning to change (Massele, Burger, et al., 2017; Massele, Tiroyakgosi, et al., 2017). Despite this, a number of insights can be made. There appears limited regulation of antimicrobial use due to either missing guidelines or, more commonly due to lack of enforcement of current guidelines(Ceyhan et al., 2010; Ren et al., 2016; Robert et al., 2012; Ann Versporten et al., 2016; Versporten et al., 2013). AMR rates were frequent in hospitals with the widespread use of antimicrobials (Lusignani et al., 2016a; Vu Dinh Phu et al., 2016; Wambale et al., 2016; Xie et al., 2015). There was also excessive use of broad-spectrum antimicrobials (Ceyhan et al., 2010; Hajdu et al., 2007; Hawkey, 2015; Magill, Edwards, Beldavs, et al., 2014; Vu Dinh Phu et al., 2016; Ren et al., 2016; Sviestina & Mozgis, 2014; Ufer et al., 2005; Usluer et al., 2005; Ann Versporten et al., 2016; Versporten et al., 2013; Xie et al., 2015). The process of rational antimicrobial prescribing appeared multifaceted and must be supported on local patterns of antimicrobial susceptibility (Fürst et al., 2015; Brian Godman, Fadare, Kibuule, Irawati, Mubita, Ogunleye, Oluka, Paramadhas, de Oliveira Costa, et al., 2017; Lob, Hoban, Sahm, & Badal, 2016; A. Sturm et al., 1997). In regions where antimicrobial susceptibility information is not available, selection of antimicrobial is challenging, even for experienced health care providers which need to be addressed (Iruka N Okeke, Klugman, et al., 2005; Iruka N Okeke, Laxminarayan, et al., 2005). In addition, monetary considerations can also influence antimicrobial selection (Kunin et al., 1987) along with the activities of pharmaceutical companies if this is the main source of information to physicians (Riaz et al., 2015). Despite this, the prescription status of antimicrobials in resource-limited settings might be main mechanism of access to antimicrobials.

The practical difference in antimicrobial prescribing within European countries and across the globe could be determined by national guidelines, cultural influences, resistance patterns, local or regional policy, knowledge on rational antimicrobial use and the availability of antimicrobials in the market. The perceived region-specific shares of antimicrobial prescribing cannot be generalized; neither its rational use can be argued because pertinent factors of antimicrobial prescribing such as patients' characteristics, bed occupancy, type of hospital, and severity of disease were not controlled for in this systematic review. For example, high proportions of antimicrobial prescribing were to be expected in Vietnam as patients in ICU of the hospital are prone to acquire the infectious disease (Vu Dinh Phu et al., 2016). In sub-Africa, there can also be an appreciable rate of HIV among admitted patients (Massele, Burger, et al., 2017). Whereas the chances of infection are limited in home-based hospital care centers or intellectual disability long-term care facilities (Miliani et al., 2014; Roche et al., 2016). As a result, the comparative analysis of results amongst surveys has been challenging.

Interventions to decrease irrational antimicrobial prescribing must be carefully handled so as not to restrict access to antimicrobials for patients with true bacterial disease as this can lead to therapeutic failure (Kollef & Micek, 2014). However, AMR rates and masking of clinical symptoms can potentially be avoided (A. Kotwani, C. Wattal, P. Joshi, & K. Holloway, 2012). In irrationally treated patients, either for the reason that they do not have a causal bacterial infection or given an inappropriate antibiotic or for a suboptimum period of therapy, patients may be susceptible to an adverse event without any gain. Even though generally seen as low-risk medicines, antimicrobials are the second most frequent reason for adverse drug events in the USA (Shehab, Patel, Srinivasan, & Budnitz, 2008). Prior use of antimicrobials is also a threat to the growth of multidrug-resistant microbes (Hawkey, 2015; Prasad, Gupta, & Singh, 2014). The over-prescribing of antimicrobials have also resulted in the wide-reaching expression of antimicrobial resistance genes (Ullah et al., 2013). Inappropriate prescription or non-prescription of antimicrobials in community, hospitals, and livestock is increasing selection pressure for antimicrobial resistance (Harada & Asai, 2010). Nations with high levels of AMR frequently have high rates of prescription and non-prescription antimicrobial use (P. Hawkey, 2008; Karthikeyan K Kumarasamy et al., 2010; Rossolini, D'andrea, & Mugnaioli, 2008; Tängdén, Cars, Melhus, & Löwdin, 2010). Comparing trends of antimicrobial prescribing between countries using patient data, allows key stakeholder groups to understand the wide range of patterns of antimicrobial use and subsequent concomitant resistance (Ann Versporten et al., 2016; P Zarb et al., 2012), as well as developing strategies to try and address this issue of AMR (Fürst et al., 2015; Brian Godman, Fadare, Kibuule, Irawati, Mubita, Ogunleye, Oluka, Paramadhas, de Oliveira Costa, et al., 2017; Goossens et al., 2006).

1.15 Burden and determinants of healthcare-associated infections

Healthcare-associated infections are among the most serious public health issues with substantial morbidity, mortality, and costs (Glance, Stone, Mukamel, & Dick, 2011; Manosuthi et al., 2017; Manoukian et al., 2018; Rothe et al., 2013). The studies conducted in various healthcare settings provide baseline information in order to develop future intervention research. Because of multi-factorial features of HAIs, healthcare settings are challenging domains in order to identify the various types of infections and microorganisms, especially in LMICs. Most of the studies were conducted in Europe and Asia. Two studies were conducted in Africa, one in Ethiopia and one in Tunisia. Previous literature surveys reported that HAIs remained a public health problem in LMICs compared with developed countries (Allegranzi, Nejad, et al., 2011). However, to date, limited studies regarding PPS of HAIs have been performed in LMICs because of lack of national surveillance systems. The main reasons for this may include a lack of human and financial resources, the absence of expertise in the interpretation of the data, the paucity of reliable diagnostic procedures, the scarcity of data obtained from patient records and the absence of software used for surveillance of HAIs (Allegranzi, Bagheri Nejad, et al., 2011).

In Canada, Denis et al. conducted prevalence surveys in both adults and pediatric settings with reportedly a high prevalence rate of HAIs in adults than in pediatric patients. One of the studies reported 3-20 times higher neonatal infection rate in developing countries compared to developed countries (A. K. Zaidi et al., 2005). Rezende and colleagues performed a prevalence survey in Brazil and reported 11.4% prevalence of HAIs, requiring inter-institutional efforts so that appropriate measures