Situation Analysis Report on Antimicrobial Resistance in Pakistan

Findings and recommendations for Antibiotics Use and Resistance

Global Antibiotic Resistance Partnership

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

SITUATION ANALYSIS REPORT ON ANTIMICROBIAL RESISTANCE IN PAKISTAN

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Contents

Abbreviations and Acronyms

ADR	Adverse Drug Reactions
AMR	Antimicrobial resistance
ARI	Acute Respiratory Infection
ASP	Antibiotic Stewardship Programs
AST	Antibiotic Susceptibility Testing
ATM	Access to Medicines
BMGF	Bill & Melinda Gates Foundation
CDC	Centers for Disease Control and Prevention, Atlanta
CDDEP	Center for Disease Dynamics, Economics & Policy
CLSI	Clinical and Laboratory Standards Institute
CME	Continuous Medical Education
DALYS	Disability-Adjusted Life Years
DDD	Defined Daily Doses
DHIS	District Health Information System
DHQ	District Headquarters
DRAP	Drug Regulatory Authority of Pakistan
DST	Drug Susceptibility Testing
EARS- Net	European Antimicrobial Resistance Surveillance Network
EML	Essential Medicines List
EMRO	Eastern Mediterranean Regional office (WHO)
EPA	Environmental Protection Agency
ESBLs	Extended-spectrum beta-lactamases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food & Agriculture Organization
FELTP	Pakistan Field Epidemiology and Laboratory Training Program
GAP	Global Action Plan
GARP	Global Antibiotic Resistance Partnership
GAVI	Gavi, the Vaccine Alliance
GLASS	Global Antimicrobial Resistance Surveillance System
HAIs	Hospital-acquired infections
HCP	Healthcare Professional
HCWs	Healthcare workers

HEC	Higher Education Commission
ICC	Intersectoral Core Committee
ICUs	Intensive Care Units
IHR	International Health Regulation
IPC	Infection prevention and control
LIS	Laboratory Information System
LMICs	Low and middle-income countries
LQMS	Laboratory Quality Management System
MBL	Metallo beta-lactamase
MDR	Multi-drug Resistant
MDROs	Multi-drug Resistant Organisms
MIS	Management Information System
MMIDSP	Medical Microbiology and Infectious Diseases Society of Pakistan
MNC	Multi-National Company
MNHS&RC	Ministry of National Health Services Regulations & Coordination
MNFS&R	Ministry of National Food Security and Research
NACP	National AIDS Control Program Pakistan
NARC	National Agricultural Research Centre
NAP	National Action Plan
NEML	National Essential Medicines List
NIH	National Institute of Health
NGOs	Non-Governmental Organizations
NTP	National TB Program
NVL	National Veterinary Laboratory
OIE	World Organization for Animal Health
OTC	Over the Counter
PARC	Pakistan Agricultural Research Council
PARN	Pakistan Antimicrobial Resistance Network
PCP	Pharmacy Council of Pakistan
PHRC	Pakistan Health Research Council
PNC	Pakistan Nursing Council
PPE	Personal Protective Equipment
PVMC	Pakistan Veterinary & Medical Council

SWOT	Strengths, Weakness, Opportunities and Threats
TB	Tuberculosis
USAID	United States Agency for International Development
UNICEF	The United Nations Children's Fund
VAP	Ventilator Associated Pneumonia
WHA	World Health Assembly
WHO	World Health Organization

About GARP-Pakistan

The Global Antibiotic Resistance Partnership (GARP) is a project of the Center for Disease Dynamics, Economics & Policy (CDDEP) that facilitates the development of actionable policy proposals on antibiotic resistance by and for low and middle-income countries (LMICs). With funding from the Bill & Melinda Gates Foundation (BMGF) and other grants, GARP supports the creation of multisectoral national-level working groups, whose mandate is to stimulate specific research and develop evidence-based proposals to encourage the introduction of measures to preserve antibiotic effectiveness, slow the spread of antibiotic resistance and improve antibiotic access. The Global Antibiotic Resistance Partnership (GARP) is multi-country collaboration currently established in eight countries in Asia and Africa. The GARP mission is to assist national governments to develop national action and implementation plans for antimicrobial resistance. GARP operates through national multi-disciplinary expert Working Groups. Major milestones for Working Groups include; completing or updating a broad-based situation analysis, and developing a national action plan (NAP) and implementation plan for antimicrobial resistance (AMR).

Pakistan Global Antibiotic Resistance Partnership (GARP) was formed in the wake of international and national efforts for AMR curtailment. A group of experts from microbiology, infectious diseases and veterinary medicine formed a core group at the organizational meeting of GARP in Kathmandu, Nepal in July 2016. In the meeting, this core group was expanded to include other members from different sectors with the selection of the Chair and co-chairs. These were asked to serve on a voluntary basis, in their own individual capacities, with no personal gains, or gains to the institutions to which they are affiliated. The first phase of GARP took place from 2009 to 2011 and involved four countries: India, Kenya, South Africa and Vietnam. Phase one culminated in the 1st Global Forum on Bacterial Infections, held in October 2011 in New Delhi, India. In 2012, phase two of GARP was initiated with the addition of working groups in Mozambique, Tanzania, Nepal and Uganda. Phase three has added Bangladesh, Lao PDR, Nigeria, Pakistan and Zimbabwe to the network to date.

Following its inaugural meeting, GARP-Pakistan has carried out a series of meetings throughout the last 12 months, related to writing the Situational Analysis Report on AMR in Pakistan and through its contribution to many AMR-related activities, across Pakistan, in both participatory and advisory roles. These included the following:

1. Antibiotic Awareness Week 2016 themed as "Antibiotics – Handle with Care" Marriot Hotel, Islamabad on 20th November 2016.

2. Symposium "*Antimicrobial Resistance in Pakistan: Current Situation and Future Approaches*" Aga Khan University December 2016.

3. Launch of the *"National Framework for Containment of Antimicrobial Resistance"* by the Ministry of National Health Services, Regulations and Coordination at the "National Consultative Meeting for Finalization of Pakistan's IHR-GHSA 5 Year National Action Plan at the Marriott Hotel, Islamabad, Pakistan on 30th November – 1st December 2016.

4. National Consultation for Developing the Antimicrobial Resistance (AMR) National Action Plan (NAP) for Pakistan, 27th February – 3rd March 2017, Islamabad.

5. Consultative workshop for the development of the National Action Plan, 27th February-3rd March, Islamabad.
6. WHO-OIE International Health Regulations National Bridging Workshop 9th-11th May 2017.
7. Technical Joint Stakeholder work-plan for Implementation of the GLASS and National Action Plan on AMR 22nd-24th May 2017, Islamabad, Pakistan.
8. Seminar: WHO: Prevention of Surgical Site Infections (Part 1 and 2): 7th and 28th October 2017.
9. Global Hand Washing Day, 13th October 2017.
10. World Antibiotic Awareness Week, November 2017. Many individual and joint activities were done (including AntiMicrobial Resistance through Environmental pathways in Pakistan (AMREPAK) Consultative meeting, Antibiotic Awareness Walk, TV Interviews, TV Live Discussion Program on "Misuse of Antibiotics and the Dangers of AMR").
11. Many "Antibiotics Stewardship and AMR related Activities/Talks" at various National professional forums.
12. Finalization of this **"Situation Analysis Report on Antimicrobial Resistance in Pakistan-*Findings and Recommendations for Antibiotic Use and Resistance.*"** This was undertaken by GARP members in late 2016. This Report will document and collate the most current data on different aspects of AMR in various fields in Pakistan and is expected to be launched in early 2018. It is hoped that this Situational Analysis Report will also help policy makers in decision making for the National Action Plan on AMR and its implementation in all relevant sectors.

GARP is thus committed to support the national and international efforts to fight AMR. It intends to do this by extending all possible scientific and technical help through the multi-disciplinary, multisectoral GARP Core Group, with prioritization of the NAP recommendations for specific AMR-related public health policies.

Dr. Ejaz A. Khan

Chair, GARP-Pakistan

Foreword

Over the years, antimicrobial resistance (AMR) has manifested itself as a major public health threat in almost all countries, including Pakistan. Multi-drug resistant organisms (MDROs) have severely limited our choices of antibiotics for treatment. Being a densely populated country with poor healthcare, the mortality and morbidity rates attributed to infections remain high. Coupled with rising and emerging AMR these are likely to escalate much further.

The burden of MDROs is huge, with poor outcomes, not only in common community acquired infections, but also in healthcare-associated infections, with a mortality rate documented as high as 50%. Lack of essential equipment and supplies, failures in sterilization and disinfection of instruments, inadequate hand hygiene, overcrowding, understaffing and the lack of knowledge, training and competency regarding infection control practices, are all identified factors that contribute to resistance within health care settings.

Increasing antibiotic consumption in humans and animals, particularly of broad-spectrum antibiotics, is one of the major underlying factors contributing to antibiotic resistance globally. In Pakistan, indiscriminate and excessive use of antibiotics in farm animals and poultry for therapeutic, prophylactic and growth promotion has also added to AMR. Most studies have shown increasing rates of resistance in both human and veterinary medicine, with MDROs being isolated, with increasing frequency, across the country. The use of antimicrobial agents in animals, poultry and agriculture has recognized benefits but overuse has potentially serious implications for human health. Antimicrobial Stewardship Programs (ASP) and Infection Control Programs are the most effective immediate options for combatting AMR. Unfortunately, in Pakistan, such initiatives have not be taken, until recently, to address AMR.

Many international and regional efforts to control AMR have been initiated over the last two decades, including the World Health Organization's Global Action Plan, in May 2015. Countries endorsed the plan and are required to make National Action Plans with a commitment to work at national, regional, and global levels to develop multi-sectoral national action plans, programs and policy initiatives. The Minister of State, Ministry of National Health Services Regulations & Coordination (NHSR&C) initiated efforts over last two years and the ***"National Strategic Framework for Containment of Antimicrobial Resistance 2016"*** was developed and then followed up with the draft "***National Action Plan on AMR***" in May 2017 through a comprehensive consultative process.

This ***"Situation Analysis Report on Antimicrobial Resistance in Pakistan: Findings and recommendations for antibiotic use and resistance"*** has been undertaken to document and collate current data on different aspects of AMR, in various fields. The literature review showed that a lot of data on AMR exists but lacks national coverage and uniformity. With a major focus on AMR surveillance and monitoring now more robust data is expected to be available that can subsequently be used for addressing many issues related to antibiotic use, resistance, antibiotic stewardship and infection control. It is hoped that this Situational Analysis Report will also help policy makers in decision making for the National Action Plan on AMR and its implementation in all relevant sectors.

Message from Director General Health

Pakistan at present has a huge burden of multi and pan-drug resistance bacterial infection limiting options for treating such infections and thus leading to significant mortality and morbidity and. The situation in animal sector is also very alarming as the broad-spectrum antimicrobials are consumed for treatment and prophylaxis in large quantities without regulatory framework. The Ministry of National Health Services, Regulations & Coordination, Government of Pakistan considers Antimicrobial Resistance (AMR) containment as a priority agenda.

The Government of Pakistan has fully endorsed the WHO Global Action Plan on AMR adopted vide the resolution WHA68.7 during the 68th WHA and other international obligations on AMR.The Ministry has accordingly initiated some of the key initiatives to address the issue of AMR in the light of the strategic objectives of the Global Action Plan on AMR. We have notified a multi-sectoral AMR oversight committee and designated National Institute of Health as the National Focal Point for AMR.

Through a consultative process we have developed national strategic framework for AMR outlining the critical needs to address the challenge of AMR based on existing strengths and weaknesses to improve awareness, strengthen surveillance, to develop infections prevention and control program, optimize utilization of antimicrobials and including AMR in the national research agenda. In order to achieve the objectives of national strategic framework, we have developed and endorsed a comprehensive National Action Plan (NAP) for AMR. The NAP for AMR provides details of the priorities and actions to minimize the impact of AMR across different sectors. The Ministry of NHSRC shall remain committed to mobilize domestic funding for implementation of NAP on AMR and encourage all the stakeholders and partners, such as GARP, to support AMR activities in Pakistan.

It thus gives me immense pleasure to welcome addition of this important document ***"Situation Analysis Report on Antimicrobial Resistance in Pakistan: Findings and recommendations for antibiotic use and resistance."*** It has been prepared by GARP-Pakistan which includes many prominent experts from the field of infectious diseases, microbiology, infection control and veterinary field. It is a very comprehensive report with an in-depth analysis of available literature on AMR, antibiotic use and misuse, infection control from human, veterinary and agricultural sectors in Pakistan and will be useful to health planners.

Dr. Assad Hafeez

Director General

Ministry of National Health Services, Regulations and Coordination

Message from Executive Director NIH

The increasing trend of Antimicrobial resistance (AMR) has emerged as major challenge for the health sector worldwide. The AMR problem has now spread to almost all countries and regions, including Pakistan due to injudicious use of antimicrobials; contributing to the increasing burden of resistant bacterial infections. The mounting AMR burden requires development of National Action Plan (NAP) by the member states aligned with the WHO resolutions and Global Action Plan (GAP) through 'One Health' approach.

The major strategic priorities of Pakistan's NAP include development and implementation of national awareness raising and behavioral change strategy on antimicrobial resistance; establishment of an integrated national AMR surveillance (human, animal usage and resistance monitoring); improve prevention and control of infections in health care, community, animal health, food, agriculture and environment; update and enforce regulations for human and veterinary antimicrobial utilization; phase out use of antimicrobials as growth promoters and provision of appropriate alternatives (such as prebiotics, probiotics); integration of AMR in all public health research agendas including research on vaccines; and estimation of health and economic burden of AMR for decision making. The NIH has also prioritized AMR in its efforts to implement Global Heath Security Agenda (GHSA). The Institute under the overall leadership of Ministry of NHSRC is in process of developing Provincial Action Plans for AMR.

The NIH has rolled out sentinel AMR surveillance through participation in Global Antimicrobial Surveillance System (GLASS) and is collaborating with different partners for sharing the representative data on the WHO GLASS platform. The NIH shall remain committed to implement NAP for AMR and provide technical assistance to the provincial and area health department to develop their respective operational plans based on the national priorities. We will continue to work closely with partners like GARP and other AMR stakeholders to achieve the objectives of the NAP and as well as provincial operational plans.

The next important step for this document ***"Situation Analysis Report on Antimicrobial Resistance in Pakistan: Findings and recommendations for antibiotic use and resistance"*** is to ensure that all relevant healthcare personnel gain access to this GARP-Pakistan Report for reference and use it for carrying forward the national efforts. The media, public and advocacy groups must be engaged as well to disseminate this document. NIH is encouraged by the support that GARP-Pakistan has lent through this document and commends it for being a strong partner during this whole process.

Prof Brigadier Aamer Ikram, SI(M)

Executive Director

National Institute of Health

Chapter 1

Executive Summary

Antimicrobial resistance (AMR) has emerged as major health crisis in all sectors, including human, veterinary, agriculture and environment, and threatens the major gains that have been made in medicine. It has spread to almost all countries and regions, including Pakistan, owing to the indiscriminate use of antibiotics and poor infection control practices. The growing burden of AMR in Pakistan has gained new focus over the last few years. No national systematic data on AMR exists but there has been a growing literature on AMR. This Report is a collective literature review of of the AMR data available from human and animal health and ongoing initiatives within Pakistan. Literature published in peer-reviewed journals over last 10 years (2006-2016) and resistance data from the Pakistan Antimicrobial Resistance Network (PARN) collected by Karachi laboratories (2013-2015) were used for selected priority bacteria and selected antimicrobial agents, as recommended by the World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS) for these microorganisms.

AMR data is lacking in Pakistan, as no national surveillance network exists. This is further compounded by the fact that laboratory facilities are limited. AMR among gram-negative bacteria is widespread within the country. This has been well documented, with a high prevalence of MDROs, specifically *Pseudomonas aeruginosa, Acinetobacter species, Escherichia coli, Klebsiella pneumoniae* and *Enterobacter species,* with rates >25-100% for most isolates. High resistance rates have been shown for metallo-β-lactamases but more worrisome is the increasing incidence of resistance against the polymyxin antibiotic, colistin, reported from many centers over the last year.

The national pharmaceutical sales data for human use correlates well with the volume of antibiotic consumption data for all major beta-lactams, beta-lactamase-inhibitor combinations (cephalosporins, amoxicillin-clavulanate and piperacillin-tazobactam) and fluoroquinolones, and shows increasing trends in sales and consumption. The rising trend shows the widespread acceptance of antibiotics, such as third generation cephalosporins and fluoroquinolones, as a "cure-all," by both physicians and the public. Also more concerning, is the use of second line agents, usually reserved to treat multidrug resistant organisms (MDROs). These include carbapenems (imipenem, meropenem and ertapenem), tigecycline, linezolid and vancomycin.

One of the integral interventions for the control of AMR in healthcare settings is an antibiotic stewardship program. Antibiotic consumption remains high in healthcare settings, including in many well-established public hospitals, across Pakistan. However, these facilities lack stewardship programs to curtail antimicrobial usage. Only a few have functioning antibiotic stewardship activities. The major limitations include a lack of awareness and a shortage of human resources. These are the major bottlenecks in establishing an antimicrobial stewardship program and, as a consequence, antibiotic stewardship program initiatives have yet to gain national importance.

Furthermore, infection control and prevention (IPC) remains one of the key elements in controlling AMR, by limiting the transmission of resistant organisms. Moreover, in Pakistan, infection control practices are not universal and even where present, are sub-optimal. Thereby, risking lives, especially in public sector health settings, in the major cities of Pakistan. Only a limited number of large private and public hospitals have functional infection control (IC) programs. National Guidelines exist but lack scope and very little is

published about experiences in infection control. Documents developed by the National AIDS Control Program, Pakistan Medical Research Council and National TB program have laid emphasis on local adaption, human resource development and the availability of equipment and solutions. Local experiences show health professionals in the country lack basic IC knowledge, there is a shortage of IC expertise at a national level, dedicated programs for IC programs are not a priority in hospitals with budgetary restraints, and healthcare facilities face a shortage of IC supplies and isolation beds. Studies indicate poor practices and insufficient knowledge about basic IC, unsafe injection usage, and high rates of Hospital-acquired infections (HAIs). Despite the existence of National Guidelines, the implementation and provision of resources for IC practices has been a hindrance.

The burden of HAIs or nosocomial infections in Pakistan is unknown but is expected to be substantial from the limited literature available. With the worrisome rise of MDROs (*Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella species, Escherichia coli* and MRSA, etc.), the risk of acquiring infection may be as high as 60% for some hospitalized patients. These aforementioned pathogens have an attributable mortality rate of 12-60% in some populations. The risk of infection to patients, healthcare workers, and even visitors can be reduced by adhering to strict infection control practices and appropriate antibiotic use. In particular, measures, such as hand hygiene, isolation precautions, needle stick injury prevention, and proper waste management. There is great potential for opportunities to educate and train, not only the health care workers (HCWs), but also the public, about IC practices, basic hygiene and infection prevention. Successful implementation of IC prevention strategies (e.g. for the prevention of ventilator associated infection) in Pakistan has been reported. IC is an essential component for the delivery of quality care to patients, relatives, visitors and all healthcare workers. Addressing specific areas related to IC, such as national surveillance, education and awareness, antibiotic stewardship, and training of personnel can help in the control of HAIs. This will help to ensure the safety of patients, visitors and HCWs.

In Pakistan, national and provincial public health related interventions were aimed at different communicable and non-communicable diseases at achieving the Millennium Development Goals (MDG). These have included provision of clean water and sanitation. However millions still lack access to clean water. Subsequently, lack of access to adequate sanitation has resulted in diarrheal illnesses, outbreaks and deaths each year. The National Sanitation Policy, National Drinking Water Policy and "Clean Drinking Water Initiative" have undertaken many projects for improving quality drinking water and sanitation. The recent 2015 WHO/UNICEF Joint Monitoring Programme "Progress Report on Sanitation and Drinking Water" showed that Pakistan has achieved its target reduction of 36% in the proportion of the population practicing open defecation. Additionally, good progress in access to clean drinking water was reported with 91% of the population having access to improved drinking sources. This will likely translate into a reduction in infection rates in the community, thereby reducing antimicrobial consumption. Immunization is one of the most effective prevention strategies for infections and the Expanded Programme on Immunization (EPI) of Pakistan and its Vision 2025 has set targets and activities in order to achieve Sustainable Development Goal 3 for the country. However, the key goals of polio eradication and measles have not been achieved and coverage of routine EPI vaccines in Pakistan has remained below targets due to poor management, governance, and service delivery performance. Serious invasive disease due to *Haemophilus influenzae type b (Hib)* and *Streptococcus pneumoniae* result in significant mortality (27% due to *Hib* and 28% due to *Streptococcus pneumoniae*) coupled with sequelae (developmental delay 37%, motor deficit 31%, hearing impairment 18.5%, epilepsy 14%, vision impairment 14%). Thus,

remaining a serious threat to children <5 years old in Pakistan. However, the effectiveness of the *Hib* vaccine for the prevention of pneumonia is high (62% reduction with 3 doses of vaccine). Similarly, pneumococcal conjugate vaccine or PCV (61-63% reduction in invasive pneumococcal disease) can have a significant impact. In children (<5 years old) rotavirus accounts for up to one third of hospitalizations. With rotavirus vaccine included in the EPI program there is potential to reduce such hospitalizations and other unnecessary interventions, including the use of antibiotics.

Hepatitis has become a significant national public health problem over the past few decades. With a prevalence of 2.5% and 4.9% for Hepatitis B and C, respectively, Pakistan is ranked 2nd amongst countries with a high burden of hepatitis. A number of public health programs have been initiated for hepatitis prevention and control. Natural disasters, such as earthquakes and floods, over the years, have exposed our vulnerable population to both communicable and non-communicable diseases. The National Disaster Management Authority, established in 2007, now coordinates all relief efforts. Similarly, regarding non-communicable diseases, collaborative interventions by WHO, and other partners, include diverse strategies, such as social mobilization, school health, information, education, and communication. These have the effect of empowering communities to manage specific situations. These efforts are indirectly linked with the control of communicable diseases, in such disasters.

The health care system in Pakistan comprises both the public sector and a large private sector. Both the federal Ministry of National Health Services Regulations & Coordination (MNHS&RC) and provincial health authorities are responsible for producer licensing, drug testing, drug registration, pricing and trade and market surveillance. Access to essential medicines, as part of the fulfillment of the right to health, is recognized in the national constitution. There are >600 registered manufacturing units and 21 multinational companies in the country and raw materials for local drug production are almost entirely imported. The total size of the pharmaceutical market stands at USD 2.2 billion and the export share of the pharmaceutical industry stands at USD 190 million. The updated National Essential Medicines List (NEML) of 2016 exists but prescriptions may not contain medicine from NEML and only one fourth of medical practitioners may be aware of NEML.

The Drug Regulatory Authority of Pakistan (DRAP) is an autonomous body under the MNHS&RC and it provides for effective coordination and enforcement of The Drugs Act, 1976. It regulates manufacturing, import, export, storage, distribution and sale of therapeutic goods including 80,000 drug products (60,000 local and 20,000 imported). Pakistan thus has many health related Policy Acts, legislations, and detailed regulatory and operative guidelines. However, there is considerable deficiency between policy and practice and between medicine policies and health systems. The autonomous and powerful body, DRAP, has been unable to perform effectively. In most doctor-patient interactions diagnosis, prescription and doses of drugs are wrong. Doctors are easily influenced by the pharmaceutical industry indulging in many different unethical practices. Of the total drugs, 20-50% of medicines are counterfeit, with wide discrepancies in quality, and 10-15% of antibiotics are spurious with quinolones and cephalosporins common. The use of counterfeit, substandard and spurious antimicrobials has grave consequences for consumers. In summary, the delivery of quality healthcare in the public sector and a large private sector remains suboptimal, despite the existence of regulatory and oversight bodies.

AMR in animals is escalating and also warrants immediate attention. In both farm animals and poultry the reported usage of antibiotics is high, including antibiotics for human use, such as penicillins, lincosamide, macrolides, aminoglycosides, sulfonamides and fluoroquinolones. However, exact usage data is lacking and the levels of AMR prevalence, and the rates and mode of its transmission between humans and animals remains to be established. Antibiotics are frequently used in veterinary medicine for prophylactic treatment and growth promotion. More importantly, as there are currently no laws governing the use of antibiotics in the veterinary field, their exorbitant usage has led to the emergence of drug-resistant pathogen strains, common to both animals and humans.

Pakistan has a huge market of livestock and poultry. Currently Pakistan has 67.3 million large ruminants (cattle and buffaloes), 89.6 million small ruminants (sheep and goats) and 1,230 million poultry. The animal products resulting from livestock include 46,440,000 tons of milk, 3,095,000 tons of meat and 12,457 million eggs. There is documented indiscriminate and extensive use of antibiotics in farm animals in Pakistan. Despite the extensive usage, there is no surveillance program for antibiotic use in animals. Measurable amounts of antibiotics have been identified in poultry and meat. Poultry meat is commonly found colonized with enteric bacteria, including *E. coli*, *Salmonella typhimurium*, *S. aureus*, and *Campylobacter* spp., the four pathogens that are also the most common causes of gastrointestinal illnesses in humans.

A study of broiler meat samples showed an approximately 48% contamination rate with different species (mostly human pathogens) of *Salmonella,* with resistance rates of 64% for the antibiotics tested. *E. coli* studies show an alarming increase in the number of poultry isolates that are significantly less susceptible to multiple antibiotics. High-level resistance has been observed for *S. aureus* to ampicillin, sulfanilamide, and ofloxacin, whereas, low resistance was observed in kanamycin, erythromycin, and chloramphenicol. Many studies have shown the presence of high levels of antibiotic residues in milk and meat, from animals in livestock. In addition, most bacteria isolated from beef and mutton showed resistance to the most commonly administered antibiotics. AMR patterns of a few bacteria originating from livestock have been reported, which include *S. aureus*, *E. coli*, *Streptococcus agalactiae, Streptococcus dysagalactiae*, *Corynebacterium bovis* among others. Continuous use of antimicrobials in aquaculture for maintaining the health of fish leads to the persistence of antimicrobials in the fish flesh that can be transmitted to consumers, together with bacteria, that are resistant to the antimicrobials used in aquaculture. The Pakistan Fisheries and Livestock Department prohibits the use of antimicrobials in aquaculture, except for the treatment of carp infections, but studies show the isolation of antimicrobial resistant bacteria from ponds and fish meat. There are currently no laws governing the use of antimicrobials in poultry in Pakistan, except for control on import and registration of marketed drugs. This results in an increased use of drugs, and subsequent increase in emergence of drug-resistant strains of pathogens, common to both poultry and humans. To maintain animal and human health, effective strategies and inventions should be introduced to check and control AMR in animals.

Global efforts are underway and Pakistan is one of the first countries, in the region, to address AMR, in line with the WHO Resolution. Pakistan's Ministry of National Health Services, Regulations & Coordination has transformed the "National Strategic Framework for Containment of Antimicrobial Resistance 2016" into the official draft "National Action Plan for Containment of AMR." This document was submitted to WHO in May 2017. This process involved the full participation of the Inter-sectoral Core Committee, representatives from the health, veterinary, and agricultural sectors, ministries, departments of health, and

other sectors at the federal, provincial and regional levels. The major strategic priorities of the NAP, which emerged from the consultation process, include:

1. Development and implementation of a national awareness raising and behaviour change strategy on antimicrobial resistance.
2. Establishment of an integrated national AMR surveillance system (use and resistance, human and animal).
3. Improvement of infection prevention and control in healthcare settings, the community, animal health, food, agriculture and the environment.
4. Update and enforcement of regulations for human and veterinary antimicrobial use.
5. Phase-out of antimicrobial use for growth promotion and provision of appropriate alternatives (such as prebiotics, probiotics) in food animals.
6. Integration of AMR into all public health research agendas, including research on vaccines.
7. Estimation of the health and economic burden of AMR, for use in decision-making.

The NAP will be shared with all stakeholders, including Health Development Partners (HDPs) at the national, provincial, and regional levels under the One Health Approach for the development and adoption of respective provincial and regional level implementation plans.

Some of the specific activities and actions that will be initiated at the national level include:

1. Acknowledge that there is an urgent need to initiate measures to tackle the growing hazards of antibiotic resistance and irrational use of antibiotics, and join international efforts to control this threat.
2. Encourage and implement initiatives to improve infection control standards in hospitals.
3. Include structured training in rational antibiotic usage and infection control in the medical curriculum at undergraduate and postgraduate levels.
4. Standardize microbiology laboratories in Pakistan.
5. Collaborate for surveillance of antibiotic resistance at private and government hospitals and university labs.
6. Partner with WHO/EMRO to interact with the government on issues related to drug resistance, antibiotic policy, and infection control.
7. Liaise with professional organizations to initiate infection control and antibiotic stewardship awareness activities.
8. Participate with electronic and print mass media to raise public awareness of the dangers of the misuse of antibiotics.

9. Evaluate the extent and regulate the use of antibiotics in veterinary practice.

10. Formulate and present a policy on rationalizing antibiotic use in the country, both in hospitals and OTC, through collaboration with all stakeholders.

These priority actions will be taken incrementally to combat AMR, in a phased process, with involvement and commitment from all stakeholders, to ensure successful implementation, in all relevant sectors and provinces. We hope that this Situational Analysis Report on AMR in Pakistan will give a comprehensive review, of the issues related to AMR, in many fields in the country, and further strengthen our efforts, in line with global objectives.

Chapter 2

Health and Economic Context

2.1 Geographic and demographic context

The total land area of Pakistan is about 796,000 square kilometers. Pakistan comprises the provinces of Punjab, Khyber Pakhtunkhawa, Balochistan and Sindh and four territories: the Federally Administered Tribal Areas (FATA), Islamabad Capital Territory Gilgit–Baltistan, and Kashmir. There were 34 divisions, 156 districts (*zillahs*), 596 sub-districts (tehsils), and several thousand union councils as of 2017.[1] Islamabad is the capital of Pakistan, located in the northern part of the country.

Pakistan's population according to the 6th population and housing census 2017 is 207.8 million people with a annual growth of 2.4%.[1] This makes it the world's sixth-most-populous country and is projected to rise to 4th place by 2050. Since independence in 1947, the population of Pakistan has grown from 34 million, as reported in the first census in 1951, to 132 million in 1998 and 183 million in 2012, with a population growth rate of 2-4% per annum. Pakistan's rapid population growth during the second half of the 20th century can largely be explained by a decline in mortality rates, combined with a gradual decline in fertility rates, following a transition to an industrialized economy.[2] This trend is likely to continue, with important implications for health service coverage. The latest census report suggests considerable growth in urban population in all provinces. The urban population in Pakistan is 36.38% of total population, with annual rate of urbanization at 2.81%.[2]

In 2017, nearly two-thirds of the Pakistani population is young and thus dependent.[1] The young age structure has been persistent in Pakistan for the last five decades. Over the next 30 to 40 years, the majority of the population will be of working age with fewer younger and elderly citizens. In 2017, 35.4% of the population was <15 years of age, 60.4% between 16-64 years and 4.2% are >65 years olds. Approximately 60% were of working age. The rising share of the working-age population may correspond to a subsequent rise in the rate of economic growth.

2.2 Health indicators

Mortality began declining in the 1950s, particularly during the first two decades following independence. Life expectancy at birth for both sexes has improved over the last five decades, from 41.2 years in 1950-55 to 66 years in 2017.[2,3] Infant mortality also declined significantly following independence, from an infant mortality rate (IMR) of 177 in 1950-55 to 65.8 per 1000 live births in 2015.[3] The maternal mortality rate also declined from 431 per 100,000 live births in 1990 to 178 per 100,000 live births in 2015.[4] The Millennium Development Goal (MDG) targets set for Pakistan however remained off track for a number of reasons, including low literacy rates, food insecurity, inadequate nutrition, and low financial priority. Thus the progress on maternal and child mortality rates was not sufficient to meet the MDG targets (Tables 1).[5] Rising security expenditures and IDPs also exerted high costs on the economy. In comparison to other regional countries its human development indicators also were poor (Table 2).[5]

Table 1. Pakistan progress on MDGs.

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Target 2015
Life Expectancy at birth , total (year)	64.7	64.9	65.2	65.4	65.6	65.8	66.0	66.1	66.3	66.4	66.6	-
Infant Mortality Rate (Per 1000)	83.0	81.6	80.1	78.8	77.5	76.1	74.8	73.4	72.1	70.6	69.0	40.0
Under 5 Mortality Rate (Per 1000)	105.5	103.4	101.4	99.4	97.5	95.6	93.6	91.8	89.9	87.8	85.5	52.0
Maternal Mortality Rate Per 100000	-	-	230.0	-	-	-	-	190.0	-	-	170.0	140.0
Population Growth Rate (%)	1.8	1.8	1.8	1.8	1.9	1.9	1.8	1.8	1.7	1.7	1.9	-

Source: World Bank.

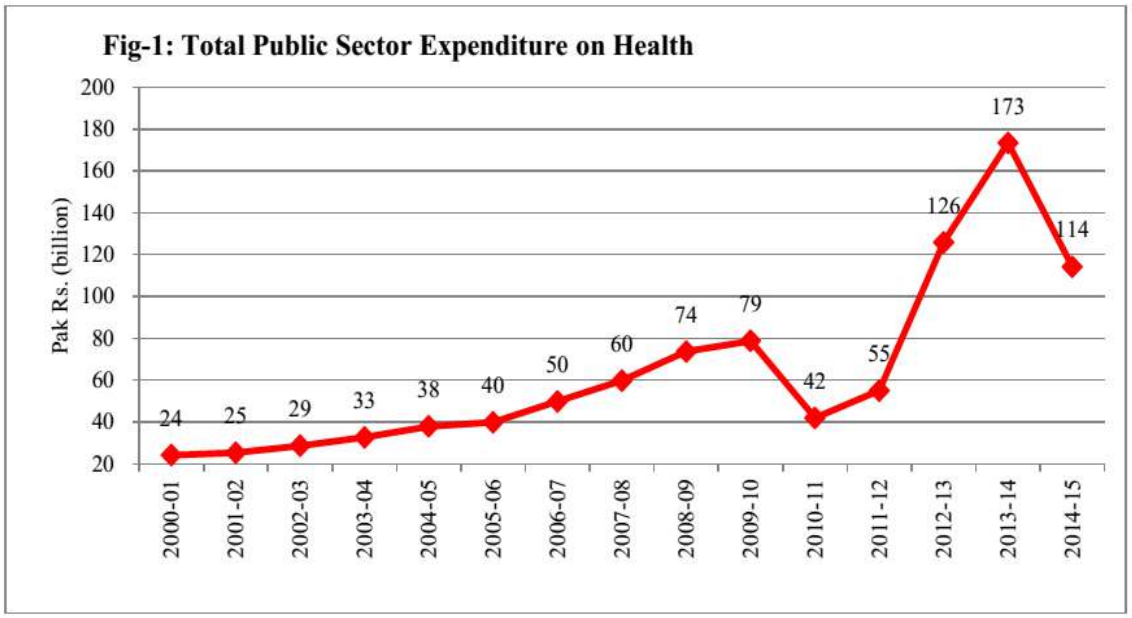
Table 2. Regional countries human development indicator.

Country	Life Expectancy 2013	Infant Mortality Rate Per 1000 2013	Under 5 Mortality Rate Per 1000 2013	Maternal Mortality Rate Per 100000 2013	Population Growth Rate(%) 2013
Pakistan	66.6	69.0	85.5	170.0	1.92
India	66.5	41.4	52.7	190.0	1.24
Bangladesh	70.7	33.2	41.1	170.0	1.22
Sri Lanka	74.2	8.2	9.6	29.0	0.76
Nepal	68.4	32.2	39.7	190.0	1.17
Bhutan	68.3	29.7	36.2	120.0	1.62
China	75.4	10.9	12.7	32.0	0.49
Malaysia	75.0	7.2	8.5	29.0	1.62
Indonesia	70.8	24.5	29.3	190.0	1.21
Philippines	68.7	23.5	29.9	120.0	1.73
Thailand	74.4	11.3	13.1	26.0	0.34

Source: World Bank

2.3 Health financing

Total public sector expenditure on health is the most significant variable affecting health status in a country. Cross-country analysis shows that infant and child mortality are lower in countries with a higher share of health care spending devoted to primary health care (Table 2).[5] Public sector expenditures in health increase yearly in any country to meet growing needs. In Pakistan, a total of Rs. 20.48 billion was provided to the health sector through the Federal *Public Sector Development Programme* (PSDP) 2014-15 and approximately Rs.22.4 billion was utilized by the end of March 2015 (Figure 1).[5] PSDP, which is under the Planning Commission of Pakistan, is the main instrument available to the government to provide budgetary resources for development projects and programmes, including health. Most recently, Pakistan spent 0.46% of its gross domestic product GDP on health care services during fiscal year 2016-17.[5] The per capita health spending is $36, compared to the WHO recommended bench mark of $86.[5]



2.4 Health system context

The health system consists of a mix of publicly financed health delivery with privately financed market delivery. The private health care sector has developed considerably and has spread across the country and provides a varying level of care. In Pakistan, 79% of the population utilizes the private health sector.[6] Provision of private health is largely due to private pharmacies and medical stores with dispensing of medicines. Of the total expenditure on medicines, private health expenditure comprises nearly three-fourths, with the burden borne by households, through out of pocket payments.[7]

In 2015, there were 119,548 hospital beds in the country and a population-to-bed ratio of 1,593.[6,8] There were 184,711 registered doctors, 16,652 dentists, 94,776 nurses, 16,448 qualified health visitors, and 34668 midwives. At the time, there was one doctor for every 1,073 people and one dentist for every 12,447 people. The number of hospitals was 1,172, while the number of dispensaries and other outlets was 5,695.[6,8] Since the majority of hospitals and doctors are located in large cities, the rural population has much lower levels of access to health facilities.

The private sector comprises various providers, including at least 20,000 registered general practice clinics, 340 dispensaries, 300 MCH centers and 450 laboratories/ diagnostic centers.[9] There are also 1,800 local NGOs providing health care services, 500 small to medium sized hospitals, and only a few large regular hospitals.[9,10] In the non-allopathic sector, there are at least 52,600 registered *unani* medical practitioners providing non-allopathic remedies. Health services in the public sector were devolved to the provinces with the passage of the 18th Amendment. Funding goes directly to the provinces through the National Finance Commission (NFC award), as well as through Federal PSDP funds for health programs.

According to the WHO Global Health Expenditure database for Pakistan the total expenditure on health (% of Gross domestic product, GDP) was 2.6%, with a total health expenditure per capita of $33 (35.2% by government and 64.8% private) in 2014.[11] The out-of-pocket expenditure, as a % of private expenditure, on health in Pakistan was 86.8 %.[11] In 2016, the National Health Insurance Initiative was launched in some districts of

Pakistan to cater to the needs of people below poverty line, by provision of free health services, in the public and private sectors.[12]

2.5 Health programs

To improve the health status of the people and to reduce the burden of disease, a series of programs and projects have been initiated. Vertical programs in the health sector have been devolved to the provinces. The following programs and projects are funded through the Federal PSDP and implemented by the provincial and area governments.[6,13]

i) Programme for Family Planning and Primary Health Care (LHWs Programme)

This program has recruited more than 100,000 Lady Health Workers (LHWs) serving over 60-80% of the population in Balochistan and Punjab, respectively. LHW services have a visible impact on the health status of women and children in particular through improved hygiene, birth spacing, iron supplementation, greater immunization coverage and through antenatal and postnatal coverage of pregnant women.

ii) **Expanded Programme of Immunization (EPI)**

The EPI program provides immunization to children, less than one year of age, against seven vaccine-preventable diseases. These include childhood tuberculosis, poliomyelitis, diphtheria, pertussis, neonatal tetanus, measles, and hepatitis B. New vaccines, like the universal pentavalent pneumococcal vaccine, and the introduction of Rotavirus vaccine, in January 2017, in some districts of Punjab, with the help of The United Nations Children's Fund (UNICEF) and Gavi, the Vaccine Alliance (GAVI), will improve coverage of some major pathogens. Though, following devolution, immunization has become largely the responsibility of the provincial governments, the federal EPI cell currently manages procurements, coordination, and technical guidance, while provincial EPI cells are largely responsible for implementation. The World Bank, along with other financial partners, such as WHO and JICA, has contributed towards implementation of the program. Still, the issue of routine immunization, in the less accessible areas of FATA and Baluchistan, needs attention. The WHO/UNICEF estimated immunization coverage for 2015-2016 for Pakistan to be: BCG 85%, DPT1 79%, DPT3 72%, oral polio3 72%, IPV 56%, measles1 61%, Hepatitis B 72%, Hib 72%, and PCV3 72%, with no data for the Rotavirus vaccine or other vaccines outside of EPI.[14] During 2015-16 eight million children (0-11 months of age) and 6.5 million pregnant women were immunized.[6]

iii) **Malaria Control Programme**

Malaria, the second most prevalent communicable disease in the country, is a major cause of morbidity in Pakistan. More than 90% of the malaria disease burden in the country is shared by 56 highly endemic districts. These are located in Balochistan (17 out of 32 districts), FATA (7 agencies), Sindh (12 districts), and Khyber Pakhtunkhwa (12 districts). *P. vivax* accounts for >80% of the reported cases from these districts. The FATA account for 12-15% of the total caseload of the country.[15]

The National Strategy for Malaria Control is based on the following 6 key Roll Back Malaria (RBM) elements:

- Early diagnosis and prompt treatment
- Multiple prevention
- Improved detection and response to epidemics
- Viable partnerships with national and international partners
- Focused operational research
- National commitment

iv) Tuberculosis Control Programme

Pakistan is ranked 6th amongst 22 of the high disease burden countries in the world, and 40% of the burden of disease is in the form of communicable diseases, such as malaria and TB. The incidence of TB stands at 231/100,000 population, with a prevalence of about 300 cases per 100,000 population.[16] The National Tuberculosis Control Program (NTP) has achieved over 85% coverage, with the Directly Observed Treatment System (DOTS) in the public sector and, in the last five years, the program has provided care to more than half a million TB patients, in Pakistan. The program is moving steadily to achieve the global target of 90% case detection. There are areas where the NTP has to improve, including suspect management, contact management, quality bacteriology services, engaging care providers through public private partnerships, inter-sectoral collaboration, monitoring and supervision, research for evidence based planning and advocacy communication, and social mobilization.

v) National AIDS Control Programme (NACP)

The prevalence of HIV/ AIDS is estimated to be as low as 1% and Pakistan is not considered a high-risk country, although the number of injecting drug users has posed a threat of increasing the number of cases. The focus of the control program is on behavior change through communication services to high-risk population groups, treatment of sexually transmitted infections (STIs), safe blood supply, and capacity building. According to NACP, at federal and provincial levels, currently there are an estimated 133,000 people living with HIV, with more than 20,000 people registered, and more than half on therapy.[17] The program is supported by the UN agencies and the Global Fund Against AIDS, TB and Malaria (GFATM).

vi) Maternal and Child Health Programme

Mother and child health has been one of the priority areas in public health in Pakistan. This health program was launched by the Ministry of National Health Services Regulation and Coordination in order to improve maternal and neonatal health services for all, particularly the poor and the disadvantaged, at all levels of the health care delivery system. It aims to provide improved access to high quality mother and child health and family planning services, train 10,000 community midwives, and provide comprehensive emergency obstetric and neonatal care (EmONC) services in 275 hospitals and health facilities and basic EmONC services in 550 health facilities.[13] However, both the maternal mortality rate, of 170/100000 live births, and the neonatal mortality rate, of 46/1000 live births, remain high.[3,4] The PDHS 2012-13 showed that neonatal mortality increased by 8% over last 20 years, with increases seen in all provinces except KPK (Table).[18]

Table. Trends in neonatal, postneonatal, infant, child and under-five mortality rates for the last 10-year period preceding the Pakistan Demographic and Health Survey by regions. Pakistan 2012-13.

Region	Survey	Approximate calendar years	Neonatal mortality (NN)	Postneonatal mortality (PNN)[1]	Infant mortality ($_1q_0$)	Child mortality ($_4q_1$)	Under-five mortality ($_5q_0$)
Punjab	2012-13 PDHS	2003-2012	63	25	88	18	105
	2006-07 PDHS	1997-2006	58	23	81	18	97
	1990-91 PDHS	1981-1990	58	46	104	32	133
Sindh	2012-13 PDHS	2003-2012	54	20	74	20	93
	2006-07 PDHS	1997-2006	53	28	81	22	101
	1990-91 PDHS	1981-1990	44	36	81	27	106
KPK	2012-13 PDHS	2003-2012	41	17	58	13	70
	2006-07 PDHS	1997-2006	41	22	63	13	75
	1990-91 PDHS	1981-1990	48	31	80	20	98
Balochistan	2012-13 PDHS	2003-2012	63	34	97	15	111
	2006-07 PDHS	1997-2006	30	18	49	11	59
	1990-91 PDHS	1981-1990	46	26	72	31	101

[1] Computed as the difference between the infant and neonatal mortality rates

In Pakistan, the overall health situation is grim, as shown in a recent article by Zaidi et al.[19] This was a review of available peer reviewed and grey literature on prescribing patterns and drug dispensing in Pakistan.[19] Problems identified include an unnecessary number of registered products (approximately 50,000),[20] 18% of advertisements being "unjustified or misleading,"[21] only 15% of promotional brochures meeting WHO criteria,[22] self-medication in 51%[23] of cases, and the presence of more than 600,000 quacks in Pakistan.[24] Diagnosis, prescription and doses of drugs are wrong in most doctor-patient interactions. Pakistan has one of the highest numbers of drugs prescribed (>3 drugs/patient),[25] highest rate of injections use (60% of patient encounters, mostly by private practitioners or quacks[25,26] and very common injection re-usage with very poor sterilization practices.[27] Even more importantly, 70% of patients are prescribed antibiotics.[26] This overuse and abuse was more common among GPs and public hospitals for costly antibiotics and 3rd generation cephalosporins.[26,28,29] The availability of over the counter (OTC) medications and especially antibiotics, without prescriptions, is common in Pakistan. These include many high end use antibiotics, now given for resistant infections. In an old study to determine whether the free availability of antimicrobial agents leads to misuse, a house-to-house semi-structured interview, in 1342 households (9209 individuals), in three different socio-economic areas of Karachi, was done.[30] It found that 3.5% had used one or more antimicrobials in the previous 4 weeks, equivalent to 43 agents per 1000 persons per month (91.4% prescribed by a physician, 2.3% by a chemist and 6.3% as self-medication). This has created a vicious cycle, with the emergence of resistance in common bacteria, as a result of antibiotic pressure. A review by Zaidi et al., on prescribing patterns and drug dispensing in Pakistan, has highlighted these issues.[19] Self-medication is very common, among university students 45% report self medication, with an antibiotic, in the preceding six months, despite knowledge in 72% of side effects, including antibiotic resistance in 43%.[31] More than 50% of nursing students from Karachi self medicated, mostly a broad spectrum antibiotic, for fever and sore throat.[32] A questionnaire-based study, from Peshawar, about the use of antibiotics in common URTI, showed that physician-prescribed antibiotics (58%), family recommendation (27%), usefulness in fever or viral infections (35-25%), and self medication (25%) were common practices.[33] Furthermore, potent drugs, including antibiotics, are misused by untrained doctors and or fraudulent medical practitioners.[34] A small but in depth qualitative community study, on treatment for minor common day

symptoms, revealed that self medication, home remedies, and spiritual healing were common, due to multiple community and cultural practices.[35]

2.6. Animal health and economics

With the per-capita GDP of 1,428.99 USD in 2015, Pakistan is classified, by the World Bank as a low to middle-income country. At least 60 million people in Pakistan live below the poverty line and rearing livestock serves as a source of income for a significant proportion of the population. In the year 2010-11, livestock accounted for approximately 55% of agriculture, at a total value of 12% of the GDP.[36] Currently, Pakistan has 67.3 million large ruminants (cattle and buffaloes), 89.6 million small ruminants (sheep and goats) and 1,230 million poultry. The animal products resulting from livestock include 46,440,000 tons of milk, 3,095,000 tons of meat and 12,457 million eggs.[37]

2.6.1 Poultry

As the number of cattle in Pakistan reaches a record low, owing to higher maintenance costs, poultry meat is gradually replacing beef or mutton. The poultry industry was established in Pakistan in the early 1960s (between 1961-1963). In the initial stages, most poultry meat was acquired from poultry grown in households. Meat and eggs obtained from home-grown chickens were fairly low in quantity, and chickens used to produce ~0.7 grams of meat at four months of age and approximately 30 eggs per-year. The increasing population and people's inclination towards eating a healthier form of meat, which included poultry and seafood, resulted in an increase in the demand for poultry meat. A tremendous amount of effort was expended to increase the volume of meat and eggs to respond to the acute dietary needs of the growing population. Several initiatives were developed to overcome the gap between supply and demand. These included developing Lyallpur Silver Black hybrid chickens by crossing local chickens (Desi chicken) with White Longhorns, White Cornish and New-Hampshire. The breed was developed by the Department of Poultry Husbandry at the University of Agriculture, Faisalabad.[38] The breed was associated with significantly higher output of both meat and eggs (150 eggs per year). To further enhance the production of eggs and meat, to fulfil growing national demands, Pakistan International Airlines, in collaboration with Shavers Poultry Breeding Farms of Canada, established the first commercial hatchery in Karachi, followed by the establishment of a commercial feed mill by Lever Brothers.[39]

Procedures were put in place to increase the number of chickens produced, which resulted in overcrowding of poultry houses. This increased density of poultry in houses resulted in increased rates of transmission of infectious diseases, among the housed birds. Results of several studies demonstrated a marked increase in both recurrent infections and outbreaks of infections from 1991 to 2000 on poultry farms. Common infections included Hydropericardium syndrome, Gumboro, avian influenza, Marek's disease, Newcastle disease, salmonellosis and enteritis, among others.[39] The poultry industry suffered great losses as a result of such infections, leading to the administration of antibiotics and vaccines for prophylaxis and treatment of severe infections.

2.6.2. Livestock

The livestock sector of Pakistan plays an important role in the national economy. Rearing livestock contributes to 35-40% of the incomes of 30-35 million people.[40] It enhances agricultural productivity and works towards alleviating poverty in the country. According to a survey in 2013-2014, the livestock sector of Pakistan added 56% to national agriculture

value and 12% (Rs. 776.5 billion) to national GDP. Livestock animals include ruminants as well as weight-bearing animals. Ruminants, which include cattle, buffalo, sheep and goat, form the majority of the country's livestock. Buffalo and cattle makeup 47% and 53% of the dairy animal population of Pakistan and produce 96% of the total milk in the country. The remaining 4% milk production is contributed by sheep and goats reared in rural areas for meat production.[41] In addition to milk and meat production, livestock animals play various other roles, which include using bulls to provide draft power in crop cultivation, using their by-products as fuel and fertilizer, and using animals as liquid assets.[42]

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Chapter 3

AMR and Antibiotic Use in Humans

Antimicrobial drug resistance has been recognized as a national concern in Pakistan since 2014. However, challenges in efforts to stringently monitor the dynamics of the spread of resistance have not been consistently and substantially addressed at a national level. The mapping of drug resistance in the absence of a surveillance network, has meant that drug resistance information, at a national level, is not available. Without such data it is difficult to develop cohesive and directed policies and strategies, at regional and national levels, including for infection control practices, antimicrobial conservation or to assess the economic impact of AMR on the health system in Pakistan.

3.1 Antibiotic consumption

It is estimated that, if antimicrobial resistance is not properly managed, it will incur a cost of 100 trillion USD on the world economy, by 2050.[1] Societies with a burdened health system are at particular risk from such emerging resistance.

While antimicrobial resistance is a natural evolutionary phenomenon, exposure to antibiotics places an increased selection pressure on microorganisms to develop mechanisms aimed at evading the action of these antimicrobial drugs thereby, decreasing the efficacy of the latter to treat infections and eventually making them redundant over time. Increased antibiotic consumption in a population is directly associated with higher rates of resistance.[2]

National pharmaceutical sales data are good correlates of in country antibiotic consumption. Moving annual sales data from Pakistan (2012 to 2016), kindly supplied by Quintiles-IMS, are presented below (Figures 1-4). However, these figures reflect sales of antibiotics registered for human-use only. As such they do not capture antimicrobial usage in animals or the agricultural sector and as such are an underestimate.

Beta-lactams

Sales data for all major beta-lactams and beta-lactamase-inhibitor combinations show increasing trends. Sales (in Standard Units) of cephalosporins, amoxicillin-clavulanate and piperacillin-tazobactam (only available as a combination) are presented in Figures 1 and 2.

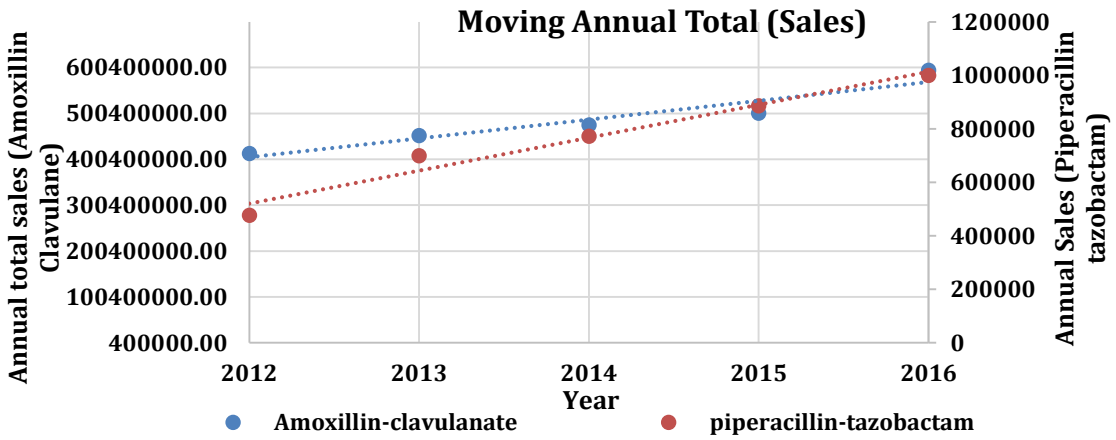

Figure 1. Moving annual total sales for amoxicillin-clavulanate, piperacillin-tazobactam (in Standard Units). Source: Quintiles IMS

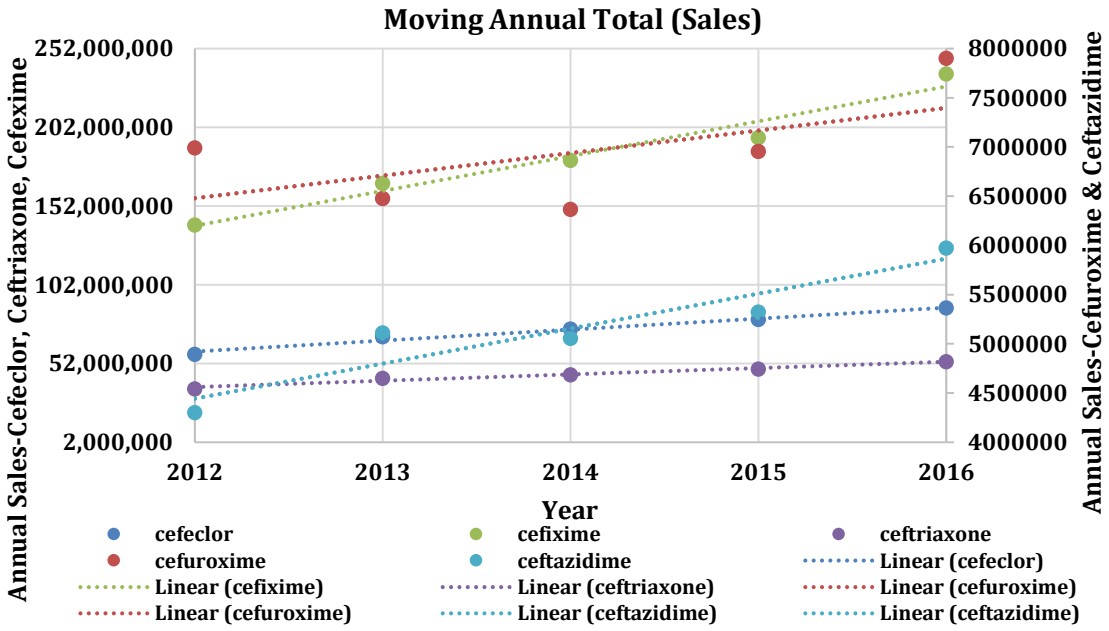

Figure 2. Moving annual total sales for cephalosporins (in Standard Units). Source: Quintiles IMS

Carbapenems, vancomycin and tigecycline

Antibiotics used to treat resistant Gram-positive and Gram-negative infections include carbapenems (imipenem, meropenem and ertapenem are all available in Pakistan), vancomycin, and the relatively new antibiotic, tigecycline. Sales trends for all three show an increase, as shown in Figure 4. However, carbapenem annual sales decreased from 2015-2016 (Figure 3).

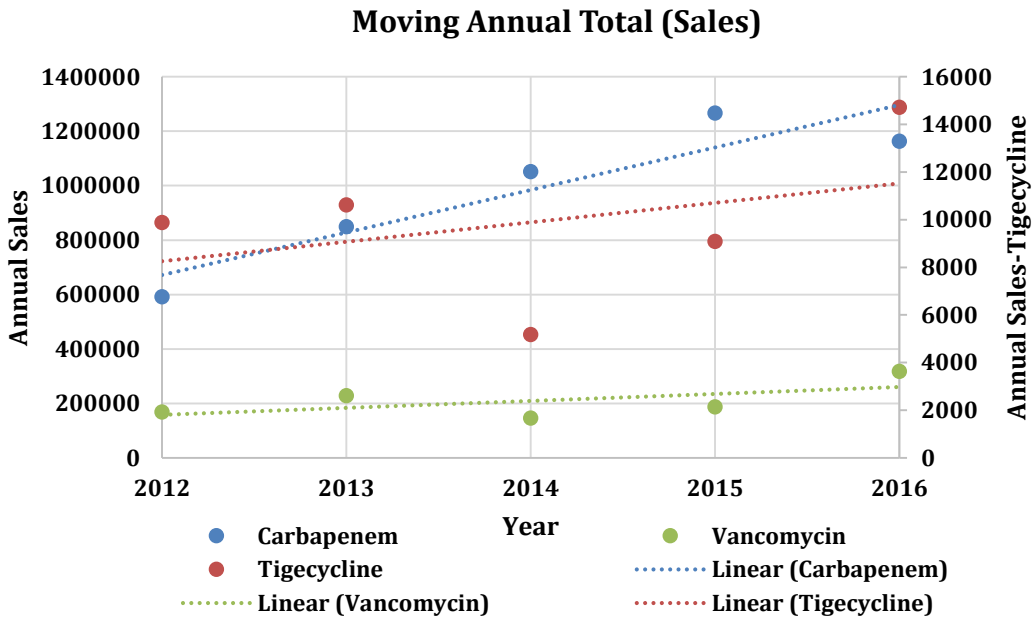

Figure 3. Moving annual total sales in Pakistan 2012-2016 for carbapenems, vancomycin, and tigecycline (in Standard Units). Source: Quintiles IMS

Fluoroquinolones

Antibiotic sales data show an increase in fluoroquinolone usage (Figure 4). Fluoroquinolones available in Pakistan include norfloxacin, ofloxacin, ciprofloxacin, moxifloxacin, levofloxacin, and gatifloxacin. The rising trend shows the widespread acceptance of fluoroquinolones as a "cure-all" antibiotic by both physicians and the public.

Macrolides

Macrolides are also popular antibiotics and commonly used to treat respiratory tract infections. Usage data show increasing sales trends and suggest a rise in consumption (Figure 4).

Co-trimoxazole

Co-trimoxazole sales and consumption appear to have plateaued over the last 5 years (Figure 4). This is in contrast to other countries, where overall use has increased, primarily because of greater usage for prophylaxis and treatment in HIV-associated infections, such as pneumocystis jerovici (PCP) pneumonia. In Pakistan one reason that this is not the case could be that prevalence of HIV remains low.

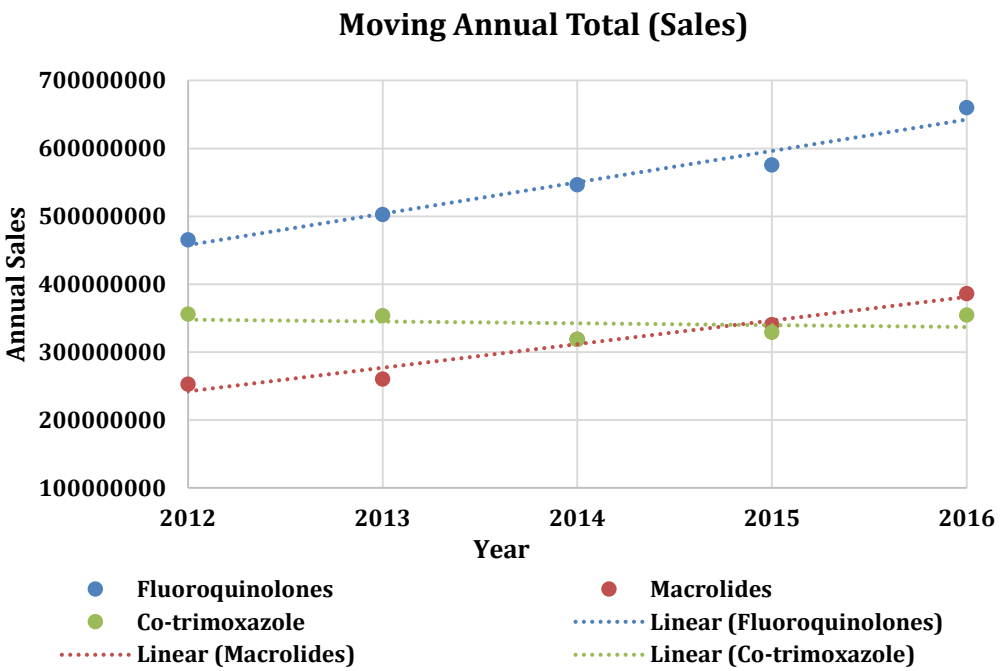

Figure 4. Comparison of moving annual total sales from 2012-2016 for fluoroquinolones, macrolides, and co-trimoxazole (in Standard Units). Source; Quintiles IMS

In the absence of regional antibiotic consumption data, trends in annual sales of antibiotics reflect high consumption rates. Several factors including; uncontrolled use due to ease of access, over the counter sales, and poor prescribing practices by physicians, contribute to the injudicious use of antibiotics. Increasing sales of next generation antibiotics, such as carbapenems and third generation cephalosporins, may reflect the inefficacy of the previous generation of antibiotics, however, fashions in antibiotic prescribing may also play a role and the true forces at work here are impossible to surmise purely from consumption data.

3.2 Antibiotic resistance

3.2.1 Methodology

To evaluate the current antimicrobial resistance (AMR) situation in Pakistan, literature published in peer-reviewed journals from 2006 to 2016 was considered. Additionally, average resistance rates of pathogens were calculated, from AMR data, reported from Karachi laboratories, for the years 2013 to 2015 by the Pakistan Antimicrobial Resistance Network (PARN).[3] Resistance data, differentiated by outpatients and inpatients, were combined and averaged (Average of outpatient and inpatient resistance data is also presented in Appendices 1 and 2). AMR of selected priority bacteria and selected antimicrobial agents, as recommended by the World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS), for these microorganisms were considered[3], alongside additional bacteria and antimicrobials (Appendix 3). The pathogens of concern, as specified by GLASS, include *E. coli, K. pneumonia, A. baumannii, S. aureus, S. pneumonia, Salmonella spp.*, *Shigella spp.* and *N. gonorrhoeae.*[4]

3.2.2 Gram-negative bacteria

Increasing antimicrobial resistance among Gram-negative bacteria is a global concern.[5] The high prevalence of multi-drug resistance (MDR) amongst Gram-negative organisms, specifically *Pseudomonas aeruginosa, Acinetobacter species, Escherichia coli, Klebsiella pneumoniae* and *Enterobacter species* has been reported globally.[6] Additionally, the emergence of carbapenem resistance, due to β-lactamase enzyme production, particularly in *Enterobacteriaceae* pathogens, further restricts the already shrinking pool of viable therapeutic options. Notably amongst these are various sub-classes of β-lactamase enzymes, with *Klebsiella pneumoniae* carbapenemase and New Delhi metallo-β-lactamase being of particular concern.[7] In a study conducted in a tertiary care hospital, MDR isolates (isolates having drug resistance to two or more classes of antibiotics to which no intrinsic resistance exists) were highly prevalent.[8] All *Acinetobacter* isolates and 72% of *P. aeruginosa* isolates were identified as MDR. Another study reported 35% metallo-beta-lactamase (MBL) resistance rates in *E. coli*, 45% in *K. pneumoniae* and 34% amongst *P. aeruginosa* isolates.[9] Resistance to third-generation cephalosporins was reportedly 85%, 84%, and 87% for ceftazidime, ceftriaxone and cefotaxime, respectively.[9] In addition, 24% of the MBL isolates carried the New Delhi Metallo-beta-lactamase-1 (blaNDM-1) gene. High resistance rates were reported for these isolates as follows; 97% resistance against imipenem, 97% against ceftazidime, 94% against ceftriaxone, and 90% to cefotaxime. Resistance against the polymyxin antibiotic colistin (3%) was also noted.[9] These data indicate the emergence of pan-drug resistance in these isolates.

Acinetobacter baumanii

A. baumanii is associated with nosocomial infections, including wound and pulmonary infections. From 2001 to 2006, studies reported resistance in *A. baumanii* against amikacin and imipenem to be 52%[10] and 65-75%[10,11] respectively. Hospital-acquired carbapenem-resistant *Acinetobacter baumannii* from different intensive care unit settings has shown $bla_{\text{OxA-23-like}}$ acquired-oxacillinase and class 1 integrase genes has been found in majority of isolates.[12] From 2010 to 2011, resistance to carbapenems was reportedly high at 96%,[13] while resistance to amikacin was 33-77%,[13,14] 83% for minocycline,[14] 12-20% for tigecycline,[13,14] and 0-50% for colistin.[13,14] Data from laboratories in Karachi suggest resistance to imipenem and gentamicin increased from 2013 to 2014, but decreased in 2015 (Figure 5), while resistance to amikacin continued to decrease from 2013 to 2015. Colistin resistance was found to be absent in 2013. Resistance in subsequent years was not reported in the antibiogram data.

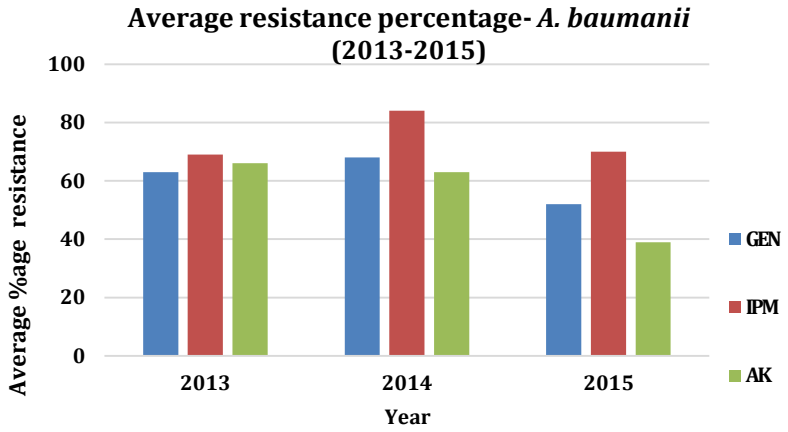

Figure 5. Average resistance percentage of *Acinetobacter baumanii* for the years 2013-2015, using data from PARN, generated by laboratories in Karachi. GEN=Gentamicin, IPM=imipenem, AK= amikacin. Colistin (CST) was not tested in the years 2014 and 2015.

E. coli

E. coli can cause life-threatening bacteremia and urinary tract infections (UTIs). The rapid emergence of *E. coli* strains, resistant to fluoroquinolones and third-generation cephalosporins, due to extended-spectrum beta-lactamase (ESBL) producing enzymes, is a major concern, in both community and health care settings.[15] The high incidence of MBL-producing *E. coli* (71% of isolates) has been reported.[16] Resistance to many of the GLASS antibacterial agents, evaluated in studies conducted between 2007 and 2008, ranged from 48-69%, 34-76% and 0-15% for cephalosporins, fluoroquinolones and carbapenems, respectively[17,18] while resistance to co-trimoxazole was 64%.[17] Data from Karachi Laboratories from 2013 to 2015 (Figure 6) show a slight decline in resistance to carbapenems and a marginal increase in resistance to co-trimoxazole. Resistance to ampicillin, ciprofloxacin and ceftriaxone remained high throughout this time interval.

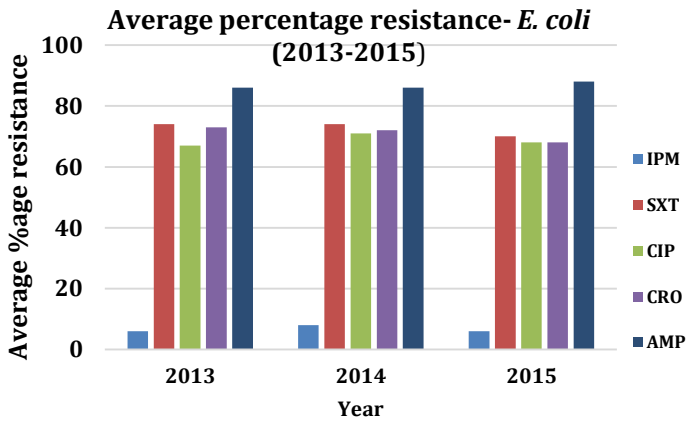

Figure 6. Average resistance percentage of *Escherichia coli* for the years 2013-2015, using data from PARN, generated by laboratories in Karachi. IPM=imipenem, SXT=co-trimoxazole, CIP=ciprofloxacin, CRO=ceftriaxone, AMP=Ampicillin. Colistin (CST) resistance was only investigated in 2013 and was not reported.

Klebsiella pneumonia

K. pneumoniae is an opportunistic pathogen commonly associated with resistance to a wide range of antibiotics.[19] In one study, 45% of ESBL-producing bacterial isolates were found to be *K. pneumoniae*, with 7 of these carrying an NDM-1 gene.[20] Reported resistance to co-trimoxazole and fluoroquinolones, ranged from 84-89% and 49-74% respectively, whereas resistance against imipenem ranged from 0-20% in different studies.[17,19] Resistance trends from 2013 to 2015 (Figure 7) confirm low resistance to imipenem amongst *K. pneumoniae*, and moderately high resistance rates against co-trimoxazole, ciprofloxacin and ceftriaxone.

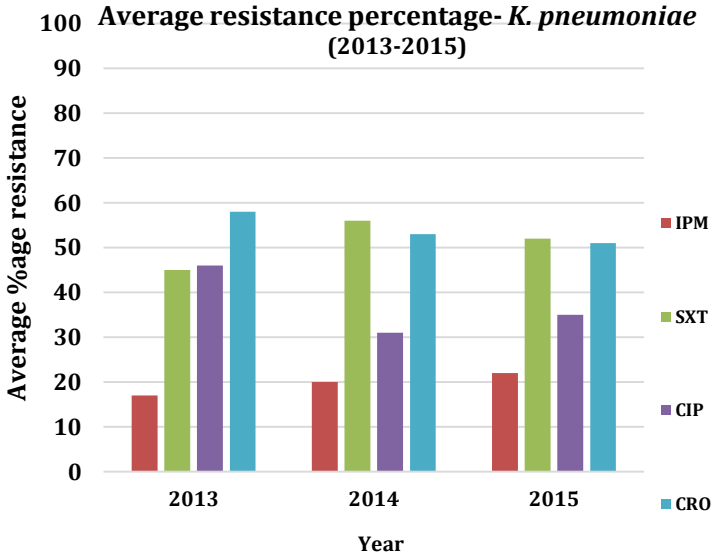

Figure 7. Average percentage resistance of *Klebsiella pneumoniae* for the years 2013-2015, using data from PARN, generated by laboratories in Karachi. IPM=imipenem, SXT=co-trimoxazole, CIP=ciprofloxacin, CRO=ceftriaxone, CST=colistin. Colistin (CST) was not tested in the years 2014 and 2015.

N. gonorrheae

In 2008, WHO reported an increase of 21% in *gonorrheae* since 2005, with 106 million new cases reported in adults, globally. [21] In a separate study, in Pakistan alone, fluoroquinolone (ofloxacin) resistance was found to have increased from 0% in 1992 to 93% in 2009.[23] However, no resistance was detected against azithromycin, spectinomycin, and ceftriaxone. The average percentage resistance 2013-2015 (Figure 8) confirms this trend, with high resistance observed against ciprofloxacin/ofloxacin i.e. 100-95% and no resistance reported against ceftriaxone.

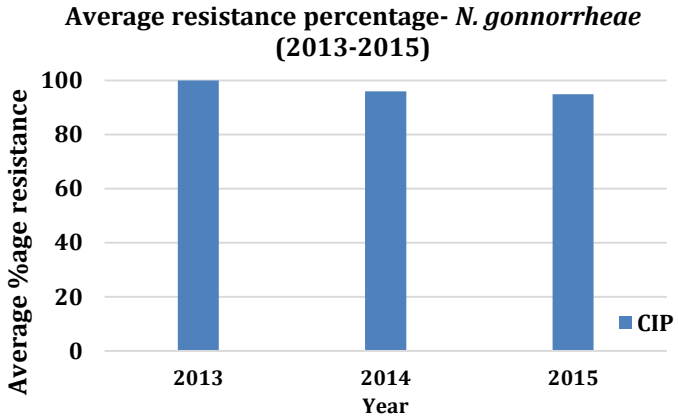

Figure 8. Average percentage resistance of *N. gonnorheae* for the years 2013-2014, using data from PARN, generated by laboratories in Karachi. CIP= ciprofloxacin, CRO= ceftriaxone.

Salmonella

It is estimated that there are 21 million cases of typhoid fever globally, with 220,000 deaths annually, worldwide.[24,25] From 2009-2011; resistance in *Salmonella* species (*Typhi* and *Paratyphi A, B* and *C*) was evaluated in a study on blood samples. Increasingly high resistance was observed against fluoroquinolones, with the average resistance rates observed for *Salmonella Typhi* and *Paratyphi* serovars being 79%, 88%, and 93% for the years 2009, 2010 and 2011, respectively. Emergence of ceftriaxone resistance was also documented at 0.08% in *S. Typhi*.[26] In comparison, the average percentage resistance for the years 2013-2015 (Figure 9) shows increasing resistance towards fluoroquinolones (ciprofloxacin) with resistance rising from 84% to 91% and no resistance being reported against ceftriaxone.

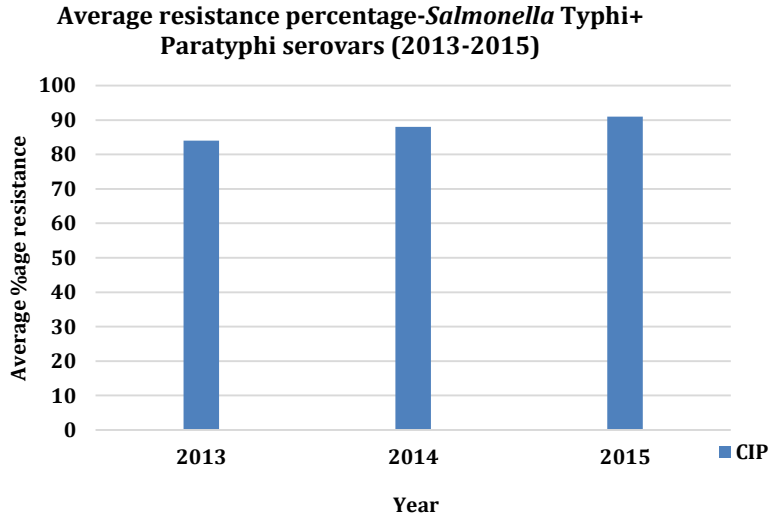

Figure 9. Average percentage resistance of *Salmonella Typhi+Paratyphi* A, B and C, from 2014-2015, using data from PARN generated by laboratories in Karachi. CIP= ciprofloxacin, CRO= ceftriaxone

These studies reveal a troublesome picture that resistant typhoid is very much rampant and likely to stay that way for a long time to come. *S. Paratyphi* and MDR strains may be becoming more prevalent and also proving difficult to treat with conventional drugs, adding to costs and morbidity.

3.2.2 Gram-positive bacteria

Emerging and evolving drug resistance in Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and penicillin-resistant *Streptococcus pneumoniae* has had serious repercussions on the health system.[27] These include; longer duration of hospital stay, increased mortality rate and higher probability of treatment failure. Increasing resistance has also been observed against aminoglycosides, glycopeptides, and penicillins in these organisms.[28]

Staphylococcus aureus

Staphylococcus aureus clinically manifests itself in different pathologies including endocarditis, osteomyelitis and bloodstream infections, as well as in community-associated infections, the majority of which are soft tissue and skin infections.[27] *S. aureus* has also gained significant notoriety with the emergence and wide spread dissemination of MRSA isolates, within both health care and community settings.[29] A study carried out from 2004 to 2005, reported the incidence of MRSA to be 43%.[30] Additionally, clindamycin resistance was reported to be 90% amongst MRSA and 6% amongst MSSA.[30] A nationwide study conducted from 2005-2007 found 79% clindamycin resistance amongst MRSA.[31] Data from Karachi Laboratories suggests (Figure 10) that clindamycin resistance increased from 17% in 2013 to 20% in 2014. Resistance to linezolid and vancomycin has not been reported to date. MRSA rates determined by cloxacillin or oxacillin susceptibility testing were 54-55% during 2013-2015.

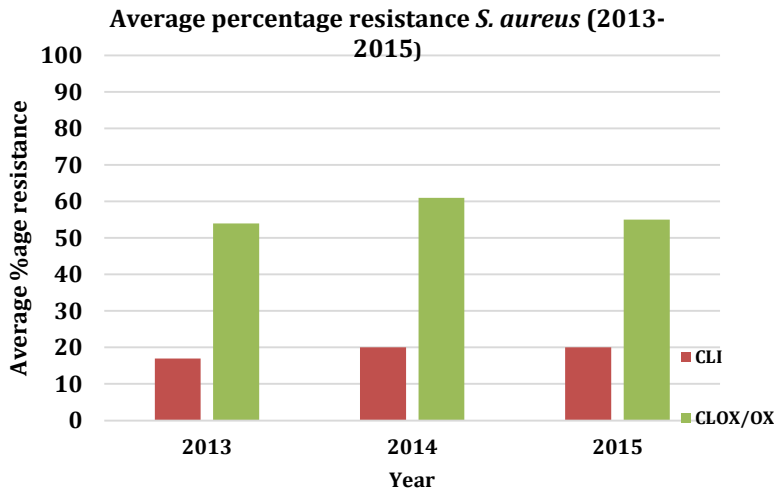

Figure 10. Average percentage resistance of *Staphylococcus aureus* from 2013-2015, using data from PARN generated by laboratories in Karachi. CLI= clindamycin, VAN= vancomycin, LZD= linezolid. Linezolid was only used in 2013 and 2014 antibiograms.

Enterococcus species

Resistance rates amongst *enterococci* are reported at 13% to vancomycin and 74% to ampicillin (2001-2006).[10] Data from Karachi (Figure 11) suggests from 2013-2015 ampicillin resistance decreased from 39% to 27% while vancomycin resistance during this period varied between 8-15%.

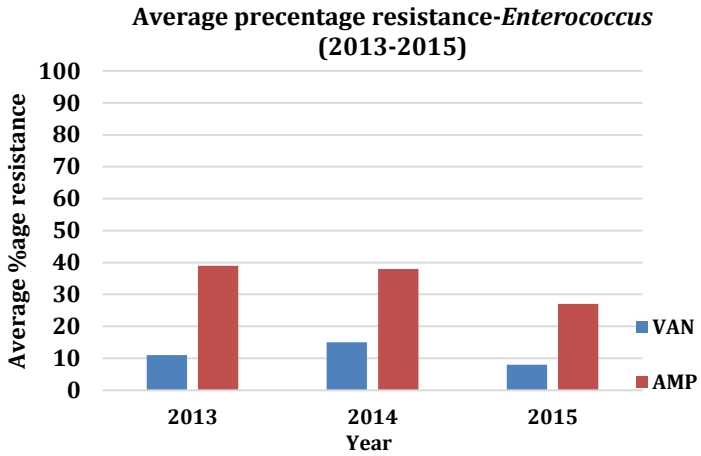

Figure 11. Average percentage resistance of *Enterococcus* from 2013-2015, using data from PARN, generated by laboratories in Karachi. VAN= vancomycin, AMP= ampicillin

Streptococcus pneumoniae

S. pneumoniae is an important pathogen in the context of respiratory and mucosal infections with resistance to pencillins, macrolides and co-trimoxazole contributing towards increasing pneumococcal disease burden.[32] Penicillin resistance was not encountered amongst community pneumococcal isolates from Pakistan in a study published in 2008.[33] Data from Karachi Laboratories (Figure 12) suggests that for 2013-2014, resistance rates for *S. pneumoniae* isolates for penicillin were 9-10%. Co-trimoxazole resistance rates decreased from 80% to 75% from 2013 to 2015.

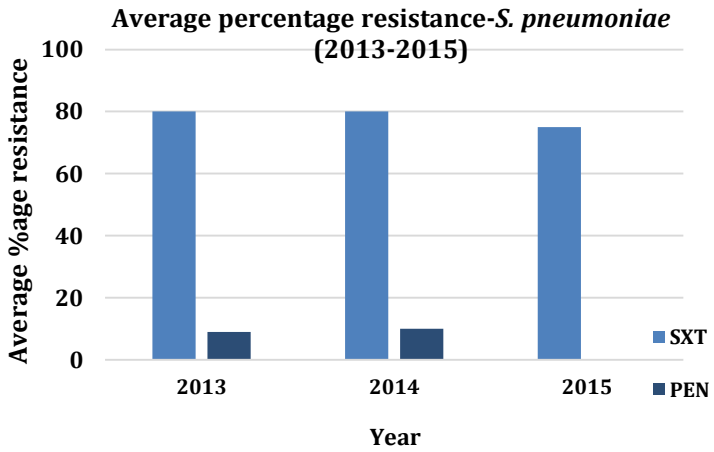

Figure 12. Average percentage resistance of *S. pneumonia* from 2013-2015, using data from PARN, generated by laboratories in Karachi. SXT= co-trimoxazole, PEN= penicillins

3.3 Laboratory and AMR surveillance capacity

Surveillance and monitoring of antibiotic resistant bacteria is essential for detecting and controlling outbreaks, identifying populations most at risk, designing and evaluating intervention strategies. Furthermore, it informs the use of scarce resources, so that they can be used most efficiently and effectively, to reduce disease burden. Monitoring AMR requires quality assured microbiology. Unfortunately, the importance of clinical microbiology laboratory services has not been recognized by the government of Pakistan, during the last 70 years, of its existence. Therefore, good standardized laboratories are very few in the country, both in public as well as private health care sector settings. Currently, many tertiary and secondary care hospital clinical microbiology laboratories have very basic facilities, which results compromised reporting.

In a Knowledge and Practices (KAP) assessment of microbiological laboratory workers from Karachi and Lahore, carried out in 2013, a clear gap between knowledge, implementation and adherence of standardized susceptibility testing was shown.[34] Even though 85% of respondents admitted to being aware of CLSI AST (antimicrobial susceptibility testing) guidelines, 68% of the respondents admitted to non-adherence to these guidelines. Moreover, awareness that non-standardized AST practices were being followed in Pakistan was present in 50% of the laboratory workers. Similarly, 21% of the respondents' laboratories did not refer to or maintain standard operating procedures (SOPs). Likewise, 66% of respondents indicated awareness that wearing gloves can prevent spread of MDR organisms, with 25% answering that personal protective equipment (PPE) was not always available to them. Moreover, reported rates of awareness regarding the role of waste disposal, disinfection, and hand-washing in limiting the spread of antimicrobial resistance were 75%, 42%, and 81%, respectively. 60% of the laboratories used an autoclave for bio-hazardous waste decontamination. Almost 47% of the respondents were unaware of the existence of a legal act for laboratory waste management in Pakistan.

A study exploring biosafety practices in microbiology laboratories in Lahore and Karachi identified a number of barriers, including lack of time to read biosafety guidelines, lack of staff authorization to change/improve practice and no career advantages for implementing optimal practices.[35] However, the predominant reason for lack of compliance appeared to be a lack of recognition for employees' rights and benefits in the workplace. Thereby, delineating the need for establishing proper laboratory management and providing workers an impetus for compliance to standardized protocols.

A more recent questionnaire-based survey conducted in 2015-2016 aimed to identify gaps in laboratory capacity for AMR surveillance.[36] The survey included public and private sector laboratories from major cities. Specific questions were included about the use of standardized methods for AST testing, quality assurance practices and readiness for AMR surveillance. The cumulative responses (Figure 13) suggest a 37% gap in AST testing, 58% gap in quality assurance practices and 60% gap in readiness for AMR surveillance. The impact of training within the longitudinal cohort showed an increase from baseline scores based on the SLIPTA checklist.[37] These studies suggest that laboratory capacity in Pakistan needs to be strengthened and standardized, in order to generate reliable and accurate data for AMR surveillance.

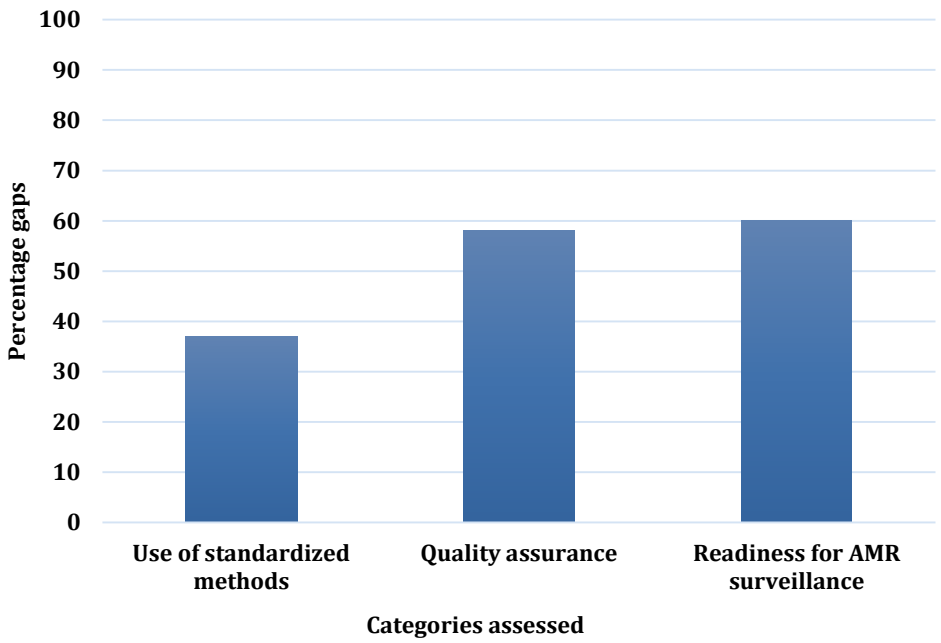

Figure 13. Gaps in AMR surveillance survey (Reference 35)

Conclusion

Although there is no national surveillance on AMR within Pakistan, PARN — a collaborative initiative — stands out as a highly effective resource for gauging AMR trends, using the antibiogram data shared by participating clinical laboratories. It is a small-scale network that can be improved upon and expanded for national surveillance.

Data on AMR within Pakistan currently has to be gleaned from informal sources and small scale published studies, and needs to be treated with caution. Whether resistance trends have changed with the passage of time or these are irregularities produced due to non-standardized AST is hard to determine. However, by and large, resistance to many antimicrobial agents included in GLASS remains high, i.e. >60% or present at intermediate levels 45-60%.

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Chapter 4

AMR and Antibiotic Use in Animals

Antimicrobial resistance in humans and animals is escalating at an exponential rate and warrants immediate attention. To sustain the health of farm animals, antibiotics were introduced in cattle and poultry farming in the late 1940s. While in use for the prevention of infections in animals, antibiotics were recognized as growth promoters, resulting in the enhanced growth of animals and increases in the yield of milk. Subsequent to this finding, antibiotics became an important component of animal feed. This indiscriminate use of antibiotics in animal farming, lead to the selection of resistant bacteria, and ultimately drug resistance, in the animal sector.[1]

Humans live at the animal-ecosystem interface and are, therefore, constantly coming in contact with animals. This occurs both indirectly, through the food chain, which includes consumption of contaminated food or food products, and directly, as a result of handling infected animals or biological substances, such as blood, urine, feces, saliva and semen. Moreover, transmission can also occur, to a lesser extent, through manure-contaminated environments, which also serve as a reservoir of resistant bacteria and can facilitate transmission to both animals and humans.[2, 3] As the antimicrobials used in animals, for growth promotion or for treatment of infections, are essentially the same as those used in humans, for the treatment of infections, transmission of such pathogens to humans can result in resistant infections and, ultimately, in cases of treatment failure.

To prevent the emergence and transmission of antimicrobial resistance, firm policies need to be developed and implemented, promoting the judicial use of antibiotics. This requires a critical analysis of the current situation to enable the development of policies that meet the current need. The following paragraphs reflect the current situation regarding antimicrobial resistance in animals in Pakistan.

4.1 Antibiotic use in food animals

Infectious diseases cause heavy losses in livestock, as a result antibiotics are often added to animal feed, for therapeutic, prophylactic and metaphylactic purposes. Additionally, antibiotics serve as growth promoters and are given to farm animals, to meet growing needs for meat and milk. Overall, livestock consumed at least 63,200 tons of antibiotics in 2010, accounting for nearly 66% of an estimated 100,000 tons of antibiotics produced annually worldwide, and livestock consumption is projected to rise to 105,600 tons by 2030.[4] Country profiles for 2010, indicated that China used the most antibiotics in animals, followed by the United States, Brazil, Germany, India, Spain, Russia, Mexico, France and Canada (Figure 1 and 2).[4,5]

Current data suggest indiscriminate and extensive antibiotic usage in farm animals in Pakistan, where, instead of sub-therapeutic levels for prophylaxis, antibiotics are being used at therapeutic levels, and in some instances at concentrations that exceed the treatment concentration used in humans.[6] This overuse/misuse leads to the selection of resistant bacteria among animals. Such resistant bacteria, can be transmitted to humans through various routes or may allow susceptible human pathogens to acquire resistance through genetic transfer, thus generating new resistant strains.

Despite extensive usage, there is no surveillance program for antibiotic use in livestock and usage data on antibiotics in farm animals is nonexistent. Furthermore, information regarding the rates and modes of transmission also remains elusive. The few available reports indicate that the most commonly used antibiotics in livestock are penicillins, lincosamide, macrolides, aminoglycosides, sulfonamides, and floroquinolones.[4]

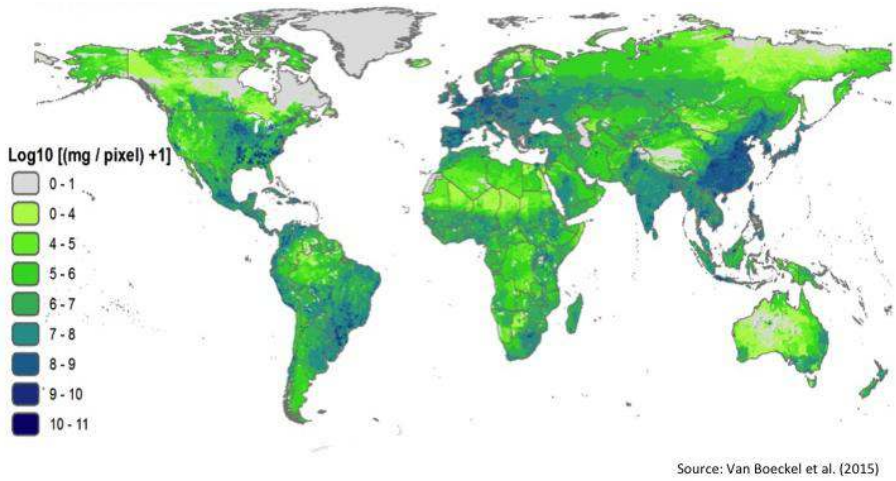

Figure 1. Global antimicrobial consumption (mg/10km pixel).

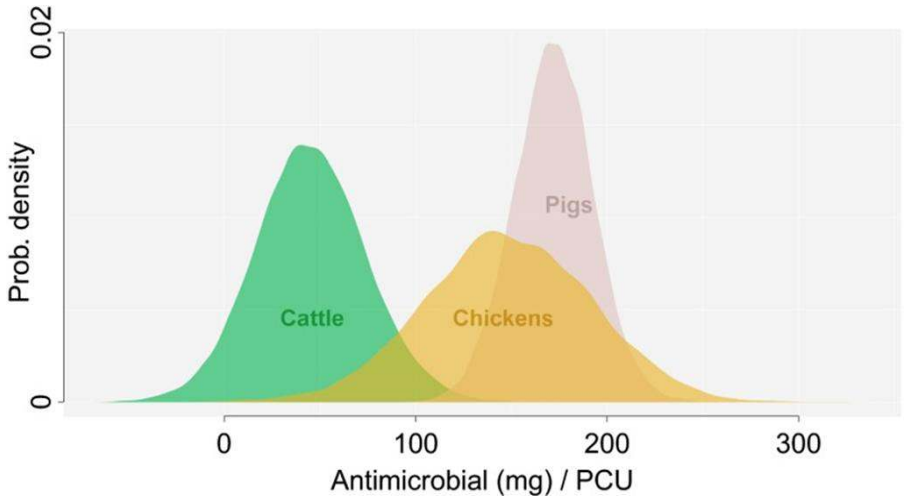

Figure 2. Posterior distributions for estimates of antimicrobial consumption in cattle, chickens, and pigs in OECD countries.[4]

4.2 AMR patterns in animals

4.2.1 Poultry

The most commonly used antibiotics in poultry are neomycin, tylosin, erythromycin, tetracycline, gentamicin, virginiamicin and bacitracin. The main purpose of these antibiotics is to prevent infections of the respiratory tract, gastroenteritis, and skin or soft tissue infections. Whereas sulfonamides are used to prevent coccidiosis fowl typhoid,

coryza and pullorun disease. Coccidiosis is also commonly treated with piperazine, oxytetracycline, amoxicillin, amprolium, ciprofloxacillin, or sulfa drugs.

4.2.1.1 Residues of antimicrobials in poultry eggs and meat

Measurable amounts of antibiotics have been identified in the egg matrix, as well as in meat. Studies performed by several authors indicated a significantly high concentration of quinolones (20-30.81 µg/kg),[7, 8] amoxicillin (16.92 – 152.62 µg/kg),[9] chloramphenicol (0.0126-0.226 µg/kg)[10] and tetraycycline (89.2 -800 µg/kg)[8, 11, 12] in poultry meat. Additionally, studies performed on fresh and frozen sample of chicken (breast and thighs) have demonstrated the presence of significant amounts of antimicrobials, such as tetracyclines (24-48%), ciprofloxacin (30-44%), enrofloxacin (18-40%) and amoxicillin (22-42%).[9]

4.2.1.2 Drug resistant bacteria in poultry

Poultry meat is commonly found colonized with enteric bacteria, including *E. coli*, *Salmonella typhimurium*, *S. aureus*, and *Campylobacter* spp. These four pathogens are also the most common causes of gastrointestinal illnesses in humans. Acquisition of such bacteria by poultry can occur via several routes, including bird feeds, farms, and slaughterhouses. Drug resistance patterns of the most commonly found pathogens are listed below.

4.2.1.2.1 Salmonella

Foodborne Salmonellosis is a major public health concern both in developed and developing countries. The disease results from the consumption of meat contaminated with *Salmonella* serovars. Globally, an estimated 20-70% of poultry has been found to be contaminated with *Salmonella* serovars. The exposure occurs in slaughterhouses, contaminated feed, and cages during transportation and through handlers. Results of several studies demonstrated that most of the isolated serovars are human pathogens and are resistant to the majority of antibiotics. Furthermore, resistance rates were also found to be higher in smaller towns as compared to large metropolitan cities. In a recent study by Korejo *et al.* a total of 78 broiler meat samples, out of 160 (approximately 48%), were found to be contaminated, with different species (mostly human pathogens) of *Salmonella*. The isolated strains demonstrated resistance to 11 out of the 17 antibiotics tested.[13] Comparable results were attained in another study performed by Rehman and colleagues. Their study showed that at least 46% of a total of 120 meat samples were positive for *Salmonella* serovars, with *S. enteritidis* being the most common serovar. Resistant patterns showed that *S. enteritidis* isolates were highly resistant to bacitracin, erythromycin and novobiocin, moderately resistant to gentamicin, kanamycin, penicillin and streptomycin, and sensitive to chloramphenicol and ampicillin.[13] In the district of Hyderabad, 42% of broiler meat samples were contaminated with *S. enteritidis*. In agreement with previous findings, high levels of ampicillin resistance were observed in strains of *Salmonella,* isolated from both meat and eggs, in addition to streptomycin and tetracycline resistance.

4.2.1.2.2 E. coli

E. coli bacteria normally reside in the intestines of poultry. Most resident *E. coli* are not infectious, however, a limited number produce extra-intestinal infections. Commonly occurring serotypes of *E. coli* associated with infections in poultry are O_1, O_2 and O_{78}. These serotypes are known to cause a range of both localized and systemic infections.

Systemic infections result when bacteria gain access to the bloodstream, either from the respiratory tract or the intestine. Antimicrobial resistance in *E. coli* is steadily increasing in Pakistan. Studies show an alarming increase in the number of poultry isolates that are significantly less susceptible to multiple antibiotics such as norfloxacin (98%) cefazolin (94%), gentamicin (87%), flumequine (80%), neomycin (79%), and oxolanic acid (77%). Moreover, sensitivity to amoxycillin, kanamycin and co-trimoxazole declined even further, with sensitivity ranging from 47% for amoxycillin to 32% for kanamycin and 8% for co-trimoxazole.[14, 15]

4.2.1.2.3 S. aureus

After *Salmonella*, *S. aureus* is the most common pathogen responsible for food poisoning and food-related infections. *S. aureus* is known to cause a variety of animal diseases, such as mastitis, arthritis and urinary tract infections, in cattle. It can cause septic arthritis, septicemia and limb infections in poultry. Contamination of food and food products by *S. aureus* indicates poor hygienic conditions. Burriro and colleagues reported high-level resistance of *S. aureus* to ampicillin, sulfanilamide, and ofloxacin, whereas, low levels of resistance were observed in kanamycin, erythromycin, and chloramphenicol.[16]

Table 1: Antibiotic resistance patterns in bacterial species isolated from poultry animals

Author	Study site	Bacterial Strain	Study population	Antibiotic (% Resistance)	Reference
M. Saleem	Faisalabad	*E. coli*	Chicken (liver & heart)	Enr (0); Cip (0); Nor (0); Cef (5); Gen (13); Flu (8); Neo (21); Oxa (23); Aml (47); Kan: (53); Sul-Tri (92)	[14]
Aijaz Hussain Soomro *et al.*	Hyderabad	*S. enteritidis*	Chicken	Amp (100); Str (94); Neo (25); Nal (62.5); Tet (94); Sul-Tri (6.25)	[17]
Aijaz Hussain Soomro*et al.*	Hyderabad	*S. typhi*	Chicken	Amp (100); Str (91); Neo (18); Nal (54); Tet (91) ; Sul-Tri 2 (18)	[17]
Aijaz Hussain Soomro *et al.*	Hyderabad	*S. pullorum*	Chicken	Amp (100); Str (85.7); Neo (57); Nal (71);Tet (100); Sul-Tri (28.5)	[17]
Aijaz Hussain Soomro*et al.*	Hyderabad	*S. typhimurium*	Chicken	Amp (100); Str (100); Neo (50); Nal (50); Tet (100); Sul-Tri (25)	[17]

Muhammad Idrees*et al.*	Pakistan	*E. coli*	Chicken	Sul-Tri(84); Tri(88); Cip(44); Nal(84); Cex(16); Ced(16); Amp(44); Nit(28)	[15]
A. H. Shah *et al.*	Karachi	*S. enteritidis*	Chicken	S. enteritidis Amp (78.9); Cex (2.6); Str (31.5); Kan (7.8); Neo (47.3); Nal (55.2); Tet (84.21); Bac (28.9); Ery (31.5); Nov (71.0);	[18]
A. H. Shah *et al.*	Karachi	*S. typhi*	Chicken	Amp (87.5); Str (68.7); Kan (6.2); Neo (62.5); Nal (87.5); Tet (93.75); Bac (12.5); Ery (62.5); Nov (6.25); Spe (12.5)	[18]
A. H. Shah *et al.*	Karachi	*S. pullorum*	Chicken	Amp (100); Str (81.2); Neo (100); Nal (31.2); Tet (93.7); Bac (50.0); Ery (56.2); Nov (68.7); Spe (6.2)	[18]
A. H. Shah *et al.*	Karachi	*S. typhimurium*	Chicken	Amp (87.5); Str (75.5); Neo (25.0); Nal (50.0); Tet (87.5); Bac (75.0); Ery (12.5); Nov (62.5)	[18]
Adnan Amin *et al.*	District DI Khan	*E. coli*	Chicken droppings	Farm A: Azt (100); Str (88); Cip (24); Ofx (36); Cro (60); Fep (56); Mem (16); Aml (76); Amc (40) Farm B: Azt (100); Str (92); Cip (28); Ofx (40); Cro (60); Fep (68); Mem (18); Aml (68); Amc (40)	[19]
Faiza Habib *et al.*	Hyderabad	*S. aureus*	Chicken	Amp (81.25); Ami (56.25); Chl (50); Sul (81.25); Ery (43.75); Gen(66.6); Kan (37.5); Neo(56.25); Pen G(66.6); Tet (66.6); Ofl (100)	[16, 18]

Amp: Ampicillin; **Ami:** Amikacin; **Chl:** Chloramphenicol; **Sul:** Sulfanilamide; **Ery:** Erythromycin; **Gen:** Gentamicin; **Kan:** Kanamycin; **Neo:** Neomycin; **Pen G:** Penicillin G; **Tet:** Tetracycline**; Ofl:** Ofloxacin; **Aml:** Amoxicillin; **Nor:** Norfloxacin; **Enr:** Enrofloxacin; **Ot:** Oxytetracycline; **Cip:** Ciprofloxacin; **Pen:** Penicillin; **Cep:** Cephradine; **Met:** Methicillin; **AmpC:** Ampiclox; **Lin:** Lincomycin; **Co-tri:** Co-trimaxazole; **Aug:** Augmentin; **Orb:** Orbenin; **Sul-Tri:** Sulphamethoxazole – Trimethoprim; **Tri:** Trimethoprim; **Nal:** Nalidixic acid; **Cex:** Cefotaxime; **Ced:** Ceftazedime; **Nit:**Nitrofurantoin; **Cel:** Cefaclor; **Dox:** Doxycycline; **Cen:** Cephalaxin; **Rox:** Roxithromycin; **Str:** Streptomycin; **Cef:** Cefzolin; **Flu:** Flumequine; **Oxa:** Oxolanic acid; **Azt:** Azteronam; **Ofx:** Ofloxacin; **Cro:** Ceftrixone; **Fep:** Cefepime; **Mem:** Meropenem; **Amc:** Amoxicillin/Clavulanic acid; **Bac:** Bacitracin; **Ery:** Erythromycin; **Nov:** Novobiocin; **Spe:** Spectinomycin

4.2.2 Livestock

Livestock animals are usually reared in poor sanitary conditions with little or no attention to disease control. In addition, these animals are in close contact with other livestock. Living in such conditions make livestock susceptible to a variety of diseases, such as diarrhea, mastitis, keratoconjunctivitis and brucellosis. Controlling these diseases is necessary to ensure animal health, human health, food security and the economic wellbeing of rural population.[20] As shown in Figure 3 and Table 2, most bacteria isolated from beef and mutton showed resistance to the five most commonly administered antibiotics. Moreover, the level of resistance to the first five antibiotics was also found to be significantly higher in beef and mutton compared to others as shown in Figure 3.

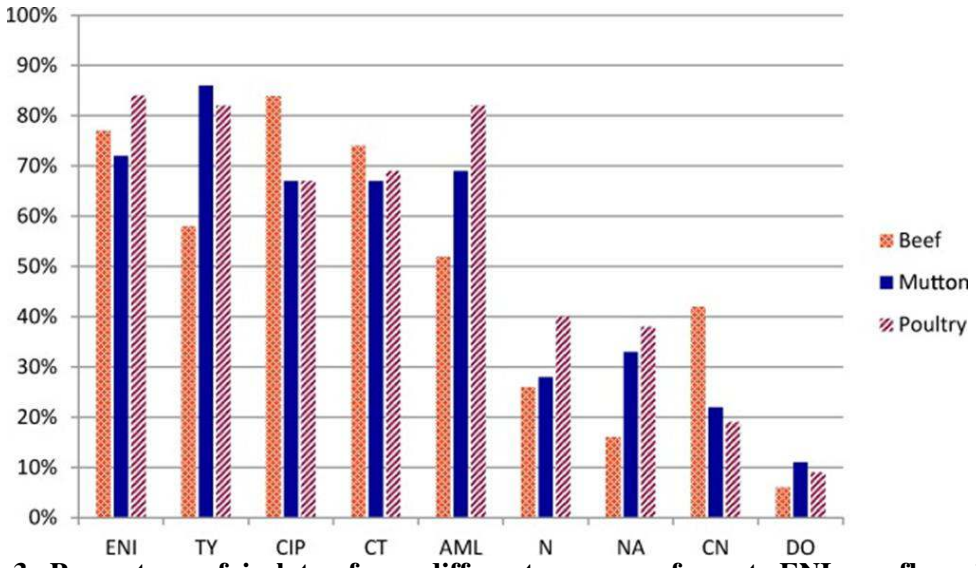

Figure 3. Percentage of isolates from different sources of meat. ENI-enrofloxacin, TY-Tylosine, AML-Amoxicilline, CIP-Ciprofloxicin, CT-Colistine, NA-Nalidixic Acid, N-Neomycin, GN-Gentamycin, DO-Doxycycline.

Table 2. Antibiotic resistance patterns in bacterial species isolated from livestock animals.

Author	Study site	Bacterial Strain	Study population	Antibiotic (% Resistance)	Reference
Faiza Habib *et al.*	Hyderabad	*S. aureus*	Buffalo	Amp (100); Ami (46.6);Chl (20); Sul (100); Ery (13.3); Gen(40); Kan (66.66); Neo (53.3); Pen G (66.6); Tet (53.3); Ofl (13.3)	[16]
Faiza Habib *et al.*	Hyderabad	*S. aureus*	Cattle	Amp (100); Ami (46.6); Chl (20); Sul (100); Ery	[16]

				(13.3); Gen (40); Kan (66.66); Neo (53.3); Pen G (53.3); Tet (53.3); Ofl (40)	
Faiza Habib *et al.*	Hyderabad	*S. aureus*	Camel	Amp (29.60); Ami (14.30); Chl (43); Sul (100); Ery (57.20); Gen (21.50); Kan (14.30); Neo (14.30); Pen G (100); Tet (0); Ofl (14.30)	[16]
Faiza Habib *et al.*	Hyderabad	*S. aureus*	Goat	Amp (100); Ami (100); Chl (55); Sul (100); Ery (25); Gen (25); Kan (50); Neo (30); Pen G (40); Tet (66.66); Ofl (100)	[16]
Faiza Habib *et al.*	Hyderabad	*S. aureus*	Sheep	Amp (38.50); Ami (53.9); Chl (96.16); Sul (100); Ery (50); Gen (3.9); Kan (77); Neo (96.16); Pen G (43); Tet (27); Ofl (0)	[16]
Abdul Qayyum*et al.*	Cholistan	*S. aureus*	Cattle	Aml (12); Amp (16); Nor (10); Enr (22); Ot (37); Gen (0); Cip (0); Pen (65); Cep (100)	[21]
S. Hameed *et al.*	Burewala	*S. aureus*	Cattle and Buffalo	Aml (39); Enr (78); Gen (96); Chl (86); Ot (69)	[22]
KalsoomFarzana*et al.*	Multan	*S. aureus*	Cattle and Buffalo	Met (10.39%); Amp (25.97%); Tet (2.60%); AmpC (18.18%); Ery	[23]

				(2.60%); Lin (57.17%); Co-tri (81.81%); Pen (24.67%); Aug (23.37%); Orb (63.63%)	
Muhammad Idrees*et al.*		*E. coli*	Buffalo	Sul-Tri (28%); Tri (28%); Cip (8%); Nal (20%); Cex (16%); Ced (4%); Amp (24%); Nit (24%)	[15]
S. Hameed *et al.*	Burewala	*E. coli*	Cattle and Buffalo	Aml (43); Enr (0); Gen (15); Chl (29); Ot (29)	[22]
Nafisa Hassan Ali *et al.*	Karachi	*E. coli*	Meat (unspecified)	Amp (71); Aml (73); Cel (60); Ofl (0); Tri (15); Dox (30); Cen (35); Rox (32)	[24]
Nafisa Hassan Ali *et al.*	Karachi	*Klebseilla*	Meat (unspecified)	Amp (100); Aml (97); Cel (83); Ofl (0); Tri (17); Dox (25); Cen (30); Rox (47)	[24]
Nafisa Hassan Ali *et al.*	Karachi	*Enterobacter*	Meat (unspecified)	Amp (75); Aml (75); Cel (55); Ofl (0); Tri (20); Dox (36); Cen (35); Rox (39)	[24]
Nafisa Hassan Ali *et al.*	Karachi	*Salmonella*	Meat (unspecified)	Amp (33); Aml (33); Cel (21); Ofl (0); Tri (17); Dox (25); Cen (21); Rox (25)	[24]
S. Hameed *et al.*	Burewala	*Streptococcus agalactiae*	Cattle and Buffalo	Aml (64); Enr (18); Gen (9); Chl (18); Ot(46)	[22]

S. Hameed *et al.*	Burewala	*Streptococcus dysagalactiae*	Cattle and Buffalo	Aml (100); Enr (0); Gen (50); Chl (0); Ot (50)	[22]
S. Hameed *et al.*	Burewala	*Corynebacteriumbovis*	Cattle and Buffalo	Aml (0); Enr (0); Gen (100); Chl (100); Ot (100)	[22]

Amp: Ampicillin; **Ami:**Amikacin; **Chl:** Chloramphenicol; **Sul:** Sulfanilamide; **Ery:** Erythromycin; **Gen:** Gentamicin; **Kan:** Kanamycin; **Neo:** Neomycin; **Pen G:** Penicillin G; **Tet:** Tetracycline**; Ofl:**Ofloxacin; **Aml:** Amoxicillin; **Nor:**Norfloxacin; **Enr:**Enrofloxacin; **Ot:**Oxytetracycline; **Cip:** Ciprofloxacin; **Pen:** Penicillin; **Cep:**Cephradine; **Met:** Methicillin; **AmpC:**Ampiclox; **Lin:**Lincomycin; **Co-tri:** Co-trimaxazole; **Aug:** Augmentin; **Orb:**Orbenin; **Sul-Tri:**Sulphamethoxazole – Trimethoprim; **Tri:** Trimethoprim; **Nal:**Nalidixic acid; **Cex:**Cefotaxime; **Ced:**Ceftazedime; **Nit:**Nitrofurantoin; **Cel:**Cefaclor; **Dox:** Doxycycline; **Cen:**Cephalaxin; **Rox:**Roxithromycin

4.2.2.1 Residues of antimicrobials in milk, feces, and meat

Many studies have shown the presence of high levels of antibiotic residues in milk and meat from animals (Figure 3). Some antibiotics are metabolized or excreted, while others accumulate in the tissue of livestock animals and, therefore, enter food chain. The monitoring and control of antibiotic residues in livestock animal meat and milk products is of prime importance. A study conducted in Sindh, Pakistan showed that 36% of 137 milk samples were positive for beta-lactam antibiotics. Out of these, 56% were positive for amoxicillin and 48% for ampicillin.[25] Another study conducted in Sindh, Pakistan showed that 38% of 300 raw beef samples were positive for antibiotic residues.[26]

4.2.2.2. Resistant bacteria in livestock

Livestock products including meat and milk have been screened for antimicrobial resistant bacteria across the globe. However, very few such studies have been carried out in Pakistan. In Pakistan, AMR patterns of a few bacteria of livestock origin have been reported, which include *S. aureus*, *E. coli*, *Streptococcus agalactiae, Streptococcus dysagalactiae*, and *Corynebacterium bovis,* among others. Their resistance patterns are shown in Table 2.

4.2.2.2.1 S. aureus

Staphylococcus aureus is an anaerobic, gram-negative opportunistic bacteria.[16] It is the most common causative agent of chronic and subclinical mastitis, a disease associated with infection of mammary tissues and a decrease in milk production, in livestock animals. *S. aureus* infections are of economic concern to the dairy industry and, therefore, various studies have been carried out to characterize *S. aureus* and to determine its resistance patterns.[21] In 2005, a study showed that 10% of *S. aureus* isolates from milk samples were resistant to methicillin, 82% to co-trimaxazole, 57% to lincomycin, 64% to orbenin, 26% to ampicillin and 25% to penicillin (Figure 4).[23] Another study, carried out in 2008, reported the AMR patterns in *S. aureus* recovered from infected cattle milk. All isolates were resistant to cephradine and sensitive to ciprofloxacin and gentamycin.[21] Another 2008 study reported that *S. aureus* isolates, from cattle and buffalo milk, were 61%, 22%, 4%, 16%,

and 31% resistant to amoxicillin, enrofloxacin, gentamycin, chloramphenicol, and oxytetraycline, respectively.[22] In another study, conducted in 2015, AMR *S. aureus* isolates from different species were reported and all isolates from buffalo, cattle and goats were resistant to ampicillin.[16] Detailed AMR prevalence from all studies is given in Table 2 above**.**

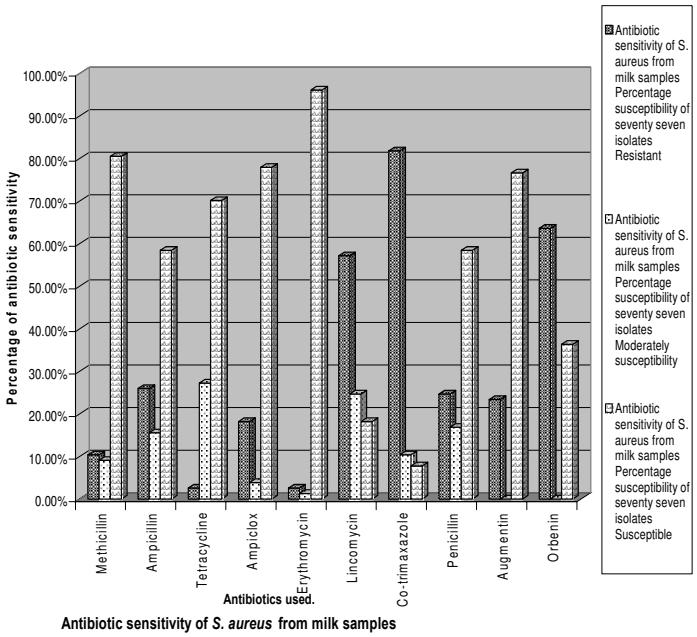

Figure 4. Antibiotic sensitivity of *S. aureus* isolated from milk samples.[23]

4.2.2.2.2 E. coli

Most strains of *E. coli*, like *S. aureus*, are commensal and reside in the gastrointestinal tracts of various species. However, many strains of *E. coli* are pathogenic. AMR prevalence in commensal *E. coli* strains can provide an insight into potential future infections. Very few studies have been carried out in Pakistan which report AMR patterns in *E. coli* isolates from livestock.[15] In 2008, AMR prevalence in *E. coli,* isolated from the milk of mastitis positive buffalo and cattle, was reported to be 43%, 0%, 15%, 29%, and 29% against amoxicillin, enrofloxacin, gentamycin, chloramphenicol, and oxytetracycline, respectively.[22] In another study, carried out in 2011, the AMR pattern in *E. coli* isolates from raw meat was reported. The highest resistance rates of 73%, 71% and 60 % were reported against amoxicillin, ampicillin and cefaclor.[24] In 2011, AMR profiles of commensal *E. coli* in buffalo were published. The highest resistance levels, of 28%, were reported for cotrimoxazole, as well as trimethoprim.[15] Resistance levels against other antibiotics from these studies are given in Table 2.

4.2.2.2.3 Mastitogens

Mastitis is the name given to inflammation of mammary glands, and its causative agents are usually referred as mastitogens. Globally, 40% of morbidity in cows and buffaloes has been attributed to mastitis. The most important bacteria that cause mastitis are *S. aureus*, *Corynebacterium pyogenes*, coagulase negative staphylococci and *Corynebacterium bovis*. In Pakistan, *Staphylococcus aureus, Streptococcus agalactiae, E. coli, Streptococcus dysagalactiae*, and *Corynebacterium bovis* are the most common mastitogens. In 2008, a study reported AMR prevalence of these agents in isolates from cattle and buffalo milk. *S. agalactiae* was the most resistant to amoxicillin, followed by oxytetracycline. Similarly, *S.*

dysagalactiae was completely resistant to amoxicillin and only 50% sensitive to oxytetracycline and gentamycin. Lastly, *Corynebacterium bovis* was 100% resistant to gentamicin, chloramphenicol and oxytetracycline.[22] Resistance levels against other antibiotics from these studies are given in Table 2.

4.2.3 AMR in aquaculture

In the last 30 years, aquaculture has emerged as an important industry providing an estimated 110 million metric tons of food per year. Fish farming is gaining momentum and a significant number of aquaculture farms are now being established to sustain the supply of fish, crustaceans and mollusks. Despite several advantages, the most important drawback of aquaculture is that it exposes fish to several stressors that result in increased susceptibility to infections. The Pakistan Fisheries and Livestock Department prohibits the use of antimicrobials in aquaculture except for the treatment of carp infections.[27] However, some of these infections can be fatal, significantly hampering the yield of fish. Therefore, to counter this situation, the use of antimicrobials in aquaculture, in doses that prevent infections, is becoming a common practice. The continuous use of antimicrobials in aquaculture, to maintain the health of the fish, leads to the persistence of antimicrobials in the fish flesh. This can be transmitted to consumers, together with bacteria that are resistant to the antimicrobials used in aquaculture. A recent study reported the isolation of antimicrobial resistant bacteria from ponds and fish meat. The study was executed in the province of Punjab, where samples were collected from fish farms around the city of Lahore (the largest city in the province of Punjab with a population of 7 million) and the city of Multan.[27] Bacteria were isolated from water, sediments, and both healthy and diseased fish. The results of the study indicated that farm water, as well as fish meat, collected at the farm, were contaminated with antimicrobial resistant bacteria. The bacteria isolated were found to express resistance to tetracycline, trimethoprim, sulfonamides, amoxicillin, oxolinic acid, streptomycin, chloramphenicol, florfenicol, and erythromycin. The emergence of resistance in bacteria, isolated from aquaculture, in Pakistan, is suggested to originate from organic waste, which is a mixture of cattle and poultry waste, and is used to line the pond. The waste-matter lining facilitates the growth of zooplankton and phytoplankton, which is important for maintenance of aquaculture.[27, 28]

4.2.3.1 Antibiotic resistant bacteria in the environment

A significant proportion of studies, involving the transmission of drug resistant bacteria, focus mainly on bacteria that are residents of human or animal organs, without consideration of bacteria residing in the water. A large proportion of antibiotics are released from both human bodies and from livestock in an unmetabolized form. Additionally, expired antibiotics and waste from pharmaceutical companies is also released into environment, from where it gains entry into water sources. The presence of antibiotic in the water, even at low levels, can contribute to selection for resistance. Water sources, including waste-water, sludge, rivers, and sewage plants, serve as "mixing pots" for genetic exchange between resistant and susceptible bacteria. Various species of bacteria are able to interact with each other and trade genes. Such genes may include the ability to be resistant to an antibiotic and thus render a susceptible bacterium resistant.[29]

4.3.1 Immunization of animals

Most commonly encountered infections in farm animals, such as cows, goats and sheeps include Foot-and-Mouth disease, Hemorrhagic sepsis, black quarter, anthrax and mastitis. Vaccines, for the prevention of infections, are locally produced by Public Sector Veterinary

Research Institutes. There are a total of eight such institutes, 3 are located in Punjab, 2 each in Sindh and Khyber PakhtoonKhwa, and one in Balochistan. Several factors, including limited human resources and limited finances, affect both the quality and volume of vaccines that are produced in these institutes. It has been shown that vaccines produced only meet the need of 25% of the animal flock each year. Due to the decrease in production and increase in demand for these vaccines, a significant proportion are imported from outside the country, to be used in both poultry and corporate dairy farms.[30]

Programs are in place at the provincial level, which facilitate and ensure the administration of vaccines to livestock. Vaccines are held in a cold facility at the public sector research institute and are distributed to District Livestock Officers who mobilize the field veterinarians and para-veterinary staff for the delivery and administration of vaccines.[30] Although the country has a fairly efficient vaccine production and immunization program, there are several aspects of infection control that still require attention.

4.4.1 Point of control for internal veterinary movement

Currently Pakistan does not have any points of control of the movement of animals and animal products, barriers for disease control, or disease free regions or zones. As a result, infection control in animals, and the surveillance of diseases among animals, is near to impossible. This leads to the more infection and increased usage resulting in AMR across the country.

4.5.1 Food Safety and Biosecurity

While an integrated framework for biosafety and food security is lacking in Pakistan, there are three ordinances that ensure the supply of clean pure food to people these include (i) Pure food ordinance, (ii) Pakistan hotel ordinance and (iii) Cantonment Pure Food Ordinance. Because these ordinances are not applicable to cantonment areas, this third rule deals with food supply to cantonment areas. However, food safety is severely compromised as a result of unsatisfactory enforcement of related laws. Proper enforcement of these laws is the responsibility of the local government at the district level. It is their responsibility to deploy food and meat inspectors to fields for inspection of the two, however, these inspectors rarely perform inspections, due to several institutional, financial, and operational constraints. In order to comply with the Agreement on the Application of Sanitary and Phytosanitary measures (SPS), Agreement on Technical Barriers to Trade (TBT), Codex Alimentarius Commission (CAC), International Plat Protection Convention (IPPC), and World Organization for Animal Health (OIE) regulations, the Government of Pakistan has established a National Food Safety Animal and Plant Health Regulatory Authority. Departmental policies were approved in June 2017 and are in the process of being implemented, at both local district level and at country level.[30]

4.6.1 Control on veterinary medicine and veterinary biologicals

Until 2012, the distribution and quality control of drugs, for both animal and human and other biologicals, was controlled under the 1976 Drug Control Act, however, in 2012, an independent Division of Drug and Regulatory Authority of Pakistan (DRAP) was established. The purpose of DRAP is to regulate the manufacture, import, export, storage, distribution, and sale of human, as well as veterinary, therapeutic goods. The Division is still in its initial developmental stages and it will take a while before it is fully operational.[30]

Conclusions

Although the precise nature of the factors governing the spread of resistance, in animal and human reservoirs, remain unknown, several studies demonstrate that humans can gain exposure to resistant pathogens through the consumption of contaminated food. Despite these observations, it is difficult to determine what proportion of this resistance is actually the result of antibiotic use in animals. Bacterial genes, encoding for antimicrobial resistance, have other metabolic functions and have been part of bacterial life cycle for an extremely long time, suggesting a broader evolutionary function. Bacterial species bearing such genes are geographically widely distributed and are likely to be present where they have never been under the selective pressure of antibiotics. It is therefore imperative to understand the background levels and distribution of specific antibiotic resistance genes in bacteria of animal origin. Moreover, understanding the role of the entire ecosystem in the spread of antimicrobial resistance should also remain a priority.

There are currently no laws governing the use of antimicrobials in poultry in Pakistan, except to control the import and registration of marketed drugs. This results in an increased use of drugs and subsequent increase in the emergence of drug-resistant strains of pathogens, common to both poultry and humans.[31] To maintain animal and human health, effective strategies and interventions should be introduced, to check and control AMR in animals and human. These interventions should include the establishment of an AMR in animals surveillance network, as well as, the implementation of strict usage regulation on antibiotics, in their roles for both prophylaxis and treatment.

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Chapter 5

Antibiotic Stewardship

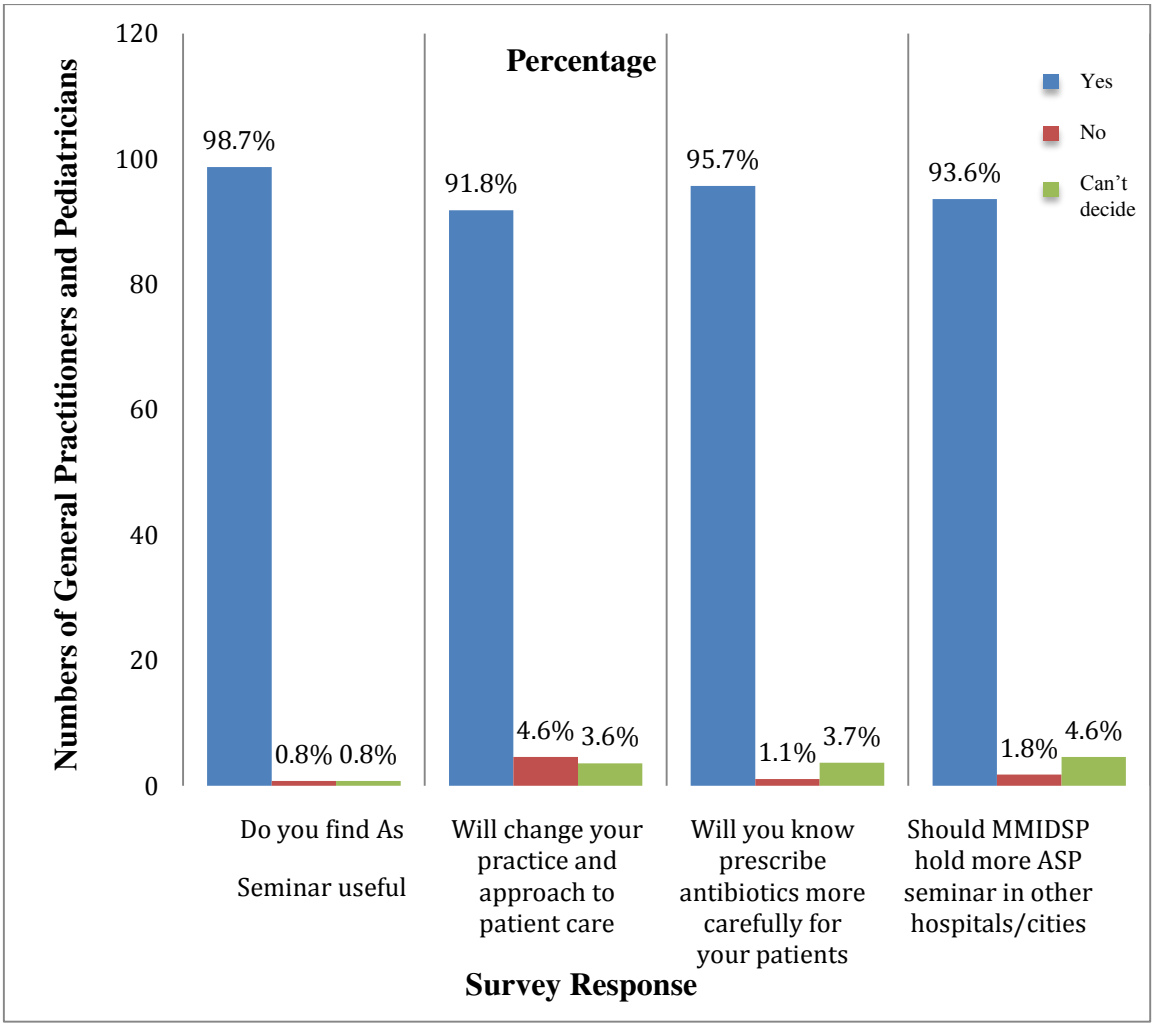
Antibiotic stewardship is defined as "coordinated interventions designed to improve and measure the appropriate use of antibiotic by promoting the selection of the optimal antibiotic drug regimen, dose, duration of therapy, and route of administration".[1,2] The major team members of Antibiotic Stewardship Programs (ASPs) are "an infectious diseases physician, a clinical microbiologist, a clinical pharmacist, with infectious diseases training, an information system specialist, an infection control professional, and a hospital epidemiologist."

Major strategies for antibiotic stewardship currently endorsed include preauthorization/formulary restriction and prospective audit with feedback, prescribing guidelines, and most importantly, education and awareness.[2] ASPs have shown a major impact on infection rates, resistance patterns, costs and clinical outcomes in many studies.[3-5] Even in community settings ASPs have been proven to have an impact.[6,7] ASPs are increasingly being advocated for and employed in some developing countries.[8,9]

Irrational antibiotic prescribing and the continuous evolution of resistant strains of microorganisms are both serious issues faced by Pakistan. Unfortunately, in Pakistan, ASP initiatives have only recently been started. In addition, there is no published literature about antibiotic stewardship within Pakistan. Given ASPs' proven efficacy and major gains in many settings, it is imperative that such initiatives and efforts be implemented across Pakistan. The Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) has addressed ASP, at both the institutional and community levels, with the involvement of major stakeholders, from professional societies, and policy makers, of public and private institutions. It launched the "Antibiotic Stewardship Initiative in Pakistan (ASIP)" in March 2014, in Islamabad, at its annual meeting.[10] Stakeholders identified and targeted included Pakistan's leading medical organizations (including the Pakistan Medical Association (PMA), Pakistan Pediatric Association (PPA) and Pakistan Academy of Family Physicians (PAFP).

Since its launch, the ASIP has initiated many ASP activities (ASP talks, workshops, initiation of weekly "ASP Rounds", awareness raising) that have led to the initiation of ASPs in many institutions in Karachi, Lahore, Rawalpindi and Islamabad. The ASIP plans to continue to advocate through print, radio and television and to seek partnerships with similar initiatives, at both national and international levels. A survey was carried out among general practitioners and pediatricians to gauge opinion on this (ASIP) initiative. This survey, by MMIDSP, involved 757 GPs and pediatricians and other clinicians, over 9 months (September 2015-May 2016). Among those who returned the survey forms, 392 GPs and pediatricians (51.8%) answered on the usefulness of this activity and 495 (65.4%) also suggested measures to combat antibiotic misuse and AMR in Pakistan. The results are shared here to depict the response from these healthcare providers (Figure 1 and Table 1, Ejaz A. Khan, unpublished data,). These results show that almost all professionals wanted to continue with such CMEs and felt there was a benefit. The majority of suggestions, for combating AMR, included regular widespread ASP activities, awareness campaigns about the dangers of antibiotics, the establishment of a national and local regulated antibiotic Strategic Framework, a ban on OTC, a comprehensive national action plan with implementation and legislation, and CMEs for professionals.

Figure 1. Survey of opinion on ASIP related educational activities from 392 General Practitioners and Pediatricians.



ASIP= Antibiotic Stewardship Initiative in Pakistan, MMIDSP=Medical Microbiology and Infectious Disease Society of Pakistan., ASP= Antibiotic Stewardship Program

Table 1. Suggested measures to combat antibiotic misuse and AMR in Pakistan from 495 General Practitioners and Pediatricians.[#]

Suggestions to combat the misuse of antibiotics and AMR	**N (%)**
• Antibiotic Stewardship in hospitals and community, including IC	100 (20.2%)
• A National and local antibiotic policy, with regulation and a ban on OTC	96 (19.4%)
• Awareness campaigns about dangers of antibiotics to GPs and community	72 (14.5%)
• CMEs for professionals	62 (12.5%)
• Take appropriate history, examination and diagnostic tests before prescribing antibiotics	44 (8.9%)
• Use of specific guidelines for infectious diseases	41 (8.3%)
• Counseling of patient about antibiotics	26 (5.3%)
• Use media/societies for awareness	22 (4.4%)
• Ban quackery and unethical practices among physicians	19 (3.8%)
• Comprehensive NAP with implementation and legislation	10 (2.0%)
• National surveillance and strengthening of Microbiology labs for AMR	8 (1.6%)
• Others	9 (1.8%)
• No suggestions given	127 (25.7)
• **Total**	495 (100)

[#]More than one response given

Despite the presence of large well-established public hospitals across Pakistan, no ASP or stewardship teams exist. A survey of 11 major private and public hospitals in large cities, carried out over three months (January-April 2016), showed that only a few have functioning stewardship activities (Table 2, Ejaz A. Khan, unpublished data). Awareness in this regard was also low. A shortage of human resources (ID physicians, microbiologists, clinical pharmacists, properly trained IPC nurses, laboratory and microbiology technologists / technicians, funding etc.) was identified in all hospitals.

Table 2. Antibiotic stewardship, AMR and MDROs related survey of 11 major private and public hospitals in 5 cities of Pakistan[*#]

Total cities surveyed	6	
	Private[1]	Public[2]
Major private and public hospitals	5	6
• Total beds capacity	2,540	8,050
• Antibiotic stewardship / management / restriction program	5	0
• Antibiotic Policy	3	2
• Infectious Diseases Physician	18	0
• Clinical Pharmacist	22	0
• Clinical Microbiologist	16	7
• Hospital Epidemiologist	2	0
• Information System Specialist	2	0
• Targeted Antibiotic Stewardship Activities	3	0
• Administrative Controls o Committee exists that looks at antibiotic usage o A formulary is in place o Regular process of formulary review o Committee has established goals o IPC Committee in place	 • 4 • 5 • 3 • 0 • 5	 • 2 • 5 • 5 • 0 • 3
▪ Number of dedicated Isolation beds	123	100
▪ Number of dedicated IPC nurses	19	10

▪ Microbiology Lab technicians	100	35
▪ IPC Policy	5	3
▪ Total cultures received by lab /day	1030	400
▪ Infection Prevention and Control Activities Done[#]	5	0
• MDROs[#] isolated in Microbiology labs (approximate % resistance of each organism) MRSA VRE Carbapenem-resistant *Klebsiella* MDR *Acinetobacter* spp. Colistin-resistant *Klebsiella*	 5-69% 7-25% 10-45% 20-97% 0-1%	 No or Poor data
• Automated laboratory systems in healthcare facility • Computerized Physician Order Entry • Electronic Medical Records • Automated Electronic Surveillance System	• 5 • 5 • 5 • 0	• 0 • 1 • 0 • 0

1. *Shaukat Khanum Hospital & Research Centre, Lahore; Aga Khan University Hospital, Karachi; Sheikh Zayed Hospital, Lahore; Shifa International Hospital, Islamabad; Indus Hospital, Karachi; Armed Forces Institute Hospital, Rawalpindi*

2. *Sheikh Zayed Hospital, Lahore; Bolan Medical Complex, Quetta; Lady Reading Hospital (LRH), Peshawar; PIMS, Islamabad; Holy Family Hospital (HFH), Rawalpindi; Civil Hospital, Karachi*

[#](MDROs; Multidrug-resistant organisms, MDR; Multidrug-resistant, MRSA; methicillin-resistant Staphylococcus aureus, VRE; vancomycin-resistant enterococci)
[#]Include: Ventilator-associated pneumonia surveillance, catheter-associated urinary tract infection surveillance, central-line-associated blood stream infection surveillance, surgical site infections surveillance, programs to reduce blood culture contaminants)

Antimicrobial stewardship is a relatively new concept for the Pakistani medical community and implementation may be challenging. Inappropriate use and OTC availability of antibiotics are key areas that need to be addressed. Most often prescription drugs such as antibiotics are sold OTC at pharmacies and even hospitals. This is despite the fact that, as per the Drug Act 1976 and the Pharmacy Act 1967, "potent and dangerous drugs" must be dispensed by registered pharmacies, through a qualified pharmacist with a licensed medical practitioner.[12,13] Pharmacies must be supervised by a qualified pharmacist and their certificate must be prominently displayed. The Drugs Act (1976) deals with the regulation

of import, export, manufacture, storage, distribution, and sale of drugs (including antibiotics). There is no specific mention of antibiotic or antimicrobial prescriptions in these Acts.

Thus the role of pharmacists, especially those working in community, is important, and their training and education needs must be adequately addressed. The following activities and actions are suggested at the national level:

a) Acknowledge that there is an urgent need to initiate measures to tackle the growing hazards of antibiotic resistance and irrational use of antibiotics, and join international efforts to control this threat.

b) Encourage and implement initiatives to improve infection control standards in hospitals.

c) Include structured training in rational antibiotic usage and infection control in the medical curriculum at undergraduate and postgraduate levels.

d) Emphasize Continuing Medical Education (CME) in rational antibiotic usage and infection control for practicing doctors.

e) Standardize microbiology laboratories in Pakistan. Hospitals must have good quality microbiology laboratories or outsource specimens, in the absence of a standardized laboratory.

f) Collaborate with Pakistan Medical Research Council to initiate surveillance of antibiotic resistance at private and government hospitals and university labs.

g) Partner with WHO/EMRO to interact with the government on issues related to drug resistance, antibiotic policy, and infection control.

h) Liaise with professional organizations to initiate infection control and antibiotic stewardship awareness activities among the society members, utilizing the extensive network of local branches of all societies.

i) Participate with electronic and print mass media to raise public awareness of the dangers of antibiotic misuse.

j) Evaluate the extent of antibiotic use and regulate it in veterinary practice.

k) Formulate and present a policy on rationalizing antibiotic use in the country, both in hospitals and OTC, through collaboration with all stakeholders.

l) Formulate a national policy to control the rise in antibiotic resistance, after consultation with all relevant stakeholders, and then take all possible measures to implement the recommendations.

After the "National Strategic Framework for Containment of Antimicrobial Resistance 2016"[11] the official AMR National Action Plan (NAP) was drafted with all relevant stakeholders by Ministry of National Health Services, Regulations & Coordination (MNHS&RC) in March 2017. One of the major strategic priorities included was "To update and enforcement of regulations for human and veterinary antibiotic use", including specific interventions, such as ASP in all major hospitals.

ASPs will be introduced, in major public and private hospitals in major cities, gradually, over the next 5 years. ASP in all sectors has been suggested, including the medical, veterinary, nursing, and pharmacy curriculum. As the ASIP program is inter-disciplinary (involving pharmacists, infectious diseases physicians, infection control specialists, physicians, microbiology staff, nursing staff, hospital administrators, and information system specialists), identifying and appointing a team will be the first priority. However, hospitals must build on existing manpower and resources in their institutions. The support of the hospital administration will be required to initiate and maintain this process. The following six specific interventions are suggested initially:

1. Creation of an antibiotic stewardship self-assessment tool
2. Implementation of an ASP in all major public and private hospitals
3. Prospective audit with intervention and feedback, at both an individual patient and a prescriber level
4. Tailoring of antibiotic therapy including
    a. De-escalation
    b. IV to PO antibiotic switches
    c. Specific disease management pathways and algorithms
5. Education and Training: Regular workshops, seminars, video-conferences on ASP
6. Collection of specific ASP data and feedback, at an both institutional and/or national program level
7. Mechanisms to evaluate the program on an ongoing basis and share results with stakeholders

In summary, one of the major specific interventions for control of AMR in healthcare settings is ASP. In Pakistan, ASP initiatives have yet to gain national health importance. The NAP has highlighted this as a key intervention strategy, which, if implemented across major healthcare institutions, will greatly help in AMR control.

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Chapter 6

Infection Control

Healthcare facilities in Pakistan lack basic amenities in delivery of quality care to patients, including infection Control (IC). In Pakistan, IC practices are not universal and maybe suboptimal. Only a limited number of large private and public hospitals have IC programs in place. Furthermore, very little is published about experiences in IC, with studies showing the lack of 1) knowledge about basics in IC, 2) budgetary allocations, 3) trained personnel, 4) shortage of supplies, and 5) isolation beds.[1-7] This was also partly due to lack of proper national guidelines, especially for public hospitals. National Guidelines did not exist until 2006, when the National AIDS Control Program published the first "National Infection Control Guidelines".[8] This initial document was an "effort to control facility based transmission of infections, training of healthcare providers" for IC guidelines. However, the lack of implementation and provision of resources for IC practices has been a hindrance.

Even though the exact burden of nosocomial infections, or Hospital-acquired infections (HAIs), in Pakistan is unknown, as major facilities lack IC programs. However, it is expected to be significant in terms of both morbidity and mortality, and may be as high as 25%.[6] IC has been proven to be cost-effective, saving on hospital budgets, length of hospital stay, and the rate of HAIs, which are commonly used now as performance indicators.[9-12] As a resource-poor country, IC practices can lead to significant reduction and prevention of such infections, by adhering to some simple measures. However, one study showed that hand washing supplies were not available in 25% of public sector hospitals.[7] Other published literature, reviewed below, relates to IC practices in multiple disciplines and settings. Past experiences show setting up IC programs and then implementing them can be a daunting task, in a country like Pakistan.

The risk of infections is high during any patient visit, whether in a hospital or in the outpatient setting. Patients are prone to infections, such as hepatitis B and C in dental procedures, if proper precautions are not followed. A cross-sectional study, based on four hundred dental IC practices, showed a poor level of infection control, however, these practices were mostly run by un-qualified practitioners.[13] For example, qualified practitioners used gloves (94.35%) compared to the un-qualified practitioners (28.2%). This study, however, showed an improvement, compared to a previous study about the use of IC measures (use of gloves, face-masks, autoclave, dry heat and chemical sterilization).[14]

The risk of acquiring blood borne infections (HIV, Hepatitis B, and Hepatitis C) through needle stick injuries (NSIs) by healthcare workers can be prevented if proper measures are taken. In hospitals healthcare workers may be at heightened risk of acquiring these blood borne pathogens. A study of approximately 500 HCWs showed that 2/3 had had NSIs in their career, with ¾ having had multiple exposures.[15] The study reported poor safety practices, inadequate vaccination coverage and unavailability of infection control guidelines. Another study, from Karachi, of dental practitioners, reported NSIs in 30%, and associated these with poor IC practices.[16]

The risk of HAIs, especially with the emergence of antibiotic resistant organisms, remains high in settings with poor IC practices, highlighting the importance of adhering to strict infection control practices and appropriate use of antibiotics. The risk of acquiring infection can be 60% (pneumonia and UTI accounting for approximately 50 and 25% respectively) and more worrisome with MDROs.[17] Ventilator associated pneumonia (VAP) is common

and carries a high fatality rate. Rates of VAP and other infections can vary (3-30%), with predominant MDROs (*Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella species, Escherichia coli* and MRSA etc.) and has a attributable mortality of 12-60% in cancer and pediatric patients.[18-21] Other infections that are equally important include UTIs, postoperative infections and SSIs, with a significant impact on patient outcomes.[21-24] Routes of infection, which can act as a vehicle for the spread of nosocomial infections (including MRSA), have been documented, not just by hands, but also by tourniquets[25] and stethoscopes.[26] Colonization rates as high as 51% have been documented, with HCWs having inadequate knowledge and poor compliance with standard precautions and IC.[25,26]

Knowledge and skills for good IC practices, along with optimal compliance, are important. Unfortunately, there is lack of these factors that determine good practice. In a cross-sectional survey, a total of 90 consultant anesthesiologists, from teaching hospitals, showed several potentially hazardous practices. These included 34% always used masks, 9% used gloves, 18% always washed their hands after every patient contact, 54% reported that they always used aseptic technique for placing an indwelling cannula, 5% reported frequently or always reusing syringes for more than one patient, and, most importantly, 58% rated their potential for contributing to transmission of infection as >5 (on a scale of 1-10), despite having knowledge of universal precautions.[27]

A cross-sectional questionnaire based KAP study was conducted among 343 HCWs at Civil Hospital, Karachi and inquired for possible modes of transmission associated with NSIs (sharing razors, NSIs, oro-fecal route, sexual contact, blood transfusion, splash of blood on eye, respiratory droplet, and eating from same utensils as a HBV-positive patient).[28] Those who were able to answer at least 5 correct modes of HBV transmission were classed as the knowledgeable group. Of these, 66% reported having a NSI at least once during their clinical practice and 57% had attended sessions on HBV awareness. The knowledgeable group was more likely to report NSIs ($p < 0.006$), more likely to have been vaccinated ($p < 0.001$), and were also more likely to attend awareness sessions ($p < 0.009$). Overall knowledge regarding transmission was inadequate, and behavior and attitude towards clinical practices were suboptimal.[28] Potentially dangerous practices and beliefs about needle stick injury, hand hygiene, and transmission of infections are also prevalent among medical students,[29] nursing students,[30] general practitioners, dispensers, the public[31] and barbers.[32,33] Knowledge about the mode of transmission and work experience alone, significantly predicted universal precaution use, in a multiple linear regression model.[31] These studies illustrate that the potential opportunity exists to educate and train, not only the HCWs at all healthcare facilities, but also the public, about IC practices, basic hygiene, and prevention.

Strategies of IC prevention have been implemented with success, within Pakistan, in a few studies. A prospective study, addressing the breach of infection control practices in the delivery room and the nursery environment, resulted in a drastic reduction in neonatal sepsis rate from 63/1000 to 14/1000 live births within 3 months.[34] Khan *et al.* used all basic IC principles as an intervention for impact on MDRO-associated ventilator-associated pneumonia (VAP).[35] VAP rates declined in the period after intervention, although the difference was not significant. Another observational pre and post-intervention study examined the effect of an educational programme focused on preventive practices for VAP.[36] VAP infection rates were reduced by 51% (from 13.2 to 6.5/1000 ventilator days). A community focused intervention study, in a rural district, to empower the community to improve unsafe injection practices, showed improved safe injection practices, increasing from a baseline of 15% to 29%.[37]

Surveillance of infections and outbreaks is an essential part of IC policy to gauge its success. An effective surveillance system meets specific, pre-set goals, focusing mostly on IC activities, and predicts their outcome, in addition to reliably identifying at risk areas, such as MDROs. Unfortunately, no National Surveillance Network exists, which contributes to difficulties in tackling AMR. Only a few studies about the surveillance of infectious diseases in Pakistan exist. A hepatitis sentinel surveillance system, by the Ministry of Health (MOH) and the Pakistan Field Epidemiology and Laboratory Training Program (FELTP), provides community education on risks associated with unsafe injections and strengthens infection control practices in health facilities.[38] Pakistan Antimicrobial Resistance Network (PARN) was initiated in 2007, to assess the prevalence of AMR, and to create awareness, through the sharing of information and development of a support group, to help address AMR. Since its establishment it has disseminated information on AMR to healthcare providers and professional organizations, promoted IC measures and performed other intervention strategies.[39]

IC is an integral part in the delivery of quality care to patients, relatives, visitors and all healthcare workers. The studies indicate poor practices and knowledge about basic IC, unsafe injection use, and high rates of HAIs. Without a full-fledged IC team, infections within a healthcare setting, due to resistant bugs, can become rampant, causing outbreaks and poor outcomes. For example, preventive measures for VAP are well documented and evidence-based, yet remain poorly implemented in most intensive care units. A multi-center 7 hospital survey about IC practices showed that, although most facilities had microbiological diagnostic facilities and a high yield of microorganisms, there was no antibiotic policy. The majority of the operation theatres lacked a proper air flow system and monitoring of autoclaves and, in addition, there was no proper disposal for sharps and needles or incineration.[40] A Karachi based study, of 44 clinical laboratories, showed that standard worker safety precautions are not followed.[41] All health care facilities should endorse National IC Guidelines, and strengthen, prioritize and implement their IC programs. Focus is needed on standard and special precautions, education and training of HCWs, immunization of health care workers, identification of hazards, and a surveillance program.[42]

After the initial document by NACP[8] on IC, the National IC guidelines were developed, by Pakistan Medical Research Council (PMRC), and tailored using WHO guidelines, National TB program, Hepatitis Program and through a consultative process of many experts.[43] These detailed guidelines have an emphasis on the local scenario and availability of equipment and solutions. These guidelines can be easily adapted and implemented in our health care settings with oversight from provincial health departments. Addressing specific areas related to IC, such as the addition of specific curricula starting at a primary level, national surveillance, education and awareness, antibiotic stewardship, and the training of personnel. These measures can help in the control of HAIs and thus ensure the safety of patients, visitors, and HCWs.[44,45]

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Chapter 7

Access to and availability of antimicrobials

The health care system in Pakistan comprises both the public sector (serving 22% of population) and a large private sector (mainly general practitioners and health facilities). Both the federal Ministry of National Health Services Regulations & Coordination (MNHS&RC) and provincial health authorities are responsible for producer licensing, drug testing, drug registration, pricing and trade, and market surveillance.[1] The Pakistan Medical and Dental Council (PMDC) and the Pharmacy Council of Pakistan (PCP) are responsible for licensing medical and pharmacy schools and practitioners.[2,3] The Pakistan Medical Association (with other associations) and the Pakistan Pharmacists Association represent the interests of the two main provider groups.[4,5] The Pakistan Pharma Bureau represents the local industry and forms an active interface for dealings with the government on drug production, pricing and trade.[6] The pharmaceutical industry in Pakistan has rapidly developed since the country's independence, in 1947. Presently there are >600 registered manufacturing units and 21 multinational companies, in the country, that meet approximately 30% of domestic demand.[6] Raw materials for local drug production are almost entirely imported.[7] The total size of the pharmaceutical market stands at USD 2.2 billion and the export share of the pharmaceutical industry stands at USD 190 million.[6,8]

Access to essential medicines, as part of the fulfillment of the right to health, is recognized in the national constitution. Pakistan has fairly well developed policy acts and operative guidelines. The Drugs Act 1976 regulates the pharmaceutical sector, setting out extensive stipulations for industry licensing, drug registration, and quality control.[9] It is intended to ensure the availability of safe, effective, and quality products, at reasonable prices. The Drug Regulatory Authority of Pakistan (DRAP) Act of November 2012 was enacted "to provide for effective coordination and enforcement of The Drugs Act 1976 and to bring harmony in inter-provincial trade and commerce of therapeutic goods".[10] A National Drug Policy exists to "develop and promote the concept of essential drugs and to ensure regular, uninterrupted and adequate availability of such drugs of acceptable quality and at reasonable prices."[11] Furthermore, it is to "inculcate in all related sectors and personnel the concept of rational use of drugs with a view to safeguarding public health from overuse, misuse or inappropriate use of drugs" and " The sale of all potent drugs shall be restricted only on prescription of registered medical practitioner" including "antibiotics shall be so restricted." However, developed in 1993, it does not have a strategic plan for implementation. The National Essential Medicine List (NEML) of 2016 contains 415 molecules with an additional list of 23 medicines.[12] It is part of the right to health and an important tool to provide access to quality medicines for the people of Pakistan. It will provide the provinces with the ability to develop their own lists and formularies for its effective implementation. However, more than one third of prescriptions may not contain medicine from the NEML and only one fourth of medical practitioners may be aware of the NEML.[13]

The Drug Regulatory Authority of Pakistan (DRAP) is an autonomous body under the MNHS&RC and it provides for the effective coordination and enforcement of The Drugs Act, 1976.[10] It regulates manufacturing, import, export, storage, distribution, and sale of therapeutic goods, and has a mandate to create harmony in interprovincial trade. Under the DRAP Act 2012, all finished drugs ready for use are required to be registered through the Drugs Registration Board. Presently, over 80,000 drug products are registered, of which 60,000 are locally produced and 20,000 are imported products. The registration under the

Policy is granted and reviewed on the basis of established criteria. This considers acceptable safety, efficacy, in terms of significant therapeutic value, quality and keeps in view the health needs of the country and the public interest. All irrational, unsafe and obsolete formulations and combinations are de-registered, based on Pharmacovigilance reports and Adverse Drug Reactions (ADR). Investigations are reported locally and internationally through stringent regulatory authorities and the WHO. Fixed drug combination products are registered only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has proven advantage over single compounds administered separately in therapeutic effect, safety or compliance. Drugs for any indication, that have been banned for safety reasons, in the USA, Canada, the European Union, Japan, Australia, China, Switzerland, or in the country of origin, by any stringent regulatory authority, are not allowed for sale in Pakistan. For products of foreign companies with parent offices abroad, the indications, adverse effects, dosing information etc., which were approved in the country of origin are accepted. Any other indication requires a separate and detailed justification. In the labeling of drugs, the use of generic names, with at least the same prominence as brand names, and necessary information in the national language, are a mandatory requirement. When a Multi-National Company (MNC) or subsidiary of MNC wishes to manufacture a drug, which is already registered in Pakistan, it may be allowed to do this, regardless of whether it produces the drug in question in its country of origin, based on the country's demand. The import of drugs is allowed to ensure availability and fair pricing, through competition. Anti-dumping laws are enforced in order to prevent dumping when necessary. The Trade Related Implications of Intellectual Property Rights (TRIPS) Agreement and its relaxation for compulsory licensing, under the agreement, are respected as internationally permitted.

Currently, antibiotic drug registration is allowed in both human and animal sectors, as per national demand and national treatment guidelines. Provision has been made, under the legislation for speedy registration of any new antimicrobial drug, to address the challenge of AMR. The Drug Registration Board (DRB) has recently issued a Healthcare Professional Advisory regarding the use of fluoroquinolones, due to serious side effects of peripheral neuropathy, tendon rupture, and irreversible damage to nerves. It has banned ciprofloxacin's use in the veterinary sector, due to its potential misuse leading to AMR. The advertisement of antibiotics is prohibited to reduce self-medication by the general public and to promote rational prescribing, through qualified medical professionals.

Provincial Governments, the pharmaceutical industry, public and private hospitals have been advised to establish pharmacovigilance centers, for the reporting of ADRs and Adverse Drug Event after Immunization (AEFI) to the National Pharmacovigilance Centre (NPC), established at the Pharmacy Services Division of DRAP, which provides assistance to the Drug Registration Board, on the Drug Safety updates. Provinces have been advised to ensure the sale of antibiotics is only by prescription. They have been further advised to develop a necessary mechanism under Drug Sale Rules.

The surveillance of antibiotic use and its relationship with the emergence of AMR has to be determined to evaluate the effectiveness of these policies. The level of AMR needs to be correlated to the level of antibiotic consumption. Hence, in order to tackle AMR via reduction of antibiotic consumption, expressed in defined daily doses (DDD), through effective prescription control is the ultimate goal of the Government. Provincial Governments are also part of this process, by making necessary amendments in their drug sale rules.

Given this background, it is clear that in Pakistan there has been considerable work in terms of health related Policy Acts, legislation, and detailed regulatory and operative guidelines. However, there remain considerable deficiencies between policy and practice and between medicine policies and health systems. For example, despite being an autonomous and powerful body, DRAP has been unable to perform effectively with evidence of "significant policy shortfalls in the DRAP's operational functions, organizational and financial structure. This limits the impact of the organization and its constituent units, in regulating the pharmaceutical industry, in Pakistan."[14] Other deficiencies, noted in this paper, were a persistent policy void between the health sector and the pharmaceutical industry, leading to uncertain dynamics and limited authority. This creates shortages in therapeutic products and access to adequate health care services. "Healthcare seekers are forced to turn to informal health services where care providers are usually unlicensed, quality of care is frequently substandard and inconsistent, and the volume, quality and authenticity of drugs prescribed and/or sold are unregulated."[14]

Furthermore, this apathy towards healthcare is reflected in the high expenditure on drugs by the poor, widespread quality concerns about drugs, widespread inappropriate prescription practices, and low drug availability in public sector facilities. The number of registered products is high (approximately 60,000-80,000),[8,10,15] there is high out of pocket expenditure on health (almost three fourths of total expenditure),[16] self-medication is high (51%),[17] a high number of drugs is prescribed (>3 drugs/patient),[18] there is a high rate of injection use (60% of patient encounters, mostly by private practitioners or quacks)[18,19] and very common injection re-usage, with very poor sterilization practices.[20] The presence of more than 600,000 quacks in Pakistan[21] gives, mostly poor, people an alternative to under funded public health centers or expensive private care.

In most doctor-patient interactions diagnosis, prescription and doses of drugs are wrong. Doctors are easily influenced by the pharmaceutical industry, often through unethical practices, such as 18% of advertisements being "unjustified or misleading,"[22] and only 15% of promotional brochures meeting WHO criteria.[23] Pakistan has one of the highest rates of antibiotic use, with 70% of patients prescribed antibiotics.[19] This overuse and abuse has been found to be more common among GPs and public hospitals for costly antibiotics and 3rd generation cephalosporins.[19,24,25] More recent studies by Atif *et al.* have indicated similar rates of >50% of antibiotics in primary care,[26] emergency department,[27] and tertiary care hospitals.[28] Using the WHO methodology of antimicrobial consumption, poor antimicrobial prescribing and utilization patterns were seen at a tertiary care hospital.[29] These included antibiotic expenditure costs (12.2% of total medicines), hospitalizations with antimicrobial(s) prescribed (82.3%), average number of antimicrobials per hospitalization (1.4), average duration of antimicrobial treatment per hospitalization (5.4 days), average cost of antimicrobials (USD 5.4), non-existent drug sensitivity testing (0.24% of records), not using standard treatment guidelines for common infections (pneumonia and cesarean section), and the frequent use of broad of broad-spectrum cephalosporins (ceftriaxone 39.6%, cefotaxime 23.1%).[29]

One of the major threats to the efforts to control AMR is the widespread availability and use of spurious or substandard antimicrobials. Most counterfeit and spurious drugs and medicines, including antibiotics, are reported in Western Pacific (48.7%), followed by Africa, Asia and Latin America (>30%) and other developing markets (10-30%).[30] Other reports says that up to 10% of the drugs worldwide may be counterfeits, with 50% of them being antimicrobials, of which 78% were from developing countries, mostly in Southeast Asia and Africa.[31,32,33] The most common substandard/counterfeit antimicrobials include beta-lactams (among antibiotics), and chloroquine and artemisin derivatives (among

antimalarials). These low quality antimicrobials have a reduced amount of the active drug and are a great danger to patients, resulting in increased mortality and morbidity. These substandard/counterfeit agents lead to therapeutic failure and may promote AMR.[34]

In Pakistan, there are more than 600 companies and more than 80,000 registered drugs.[8,10] Of these 20-30% medicines are counterfeited, with wide discrepancies in quality, and 10-15% of antibiotics are spurious.[35,36] Other studies report 40-50% of total supply as being spurious, in Pakistan.[37,38] The most commonly documented spurious antimicrobials, in Pakistan, include quinolones[39-41] and cephalosporins.[42,43] Both have very high usage and are thus easily exploited, leading to poor outcomes. Systematic reviews have highlighted that the prevalence of poor-quality antimicrobial medicines is widespread throughout Africa and Asia, with a significant impact on public health.[44-46] Examples of poor outcomes have been well documented by the failure of patients to improve with the use of counterfeit anti-malarials, and an increase in the risk of selection for drug-resistant pathogens, with anti-infectives.[47,48] Even in veterinary medicine, poor quality antibiotics may lead to variable pharmacokinetic profiles and the potential for the spread of resistance and poor outcomes.[49] As a national policy, it is imperative that we educate prescribers (doctors, pharmacists, dispensers, and others) about why safe and appropriate prescription of antibiotics is crucial in curtailing AMR. A study was performed in a rural setting on how the education of private drug sellers, as an intervention tool, can promote the rational use of antibiotics for diarrhea, at private drug outlets.[50] Prescriptions for common medications, including multiple antibiotics, decreased significantly, with an increase in referrals for sick patients, after the interventional education program.

In summary, the delivery of quality healthcare, in the public sector and a large private sector, remains suboptimal, despite the existence of regulatory and oversight bodies. Evaluating determinants of responsiveness, empathy, tangibility, reliability, and assurance it has been found that "little attention has been paid on service quality dimensions by public health care centers" compared to military and private centers.[51,52] Similarly, the Pakistan Access to Medicines (ATM) priority setting study found "evidence of major gaps in essential medicine access in Pakistan driven by weaknesses in the health care system as well as weak pharmaceutical regulation."[53] Major concerns included weak regulation related to drug registration and market quality surveillance, drug pricing and provider prescribing practices, budget insufficiency for drugs, procurement, storage and dispensation gaps, low deployment of pharmacists, lack of community level actions and impact on essential medicines of decentralization of health to the provinces.[53] The use of counterfeit, substandard and spurious antimicrobials has grave consequences for consumers. It has a direct link to the problem of AMR. It is thus essential that broad and wide initiatives, for increased international collaboration, legislation, regulations, enforcement, technology, and communication strategies, be taken at country level, to improve patient outcomes.

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Chapter 8

Public Health Interventions in Pakistan

In Pakistan there have been many national and provincial public health related interventions. These have been broad and addressed many public health issues including specific populations, different communicable and non-communicable diseases, different emergencies, education and community development. Most of these interventions had set aims to achieve the Millennium Development Goals (MDG).[1]

8.1 Sanitation and clean water

Pakistan is a populous country, which can create challenges in the provision of basic amenities, such as clean water and sanitation. Provision of clean water and sanitation is the responsibility of provincial and local governments. This challenge is compounded by insufficient allocation of funds, diverse geography, rapid urbanization, and an unstable political environment. It is estimated that 21.6 million people lack access to clean water and 78.9 million do not have access to adequate sanitation. This results in diarrheal illnesses, which cause 19,000 deaths, each year, in children.[2] Major outbreaks have occurred in major cities.[3] Such a huge infectious disease burden needs a nationwide clean water and sanitation policy. The National Sanitation Policy (2006) had the target of meeting the Millennium Development Goal by 2015 and universal access by 2025.[4] It aimed to promote community-led total sanitation (CLTS) at a grassroots level in communities. The National Drinking Water Policy (2009) was developed to provide universal access to drinking water in an equitable, efficient, and sustainable manner, by 2025.[5] A large initiative "Clean Drinking Water Initiative" also was undertaken in 2004 for improving quality drinking water by building 445 water treatment facilities in all tehsils of Pakistan.[6]

Successful sanitation projects have been developed in some of the major slums and communities in Pakistan. These include the Orangi Pilot Project, initiated in 1980, that involved the community, and led to 100,000 households having their own sanitation systems in Orangi, Karachi, one of the largest slums of Asia.[7] This was successfully replicated in other cities and included the Lodhran Pilot Project, in 100 villages in Southern Punjab, in 1999, with its own sanitation model and technical assistance and training.[8,9] Similarly, CLTS was initiated in 2003 in Mardan District by UNICEF and a local NGO, Integrated Regional Support Program, with the creation of open defecation free villages through behavioral change.[10] Being highly successful, it was implemented in other parts of the country and is now the main feature of the National Sanitation Policy, in addition to being used by other organizations.

The World Health Organization and UNICEF, in their Joint Monitoring Program for Water Supply and Sanitation, estimated that access to improved water sources improved from 85% in 1990 to 92%, in 2010, and sanitation coverage improved from 27% to 48%, during the same time period.[3] Furthermore, through CLTS, 15,000 villages, covering a third of rural Pakistan, are expected to have achieved "open defecation free status" by 2010.

Another program the UNICEF "Sanitation Programme at Scale in Pakistan - Rural (SPSP Rural)" (2013-17) programme aimed that, by 2017, most vulnerable and marginalized children and women would be using safe drinking water, and improved sanitation and hygiene practices.[11] In the evaluation report, strategies for community mobilization, behavior change, and communication were found to be most effective in organizing,

educating and sensitizing the community. For instance, 41% more people responded that they had received health and hygiene messages, compared to the baseline numbers. Those who adopted improved hygiene practices also increased by 39% (compared to baseline). Receptiveness to the messages, as well as recall ability (including practice) has shown significant increase. In programme areas, 65% population now has access to sanitation facilities, significantly higher than the national average and two per cent short of the MDG sanitation targets.

The recent 2015 WHO/UNICEF Joint Monitoring Programme Progress Report on Sanitation and Drinking Water showed a major global achievement, with >90% of the world's population now having access to improved sources of drinking water. However, it has fallen short of the sanitation target of a 25% reduction, leaving 2.4 billion people without access to improved sanitation facilities.[12] Pakistan has achieved that target, with a reduction of 36% in the proportion of population practicing open defecation from 1990 to 2015.[12] Pakistan also showed good progress in access to clean drinking water, with 91% of the population having access to improved drinking sources and an increase of 40% of the population having gained access in 2015 compared to 1990.[12]

Hand hygiene is considered a very important but a simple and inexpensive intervention for the prevention of major diarrheal and respiratory infections. A recent meta-analysis showed that multi-level interventions can have significant reduction in not only respiratory and gastrointestinal infections but also school absenteeism.[13] In the squatters of Karachi, simple hand washing, using soap distributed at homes, reduced diarrheal illnesses among children by 56% and 35% in two subsequent years.[14] Such interventions can have huge impacts on the reduction of the burden of these communicable diseases in developing countries.

8.2 Immunization

Immunization is one of the most effective prevention strategies in children and has an immense impact on the public health in particular. The most recent examples of the dramatic benefits of appropriate immunization are the marked decrease in cases of invasive *Haemophilus influenzae type b (Hib)* infection and significant reduction of pneumonia and invasive pneumococcal disease, in countries where the *Hib* conjugate vaccine and pneumococcal conjugate vaccine (PCV), respectively, have been routinely administered.

In Pakistan, few studies show the importance of *Hib* and PCV vaccines in the prevention of serious invasive disease. Mortality (overall 34%; 27% due to *Hib* 28% due to *streptococcus pneumonia*), coupled with sequelae (developmental delay 37%, motor deficit 31%, hearing impairment 18.5%, epilepsy 14%, vision impairment 14%), remains a serious threat to children <5 years old, in Pakistan.[15] A significantly higher risk for all sequelae was observed, in cases compared to controls, after pneumococcal meningitis (73%) and Hib meningitis (53%). A multi-center study on the effectiveness of the *Hib* vaccine showed that vaccine effectiveness for the prevention of radiologically confirmed pneumonia was 62% with 3 doses of vaccine using hospital controls and 70% using neighborhood control.[16] The pneumococcal serotypes, among 111 episodes of invasive disease, from Pakistan, show that the most common was serogroup 18, causing meningitis in children <5 years.[17] The 10-valent pneumococcal conjugate vaccine (PCV 10), or PCV10-related serotypes, were found in 61% of childhood meningitis episodes while PCV-13 increased this to 63% indicating probable coverage and that PCV will have significant impact on reducing invasive pneumococcal disease.

The Expanded Programme on Immunization (EPI) of Pakistan, launched in 1978, covered major childhood vaccines, such as tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus, and measles and added new antigens of hepatitis B, *haemophilus influenzae type b (Hib)*, pneumococcal vaccine (PCV10), inactivated polio vaccine and rotavirus vaccine 2002, 2009, 2012, 2015, and 2017 respectively.[18] With these vaccines up to 17% of childhood mortality may be reduced in Pakistan. A programme policy/guideline document was developed in 2015 and the new immunization policy envisages Pakistan's Vision 2025 by addressing its key goal - to reduce the infant mortality rate from 74 to less than 40 (per 1000 births), through immunization targets and activities, in order to achieve Sustainable Development Goal 3 for the country.[18]

However, the key goals of polio eradication, and measles, have not been achieved. The coverage of routine EPI vaccines in Pakistan has been poor. Reporting from provinces and other areas indicates an overall coverage of about 80%.[18] The Pakistan Demographic Household Survey (PDHS) 2012-13 and Pakistan Social and Living Standards Measurement Survey (PSLM, 2014–2015) showed are the current EPI overall national full child vaccination coverage to be 65% and 88%, respectively. The Province-wide coverage is similarly suboptimal (Punjab: 65.6%, Sindh: 29.1%, KP: 52.7%, Balochistan: 16.4%).[19,20] Punjab is the first province to achieve elimination of maternal and neonatal tetanus in 2016. According to WHO in 2015 the coverage for DPT3 for children under 1 year old was 73% and for measles coverage was only 68%.[21] Pakistan is third among countries with the most unvaccinated and under-vaccinated children. This can cause significant outbreaks, such as measles.[22]

EPI services are being strengthened by WHO and other partners, through a comprehensive multi-year plan, for federal and provincial EPI programmes that will involve capacity-building, effective vaccine management, and improvement in data quality.[21]

8.3 Hepatitis

Hepatitis has become a significant national public health problem over last few decades, with few surveillance studies that provided data for its prevention and control.[23-25] The largest community-based study, by PMRC, of 7,000 households, and a survey of 47,043 people, on the prevalence of hepatitis B and C, in Pakistan, and found a prevalence of 2.5% and 4.9% respectively.[26] Global estimates put Pakistan as 2nd high burden countries.[27] For hepatitis prevention and control, a number of public health programs have been initiated.

The Ministry of Health launched a National Program for Hepatitis Prevention and Control (NPHPC) in 2005 for the screening and treatment of HCV infection.[28] It has since expanded into the Prime Minister's Program (2005-2010) and Chief Minister's Program (2010-2015). The CDC and DVH collaborated for another sentinel surveillance program in 2009.[25] A number of national and provincial strategies were formulated, through various steps, including formation of a Technical Advisory Group (2013-14), initiation of Sindh Hepatitis Program (2013) and Infection Control Training in 25 high-risk districts, by WHO and PMRC (2014).[29] The Drug Registration Authority Pakistan (DRAP) granted registration of Sofosbuvir for local manufacture. This drug is used for the treatment of Hepatitis C and the government allowed it to be introduced at discounted rates in 2014, causing a resultant surge in its sales.[30]

8.4 National Disaster Management

Natural disasters, such as earthquakes and floods, and the resulting migration of populations, place them at risk of many diseases, especially infections. The earthquake of 2005, in Northern Pakistan, caused major damage to life and property, including 87350 deaths, >38,000 injured, and over 3.5 million homeless.[31] The aid and relief efforts that followed became more coordinated after the formation of Federal Relief Commission, the Earthquake Relief and Rehabilitation Authority in 2005, and, subsequently, the National Disaster Management Authority in 2007.[32,33] Healthcare delivery was difficult, however, massive national and international relief efforts were undertaken and both communicable and non-communicable diseases were encountered.[34,35]

The floods of August 2010 in Pakistan caused 1,800 deaths, destroyed thousands of homes and property across 78 districts, and displaced 2 million people.[36] 514 health facilities were also affected, with resultant strain on an already poor health delivery system. Massive efforts by governmental, non-governmental, and international organizations for relief activities were undertaken. Approximately 6.2 million consultations for gastroenteritis, respiratory infections, malaria, and dermatologic conditions were reported. Outbreaks of other diseases like Crimean-Congo hemorrhagic fever, dengue fever, diphtheria, cholera, falciparum malaria, measles, and polio were reported.[37]

As part of health promotion for non-communicable diseases, many including WHO and other partners, have had collaborative interventions, using different strategies, such as social mobilization, school health and education, with a large impact, empowering communities to manage specific situations.[38] These include health subjects of public importance, especially for internally displaced persons, such as respiratory and gastrointestinal diseases, dengue, malaria and others. A recent systematic review showed that promotional material, aimed at hand washing and sanitation behavior change, can be effective in low- and middle-income countries.[39]

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Chapter 9

Way Forward and Recommendations

All studies, from both human and animal sectors, on AMR, reinforce the fact that this crisis in Pakistan is already out of control. A National Action Plan with strategies and solutions is thus a dire need to stem the rapid spread of AMR across human, animal and agriculture sectors. Multiple strategies have to be adopted that encourage the prudent use of antimicrobials while limiting their random and irrational use in all human and veterinary settings. This will have a major impact on infection rates, resistance patterns, costs, and clinical outcomes. This can be achieved at both institutional and community levels, through multi-sectoral involvement of all key stakeholders, from the Government, professionals, societies and policy makers of public and private institutions. In this regard, it is necessary, that the multi-sectoral AMR oversight committee designated by Ministry of NHSR&C remain engaged in the process of AMR NAP development and subsequent implementation, at all levels, including Federal, Provincial/ Regional, district, and community levels. Furthermore, deliberations during the National AMR Framework Development revealed that at the national level there is a lack of relevant AMR experts, including an almost complete lack of AMR awareness among professionals, from both human and veterinary health, and the community. In public and private hospitals, there are no Antibiotic policy or Antibiotic stewardship programs. IPC is compromised due to poor practices in antibiotic use and basic hygiene. Microbiology laboratories are not standardized, a national AMR surveillance system is nonexistent, and there is lack of collaboration between human health and other sectors, such as the veterinary, poultry and agricultural sectors, for the containment of AMR. Other threats to AMR include a lack of data on the consumption and quality of antibiotics and vaccines. Additionally, the enactment for legislation related to education, programs for hospitals, antibiotic use and quality, phamacies, and laboratories are some of the additional challenges.

However, there is hope, as some existing health and livestock infrastructure and facilities can be upgraded for use in AMR surveillance. This can be done with the existing National Programs serving as model. Similarly, available specific expertise in the human and animal health can be garnered to establish national bodies for the implementation of AMR activities using the “One Health Approach.” Furthermore, many professional national and international organizations are interested in working together and supporting the Government of Pakistan, in addressing AMR, through implementation of the National Action Plan.

Focus should be on major areas, such as AMR burden and surveillance, IPC practices, antimicrobial stewardship efforts, and the judicial use of antibiotics in all fields, including human, poultry, agriculture, veterinary medicine and other fields. Specifically, emphasis should be placed on “low hanging fruit”, with a focus on improving awareness and understanding of AMR, and education and training at all levels, beginning with school through to undergraduate levels. Optimal use of antimicrobials, both in human and animal health, is essential. Simple measures, such as effective sanitation and hygiene in community and healthcare settings, can greatly reduce the incidence and transmission of infections.

In many developed countries there have been recent initiatives, at a national level, to address AMR. These include the USA, where an Executive Order in 2015, with objectives and activities calling for sustained, coordinated, and complementary efforts of individuals and groups, around the world, including healthcare providers, healthcare leaders,

veterinarians, agriculture industry leaders, manufacturers, policymakers, and patients to detect, stop, and prevent the emergence and spread of resistant bacteria.[1] Others have shown similar urgency in the call for action, including the G7 countries (Canada, France, Germany, Italy, Japan, the United Kingdom and the United States),[2] the European Council,[3] and the Trans Atlantic Task Force on Antimicrobial Resistance (TATFAR), which aims to enhance cooperation between the USA and Europe in the field of AMR.[4] In other countries initial steps for National Action Plans have been taken over the last few years to include all key stakeholders and priority areas, especially in view of the "One Health Approach" and the GHSA. These include India, Kenya, Cambodia, Fiji, Japan, Philippines, Vietnam, Ethiopia, and South Africa.[5]

A significant global step towards tackling AMR was achieved during the 71st Session of United Nations General Assembly (UNGA), in 2016, in a declaration on AMR.[6] The declaration was widely hailed as a milestone in the global effort to confront AMR. There was a commitment to work at national, regional, and global levels to develop, as per resolution WHA 6 8.7, multi-sectoral national action plans, programs and policy initiatives. This will also be in line with a "One Health Approach" and with the WHO Global Action Plan on AMR[7] and its five overarching strategic objectives. The declaration includes a plan to bring together a new governance structure, which will report on the progress that has been made in two years time.

In the past, in Pakistan, there has been limited attention or political prioritization of AMR. Pakistan's Ministry of NHSR&C has transformed the "National Strategic Framework for Containment of Antimicrobial Resistance 2016" into the official AMR National Action Plan.[8] This process involved the full participation of the Inter-sectoral Core Committee, representatives from the health, veterinary, and agricultural sectors, ministries, departments of health, and other sectors at the federal, provincial and regional levels.

A consultative workshop for the development of the National Action Plan took place in March 2017. The workshop was conducted in close collaboration with the National Institute of Health, the National Agricultural Research Centre, and the National Veterinary Laboratory - the designated focal points for AMR in the health and veterinary sectors, respectively. The workshop was technically supported and financed by the WHO, and a team of international consultants and national experts facilitated technical discussions during the workshop with all relevant national, provincial and regional stakeholders. Partners interested in supporting AMR containment and the implementation of national action plans, including the CDC, GARP and USAID, also participated in the process.

Some of the major findings and observations during these meetings and workshops are listed below:

- Health structure and healthcare systems are very weak, less efficient and lack standards.
- "One Health Approach" integration at federal and provincial levels is poor.
- Legislation and implementation for specific aspects (e.g. for non-prescription use of antibiotics) are lacking.
- Priority for AMR, responsibility and accountability and monitoring mechanisms are less clear or developed.

- There are a large number of unregistered medical and veterinary practitioners who often have weak training and poor practice relating to the management of infectious disease.
- There are weak or non-existent curricula, and awareness in professional education and the general public, regarding AMR at different levels, is low.
- In public and private health hospitals there is commonly no Antibiotic Policy, Antibiotic Stewardship Programs are usually non-existent, and Infection Control Programs have poor practice in antibiotic use and hand hygiene.
- Qualified human resources are lacking, including infectious diseases physicians, microbiologists, clinical pharmacists, and properly trained infection control nurses, amongst others.
- There are inadequate or poor microbiologic facilities, with a lack of dedicated funds that hamper efforts for appropriate infection control practices, surveillance and diagnostics.
- There is inadequate or poor AMR surveillance and research with no federal or provincial laboratories that can serve as reference labs.
- Human and veterinary health, poultry and agriculture sectors lack collaboration on AMR containment efforts.

Some specific recommendations in the Strategic Framework included:

- Federal Government shall have political priority for AMR at all levels under a "One Health Approach".
- Professional, Educational and Regulatory Bodies will carry out awareness campaigns in society and ensure AMR related curricula are incorporated and implemented in education and training at all levels.
- An Integrated AMR surveillance system shall comprise of national and provincial coordinating and communication centers, national and provincial reference laboratories, data collection and management units, and Quality Assurance Systems.
- Establishment and strengthening of microbiology laboratories (including veterinary and agriculture laboratories) across Pakistan should be ensured.
- The Federal Government and an Advisory Body shall be established to formulate National Infection Prevention and Control Guidelines for all health care settings and develop a framework and mechanism for its implementation and monitoring by relevant authorities.
- The Drug Act 1976 shall be fully implemented, in true letter and spirit, by relevant authorities, with an emphasis on limiting the availability of antimicrobials to prescription-only status.
- Antimicrobial consumption in humans, animals, and plants shall be monitored at Federal and Provincial levels.
- There shall be promotion of strong media campaign against inappropriate use of antibiotics.

- Non-therapeutic use of antibiotics in livestock, poultry and plants shall be discouraged at all levels and the evidence-based use of antimicrobials shall be encouraged.
- Healthcare institutions and the agriculture industry shall establish Antibiotic Stewardship Programs (ASPs) and shall develop mechanisms for the auditing of antibiotic use in humans, livestock, milk products, poultry, and plants.

The major strategic priorities of the NAP, which emerged from the consultation process, include:

1. Development and implementation of a national awareness raising and behaviour change strategy on antimicrobial resistance.
2. Establishment of an integrated national AMR surveillance system (use and resistance, human and animal).
3. Improvement of infection prevention and control in health care settings, the community, animal health, food, agriculture and the environment.
4. Update and enforcement of regulations for human and veterinary antimicrobial use.
5. Phase-out of antimicrobial use for growth promotion and provision of appropriate alternatives (such as prebiotics, probiotics) in food animals.
6. Integration of AMR into all public health research agendas, including research on vaccines.
7. Estimation of the health and economic burden of AMR, for use in decision-making.

The AMR NAP is now being shared with all stakeholders, including Health Development Partners (HDPs) at the national, provincial, and regional levels under the "One Health Approach" for the development and adoption of respective provincial and regional level implementation plans. Two activities followed immediately after the NAP was drafted. A WHO-OIE International Health Regulations National Bridging Workshop was held on 9-11 May 2017, in Islamabad, so that, at country level, the joint use and/or refinement of respective WHO IHR Monitoring and Evaluation Framework (IHRMEF) and OIE Performance of Veterinary Services (PVS) Pathway tools would be better aligned for a capacity building approach and strategies between human and animal health sectors. The main objective of the IHR-PVS Pathway National Bridging Workshop was to provide an opportunity to human and animal health services to build on the assessments conducted in the human and animal health sectors respectively, explore options for improved coordination, and jointly strengthen preparedness for, and control of, the spread of zoonotic diseases.

A Technical Joint Stakeholder work-plan for the implementation of the GLASS and National Action Plan on AMR in Pakistan was held in Islamabad, Pakistan, on 22-24 May 2017. GARP Pakistan participated, along with multiple partners, including WHO, CDC, and Health Security Partners, that have expressed their interest in assisting Pakistan, to detect, prevent and respond to the issue of AMR in the country. It was agreed that Pakistan's National Action Plan on AMR would be the reference for supporting AMR related interventions by all partners.

The main objectives included:

- Identify priority areas for support by primary stakeholders in 2017, including an assessment and training plan for NIH and GLASS sentinel sites;
- Create a network of partners working in, or with capacity and interest in working in, AMR, in Pakistan, for harmonization and synergy of interventions; and,
- Initiate discussion to develop an all-partner Pakistan work plan for the implementation of the National Action Plan on AMR, aligned with national priorities, as well as other relevant programs (e.g. GHSA), with clear roles and responsibilities.

Thus with this National Action Plan that was developed after an extensive consultative process the focus has shifted to address an important public health crisis. GARP-Pakistan report ***"Situation Analysis Report on Antimicrobial Resistance in Pakistan: Findings and recommendations for antibiotic use and resistance"*** prepared by prominent experts is an in-depth analysis of available literature on AMR, antibiotic use and misuse, infection control from human, and veterinary sectors in Pakistan and will be useful to health planners. Relevant federal and provincial health authorities must use this GARP- Pakistan Report for carrying forward the national efforts on AMR. It will help to implement national measures for strengthening and developing steps to curtail antibiotic use in humans and animals and thus AMR. It will further assess resource needs, sustained technical and financial investment in shared research, laboratories and regulatory capacities, as well as professional education and training. It is now expected that this joint effort of all relevant sectors from healthcare, animal and agriculture sectors will galvanize national efforts to deal with AMR comprehensively.

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Appendix 1

Table A1. Summary of reported resistance rates presented in this study for priority microorganisms against studied GLASS antimicrobials.

Microorganism	Year of study	Site of infection	Isolates	Hospital/ Community acquired/lab based study	City	Reported percentage resistance	Ref*
A. baumanii	2003-2006	Blood, stool, urine, tracheal aspirate, sputum or wound	10	Hospital acquired	Lahore	IMP; 2003: 80%, 2006: 75%	11
	Nov 2007-Aug 2008	Tracheal aspirate, BAL, CVL, wound swabs, urine	50	Hospital acquired	Karachi	AK; 91-100%, GEN; 97-100%, PB; 0%	12
	Jan-Aug 2011	Multiple site of infections; urine, blood, tracheal, sputum, stool	26	Hospital acquired	Islamabad	carbapenems; 96%, AK; 50%, TIG; 12%,CST; 0%	13
	July 2010-August 2011	Tracheal aspirate, blood, pus, wound, endotracheal tube, catheter tip, various body fluids, drain tip	90	Hospital acquired	Lahore & Islamabad	TIG; 20%, CST; 50%, AK; 77%, MIN; 83%	14
E. coli	May 2007-April 2008	Tracheal aspirate, sputum, urine, urine catheter tips, CVL tips, blood, body fluids, pus	53	Hospital acquired	Rawalpindi	CRO; 72%, CAZ; 72%, CFX; 62%, CIP; 76%, IMP; 15%	17
	Jan-Dec 2008	Post-operative wound infections	68	Hospital acquired	Lahore & Hyderabad	carbapenems; 0%, quinolones; 50%, cephalosporins; 71%, aminoglycosides; 50%	18

K. pneumoniae	Jan-Dec 2008	Post-operative wound infections	23	Hospital acquired	Lahore & Hyderabad	Quinolones; 44%, cephalosporins; 61%, aminoglycosides; 22%, carbapenems 0%	18
	2007-2008	Blood cultures, tracheal aspirates, urine, wound swabs, pus and tissue	61 (ESBL)	Hospital acquired	Karachi	CIP; 49%, SXT; 84%	20
N. gonnorrheae	1992-2009	Urethral, high vaginal and cervical swabs. A small percentage (1%) of pus, blood, urine and eye swabs also included	804	Laboratory surveillance	Countrywide	OFX; 1992: 0%-2009: 93%, AZM, SPT & CRO; 0%	23
***S. Typhi*+ *Paratyphi* serovars**	2009 & 2011	Blood samples	4323	Laboratory surveillance	Country wide	FQ: 2009; 79%, 2010; 88%, and 2011;93%	25
S. aurues	March 2004-Feb 2005	Multiple sites	190	Hospital & Community	Karachi	MRSA=43%, VAN=0%, DA=90%	29
	Jan2005-Jun2007	Skin and soft tissue	501	Laboratory surveillance	Country wide	DA=79%	30
S. pneumoniae	2006	Respiratory samples	78	Community acquired	Country wide	PEN=0%	32
***Enterococcus* species**	2001-2006	Blood	60	Hospital acquired	Karachi	VA=13%, AMP=74%	10

Key; MRSA= Methicilin Resistant *Staphylococcus aureus*, CRO=ceftriaxone, CAZ=ceftazidime, CFX= cefotaxime, FQ=fluoroquinolones, OFX=ofloxacin, CIP=ciprofloxacin, IMP=imipenem, AZM=azithromycin, SPT= spectinomycin, TIG=tigecycline, MIN=minocycline, AK=amikacin, GEN=gentamicin, PB=polymyxin B, CST=colistin, VA= vancomycin, DA= clindamycin.

* References from Chapter 3.

Appendix 2

Table A 2.1 Average percentage resistance from inpatient data reported in antibiograms published in Pakistan PARN (2011-2015) by Karachi Labs.

Microorganism	Year	SXT	CIP	CRO	IPM	MEM	AMP	GEN	AMK	PEN	CLOX	CLI/ DA
K. pneumoniae	2013	59.5	39.5	69.5	9.7							
	2014	60	29	58	18							
	2015	53	35	52	22							
E. coli	2013	78	72.5	81.5	3.00	3	94.5					
	2014	73	74	74	5		88					
	2015	70	68	68	6		88					
***Acinetobacter* species**	2013				85.5	82		66.5	39			
	2014				90			72	50			
	2015				87			56	41			
N. gonnorheae	2013		100	0								
	2014		96	0								
	2015		95	0								
Typhoidal *Salmonella*	2013		92	0								
	2014		91	0								
	2015		91	0								
S. pneumoniae	2013	76.5								9		
	2014	80								10		
	2015	75								0		
S. aureus	2013										56	20
	2014										58	23
	2015										59	20

Table A2.2 Average percentage resistance from outpatient data reported in antibiograms published in PARN (2011-2015) by Karachi labs.

Microorganism	Year	SXT	CIP	CRO	IPM	MEM	AMP	GEN	AMK	CLOX/ OXA	CLI/DA
K. pneumoniae	2011	55	36.5	55.5	13						
	2012	53	37	49	10						
	2013	59.5	33	47.5	10	6					
	2014	51	33	47	21						
	2015	50	35	50	22						
E. coli	2011	70.5	65.5	59	1.5		83.5				
	2012	70	65.5	59	0.88						
	2013	70	64.5	69			88				
	2014	68	68	64	2		85				
	2015	70	67	67	5		87				
Acinetobacter sp.	2011				44.5			54	51		
	2012				54	82		53.5	50.5		
	2013				32	39		66.5	16		
	2014				64			40	24		
	2015				53			47	36		
S. aureus	2011									43	27.5
	2012									44	19
	2013									52	19
	2014									55	17
	2015									59	19

Appendix 3

Table 3.1 Priority bacteria and corresponding antimicrobial agents as specified by GLASS considered for antibacterial resistance trends in this situation analysis. *Indicates pathogens and antimicrobials not included in GLASS.

Priority microorganisms		**GLASS antimicrobials**	**Antimicrobial agents**
Escherichia coli		Sulfonamides and trimethoprim Fluoroquinolones Third-generation cephalosporins Fourth-generation cephalosporins Carbapenems Polymyxins Penicillins	Co-trimoxazole Ciprofloxacin Ceftriaxone/cefotaxime and ceftazidime Cefepime Imipenem Colistin Ampicillin
Klebsiella pneumonia		Sulfonamides and trimethoprim Fluoroquinolones Third-generation cephalosporins Fourth-generation cephalosporins Carbapenems Polymyxins	Co-trimoxazole Ciprofloxacin Ceftriaxone, cefotaxime and ceftazidime Cefepime Imipenem Colistin
Acinetobacter baumannii		Tetracyclines Aminoglycosides Carbapenems Polymyxins	Tigecycline or minocycline Gentamicin and amikacin Imipenem Colistin
Staphylococcus aureus		Penicillinase-stable beta-lactams Glycopeptides*,Oxazolidinone*, Lincosamides*	Cefoxitin, Oxacillin/Cloxacillin* Vancomycin*, Linezolid*, Clindamycin*
Streptococcus pneumonia		Penicillins Sulfonamides and trimethoprim	Oxacillin, Penicillin G Co-trimoxazole
Enterococcus spp.*		Glycopeptides* Penicillins*	Vancomycin* Ampicillin*
Salmonella Typhi and *Paratyphi* A, B and C		Fluoroquinolones Third-generation cephalosporins Carbapenems	Ciprofloxacin Ceftriaxone, cefotaxime and ceftazidime Imipenem
Neisseria gonorrhoeae		Third-generation cephalosporins Macrolides Aminocyclitols Fluoroquinolones Aminoglycosides	Cefixime, Ceftriaxone Azithromycin Spectinomycin Ciprofloxacin Gentamicin

Ref: Global Antimicrobial Resistance Surveillance System. World Health Organization. 2015.

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Six strategies needed in national antibiotic policies.

1. **Reduce** the need for antibiotics through improved water, sanitation and immunization

2. **Improve** hospital infection control and antibiotics stewardship

3. **Change** incentives that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship

4. **Reduce** and eventually phase out subtherapeutic antibiotic use in agriculture.

5. **Educate** health professionals, policy makers and the public on sustainable antibiotic use

6. **Ensure** political commitment to meet the threat of antibiotic resistance

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