Ministry of
National Health Services
Regulations & Coordination
Government of Pakistan

NATIONAL STRATEGIC FRAMEWORK FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE (AMR)

Table of Contents

List of Abbreviations and Acronyms

AFIP	Armed Forces Institute of Pathology
AMR	Antimicrobial resistance
ARI	Acute Respiratory Infection
ASP	Antibiotic Stewardship Programs
AST	Antibiotic Susceptibility Testing
CDC	Centre for Disease Control, Atlanta
CLSI	Clinical and Laboratory Standard Institute
DGHS	Directorate General of Health Services
DRAP	Drug Regulatory Authority of Pakistan
EARS-Net	European Antimicrobial Resistance Surveillance Network
EMRO	Eastern Mediterranean Regional office (WHO)
ESBLs	Extended spectrum beta lactamases
FAO	Food & Agriculture Organization
FELTP	Pakistan Field Epidemiology and Laboratory Training Program
GAP	WHO Global Action Plan for AMR
GLASS	Global Antimicrobial Resistance Surveillance System
HAIs	Hospital-acquired infections
HCWs	Healthcare workers
HCP	Healthcare Professional
ICC	Inter-sectoral Core Committee
IPC	Infection Prevention &Control
IHR	International Health Regulation
ICUs	Intensive care units
LIS	Laboratory Information System
MDR	Multi-drug Resistant
MDROs	Multidrug-resistant organisms
MIS	Management Information System
MMIDSP	Medical Microbiology and Infectious Diseases Society of Pakistan

MNHSR&C	Ministry of National Health Services, Regulations & Coordination
MNFS&R	Ministry of National Food Security and Research
NARC	National Agricultural Research Centre
PARC	Pakistan Agricultural Research Council
NACP	National AIDS Control Program Pakistan
NIH	National Institute of Health
NGOs	Non-Governmental Organizations
NTP	National TB Program
OIE	Organization for Animal Health
OTC	Over the counter
PARN	Pakistan Anti-Microbial Resistance Network
PMRC	Pakistan Medical Research Council
PNC	Pakistan Nursing Council
PVMC	Pakistan Veterinary & Medical Council
TB	Tuberculosis
USAID	United States Agency for International Development
VAP	Ventilator Associated Pneumonia
WHA	World Health Assembly
WHO	World Health Organization

Message

AMR has emerged as a major public health problem worldwide leading to significant morbidity and mortality. The growing problem of AMR has resulted in significant health crisis in almost all the countries of the world including Pakistan, resulting in an alarming increase in the burden of infections due to multi-resistant organisms and severely limiting the choice of antimicrobial agents available for treatment. The emergence and spread of resistance among the micro-organisms is a complex phenomenon and hence requires multi-pronged approach to contain this phenomenon.

Accordingly, the WHO through resolution WHA/67.25 in May 2014 stressed the need for development of Global Action Plan which reflects the global consensus on the profound threat of AMR to human and animal health. Accordingly, the 68th WHA through a resolution A68/20 adopted the Global Action Plan on AMR in May 2015. The Global Action Plan aims to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. The first follow-up action to the commitment of the Government of Pakistan was the development of the "National Strategic Framework for Containment of Antimicrobial Resistance".

In line with the five strategic objectives of the WHO Global Action Plan (GAP) for AMR, the Ministry has steered the development of National Strategic Framework for AMR Containment through a consultative process adopting "One Health Approach". It is indeed a matter of appreciation that a broad range of stakeholders representing health, agriculture, livestock, environment, academia, armed forces and private sectors participated in the process of development of strategic framework.

The national strategic framework addresses the five objectives of the GAP and includes; improve awareness and understanding of antimicrobial resistance; strengthen knowledge through surveillance and research; reduce the incidence of infection; optimize the use of antimicrobial agents; and ensure sustainable investment in countering AMR. The document also provides in-depth situation analysis of AMR in human and animal sector as well as a detailed analysis of strength, weakness, opportunities and threats (SWOT) of the five strategic objectives. The process also involved consensus building on the policy statements for each objective, which are now being translated into a comprehensive National AMR action plan with strategic, operational and monitoring/ evaluation framework that will be presented before the 69th World Health Assembly. The Government of Pakistan shall remain committed to the WHO resolutions on AMR as a responsible member state to comply with the global health security challenges.

- Saira Afzal Tarar, Minister for State

Foreword

Emergence of Antimicrobial Resistance (AMR) is a complex phenomenon that follows use of antimicrobials and has been accelerated by inappropriate antimicrobial use. Higher consumption of antimicrobials especially antibiotics is associated with higher levels of resistance. Antimicrobial resistance (AMR) has emerged as one of the world's most serious public health problems and WHO has called it as "The greatest threat to human health". The growing AMR problem represents failure in public Strategic Framework, global governance, research prioritization and the market system at the global level. A number of microorganisms including bacteria, viruses, parasites that cause infectious disease no longer respond to common antimicrobial drugs. The factors responsible for AMR includes lack of knowledge on AMR, irrational/inappropriate use, lack of information and awareness on its proper use, absence of Strategic Framework on antimicrobial use, spurious, substandard, falsified, fake and counterfeit antimicrobials in the market and unregulated access and availability of all the antimicrobials over the counter without prescription. These factors are directly or indirectly related in human, animal and industrial consumption. Other implicating factors are use of antibiotics in agriculture as growth promoters, lack of infection prevention and control programs in health facilities, poor environmental sanitation and inadequate surveillance on antimicrobials use.

At the Sixty-eight World Health Assembly (WHA) in May 2015, it endorsed a Global Action Plan (GAP) vide resolution (A68/20 Corr.1) to address the issue of antimicrobial resistance. The goal of the draft GAP is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. To achieve this goal, the GAP sets out five strategic objectives:

i. Improve awareness and understanding of antimicrobial resistance through effective communication, education and training
ii. Strengthen the knowledge and evidence base through surveillance and research
iii. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures
iv. Optimize the use of antimicrobial medicines in human and animal health
v. Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

This "National Strategic Framework for Containment of Antimicrobial Resistance" has been developed under guidance of an Inter-sectoral Core Committee (ICC) in line with strategic objectives of the GAP for AMR. A well-functioning AMR containment system requires coordination and supervision of key stakeholders at the national level, as well as the implementation of and adherence to the national AMR containment Strategic Framework.

National AMR containment system can be strengthened by developing national policies, strategies and standards, supported by sustainable training programs for the key stakeholders.

The development of this Strategic Framework covering all involved in human and animal health is a crucial first step in addressing the needs of the AMR system as a whole. It provides direction to strengthening efforts and ensures efficient use of government funds and donor investments as well as the development of a sustainable system of AMR containment.

It is the responsibility of the Ministry of National Health Services, Regulations & Coordination (MNHS&RC) to provide leadership through regulation, Strategic Framework and collaboration as well as direct service provision to assure that within resource limitations the most appropriate AMR containment system involving major stakeholders is developed to achieve the best outcomes in health. This AMR Containment Strategic Framework is designed to guide best choices in achieving health for all.

Based on the GAP, this Strategic Framework document was developed after an extensive multi-sectoral consultative process over last few months with principal stakeholders. The document will provide a framework to develop strategic and operational plans, which could be implemented effectively. This Strategic Framework document also endorses the concept of "One Health Approach" to include all the sectors involved in the consumption of antimicrobials (human and veterinary medicine, agriculture), or affected by it (finance, research, environment).

- Dr Assad Hafeez, Director General Health

Executive Summary

The rising global challenge of antimicrobial resistance (AMR) has been rightly called as a major health crisis. It has spread in almost all countries and regions, including Pakistan. In Pakistan the "misuse and overuse" of antibiotics is rampant with upto 70% being used inappropriately. It has contributed to the rise of resistant bacteria or "superbugs" making it difficult to treat yesterday's common infections. A National Strategic Framework was thus needed to tackle AMR through consensus policies. The Government of Pakistan in line with World Health Resolution of May 2015 has formulated this "National Strategic Framework for Containment of Antimicrobial Resistance" to address the AMR crisis.

An Inter-Sectorial Core Committee (ICC) comprising relevant experts and stakeholders from different ministries and sectors of health and provincial authorities oversaw this whole consultative process. Major stakeholders and relevant experts were identified, literature review of available studies in Pakistan on AMR done, visits to major institutions, major hospitals and different stakeholders for gap analysis carried out, two consultative workshops for detailed SWOT analysis for the formulation of Strategic Framework topics and statements was finally held. This process ensured national ownership for the Strategic Framework as well as the commitment of all relevant stakeholders.

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.
- Large number of unregistered medical and veterinary practitioners who usually have weak training and poor practices related to management of infectious diseases.
- There are weak or non-existence curriculum and awareness in professional education and general public regarding AMR at different levels.
- In public and private health hospitals there is mostly no Antibiotic Policy, Antibiotic Stewardship Programs, Infection Control Programs with poor practices in antibiotic use and hand hygiene.
- There is lack of qualified human resource including infectious diseases physicians, microbiologists, clinical pharmacists, properly trained infection control nurses etc.
- There are inadequate or poor microbiologic facilities with 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 and 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 include:

- Federal Government shall have political priority for AMR at all levels under "One-Health" concept.
- Professional, Educational and Regulatory Bodies will do 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 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.
- Drug Act 1976 shall be fully implemented in true letter and spirit by relevant authorities with emphasis to limit the availability of antimicrobials to prescription-only status.
- Monitoring of antimicrobial consumptions in humans, animals and plants shall be monitored at Federal and Provincial levels.
- There shall be promotion of strong media campaign against in-appropriate use of antibiotics.
- Non-therapeutic use of antibiotics in livestock, poultry and plants shall be discouraged at all levels and evidence based use of antimicrobials shall be encouraged.
- Healthcare institutions and agriculture industry shall establish Antibiotic Stewardship Programs (ASPs) and shall develop mechanisms for auditing of antibiotic use in humans, livestock, milk products, poultry and plants.

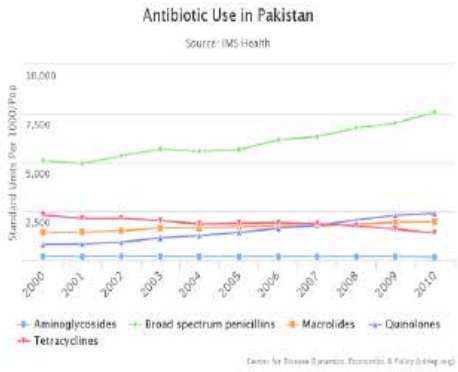
In summary the vision of the "National Strategic Framework for Containment of Antimicrobial Resistance" is to establish a coordinated, collaborative and sustainable AMR containment system with measurable outcomes under "One Health Approach" concept, involving all relevant stakeholders. It lays emphasis on key Strategic Framework areas and will tackle current and future threats posed by AMR. The primary objective is to ensure that antimicrobials remain effective as long as possible and minimize the costs associated with its indiscriminate use.

Background

Introduction

Antibiotic resistance has risen alarmingly and emerged as a major health threat in the developed world but more so in resource poor countries including Asia.[1-3] This increasing trend has been documented over the last two decades in all health care settings, particularly in high-risk areas such as intensive care units, surgical units and neonatal intensive care units. Realizing the global threat of drug resistance, WHO in 2001 developed "The WHO Global Strategy for Containment of Antimicrobial Resistance" that provided some key interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms[1]

Pakistan like other countries also faces the crisis of antibiotic resistance as well.[4,5] There is an urgency for many healthcare settings because of associated higher morbidity, mortality and costs.[6,7]Antibiotic misuse and overuse has contributed tremendously to this major health crisis (Figure 1). As an array of newer "superbugs" especially the enterobacteriaceae continues to spread in healthcare, community settings and environment alike the challenges and goals to combat AMR now seems to be out of reach.8 Tackling antibiotic misuse in the country will need a huge effort and undertaking it will be an equally daunting and challenging task.[4,5] Potential hurdles includes weak health infrastructure and expertise, illiteracy, lack of access to basic health needs and lack of clean water and sanitation lead to a continuous "explosion" of infectious diseases that are mostly preventable. A series of strategies that includes national Infection Prevention & Control (IPC) policies and Antimicrobial Stewardship Programs (ASP) are an emerging concept.[9,10] All such interventions are aimed towards improving appropriate prescription of antibiotics in all healthcare settings. The ultimate goal is the preservation of current and future antibiotics against the threat of AMR with improving patient safety and reducing healthcare costs.



Global Overview

The 2001 "WHO Global Strategy for Containment of Antimicrobial Resistance" had made comprehensive recommendations.[1] In the 2012 report "The evolving threat of antimicrobial resistance: Options for action" WHO further highlights the lessons learnt with gaps and urges countries to commit to a comprehensive financed national plan to combat antimicrobial resistance, engaging all principal stakeholders including civil society.[11] The report had made the following major observations:

"Antimicrobial resistance: Kills, hampers the control of infectious diseases, increases the costs of health care, jeopardizes health care

gains to society and has the potential to threaten health security, and damage trade and economies." It also noted that drug-resistant tuberculosis (TB) has also risen. There is an estimated 450 000 new cases of MDR-TB with around 6% in new and among 20% in previously treated TB cases. Extensively drug-resistant TB (XDR-TB) has been reported in 92 countries. Resistance in malaria is also beginning to be of concern for global effort to control malaria with emergence of P. falciparum resistance to artemisinin in the Greater Mekong sub-region. Resistance in HIV is emerging with increasing levels of resistance to the non-nucleoside reverse transcriptases (NNRTI) from Africa in Europe and the USA with prevalence of 3.4–20%. Influenza viruses are resistant to traditional drugs (amantadine and rimantadine) with resistance to neuraminidase inhibitor (oseltamivir) emerging (1-2%).[11]

WHO global surveillance study "Antimicrobial resistance: global report on surveillance" reported data from 114 countries with resistance now documented "in every region of the world."[12] It was observed that "we are in a post-antibiotic era", in which people would die from simple infections. Studying further two key antibiotics, it was noted to be ineffective in 50% people in some countries. These included carbapenems (for pneumonia, blood stream infections, urinary tract infections (UTIs) and neonatal infections) and ceftriaxone being used as last resort for gonorrhoea. It noted with concern that the data is "devastating" unless significant action was taken urgently with overall message being that an "urgent global plan of action is needed for the rational use of antibiotics."[12] As per this WHO report the increasing high proportions of bacteria that cause common infections are becoming resistant with high treatment failures, worse clinical outcomes and death. The risk of death with some resistant enterobacteriaceae to specific key antibiotics is almost two fold. Estimates from Europe of the health and economic burdens resulting from resistant infections indicate that the excess mortality due to resistant hospital infections exceeds 25,000 annually.[13] Apart from additional patient morbidity and mortality, the attributable healthcare costs and productivity losses are estimated to be at least €1.5 billion each year.[13] Estimates from Canada also show very high excess costs associated with resistant infections.[14]

AMR situation in Pakistan

Antibiotic resistance is one of the major health crises in Pakistan with overall situation much more grim as depicted in many published studies over last two decades.[15-25] A number of factors may be contributory. Problems identified include unnecessary number of registered products (approximately 50,000),[16] 18% advertisements being "unjustified or misleading"[17] only 15% promotional brochures meet WHO criteria,[18] self-medication in 51%[19] and the presence of more than 600,000 quacks in Pakistan.[20] Pakistan has one of the highest numbers of drugs prescribed (>3 drugs/patient),[21-23] However more importantly 70% of patients are prescribed antibiotics.[21] This overuse and abuse was more common among GPs, public hospitals for costly antibiotics and 3rd generation cephalosporins.[22,24,25] Availability of over the counter (OTC) medications and especially antibiotics without prescriptions is common. These include many high end use antibiotics

now given for resistant infections. This has created a vicious cycle with emergence of resistance in common bacteria as a result of antibiotic pressure. A National Antibiotic Policy or IPC Policy is lacking. Few institutions may have full or partial institutional policies but unless majority has in place such policies with full implementation any impact at country level will be minimal.

Almost a decade ago resistance in Gram-negative organisms was increasing being recognized with extended spectrum beta lactamases (ESBLs) being a major concern.[26-28] A recent study from Aga Khan University, Karachi showed an increase in ESBL and multidrug-resistant organisms (MDR) producing K. pneumoniae to >30% (p=<0.0001) and 0.4% carbapenem resistant.[29] A study of blood stream infections (BSIs) from Lahore showed an alarming high resistance of 93.7% in Enterobacteriaceae against 3rd generation Cephalosporins with 6.5% carbapenem resistance among Pseudomonas and Acinetobacter isolates.[30] Muti- and pan-drug resistant Acinetobacter infections are now common in many hospital settings across Pakistan with high mortality as treatment options are few and limited. For example neonatal Acinetobacter infections resulted in 47% mortality in Karachi.[31] Increasing resistance in Shigella to common antibiotics is now also a reality.[32]

Typhoid continues to an important public health threat with increasing concern for resistance documented from many cities across Pakistan.[33-35] An AKU study of more than 5,000 isolates of Salmonella typhi and S. paratyphi A showed that MDR rate increased significantly in S. typhi (34.2 to 48.5% p<0.001) and that quinolone resistance increased in both S. typhi(1.6 to 64.1% p<0.001) and S. paratyphi A (0 to 47% p<0.001).[35] Methicillin-resistant S. aureus (MRSA) may be responsible for soft tissue and skin infections (SSTIs) and bone and joint infections. In Pakistan the prevalence of MRSA will determine the management of patients presenting with such infections. High prevalence (35-40%)[36,37] of MRSA isolates in different hospitalized patients means increasing use of second line drugs and higher cost. Anecdotal evidence suggests that MRSA infections within the community maybe on the increase. One study in our general population has shown that MRSA carriage rate (14.8%)[38] to be concerning for future management options.

A review of bacterial resistance among children in Pakistan from available literature also highlighted this issue.[39] Tuberculosis and malaria are also rampant in Pakistan. Resistance has emerged with potential negative fallout on the National Programs with grave implications for the public at large. Drug-resistant tuberculosis is increasingly being encountered in Pakistan due to wrong practices. WHO estimates that in Pakistan there are 15,233 MDR TB cases (5% of total).[40] Other reports suggest increasingly high rates (2-32%) as well.[41-45] More recent trends in malaria suggest the same pattern that probably is a result of overuse of antimalarials.[46,47]

The use of antimicrobial agents in animals, poultry and agriculture has benefits but overuse has potential implications for human health with sharp rise because of

high global demand.[48] The appropriate use of antimicrobials (selection, administration, monitoring and assessment) is a highly skilled discipline needing the experience and expertise of veterinarians and farmers. Practices to increase production have involved regular use of antimicrobials, potentially increasing selection pressure on bacteria to become resistant. Transmission of resistant bacteria of animal origin to humans is possible through the environment[49] and food products[50] and to agricultural workers by direct contact.[51] Causality due to antibiotic use in animals is difficult to establish but there is some direct evidence to show a close association between the prevalence of livestock-associated resistant bugs in animals and in humans,[52] levels of antimicrobial use in animals and the prevalence of resistant bacteria in animals[53] and in humans.[54] A recent European study showed a strong correlation between consumption of different antimicrobials and the prevalence of antimicrobial-resistant commensal Escherichia coli in pigs, poultry, and cattle.[55]

In low- and middle-income countries there is a huge and unprecedented growth in demand for animal protein.[56] The global consumption of antimicrobials in food animal production estimated at 63,151 (±1,560) tons in 2010 is projected to rise by 67%, to 105,596 (±3,605) tons, by 2030.[57] Pakistan is one of the top ten producers with increase production of livestock and poultry.[57,58] The overuse of antibiotics is common with potential public health hazards including compounding AMR. Few old studies have been done on antibiotic residues in poultry.[59-61] Experts in the field have warned against this threat and for the government to take notice and address this pressing issue.[62-65]

Most important from a public health perspective, there is well documented the spill over of resistance genes and resistant bugs from food animals into human populations via the environment,[66] the food chain[67] through direct contact with food animals.[68] In fast growing Asian countries, this will constitute a significant challenge because of the rapid demand for meat products.[69] The widespread resistance has grave implications for densely populated countries such as India and Pakistan. Recent studies in India have discovered antimicrobial residues in food animal products (such as chicken meat and milk), indicating that antibiotic use in food animal production is widespread and current regulation is non-existent for domestic production.[70]

This is further compounded by the fact that regulations on antimicrobial use are lacking and surveillance information on antimicrobial consumption does not exist. A survey of World Organization for Animal Health (OIE) in 2012 of OIE Member Countries revealed that only 27% countries have quantitative data on antimicrobial use in livestock with no regulations controlling the use of antimicrobial agents.[71] Limiting antimicrobial consumption in countries such as Pakistan, Bangladesh, Nepal, and Sri Lanka are likely to be also beneficial given the interconnectedness of the region's pharmaceutical commerce and trade.[72] In Canada there was a significant drop in cephalosporin resistance after stopping its use in poultry.[73] This has also been documented in a review from Europe.[74] Pakistan and other countries must learn these lessons for better surveillance to

collect data, resistant patterns, improve diagnostics and help in implementation and regulation that is acceptable and applicable. In summary antibiotic use in animals, poultry and agriculture can be detrimental for AMR. However non-essential use can mean safe and secure food and also help in controlling the spread of AMR. Monitoring and regulatory framework in all sectors including animal and agriculture health is a must that needs to be in place in line with the World Health Assembly (WHA) endorsed GAP to tackle AMR to succeed.[75]

All studies from human and animal sectors on resistance reinforce the fact that the problem of AMR is out of control. Unless contributing factors such as antibiotic misuse and poor IPC are not tackled we will become helpless in treating even the most common infections highlighted. A National Action Plan with strategies and solutions is thus a dire need to stem the rapid spread of these "superbugs." Multiple strategies that encourage the prudent use of antibiotics, anti-malarials, and anti-tuberculosis drugs and discourage their random and irrational uses in all healthcare settings have to be adopted. This will have major impact on infection rates, resistance patterns, costs and clinical outcomes. This can be achieved at both institutional and community levels by multi-sectoral involvement of all key stakeholders from the Government, professionals, societies and Policy makers of public and private institutions. At the 68th session in Geneva (18–26 May 2015), delegates at the WHA endorsed a GAP to tackle AMR.[75] Through adoption of the global plan all governments are committed to a National Action Plan on antimicrobial resistance aligned with the GAP by May 2017.[76] A WHO manual in collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) will assist countries in preparing their national action plans with participation of all relevant sectors and an incremental approach.[77] Pakistan in line with World Health Assembly Resolution in May 2015 has initiated efforts to take up the challenges of AMR. This **"National Strategic Framework for Containment of Antimicrobial Resistance"** under the Ministry of National Health Services, Regulations and Coordination (MNHS&RC) has been developed after due consultative process. A multi-sectoral committee that had oversight over this process involved consultations and meetings with major stakeholders from different sectors, literature review, surveys, assessments and gap analysis in public hospitals and in-depth Strengths Weaknesses Opportunities and Threats (SWOT) analysis with technical working groups. The process followed for Strategic Framework development is summarized in Annexure 1.

Situation analysis was done through literature review (Annexure 2). Most studies showed secular upward trends in resistance in all fields of human and veterinary medicine. MDROs have been isolated with increasing frequency across the country. However there is no nationwide surveillance to capture data for action plans to address the growing threat from AMR. Visits to major institutions, tertiary care hospitals and different stakeholders for assessment (Annexure 3), two in-depth SWOT consultative workshops with experts from relevant fields and representatives from

provinces for broader consensus on key issues (Annexure 4) and use of WHO checklist for National Action Plan development support tools for the formulation of Strategic Framework topics and statements (Annexure 5) was done.

These deliberations revealed that at the national level there is lack of relevant AMR experts; almost complete lack of AMR awareness among both relevant professionals from human and veterinary health, and the community. In public and private health hospitals there is mostly no Antibiotic Policy, Antibiotic Stewardship Programs, Infection Control Programs with poor practices in antibiotic use and basic hygiene practices. Microbiology laboratories are not standardized, national surveillance is not being carried and collaboration between human health and other sectors such as veterinary, poultry and agriculture sector for AMR containment is lacking. Many other threats to AMR include lack of data, quality of antibiotics and vaccines, misuse of funds, ability to sustain and implement programs such as Infection Prevention and Control in healthcare settings. Similarly the enactment for legislation related to education, programs for hospitals, antibiotic use, quality of antibiotics, establishment of national laboratories and incorporating into provincial health structure might be challenging. General apathy exists towards healthcare and especially specifically for AMR with poor political will.

However there is optimism as well with some established health and livestock infrastructure that can be used for surveillance system with upgrading of existing facilities. Existing National Programs can serve as models to be replicated as well. Similarly specific expertise exists in human and animal health. These can be garnered to establish national bodies and have shown willingness for AMR related activities including One Health Approach concept. Many professionals and national and international organizations are willing to work together for National Action Plans for AMR as well.

This document addresses all the five objectives outlined in WHO GAP for AMR.[75] Focus has been on major areas such as AMR burden and surveillance, IPC practices, antimicrobial stewardship efforts and the use of antibiotics in all fields including human, poultry, agriculture, veterinary medicine and other fields. Specifically emphasis has been on "low hanging fruits" approach with direction to improve awareness and understanding of antimicrobial resistance, education and training at all levels starting from undergraduate levels and schools. Strategic Framework related to establishing and strengthening of AMR surveillance and research has been outlined. Simple measures such as effective sanitation and hygiene in the communities and healthcare settings can greatly reduce the incidence and transmission of infections. Such measures complemented by additional disease specific precautions must be implemented for infection prevention measures in large public and private hospitals through this detailed Strategic Framework. Optimal use of antimicrobials both in human and animal health is essential and delineated here. Long term AMR containment has been addressed by focusing on investment in local solutions for new medicines, diagnostic tools, vaccines and other innovative interventions.

This "**National Strategic Framework for Containment of Antimicrobial Resistance"** has laid emphasis on key Strategic Framework areas and is envisaged to tackle current and future threats posed by AMR. The primary objective is to ensure that current antimicrobials remain effective as long as possible for all those who need them and minimise the costs associated with its indiscriminate use. We need to have consistent, coherent, comprehensive and integrated approach at national level to address AMR and to supplement the global and regional efforts. The "One Health" AMR approach involves an AMR containment system that will ensure reduction of adverse impact of inappropriate antimicrobial use on health in terms of cost, resistance and poor outcomes in human and veterinary medicine, agriculture and on finance, environment and consumers. Accordingly, Pakistan in line with "One Health Approach" has addressed AMR challenges through this Strategic Framework document.

Vision of National Strategic Framework

To establish a coordinated, collaborative and sustainable AMR containment system or programme with measurable outcomes under "One Health Approach" concept, involving all relevant stakeholders, on priority, in line with WHO Global Action Plan. This system shall be implemented, governed and monitored with specific strategic and operational plans.

Strategic Framework Objectives

To minimize AMR related consequences the Strategic Framework will focus on involving all stake holders under "One Health Approach" concept for developing AMR awareness, education and training, establishing AMR surveillance system, infection prevention and control (IPC), preventing in-appropriate use of antimicrobials, and carrying out AMR related research and development.

The Strategic Framework focuses on the following areas:

a. Well-coordinated awareness and educational program on AMR for all levels through relevant authorities.
b. Cross-sectoral coordination and establishing linkages for an integrated AMR surveillance system for evidence-based interventions and research. Establishment and strengthening of Microbiology laboratories as per proposed National Laboratory Strategic Framework.
c. Infection prevention and control standards by relevant experts, including provincial representation. To develop a framework for IPC implementation and monitoring by relevant authorities.
d. Rationalizing and promoting appropriate antimicrobial therapy through education of all relevant professionals, antimicrobial stewardship programs, and restriction on OTC antimicrobial and monitoring of antimicrobial consumption in humans, animals and plants.
e. Relevant academic institutions shall be encouraged and facilitated for funding of innovative research, development for vaccines, new or alternative antimicrobials and rapid and accurate inexpensive diagnostic tools of infectious diseases.

Definitions

Antimicrobial resistance (AMR): The ability of microorganisms, especially bacteria, to resist or to become tolerant to antimicrobial agents or antibiotics by acquired through genetic means especiallyplasmids.

Surveillance: Systematic and continuous collection, analysis, and interpretation of data of infectious diseases, specific pathogens of interest closely integrated with timely dissemination of results for use in planning, implementing, and evaluating health systems in hospital and community settings.

Multiple drug resistant organisms (MDROs): A bacterial isolate (organism) which is resistant to one or more antimicrobial agents in three or more different classes that the isolate is expected to be susceptible to; e.g., penicillins, cephalosporins, aminoglycosides, fluoroquinolones and carbapenems.

Multidrug-resistant tuberculosis (MDR-TB): Amycobacterial isolate that is resistant to both isoniazid and rifampicin, two of the first-line drugs used in treating smear-positive pulmonary tuberculosis.

Isolation: Placement of a patient in a single room with toilet facilities.

Isolation room: An isolation room indicated for the MDRO infected patient in a single room with toilet facilities, including dedicated washing/bathing facilities for the patient.

Hospital-acquired infections (HAIs): An infection acquired from the environment or staff of a healthcare facility, usually is spread to the susceptible patient by various means such as contaminated equipment, bed linens, or air droplets mostly after 48 hours of stay.

"One Health Approach": It is a concept that recognizes that the health of humans, animals and ecosystems are interconnected. It involves applying a coordinated, collaborative, multidisciplinary and cross-sectoral approach to address potential or existing risks that originate at the animal-human-ecosystems interface.

STRATEGIC FRAMEWORK STATEMENTS BASED ON WHO'S AMR OBJECTIVES

Objective 1:

Improve awareness and understanding of AMR through effective communication, education and training

Objective 1:

Improve awareness and understanding of AMR through effective communication, education and training

Potential measures of effectiveness

Extent of reduction in National human consumption of antibiotics (with allowance for the need for improved access in some settings), and reduction in the volume of antibiotic use in animal sector and food production.

Statements

1. Antimicrobial resistance shall be prioritized with political commitment as cross-sectorial public health threat at all levels.

2. The Governments shall promote, facilitate and support establishment of "One-Health" coalitions to address antimicrobial resistance at provincial, national and local levels with legislation for nation-wide antimicrobial program.

3. All relevant authorities and partners will create community awareness of the risks associated with antimicrobial misuse through effective communication.

4. Educational authorities will include antimicrobial resistance, infection prevention, sanitation and hygiene in the curricula as training of undergraduate and postgraduate students in medical, dental, nursing, veterinary and pharmacy institutions.

5. Regulatory authorities including Higher Educational Commission (HEC), Pakistan Medical & Dental Council (PMDC), Pakistan Veterinary & Medical Council (PVMC), Pakistan Nursing Council (PNC), Pakistan Pharmacy Council and Agriculture Councils to make ensure antimicrobial resistance related curricula are incorporated and implemented in professional education and training at all levels.

Objective 2:

Strengthen the knowledge and evidence base through surveillance and research

Objective 2:

Strengthen the knowledge and evidence base through surveillance and research

Potential measures of effectiveness

Extent of reduction in the prevalence of antimicrobial resistance, based on interventions following data collection, compilation and analysis through integrated programs for surveillance of antimicrobial resistance.

Statements

1. Cross-sectoral system under "One-Health" concept for AMR surveillance shall be established at federal and provincial levels.

2. Federal Government shall establish a Central Advisory Body of relevant experts including provincial representation tasked with identifying surveillance indicators for AMR. The advisory body shall carry out overall monitoring and evaluation of the AMR surveillance network. This body shall also formulate stewardship strategies for infectious diseases diagnostics and treatments.

3. 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. The reference labs shall also maintain Quality Control strains inventory & resistant strains repository.

4. There shall be mandatory establishment and strengthening of Microbiology laboratories (including veterinary and agriculture microbiology laboratories) network at different tiers of health care system in accordance with proposed National Laboratory Strategic Policy developed by the Ministry of NHSR&C.

5. The surveillance system shall be integrated with academia and research bodies / organizations for AMR related research and development.

6. For specific surveillance for MDROs the GLASS protocol for surveillance will be initiated.

Objective 3:

Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures

Objective 3:

Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures

Potential measures of effectiveness

Extent of reduction in the prevalence of preventable infections, and in particular the incidence of drug-resistant infections in health care setting and community.

Statements

1. Federal Government shall establish a Central Advisory Body of relevant experts including provincial representation tasked with infection prevention and control in all healthcare settings.

2. The Advisory Body shall formulate the national IPC guidelines for all health care settings. The said body will also develop a framework and mechanism for IPC implementation and monitoring by relevant authorities.

3. Strategic planning for IPC by the relevant authorities shall include mechanisms for implementation of surveillance for healthcare associated infections; prepare budgetary requirements and identification of resources for IPC programs.

4. Relevant authorities shall ensure preventive vaccination at all tiers as per existing programs (public and animal health).

5. Provision of clean drinking water, proper sanitation and hygiene shall be ensured at local, federal and provincial levels.

Objective 4:

Optimize the use of antimicrobial medicines in human and animal health

Objective 4:

Optimize the use of antimicrobial medicines in human and animal health

Potential measures of effectiveness

Extent of reduction in global human consumption of antibiotics (with allowance for the need for improved access in some settings), the consumption of antibiotics used in food production (terrestrial and aquatic livestock, and other agricultural practices), and the use of medical and veterinary antimicrobial agents for applications other than human and animal health.

Statements

1. All relevant authorities and associations shall ensure Antibiotic Stewardship is promoted in institutions, community and veterinary settings.
2. Drug Act 1976 and DRAP Act 2012 shall be fully implemented in true letter and spirit by relevant authorities with emphasis to limit the availability of antimicrobials to prescription-only status as given in WHO Global Strategy for Containment of Antimicrobial Resistance.
3. Monitoring of antimicrobial consumptions in humans, animals and plants shall be monitored at Federal and Provincial levels.
4. Relevant authorities and associations shall make sure that pharmacies have AMR awareness and personnel training for dispensing antibiotics.
5. Alternate medicine practitioner shall be regulated under relevant rules of PMDC and PVMC; and AMR awareness shall be created among them.
6. Ethical norms shall be promoted in order to discourage promotion of brands of antimicrobials.
7. There shall be promotion of strong media campaign against in-appropriate use of antibiotics.
8. Non-therapeutic use of antibiotics in livestock, poultry and plants shall be discouraged at all levels and evidence based use of antimicrobials shall be encouraged.
9. Health institutions and agriculture industry shall establish Antibiotic Stewardship Programs (ASPs) and shall develop mechanisms for auditing of antibiotic use in humans, livestock, milk products, poultry and plants.
10. There shall be mandatory inclusion of relevant experts in infectious diseases, clinical and veterinary microbiology for approval of national formulary of drugs with reference to antimicrobials.
11. Relevant authorities shall randomly conduct testing for antibiotic residues in food items.
12. The concept and details should be made part of curricula for teaching of all concerned tiers.
13. Monitoring and availability for quality assured antimicrobials in humans, animals and plants should be done at local, federal and provincial levels.

Objective 5:

Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

Objective 5:

Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

Potential measures of effectiveness

Extent of increase in sustainable investment in capacity to counter antimicrobial resistance in Pakistan, including investment in development of new medicines, diagnostics and other interventions.

Statements

1. Institutions shall be encouraged and facilitated for seeking funding for research on new and re-purposed antibiotics, vaccines and diagnostic tools.

2. Academia with teaching and training institutions shall offer opportunities for enhancing research capacity.

3. There shall be enhancement of linkages between research institutions and pharmaceutical industry and manufacturer of diagnostics for supporting AMR related R&D through public private partnership.

4. There shall be enhancement of vaccine development capacity at public and private sector according to international standards.

Limitations

Because of largely unregulated and fragmented healthcare system it was not possible to assess AMR situation across the country. Moreover, due to the devolved health care system, with the responsibility essentially at provincial level, it is difficult to give one overarching picture of the AMR system situation in Pakistan. However, visits to federal and provincial health authorities, NARC, DRAP and some tertiary care hospitals for extensive interviews with the relevant officials were carried out to collect the relevant information. From the discussions during workshops it became evident that the situation is quite heterogeneous. The observations during the visits were also shared with the participants of second workshop to formulate Strategic Framework statements.

Currently only few countries have developed National Action Plans or have Strategic Framework in place for AMR. According to WHO only 26% of the countries have some plans for AMR in their countries. Unfortunately few if any model exists for National AMR and we have to adapt to local needs and resources. Given the complexity and many areas to cover a coordinated, integrated and collaborative approach is required at national, regional and international level to effectively tackle AMR. Countries such as Pakistan with poor health structures and care may face much more difficulties in incorporating recommendations that will be forth coming. Unfortunately such countries face the brunt of AMR related costs, which is likely to spiral further out of control. Even incorporating generic best practice principles of AMR for **"National Strategic Framework for Containment of Antimicrobial Resistance"** will require workforce development and capacity building, funding, team of experts, reference labs, close coordination with many sectors such as animal and veterinary sciences, environmental, regulatory authorities and approval of all provinces and federal governments. All these gaps have been identified in this document through consultations with many stakeholders, SWOT analysis, visits to major public hospitals, surveys and the WHO checklist of "National Action Plan development support tools."[76] Many additional obstacles and barriers may need to be overcome for tackling AMR across Pakistan.

Way forward

The Strategic Framework on AMR containment in Pakistan is first and the essential step towards the commitment of Government of Pakistan to develop and sustain a comprehensive program based on the WHO Global Action Plan (GAP).[76] More importantly it reflects the vision of the government for the protection of health of the people of Pakistan. This Strategic Framework document is generic that was developed through the consultative process with wider range of stakeholders under the ICC. The Strategic Framework document has been shared with all the provincial/area and territories health departments. The Strategic Framework statements in the document are generic and as such may adopted by the respective provinces and areas health departments or customized to the local needs if required. It provides the framework for developing National strategic plans and provincial operational plans for an AMR containment system. Specific next steps would include:

1. Promoting and sustaining awareness and educational activities for public and professionals from all sectors
2. Estimating burden and dynamics of AMR
3. Establishing an infrastructure of AMR surveillance
4. Establishment of a national reference laboratory for human and animal health
5. Estimating the antibiotic production, distribution and use in humans, animals and plants
6. National Antibiotic guidelines for all sectors with stewardship strategies
7. Promoting and implementing IPC practices in all healthcare settings
8. Investing in AMR related research within the country

To accomplish these it is imperative that the role of ICC be expanded to have a wider representation of all relevant areas of health from different Ministries and Councils, concurrent and complimentary AMR projects and different societies. Specifically advisory bodies and working groups with relevant expertise such as human and animal health be formed who shall be tasked to coordinate and identify priority areas to fill gaps in AMR system and choose operation action plans incrementally. The ICC will oversee and monitor the implementation of endorsed key steps and report to the MNHS&RC. The Intersectional collaborative efforts will need to continue with a huge responsibility to monitor and oversee the whole AMR Strategic Framework implementation process. All stakeholders and ICC are expected to give their full support to ensure that practical and locally applicable solutions for AMR are endorsed and implemented that will improve healthcare service delivery in Pakistan.

Acknowledgments

The Ministry of NHS&RC acknowledges the technical, advisory and scientific contributions of Inter-sectoral Core Committee members, workshop participants, facilitators, Provincial Directorates General of Health, National Agricultural Research Centre / Pakistan Agricultural Research Council, Ministry of National Food Security and Research (MNFS&R),Drug Regulatory Authority of Pakistan, Pakistan Field Epidemiology and Laboratory Training Program, Provincial Ministries of Livestock and Dairy Development, Pakistan Medical Research Council, Medical Microbiology &Infectious Diseases Society of Pakistan, Armed Forces Institute of Pathology, Pakistan Medical Association, Pakistan Poultry Association, National Health Programs, Pakistan Nursing Council, Pakistan Pharmacy Council, Provincial Directorates General of Animal Health and other representatives from other ministries and associations. The Ministry also acknowledges the support it received from United States Agency for International Development (USAID) and implemented by JSI Research & Training Institute, Inc. as part of their Health Systems Strengthening Component of USAID's MCH Program.

References

1. WHO Global Strategy for Containment of Antimicrobial Resistance. Geneva, World HealthOrganization,2001,WHO/CDS/CSR/DRS/2001.2http://www.who.int/csr/resources/publications/drugresist/en/ EGlobal_Strat.pdf.
2. World Health Day 2011: Policy briefs. Geneva, World Health Organization, 2011 (http://www.who.int/world-health-day/2011/Strategic Frameworkbriefs/en/index.html.
3. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1–12.
4. Huttner A, Harbarth S, Carlet J, Cosgrove S, Goossens H, et al, World Healthcare-Associated Infections Forum. Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum. Antimicrobial Resistance and IPC 2013, 2:31.doi: 10.1186/2047-2994-2-31. eCollection 2013.
5. Khan E, Ejaz M, Shakoor S, Inayat R, Zafar A, et al. Increased isolation of ESBL producing Klebsiella pneumonia with emergence of carbapenem resistant isolates in Pakistan: Report from a tertiary care hospital. JPMA 2010 Mar;60(3):186-90.
6. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay. Clin Infect Dis 2006 Jan 15;42, Suppl 2:S82-9.
7. McGowan JE Jr. Economic impact of antimicrobial resistance. Emerg Infect Dis 2001;7:286–92.
8. Khan GA, Berglund B, Khan K, Lindgren P, Fick J. Occurrence and abundance of antibiotics and resistance genes in rivers, canal and near drug formulation facilities – A study in Pakistan. PLoS One 2013; 8(6): e62712.
9. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. ClinMicrobiol Rev 2005 Oct;18(4):638-56.
10. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, et al, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America: Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship: Clin Infect Dis 2007;44:159-77.
11. World Health Organization 2012. The evolving threat of antimicrobial resistance: options foraction.Available at http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf
12. World Health Organization 2014. Antimicrobial resistance: global report on surveillance 2014. Available at http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf
13. European Centre for Disease Prevention and Control (ECDC) and European Medicines Agency (EMEA). ECDC/EMEA Joint Technical Report—The bacterial challenge: time to react. Stockholm, 2009.Availableat(http://www.emea.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf
14. Birnbaum D. Canadian Committee on Antibiotic Resistance. Antimicrobial resistance: a deadly burden no country can afford to ignore. Canada Communicable Disease Report 2003;29(18):157-64.
15. Zaidi S, Nishtar NA. Rational prescription and use: a snapshot of the evidence from Pakistan

and emerging concerns. International Journal of Pharmacy and Pharmaceutical Sciences 2013;5(1):131-5.
16. Ministry of Health and WHO. Pakistan KB: Pharmaceutical Country Profile. Pakistan; 2010.
17. Rohra DK, Gilani AH, Memon IK, Perven G, Khan MT, et al: Critical evaluation of the claims made by pharmaceutical companies in drug promotional material in Pakistan. J Pharm Pharmaceut Sci 2006;9:50-59.
18. Hafeez A, Mirza Z. Responses from pharmaceutical companies to doctors' requests for more drug information in Pakistan: postal survey. BMJ 1999;319:547.
19. Haider S, Thaver IH. Self-medication or self-care: implication for primary health care strategies. JPMA 1995;45(11):297-8.
20. Pakistan Medical and Dental Association (PMDC). Unpublished data December 2014. http://www.pmdc.org.pk/Home/tabid/36/Default.aspx
21. WHO: The World Medicines Situation 2004. Available at http://apps.who.int/medicinedocs/en/d/Js6160e/
22. Amin A, Khan MA, Azam SM, Haroon U: Review of prescriber approach towards rational drug practice in hospitalized patients. J Ayub Med Coll Abbottabad 2011;23:19-22.
23. Samad L. Rapid Assessment Survey of injection practices in Northern Areas of Pakistan. JPMA 2006;56(11).
24. Siddiqi S, Hamid S, Rafique G, Chaudhry SA, Ali N, Shahab S, Sauerborn R. Prescription practices of public and private health care providers in Attock District of Pakistan. Int J Health Plann Manage 2002;17:23-40.
25. Khan MS, Ahmed Z, Jehan S, Fassehuz Z, Khan S, et al. Common trend of antibiotics usage in a tertiary care hospital of Peshawar, Pakistan. J Ayub Med Coll Abbottabad 2010;22:118-120.
26. Shah AA, Hasan F, Ahmed S, Hamed A. Prevalence of ESBL in nosocomial and outpatients. Pak J Med Sci 2003;19(3):187-191.
27. Ali AM, Rafi S, Qureshi AH. Frequency of extended spectrum beta-lactamase producing gram-negative bacilli among clinical isolates at clinical laboratories of Army Medical College, Rawalpindi. JAMC 2004;16(1):35-37.
28. Jabeen K, Zafar A, Hasan R. Frequency and sensitivity pattern of extended spectrum beta-lactamase producing isolates in a tertiary care hospital laboratory of Pakistan. JPMA 2005;55(10):436-439.
29. Khan E, Ejaz M, Shakoor S, Inayat R, Jabeen K, Zafar A, Hasan R. Increased isolation of ESBL producing Klebsiellapneumoniae with emergence of carbapenem resistant isolates in Pakistan: Report from a tertiary care hospital. JPMA 2010 Mar;60(3):186-90.
30. Nafees M, Farooq M, Ghazala Jafferi. Bacterial pathogens responsible for blood stream infection (BSI) and pattern of drug resistance in a tertiary care hospital of Lahore. BiomedicaJul-Dec 2009;25(2):101-5.
31. Saleem AF, Ahmed I, Mir F, Ali SR, Zaidi AK. Pan-resistant Acinetobacter infection in neonates in Karachi, Pakistan. J Infect DevCtries 2009 Nov 5;4(1):30-7.
32. Zafar A, Hasan R, Nizami SQ, von Seidlein L, Soofi S, et al. Frequency of isolation of various

subtypes and antimicrobial resistance of Shigella from urban slums of Karachi, Pakistan. Int J Infect Dis 2009 Nov;13(6):668-72.
33. Butt T, Ahmad RN, Salman M, Kazmi SY. Changing trends in drug resistance among typhoid salmonellae in Rawalpindi, Pakistan. East Mediterr Health J 2005 Sep-Nov;11(5-6):1038-44.
34. Ali AM, Qureshi AH, Rafi S, Mirza SH. Changing frequencies and current status of Multiple-Drug Resistant Typhoidal Salmonellae in year 2001-2003 at Rawalpindi. Infect Dis J Mar 2005;14(1):3-6.
35. Hasan R, Zafar A, Abbas Z, Mahraj V, Malik F, Zaidi A. Antibiotic resistance among Salmonella enteric serovars Typhi and Paratyphi A in Pakistan (2001-2006). J Infect DevCtries 2008 Aug 30;2(4):289-94.
36. Hafeez R, Chughtai AS, Aslam M. Prevalence and antimicrobial susceptibility of methicillin resistant staphylococcus aureus (MRSA). Int J Pathol Jun 2004;2(1):10-5.
37. Hussain S, Shams R, Ahmad K, Perveen R, Riaz B. Prevalence of methicillin resistant staphylococcus aureus (MRSA) in surgical site infections in a tertiary care hospital. Int J PatholDec 2005;3(2):81-5.
38. Anwar MS, Jaffery G, Tayyib M, Bokhari SR. Staphylococcus aureus and MRSA nasal carriage in general population. J Coll Physicians Surg Pak Nov 2004;14(11):661-4.
39. Khan EA. A literature review and analysis of antimicrobial resistance in Pakistani children-Time for pediatricians to do more! Infect Dis J Oct-Dec 2013; 22(4):613-27.
40. World Health Organization. Global tuberculosis control: surveillance, planning, financing: WHO report 2008. "WHO/HTM/TB/2008.393".
41. Butt T. Frequency and antibiotic susceptibility pattern of Mycobacterial isolates from extra-pulmonary TB cases. JPMA Aug 2003;53(8):328-32.
42. Iqbal R, Shabbir I, Mirza MN, Hasan M. TB drug resistance an alarming challenge - answer DOTS. Pak J Med Res Sep 2003;42(3):134-8.
43. Javaid A, Hasan R, Zafar A, Ghafoor A, Pathan AJ, et al. Prevalence of primary multidrug resistance to anti-tuberculosis drugs in Pakistan. Int J Tuberc Lung Dis. 2008 Mar;12(3):326-31.
44. Ejaz M, Siddiqui AR, Rafiq Y, Malik F, Channa A, et al. Prevalence of multi-drug resistant tuberculosis in Karachi, Pakistan: identification of at risk groups. Trans R Soc Trop Med Hyg 2010 Aug;104(8):511-7. doi:10.1016/j.trstmh.2010.03.005. Epub2010 Apr 28.
45. Ayaz A, Hasan Z, Jafri S, Inayat R, Mangi R, et al. Characterizing Mycobacterium tuberculosis isolates from Karachi, Pakistan: drug resistance and genotypes. Int J Infect Dis 2012 Apr;16(4):e303-9. doi:10.1016/j.ijid.2011.12.015. Epub 2012 Feb 23.
46. Ahmed S, Adil F, Shahzad T, Yahiya Y. Severe malaria in children: Factors predictive of outcome and response to Quinine. JPMA 2011;61:54
47. Ghanchi NK, Ursing J, Beg MA, Veiga MI, Jafri S, et al. Prevalence of resistance associated polymorphisms in Plasmodium falciparum field isolates from Southern Pakistan. Malar J 2011 Jan 28;10(1):18. doi:10.1186/1475-2875-10-18.
48. Evans T, Chapple N, Kidd C, Wernham J. & Lloyd J. 2008 – Animal health service. Anti-

infectives. Vetnosis, Edinburgh.
49. Graham JP, Evans SL, Price LB, Silbergeld EK. Fate of antimicrobial-resistant enterococci and staphylococci and resistance determinants in stored poultry litter. Environ Res 2009;109(6):682–689.
50. Price LB, Johnson E, Vailes R, Silbergeld E. Fluoroquinolone-resistant Campylobacter isolates from conventional and antibiotic-free chicken products. Environ Health Perspect 2005;113(5):557–560.
51. Smith TC, et al. Methicillin-resistant Staphylococcus aureus in pigs and farm workers on conventional and antibiotic-free swine farms in the USA. PLoS ONE 2013;8(5):e63704.
52. Vieira AR, et al. Association between antimicrobial resistance in Escherichia coli isolates from food animals and blood stream isolates from humans in Europe: An ecological study. Foodborne Pathog Dis 2011;8(12):1295–1301.
53. Aarestrup FM. Veterinary drug usage and antimicrobial resistance in bacteria of animal origin. Basic Clin Pharmacol Toxicol 2005;96(4):271–281.
54. Schwarz S, Kehrenberg C, Walsh TR. Use of antimicrobial agents in veterinary medicine and food animal production. Int J Antimicrob Agents 2001;17(6):431–437.
55. Chantziaras I, Boyen F, Callens B, Dewulf J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: A report on seven countries. J Antimicrob Chemother 2014;69(3):827–834.
56. Tilman D, Balzer C, Hill J, Befort BL. Global food demand and the sustainable intensification of agriculture. Proc Natl AcadSci USA 2011;108(50):20260–20264.
57. Boeckel TPV, Brower C, Gilbert M, Grenfell BT, Levin SA, 2015 Robinson TP, et al. Global trends in antimicrobial use in food animals. Proc Natl Acad Sci 2015 Mar 19;201503141.
58. FAOSTAT. Live animal statistics. Available at http://faostat3.fao.org/home/E.
59. Maqbool, J. Residues of Sulfachloropyrazin in Poultry Products. 1988. M.Sc. Thesis, Deptt. Vet. Pharmacology, Univ. Agri., Faisalabad.
60. Muhammad G, et al. Testing milk and meat for antibiotic residues. Pakistan J Food Sci 1997;7:35–8.
61. Nawaz R., R Ahmed. Residues of sulfamethoxine in blood, eggs, and tissues of poultry birds. 1996 Pakistan Vet. J., 16: 181–5.
62. Ahmed Din Anjum, Professor, Department of Veterinary Pathology, University of Agriculture, Faisalabad. Misuse of drugs and development of their resistance. Available at http://www.pakissan.com/english/allabout/livestock/poultry/misuse.of.drugs.and.development.of.their.resistance.shtml
63. Alamdar Hussain Malik. Drugs residue in food. Available at http://www.pakissan.com/english/news/newsDetail.php?newsid=15325
64. Hafiz Muhammad Matiullah. Injections to animals harmful for human health: Expert
65. Mumtaz A, Awan JA, Athar M. Rational Use of Drugs in Broiler Meat Production. Int J AgriBiol 2000;2(3):269–272.
66. Berendonk TU, Manaia CM, Merlin C, Fatta-Kassinos D, Cytryn E, Walsh F, et al. Tackling

antimicrobial resistance: the environmental framework. Nat Rev Microbiol [Internet] 2015 Mar 30 [cited 2015 Apr 13]. Available from: http://www.nature.com/nrmicro/journal/vaop/ncurrent/abs/nrmicro3439.html
67. Aarestrup FM, Wegener HC, Collignon P. Resistance in bacteria of the food chain: epidemiology and control strategies. Expert Rev Anti Infect Ther 2008 Oct;6(5):733–50.
68. Van Cleef BAGL, Graveland H, Haenen APJ, van de Giessen AW, Heederik D, Wagenaar JA, et al. Persistence of Livestock-Associated Methicillin-Resistant Staphylococcus aureus in Field Workers after Short-Term Occupational Exposure to Pigs and Veal Calves. J Clin Microbiol 2011 Mar;49(3):1030–3.
69. Robinson TP, Pozzi F. Mapping Supply and Demand for Animal-Source Foods to 2030, Animal Production Health Working Paper (Food Agric Org, Rome), 2011, No 164.
70. Kakkar M, Rogawski L. Antibiotic Use and Residues in Chicken Meat and Milk Samples from Karnataka and Punjab, India: 2013 Research Scheme 34 (Public Health Found, New Delhi).
71. Diaz. Antimicrobial use in animals: Analysis of the OIE survey on monitoring of the quantities of antimicrobial agents used in animals [Internet]. 2013; Paris. Available from: http://www.oie.int/eng/A_AMR2013/Presentations/S2_4_Fran%C3%A7oisDiaz.pdf
72. Basnyat B. Antibiotic resistance needs global solutions. Lancet Infect Dis 2014;14(7):549–550.
73. Dutil L et al. Ceftiofur resistance in Salmonella entericaserovar Heidelberg from chicken meat and humans, Canada. Emerging Infectious Diseases 2010;16(1):48-54.
74. Cogliani C, Goossens H, Greko C. Restricting antimicrobial use in food animals. Lessons from Europe. Microbe 2011;6(6):274–279.
75. WHO 2015. World Health Assembly addresses antimicrobial resistance, immunization gaps and malnutrition. http://www.who.int/mediacentre/news/releases/2015/wha-25-may-2015/en/
76. WHO 2015. Global Action Plan on antimicrobial resistance. Available at http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf
77. WHO 2016. Antimicrobial resistance: A manual for developing national action plans. Available at http://apps.who.int/iris/bitstream/10665/204470/1/9789241549530_eng.pdf

Annexure 1:

The process of Strategic Framework Development

Phase 1:
Preparatory activities

A national multi-sectoral AMR containment steering committee called Inter-sectoral Core committee (ICC) was officially established vide MNHS&RC notification in November 2015. Essential information on the country's AMR containment system was gathered and available literature was reviewed in light of WHO Global Action Plan 2015. This information was analysed to identify the key issues and stakeholders and relevant experts for conducting consultative workshops were identified in addition to the members of the AMR oversight committee. Visits to major institutes and tertiary care hospitals were also conducted to assess the current healthcare structure with gap analysis.

Phase 2:
Workshops and visits for the development of "National Strategic Framework for Containment of Antimicrobial Resistance"

This phase involved 2 consultative workshops of 2 days each and a total of 17 visits including visits to NARC, DRAP, Provincial Health Care Authorities and tertiary care hospitals in different cities of the country. During the workshops participants worked together on the development of the "National Strategic Framework for Containment of Antimicrobial Resistance" keeping in view five objectives of WHO GAP 2015. The first Strategic Framework development workshop was held in Islamabad in February 2016 and the second workshop in April 2016. Experts from relevant fields and representatives from provinces were engaged to develop broader consensus on key issues. The workshops were conducted under the guidance of Dr. Assad Hafeez, Director General, Ministry of National Health Services, Regulations & Coordination through AMR Focal Person Dr. Muhammad Salman, Consultant Microbiologist at National Institute of Health. Dr. Ejaz Ahmed Khan, Infectious Diseases Consultant and Dr. Muhammad Usman, Consultant Microbiologist served as facilitators for the workshops. During these workshops the foundation for a National Strategic Framework was built, through development of consensus, SWOT analysis and formulation of Strategic Framework topics and statements. Findings of visit reports were also shared with participants during the workshop.

Phase 3:
Strategic Framework dialogue and final draft preparation

After the second workshop a Strategic Framework dialogue process was started to discuss the draft "National Strategic Framework for Containment of Antimicrobial Resistance" before endorsement. Input and suggestions through phone and email by key members of ICC and relevant ministries were incorporated. This process ensured national ownership as well as the commitment of all relevant stakeholders to the Strategic Framework.

Annexure 2:

Literature Review

One of the foremost steps for any Strategic Framework development is one must know the extent and magnitude of any problem such as AMR. In Pakistan despite lack of systematic National AMR data there is enough in published literature in all settings including healthcare, communities, agriculture, veterinary and basic research that can be used as a basis for making some recommendations for "National Strategic Framework for Containment of Antimicrobial Resistance" (see separate Full Literature Review for details). Specific areas that are of prime interest are AMR surveillance studies, IPC practices, antimicrobial stewardship efforts, human resources and the use of antibiotics in other fields such as agriculture, veterinary medicine and other fields. Relevant articles from both international and local literature were selected in PUBMED and Pak Medinet. We acknowledge that some of these and similar studies may not have been well designed, without proper microbiologic standards and may have certain other limitations.

However this available AMR data available in Pakistan was gathered and will serve as useful point for Strategic Framework makers to gauge the extent of some major gaps that must to be addressed when strategizing action plans. In Pakistan nearly all infections have consistently shown a rise in resistance to antimicrobials. These include common bacterial infections, tuberculosis, malaria and paediatric infections. The presence of these resistant organisms translates into a high morbidity and mortality besides significant economic burden. Most of these studies have shown resistance in all fields of human and veterinary medicine. Microbiologic methods for isolation of organisms may have differed in most studies but etiologic agents for different infections have showed same secular trends and some geographic variations in the last few decades. Most organisms have shown increasing drug resistance with poor outcome with main clinical syndromes recording newer resistance patterns. Major contribution to the increasing drug resistance include indiscriminate and overuse of antibiotics in all sectors of health, inappropriate antibiotic selection, poor IPC practices or non-existent institutional antibiotic policies, substandard antibiotics in the market, non-existent microbiologic facilities and research. As International health authorities are focused on AMR related threats it is expected that by initiation of these efforts by Government of Pakistan more useful data is expected to be forthcoming.

Annexure 3:

AMR Containment System Assessment

As an assessment and gap analysis the AMR Team consisting of two consultants visited key stakeholders, public health officials, major public and private hospitals, provincial health departments, drug regulatory authority, animal and agriculture institutions and other related individuals. Specific information was sought related to awareness about AMR, hospital beds, personnel, laboratory and other facilities etc. Below are key assessments, observations and summary of these visits done over three months (January-April 2016):

- A total of 17 visits were done in 5 cities (Islamabad, Rawalpindi, Lahore, Peshawar, Quetta and Karachi)
- A total of 11 major private and public hospitals, 11 institutions and organizations were visited with meetings and interviewing approximately 40 individuals
- **Public Hospital Visits**
  - Six Public Hospitals had a total bed capacity of 8050 (equivalent to ~10% of all beds in Pakistan).
  - Most tertiary care public teaching hospitals had high turnover of patients and were operating beyond their capacity.
  - **Isolation Areas/Beds Negative Pressure rooms/PPEs:**
    - Only half of the hospitals had some isolation rooms or dedicated wards for infected patients. Most of these are for patients with tuberculosis, dengue, CCHF and H1N1 influenza. Infected patients are mostly kept in open wards where isolation precautions are difficult.
    - A total of less than 100 isolation beds where identified in all the hospitals visited. The quality and maintenance of these dedicated beds was well below international standards.
    - None of the hospitals visited had Negative pressure rooms.
    - Availability of Hand Hygiene solutions and PPEs was also not consistent and lacking most of the time.
    - General cleanliness and attention to sanitation etc. was extremely wanting with major flaws creating major risks to the patients. One large hospital had >200 cleaners/sweepers for 2000 beds but cleanliness level showed that much more needed to be done to improve this aspect of AMR.
  - **IPC Teams:**
    - IPC teams (ICT) were constituted in most hospitals only recently and IPC policies / guidelines were present in some hospitals. However, gaps existed in implementation of IPC measures in most setups. There was some structure in these ICT but functioning was poor with mostly no regular meetings.
    - Only one hospital had written IPC written guidelines in a booklet form.

- **Hospital Surveillance/HAIs Indicators:**
  - Interviews with the team members of ICT revealed that only some daily activities were done in some hospitals. These included monitoring for IPC practices, some infected patients' identification, ensuring availability of PPEs, sterilization and hand washing / hand sanitizer facilities at bedside, barrier precautions during procedures, proper disposal of waste management and keeping separate colour coded containers. There is some teaching for nurses but there was no structured training for such activities. However, compliance was generally variable and nurses were not empowered to enforce isolation precautions and hand hygiene for all including physicians.
  - None of the hospitals used any of the defined indicators for surveillance of Hospital-acquired infections.
  - Electronic Lab information system (LIS) is not available in most hospitals. In one hospital only both manual and Electronic Lab information management system was available.
- **Hospital Surveillance/HAIs Indicators:**
  - Only one hospital had Antibiotic Policy / guideline in place but its implementation was partial.
  - In all the hospitals antibiotics (mostly broad spectrum antibiotics) were being empirically used at the discretion and preferences of treating physician. The rationale for antibiotics use, its duration and dose was not clear due to non-availability of consultation by infectious diseases physicians in infected cases.
  - Reasons for this massive use of high-end antibiotics were non-existent Antibiotic Policy, fears of "super-infections", availability of OTC antibiotics without a prescription and inadequate or poor microbiologic diagnostic facilities.
  - The use of hospital pharmacy for available antibiotics (including broad spectrum) was mostly functional and formulary was available.
  - All these factors were pointed by most hospitals as probably contributing towards misuse of antibiotics along with non-regulation of labs and pharmacies outside most major public hospitals.
  - Antibiotic Stewardship was either not present or was rudimentary. Awareness in this regard was also low.
- **IPC:**
  - Only 13 nurses were "dedicated" for IPC among all major public hospitals visited. This is equivalent to 1 per 615 patient beds rather than the recommended 1 per 100-150 beds.
  - Most hospitals did not have any formal full-time vacancy created for IPC nurses.
  - Some dedicated nurses were working in some hospitals but did not have any clear

defined job description and mostly had limited role of observations, lab coordination and some education and training.

- The ICT also said that there was poor nurse to patient ratio (30 nurses per 100 beds rather that the allotted post of 42 nurses per 100 beds in one hospital).
- Only 2 hospitals reported IPC Policy with one having written Policy that was shared with the team.
- IPC Policy was being developed in some but implementation witnessed in only few areas and was not satisfactory.
- **Hand Hygiene education and other preventive aspects training to HCWs:** There was inadequate Hand Hygiene facilities in some of the areas that was visited. The ICT also pointed to the fact that there was poor compliance and enforcement of such Policy and educational programs such as CMEs is do not exist or problematic in their setup.
- Some education and training sessions were reported but these were mostly not regular and probably not enough or optimal.
- **Protocols for Healthcare workers regarding exposure (needle stick, infectious diseases etc.):** Protocols did not exist to address work related exposures such as needle stick injuries. Only one hospital had written protocol to that effect.

o **Human Resources:**

- Shortage of human resource (ID physicians, microbiologists, clinical pharmacists, properly trained IPC nurses, laboratory and microbiology technologists / technicians etc.) was pointed by all hospitals.
- Shortage of human resource and funds hampered surveillance and IPC.
- **ID Physicians:** None of the hospitals had any certified Infectious Disease Physician. Instead either a medical specialist or a pulmonologist, if any, carried these responsibilities.
- **Clinical Pharmacists:** None of the hospitals had any clinical pharmacist. Balochistan was the only province where law for regulation of pharmacies and labs existed but had not been implemented yet.
- **Microbiologists:** Microbiologists are considered as the most important position in any major hospitals especially with regards to IPC and lab diagnosis of infections. However, the hospitals visited had only 7 trained microbiologists in all. This is equivalent to 1 per 1150 patient beds rather than the recommended 1 per 100-200 beds.
- **Trained Lab Technicians:** Hospitals did not have properly trained technologists / technicians in clinical microbiology. These responsibilities were carried by mostly partially trained persons or with no proper background.

- **Microbiology Lab/facility:**
  - Only two hospitals generated cumulative data of antimicrobial susceptibility but less regularly, but proper antibiograms were not generated.
  - Most microbiology labs are equipped to perform basic bacterial identification & drug susceptibility testing by basic conventional culture methods. Advanced blood culture systems like Bactec 9240 was used in two hospitals. Some labs were in process of acquiring automated drug susceptibility testing. Quality management system was insufficient in most hospital labs visited. Uniform standards were not used in Microbiologic diagnostics. The labs in most instances reported MDRO, once isolated, directly to the ward / unit, who also in turn would inform the ICT for barrier precautions or the patient transferred to the isolation area for IPC measures.
  - The total number of cultures received in these public hospital microbiology labs was variable (10 to 100 / day). The underutilization of hospital labs was due to the fact that samples were also being sent to private labs outside the hospital. Few laboratories reported that due to non-availability of supplies and equipment they could not cater to all the cultures requested as it easily exhausted their supplies.
  - No lab was participating in any MDROs surveillance network. Surveillance coordinating unit was non-existent in the provinces.
  - Reference labs were also non-existent at national and provincial levels.
- **Multi-drug resistant organisms (MDRO) Problems:**
  - Public hospitals visited had inadequate surveillance system for MDROs. However, carbapenem resistance in enterobacteriaceae (CRE), Acinetobacter and Pseudomonas were prevalent in hospitals. ESBLs (some reported 60%) among Gram negatives infections were most prevalent problem in most of the patients.
  - Other cases of major MDROs were also being isolated in the lab and included MRSA and VRE.
- **Waste Disposal Management/Hospital incinerator:**
  - Hospital Waste disposal was being done in most hospitals with different arrangements. But mostly waste disposal was not being disposed properly. In some it was being done by outsourcing to a third party who were doing better job by following some protocols.
  - Hospitals corridors and wards were mostly either not cleansed or were partially done with areas and corners dirty, floors and walls stained, windows and doors broken or dirty, wash basins inadequate or broken and leaky, roofs dirty or leaky from clean pipes or even gutters and strong stench. This was more evident unfortunately in some high-risk areas such as intensive care units and ORs.
  - Incinerator was mostly not present, non-functional or by outsourcing to a third party for this purpose.

- **Funding issues:**
  - Funding for AMR related activities appeared to be an issue also. Most concerned person interviewed consistently talked about lack of funds for major activities that including basic lab diagnostics, hiring of properly trained personnel, equipment, IPC (PPEs), surveillance etc.
- **Involvement of administration**

  The Hospital administration was mostly not part of the activities such as ICT, ASP etc. AMR seemed a low priority of the hospitals.
- **Examples of some well-functioning units**

  There may have been many examples of good and well functioning units in these and other hospitals but some examples that were assessed in these visits include the following:
- **Microbiology Lab, Civil Hospital, Karachi**
  - This laboratory caters to the needs of >1200 beds Civil Hospital. Situated within the hospital the lab has adequate staff with trained technicians and microbiologists. The lab is equipped with latest diagnostic culture system. The workload was considerable with total cultures being received >100/day. Most routine and special cultures were done in the hospital lab and not from outside unless fungal and TB cultures were needed or further testing was needed for some isolates.
  - The lab was well funded by both government and Dow Medical College Alumni since many years. Fungal and TB cultures were not done which was a drawback. However TB cultures were being sent to TB Lab that was part of the National TB Control Program. The lab otherwise has been maintained and functioning well overall.
- **Dengue/Isolation Ward, Holy Family Hospital, Rawalpindi**
  - Situated within the new building of Holy Family Hospital, Rawalpindi this dengue ward was part of the recently established "Infectious Disease Department." It was run by a dedicated Medical Specialist. The need for this special unit was the initiative of Government of Punjab after the dengue epidemic that became rampant over last few years.
  - This 25-bed unit had separate rooms as well wards. It was well maintained and clean. It was equipped with all PPEs with excellent Hand Hygiene facilities. The staff to deal was adequate and well trained. Regular educational activities were being done almost on daily basis mostly related to Dengue Prevention and Management. The unit also had a small lab, x-ray and ultrasound machine for these patients. It was also capable to expand to more beds in case of any epidemic.
- **Children emergency run by Child Life Foundation at National Institute of Child Health, Karachi**
  - National Institute of Child Health is one of the largest children hospitalsin Pakistan.

Emergency rooms/centres have the past been overburdened, poorly equipped and delivering sub-optimal emergency care to children of all ages with poor outcome. Child Life foundation, a private NGO, took the initiative and collaborated with Government of Sindh to improve its functioning.

- Now this Emergency Centre is 50+bed unit, one of the largest of its kind with number of patients being seen doubled compared to those in the past. It has well trained adequate staff including doctors, nurses and paramedics. It is equipped with lifesaving equipment, has its own pharmacy, lab, x-ray machine etc. It has focused on rapid triage of sick children and efficient enough to deliver immediate care. It is a paperless unit with all record being computerized.
- IPC and prevention are being done despite the huge load of patients and high turnover. However space constraint that was visible was being addressed with recent approval to expand and have more isolation beds and areas. Antibiotic use was being monitored with mostly first line therapy being utilized.
- Funding was not a major issue, as sources existed that catered to all the needs of such a big unit within a public hospital.

General Recommendations/Suggestions

- **Recommendations for AMR given by the Hospital Team included:**
  - Countrywide surveillance data on MDROs to make evidence based recommendations using local data, provision of diagnostics, opportunity for training, creating posts for microbiologists, pharmacists and inducting Infectious disease person in each hospital, ban on the use of doing lab facilities from outside rather than these major public hospitals.
  - There was lack of political will to implement health policies such as AMR related major decisions. There was also major concern for the political meddling in healthcare related decisions in these major hospitals (procurement of antibiotics from companies, hiring of appropriate staff, use of lab and radiology facilities).
  - Poor lab facilities and funds hampered efforts for appropriate IPC practices, surveillance and diagnostics. Therefore upgrading and adding all main components of lab facilities for microbiologic diagnosis and using automated system to improve surveillance and diagnostics was needed.
  - Regular education and training related to AMR containment, a full-fledged IPC Team and regular surveillance for HAIs.
  - Appropriate and regular funding for upgrading lab facilities and diagnostics, imparting education and training to relevant HCWs, creating posts for microbiologists, pharmacists and inducting Infectious disease person in the hospital and improving nurse to patient ratio.

- Awareness and education about judicious use of antibiotics through regular sessions. ASP teams should be established for such an important task that should be empowered and properly funded.

Visit to Drug Regulatory Authority of Pakistan (DRAP), Islamabad

- **Discussions and observations:**
  - The role of DRAP is
- To regulate the import, export, manufacture, storage, distribution and sale of drugs through the Drug Act, 1976 and DRAP Act 2012.
- Registration, quality assurance and lab testing of antibiotics are being done by DRAP under the Drug Act and relevant government rules.
- Licensing for sale of drugs and monitoring of Medical stores / Pharmacies is a provincial/ local matter under Provincial Chief Drug Controllers and Drug Inspectors and not under DRAP.
  - Gaps exists in implementation of Drug Act and policies made under the Act.
  - DRAP was already doing activities related to the judicious use of antibiotics.
  - Antibiotics used in animals are also registered/approved by DRAP.
  - OTC sale of antibiotics is not regulated properly, as all antibiotics are available OTC, without prescription by qualified health care professionals.
  - Registration of new drugs is done on recommendations of advisory board; however, in case of antibiotics Infectious Diseases specialists/clinical microbiologists are usually not involved in advisory process.
  - Antibiotic are also added to herbal medicines, which creates difficulties in registering these products.
  - Data regarding overall sale of antibiotics is not available at provincial or national level.

- **Recommendations and considerations:**
  - DRAP will nominate a person for AMR related activity.
  - More awareness about appropriate use of antibiotics and involvement of others will be undertaken.
  - DRAP will consider addition of microbiologists and an ID physician to advisory board for registration of antibiotics used both for human and animal health activities.

Visit to Pakistan Agricultural Research Council (PARC), Islamabad

- **Discussions and observations:**
  - PARC is the apex national organization working in close collaboration with other

federal provincial institutions in the country to provide scientific-based solutions to agriculture of Pakistan through its statutory functions.

- PARC has seven divisions; five technical divisions: "Plant Sciences", "Animal Sciences", "Social Sciences", "Natural Resources", "Agricultural Engineering" and Two services divisions: "Finance" and "Coordination & Monitoring".
- There are an estimated 7000 veterinarians besides other para-veterinarians.
- Approximately 5-10% farmers acquire zoonosis.
- Zoonosis such as influenza, CCHF, tuberculosis, brucellosis, salmonellosis and other tick borne diseases are very common and documented.
- Antibiotics use in animals, poultry and agriculture is indiscriminate and huge. Antibiotics are being extensively used in animals for growth promotion and prophylaxis of infections.
- Many broad-spectrum antibiotics are used including quinolones, third generation cephalosporins and even colistin.
- Major dispensers of antibiotics are veterinarians but also OTC antibiotics by farmers. Use of antibiotics in animals is mostly unregulated and is available OTC and without prescription.
- Poultry Industry is huge but >90% are in Private setup and is very powerful and resourceful.
- Antibiotics use in animal and poultry feed is huge. Exact usage is unknown. However there was little use of the National Veterinary Lab at federal level and other veterinary research labs to document relationship between amount of antibiotic residue in meat and poultry and drug resistance in humans.
- There is very poor awareness of the dangers of antibiotics misuse and problems of resistance among veterinarians.
- National / local guidelines for use of antimicrobials are not available.
- Some research has been done in many aspects related to AMR related to human health.
- Veterinary basic diagnostic Microbiology labs do exist at district level in most of the places in Pakistan with the capacity of identification & drug susceptibility testing of common pathogens.
- Data sharing for surveillance of zoonotic infections is limited to a few projects addressing CCHF, brucellosis, salmonellosis and bird flu but there is no integrated surveillance system of AMR in animal health sector.
- Surveillance studies carried out in this regard are fragmented.

- **Recommendations and considerations:**
  - Many aspects of animal-human interface regarding transfer of drug resistance

factors need to be studied to establish any link between the impacts of use of antibiotics in animals on creating resistance in microorganisms infecting humans.
- More involvement of veterinary, poultry and agriculture sector is needed in the process to strengthen collaboration on AMR containment efforts.
- Funds and adequate trained staff are needed to carry out nationwide efforts and influence the Strategic Framework regarding judicial usage of antibiotics in animals.

Other General Observations

- Overall health structure is very weak and lacks standards that make it less efficient. This was evident by visits to these large public hospitals.
- Strategic Framework for overall healthcare systems is partial and is largely un-regulated with insufficient legislation (e.g. for antibiotic use, OTC), poor implementation of available legislation, certified and qualified healthcare workers are not available especially for AMR containment.
- Priority for AMR, responsibility and accountability, feedback and monitoring mechanisms are less clear and less developed.
- Given this situation specifically for AMR the Strategic Framework should be realistic, sustainable and practical given current assessment as narrated above. The Strategic Framework should therefore be objective-oriented, flexible and progressive.

Annexure 4:

SWOT Analysis

Two workshops were conducted in February and May 2016 with members of the ICC, technical working group, representations from different sectors and all the four provinces and federally administered areas of Pakistan. A summary of this SWOT analysis as 5 strategic objectives is presented below:

Objective 1: To improve awareness and understanding of antimicrobial resistance through effective communication, education and training

Strengths	Weaknesses
1. Availability of some relevant expertise within the country 2. Proactive media, availability and widespread use of internet across the country 3. Educational infra-structure available 4. Health infrastructure available	1. No Strategic Framework available at national and provincial levels 2. Shortage of skilled human resource regarding AMR related issues 3. Weak curriculum of professional education 4. Low quality of education regarding AMR at different levels 5. Weak understanding and lack of awareness of AMR among professionals 6. Poor general public awareness regarding AMR related problems

Opportunities	Threats
1. NGO and community based organizations can be engaged to improve AMR awareness 2. Expertise available at certain levels can be engaged for advisory and educational purpose 3. Experience from vertical programs like TB can be used to promote awareness and education regarding AMR 4. Strategic Framework makers and politicians can be sensitized to address the AMR related problems 5. Engagement of Federal and Provincial Governments for legislation and implementation 6. Integration of academia and research institutions with clinical / field professionals 7. Highly proactive electronic media can carry out Positive media campaigns 8. International agencies and donors for funding to carry out awareness activities related to AMR 9. International commitments by the Government of Pakistan, and AMR inclusion in the Global Health Security Agenda (GHSA) as a major action package and priority agenda by the NHSRC	1. Security situation in certain areas 2. Conflict of interest among stake holders 3. Non availability of specific funds for AMR 4. Weak political will

Objective 2: Strengthen the knowledge and evidence base through surveillance and research

Strengths	Weaknesses
1. Available expertise can be used for establishing surveillance system 2. Established health and livestock infrastructure can be used for surveillance system 3. Labs doing Drug Susceptibility Testing (DST) exist at different levels of human and animal health care and system (in both private and public sector) can be involved in surveillance system. Some of them are Quality Assured 4. Existence of regulations and models for surveillance in place e.g. for TB program, other communicable diseases (including those under One Health Approach) 5. Disease surveillance systems that can be adapted / modified for AMR surveillance include DHIS and FELTP programs 6. Established research and academic base at institutions like NIH, PMRC, PARC, Academia can contribute towards system development	1. No AMR related central coordinating body /unit/cell/ data centre 2. Partial diagnostic infrastructure available 3. Weak microbiology lab system with variable standardized system for DST 4. Lack of resources for performing DST 5. Limited EQA for labs 6. Cultures / DST are not uniformly requested for diagnosing infection due to lack of diagnostic guidelines 7. Institutions reluctant to share AMR data 8. Limited AMR related diagnostic stewardship 9. Lack of federal & provincial labs that can serve as reference labs for AMR 10. Inadequate AMR surveillance infrastructure 11. Lack of lobbyist for AMR surveillance & research 12. Limited awareness /education / training regarding AMR surveillance 13. Lack of AMR research training / programs 14. Weak political will and motivation

Opportunities	Threats
1. Willingness at different levels (national & international & donors) exist for AMR surveillance including One Health Approach concept 2. National Lab Strategic Framework has been developed 3. Interest in lab strengthening at national level by government 4. Provincial health regulatory authorities (KPK, Punjab) and Sindh Health Care Commissions are in place 5. IHR related provisions, programs and Global demands for food safety can be utilized for strengthening surveillance system 6. Available labs can be upgraded to do DST through public private partnership models 7. DHIS/MIS can be modified for AMR surveillance in provinces 8. Several Academic Research units for AMR research are available for high level research 9. WHO guidelines for surveillance under GLASS protocol available and can be adopted 10. Initial assessment for setting up sentinel surveillance for AMR in Pakistan using GLASS protocol conducted by WHO	1. Vested interests of professionals, Pharmaceutical, veterinary and agriculture industry may influence AMR surveillance system 2. Conflict of interest in antimicrobial prescription 3. Pressure to conceal information in some situations 4. Lack of sustainable resources for doing surveillance, which should be provided by the public sector rather than by donors 5. New extreme resistance may create panic 6. Inadequate bio-risk management in surveillance network labs 7. High cost for existing and new diagnostics

Objective 3: Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures

Strengths	Weaknesses
IPC 1. Awareness among health care professionals in some settings 2. Expertise available within country 3. Media support to communicate at mass level **Hygiene and sanitation** 1. Religious and social beliefs 2. Existing sanitation in urban areas in some cities 3. Awareness through media 4. Know-how about Bio-remediation of waste water available at some institutions (NARC, QAU etc.) **Vaccination** 1. Awareness among general public 2. Availability / support to masses 3. Parental intent 4. Fear of infections 5. Manufacturing facilities available at some institutions **National standards for IPC** 1. Expertise available **Sustainable animal husbandry practices** 1. Veterinary Hospitals Network existing at provincial level and some coordination with national institutions 2. Awareness in professionals 3. Trained manpower available 4. Vaccines available and routine vaccination is carried out in some parts of the country **Public health** 1. National Institute of Health (NIH) may play a role at National level 2. Availability of trained manpower through Master degree program at some academic institutions and other training programs like FELTP (NIH) 3. Willingness and on-going campaigns by majority of the stakeholders	**IPC** 1. No institutional, Provincial, National IPC policies / programs 2. No waste management Strategic Framework Implementation 3. Non-availability of accountability / audit systems 4. Shortage of trained IPC professionals/ PPE 5. Negative attitude / behaviour towards IPC and prevention 6. Weak political will 7. Lack of dedicated funds 8. Lack of vaccination of HCW in most hospitals 9. No positions in health care facilities for IPC Staff 10. Lack of HCW, PPE & Safety eqipments. 11. Lack of decontamination, disinfection sterilization facilities in most regions **Hygiene and sanitation** 1. Weak sanitation systems 2. Untreated dumping of contaminated water 3. Poor awareness of personal and food hygiene 4. Limited funding **Vaccination** 1. Inadequate transportation facilities 2. Inadequate local manufacturing 3. Vaccination records and ledgers poorly maintained

Strengths	Weaknesses
	National standards for IPC 1. Inadequate and weak IPC programs 2. No National Policy on IPC 3. No proper training programs 4. No allocated and dedicated funds 5. No system of surveillance for epidemiology of microbes **Sustainable animal husbandry practices** 1. Unhygienic practices 2. Financial constraints 3. Weak implementation of existing national livestock policies 4. Quality of vaccines is not according to international standards and supply of vaccines is irregular 5. Low vaccination coverage 6. Lack of proper surveillance and monitoring systems for animal communicable diseases and zoonosis **Public health** 1. One Health Approach integration at federal and provincial levels is poor 2. Weak public health system due to improper public health legislation

Opportunities	Threats
IPC 1. Availability of guidelines at international level 2. Availability of donors to support IPC 3. Availability of materials / PPE for IPC **Hygiene and sanitation** 1. Support from donors available in public health sector **Vaccination/Immunizations** 1. International donors support available 2. Requirement at international level under Global Health Security Agenda (GHSA) **National standards for IPC** 1. International guidance can be availed through WHO or other organizations 2. Engagement of NGOs **Sustainable animal husbandry practices** 1. Evidence based research can help in improving practices 2. Public / private partnership in Research & Development 3. Capacity building on existing resources **Public health** 1. Support of Donors and international sources 2. Governmental requisites	**IPC** 1. Misuse of funds and wrong re-direction of funds 2. Lack of local production of IPC-supplies **Hygiene and sanitation** 1. Misuse of funds and resources 2. Poor infrastructure **Vaccination** 1. Terrorists attacks on vaccination of workers, especially polio teams and fear among HCWs to work in difficult areas 2. Mind set in certain groups opposing vaccination 3. Lack of most of the Vaaccines production **National and International standards for IPC** 1. Misuse of funds 2. Implementing, Guideline without local adaptation **Sustainable animal husbandry practices** 1. Large number of Quacks 2. Irrational use of antimicrobials as therapeutics, prophylaxis and growth promoters **Public health** 1. Outbreaks can occur and cause panic

Objective 4: Optimize the use of antimicrobial medicines in human and animal health

Strengths	Weaknesses
1. DRAP published guidelines with defined PMRC criteria for voluntary ethical marketing code 2. DRAP activities related to regulation and quality management improved in past 3 years 3. Some poultry farms have established labs and practicing culture based antibiotic use 4. Development of the One Health Approach forum/network on the National and Provisional level 5. Research and Development and production of veterinary vaccines within Pakistan 6. Increase in number of trained ID physicians and microbiologists in last 5-6 years 7. ASP in some hospitals showing benefit in prudent use of antibiotics	1. Large number of unregistered medical and veterinary practitioners 2. Weak training and poor practices in healthcare provider (HCP) 3. Unethical incentives to doctors from drug industry 4. Laboratory methodology not uniform 5. Community certified pharmacies are insufficient in number and run by un-trained personnel 6. Easy accessibility to over-the-counter antibiotics 7. Overuse of antibiotics in veterinary use responsible for drug resistance in human 8. Farmers self-prescribing antibiotics as growth enhancers 9. Lack of efforts to introduce antibiotics replacement products as growth promoters in animals

Opportunities	Threats
1. Inclusion of certified infectious diseases specialists in the DRAP Advisory Committee for essential drugs 2. List of drugs that are to be dispensed only on prescription by Registered Medical Practitioner to include antimicrobials 3. Standardized prescriptions bearing physician's name, address, telephone # and PMDC & PVMC registration number 4. Specific syndrome- related messages for health care providers, e.g. URTI, AGE, UTI 5. Discourage production of irrational antibiotic combinations in human and veterinary practices 6. Media campaign for general public explaining the problems associated with antibiotic use 7. Strengthening and upgrading of community pharmacies 8. Optimal harmonization of diagnostic kits and microbiology lab procedures 9. Remove obsolete tests like typhoid and TB serology 10. Learning modules/programs for HCPs and farmers 11. Certification program and incentives for institutions and individuals embarking on ASP 12. Certification of antibiotic- free poultry, meat and milk products 13. PVMC and/or FAO guidelines to be implemented through the Ministry of National Food Security and Research (MNFS&R) 14. Education of farmers for judicious antimicrobial use in livestock and poultry 15. Drug sale rules should be implemented in letter and spirit to check injudicious use of antibiotics 16. Un-registered medical practitioners should be given training in performing safe procedures where such qualified persons are not available	1. Enforcement / implementation of over the counter drug list of antibiotics will not be easily accepted by community pharmacists 2. Lack of infrastructure to implement an electronic record of antibiotic prescription 3. Lack of current human resources for building an ASP (trained ID specialist, microbiologist, IPC nurse, pharmacist) in most hospitals 4. Financial support for ASP is unlikely at this time 5. Lack of general health infrastructure in the country 6. Resistance from the farmers as lack of replacement of antibiotics as growth promoters 7. Drug companies may resist wide-spread implementation

Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

Strengths	Weaknesses
1. Availability of vaccine development in public and private sector in veterinary sector Veterinary research Institutes (VRI) in all provinces and NARC. 2. Availability of lab for drug residue testing in food of animal source (National Veterinary Laboratory (NVL) 3. Availability of provincial vaccine production e.g. Sindh Poultry Vaccine Production. 4. Availability of skilled personnel in diagnosis and vaccine production. 5. Reports of several new antimicrobials under research in Pakistan 6. Availability of strong research system in agriculture including plant and animal health coordinated by PARC throughout out the country. 7. Availability of funds through academia interest linkage programmes (e.g. through HEC) 8. Availability of Patent filing and intellectual property rights organization	1. Lack of evidence based research for proper intervention and therapeutics 2. Personnel available for diagnosis and vaccine are not well trained 3. No organization to regulate import of diagnostic kits/equipment according to WHO recommendation 4. Lack of data for financial impact of infectious diseases (e.g. DALYS) 5. No state of the art reference lab and weak microbiological support for diagnosis of infectious disease 1. Lack of interprovincial and interdepartmental harmony, collaboration and coordination 6. Lack of sustainability of diagnostic or treatment strategy due to ad-hoc solutions 7. No national proficiency scheme for standardized AMR testing in public and animal health sectors

Opportunities	Threats
1. International interest to develop regional and international linkages for AMR research 2. Need to develop AMR reference lab with research facilities 3. National need to develop cost effective drug designing and prescribing algorithms for containment of AMR and for development of new antimicrobials	1. Massive negative economic impact of the country 2. Some stakeholders can create hurdles 3. Weakness of political will 4. Imported antimicrobials and diagnostic kits do not fulfil the local requirements 5. Insufficient investment in Research & Development by local pharmaceutical industry

Annexure 5:

Checklist-National Action Plan Development support tools

The following WHO checklist1 was used by participants at the 2nd Workshop on **"National Strategic Framework for Containment of Antimicrobial Resistance"** on 28-29th April 2016 to assist with the development of our national action plan on AMR and reviewing any existing activities. Please note that we went to part 5 of the WHO checklist, as there was no existing National Strategic Framework.

Objectives of Checklist Tool

To assist with the development of our national action plan on AMR and reviewing any existing activities.

Governance and multi-sectoral "One Health Approach" coordination

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
Step 1:There is national coordination on activities in the country among AMR focal points, with defined roles and responsibilities	1. Formation of a national multi-sectoral coordinating group (NMCG) or ICC 2. Facilitate and coordinate development of the national AMR action plan through the ICC.	1. Facilitate and oversee implementation, monitoring and evaluation of the AMR action plan through the ICC. 2. Ensure regular data collection and information-sharing among all relevant sectors and stakeholders	1. Political commitment is weak due to lack of awareness 2. Shortage of Human Resource is a major issue 3. Uniform standard Guidelines in both Health sector and Veterinary Microbiology for drug susceptibility not available 4. Provinces need to develop coordinating centres / units for all labs including academia and to allot resources for this purpose. 5. Participation from Provinces will be major challenge and so there is need to keep them on board.	Implementation, monitoring and evaluation of AMR action plan will be done by the relevant authorities (Federal/ provincial/ local) after approval of the Strategic Framework.
Step 2: A national multi-sectoral coordinating group (NMCG) or ICC is established.	1. The ICC is supported by technical experts.	7. The ICC has strong political support, has authority to act, is accountable to the government, has dedicated funds and has a secretariat.	1. Not in provinces from all relevant sectors 2. Academia, economist, health education, legal & communication need to be included as well. 3. AMR may not be a priority unless the gravity of the situation is advocated vociferously to the political decision makers 4. Appropriate and sustainable funds would need to be made available.	Political backing is major prerequisite for AMR-related decisions that will need be quick and bold.

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
Step 3: ICC ensures ownership of activities in multiple sectors and considers the perspectives of the following bodies and institutes at national and sub-national levels	1. Main relevant Ministries are involved 2. Regulatory authorities are involved	The following have to be engaged 1. Public agencies 2. Laboratories 3. Universities, academic, and research institutions 4. Private sector 5. Civil society 6. NGOs, electronic & print media	1. National & Provincial legislation may need to be made and so appropriate expertise in planning and devising legal aspects related to AMR may be a hurdle 2. Lack of funds, resources will be huge for some of the activities mentioned here 3. Approach and engage of professional societies who are major prescribers of antibiotics is a must 4. Advocacy still weak but expected to be boosted as AMR is given top health priority 5. Training system or CME activities will also needs to be made available and mandatory which some professional bodies can disapprove	Establishment of National Reference lab for AMR is in process.
Step 4: Technical working groups are created as needed. Members may represent the following areas	1. Human health 2. Animal health, welfare, and production including fisheries 3. Technical disciplines	1. Food safety and security, including food production and processing 2. Agriculture 3. Environment, including water and sewage and waste management 4. Academia and R & D	1. Insufficient expertise is a major negative aspect for a country like Pakistan but then training and supervising may be an answer. 2. Technical working groups are already spelled but may need expansion to include individuals and also other key stakeholders who are left out (EPA, Academia, etc.) 3. Time and commitment from these members will be a challenge as this can be a very exhaustive process.	

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
Step 5: Guidance, tools, data and case studies are available to form a basis for preparation of a national action plan on AMR.	1. Stakeholder mapping and analysis 2. Review of existing tools and projects and guidelines 3. Situational analyses 4. Gap analysis and needs assessment 5. Determining strategic priorities, objectives, interventions, activities	1. Drafting key documents 2. Validation of key documents 3. Implementation, monitoring and evaluation	4. General Practitioners are one of major stakeholders and can be addressed through associations like PMA, Pakistan Paediatric Association and other institutions/organizations like CPSP, HEC, PMDC for CME activities. PPA, PVMC, PVMA, PPMA, Pharma Bureau of Statistics, academia & research organizations, Health care commissions (KPK, Punjab, Sind), and Drug Regulatory Authority (DRAP) can also play a role. 5. Other possible stakeholder include Quacks, Homeopaths & Hakims 6. Veterinary and academia data not available, though some data is available from research publications 7. Data can be obtained from Provincial Secretaries of the departments and DCOs.Data from Homeopathy and Unani Councils etc. can also be obtained 8. NARC, Private poultry labs, VRI, Poultry, Livestock, Fisheries may need to provide relevant AMR data	

GAP Strategic Objective 1. Improving awareness and understanding of antimicrobial resistance through effective communication, education and training

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
A. Activities to increase national awareness of AMR are planned	1. Main relevant Ministries 2. Regulatory authorities	1. Public communication programmes targeting audiences in human health practice, animal health practice, plant production and crops, along the food chain and in the environmental sector. 2. Country participates in an annual world or regional AMR awareness campaign	1. National AMR week, Hand hygiene day in line with global/regional notification 2. Previous publicity / advocacy campaigns (TB, Polio, Hepatitis, Dengue) can be assessed for future planning	
B. AMR and related topics are core (mandatory) components of education, training, and development in Human and animal health, Plant production, Food chain and Environment		1. AMR and related topics included in undergraduate curricula, continuing education programmes, quality assurance programmes and education/training provided outside formal academic settings	1. Mandatory training of relevant staff in all food tested for drug residues. 2. Deceptive marketing legislation should be in place. 3. HEC to design and implement AMR related educational / training activities including development of curricula in all related fields as part of Global Health Agenda (health, animal & food security).	
C. Education and information on AMR provided to the general public.		1. Include antimicrobial use and resistance in school curricula. 2. Provide accurate, relevant information on AMR to public.	1. Hygiene standards including infection prevention and hygiene to furnish recommendations by educationists.	

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
D. AMR is recognized as a national priority.		1. Use effective mechanisms to ensure inter-ministerial collaboration and commitment. 2. Promote and support establishment of public-private, multi-sectoral ("One Health Approach") coalitions to address AMR at local and national level. 3. Promote and support participation in public-private, multi-sectoral ("One Health Approach") coalitions to address AMR at regional and global level.	1. Advocacy to a political leadership may be difficult as priority for them maybe different unless efficient and effective ways are used to attract their attention.	

GAP Strategic Objective 2. Strengthen the knowledge and evidence base through surveillance and research.

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
A. National AMR surveillance and use monitoring systems exist or are planned, comprising:		1. Surveillance of AMR in isolates from humans, animals, food, plants and the environment. 2. Monitoring of use of antimicrobial agents in humans, animals and plants. 3. Special studies to provide information not covered by routine surveillance to provide supplementary information.	1. Ministry of commerce (Trade Development Authority of Pakistan) can provide information regarding antimicrobial consumption in the country. 2. Un-organized studies or some may lack standards to be of any value.	

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
B. Data on the extent and impact of AMR are available		1. Incidence and prevalence of AMR in humans, animals, plants, food, and environment. 2. Human morbidity, mortality and other health outcomes in relation to AMR. 3. Data on economic impact of AMR in humans, animals, plants, food, and the environment.	1. Large-scale specific AMR data generation is a challenge but surveys and point prevalence data may be more feasible. 2. Economic expert and epidemiologist can help to generate this kind of data.	
C. A national AMR surveillance and antimicrobial use (AMU) report (within the past 5 years) publicly available, including		1. AMR in isolates from humans, animals, plants, food and the environment. 2. Antimicrobial use in humans, animals and plants.	1. Purposeful collection of antimicrobial use data has not been done. 2. Linkages between different health sectors are weak and will need to be established for long-term purpose.	
D. A national mechanism coordinates the different national AMR surveillance and antimicrobial use (AMU) monitoring systems		1. Defines the objectives of the national surveillance systems based on intergovernmental standards 2. Reviews and coordinates dissemination of existing national AMR surveillance and AMU monitoring protocols 3. Coordinates AMR data collection, analysis, reporting and sharing across the human health, animal health, food, plant and environmental sectors 4. Monitors data on the use of antimicrobial agents in humans, animals, and plants, and continuously evaluates the national surveillance systems 5. Links and coordinates AMR surveillance in the human health, animal health, plant, food, and environment sectors	1. Regular sustainable interaction between stakeholders is recommended which will be a major challenge. 2. Coordination between the many related sectors will have to be much more robust and structured.	

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
A. **One or more national reference laboratories have been nominated for surveillance of AMR, to**		1. Accurately confirm diagnoses 2. Develop, maintain and share relevant reference material 3. Serve as a resource and coordination point for expertise and for sharing information and advice with relevant stakeholders 4. Engage in collaboration and research 5. Provide guidance and technical support for the management of quality, including participation in external quality assurance schemes 6. Liaise with the national AMR coordinating mechanism	1. Establishing reference lab at NIH supported technically by AFIP, AKU, Shifa, other private and public institutions and related experts from both human and animal health and others including academia.	
B. **A national research agenda implemented, including**		1. Social science and behavioural studies and other research to support achievement of the global objectives 2. Research to develop new treatments, diagnostic tools, vaccines and other interventions in humans, animal, and plants related to infectious diseases 3. Research to identify alternatives to non-therapeutic uses of antimicrobial agents in animals and plants 4. Economic research	1. Only some research on these specific aspects is currently being done but potential is much more. 2. Engaging experts and relevant fields and initiating some major AMR related research activities may be hurdle	

GAP Strategic Objective 3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures.

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
A. Infection prevention and control (IPC) programmes introduced across the spectrum of human health settings, including		1. A national program for IPC in health care 2. IPC programmes in hospitals, long-term care and outpatient and community health settings and congregate settings	1. Current lack of specific personnel related to IPC and sustained funding for such IPC activities may become an issue. 2. Some models currently being practiced in private setups may need to be adopted and modified for public settings.	
B. Intergovernmental standards and guidelines related to infection prevention and control implemen		1. The animal health sector, plant sector, food sector and environment sector	2. Engaging all sectors may be a big challenge. 3. Political willingness to initiate such guidelines is weak.	
C. The infection prevention and control (IPC) programmes for human health adapted to local conditions and include the following essential (core) components:		1. A formal organizational structure to facilitate proper development and management of IPC policies and strategies 2. IPC guidelines and policies 3. Training of health care providers in the principles and practice of IPC 4. Appropriate environment for application of IPC principles and practices 5. Laboratory and diagnostic support for prescribing antimicrobial agents and accurate, timely detection of infections caused by resistant pathogens 6. Surveillance systems 7. Monitoring and evaluation framework to monitor implementation and enable timely adaptation of IPC strategies 8. Links with public health, other services and societal bodies to facilitate communication	1. A major challenge will be how to sustain funding and ensure availability of relevant expertise on a large scale. 2. Data management may pose potential problem. 3. Training of health care providers in IPC done by PMRC, PHRC, MMIDSP and other associations in some forms.	

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
D. Training and education in hygiene and IPC are core (mandatory) components of education, training, and development in Human		1. Hygiene and IPC included in undergraduate curricula, CMEs, education/ training provided outside formal academic settings	1. Although mostly core components of IPC are available but national and formal systems still are lacking. 2. Making Mandatory components may not be possible or applicable.	
E. Hygiene and infection prevention and control (IPC) measures are planned outside health settings		1. Promotion of personal hygiene by social mobilization and behavioural change activities at home, at work and in social settings 2. Prevention of infections in humans transmitted through sex or drug injection 3. Provision of safe, sufficient drinking-water and adequate sanitation 4. Strengthening of vaccination programmes to reduce the burden of infectious diseases 5. Promotion of good hygiene practices along the food chain 6. Good practices in place in animal health, welfare and production including vaccination, the plant production and the environment sector	7. Key role will be from Governments and political leadership. 8. Key sectors may not be ready to implement some of the policies yet for various reasons.	

GAP Strategic Objective 4. Optimize the use of antimicrobial agents in human and animal health

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
A. Effective, enforceable regulation and governance are planned for licensing, distribution, and quality assurance of antimicrobial agents in human, animals, and plants	1. There is a national human drug regulatory authority and national animal drug regulatory authority 2. Marketing authorization is given following international standards and guidelines to ensure that antimicrobial agents are quality assured, safe and effective 3. Mechanisms or requirements are in place for detecting and combating counterfeit antimicrobial agents 4. Promotional practices by industry are regulated and controlled	1. There are regulations in place for antimicrobial agents used in the plant sector 2. There is a quality management system for the antimicrobial agents supply chain 3. There is a regulatory framework for preservation of new antimicrobial agents 4. Economic incentives that encourage inappropriate use of antimicrobial agents are being identified and addressed in all sectors. 5. Economic incentives to optimize use of antimicrobial agents are being introduced in all sectors	1. Legislation may be problematic as consensus building difficult or too long. 2. Implementation is not uniform in quality management system for the antimicrobial agents supply chain. 3. Data generation through voluntary code for ethical processes for the drug companies and code of Medical ethics may be way forward.	Smuggled drugs: Customs department and Border security forces are responsible

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
B. Purchasing and prescribing of antimicrobial agents guided and supported by	1. A national essential medicine list 2. Institutional essential medicine lists	1. Reimbursement lists for human health 2. National Health Insurance approved recently 3. Standard treatment guidelines for use of antimicrobial agents in humans, animals and plants 4. Medical or veterinary supervision. 5. Standard treatment recommendations are developed for animals and plants 6. Policies that promote the prudent and responsible use of antimicrobial agents based on existing intergovernmental standards and guidelines	1. Relevant expertise are either not available, unknown or not on board for major decisions that have far reaching implications for manufacturing, registration and licensing or distribution of antimicrobials.	
C. Policies on use of antimicrobial agents in animals and plants prepared, including		1. Policies on the use of critically important antimicrobials 2. Policies on phasing out use of antimicrobials for animal growth promotion and crop protection in the absence of risk analyses 3. Policies on reduction in non-therapeutic use of antimicrobial agents in animal health	1. Major sectors have to commit to adhere to international standards and this maybe a difficult target.	

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
D. Antimicrobial stewardship programmes set up for human health at national and local levels, including		1. A formal multidisciplinary organizational structure responsible for antimicrobial stewardship 2. Qualified human resources. 3. Facility/specialty-specific treatment recommendations/guidelines 4. Review of appropriateness of antimicrobial agents 48–72 h after administration 5. Direct communication of the results of audits and reviews to all sectors using antimicrobial agents	1. Antimicrobial stewardship is a new concept in Pakistan and adapting locally may be possible but community practices are difficult to change. 2. National computerized database for prescribing of antimicrobials is a challenge.	

GAP Strategic Objective 5. Develop the economic case for sustainable investment to take into account the requirements of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

WHO's AMR Steps	Steps or measures taken	Steps in process or not done	Gaps and challenges	General comments
A. An economic case for sustainable investment in new medicines, diagnostic tools, vaccines and other preventions and/or interventions prepared.		1. The investment required for implementation of the national action plan has been assessed, and plans to secure and use the required financing have been prepared 2. Participation in international collaboration, based on fair and equitable benefit-sharing as mutually agreed, in the investigation of natural sources of biodiversity and bio-repositories as sources of new antimicrobial agents 3. Strengthening existing and creating new public–private partnerships for encouraging research and developing new antimicrobial agents, vaccines and diagnostics 4. Pilot testing of innovative ideas for financing research and development and for new market models to encourage investment and ensure access to new antimicrobial products	1. Current healthcare even lacks basics such as in availability of medicines; vaccines or diagnostics and introducing something new will be a hurdle in many ways.	

1. WHO (February 2016). Antimicrobial resistance: A manual for developing national action plans. Available at http://www.who.int/drugresistance/action-plans/sample-checklist.pdf

Annexure 6:

Provincial Health Structure and Roll out Plan

As AMR Strategic Framework has to be implemented by Provincial Health Authorities it is important that the AMR development process include stakeholders from all provinces and regions of Pakistan, including both human and animal health. The provincial health structure has to be taken in account when policies are amended for strategizing and implementing of **"National Strategic Framework for Containment of Antimicrobial Resistance".** Visits to provincial capitals were made with introduction and input sought about AMR Strategic Framework from Provincial Stakeholders (DG Offices, microbiologists and clinicians).The following were some of the recommendations made by provincial health authorities for rolling out the provincial plans under the AMR Strategic Framework.

- Legislation for antibiotic misuse. Presently such legislation does not exist in any province.
- Coordination Body between Health, Livestock and Agriculture Department for One Health Approach needs to be established.
- Improve awareness through AMR related education and training in healthcare settings, especially hospitals, and veterinary settings.
- Establishment of active IPC Teams, and to ensure hygiene/sanitation standards.
- Hospital waste management should be mandatory.
- Establishment of surveillance and research in each province at tertiary care and large hospitals (divisional / district level).
- Full support and funding for establishing and facilitating quality microbiology labs at tertiary care and Divisional /District Headquarter Hospitals.
- Promote public-private partnerships.
- Regulating pharmacies/drug store and clinical labs.
- Discouraging OTC sale and self-medication with antibiotics.
- Ensuring availability of clinical pharmacists at tertiary care / large hospitals.

The Strategic Framework document shall be shared with all the provincial and territories health departments for approval and adapting in their respective provinces based on their priorities. The Strategic Framework statements in this document are generic and may be customized to the local needs if required.

Annexure 7:

AMR Surveys

As part of assessment process the following two surveys were also done and included here:

1. Private hospitals in Pakistan have better facilities for patients seeking better care compared to public hospitals in some aspects. This survey was done from representatives, mostly microbiologists, of five major private hospitals from different cities of Pakistan. As Table 1 shows most AMR related activities were being done with some gaps such as human resources but much better than public hospitals.

Table 1. AMR and MDROs related Survey of 5 major Private Hospitals in Pakistan*#

Total beds capacity	2,540
Automated laboratory systems in healthcare facility	2/5
Computerized Physician Order Entry	5/5
Electronic Medical Records	5/5
Automated Electronic Surveillance System	0/5
Antimicrobial stewardship / management/restriction program	5/5
Antibiotic Policy	3/5
Infectious Diseases Physician	18/5
Clinical Pharmacist	22/5
Clinical Microbiologist	16/5
Hospital Epidemiologist	2/5
Information System Specialist	2/5
Targeted Antimicrobial Stewardship Activities	3/5
Administrative Controls a. Committee exists that looks at antibiotic usage b. A formulary is in place c. Regular process of formulary review d. Committee has established goals e. IPC Policy	4/5 5/5 3/5 0/5 5/5
Number of dedicated Isolation beds	123
Number of dedicated IPC nurses	19
Microbiology Lab technicians	100
IPC Policy	5/5
Total cultures received by lab / day	1030
Approximate MDROs isolated in Microbiology labs# a. MRSA b. VRE c. Carbapenem Resistant Klebsiella d. MDR Acinetobacter spp. e. Colistin resistant Klebsiella	5-69% 7-25% 10-45% 20-97% 0-1%
Infection Prevention and Control Activities Done	5/5

**Positive or yes answer*

#More than one response given

* (ShaukatKhanum 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)
#(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)

2. A survey of 25 participants of the AMR workshop in April 2016 was done. Participants were asked about most important suggestions for AMR containment. Many suggestions were given but most suggested regulation and ban on OTC antibiotics (8/25, 32%),need for national surveillance for AMR and other data (4/25, 16%) and multi-sectoral collaboration (3/25, 12%).

3. An ongoing antibiotic stewardship activity "Antibiotic Stewardship Initiative in Pakistan (ASIP)" by Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) also carried a survey about ASP from 757 GPs and paediatricians and other clinicians over 9 months (September 2015-May 2016). Among these 392 GPs and paediatricians (51.8%) returned the survey forms. The results are shared here to depict the response from these healthcare providers (Table 2). These results show that almost all professionals wanted to continue with such CMEs and felt benefitted. The major suggestions for combating AMR included regular widespread ASP activities, awareness campaigns about dangers of antibiotics, a national and local antibiotic Strategic Framework with regulation and ban on OTC, a comprehensive national action plan with implementation and legislation and CMEs for professionals (Table 2).

Table 2. Survey of opinion on ASP related educational activities and suggested measures to combat antibiotic misuse and AMR in Pakistan from 392 General Practitioners and Paediatricians

Positive responses about ASP activity (N=392)	**N (%)***
Did you find ASP seminar useful	387 (98.7)
Will it change your practice and approach to patient care	360 (91.8)
Will you now prescribe antibiotics more carefully for your patients	375 (95.7)
Should more ASP seminar be held in future and in other hospitals/cities	367 (93.6)
No Response	5 (1.3)
Suggestions to combat misuse of antibiotics and AMR (N=382)#	
Antibiotic Stewardships in hospitals and community	72 (18.8)
Awareness campaigns about dangers of antibiotics to GPs and community	64 (16.8)
A National and local antibiotic Strategic Framework with regulation and ban on OTC	50 (13)
Comprehensive NAP with implementation and legislation	40 (10.5)
CMEs for professionals	38 (9.9)
Take appropriate history, examination and diagnostic tests before prescribing antibiotics	34 (8.9)
Use of specific Guidelines for infectious diseases	29 (7.6)
Use media/societies for awareness	18 (4.7)
Counselling of patient about antibiotics	15 (3.9)
National surveillance and strengthening of Microbiology labs for AMR	7 (1.8)
Ban unethical practices among physicians	7 (1.8)
Others	8 (2.1)
No suggestions given	95 (24.5)

*Positive or yes answer

#More than one response given

Annexure 8:

List of participants in workshops

Dr Bashir Choudhry	Director Health Services, DHS (CDC), DSH Office, Muzaffarabad
Dr Muhammad Zakria	Principal Scientific Officer, CDRI, DPEP, NARC, Islamabad
Prof Ghulam Sarwar Pirkani	Head of Microbiology, Bolan Medical Complex Hospital, Quetta
Prof Aamer Ikram	Microbiologist AFIP, National Laboratory Working Group, Rawalpindi
Prof Asim Beg	Clinical Parasitologist, Agha Khan University Karachi
Brig Dr Gohar Zaman	Head of Microbiology, AFIP, Rawalpindi
Dr Zulfiqar Baloch	Director Health Services, Health Directorate, Quetta
Dr SabiraTahseen	Tech Advisor, (Lab), National TB Program, Islamabad
Dr Faisal Sultan	Infectious Disease Consultant & CEO, Shaukat Khanum Hospital, Lahore
Dr Muhammad Usman	Microbiologist, Shifa International Hospital, Islamabad
Dr Muhammad Afzal	Project Coordinator, FAO Pakistan, NARC Building, Islamabad
Dr Ihsan Ullah Khan	Epidemiologist, Directorate General, Islamabad
Prof Ejaz A Khan	Infectious Disease Consultant, Shifa International Hospital, Islamabad
Col Irfan Ali Mirza	Consultant Microbiologist & Associate Prof, PNS Shifa, Karachi
Dr Ali Ahmed Sheikh	Assistant Professor, Univ. of Veterinary & Animal Science, Lahore
Dr Saleem Memon	Program Director CDD, DG HSS, Karachi
Dr Shahid Rafiq	Member, ASD, PARC, G-5/1, Islamabad
Dr M Athar Abbas	Senior Scientific Officer NRLPD, Veterinary Microbiologist, Animal Sciences, NARC, Islamabad
Dr Naseem Salahuddin	Infectious Disease Consultant, The Indus Hospital, Karachi
Dr Muzaffer Ali	Project Director, Directorate of Animal Breading Sindh, Hyderabad

Umar Zia	Pharmacist, Shaukat Khanum Hospital, Lahore
Dr Altaf Ahmed	MMIDSP Rep, Microbiologist, The Indus Hospital, Karachi
Col Nasrullah Malik	Microbiologist, Shaukat Khanum Memorial Hospital Lahore
Dr Ahmed Mahmood Mumtaz	DDG Pharmacovigilance, DRAP, Islamabad
Dr Farnaz Malik	ED / NIH, Islamabad
Dr Huma Qureshi	ED, PMRC, Islamabad
Dr K Naeem Khawaja	Consultant Microbiologist, Islamabad
Dr Zahida Fatima	Deputy Director PARC, Veterinary Epidemiologist, Animal Sciences Division, PARC, Islamabad
Dr Aman Ullah	AHD, NARC, PARC, Veterinary Epidemiologist, Islamabad
Dr Sheikh Ansar	Director Pharmacy, Division of Pharmacy, DRAP
Dr Ahmed Din Ansari	DDC (PS), DRAP, Islamabad
Dr Rani Faryal	Associate Professor, Department of Microbiology, Quaid-i-Azam University, Islamabad
Dr Mumtaz Ahmed	Microbiologist, AIMS, Muzaffarabad
Dr M Arshad	President, PMA House, Rawalpindi
Fouzia Mushtaq	Acting Registrar, Pakistan Nursing Council, Islamabad
Dr Afia Zafar	Microbiologist. Agha Khan University Karachi
Dr. Faisal Mahmood	Infectious Disease Consultant. Agha Khan University, Karachi
Dr. Anisa Afridi	Deputy Director, FATA Health Secretariat, Peshawar
Dr Najma Javed	SMO, PMRC, Islamabad
Dr Fazle Bari	Associate Prof, Microbiology, Lady Reading Hospital, Peshawar

Dr Aamir bin Zahur	Veterinary Microbiologist NARC, Islamabad
Dr Zaka Ullah	PMA House, Rawalpindi
Dr Bashir Ahmad	Secretary General, PPA, Islamabad
Prof Rumina Hassan	Microbiologist, Aga Khan University Karachi
Dr Muhammad Salman	Focal Person, AMR, NHSRC, NIH, Islamabad
Dr Faiza Bashir	MO, PMRC, Islamabad
Dr Arsalan Ahmad	MO, PMRC, Islamabad
Dr Mohsin Ahmad	HEO/LHW Program, Health Department, KP, Peshawar
Prof Saleem Ullah	Professor of Medicine, Karachi Medical and Dental Collage, Karachi
Dr Shahad Hussain	Acting Chief, DCDID, NIH, Islamabad
Dr Naveed	NHR&C, Islamabad
Pro Aamir Ali Khan	Department of Pathology, Multan
Dr S Jamal Akbar	ADPH/DOHKP, Islamabad
Dr Muhammad Nazeem	Director Health, Gilgit Baltistan
Dr Rabaab Zahra	Associate Professor, Quaid-i-Azam University, Islamabad
Dr Rehana Anjum	SSO, National Veterinary Laboratories, Islamabad
Dr M Fatah Ullah Khan	Senior Director, National Veterinary Laboratories, Islamabad
Dr Sumera Abid	Research Officer, PHRC Head Office, Islamabad
Dr Hajira Gul	Assistant Registrar PNC, Islamabad
Dr Tayyab Razi	Senior Officer, NIH, Islamabad
Dr Mumtaz Ali Khan	MO FE & DSD, NIH, Islamabad

Ministry of National Health Services, Regulations & Coordination,
Government of Pakistan
LG&RD Complex, G/5-2, Islamabad. Tel: 051 9245933
Website: www.nhsrc.gov.pk