AMR-POLICY BRIEF

UNIVERSITY OF VETERINARY AND ANIMAL SCIENCES LAHORE

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Preventing antimicrobial resistance together

ANTIMICROBIAL RESISTANCE (AMR): CURRENT STATUS AND FUTURE ROAD MAP FOR PAKISTAN

Policy Message

- Quadripartite platform (WHO, FAO, WOAH and UNEP) has declared AMR as one of the top global threats to human and animal health and ecosystems.
- Combating AMR is pivotal to reduce resistant-pathogen-associated morbidity and mortality in humans and animals.
- Identification of the important gaps is necessary to establish an integrated national AMR control program.
- Multisectoral collaboration is direly needed to prevent the spread of resistant micro-organisms and to promote the infection control programs.
- There is a need to highlight this emerging health problem at all levels through print and electronic media.

Antimicrobial resistance (AMR) is one of the most important emerging problems worldwide. Irrational use of antimicrobials in medical and veterinary practice, and improper disposal of antimicrobial drugs have led to the development of AMR posing a serious threat to human, animal, and environmental health. Antimicrobial resistance is not merely a biological or a medical problem, instead, it is equally a social as well as an economic plight as the sustainable development goals are unlikely to be achieved without the containment of AMR. Efficient containment of AMR can benefit the community by reducing the burden of resistant infectious organisms and ultimately preventing the spread of infectious diseases.

Antimicrobial Resistance and its public health significance

Antimicrobials (including antibiotics, antivirals, antifungals, and antiparasitics) are medicines used to prevent and treat infections in humans, animals and plants. Antimicrobial resistance develops when microorganisms change over time, and make infections difficult or impossible to treat and results in increased risk of disease spread, severe illness and death. The main drivers involve in development of AMR are irrational usage including under dosage and treatment for a short duration, availability of antimicrobial drugs over the counter, wrong methods for drug disposal, pharmaceutical waste material in the environment, antibiotic residues in the food, and lack of preventive measures and infection control.

The emergence and rapid spread of drug-resistant pathogens have reduced the efficacy of antimicrobial therapies leading to increased morbidity and mortality. The outbreak of extensively drug resistant (XDR) bacterium *Salmonella* Typhi in Pakistan is the perfect depiction of changes and resistance development in microorganism over time (from multi-drug resistant (MDR) serovar to XDR serovar).

Featured case studies

Below are some successful initiatives for controlling AMR taken by the developing economies (Tajikistan, Burkina Faso, Jordan) and developed economies like G7 countries.

Tajik National Action Plan on AMR

In May 2018, the Tajik National Action Plan on AMR was endorsed by the Tajikistan's Mnistry of Health, Ministry of Agriculture and Committee on Food Security. Several seminars, consultation meetings and workshops were conducted to identify the country's priority areas and required actions for AMR containment and control of antimicrobial consumption. The country has successfully implemented the planthrough State Surveillance Service.

Burkina Faso National Action Plan on AMR

Burkina Faso's AMR Committee has successfully enacted several key actions to address AMR, including strengthening surveillance, ensuring safer antimicrobial prescribing practices, and improving water and sanitation, highlighting the important role of a dedicated governance structure to drive action on AMR.

National Action Plan for Combating AMR in Jordan

The AMR and AMC surveillance systems in Jordan established the AMR surveillance sites and identified the targeted actions for antimicrobial stewardship interventions, including guidance and regulations aimed at ensuring safer prescribing practices among healthcare workers.

National plans and efforts to tackle AMR in G7 countries

The Group of Seven (G7) is an intergovernmental political forum consisting of Canada, France, Germany, Italy, Japan, the United Kingdom and the United States. France has issued three national plans, publishing the first targeted plan in 2001. Germany has issued two national plans, publishing its first national strategy in 2008 and the most recent plan integrates actions proposed in the WHO global action plan. G7 countries show sustained commitment to AMR plans, which currently encompass a 5-year plan by Canada, Germany, France, the United Kingdom and the United States, and a 4-year plan by Italy.

How important is to control Antimicrobial Resistance

AMR is an irrevocable problem and recognized as one of the most serious threats to global health in the 21st century that needs to be addressed on a priority basis through intersectoral collaboration, as antimicrobial agents are not only used in human medicine but also in veterinary practice and animal-derived food production systems. The Global Antimicrobial Surveillance System (GLASS) of WHO reported antimicrobial-resistant bacterial infections in 500,000 people across 22 countries including Pakistan in 2018 (World Health Organisation, 2018).

In 2019, WHO included AMR among the top ten public health threats that humanity is currently facing. It is estimated that in 2050 health care costs due to AMR are likely to surge by 25%, 15% and 6% in low-income, middle-income and high-income countries, respectively. Moreover, higher AMR is likely to cause 10 million annual deaths by 2050 and push as many as 24.1 million people in extreme poverty by 2030 of which 77.6% will be in low-income countries (World Bank, 2017). The livestock production is projected to decline by 9.5% attributed to higher AMR by 2050.

Existing legal framework to control AMR in Punjab, Pakistan

In countries like Pakistan, unhygienic environment, poor sanitation systems at slaughtering sites, storage and transportation systems mainly cause the spread of different pathogenic organisms in animal products. In addition, poultry products are suspected to be a major source of antimicrobial-resistant organisms due to irrational use of antibiotics. However, several legislative frameworks for better animal health and improved feed and food quality have been developed and approved by the governing bodies that will help to reduce AMR.

i.Punjab Poultry Production Act 2016 and Poultry Production Rules 2017; ensure judicious use of antimicrobial drugs in poultry to meet the international guidelines, strict observance of antimicrobial withdrawal time before marketing of end products and bounds poultry feed manufacturers to introduce and mark "non-medicated feed" on each package.

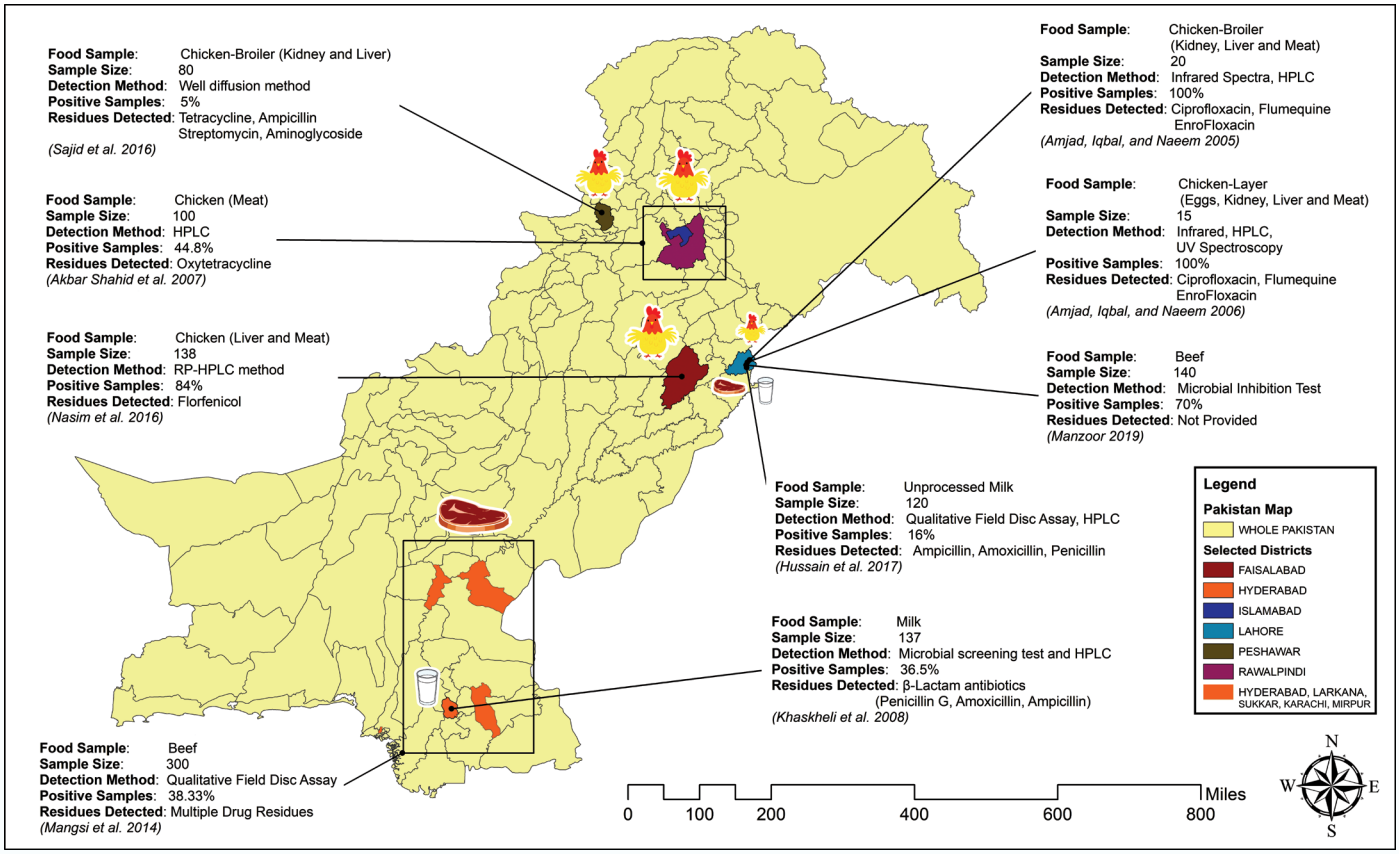
ii.The Punjab Animal Feed Stuff and Compound Feed Act 2016; check adulteration/ misbranding and make sure quality production of poultry and livestock feed stuff by strict observance of feed stuff ingredients (particularly macro & micro ingredients including feed additives and drugs).

iii.The Punjab Animal Health Act 2019; regulates the welfare of animals and prevention, control, containment, and eradication of animal diseases to meet the international standards of import and export.

Initiatives: The first action plan, development of "National Strategic Framework for Containment of Antimicrobial Resistance" to tackle AMR was endorsed by Ministry of NHSR&C in 2016. Pakistan was one of the leading countries among low- and middle-income countries (LMICs) to develop National AMR Plan (in 2017) and design policies on AMU. National AMR plan was developed in collaboration with NIH, NARC, NVL, and WHO. However, strict implementation of AMR National Action Plan (NAP) for adoption and development of respective provincial and regional plans is the dire need of time. However, this issue could

Table 1: Hospital based studies reporting antimicrobial-resistant bacterial isolates from human samples in Pakistan

Area/Hospitals	**Sample size**	**Bacterial isolates**	**Results** (Resistant to)
Mayo hospital, Lahore	500	*E. coli, S. aureus, Proteus, Pseudomonas*	Penicillin, Cephalosporins, Tetracyclines, Aminoglycosides
Hyderabad	486	*Salmonella enterica serotype Typhi*	Ceftriaxone-resistant
Peshawar	1598	*E. coli, S. aureus, Pseudomonas, Klebsiella, Proteus, Listeria monocytogenes*	Highly resistant to Ampicillin, Augmentin, Gentamycin. Moderately resistant to Cephalosporins. Low resistance to Ciprofloxacin.
Faisalabad	80	*Staphylococcus epidermidis*	Aminoglycosides, Tetracyclines, Penicillin, Cephalosporins, Vancomycin
Karachi	312	*E. coli, S. aureus, P. aeruginosa, Pneumonia, Proteus, Candida, Enterobacter*	Aztreonam, Aminoglycosides, Carbapenems, Cephalosporins, Penicillin, Fluoroquinolones
	1573	*Shigella*	Ampicillin resistance
	501	*S. aureus*	Tetracycline and Clindamycin resistance
	889	*Helicobacter pylori*	Resistance to Metronidazole and Ofloxacin
Rawalpindi	1400	*E. coli, K. pneumonia, S. aureus, P. aeruginosa*	Ampicillin, AMC, and Doxycycline resistance
Sukkur	465	*Salmonella typhi, Salmonella Para-typhi*	Ampicillin resistance
Azad Kashmir	1210	*E. coli*	Penicillin, Tetracycline Macrolides, Nalidixic acid, Aminoglycosides, Chloramphenicol, Cephalosporins



Map of Pakistan showing antimicrobial residues detection in various food samples in different parts of the country.

not get required attention to be on the priority list for implementation largely due to lack of funds, poor command of regulatory authorities and lack of political will.

Fleming fund accomplishments:

Under the FF project, AMR National Surveillance Strategy for Healthy/ Diseased Food Animals/ Aquaculture/ Environment, Pakistan Veterinary Laboratories, AM Prescription Guidelines, Sampling Plans and Antibiotic Footprints Analysis were developed and disseminated among stakeholders. FF conducting advocacy to strengthen AMR policy and enabling environment. National Lab Networking Group (NLNG) developed with the objective to track the progress of labs on standardization and harmonization of protocols and initiated the National External Quality Assurance Scheme (NEQAS).

How can existing framework for the control of AMR in Pakistan be improved

Since the global action plan on AMR emphasizes awareness regarding AMR, strengthening surveillance and research programs and optimization of the use of antimicrobial agents, Pakistan needs to devise the appropriate strategies at the national level that minimizes the emergence of AMR and rational use of antimicrobials in agricultural and medical settings. Replication of successful federal antimicrobial stewardship programs for combating AMR in all the provinces to ensure effectiveness and sustainability is very important. Since the role of the federal government in policymaking and implementation of initiatives within health and livestock domains is limited as both the sectors are primarily driven by the respective provincial governments.

There is also a need of furthering the research on exploring AMU in various components of human, animal and environmental health with more robust epidemiological approaches in order to make informed decisions in a timely manner. The national policies need to be largely based on evidence-based decision-making backed by applied policy research.

Current status of AMR in Pakistan

Table 2: Studies that isolated antimicrobial-resistant microorganisms from various animal-origin food commodities in Pakistan.

Food commodity	Area	Sample size	Bacterial isolates	Resistance against antibiotics
Milk products	Multan	30	*S. aureus, E.coli, Klebsiella*	Urixin, Chloramphenicol, Ampicillin
Poultry meat	Karachi	160	*Salmonella* spp.	Ampicillin, Streptomycin, Cefotaxime, Kanamycin, Neomycin, Nalidixic acid, Tetracycline, Bacitracin, Erythromycin, Novobiocin, Spectinomycin.
	Hyderabad	100	*Salmonella* spp.	Ampicillin
	Faisalabad	340	*S.Typhimurium, S. Enteritidis*	Pefloxacin, Ofloxacin,Norfloxacin, Ciprofloxacin, Levofloxacin,Imipenem, Doripenem, Meropenem, Ertapenem, Ceftazidime, Cefepime, Ceftazidime, Cefotaxime, Cefixime,Piperacillin,Ampicillin,Ticarcillin, Tobramycin, Gentamicin, Amikacin,Chloramphenicol
Eggs	Haripur	300	MDR *Staphylococcusaureus*	Moxifloxacin, Levofloxacin, Tigecycline, enicillin, Oxacillin, Gentamicin, Erythromycin,Cefoxitin
	Peshawar	100	*Escherichia coli*	Tetracycline, Streptomycin, Amoxicillin, Gentamicin, Kanamycin
	Faisalabad	240	*Salmonella* spp.	Bacitracin, Erythromycin and Novobiocin.
Drinking water	Khairpur	72	Thermoresistant *Escherichia coli*	Penicillin, Streptomycin,Meropenem, Lincomycin, Fusidic acid, Bacitracin, Monensin, Cefuroxime, Amoxil, Cefaclor, Augmentin, Cephradine, lindamycin

Can potential alternative to antimicrobials provide real solution?

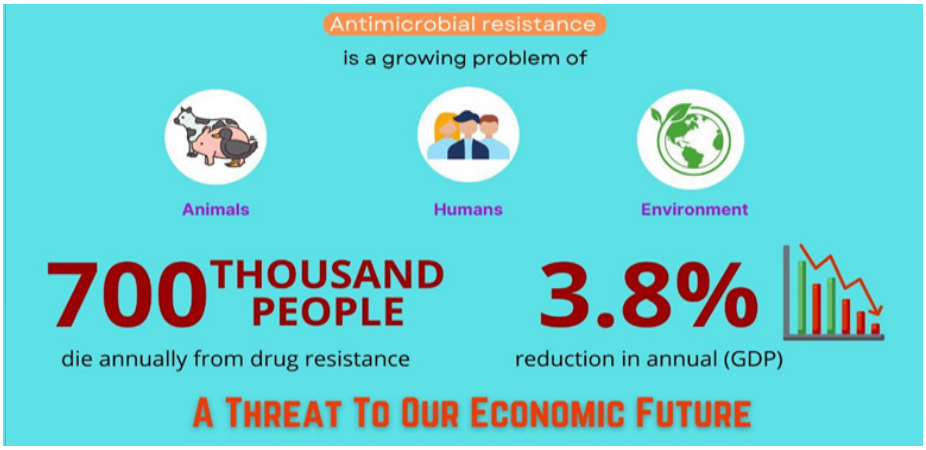
Various potential alternatives to antimicrobials exist for treating specific diseases, including bacteriophage therapy, immunotherapeutics, prebiotics, probiotics, and synbiotics. The only advantage to these therapies is that they don't have collateral effects on commensal organisms (contrasting to antibiotics).

Bacteriophage, or phage, therapy is

among the most researched alternatives having specificity for a target bacterial population. But the therapy requires knowledge of the target bacterium and sufficiently high populations of the target bacterium.

Immunotherapeutics are molecules that prevent a disease at infection-prone times by boosting the host immune system. The limitation is that the timing of delivery needs to be precise, which is a potential challenge.

Probiotics, prebiotics, or synbiotics are used to modulate the gut microbial community to improve health. However, the gut microbial community is a complex consortium of >500 different bacterial species, and all these –biotics have revealed inconsistent efficacy due to lack of knowledge on precise mechanism of how each member contributes to host health. The solutions to the antibiotic-resistance problem are multifaceted but unfortunately, none have consistently demonstrated efficacy comparable to antimicrobials. However, further development of these specific approaches for disease treatment is warranted to improve deliverability, potency, and reliability as antimicrobials alternatives.



Policy Recommendations

Antimicrobial resistance is an emerging threat in Pakistan but ensuring the effective implementation of following recommendations can reduce AMR development.

1—A comprehensive and integrated national AMR and AMU surveillance plan to tackle the threat of AMR to health, agriculture, environment and socio-economic development of Pakistan.

2—Firm enforcement of legislative actions to ensure the rational usage of antimicrobials particularly critically important antimicrobials in medical and veterinary sectors.

3—Capacity building of personnel and food safety laboratories for antimicrobial susceptibility testing and detection of antimicrobial residues in food items.

4—Educational interventions to improve the practicing code of conduct,perceptions and attitude regarding AMU both in medical and veterinary professionals, and community.

5—Estimation of the economic impact and health burden of AMR in medical and veterinary sectors.

6—Alternative therapies (prebiotic, probiotics) and techniques to combat AMR should also be extensively explored by the Pakistani researchers.

Researchers Featured

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Further reading

https://www.who.int/publications/m/item/jordan-national-action-plan-for-combating-antimicrobial-resistance-in-the-hashemite-kingdom-of-jordan

https://www.fao.org/antimicrobial-resistance/quadripartite/who-we-are/en/

https://www.who.int/news/item/17-10-2022-sustaining-action-against-antimicrobial-resistance-a-case-series-of-country-experiences

https://www.woah.org/fileadmin/Home/eng/Media_Center/docs/pdf/PortailAMR/EN_OIE-AMRstrategy.pdf

https://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf

Explained terminologies

Probiotics are living organisms that are intentionally fed to a host and are typically known as“good” bacteria

Prebiotics are molecular precursors to expand the presence of the existing “good” gut microbiota of a host.

Synbiotics are a combination of both pre- & probiotics.

Phage therapy is the therapeutic use of bacteriophage for the treatment of pathogenic bacterial infections.

Immunotherapeutics is the treatment of diseases by using substances that activate or suppress the immune system.

Extensively drug-resistant bacteria, or XDR bacteria, are a type of organisms that are resistant to almost all or all approved antimicrobial agents.

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