The Pharma Innovation Journal 2024; 13(3): 246-253

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
TPI 2024; 13(3): 246-253

www.thepharmajournal.com
Received: 23-01-2024
Accepted: 14-02-2024

Shingini Sharma
CCS National Institute of Animal Health, Baghpat, Uttar Pradesh, India

Aditi Sharma
Council of Environment and Sustainable Development, Uttarakhand, India

Honey Krishna Gaur
DoE, State government of Madhya Pradesh, India

Kusum Rani
Centre for Drug Design Discovery and Development (C4D), SRM University, Sonepat, Haryana, India

Rashmi Tyagi
GNIT College of Pharmacy, Knowledge Park 2, Greater Noida, Uttar Pradesh, India

Shyam Tripathi
Centre for Drug Design Discovery and Development (C4D), SRM University, Sonepat, Haryana, India

Rajesh Kumar
Department of Veterinary Microbiology, G.B. Pant University of Agriculture and Technology, Pantnagar, Uttarakhand, India

Corresponding Author:
Shingini Sharma
CCS National Institute of Animal Health, Baghpat, Uttar Pradesh, India

Antimicrobial Resistance (AMR): An overview with One Health perspective

Shingini Sharma, Aditi Sharma, Honey Krishna Gaur, Kusum Rani, Rashmi Tyagi, Shyam Tripathi and Rajesh Kumar

Abstract
The emergence of antimicrobial resistance in bacterial species is an evolutionary process which has been proliferated by the improper use and over use of therapeutic agents. AMR involve the transfer of microbes and genes between human animal and the environment. AMR being a global public and animal health concern is influenced by the prevalence of antimicrobial in all ecosystems comprising human, animals and environment. Here we describe the present situation of AMR with One Health perspective which includes inter-sectoral approach to tackle the human and animal health together in interaction with the environment in an integrated manner. The increasing bacterial resistance and the loss of antibiotic effectiveness is a significant challenge for both animal health and public health safety. The existence of Antimicrobials and Antimicrobial resistance (AMR) go hand in hands since the antibiotics were discovered as the therapy for the dreadful human infections. Though the resistance was noticed just after the few years of initiation of antibiotic use as a therapy in human but the infections caused by resistant bacteria was significantly increased in later years as a result the treatment of infections became difficult. In present world the constant increase in AMR and failure of existing antibiotics in treating the diseases is posing a serious threat of reversal of world to pre-antibiotic era. Antimicrobial compounds are widely used in human and veterinary medicine since middle of the twentieth century for treatment of various diseases as a result there is increasing resistance in microbes towards them in both the ecosystems. The different ecosystems comprising human, animals and environment are interconnected in one or other way so the transmission and exchange of bacteria and other microbes among them is continuous so AMR problem is no longer limited to human only but involves the other ecosystem as well so the medical science alone is not sufficient to address the issue of AMR but it requires effective collaboration among several disciplines to tackle this challenge. In summary we provide the important information about the Antimicrobial resistance and its effect on the health of people, animals, and the environment under one health perspective.

Keywords: Antimicrobial resistance, AMR, one health, antibiotics, antibacterial

Introduction
Antimicrobial resistance (AMR) and its relationship to medical and veterinary morbidity is one of the biggest challenges facing modern medicine [1]. As a result, standard treatments become ineffective, infections persist and may spread to others. The indiscriminate use of antimicrobials in human is suspected to be the major cause of rising problem of AMR [2, 3] and the use of antibiotics for veterinary applications as therapeutic [4], prophylactic, metaphylactic and as animal growth promoters has also greatly proliferated the problem [5, 6]. Antimicrobial resistance (AMR) is a global health [7] and development threat [8]. It requires urgent multisectoral action in order to achieve the Sustainable Development Goals (SDGs) [9] and this leads to One Health approach that explain the interconnection and interdependence of different ecosystems.

Antimicrobial Resistance (AMR)
Antimicrobials including antibiotics, antivirals, antifungals and antiparasitics are medicines used to prevent and treat infections in humans, animals and plants [7]. AMR is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it [10]. The details of classes of antimicrobial are given in Table 1 with their mechanism of action on various species. Microorganisms that develop antimicrobial resistance are sometimes referred to as "superbugs" [9]. The details of mechanism of resistance is described in Table 2.

Resistance is basically of two types, Endogenous and Exogenous. Endogenous resistance comprises point mutation in a promoter or operator of genes encoding antimicrobial targets whereas exogenous resistance is encoded on plasmids, integrons, phage, and transposons and can be horizontally transmitted by transformation, conjugation, or transduction. The mechanism of resistance usually comprises three categories: (a) inactivation of antimicrobial (b) Efflux or changes in permeability or transport of the antimicrobial or (c) modification or replacement of antimicrobial target [11], [12], [13-15]. Both Endogenous and Exogenous resistance encode for all three categories of resistance. Apart from this there is a significant rise in the Multidrug resistance (MDR) bacteria. MDR in bacteria is defined as non-susceptibility to one or more antimicrobials or three or more antimicrobial classes [9]. The microorganisms that are mainly *inv*olved in the resistance process are the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae*) [16] emphasizing their capacity to escape from common antibacterial treatments [16-18]. Plasmids do play a vital role in spreading the AMR [19]. Plasmids are important for not only storing the genetic information but also for the dissemination of genetic information including antibiotic resistance [20, 21]. MDR in bacteria occurs by the accumulation on resistance (R) plasmids or transposons, of genes, with each coding for resistance to a specific agent [19]. The reservoir of resistance genes is established due to the transfer of resistant genes in between strains of same or different species of bacteria in animals and the environment [22]. Since plasmids of similar incompatibility groups were found among plasmids from the pre-antibiotic era and current plasmids coding for antibiotic resistance, it can be assumed that the later evolved from the former ones by acquisition of new genetic elements.

Antimicrobial resistance (AMR) is emerging as a serious challenge in treatment of infectious diseases. The over use and misuse of antibiotics over the last number of decades has increased patient morbidity and mortality rates globally and has thus generated a serious problem with no immediate solution [2, 3]. The increasing AMR in community and hospital settings contribute in increasing morbidity and mortality. The deaths from Antimicrobial Resistance (AMR) in low income countries are predicted to rise drastically by 2050 [7, 23, 24], thereby leading to urgent requirement of new antimicrobial compounds. The antibiotics create selective pressure that is considered as a major factor for the emergence of resistance against them [25]. As per World Health Organisation (WHO) only few antibiotics that are currently in development address the serious and growing threat of AMR. WHO has published its first ever list of antibiotic-resistant "priority pathogens" [26]. It comprises a catalogue of 12 families of bacteria that pose the greatest threat to human health. The most critical group of all includes carbapenam resistant and ESBL producing *Enterobacteriaceae* (including *Klebsiella* spp., *E. coli*, *Serratia* and *Proteus*, *Acinetobacter*, *Pseudomonas*) [27]. These bacteria have become resistant to a large number of antibiotics, including carbapenems and third generation cephalosporins which are the best available antibiotics for treating multi-drug resistant bacteria. Fluoroquinolone-resistant *Salmonellae* is placed into High priority category [26] [28] and Fluoroquinolone-resistant *Shigella* is placed into medium priority [26]. Human and animals share the same bacteria [29] which need to be combated and prevented at the national, regional and global levels [8]. The use of antimicrobials in veterinary medicine for disease treatment and prevention in domestic and non- domestic animals also contributes significantly to the AMR. Additionally, antibiotics are widely used as growth promoters in aquaculture and for promoting the faster growth of livestock in agriculture. WHO launched new guidelines on use of medically important antimicrobials in food-producing animals, recommending that farmers and the food industry should stop using antibiotics routinely to promote growth and prevention of diseases in healthy animals [6]. These guidelines aim to help preserve the effectiveness of antibiotics that are important for human medicine, by reducing their indiscriminate use in animals that add in rise of the AMR.

One Health

The interconnection and interdependency between the different ecosystems comprising human [30], animals [31] and the environment [32] affect the health outcomes so the concept of One Health emerged which is a collaborative, multisectoral and transdisciplinary approach that work at local, regional, national and global level to achieve the optimal health of all by recognizing the interconnections and interdependency between the health of different ecosystems [31, 33]. Antimicrobial resistance is also a global public and animal health concern [7] that is influenced by both human and non-human antimicrobial usage. This promotes the 'one health' concept that is essential [30]. Curbing the emergence of antimicrobial resistance therefore requires global, multi-sector harmonisation of the strategies and measures designed to improve the coordination of public health, animal health and environmental policies [34]. The human, animal and plant sectors have a shared responsibility to prevent or minimise antimicrobial resistance selection pressures on both human and animal pathogens [33]. The study of ecology of antimicrobial resistance is of paramount importance that is playing a significant role in contributing new models and solutions to combat this uncontrolled pandemic [35]. The antibiotics resistant bacteria can be transferred in between human and animals through contact, via food, and from the environment [29]. High levels of resistance were also found in bacteria that have been deemed "priority pathogens" by WHO [36]. The ecosystems comprising human, animals, environment are interconnected due to which the exchange of bacteria is continuous thus AMR is no longer limited to the bacteria of importance in medical science alone [1] but it also *inv*olve bacteria of importance in Veterinary science [6] and also in environmental sciences [29]. The antimicrobials used in human and animal therapeutics are same so overuses of one antibiotic in one system immensely contribute in rise of AMR in the other so it is of paramount importance to contain the indiscriminate use and to classify the critical antimicrobials. The third and fourth generation cephalosporins, fluoroquinolones and macrolides are considered highest priority critically important antibiotics in human and veterinary medicine as per WHO and OIE [37]. AMR is observed in all microbes comprising pathogenic, non-pathogenic and commensal bacteria. The non-pathogenic or commensal bacteria may be a reservoir for antimicrobial resistance. AMR genes can spread from pathogenic and resistant microbes to the non-pathogenic and non-resistant microbes and vice versa. The AMR can be genetically transferred or encoded. It can be horizontally transferred or

can be inherited by the progeny of the resistant bacteria [38]. Polymyxins were banned from human use in the 1970s due to its nephrotoxic effect on the kidneys but it is reused now to control the dreadful infectious organisms that have become resistant to all the existing antibiotics. But more serious concern arises when it was reported that AMR is also observed for colistin leading to emergence of colistin resistant superbugs. A maor reason may be the indiscriminate use in prophylaxis and as a growth promotion in pigs [39] increasing the AMR in human to the alarming levels. One Health approach is of paramount importance in containing the spread of AMR in different ecosystems which can be achieved by carrying out global public awareness campaigns, observing strict hygiene, avoiding the indiscriminate use of antimicrobials in agriculture thereby reducing their dissemination in the environment. In medical and veterinary science, the rapid diagnostic methods may help in early clinical diagnosis leading to correct use of antibiotics. The development of vaccine against the resistant bacteria is a good alternative to AMR apart from promoting investment in the research on new treatments and the antimicrobial drugs. Strengthening of Global surveillance of AMR and increase in competent manpower to handle AMR are few important parameters that may help to combat the continuously rising AMR on global level.

AMR with One Health perspective

In world

World Health Organization worked closely with Food and Agriculture Organization (FAO) of the United Nations and the World Organisation for Animal Health (OIE) in a 'One Health' approach to promote best practices to avoid the emergence and spread of antibiotic resistance, including optimal use of antibiotics in both human and animals. These agencies have worked as surveillance network to formulate and implement the policies to contain AMR globally [40]. To pace up the political action in containing the AMR a group was formed as Global Leaders Group on Antimicrobial Resistance, which comprises world leaders and experts from across the globe and from different sectors. This group carry out an independent global advisory and advocacy role and works to maintain urgency, public support, political momentum and visibility of the AMR challenge on the global health and development agenda [41, 42]. The world health assembly in its sixty eight assembly endorsed a global action plan (GAP) [43] to tackle antimicrobial resistance [36, 44] including antibiotic resistance the most urgent drug resistance trend. There is a constant increase in the huge burden of antimicrobial resistant infections [45, 46]. WHO launched the Global antimicrobial resistance surveillance system (GLASS) [47] the first global collaborative effort to standardise AMR surveillance. and published its first ever list of antibiotic-resistant "priority pathogens" that comprises a catalogue of 12 families of bacteria that pose the greatest threat to human health [7]. The most critical group of all includes carbapenem resistant and ESBL producing *Enterobacteriaceae* (including *Klebsiella*, *E. coli*, *Serratia* and *Proteus*, *Acinetobacter*, *Pseudomonas*). These bacteria have become resistant to a large number of antibiotics, including carbapenems and third generation cephalosporins which are the best available antibiotics for treating multi-drug resistant bacteria. Thus this issue of increasing AMR in these groups require immediate attention and urgent solution [48]. The second and third tiers in the list comprise the high and medium priority categories that include fluoroquinolone-resistant *Salmonellae* and fluoroquinolone-resistant *Shigella* spp. WHO launched new guidelines on use of medically important antimicrobials in food-producing animals, recommending that farmers and the food industry stop using antibiotics routinely to promote growth and prevent disease in healthy animals [36]. These guidelines aim to help preserve the effectiveness of antibiotics that are important for human medicine by reducing their use in animals. The restriction on the use of antibiotics in food producing animals is important as it has an impact on the AMR in animals and human [6]. In new surveillance data released by WHO revealed the widespread and in some cases high levels of antibiotic resistance across the globe in the most common bacterial infections [7, 49].

In India

AMR gained attention in India in the year 2010, when a controversy broke out due to New Delhi Metallo-β-Lactamase (NDM-1), an enzyme that was isolated in US from a Swedish patient of Indian origin who returned to US after a vacation in India, so the enzyme was named after the India's capital New Delhi [50] that later received objections from Government of India. This enzyme make bacteria resistant to large number of β-Lactam antibiotics comprising carbapenems even, that are considered last resort in treatment of the serious infections [51]. A National Policy on Containment of AMR in addition other NGO initiatives was first published in 2011 and thereafter in April 2017 a comprehensive National Action Plan for Containment of AMR was launched in India [52].

India has some of the highest antibiotic resistance rates among bacteria that commonly cause infections in the community and healthcare facilities. The non-prescription use of antibiotics are the major source of misuse and indiscriminate use of antibiotics throughout the world has immensely contributed in emergence of AMR [9],[2] [53]. Apart from the misuse the poor quality of the antimicrobials too has contributed in rise of AMR [3]. A recent national scale laboratory-based study [54] and data from the newly established ICMR, AMR surveillance network showed high levels of resistance to first line and broad spectrum antibiotics among various bacteria isolated from bloodstream infections. The highest carbapenem resistance (Meropenem/imipenem) was observed in *A. baumannii* (67.3%; 70.9%) followed by *K. pneumoniae* (56.6%, 56.6%), *P. aeruginosa* (46.8%, 41.8%) and *E. coli* (11.5%;16.2%) [54]; ICMR 2015 [52].

AMR is widespread in animals in India [55]. In terms of animal health, the responsible and prudent use of antimicrobial agents is essential for maintaining their therapeutic efficacy and minimising the AMR. It is estimated that India was the fifth largest consumer of antibiotics in food animals (poultry, pigs, and cattle) in 2010 and will be the fourth largest consumer of antibiotics in food animals by 2030 [56]. Antibiotics such as tetracycline, doxycycline, and ciproflocacin, which are critical to human health, are commonly used as growth promotor in poultry [57, 58]. A more concerning issue is the use of colistin for growth promotion propylaxis and therapeutic purposes in poultry [58]. Government of India following One Health approach has banned manufacture, sale and distribution of the drug colistin and its formulations for food-producing animals, poultry, aqua farming and animal feed supplements because such use

is likely to involve risk to human beings [59]. The indiscriminate use of antibiotics has resulted in sharp increase in emergence of resistant bacteria in different species [9, 2]. M-1 [60] and ESBL producing gram negative bacteria [61] and Vancomycin resistant Staphylococcus aureus (VRSA) strains have been isolated from milk samples obtained from cattle with mastitis [62]. ESBL producing *E. coli* strains from have been isolated from fecal samples of chickens [57, 63, 64].

Environment plays a major role in the evolution of resistance and its transmission to different ecosystems comprising human and animals. The environment is contaminated from many sources that contribute to the emergence of AMR in the microbes towards the last resort antibiotics, though the microbes have evolved the mechanisms to tolerate the antibiotics since pre-antibiotic era [29]. Though there are limited studies on environment but studies indicated that major rivers in India have bacteria with high levels of resistance to broad spectrum antibiotics. The effluents from the antibiotic manufacturing units contain a substantial amount of antibiotics, leading to contamination of rivers and lakes in India [65, 66, 67], one of the major cause is that existing good manufacturing practices (GMP) framework is restricted to drug safety and does not include environmental safeguards. The current standards do not include antibiotic residues and thus they are not monitored in the pharmaceutical industry effluents [68, 52]. Another common cause is that more than 50% of the Indian population do not have access to sanitation facilities for safe disposal of human waste [69], in addition a large proportion of sewage is disposed untreated into receiving water bodies leading to gross contamination of rivers with antibiotic residues and antibiotic resistant organism [70].

Table 1: Antibiotic Classes [71, 72, 73]

Classes	Groups	Subclasses	Member	Mechanism of Action	Bacterial species	References
β–Lactam family	Penams Penems Cephems monocyclic β–lactams	Pencilillins Oxa-1-penams/ β–Lactamase inhibitors Carbapenems Carbapenems Cephalosporins First generation Second generation Third generation Fourth generation Fifth generation Monobactams Monocarbams Monophosphatams	Pencilillin G, Pencilillin V, Methicillin, Oxacillin, Cloxacillin, Ampicillin, Amoxicillin, Carbenicillin, Ticarcillin, Mezlocillin, Piperacillin, Aocillin, Temocillin, Nafcillin Clavulanic acid Meropenem, Imipenem Cephalothin, Cephradine, cefazolin Cefamandole, cefuraoime, cephalexin, cefprozil, cefaclor, cefoxitin Cefotaxime, Ceftriaxone, Cefoperazone, Ceftazidime, Cefixime, Cefpodoxime Cefpirome, Cefepime Ceftaroline, Ceftobiprole Aztreonam	Inhibition of cell wall sysnsthesis Production of β-lactamases i.e. Enzymatic degradation; Alteration of new penicillin binding proteins (PBP); Bind β-lactamase enzymes Decreased uptake i.e. Porin channel formation is decreased	*Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, Salmonella* Typhimurium DT *104, (ESBL)- producing Enterobacteriaceae, Enterococcus faecium, Pasteurella* spp., *Brucella* spp., *Staphylococcus aureus, Clostridium difficile, Campylobacter* spp.	[74] [75] [76] [77]
Aminoglycosides	Group I Group II Group III Group IV Group V Group VI	-	Trehalosamine, Streptomycin and derivatives Apramycin Neomycin Kanosamine (Kanamycin, Tobramycin, Amikacin) and Gentamicin Spectinomycin	Inhibition of Protein Synthesis Cell membrane modification - decreased permeability Alterations at the ribosomal binding sites Production of aminoglycoside modifying enzymes (AMEs). Drug efflux	*Salmonella* Typhimurium DT *104, Klebsiella* spp., *Acinetobacter baumanii, Escherichia coli, Pasteurella* spp., *Campylobacter* spp., *S. aureus, Enterococci* spp. *(E. faecalis)*	[78] [79] [80] [81]
Macrolides and Ketolides	-	-	Erythromycin, Azithromycin, Clarithromycin Tylosin and spiramycin, Tilmicosin, Tulathromycin	Inhibition of Protein Synthesis Target site modification i.e. binding to the 50S subunit of the ribosome Horizontal Gene transfer Drug efflux	*Enterococci* spp. *(E. faecalis, E. faecium), Campylobacter* spp, *M. Bovis, Pasteurell multocida, Mannheimia haemolytica, Bartonella* spp., Most gram-negative organisms	[82] [83]
Quinolones	Group I Group II Group III Group IV Group V Group VI	-	Nalidixic acid Pipemedic acid Enoxacin, Norfloxacin, Ciprofloxacin Ofloxacin Moxifloxacin	Inhibition of DNA function Mutational alterations in target enzymes – DNA gyrase and topoisomerase IV Horizontal gene transfer	*Escherichia coli, E. faecium, Neisseria gonorrhoeae, Campylobacter* spp *(C. jejuni and C. coli), Salmonella* Typhimurium DT 104, *Pseudomonas aeruginosa,*	[75] [20] [84] [85]

			Levofloxacin, Gatifloxacin	Drug efflux	*Klebsiella pneumoniae, Acinetobacter baumanii*	
Peptide Antibiotics	-	-	Gramicidin, Vancomycin, Polymyxin E (Colistin), Polymyxin B and Daptomycins	Inhibition of Cell membrane function Lipopolysaccharide (LPS) modifications - covalent modifications of the lipid A moiety of LPS Drug efflux	*Enterobacteriaceae* spp.*; Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Salmonella enterica, Acinetobacter baumanni*	[86] [87]
Ansamycin	-	-	Rifamycin			
Tetracycline	-	-	Chlortetracycline, Doxycycline, Oxytetracycline, Minocycline, Tigecycline, Tetracycline	Inhibition of Protein Synthesis Protection of ribosomes Enzymatic inactivation Drug efflux	*Pasteurella* spp., *Pseudomonas* spp., *S. aureus Salmonella* Typhimurium DT 104, *Brucella* spp., *Campylobacter* spp., *Klebsiella* spp., *Escherichia coli, Acinetobacter baumanii, Enterococci* spp. *(E. faecalis)*	[88] [89] [90] [91]
Lincosamide	-	-	Lincomycin, Clindamycin	Inhibition of Protein Synthesis Target site modification i.e. binding to the 50S subunit of the ribosome Horizontal Gene Transfer Drug efflux	*Campylobacter* spp., *Pseudomonas aeruginosa, Acinetobacter, Staphylococci, Enterococci, Pasteurella multocida, Mannheimia haemolytica, Escherichia coli,*	[83]
Chloramphenicol	-	-	Chloramphenicol	Inhibition of Protein Synthesis Target site modification i.e. binding to the 50S subunit of the ribosome Enzymatic inactivation by acetylation by chloramphenicol acetyltransferases (CATs) Drug efflux	*S. aureus, Salmonella* Typhimurium DT 104, *Pseudomonas aeruginosa, Proteus* spp., *Klebsiella* spp, *Campylobacter* spp., *Escherichia coli, Enterococci* spp. *(E. faecalis)*	[75] [92]
Benzylpyrimidines	-	Sulfonamides	Sulphanilamide, para-aminobenoic acid, sulfadiazine, sulfisoxazole, sulfamethoxazole sulfathalidine	Inhibition of DNA function Alteration of Enzyme (dihydropteroate synthetase) Over-production of para-aminobenzoic acid (PABA) - inhibition of dihydropterate synthetase enzyme Horizontal gene transfer	*Pasteurella* spp. *Salmonella* Typhimurium DT 104 *Neisseria meningitidis, Pseudomonas aeruginosa, Campylobacter* spp., *Bacillus* spp., *Escherichia coli, Shigella., Klebsiella*	[75] [93] [89] [94]
5-Nitroimidazoles	-	.	5-or 2-nitroheterocycles, metronidazole			
Oxazolidinone	-		Linezolid, Tedizolid			

Table 2: Mechanism of action and resistance in microbes [11, 13, 15]

S.no.	Antibiotics	Mechanism of Action /Targets	Mechanism of Resistance
1.	B-lactams	Inhibit Cell wall synthesis	Inactivate enzymes/ Efflux
2.	Vancomycin	Inhibit Cell wall synthesis	Modify Targets / Immunity and bypass
3.	Fluroquinolones	Inhibit DNA/RNA Synthesis	Modify Targets/Efflux
4.	Rifamycin	Inhibit DNA/RNA Synthesis	Inactivate enzymes/ Modify Targets
5.	Trimethoprim	Inhibit Folate Synthesis	Immunity and bypass
6.	Sulphonamides	Inhibit Folate Synthesis	Immunity and bypass
7.	Tetracycline	Inhibit Protein synthesis	Immunity and bypass/ Efflux
8.	Aminoglycosides	Inhibit Protein synthesis	Inactivate enzymes/ Modify Targets / Efflux
9.	Macrolides	Inhibit Protein synthesis	Inactivate enzymes/ Modify Targets / Efflux
10.	Penicillin	Inhibit Cell wall synthesis	Modify Targets

Conclusion

AMR is among top ten health hazard the mankind is facing today. Stringent action plans are required on global basis to contain the rapid spread of AMR. World Health Organization, Food and Agriculture Organization (FAO) of the United Nations and the World Organisation for Animal Health (OIE) are working with 'One Health' approach to contain the menace of AMR but more stringent guidelines are required to be formulated based on the prevalence of the AMR in different regions and countries of the globe in a collaborative manner recognizing the interconnection and interdependency of the health of people, animals and their environment.

Acknowledgements

We thank the Centre for drug design, discovery and development (C4D) of SRM University, Haryana for

providing the necessary research facilities and the Government of India, CCS National Institute of Animal Health, Baghpat (U.P.) for their support for this study. The observatios and conclusions in this report are those of authors and do not represent the official position of any of the above organization.

Funding - No specific funding
Conflict of Interest-None to declare
Transparency declaration-None to declare

References

1. CDC. Antibiotic resistance threats in the United States, 2019, Atlanta, GA: U.S. Department of Health and Human Services. Cent Dis Control Prev; c2019.
2. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: A systematic review. Lancet Infect. Dis; c2011.
3. Kelesidis T, Falagas ME. Substandard/counterfeit antimicrobial drugs. Clin Microbiol Rev; c2015.
4. Johnston AM. Use of antimicrobial drugs in veterinary practice. Br. Med. J; c1998.
5. Palma E, Tilocca B, Roncada P. Antimicrobial resistance in veterinary medicine: An overview. Int. J Mol. Sci; c2020.
6. Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, *et al*. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: A systematic review and meta-analysis. Lancet Planet Heal; c2017.
7. Coates A, Hu Y. Antibiotics and AMR: A global perspective. Drug Discov. World; c2018.
8. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: A global multifaceted phenomenon. Pathog. Glob. Health; c2015.
9. Https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Antimicrobial resistance. 2021;
10. Https://www.who.int/health-topics/antimicrobial-resistance. No Title. 2022.
11. Mc Dermott PF, Walker RD, White DG. Antimicrobials: modes of action and mechanisms of resistance. Int J Toxicol. 2003;22(2):135-143.
12. Foley SL, Lynne AM. Food animal-associated Salmonella challenges: Pathogenicity and antimicrobial resistance. J. Anim. Sci; c2008.
13. Walsh, C. Antibiotics: actions, origins, resistance. Am. Soc. Microbiol; c2003.
14. Brötz-Oesterhelt H. Antibiotics. Actions, Origins, Resistance. By Christopher Walsh. Angew Chemie Int Ed; c2004.
15. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, *et al*. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet; c2016.
16. Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. Expert Rev. Anti. Infect. Ther; c2013.
17. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, *et al*. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. Clin Infect Dis 2009;
18. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, *et al*. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Clin Infect Dis; c2009.
19. Bennett PM. Plasmid encoded antibiotic resistance: Acquisition and transfer of antibiotic resistance genes in bacteria. In: British Journal of Pharmacology; c2008.
20. Vingopoulou EI, Delis GA, Batzias GC, Kaltsogianni F, Koutinas A, Kristo I, *et al*. Prevalence and mechanisms of resistance to fluoroquinolones in Pseudomonas aeruginosa and Escherichia coli isolates recovered from dogs suffering from otitis in Greece. Vet Microbiol. 2018.
21. Stephens C, Arismendi T, Wright M, Hartman A, Gonzalez A, Gill M, *et al*. F Plasmids Are the Major Carriers of Antibiotic Resistance Genes in Human-Associated Commensal Escherichia coli. mSphere 2020;
22. Su LH, Chu C, Cloeckaert A, Chiu CH. An epidemic of plasmids? Dissemination of extended-spectrum cephalosporinases among Salmonella and other Enterobacteriaceae. FEMS Immunol. Med. Microbiol; c2008.
23. de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? PLoS Med; c2016.
24. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations: the review on antimicrobial resistance; 2016 [Available from: https://amr-review. org. Publ html; c2019.
25. Alanis AJ. Resistance to antibiotics: Are we in the post-antibiotic era? Arch. Med. Res; c2005.
26. Tacconelli E, Magrini N. WHO (2017) Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Cad Pesqui; c2017.
27. Tacconelli E. WHO (2017) Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics; c2013.
28. Hopkins KL, Davies RH, Threlfall EJ. Mechanisms of quinolone resistance in Escherichia coli and Salmonella: Recent developments. Int. J. Antimicrob. Agents; c2005.
29. Larsson DGJ, Flach CF. Antibiotic resistance in the environment. Nat. Rev. Microbiol; c2021.
30. Https://www.who.int/news-room/questions-and-answers/item/one-health. One Health.
31. Https://www.oie.int/en/what-we-do/global-initiatives/one-health/. One Health.
32. Https://www.fao.org/one-health/en/. One Health.
33. Mackenzie JS, Jeggo M. The one health approach-why is it so important? Trop. Med. Infect. Dis; c2019.
34. Buschhardt T, Günther T, Skjerdal T, Torpdahl M, Gethmann J, Filippitzi ME, *et al*. A one health glossary to support communication and information exchange between the human health, animal health and food safety sectors. One Heal; c2021.
35. González-Zorn B, Escudero JA. Ecology of antimicrobial resistance: Humans, animals, food and environment. Int. Microbiol; c2012.
36. Khabbaz R, Cars O, Kumar S, Perovic O, Song J-H, Thamlikitkul V, *et al*. Implementation of the global action plan on antimicrobial resistance. WHO GAP AMR Newsl N°32 2017.

37. Http://apps.who.int/iris/bitstream/handle/10665/77376/9789241504485_eng.pdf;jsessionid=D835CFE9904BBFD6F68F40648D40D3D9?sequence=1. Critically important antimicrobials for Human medicine.
38. Linton AH. Animal to man transmission of enterobacteriaceae. J R Soc Promot Health; c1977.
39. Rhouma M, Beaudry F, Letellier A. Resistance to colistin: what is the fate for this antibiotic in pig production? Int. J. Antimicrob. Agentsl; c2016.
40. Oldenkamp R, Schultsz C, Mancini E, Cappuccio A. Filling the gaps in the global prevalence map of clinical antimicrobial resistance. Proc Natl Acad Sci U S A; c2021.
41. Https://www.who.int/groups/one-health-global-leaders-group-on-antimicrobial-resistance. Resistance., Global Leaders Group on antimicrobial. 2021;
42. United Nations Secretary-General. Interagency Coordination Group on Antimicrobial Resistance. 2017.
43. Global Action Plan on Antimicrobial Resistance. Microbe Mag; c2015.
44. Mundy LM, Sahm DF, Gilmore M. Relationships between Enterococcal Virulence and Antimicrobial Resistance. Clin Microbiol Rev; c2000.
45. Dunachie SJ, Day NP, Dolecek C. The challenges of estimating the human global burden of disease of antimicrobial resistant bacteria. Curr. Opin. Microbiol.2020;
46. Limmathurotsakul D, Dunachie S, Fukuda K, Feasey NA, Okeke IN, Holmes AH, *et al*. Improving the estimation of the global burden of antimicrobial resistant infections. Lancet Infect. Dis.2019;
47. WHO. Global Antimicrobial Resistance Surveillance System (GLASS) Report. 2017.
48. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, *et al*. Antibiotic resistance-the need for global solutions. Lancet Infect. Dis.2013;
49. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, *et al*. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control 2018;
50. Savard P, Gopinath R, Zhu W, Kitchel B, Rasheed JK, Tekle T, *et al*. First NDM-positive Salmonella sp. strain identified in the United States. Antimicrob. Agents Chemother.2011;
51. Walsh TR. Emerging carbapenemases: A global perspective. Int J Antimicrob Agents 2010;
52. Sumanth Gandra, Jyoti Joshi, Anna Trett, Anjana Sankhil Lamkang and R, Laxminarayan. Scoping Report on Antimicrobial Resistance in India. 2017;
53. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, *et al*. Global Antibiotic Consumption in Humans, 2000 to 2018: A Spatial Modelling Study. SSRN Electron J 2021;
54. S. G, N. M, E.Y. K, A. A, V. N, M. K, *et al*. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. Int J Infect Dis 2016;
55. Gandra S, Joshi J, Trett A, Sankhil Lamkang A. Scopig Report on Antimicrobial Resistance in India. Cddep 2017;
56. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, *et al*. Global trends in antimicrobial use in food animals. Proc Natl Acad Sci U S A 2015;
57. Brower CH, Mandal S, Hayer S, Sran M, Zehra A, Patel SJ, *et al*. The prevalence of extended-spectrum beta-lactamase-producing multidrug-resistant Escherichia coli in poultry chickens and variation according to farming practices in Punjab, India. Environ Health Perspect 2017;
58. Http://www.cseindia.org/, Userfiles/factsheets/factesheet%206.pdf. CSE (Center for Science and Environment). Food Saf 2014;
59. Http://www.egazette.nic.in/WriteReadData/2019/207345.pdf. No Title.
60. Ghatak S, Singha A, Sen A, Guha C, Ahuja A, Bhattacharjee U, *et al*. Detection of new delhi metallo-beta-lactamase and extended-spectrum beta-lactamase genes in escherichia coli isolated from mastitic milk samples. Transbound Emerg Dis 2013;
61. Das A, Guha C, Biswas U, Jana PS, Chatterjee A, Samanta I. Detection of emerging antibiotic resistance in bacteria isolated from subclinical mastitis in cattle in West Bengal. Vet World 2017;
62. Debaraj B, Jaydeep B, Samiran B, Bimalendu M, Nanda PK, Indranil S, *et al*. First report on vancomycin-resistant Staphylococcus aureus in bovine and caprine milk. Microb Drug Resist 2016;
63. Kar D, Bandyopadhyay S, Bhattacharyya D, Samanta I, Mahanti A, Nanda PK, *et al*. Molecular and phylogenetic characterization of multidrug resistant extended spectrum beta-lactamase producing Escherichia coli isolated from poultry and cattle in Odisha, India. Infect Genet Evol 2015;
64. Shrivastav A, Sharma RK, Sahni YP, Shrivastav N, Gautam V, Jain S. Study of antimicrobial resistance due to extended spectrum betalactamase- producing Escherichia coli in healthy broilers of Jabalpur. Vet World 2016;
65. Larsson DGJ, de Pedro C, Paxeus N. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J Hazard Mater 2007;
66. Lübbert C, Baars C, Dayakar A, Lippmann N, Rodloff AC, Kinzig M, *et al*. Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. Infection 2017;
67. Gothwal R, Shashidhar. Occurrence of high levels of fluoroquinolones in aquatic environment due to effluent discharges from bulk drug manufacturers. J Hazardous, Toxic, Radioact Waste 2017;
68. CPCB Effluent Standards. Environ Rules 1986;(CPCB Effluent Standards. In "The Environment (Protection) Rules, 1986." http://www.cpcb.nic66 in/Industry-Specific-Standards/Effluent/469-1. pdf.).
69. World Bank. World Bank. "Improved Sanitation Facilities (% of Population with Access). http:// data.worldbank.org/indicator/SHSTA ACSN?end=2015&locations= IN&start=2015&view=map 2017;
70. Marathe NP, Pal C, Gaikwad SS, Jonsson V, Kristiansson E, Larsson DGJ. Untreated urban waste contaminates Indian river sediments with resistance genes to last resort antibiotics. Water Res 2017;
71. Adzitey F. Antibiotic Classes and Antibiotic

Susceptibility of Bacterial Isolates from Selected Poultry; A Mini Review. World s Vet J 2015;
72. Moore AD. Antibiotic Classification & Mechanism. OrthoBullets 2016;
73. Meade E, Slattery MA GM. Antimicrobial resistance: an agent in zoonotic disease and increased morbidity. J Clin Exp Tox 2017;1(1):30–7.
74. Karam G, Chastre J, Wilcox MH, Vincent JL. Antibiotic strategies in the era of multidrug resistance. Crit. Care2016;
75. Economou V, Gousia P. Agriculture and food animals as a source of antimicrobial-resistant bacteria. Infect. Drug Resist.2015;
76. Kumar S, Singh B. An overview of mechanisms and emergence of antimicrobials drug resistance. Emergence 2013;
77. Li XZ, Mehrotra M, Ghimire S, Adewoye L. β-Lactam resistance and β-lactamases in bacteria of animal origin. Vet. Microbiol.2007;
78. Wang Z, Kong LC, Jia BY, Liu SM, Jiang XY, Ma HX. Aminoglycoside susceptibility of Pasteurella multocida isolates from bovine respiratory infections in China and mutations in ribosomal protein S5 associated with high-level induced spectinomycin resistance. J. Vet. Med. Sci.2017;
79. Müller S, Janßen T, Wieler LH. Multidrug resistant Acinetobacter baumannii in veterinary medicine-emergence of an underestimated pathogen? Multiresistente Acinetobacter baumannii in der Veterinär-medizin-Vormarsch eines unterschätzten Krankheits-erregers? Berl Münch Tierärztl Wochenschr 2014;
80. Endimiani A, Hujer KM, Hujer AM, Bertschy I, Rossano A, Koch C, *et al*. Acinetobacter baumannii isolates from pets and horses in Switzerland: molecular characterization and clinical data. J Antimicrob Chemother 2011;
81. Day M, Doumith M, Jenkins C, Dallman TJ, Hopkins KL, Elson R, *et al*. Antimicrobial resistance in Shiga toxin-producing Escherichia coli serogroups O157 and O26 isolated from human cases of diarrhoeal disease in England, 2015. J Antimicrob Chemother 2017;
82. Kong LC, Gao D, Jia BY, Wang Z, Gao YH, Pei ZH, *et al*. Antimicrobial susceptibility and molecular characterization of macrolide resistance of Mycoplasma bovis isolates from multiple provinces in China. J Vet Med Sci 2016;
83. Pyörälä S, Baptiste KE, Catry B, van Duijkeren E, Greko C, Moreno MA, *et al*. Macrolides and lincosamides in cattle and pigs: Use and development of antimicrobial resistance. Vet. J.2014;
84. Redgrave LS, Sutton SB, Webber MA, Piddock LJV. Fluoroquinolone resistance: Mechanisms, impact on bacteria, and role in evolutionary success. Trends Microbiol.2014;
85. Pallo-Zimmerman LM, Byron JK GT. Fluoroquinolones: then and now. Compend Contin Educ Vet 2010;9.
86. Poirel L, Jayol A, Nordmanna P. Polymyxins: Antibacterial activity, susceptibility testing, and resistance mechanisms encoded by plasmids or chromosomes. Clin. Microbiol. Rev.2017;
87. Olaitan AO, Morand S, Rolain JM. Mechanisms of polymyxin resistance: Acquired and intrinsic resistance in bacteria. Front. Microbiol.2014;
88. Marosevic D, Kaevska M, Jaglic Z. Resistance to the tetracyclines and macrolide-lincosamide-streptogramin group of antibiotics and its genetic linkage – A review. Ann. Agric. Environ. Med.2017;
89. Nhung NT, Chansiripornchai N, Carrique-Mas JJ. Antimicrobial resistance in bacterial poultry pathogens: A review. Front. Vet. Sci.2017;
90. Shin SW, Shin MK, Jung M, Belaynehe KM, Yoo HS. Prevalence of antimicrobial resistance and transfer of tetracycline resistance genes in Escherichia coli isolates from beef cattle. Appl Environ Microbiol 2015;
91. Hao H, Sander P, Iqbal Z, Wang Y, Cheng G, Yuan Z. The risk of some veterinary antimicrobial agents on public health associated with antimicrobial resistance and their molecular basis. Front. Microbiol.2016;
92. Schwarz S, Kehrenberg C, Doublet B, Cloeckaert A. Molecular basis of bacterial resistance to chloramphenicol and florfenicol. FEMS Microbiol. Rev.2004;
93. Wang Y, Lv Y, Cai J, Schwarz S, Cui L, Hu Z, *et al*. A novel gene, optrA, that confers transferable resistance to oxazolidinones and phenicols and its presence in Enterococcus faecalis and Enterococcus faecium of human and animal origin. J Antimicrob Chemother 2015;
94. Zhang X, Li Y, Liu B, Wang J, Feng C, Gao M, *et al*. Prevalence of veterinary antibiotics and antibiotic-Resistant Escherichia coli in the surface water of a livestock production region in northern China. PLoS One; c2014.