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Antimicrobial Resistance

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Preface

Antimicrobial resistance is emerging as a major threat to global public health. Since the discovery of penicillin in 1928, and subsequently, several new groups of antimicrobials including tetracyclines, aminoglycosides, cephalosporins, fluoroquinolones, macrolides and antibiotics have played an important role in saving billions of human and animal lives. Besides, by reducing the disease burden, these antimicrobials have been contributing towards ensuring the quality of life, in terms of better health, nutrition and environment. Antibiotics have been the most widely used class of drugs, and without these, the treatment of several communicable diseases and advances in surgeries, including transplantation of vital organs and cancer, could not have been possible. However, the excess, injudicious, indiscriminate and prolonged use of antimicrobials can lead to the emergence of resistance in pathogens. The poor hygiene and sanitation, ineffective infection control standards, spurious drugs, and non-availability of diagnostics and vaccines may further compound the problem.

The National Academy of Agricultural Sciences (NAAS) organized a brainstorming session on August 20, 2020, to discuss the problem of antimicrobial resistance, its consequences and possible solutions. The session was attended by a number of scientists, academicians and professionals, and their inputs and suggestions have led to a set of recommendations that I feel, if implemented, may herald a paradigm shift in the management of antimicrobial resistance. I sincerely acknowledge the contributions of Prof A.K. Srivastava, Convenor and Dr A.K. Arora, Co-Convenor, and all those who participated in this session. I also thank Dr Gaya Prasad for his valuable comments on the document. My sincere thanks to Drs Pratap S. Birthal and Malavika Dadlani for their editorial support.

Trilochan Mohapatra
(President, NAAS)

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Antimicrobial Resistance

1. BACKGROUND

The discovery of antimicrobials and their introduction as clinical medicine was one of the greatest medical triumphs of the 20th century that revolutionized the treatment of bacterial infections. Alexander Fleming discovered penicillin-G in 1928. Although the Penicillin-G remains extensive in clinical utility, several changes have occurred with the development of broad-spectrum penicillins such as ampicillin and amoxicillin. Antibiotic treatment is still a mainstay of antimicrobial therapy for combating bacterial and other microbial infections. The success of antimicrobial therapy depends on the concentration of the antibiotic at the site of infection, which must be sufficient to inhibit the growth and multiplication of offending microorganisms. The concentration of the antibiotics at the site of infections should be such that it is effective against microbes but also must remain below the level that is toxic to human cells. Antimicrobial agents, based on the mechanism of action and chemical structure, are classified as:

- Agents that inhibit the synthesis of bacterial cell walls, e.g., β-lactum antibiotics (penicillin, cephalosporins and carbapenems) and cycloserine, vancomycin and bacitracin.
- Agents that act directly on the cell membrane of the organisms, increasing permeability leading to leakage of intracellular compounds, e.g., polymyxin, nystatin, amphotericin-B and daptomycin.
- Agents that disrupt or inhibit protein synthesis, e.g., tetracyclines, aminoglycosides and macrolides antibiotics.
- Agents that inhibit bacterial nucleic acid metabolism, e.g., rifamycin, quinolones.
- Agents that act as antimetabolites for bacterial cells, e.g., sulphonamides and trimethoprim which block essential enzymes of folate metabolism.

Antimicrobials have been used in reducing the disease burden and sufferings of animals and humans and also in production agriculture to contain insect pests and diseases. Quantitatively, antibiotics have been one of the most widely used classes of drugs to control infections. Antimicrobial agents have revolutionized the field of medicine, as without them the surgeries including organ transplantation and cancer therapy could not have been possible. During the last 90 years, antibiotics have saved billions of human and animal lives. The first antibiotic “Penicillin” was discovered in 1928, and was termed the “magic bullet”. The discovery of penicillin heralded the golden era for antibiotics development leading to the discovery of several new antibiotics subsequently. The important antibiotics used in human and veterinary medicine are shown in Table 1.

In a strict sense, antibiotics are antibacterial substances produced by various species of microorganisms (bacteria, fungi, actinomycetes) that suppress and inhibit the growth of other micro-organisms. The common usage of antibiotics often extends the use of the term also for the synthetic antimicrobial agent. sulphonamides and quinolones in the group of antibiotics.

Table 1. Important antibiotics/antimicrobials used in human and veterinary health sectors

Sulfonamides: Sulfanilamide, Sulfadimidine, Sulfadoxine, Sulfisomidine, Sulfadimethoxine, Sulfamethoxypyridazine, Sulfadiazine, Sulfamethoxazole, Sulfamathazine, Sulfapyridine, Sulfacetamide, Sulfisoxazale, Cotrimoxazole(Sulfa+Trimethoprim)
Penicillins: Penicillin G, Penicillin V, Ampicillin, Amoxycillin, Cloxacillin, Oxacillin, Methicillin, Mezlocillin, Carnbenicillin, Nafcillin, Piperacillin
Tetracyclines: Oxytetracycline, Minocycline, Doxycycline, Demeclocycline, Methacycline
Aminoglycosides: Amikacin, Neomycin, Gentamycin, Kanamycin, Tobramycin, Netilmicin, Plazomycin
Cephalosporins: Cefalexin, Cefotaxime, Cefuroxime, Ceftizoxime, Cephaloridine, Ceftriaxone, Cefoperazone, Cefoperazone, Cefadroxil, Cefdinir, Cefepine, Cefaclor, Ceftazidime, Cefprozil, Cefotetam, Ceforanide, Cefoperazone, Cefsulodin, Cefoxitine
Fluroquinolones: Enrofloxacin, Pefloxacin, Ciprofloxacin, Oflaxacin, Levofloxacin, Norfloxacin, Nalidixic acid, Enoxacin, Gemifloxacin, Oxolinic acid, Garenoxacin, Difloxacin, Danofloxacin, Flumequine, Orbifloxacin, Cinoxacine, Marbofloxacin, Rosoxacin
Macrolides: Erythromycin, Clarithromycin, Azithromycin, Telithromycin, Tobramycin, Clindamycin,
Other Antibiotics: Chloramphenical, Carbapenems, Cycloserin, Vancomycin, Bacitracin, Polymyxin, Nystatin, Amphotericin, Linozolid, Daptomycin, Teicoplanin, Mupricrocin, Isoniazide, Ethambutol, Rifampin, Rifabutin, Pyrazinamide, Ethionamide

Antimicrobial resistance (AMR) is the ability of microorganisms to resist the effects of antimicrobials, to which they were sensitive earlier. AMR is now the major cause of concern for global public health. It is not a new phenomenon and evolves naturally through genetic changes. Resistance to penicillin was reported in the same year in which it was discovered. Indiscriminate, excessive and inappropriate use of antimicrobials in human, animal and plant health sectors is one of the causes of the emergence of AMR, consequently the reduced efficacy of antibiotics in treating the infections.

Antimicrobial Resistance
• Antimicrobial resistance happens when microbes like bacteria, fungi, viruses and parasites develop the ability to defeat the drugs designed to kill them. Infections caused by antibiotic-resistant microbes are difficult and sometimes impossible to treat with the available drugs.
• Antibiotic resistance or antimicrobial resistance is also understood as “drug resistance”.
• A WHO multi-country survey reveals a widespread public misunderstanding of AMR.
• More than 60% of hospitalized patients receive antimicrobial agents, and most achievements in medical sciences are attributed to the use of antibiotics.
• Permanent resistance by bacteria, fungi and other microbial pathogens against antibiotics cannot be prevented in the long run unless the use of antibiotics is completely stopped.
• The WHO report confirms that the world is running out of antimicrobials.
• Antimicrobial resistance is the biggest threat to global health, food security and development.
• Antimicrobial resistance can affect anyone at any location. It is rising to a dangerously high level, and new resistance mechanisms are also emerging.
• Infections such as pneumonia, tuberculosis, gonorrhoea and salmonellosis are becoming harder to treat as the antibiotics have become less effective or ineffective.
• Antimicrobial resistance leads to longer hospital stays, higher medical costs and increased mortality.
• “World Antimicrobial Awareness Week” (WAAW) is a global campaign and it is observed during November 18-24 every year since 2015.

Bacterial pathogens of animal and human origins are becoming increasingly resistant to most of the frontline antimicrobials, including aminoglycosides, expanded spectrum cephalosporins and fluoroquinolones. More than 80% of the bacteria associated with hospital-acquired infections are resistant to one or more drugs previously used to treat them. Penicillin resistant strains of pneumococci account for 50% or more of isolates in European countries. The emergence of haemophilus and gonococci (that produce β lactamase) has become a major therapeutic problem. Methicillin-resistant *S. aureus* is endemic in hospitals and is isolated increasingly in community-acquired infections (Naimi et al., *2003*). Now there are strains of Enterococci, Pseudomonas and Enterobacter, that are resistant to all available antibiotics. Epidemics of multiple drug-resistant of *Mycobacterium tuberculosis* have been reported in several countries, including the US and the EU (WHO, 2020)

The problem gets aggravated in the absence of any new antibiotics in the pipeline. Unfortunately, the discovery of antibiotics has not kept pace with the emerging resistant pathogens. As per the WHO, declining private investment and lack of innovation in the development of new antibiotics, have been aggravating AMR and ultimately negating the efforts to combat drug-resistant infections**.** The absence of new antibiotics in research programs and continuous non-judicious use of existing antibiotics have fuelled a catastrophic rise in antibiotic resistance. *Recognising the sensitivity of the issue, WHO has rightly identified AMR as the most critical threat to global public health, food security and economic development.*

In animal production systems, antimicrobial drugs are widely used, and antimicrobial resistance has been increasing against zoonotic and commensal bacteria. This has raised concerns about the risks of transmission of resistant zoonotic bacteria as well as resistant bacterial genes from animals to humans or vice-versa. A steady increase in the resistance across species of microbes has been a major concern for health professionals and policymakers.

We Are Very Near to Post-antibiotic Era

- There is a dwindling trend in the development of antibiotics. Between 1935 and 1968, a total of 14 new classes of antibiotics were developed and introduced, but in clinical therapy, since 1965 only 5 new antibiotics were developed.
- After 1987, no new class of antibiotics was discovered, and as of now, there is no new antibiotic in the pipeline of research and development. Further, only 1 out of 5 new antimicrobials that reach the phase of testing in humans receives approval from the Food and Drug Administration (FDA).
- There is a lack of incentives for pharmaceutical companies to develop newer antibiotics. Further, there is less investment both from public or private sectors in antimicrobials R&D than drugs used in the treatment of non-communicable diseases like obesity, diabetes and heart diseases.
- Out of 35 companies engaged in the development of antibiotics, only one ranks among the top 50 pharmaceutical companies. Approximately 95% of the products development is studied in small countries. The approval of new antibiotics has also declined in the past three decades. No antibiotic was approved after 2009 (Figure 1).

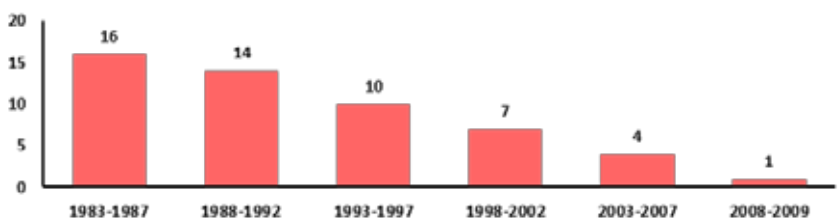


Fig 1. Declining Antibacterial Approvals (Past 25 Years)

2. PHYSICAL AND ECONOMIC IMPACT OF AMR

Antimicrobial resistance poses a substantial economic burden. However, estimating the exact economic impact of resistant bacterial infections is a challenge. In the US, antibiotic-resistant pathogen-associated hospital-acquired infections (HAIs) cause 99,000 deaths annually, leading to an economic loss of around the US $20 billion. Further, an annual loss worth the US $35 billion has been reported in terms of lost productivity due to antibiotic resistance in the health care systems (Ventola, 2015). According to the Research and Development Corporation, a US organization, a worst-case scenario may evolve in the future, where the world might be left without any potent antimicrobial agent to treat bacterial infections. In this situation, the global economic burden of AMR would be about the US $120 trillion by 2050, about 444 million people would succumb to infections of resistant microbes, and birth rates would decline rapidly (Founou et al., 2017).

At present, in India, the infectious disease mortality rate is 416.75 per 100,000 persons, which is twice the rate prevailing in the US (roughly 200 per 100,000 persons) when the antibiotics were introduced (Armstrong et al., 1999). India will face a bigger challenge of AMR. It is predicted that by 2050 about 2 million people would die annually because of the AMR. These include the death of more than 50,000 newborns from sepsis due to AMR pathogens. At present, around 33000 people die every year because of AMR. The India TB Report-2021 estimated 24.04 lakh people suffering from tuberculosis and 79144 dying from it. India spends only 4.7% of its gross domestic product (GDP) on health.

Several studies have demonstrated an alarming increase in the AMR. As per the latest report, the extended Spectrum of Beta-Lactamase (ESBL) production rate is 70% in *E.coli* and 60% in *Klebsiella*. In India, an estimated 58,000 neonatal sepsis deaths are attributed to drug-resistant infections (Laxminarayan et al., 2013). Worldwide, every year about 700,000 people die from antimicrobial-resistant infections, and it is projected to reach 10 million by 2050 with an economic loss of 100-250 trillion US $ (O'Neill, 2015). About 2.4 million people in high-income countries would die by 2050 if the current trends of antimicrobial resistance continue. Even in the US, the AMR bacteria and fungi cause at least 28,68,700 infections and 35900 deaths every year. By 2050, the AMR would lead to at least a 25% increase in health expenditure in low-income countries. In 2017, it was reported that among 600,000 cases of rifampicin (most

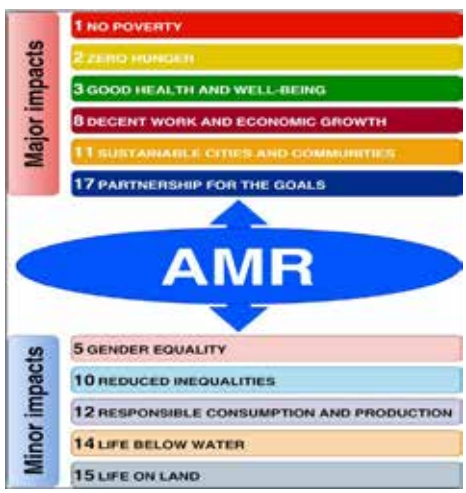


Fig. 2. Impact of AMR on Sustainable Development Goals

effective first-line drug) resistant Mycobacterium tuberculosis (the causative organism of TB), 82% had MDR-TB (multidrug-resistant tuberculosis) (Tasbiti et al., 2018; WHO, 2020).

In addition to the health and economic outcomes, other impacts of AMR are intangible. The available evidence indicates that if the AMR is left unaddressed, its scourge may evolve into a developmental challenge (Figure 2). A World Bank report points that infections by AMR pathogens could neutralize the health achievements of the past century. The AMR has been recognized as a major impediment in ending extreme poverty and hunger, promoting well-being and healthy life, and achieving sustainable economic development. It is further reported that if the AMR is not contained, it is also likely to aggravate gender inequities as the probability of drug-resistant infections is higher in females during pregnancy and child-birth, besides the sepsis and urinary tract infections, which are more common among women (CDC, 2016).

However, the achievements of some Sustainable Development Goals (SDGs) may positively contribute towards the containment of AMR. For example, when the availability of clean and potable water is ensured and when hygienic living is provided, the incidences of infectious diseases to poor people will drop, thus limiting the necessity of antibiotic usage and thereby ensuring antimicrobial stewardship at the community level.

AMR is a Cause of Great Concern
• Antimicrobials are essential for sustainable food production. In the absence of an AMR control strategy, its economic consequences would be severe on food supplies.
• Human and animal health management is at risk due to AMR. Without the availability of effective antibiotics, cancer chemotherapy, surgeries and organ transplant would be at great risk because of post- and pre-procedure/ post-operative infections.
• In 2016, the UN General Assembly had a high-level meeting to develop and implement the "International Action Plan on AMR". This was the 4th health issue taken up by UN General Assembly in past 72 years.

3. THE WORLD OF SUPERBUGS

The anomalous use of antibiotics has resulted in evolving resistant bacterial pathogens. Because of several mutations, the pathogens develop resistance to different classes of antimicrobials, and such pathogens are frequently associated with higher morbidity and mortality. The emergence of "superbugs" —ranging from multidrug-resistant (MDR), extensively drug-resistant (XDR) to totally drug-resistant (TDR) pathogens —is a cause of grave concern. XDR *Mycobacterium tuberculosis* is the most dangerous pathogen in developing as well as developed countries (Sotgiu et al., 2009).

The 'ESKAPE' pathogens (*Enterococcus* spp., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii, Pseudomonas aeruginosa* and *Enterobacter* spp.) are the most important identified antimicrobial-resistant pathogens involved in a majority of the hospital-acquired infections. These microorganisms are associated with the presence of specific mechanisms of chromosomal or transferable resistance and show multi-drug resistance to most antibact erial agents. In some cases, the ESKAPE microorganisms even show resistance to all the scheduled antibacterial agents, necessitating the use of the "last resort" antibacterial agents for the management of infections. The antibiotic-resistant gene may remain occult and silently introduced in a commensal microbiomes, and thereafter transmitted to pathogenic microorganisms. CDC has reported dangerous AMR in ESKAPE and emphasized the need for the development of new antimicrobial drugs in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), fluoroquinolone-resistant *Pseudomonas aeruginosa*, extended-spectrum *β*-lactamases (ESBL) producing and

carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter* (National Nosocomial Infections Surveillance, 2004; INSAR, 2013).

Staphylococcus aureus is considered one of the most notorious superbugs. More people die because of the infection of methicillin-resistant *Staphylococcus aureus* (MRSA) than of HIV/AIDS and tuberculosis combined (Boucher and Corey, 2008). Community-associated MRSA (CA-MRSA) with increased acquired virulence has emerged as a major threat to public health. Although most of the properties of CA-MRSA are similar to that of MRSA, the CA-MRSA has two additional genes, i.e., *mec* gene clusters and genes encoding the cytotoxic Panton-Valentine Leukocidin **(**Watkins et al., 2012)**.** Methicillin-resistant *Staphylococcus* is considered to be endemic in India. In the past few years, the infection of MRSA in India has increased from 29% of *S. aureus* isolates in 2009 to 47% in 2014 (CDDEP, 2015), while its incidence has declined in Europe and the US.

In 2017, the WHO listed ESKAPE pathogens in the list of 12 bacteria that pose increasing risks to human health because these are resistant to most of the existing antibiotics. The WHO also emphasized the development of new antibiotics to treat infections of these resistant microbes. To foster research, discovery and development of new antibiotics, the WHO published a list of "global priority pathogens". The WHO described the three categories of pathogens: (i) critical, (ii) high and (iii) medium priority, according to the species of pathogens and the class of antibiotics against which the pathogens have developed resistance and the urgency for development of new antibiotics. Carbapenem-resistant *A. baumannii* and *P. aeruginosa* along with extended-spectrum β-lactamase (ESBL) or carbapenem-resistant *K. pneumoniae* and *Enterobacter* spp. are in the critical priority list of pathogens; whereas, vancomycin-resistant *E. faecium* (VRE) and methicillin and vancomycin resistant *S. aureus* (MRSA and VRSA) are in the high priority list (Tacconelli et al., 2018).

12 Pathogens Prioritised by WHO for Development of New Antibiotics

Critical Priority

- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*

} *Carbapenem-resistant*

- Extended-spectrum beta-lactamase-producing *K. pneumoniae*
- Extended spectrum beta-lactamase-(ESBL) producing *Enterobacteriaceae*

High Priority

- *Enterococcus faecium: vancomycin-resistant*
- *Staphylococcus aureus: methicillin-and vancomycin-resistant*
- *Helicobacter pylori: clarithromycin-resistant*
- *Campylobacter spp. and Salmonella spp.: fluoroquinolone-resistant*
- *Neisseria gonorrhoeae: cephalosporin-and fluoroquinolone-resistant*

Medium Priority

- *Streptococcus pneumoniae: penicillin-non-susceptible*
- *Haemophilus influenzae: ampicillin-resistant*
- *Shigella spp.: fluoroquinolone-resistant*

4. DRIVERS OF AMR

Bacterial pathogens of animal and human origin are becoming increasingly resistant to most of the frontline antimicrobials. Resistance happens when microorganisms change their metabolic pathway after their exposure to antimicrobial drugs. The misuse and overuse of antimicrobials are

increasing, especially in the developing countries where the antimicrobials are freely accessible to the public without any prescription from the medical practitioners, and poor hygiene facilitates the transmission of the resistance from one microbe to another microbe (Rossolini et al., 2014).

How Antibiotic Resistance Develops in Microorganisms

A. Natural Resistance: Some bacteria are naturally resistant to a certain type of antibiotics e.g. Gram^{+ve} bacteria will not be inhibited/killed by narrow-spectrum antibiotics (e.g., streptomycin); effective only against Gram^{-ve} bacteria.

B. Acquired Resistance: Any bacterium that acquires resistance genes, whether by spontaneous mutation or through the genetic exchange, can resist one or more antibiotics. Because it can have multiple resistance traits in its genetics, it can become resistant to many different families of antibiotics.

1. Biochemical Mechanisms:

- Reduce the entry of antibiotics into a pathogen, by altering the mechanism/ process of transport of drugs.
- Enhance the export of antibiotics from microorganisms by efflux pumps.
- Synthesis and release of some microbial enzymes that denature and destroy the antibiotics.
- Alteration and modification of target microbial proteins, so there is no site for action of antibiotics.
- Development of an alternative metabolic pathway, which is not affected/ inhibited by the antibiotics.

2. Mutation

- Antimicrobial resistance may be acquired by mutation and selection, with the passing of the trait. The mutant gene is transferred vertically to daughter cells and also in horizontal way through transduction, transformation and conjugation. Resistance acquired by clonal spread of the resistant strain or by subsequent transfer to other susceptible recipient strains e.g., the plasmid-encoded staphylococcal β lactamase gene is distributed widely among many unrelated strains.

Can Bacteria Lose their Antibiotic Resistance?

Yes, the antibiotic resistance traits can be lost, but this reversal process occurs very slowly. If the selection pressure of an antibiotic is removed (i.e., complete stopping of antibiotics used for long, may be for several decades), the bacterial population can potentially revert to a population of bacteria that responds to antibiotics.

Issues of Cross Antimicrobial Resistance and Co-resistance

Cross-resistance means when the resistant microorganism to one antibiotic develops resistance to all other antibiotics belonging to the same class due to the same mechanism of action. For example, the resistance of pathogens to one sulfonamide means resistance to all sulfonamides. Similarly, the resistance of pathogens to one tetracycline means resistance to all tetracyclines. Sometimes, this cross-resistance is seen in unrelated drugs, e.g., between tetracyclines and chloramphenicol or between erythromycin and lincomycin.

In the pharmacology of antibiotics, the concept of cross-resistance was used first time in 1946. Cross-resistance may be:

- Two-way cross-resistance, e.g., between erythromycin and clindamycin. If a pathogen is resistant to erythromycin, it will be resistant to clindamycin or *vice versa*.
- One-way cross-resistance, e.g., the development of neomycin resistance by *Enterobacteriaceae* makes them resistant to streptomycin but streptomycin-resistant organisms remain susceptible to neomycin.

Difference Between Cross Resistance and Co-resistance
• Cross-resistance: where one resistance system confers resistance to both antimicrobials. • Co-resistance: where the resistance of one antibiotic (antibiotic-A) and another antibiotic (antibiotic-B) is physically co-located on the same genetic element, as on plasmid. Co-resistance is also generally seen in the development of bacterial resistance against an antimicrobial and metals (e.g., Cu) • Co-regulation/ Co-expression: It applies only to co-resistance, where the expression of the resistance system to both antibiotics are controlled by a common regulator. **Multidrug-Resistant (MDR), Extensively Drug-Resistant (XDR) or Totally Drug-Resistant (TDR), "Superbugs" are different terms used to represent the extent of resistance in microorganisms.**

Most of the antibiotics are produced naturally by saprophytic bacteria or fungi. It is opined that various antimicrobial molecules produced by saprophytic bacteria and fungi impede the growth of other competitive organisms in the environment. The functional metagenomic analysis of several microbes has revealed an extensive diversity in the genetic determinants associated with antibiotic resistance. The microorganisms appear to undergo the 'Darwinian selection' to develop stringent mechanisms to escape the lethal effects of antimicrobial substances (Holmes et al., 2016). Against the last generation of antibiotics, i.e., fluoroquinolones (ciprofloxacin, enrofloxacin, pefloxacin, etc.), the organisms have evolved a multitude of defensive phenomena, including alteration of the target (DNA-gyrase), increased efflux (export of drug out of microorganism), synthesizing fluoroquinolone inactivation enzyme (aminoglycoside N-acetyltransferase), and protection of the target by DNA-binding proteins.

Although the emergence of antimicrobial resistance in microorganisms is a natural phenomenon, the injudicious use of antimicrobials in human, animal and plant health care systems and the antibiotic residues in the environment have been the prominent causes of the development of resistance in microorganisms. The selection pressure exerted by the antimicrobial exposure allows microorganisms with inherent resistance or newly acquired mutations or resistance genes to survive and proliferate (Aminov, 2009). Other important factors which are potent drivers of antibiotic resistance include poor sanitation settings, ineffective infection control standards, poor water hygiene, spurious drug quality, non-availability of diagnostics and vaccines, and non-implementation of travel or migration quarantine. The situation is compounded by many other factors, including the interaction of the pathogen with the drug and the host, mutation rates, emergence of successful antimicrobial-resistant clones, the transmission rate of the pathogen between humans and animals, cross-resistance, and selection of co-resistance to unrelated drugs (Holmes et al., 2016). There might be a genetic linkage between resistance gene and virulence gene, resulting in increased virulence of resistant strains. Co-transfer of resistant traits and virulence genes could make drug-resistant pathogenic strains intrinsically more virulent than drug-susceptible strains.

Irrational use (misuse and overuse) of antimicrobials in poultry and farm animals is directly associated with the transmission of resistance as well as resistant microbes to humans via animal-source foods. The most important pathogens which are transferred through animal-source foods are *Salmonella* spp. and *Campylobacter* spp. Resistant bacteria and their mobile genetic elements make an easy transfer from the animals to humans through animal-source foods. Further, similar mechanisms of resistance development have been reported in the bacteria isolated from humans as well as from animals. The roles of sewage systems and waste management procedures of the pharmaceutical industry in the development of antimicrobial resistance are well documented. Several resistant pathogens have been isolated from pre-and post-treatment sewage (Schwartz et al., 2003).

It is reported that from animals over 75% of the total administered antibiotics is excreted unmetabolised in urine and faeces and enter into sewage systems and water bodies. Thus, the animal waste not only contains resistant bacteria but also antibiotic residues which can trigger the development of resistance in new bacteria. Similarly, a large amount of unmetabolized antibiotics is also released into municipal waste through urine and faeces of antibiotic-treated humans. In India, a study detected plasmid-borne *bla*NDM-1resistant genes in *Shigella* spp and *Vibrio* spp. in 2 of 50 drinking water samples and 51 of 171 seepage samples (Andremont and Walsh, 2015). Further, *E. coli* resistant to extended-spectrum cephalosporins have been detected in the samples from rivers and sewage treatment plants (STPs) (Akiba et al., 2015).

Non-Human Antibiotic Use: The Key Driver of AMR

- Quantitatively, antibiotics are the most used drugs in human medicine. Whilst the use of antibiotics in human medicine is identified as a strong risk factor in the development of antibiotic resistance, the use of antimicrobials outside of human medicine is also responsible for AMR.
- Antibiotics are commonly used in veterinary medicine, animal husbandry, apiculture, aquaculture, ethanol production, horticulture, crop production, anti-fouling paints, food preservation and other domestic uses.
- Antimicrobials are more used in animal husbandry than in managing human health. Non-human antimicrobial use (AMU) leads to the development of resistant microbes in humans.
- In the US and the EU, animal food production accounts for 70% of total antimicrobial consumption as compared to 30% as human medicine.
- The amount and pattern of AMU have a direct impact on resistant bacteria in animals and humans.
- The food-borne route is the major transmission pathway for AMR bacteria and antibiotic-resistant genes from animals to humans.
- Surveillance of AMR and antimicrobial use (AMU) in non-human (livestock, aquaculture and agriculture) species is most important for combating the AMR
- The publication of the first global report on surveillance of AMR by WHO in 2014 indicated that surveillance data, where available, could be of immense value for understanding the trends, identifying the priority areas for interventions, and monitoring the impact of interventions to check the antibiotic resistance. Lack of adequate surveillance of AMR in many parts of the world leaves a very huge gap in knowledge of the distribution and extent of the AMR phenomenon.

Source: O' Neill, 2014)

What are the Main Reasons for AMR Threat

A serious menace of antimicrobial resistance prevails across the world. While the full impact of AMR is yet to be understood, there is no reporting and testing system to track AMR. Some important reasons for the AMR threat are given below:

- Antimicrobial use (AMU) in humans and animals often overlaps as the infections are caused by the same pathogens, and the line of treatment is also with the same antibiotics.
- The extensively used antibiotics like penicillin, cephalosporins and tetracyclines in dairy animals, are also important and lifesaving antibiotics in treating pathogenic infection in humans.
- About 75% (31/41) of approved veterinary drugs are also classified as essential drugs for human treatment.
- The global antimicrobial consumption in livestock health care is predicted to increase by 67% by 2030, reaching 240,000 tons.
- Despite a serious threat of AMR, antibiotics, the manufacturing of veterinary-specific pharmaceuticals is not receiving attention.

The untreated pharmaceutical waste is a dangerous reservoir of antibiotic resistance. Globally, an estimated 30,000 – 70,000 tons of pharmaceutical waste with antimicrobial residues are annually generated by nearly 200 antibiotic pharmaceutical industries, most of which are located in China and India. This quantity represents about 10-20% of the total antimicrobial activity in the manufacturing of the global antibiotic demand of around 250,000 tons a year. It is reported that more than 95% of the antibiotic manufacturing waste is in liquid form and it needs necessary treatment before its release to the environment (O'Neill, 2016). A study on the wastewater treatment plant in India that received effluent from 90 bulk Active Pharmaceutical Ingredients (API) manufacturers revealed high levels of APIs being discharged into a nearby river. The study also revealed a very high concentration of ciprofloxacin, a commonly used antibiotic, (31 mg/l) in the river, which was about 1000 times higher than the concentration required for bactericidal effect in the patients and approximately one million times greater than the levels that are generally reported in treated municipal sewage effluent (Larsson et al., 2007; Larsson, 2014).

In addition to antibiotics, disinfectants, heavy metals and biocides also play an important role in the development of resistance in bacteria. The sub-lethal concentration of herbicides has been shown to increase the efflux pumps in bacteria. As such, the varied uses of antimicrobials in humans, animals, agriculture along with its environment interface underline the development and transmission dynamics of antibiotic resistance.

5. HOW MUCH ANTIBIOTICS ARE USED IN HUMANS AND LIVESTOCK?

5.1 Use of Antibiotics in Humans

A global study, (Klei et al., 2018) that aimed to determine the trends in antibiotic consumption from 2000-2015 in 76 countries, compared the consumption between the low-middle income countries (LMIC) such as China and India, with high-income countries (HIC) such as the UK and the US. This study found that over 16 years, global antibiotic consumption has increased by 65% from 21.1 billion to 34.8 billion defined daily doses (DDDs). Further, as compared to HICs, the total consumption of antibiotics was higher in LMICs. Another very interesting observation is that the consumption of newer and “last resort” antibiotics has increased across all countries. Assuming that there is no change in the policy, antibiotic consumption, has been projected to increase by 200%, reaching 128 billion DDDs by 2030 (Eli et al., 2018).

Several studies have also projected high usage of antibiotics in India. The per capita antibiotic consumption in the retail sector has increased to the extent of about 22% (from 13.1 DID in 2008 to 16.0 DID in 2012). In addition, there has been a rise in the use of a newer class of antibiotics like carbapenems, lincosamides, glycopeptides, third-generation cephalosporins and penicillin with beta-lactamase inhibitors. However, the per capita antibiotic consumption in India is low (16.0 DID) as compared to European countries (21.54 DID) (Farooqui et al., 2018). Laxminarayan and Chaudhury (2018) found that in 2010, India was the world’s largest consumer of total antibiotics for human health, and also the highest over-the-counter non-prescription user of lifesaving antibiotic carbapenems. The overuse of antibiotics contributed to the growing carbapenem-resistance among Gram-negative organisms.

Antibiotics are often viewed as “magic bullets” not only in the treatment of infections of bacterial pathogens but also of viral infections, where an antibiotic may not have any direct effect but is frequently used to check the secondary bacterial infections. Ray et al.(2019) reported that in the US, 43% of the antibiotic prescriptions in ambulatory care are without documentation,

hence, “inappropriate” use of antibiotics. The situation may be more serious in India where the disease burden is high, diagnostic facilities don’t have a wider reach and antibiotics are easily available without prescription by the medical practitioner

5.2 Use of Antimicrobials in Livestock and Poultry

In the animal food production system, antimicrobial drugs are widely used, resulting in an increase in antimicrobial resistance both in zoonotic and commensal bacteria. This has raised concerns about the risks of transmission of ‘resistant zoonotic bacteria’ as well as ‘resistance genes’ through commensal bacteria from animals to humans. Thus, a steady increase in the resistance across microbial species has been the major concern for veterinary and human health professionals.

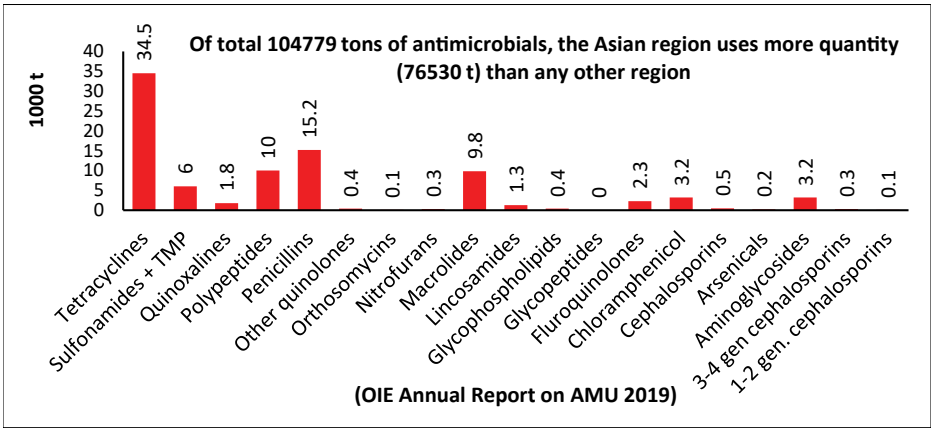


Fig.3. Share of differet antimicrobials (quantity) used in veterinary pracatice (Report from 116 countries)

Globally, antibiotics are used in livestock not only as therapeutics but also as metaphylaxis, prophylaxis and as growth promoters. According to Lander (2012) and Martin (2015), in the US about 93% of the medically-important antibiotics are administered in poultry and animals *via* feed and/or water. In a global map on antibiotic consumption in livestock in 228 countries, it is predicted that the use of antimicrobials in food animals will increase by 67%, from 63,151 tons in 2010 to 105,596 tons in 2030; and the consumption will be nearly double in Brazil, Russia, India, China, and South Africa (Van Boeckel et al., 2015). The estimated annual consumption of antimicrobials to produce one kilogram of beef, chicken and pork is 45, 148 and 172 mg, respectively. According to an estimate, in the US about 80% of the total antibiotics in livestock practice are sold as growth supplements and for prophylaxis to control infection. The non-therapeutic usage of antibiotics is common in poultry and aquaculture. In India, by 2030, the use of antibiotics in animal feed is predicted to increase by 82%, and in poultry production by three times.

In India, the exact burden of AMR in livestock and food-producing animals has been poorly documented, but several studies have reported widespread occurrence of multi-drug resistance among bacterial pathogens from livestock and poultry. In one study (unpublished) 32.1% of *E. coli* isolates from cattle, buffalo, poultry and dogs have been found positive for the production of ESBLs. Although antimicrobials are used to treat a range of bacterial diseases in animals the

mastitis is one of the most common for antibiotic usage. Penicillins and their combinations are commonly used antimicrobial for clinical mastitis followed by fluoroquinolone, aminoglycosides and cephalosporins *(*Srivastava et al., 2015*)*.

A study by the Centre for Science and Environment (2017) reports that 100% of the *E. coli*, 92% of *K. pneumoniae* and 78% of *S. lentus* isolated from poultry were multi-drug resistant, with 40% of *E. coli* and 30% of *K. pneumoniae* isolates being resistant to at least 10 of the 13 antibiotics tested. These isolates showed a high degree of resistance to penicillin, fluoroquinolones, 3rd and 4th generation cephalosporins and carbapenems. Further, the *E. coli* isolates from the poultry litter and surrounding soil samples indicated the spread of *E. coli* to the environment.

There is Problem of AMR in Livestock Food Production System: Antibiotic-Resistant Pathogens are Isolated from Livestock

In livestock and poultry, in addition to the therapeutic, prophylactic and metaphylactic uses the antibiotics are also used as growth promoters, and as food preservatives, disinfectants and antiseptics. Although, the FSSAI has banned the use of antibiotics and several pharmacologically active substances in aquaculture, but not in poultry and dairying (NAP-AMR 2017). Since India has one of the largest livestock sectors in the world and given the fact that there is unregulated use of antibiotics in animals the livestock sector is likely to play a significant role in the emergence of AMR. About 10-11% of the total prevalence of antibiotic residues in milk is due to β-lactams and tetracycline group of antibiotics.

1. Intensive livestock farming is associated with more disease incidences, and thus requires more AMU. As such, in commercial farms, injudicious use of antibiotics is more prevalent than in unorganized farms.
2. Antimicrobial use is more in poultry and monogastric animals (pigs) than in ruminants. Hence, the incidence of AMR is higher in poultry, followed by pigs and cattle.
3. There are more AMR and MDR microbial isolates from commercial chicken farms.
4. The enteric bacterial isolates of *E. coli, Enterococcus spp* from food-producing animals are resistant to ampicillin, tetracycline, co-tromoxazole and streptomycin.
5. The carbapenem-resistant Gram-negative pathogens and 3rd generation cephalosporines resistant extended-spectrum β lactamase (ESBL) pathogens have been isolated from dairy animals.
6. There are many genetic similarities between the extended-spectrum β-lactamase (ESBL) positive *E. coli* isolated from humans and poultry.
7. There is a direct correlation between antibiotic usage and the development of resistance in *E. coli* isolated from animals.

Source: CDC (2019)

Use of Antimicrobials as Growth Promoter

- In an international survey conducted by the OIE (2019), most of the countries have reported the use of antibiotics for the growth promotion of dairy animals and poultry birds.
- In India, the BIS in 2017 has recommended that antibiotics with systemic action should not be used as a growth promoter in poultry feed and the use of gut acting antibiotics should be phased out in 5 years. The Department of Animal Husbandry, Dairying and Fisheries has directed the state governments to stop the use of antibiotics as a growth promoter in feed or use of any antibiotic as feed supplements. The FSSAI in 2015 has also banned antibiotic growth promoters in the animal/ poultry feed industry.

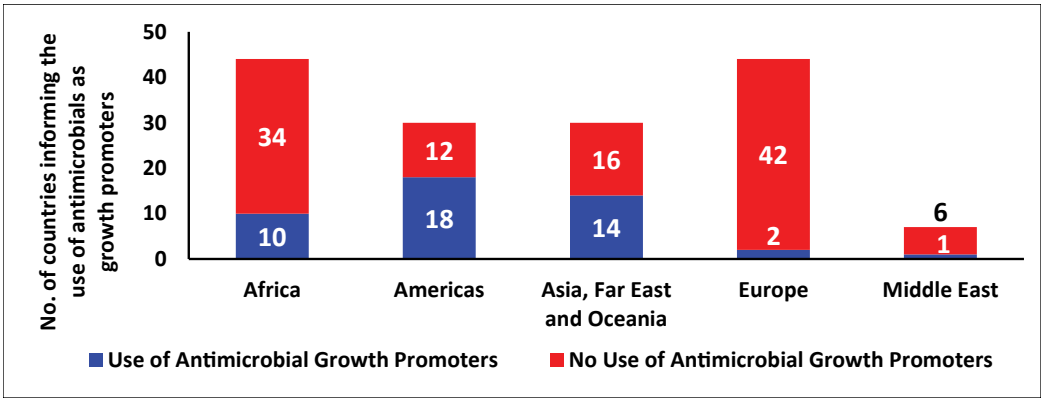


Fig.4. Global use of antibiotics in animal feed as a growth promoter

Is there a Correlation between Antimicrobial Use (AMU) and Antimicrobial Resistance (AMR)?

- The 3rd and 4th generation cephalosporins and fluoroquinolone resistance in *E. coli* isolates from humans is directly associated with their use in humans.
- The consumption of macrolide antibiotics in animals is directly and significantly associated with macrolide resistance in *Campylobacter* species isolated from animals and humans.
- The fluoroquinolones resistant *Salmonella* and *Campylobacter* species isolated from humans is directly related to the use of fluoroquinolones in animals of the region.

Contrary to these, there are also reports that:

- In 2015 the use of tetracycline in cattle remained the same as in 2014, but the prevalence of tetracycline-resistant *C. jejuni* was significantly increased in 2015 as compared to 2014.
- The use of Fluoroquinolones in food-producing animals decreased from 114 kg in 2001 to 18 kg in 2005, but the fluoro-quinolone-resistant *C. jejuni* infection increased during the said period.

Source: CDC (2019)

Resistant bacteria are transmitted from farm animals to humans either through direct contact or indirect contact through the foods of animal origin and the environment. The excreta of the animals treated with antibiotics may contaminate the environment with antibiotic residues, resistant pathogens and resistance genes. Animal excreta may also contaminate the soils and crops (mainly vegetables) when used as manure.

The commensal bacteria may also acquire resistance genes and play an important role in the transmission of resistant organisms and resistance genes to humans through the environment (Marshall and Levy, 2011). In a study from seven European countries, a clear positive correlation has been established between antibiotic use and prevalence of resistance gene in *E. coli* isolated from cattle, pig and poultry and *E. coli* from the environment by (Chantziaras et al., 2014).

Environmental Contamination of Antibiotics is of great Concern for Antimicrobial Resistance

- Resistant genes, as well as resistant bacteria in the environment, are increasingly seen as an ecological problem. The most prominent medical threats are the presence of vancomycin-resistant *Enterococci* (VRE), methicillin-resistant *Staphylococcus aureus* (MRS) and multidrug-resistant *Pseudomonas* in the environment.
- About 75-90% of antimicrobials are excreted as such unmetabolized in faeces and urine of humans and animals.
- About 93% of antibiotic residues in milk is because of the treatment of mastitis with antibiotics.
- Environmental pollution with antimicrobial residues from the antibiotic manufacturing pharmaceutical industries leads to the problem of AMR development. India and China are manufacturing about 90% of global antibiotics.
- The environment around antibiotic manufacturing pharmaceutical plants is identified as a big source of AMR pathogens in India and China. Although the Ministry of Environment, Forests and Climate Change, the Government of India has stringent standards on antibiotics residues in the waste discharged by pharmaceutical factories.
- Medicated cleansing products are also responsible for environmental contamination (Martinez, 2009; Kraemer et al., 2019)

5.3 Use of Antibiotics in Agriculture

For a long, antibiotics have been used to control specific and non-specific bacterial diseases of rice, vegetables and ornamental plants. However, the amount of antibiotics used on crops is relatively low, 0.2–0.4% of total agricultural antibiotic consumption. The most commonly used antibiotics on plants include kasugamycin, oxytetracycline and streptomycin. Although there is no clinical use of kasugamycin in humans and animals, streptomycin and tetracycline have been classified by WHO as “critically” and “highly” important antibiotics in human medicine. As such, there is always a chance that the residues of antibiotics are carried in edible parts of the plants and fruits, which may lead to the development of AMR in human and animal pathogens.

Use of Antibiotics in Crop Production: Great Concern for AMR

Indiscriminate use of antibiotics on food crops in several parts of India could result in resistant microbes for the environment and humans. A few antibiotics considered critically important for human medicine are being recommended for use in crops. As such antibiotics and resistant bacteria along with resistant genes remain in harvested crops and enter into the human food chain (Taylor and Reeder, 2020). Additionally, after spraying much of the antibiotic remain unspent in the soil. There is a growing concern, as this creates a reservoir of resistance in the environment.

- In 2019, the US Environmental Protection Agency (EPA) controversially allowed farmers to spray hundreds of tons of human antibiotics, including streptomycin in the orchard to combat the disease “citrus greening”.
- An investigation by the FAO, WHO and OIE found that only 3% of the countries did a regular assessment of the types and amounts of antibiotics used on crops.
- The spray of streptocycline, a mixture of 2 antibiotics i.e., streptomycin and oxytetracycline on cauliflowers, radish, spinach, fenugreek and bottle gourds is a common practice. Here, it is important to mention that both these antibiotics are very critical, lifesaving and highly important as human medicine.
- Surprisingly, the Central Insecticide Board and Registration Committee (CIBRC) has registered streptocycline as a fungicide and to make the matter worse, it is classified as a fungicide with low toxicity.
- Hindustan Antibiotic Limited produces 106 tons sytreptocycline every year and about 50% of total production is used in India. It is reported that in 2016-17, about 25 tons of streptocycline was used in crop production. Here it is noteworthy to mention that in the EU, streptocycline is not approved for its use in crop production.

Source: Khullar et al.(2019)

AMR in Aquatic Animal Species

- Fish is the most traded food commodity in the international market, and the development of resistance to fish pathogens has created panic.
- Although the quantity of antibiotics used in fisheries is small, clinically it is threatening to human health because of several recent reports of MDR isolates from fishes.
- However, the existence of somewhat stringent legislative provisions with frequent inspection of AMR in aquatic animals than in dairying and poultry may probably provide some relief.
- In shrimp hatcheries, mass mortality due to antibiotic-resistant *luminous* bacteria (*vibrio species*) is a problem.
- In Italy, over 80% of *Vibrio harveyi* from aquaculture showed resistance to amoxycillin, ampicillin, erythromycin and sulfadiazine.
- Several mobile genetic elements like plasmids, transposons and integrons carrying the AMR genes have been detected in *Aeromonas species*.
- Acquired resistance in *Aeromonas salmonicida* in temperate water fish has been reported from several countries.

Sources: FAO (2018; FAO, 2019)

5.4 Use of Biocides and Heavy Metals *vis a vis* AMR

In addition to antibiotics, biocides and heavy metals have also been identified as supplementary chemical drivers of resistance genes. Present-day biocides are not used only in spheres of human life (e.g., toothpaste, hygiene-related products, household cleaners etc.), but also in animal husbandry and food industries. The presence of biocides in the environment may lead to the selection of resistance genes that can also be involved in cross-resistance or co-resistance to antimicrobials (Pal et al., 2015; Alonso-Calleja et al., 2015). The development of acquired tolerance to biocides, increase in antibiotic resistance and ability to form strong biofilms have been reported in *Cronobacter sakazakii* and *Yersinia enterocolitica* pathogenic organisms exposed to sub-MICs of many disinfectants such as sodium hypochlorite, peracetic acid and benzalkonium chloride (Capita et al., 2019). Similarly, potent induction of VanA-type vancomycin resistance genes and the genes associated with daptomycin resistance have been reported upon continuous exposure to chlorhexidine, a bisbiguanide antiseptic incorporated into many infection control products (Pooja et al., 2016). Exposure to triclosan, a common biocide used in more than 2,000 different kinds of products (toothpaste, hand-washing liquid etc.), also leads to hereditable multiple-antibiotic resistance in *E. coli* due to increased mutation frequency (Lu et al., 2018).

Anthropogenic contamination of the environment with heavy metals is a serious problem. Application of metal-containing fertilizers, sewage sludge and liquid manure is a common practice in agriculture, due to which heavy metals (Hg, Cd, Cu, Zn, Cr, Ni etc.,) are transferred to arable soils. Also in aquaculture, the copper (Cu) containing materials are used as anti-fouling agents for farm cages. The mechanisms of development of antimicrobial resistance to metals are similar to that for antimicrobials, i.e., increasing efflux pumps, reduced membrane permeability, and alteration of the target. As such the microbial communities exhibit both cross-resistance and co-resistance between heavy metals and antibiotics, and heavy metals appear to "co-select" indirectly for antibiotic resistance. A genetic linkage of Cu resistance (*tcrB*), macrolide (*erm*(B) and glycopeptide resistance (*vanA*) has been observed in *E. faecium* isolated from farm animals (Palomino, 2014).

5.5 Environmental Pathways for Dissemination of Antimicrobial Resistance Genes (ARGs)

There are numerous genes responsible for antimicrobial resistance in several pathogens. These genes are often located on the mobile genetic elements of the organisms and traverse across species and genera resulting in the dissemination of antimicrobial resistance even in a distantly related microorganism. Another mechanism of the flow of resistance genes is through a direct clonal transfer of resistant organisms (Figure 5).

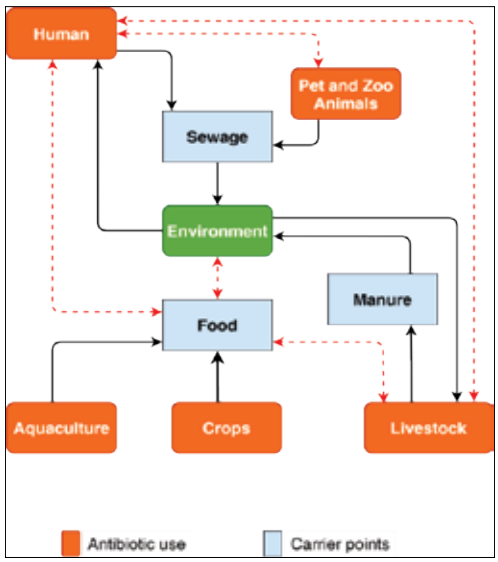


Fig.5. Pathways of transfer of AMR in the environment

Sewage and animal manures are two potent sources of environmental contamination with AMR bacteria. Although, the sewage and manures originating from urban regions are treated before their release into the environment, but the evidence suggests that the treatment is not sufficient to neutralize the risks of the spread of the AMR organisms. Moreover, in developing countries, a large quantity of sewage and animal manures with AMR bacteria are directly released into the environment without any treatment. It has been reported that contamination of the environment (soil and water) and riverine water with AMR bacteria not only facilitate the dissemination of antimicrobial resistance, but also the contaminated water sediments act as a potential reservoir of AMR bacteria allowing long-term release into other ecological niches. In addition to sewage and manures, foods of animal, plant and aquatic origin also play important role in the clonal dissemination of AMR bacteria. In the past two decades, numerous studies have isolated antibiotic-resistant bacteria from foods of animal, plant and aquatic origin.

Further, the direct transfer of AMR bacteria from pets to humans is also possible. When pets are under long-term antibiotic treatment, the resident flora of the pets is replaced by drug-resistant organisms and thus poses considerable risk of transmission of AMR bacteria to their owners/handlers. With shrinking urban space and rising pet ownership, this mode of transfer of antibiotic-resistant infections is assuming greater importance than ever.

From the available evidence, it appears that the milieu through which the spread of AMR bacteria and/or AMR genes is mediated is complex (Figure 5.) and intricately linked to many

factors, including antimicrobial usage patterns (in human and veterinary medicine, agriculture, animal husbandry and aquaculture), waste disposal (sewage and farm manure), food production system and changing relationships between humans and their pets.

6. GLOBAL AND NATIONAL IMPLICATIONS

Antimicrobial resistance (AMR) is a multifaceted complex problem with momentous consequences for individuals as well as the healthcare systems. Understanding the gravity of the problem, the "World Health Assembly" adopted the Global Action Plan (GAP) on AMR in 2015 as a part of the tripartite collaboration among WHO, FAO, and OIE (World Organization for Animal Health). It sets out strategic objectives: (i) to improve awareness and understanding of antimicrobials and antimicrobial resistance, (ii) to strengthen knowledge of AMR through surveillance and strategic research, (iii) to reduce the incidence of common infection by improving the infection control and eradication program, (iv) to optimize the use of antimicrobial agents also by computing the dosage regimen, (v) to develop an economic model for sustainable investment to meet the needs of countries, and (vi) to increase investment in the development of new antibiotics, diagnostic tools and vaccines.

All member countries of WHO had committed to support the WHO Global Action Plan on Antimicrobial Resistance, by developing their National Action Plans. Following this, many countries have formulated their own National Action Plans (NAPs). Consequently, the Government of India too has prioritized the AMR in the National Health Policy. The National Action Plan of India for AMR was released and launched in April 2017 by the Ministry of Health and Family Welfare. The major objectives of the NAP are aligned with GAP.

6.1 Regulatory Policies on Antibiotic Use in Human and Animals

Since the drivers of AMR include multifactorial "use and abuse" of antimicrobials across the human, animal and environment interface, the possible solution for addressing this problem is the application of collaborative efforts through the "One Health" approach. The effectiveness of the existing antimicrobials has to be compulsorily preserved for mankind. As such, WHO in a 'Tripartite Alliance' with FAO and OIE has validated the One Health approach to addressing the problem of AMR. WHO has further endorsed the 'Global Action Plan (GAP) on AMR' which was launched during the 8th meeting of the World Health Assembly in May 2015, to ensure the successful treatment and prevention of infectious diseases with effective and safe medicines, used responsibly. WHO again reassures to work with partner countries and new partners to improve infection prevention and control and to foster appropriate use of existing and future antibiotics (Mc Ewan and Collignon, 2018).

To ensure prudent use of all antimicrobials in both human and veterinary medicine, WHO has earlier ranked the available antimicrobials as per their importance in human medicine. A list of Critically Important Antimicrobials (CIA) was developed in the 1st WHO Expert Meeting of the "Advisory Group on Integrated Surveillance of Antimicrobial Resistance' (AGISAR) on CIA for Human Medicine", held in 2005 in Australia. Now in the latest version of the CIA list (6th revision, 2018), the antimicrobials belonging to certain classes (fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and ketolides, glycopeptides, and polymyxins) have been classified as "Highest Priority Critically Important Antimicrobials" for human medicine.

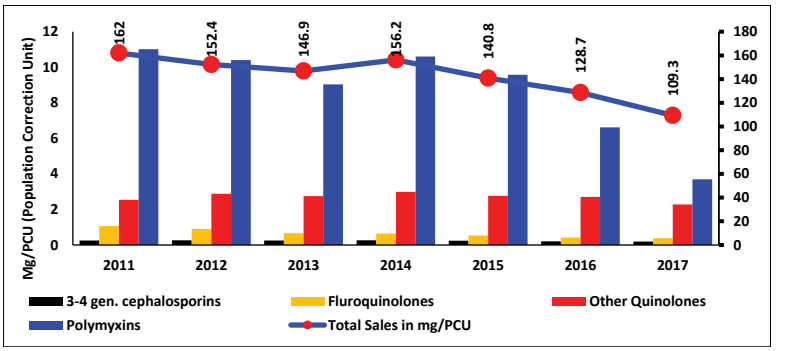
Parallel to the list of WHO for human medicine, the OIE in 2007 also developed a list of antimicrobial agents of veterinary importance. OIE has emphasized the implementation

of veterinary legislation and regulations for judicial use of 'Veterinary Critically Important Antimicrobial Agents (VCIA), Veterinary Highly Important Antimicrobial Agents (VHIA) and Veterinary Important Antimicrobial Agents (VIA)'. This list was further updated in 2013, 2015 and 2018. Among the VCIA, the fluoroquinolones and the 3rd & 4th generation cephalosporins are considered critically important for both human and animal health. Therefore, OIE recommended that these antimicrobials, which are already in the WHO category of Highest Priority Critically Important Antimicrobials, are not to be used (i) as a preventive treatment in animals, (ii) as a first-line treatment and (iii) prohibited for use as growth promoters. The objectives of the OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials also align with the principles of the Global Action Plan on AMR.

Recent Strategies of European Union to Reduce the Antimicrobial Use (AMU)

The surveillance of AMR pathogens is also poor in the EU countries. Only 13 out of 31 countries have an exclusive program on surveillance of AMR pathogens. Following new regulations will enter into force in European Union from January 2022.

- Ban on the preventive and prophylactic use of antimicrobials in livestock as well as in medicated feed of poultry and dairy animals.
- Restricted use of antimicrobials for metaphylaxis.
- Reinforcement of the ban on the use of antimicrobials as growth promoters to increase yield in animals and poultry.
- Compulsory collection of data on sale and use of antimicrobials in the food production system (crop, animals, aquatic etc.).
- Restricted use of "human important antimicrobials" in livestock, poultry and aquatic animals.
- Reservation of certain antimicrobials only for human use.



In the EU, during 2011-2017, the slaes of 3rd & 4th generation cephalosporins decreased y 21%, polymyxins by 66%, and fluoroquinolones by 10% and other quinolones by 65%

Fig.6. Trend in the use of critical antimicrobials in food animals in the EU

7. STRATEGIES FOR MANAGING AMR

Taking cognizance of the complexities of numerous factors that promote and perpetuate the AMR, it is obvious that the challenges of AMR may not be solved forever, but can only be managed sustainably. Further, AMR must require multi-pronged efforts backed by a bulwark of unwavering political will and societal engagement. The following actions merit attention:

Antibiotic Use Policy: The policy on judicious and prudent use of antibiotics in human and veterinary medicine along with a standard and evidence-based treatment guideline and protocol for targeted disease(s) with lesser critical but sensitive antibiotics should be developed immediately. Further, strict implementation of drug withdrawal periods must be ensured to safeguard the antibiotic-residue free food products. The regulatory provision for compulsory submission of data on the sale of antimicrobials from pharmaceuticals and pharmacies should be mandatory. In addition, there should be a separate regulatory policy (i) for premix, oral solution and oral powder preparations of antimicrobials for their use in the poultry sector, (ii) for complete ban/regulated use of antibiotics in the crop production system and strict compliance of guidelines on the use of antibiotics in Fishery sector, and (iii) for control of environmental pollution from antimicrobials manufacturing plants.

Further, it is imperative to reduce the over-prescribing of antimicrobials. A reduction in antibiotic consumption will lead to the reduction of antimicrobial resistance (Bergman et al. 2004).

The excessive use of antimicrobials in veterinary medicine and its associated human health consequences justify the importance of limiting the use of those antimicrobials in veterinary medicine, which are critically important for humans, viz., 3rd and 4th generations cephalosporins and fluoroquinolones.

The vaccination guidelines and protocol for all livestock species should be in place and made mandatory to reduce the need for antibiotics in veterinary medicine.

Surveillance and Monitoring of Pathogens and their Susceptibility: Surveillance of pathogenic microbial organisms and their antimicrobial susceptibility should be initiated on priority as it allows early detection of resistant strains and is very vital to make the clinical decisions to control the AMR. As such the “ongoing ICMR surveillance programme” on AMR should be strengthened as per WHO/FAO/OIE guidelines and the data on antimicrobial susceptibility must be shared at national and international levels to predict, prevent and devise the interventional strategies. An “AMR Regulatory Platform” should also be established at the National level and a coordinated “Regional Network Programme”, to track and detect antimicrobial resistance at the human, animal and environment interface should be launched. Further, the establishment of a “National Surveillance Programme” on human and non-human AMU of antimicrobials is the need of the day. Although the said surveillance network under the aegis of ICMR is currently operational, there is no such program in the agriculture and animal husbandry sector, which is a very important contributor to AMR. As such, there is an urgent need to generate quality surveillance data on AMR in agriculture (crops, dairy, animal husbandry, poultry and fishery).

Robust Immunisation Programmes: The incidence of bacterial and viral infections can be substantially reduced by the adoption of strategies and programmes on the prevention and control of infectious diseases that will directly be translated into reduced use of antimicrobials and AMR.

Curbing the Production and Sale of Poor Quality and Sub-standard Antimicrobials: Continuous exposure of bacteria to a sub-therapeutic level of drugs, which is achieved with the use of substandard antimicrobials, always triggers the development of resistance. So vigorous enforcement of the policy to curb the manufacturing, distribution and sale of substandard antimicrobials is need of the hour. At present, controlling and regulating the sale of substandard and illegitimate antimicrobials is a difficult challenge (Bate et al., 2009).

Educational and Awareness Programme: The efforts to contain antimicrobial resistance will be futile in the absence of education and awareness on "prevention and control of antimicrobial resistance" among those involved in antimicrobial use. There is a need to strengthen information and resources by involving all stakeholders i.e., policymakers, pharmaceutical industries, medical and veterinary professionals, producers and consumers.

Physicians, health workers and veterinarians can help in combatting AMR by (a) ensuring that hands, instruments and surrounding hospital environment are clean, (b) prescribing antibiotics according to current guidelines only when these are needed, (c) prescribing the right antibiotic, (first narrow-spectrum antimicrobial rather than broad-spectrum) with right dose and duration, (d) ensuring periodic antimicrobial susceptibility test of local bacterial isolates, (e) ensuring that antibiotics are prescribed only to treat infections and not for prophylaxis and (f) reporting antibiotic-resistant infections to surveillance team.

Policymakers can help in combatting the AMR by (a) ensuring availability and implementing of a national plan to tackle AMR, (b) regulating the sale of quality antimicrobials, (c) shortening the timeline for approval of new antimicrobials, (d) providing investment in research and development of new antibiotics, (e) encouraging and incentivising pharmaceutical industries for the development of a new class of antimicrobials by strengthening policies, programmes and implementation of infection prevention and control measures, and (f) regulating and promoting appropriate disposal of hospital and medical waste.

Consumers can help in combating AMR by (a) making sure to complete the dose and duration of antibiotic, even if they feel better, (b) using antibiotics only when prescribed by certified health professionals (no self-medication), (c) washing hands regularly, and (d) avoiding contact with sick people to prevent infection.

Use of Alternatives to Antibiotics: To reduce human and animal disease burden, the research on an appropriate alternative substitute to antimicrobials should be promoted. Natural agents such as prebiotics, probiotics, organic acids, enzymes, antimicrobial peptides (AMPs) and host-defence peptides (HDPs), bacteriocins, bio-enhancers, essential oils, and phytogenic feed additives (PFAs) could be promising alternatives. Nanoparticles of silver and copper and oxidized metals have also been used as alternatives to antimicrobials in the animal feed industry.

Augment Investment in Research: The government and the pharmaceutical industry must strengthen their research activities leading to the development of (i) new rapid diagnostic tools for identification of pathogens for AMR surveillance, (ii) new antimicrobial drugs, and (iii) new alternatives to treat diseases of multi-drug resistant bacteria like bacteriophages and genetically modified bacteriophage, synthetic mimics of antimicrobial peptides (SMAPs), antimicrobial antisense and oligonucleotides.

The experts predict that if adequate measures are not taken our future will resemble pre-antibiotic era as the resistance to antibiotics is increasing at a fast pace.

Antimicrobial Resistance: If No Action Today, No Cure Tomorrow

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