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Antibiotic Resistance in Non-humans and its Impact on Human Health

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Abstract:

Antimicrobial drugs are magic bullets which are used in humans, animals and plants to treat and prevent bacterial infections. The inevitable side effects of the use of antibiotics are the emergence and dissemination of resistant bacteria. Their level of resistance is considered to be a good indicator for selection pressure by antibiotic use and for resistance problems to be expected in pathogens. At least twelve classes of antimicrobials namely arsenicals, polypeptides, glycolipids, tetracyclines, elfamycins, macrolides, lincosamides, polyethers, beta-lactams, quinoxalines, streptogramins, and sulfonamides have been used in veterinary practice. The effect of this selection pressure has been the appearance of numerous resistant strains of *Escherichia coli*, *Salmonella species*, *Staphylococcus aureus*, *Pasteurella hemolytica*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Clostridium perfringens* and many other bacterial species. Bacteria also acquire genes conferring resistance by a variety of mechanisms including acquisition of extrachromosomal plasmids that replicate apart from the chromosomal DNA. Damage caused by antibiotic resistant bacteria is a kind of pollution. The precise effect of agricultural antibiotic use on resistance levels in the general population is not known, but the evidence points to a link. Considerable attention has been focussed on a very small minority of bacteria that cause disease but a vast sea of commensal and environmental bacteria continuously and promiscuously exchange genes totally unnoticed.

Immediate action has to be taken to prevent the antibiotic resistance in bacteria by judicious and rational use of antibiotics, effective hospital infection control programs and research for the development of new antibiotics or by combination therapy.

Key words: Antibiotics, Agriculture, Bacterial resistance, Non-human use, Veterinary

Everyone, a city dweller or a farmer knows about the uses of antibiotics in medicine. Antimicrobial drugs are magic bullets which are used in humans, animals and plants to treat and prevent bacterial infections. These drugs are the most important tools available to modern medicine.[1] Antibiotics became available for the treatment of humans disease in mid 1940s before being used in veterinary practice.[2] Penicillin was used to treat mastitis before 1940. Ten years later, antibiotic resistant strains were recognized in 1950.[3] The inevitable side effects of the use of antibiotics are the emergence and dissemination of resistant bacteria.

Most retrospective and prospective studies show that after introduction of an antibiotic, the level of resistance of pathogenic bacteria and commensal bacteria has increased considerably. Commensal bacteria constitute a reservoir of resistance genes for potentially pathogenic bacteria. Their level of resistance is considered to be a good indicator for selection pressure by antibiotic use and for resistance problems to be expected in pathogens.[4]

Resistant commensal bacteria of food animals may contaminate meat and reach the intestinal tract of humans. Monitoring the prevalence of resistance in indicator bacteria such as *E.coli* and *Enterococcus* in different population of animals, plants, and healthy humans makes it feasible to compare the prevalence of resistance and to detect transfer of resistance genes from animal and plants to humans and vice-versa.[5]

A large amount of drugs are being used worldwide annually to secure sufficient quantities of food to feed fast growing population.[5] The widespread use of antibiotics in humans and animals has been followed by increased emergence of resistance to antibiotics.[6] A causal relationship between increased use of antibiotics and increased prevalence of resistant bacteria has been demonstrated.[7] Transmission of resistance may be person to person, animal to animal and animal to person.[8, 9]

Drug resistant strains of bacteria may transfer their resistance to the drug susceptible strains of bacteria that ultimately act as reservoir of resistance to pathogenic organisms. Thus the occurrence of antibiotic resistant bacteria in humans and animals is a great concern.[2]

Indications of non-human antibiotic usage:

A very wide range of antibiotics is used for many different reasons in animal husbandry, agriculture and in veterinary practice. Antibiotics are used in animal husbandry and veterinary practice as therapeutic, prophylactic and sub-therapeutic doses for treating clinical disease, as a preventive measure for common diseases and as growth promoters either for a single animal or large group of animals. [10, 11]

Apple orchards and pear trees may be treated with the antibiotics like gentamicin, streptomycin and tetracycline to control fire blight and also as pesticides. This can increase the likelihood that bacteria causing human diseases will be resistant to those antibiotics as well.[12]

At least twelve classes of antimicrobials namely arsenicals, polypeptides, glycolipids, tetracyclines, elfamycins, macrolides, lincosamides, polyethers, beta-lactams, quinoxalines, streptogramins and sulfonamides have been used in veterinary practice.[13] Tetracyclines, penicillins, and sulfonamides, have been used in the treatment of infections in humans while other antimicrobials used in animals are not currently used to treat human disease.[14] WHO has classified the antibiotics as “critically important,” “highly important,” and “important” according to the priority of usage in human diseases.[15,16] The list of some of the antimicrobials used in non-humans are shown in the **Table I**.[12, 17, 18, 19]

Common antibiotic resistant bacteria

The development of bacterial strains resistant to antibiotics was recognized in the late 1950s. Microorganisms such as *Salmonella typhimurium* and *Salmonella enteritidis* which were resistant to one or more antibiotics can be transferred to other bacteria.[20] Studies have shown that the use of antibiotics as feed additives results in an increase of both proportion and persistence of antibiotics resistant bacteria.[21] Feeding of low levels of antibiotics creates a selection pressure to the bacterial flora of livestock. The effect of this selection pressure has been the appearance of numerous resistant strains of *Escherichia coli*, *Salmonella species*, *Staphylococcus aureus*, *Pasteurella hemolytica*, *Pasteurella multocida*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Haemophilus pleuropneumoniae*, *Clostridium perfringens* and many other bacterial species.[21] The common bacteria present in the foodstuffs are listed in **Table II**.

The prevalence of multidrug resistant bacteria (MDR) is a serious problem. Its prevalence among Enterobacteriaceae particularly *E.coli*, *Salmonella*, *Shigella*[22], and Ciprofloxacin resistant *Campylobacter spp.*[23,24] isolated from 10-14% of consumer chicken products [23,24] and MRSA in 12% of beef, veal , lamb, mutton, pork , turkey , fowl and game meat samples makes it of even greater concern to clinicians in curbing infections in medical and veterinary practice.[25]

Table I: Antimicrobials used in non-humans [12, 17, 18, 19]

Treatment of diseases		
Sl. No.	**Drugs**	**Species**
1.	Oxytetracycline	Fish
2.	Trimethoprim	Fish
3.	Bacitracin	Swine and poultry
4.	Ampicillin	Fish and farm animals
5.	Amoxicillin	Fish and farm animals
6.	Erythromycin	Fish and farm animals
7.	Gentamicin	Swine and poultry
8.	Furazolidone	Fish
9.	Neomycin	Poultry
10.	Streptomycin	Fish and fruits
Growth promoters		
Sl. No	**Drugs**	**Species**
1.	Virginamycin	Chicken
2.	Bambermicin	Chicken
3.	Penicillins	Farm animals and fruits
4.	Tetracyclines	Farm animals and fruits
5.	Avoparcin	Farm animals
6.	Bacitracin	Poultry
7.	Avilamycin	Broilers
8.	Ardacin	Bovine
9.	Lasalocid	Poultry and farm animals
10.	Monensin	Bovine

Table II: Bacteria commonly present in foodstuffs [26, 27]

Sl. No	Name of bacteria	Food stuffs
1.	*Salmonella enterica* var. Enteritidis	beef, pork, eggs, poultry and dairy products
2.	*Salmonella enterica* var. Typhimurium	beef, pork, eggs, poultry and dairy products
3.	*Campylobacter jejuni*	broiler chickens and their meat, pigs and cattle
4.	*Campylobacter coli*	broiler chickens and their meat, pigs and cattle
5.	*Escherichia coli*	Cattle, poultry and broiler chickens
6.	*Enterococcus faecalis*	Meat
7.	*Enterococcus faecium*	Meat
8.	*Proteus* species	Meat
9.	*Staphylococcus* species	Meat and dairy products
10.	*Bacillus* species	Meat

Mechanism of antibiotic resistance

A probable mechanism of spread of antibiotic resistance from the humans, veterinary and agriculture to other humans is depicted in **Figure I**.

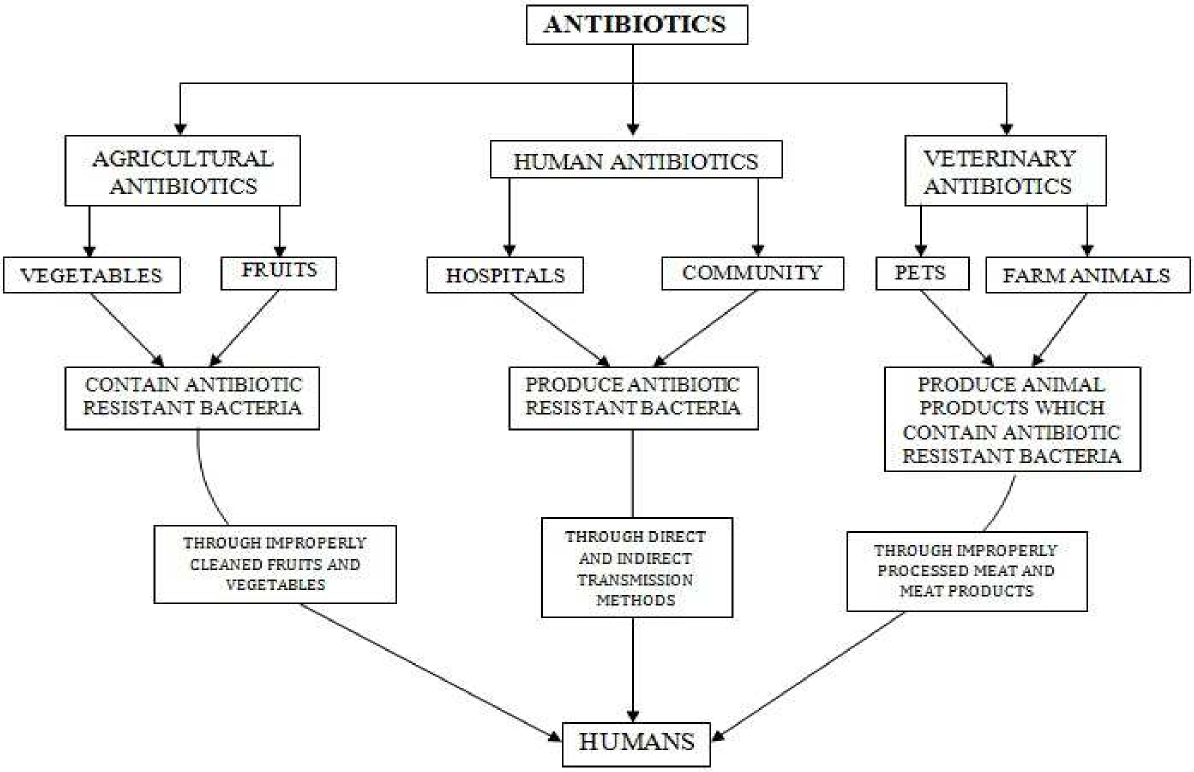
Bacteria can be resistant to the action of antimicrobial drugs because of the inherent structure, physiology of bacteria or can develop mechanisms to circumvent action of drugs through genetic mutation. Genetic mutation is a normal process that occurs during bacterial replication at the rate of 1 mutation per million bases per cell division. Most mutations are detrimental to the organism by random chance; mutation can develop that provides selective advantage to bacteria exposed to antimicrobial drugs leading to survival of strains less susceptible to the antimicrobial drug. Number of mechanisms are associated with acquired antibiotic resistance like drug inactivation, drug modification, production of competitive metabolites, target mutation, production of competitive metabolites, target mutation, target substitution, target modification, decreased cell wall permeability to drugs, active efflux of drugs and failure to metabolize a drug to its active form.[28]

Bacteria also acquire genes conferring resistance by a variety of mechanisms including acquisition of extra chromosomal plasmids that replicate apart from the chromosomal DNA. Plasmids can contain smaller mobile genetic elements called transposons that have the ability to move from plasmids to chromosomes and vice-versa. Smaller elements within transposons can further facilitate acquisition of MDR genes. Resistance genes are believed to transfer among bacteria of different species or even from different genera. Therefore genetic elements have the ability to transfer resistance among bacteria and exchange

among bacteria in animals of same species or different species.[28] Once bacteria acquire genetic material conferring resistance, continued exposure of bacterial population to antimicrobial drugs provides selection pressure that might allow the resistant population to increase in prevalence and subsequently become the dominant clone in the population.[29]
R-plasmids (R-factor) are the extra chromosomal substance responsible for antibiotic resistance. These R-plasmids are spread to other bacterial cells by transformation, transduction, conjugation or transposition. [30]

R-plasmids can circulate in humans, in animals and in the environment and possibly between animals and humans. [31]
Transmitted antibiotic resistance in disease causing bacteria may cause zoonotic infections.[29] R factors were found in members of the genus *Shigella* in Japan; since then, they have been found in all other genera of the family Enterobacteriaceae and in the genera of *Pasteurella*, *Vibrio*, *Campylobacter*, *Haemophilus*, *Neisseria*, *Staphylococcus* and *Pseudomonas*.

Figure I: Mechanism of Antibiotic Resistance



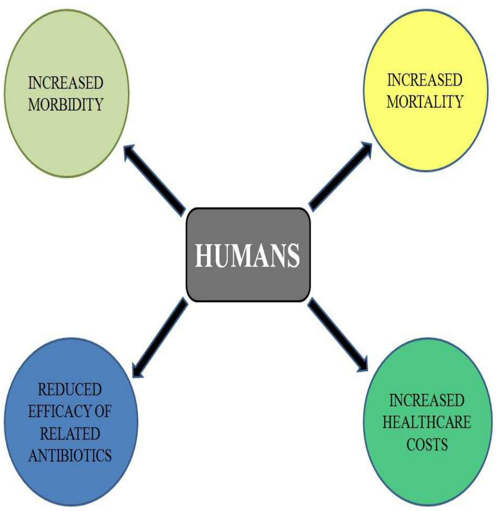
R plasmids possess regions with the resistance genes and resistance to different antibiotics can be mediated by the R-plasmid which confers multiple drug resistance. [32]

Impact of antibiotic resistance on public health:

Multiple factors contribute to the pathways by which antibiotics used in food animals could cause risk to human health.[30] Persistent asymptomatic carriage plays a key role in bacterial resistance for hospital acquired infections. Antibiotic resistant bacteria can colonize a person for years. New carriers are discharged from one hospital to another hospital later. Damage caused by antibiotic resistant bacteria is a kind of pollution. Bacteria with resistance genes are a general threat to the population in both humans and animals.[33,34,35,36,37,38] Abundant quantities of resistant bacteria and their resistant genes are transmitted during different stages of processing of food from different animal sources. Increase of antibiotic resistant bacteria among farm animals and consumers of meat has been reported in different studies.[39,40,41,42] Antibiotic resistant genes identified in food bacteria have also been detected in humans which provide direct evidence for transfer by food handling or consumption.[18]

Antibiotic use in non-humans may have many effects on humans as shown in **Figure II**.[43] This has been divided into two effects like direct and indirect effects.[38]

Figure II: Impact on humans due to antibiotic resistance in non-humans [43]



Direct effects

- Infection or colonization by the antibiotic resistant bacteria on exposure to animals treated with antibiotics.
- Outbreak of resistant diarrhoeal disease after eating food contaminated with such bacteria.
- Development of drug resistance in the normal flora of the human gastrointestinal tract after consumption of the contaminated foodstuffs.

Indirect effects

Dispersion of resistant bacteria during transportation.

- Transfer of mobile genetic elements from animal bacteria to pathogenic bacteria of humans.
- Alterations in human flora due to contamination of water supply by the resistant bacteria from animal waste used as fertilizer.
- Humans may colonize or get infected after handling the animal food or carcasses.

The precise effect of agricultural antibiotic use on resistance levels in the general population is not known, but the evidence points to a link. In 2003, an expert committee convened by WHO, the UN Food and Agriculture Organization, and the World Organization for Animal Health concluded, ‘there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death), and increased severity of infections.[44]

Prevention of spread of antibiotic resistance:

Considerable attention has been focused on a very small minority of bacteria that cause disease but a vast sea of commensal and environmental bacteria continuously and promiscuously exchange genes totally unnoticed. These bacteria which are largely ignored are a reservoir of resistance genes.

Immediate action has to be taken to prevent the antibiotic resistance in bacteria by judicious and rational use of antibiotics, effective hospital infection control program and research for the development of new antibiotics.[45] Combination therapy can be another approach for this.[46]

To maximize the therapeutic efficacy and lessen the antibiotic resistance, some of the steps which can be done in veterinary settings are:

1. Improve hygiene and limit the density of animals, these include cleaning procedures, disinfectant practices, animal and personnel movement, housekeeping practices and waste disposal; however recommendations need to be tailored depending on the type of animal population and premises.
2. Disease prevention efforts should be promoted and preference for conservative treatment and education to the animal owners regarding antibiotic use.
3. Avail alternatives to antibiotics in human usage as well as animals like vaccines, probiotics, prebiotics, enzymes etc.
4. Avoid unnecessary antibiotic prescription, and if required use it in proper dosage.
5. Laboratory should test resistance patterns of certain bacteria that are of concern in human and veterinary medicine for example VRE and MRSA.
6. Laboratory should communicate about emergence of MDR to infection control and infectious disease specialists
7. Eliminate the suboptimal usage of antibiotics as pesticides in agricultural industry.
8. Formulating regulations regarding the usage of antibiotics in veterinary hospitals
9. Establishing hospital antibiotic policy and implementing the same in practice
10. Strict surveillance of the regulations and taking necessary actions required in case of a lapse.
11. Educating about antimicrobial resistance and conservative antimicrobial drug use to all veterinary professionals, owners and managers of animal husbandry.
12. Promoting research regarding antibiotic use and drug resistance alternatives to antibiotic treatment and infection control practices.

Regulations have been made to curb the antimicrobial resistance in non-human use by both international and national bodies.

International regulations: [47]

In 1995, Denmark had started a process to end the use of antibiotics as growth promoters in livestock production involving both voluntary and legislative elements. This led to a total ban of growth promoters in the year 1999 in Denmark.

The European Union (EU) had recognized the serious health threat due to antibiotic resistance and had banned the use of growth promoting antibiotics in animal feed. In December 1997, the EU banned the Animal Growth-Promoter (AGP) avoparcin in all its member states. In July 1997, the EU banned another four AGPs (tylosin, spiramycin, bacitracin and virginiamycin) because these antimicrobial drugs were being used in human medicine also. United States is yet to pass a decision on antibiotics use in livestock production but the Food and Drug Administration (FDA) had banned use of fluoroquinolones in the year 2005 based on the study that showed high levels of fluoroquinolones in poultry led to drug resistance in humans.

National regulations:

As of now, there is no regulation in India for the use of antibiotics in livestock. Prevention of Food Adulteration Rules (1995), Part XVIII: Antibiotic and Other Pharmacologically Active Substances applies only to the use of antibiotics in certain types of seafood[48], and the Export

Inspection Council of India prohibits the use of certain antibiotics in the feed and medication of poultry intended for export only.[49]

The amount of antibiotics for sea foods including shrimps, prawns or any fish and fishery products, should not exceed the prescribed tolerance limit (mg/Kg[ppm]) as suggested below: [47]

a. Tetracycline (0.1)
b. Oxytetracycline (0.1)
c. Trimethoprim (0.05)
d. Oxolinic acid (0.3)

A committee of experts from inter-sectoral coordination committee is formed, which comprises of the following agencies: [47]

- Central Council for Scientific and Industrial Research (CSIR) (Chairperson: DG, CSIR)
- Ministry of Health and Family Welfare
- Ministry of Agriculture
  i. Indian Council for Agricultural Research
  ii. Department of Animal Husbandry
- Food Safety and Standards Authority of India (FSSAI)
- Agricultural and Processed Food Products Export Development Authority (APEDA)
- Marine Products Export Development Authority (MPEDA)
- Drug Controller General of India (Member Secretary)

  This committee may undertake the following activities: [47]
- Review of available data regarding the use of antimicrobials.
- Generation of data by undertaking studies on the use of antimicrobials as Animal Growth-Promoters.
- Specify the antibiotics for use in Livestock
- Review of current laws on use of AGPs in other countries and feasibility of their implementation in India.
- Development of regulations on usage of antimicrobials in poultry and other animals as well as the requisite labelling requirements in food.
- Review of Prevention of Food Adulteration Rules, 1995-part XVIII: Antibiotic and other pharmacologically active substances, if required, to enhance the scope (inclusion of other food products and antimicrobials).
- Any other related issue.

Conclusion:

Antibiotic resistance is acquired not only through the use of antibiotics in humans but it can be transferred from the non-human use to humans by genetic or plasmid route by selective pressure. Because of this, treatment of human infections will be an uphill task. Prevention is better than cure. So private and government agencies are trying to prevent the antimicrobial resistance by formulating policies for antibiotic use in non-humans and find alternatives for the antibiotics.

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