Veterinary Use of Antibiotics vis-à-vis Anti-Microbial Resistance (AMR)

Indian Animal Healthcare Industry Perspective

Indian Federation of Animal Health Companies

INFAH

Dedicated to

All public officials, Regulators, AMR Working groups, Academicians, Veterinary Institutes and Animal Health Companies, who are working to address the concerns of AMR while at the same time provide Veterinarians with treatment options for better animal health.

Compiled and prepared by
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Preamble

With the largest livestock population of the world (536 plus million heads) India's livestock sector is evolving in response to rapid increase in demand for animal produce and the demand for livestock products. The sector will continue to grow with ever-increasing population, rapid urbanization, increasing disposable incomes and changing socio-cultural values. Government of India has also undertaken many initiatives with increased financial budget for the growth of the sector.

A major limiting factor in profitable livestock production in India is the burden of infectious diseases. These livestock diseases cause great socio-economic impact, and many times the conditions are further complicated by sub-optimal biosecurity in both intensive and open production systems. This has made the use of antimicrobials for the treatment of sick animals indispensable.

Antibiotics in Animal Healthcare in India

Bacterial infections make up a significant proportion of animal essential part of therapeutic management of infectious diseases in both farm and companion animals, ensuring better animal health and welfare; also assures healthy and safe food from the animal sources. Although treatment of individual animal is preferred, however for animals like poultry and fish, mass medication is the most feasible means of treatment. Furthermore, certain mass-medication are essential to treat the sick animals while medicating others in the group that may not be sick but exposed to the infection or suffering from sub-clinical infection. Other prophylactic antimicrobial treatments are typically used during high-risk periods for infectious diseases.

- In India, a wide range of antibiotics are available in the Veterinary practice viz. Penicillin, Semi-synthetic penicillin like Ampicillin, Amoxycillin, Aminoglycosides like Streptomycin, Gentamicin, Neomycin; Tetracycline, Kanamycin, Erythromycin; Fluoroquinolones like Enrofloxacin, Norfloxacin, Ciprofloxacin, Levofloxacin, Marbofloxacin; 1st, 2nd and 3rd generation Cephalosporins - Cephalexin, Cefrtiaxone, Cefoperazone, Ceftiofur, Cefoquinome etc. Most of the antibiotics are common for both human & veterinary use. Indiscriminate use of such antibiotics may increase possibilities of spread of resistant bacteria in both human & animal population.
- According to the World Organisation for Animal Health, tetracyclines and penicillins represent about 55% of global animal antibiotic use, and neither of these classes are on the WHO list of highest priority critically important antimicrobials for humans. Furthermore, WOAH does not include 'animal only' antibiotics in their measurements. These are antibiotics that are only authorized for use in animals and not considered contributors to human AMR (HFA).
- Many antibiotics are being used in livestock since their introduction and are still found reliable to treat infectious bacterial diseases, with little resistance being encountered. For example, tetracycline classes of antibiotics makes up to 40 percent of the total Veterinary antibiotic market but have limited use in humans in many countries. Nonetheless, despite their use in animals since long, Veterinarians have found little evidence of resistant strains causing hard to treat infections.

- New generation antibiotics like Carbapenem, Quinolones and Cephalosporins which are considered for life threatening infections in human are not allowed in Veterinary use. However, "There may be overlap in the use of medically-valuable antibiotic for humans such as fluoroquinolones and cephalosporins. For example - Veterinary fluoroquinolones" are effective treatments for livestock with respiratory diseases but are only available for use through a Veterinarian's prescription.

AMR Concerns

Drug selection pressure is the single most important factor in the evolution of drug resistance in bacteria. The reasons for drug pressure are multi-factorial and involve both human and animal use. The factors that influence the spread of resistance can be ecological, epidemiological, cultural, social, and economic.

Many a times, over-use of antibiotics in animal husbandry is presumed to drive in emergence of drug resistant bacteria, which in fact is not true. In general, the effect of antibiotic residues in meat, eggs and milk are insignificant when compared with the issue of selection and amplification of antibiotic resistant strains of bacteria. Besides, antibiotics used for treating livestock carry a statutory withdrawal period stating the minimum amount of time to lapse after the treatment before meat, milk or eggs can enter the human food chain.

There are multiple potential sources of antimicrobials entering the environment. Among the most important contributors to environmental pollution by antimicrobials are waste from pharmaceutical manufacturing plants, hospitals, wastewater treatment plants, untreated human wastes, waste and runoff from aquaculture, livestock, and plant-based food production and processing facilities. However, the attributable fraction of each source and factors governing transfer of AMR organisms, antibiotic resistant genes (ARGs), and residues in the environment from agricultural sources are unclear.

While it is imperative to follow AMR stewardship through rational and circumspect usage of antimicrobial in animals, it is also important to bear in mind that human also present risk to animals. The USFDA described the phenomenon of AMR as a very complex and non-victimless phenomenon, affecting both human and animal health.

Antibiotic Consumption in Indian Animal Healthcare

As per recent report published in 2010 'Antibiotic Use and Resistance in Food Animals- Current Policy and Recommendations' from Center for Diseases Dynamics, Economics & Policy (CDDEP), reveals India accounts for 3 percent of the global livestock antimicrobial consumption i.e. around 2000 MT (hosts 11.6 percent of world's animal population). However, the methodology adopted in the study is not clear and seemingly, no major stakeholders were consulted in the process. Recently, Indian Federation of Animal Health Companies (INFAH) that represent around 85 percent of the Animal Health Industry of India compiled an estimated usage of antibiotics in organized Animal healthcare for the year 2020 and 2021 and submitted to Department of Animal Husbandry and Dairying (DAHD), MoFAHD. The estimated data on antibiotic usage in 2020 and 2021 are 912 MT and 963 MT respectively (details in Annexure A).

Impact of Veterinary Use of Antibiotics on AMR Emergence in Humans

Significance and relevance of the use of antibiotics in animals which is presumed to impact efficacy in human antimicrobial therapy has been scientifically debated for decades.

The key question regarding antimicrobial use in farm animals is whether and to what degree it poses a threat to human health. Numerous research studies conducted on AMR, do not provide information on the origin of AMR in pathogens. Also, there is no systematic, comprehensive data on the prevalence of AMR infections in livestock. Therefore, it is not known to what extent the presence of AMR in agriculture systems is due to veterinary use of antimicrobials.

- The UK Government in a five-year antimicrobial strategy reported "Increasing scientific evidence suggests that the clinical issues with antimicrobial resistance that we face in human medicine are primarily the result of antibiotic use in people, rather than the use of antibiotics in animals. Nevertheless, use of antibiotics in animals (which includes fish, birds, bees and reptiles) is an important factor contributing to the wider pool of resistance which may have long term consequences." (UK Deptt of Health and DEFRA)
- In 2019, the U.S - CDC published a report on 'Antibiotic Resistance Threats' confirmed that out of the 18 species of antibiotic resistant bacteria that pose the greatest threat to human health, only two have their potential source in food animals. (U.S - CDC)
- In a landmark study, the European Centre for Disease Prevention and Control found that "75 percent of disease linked to resistant bacteria is due to healthcare-associated infections"
- Bywater and Casewell (2000) explains "Out of the 20 most serious bacterial infections exhibiting problems with antibiotic resistance in human medicine, 12 are in no possible way related to antibiotic use in food-producing animals as these bacteria cannot be acquired via the food chain. Of the remaining 8, assuming that transfer of bacterial resistance from animals to people occurs (an unproven assumption in most cases), the calculated percent contribution to antibiotic resistance in all cases is 1 percent or less and in most cases is less than 0.5 percent."

Indian Reports

A Delhi based organization, released its findings 'Antibiotics in Chicken Meat' in 2014 and 'Antibiotics Resistance in Poultry Environment' in 2017

- In the 2014 study, 70 chicken samples were tested from Delhi and NCR were analysed for the presence of antibiotics. 28 samples (40 percent) were found to contain residues of one or more antibiotics. About 23 percent (16/70) chicken had residues of one antibiotic while about 17 percent (12/70) had residues of more than one antibiotic. The antibiotic residues found and documented were as follows:

Table - 1: Antibiotic residues found in chicken meat (mcg/kg)
(70 samples collected from Delhi and NCR)

Antibiotic	Muscle	Liver	Kidney
Oxytetracycline	8.45 - 13.60	9.13	8.25
Chlortetracycline	10.20	ND	ND
Doxycycline	14.61 - 20.66	11.94	15.73
Enrofloxacin	3.84 - 58.06	3.37 - 131.75	ND
Ciprofloxacin	3.55 - 26.27	7.55 - 64.59	ND

The antibiotic residues (mcg/kg) found in chicken meat were found to be much lower than the permissible Maximum Residue Limits (MRLs) permitted for poultry as per CODEX (International) standards, as revealed below:

Table 2: Maximum Residue Limits for Poultry as per EU and US Standards (mcg/kg)

Antibiotic	Muscle		Liver		Kidney	
	EU	US	EU	US	EU	US
Chlortetracycline	100		300		600	
Oxytetracycline	100		300		600	
Tetracycline	100		300		600	
Doxycycline	100		300		600	
[1]All tetracyclines		2000		6000		12000
Enrofloxacin/ Ciprofloxacin	100		300		200	
Enrofloxacin		300				
Neomycin	500	1200	500	3600	5000	7200
[1]Chlortetracycline + Oxytetracycline + Tetracycline						

- The 2017 report evaluates the poultry environment (poultry litter, poultry farm soil and nearby agricultural soil). The study documents highest resistance of *E. coli* followed by *K. pneumoniae* and *S. lentus* and suggests that multidrug resistance is moving from farm to agricultural fields. The study was undertaken in the farm surroundings not from animal body, that documents 62 *E. coli* isolates were resistant to Meropenem. Meropenem belongs to carbapenems class of antibiotics used in human only. The study also documents similar resistance to Linezolids, again an antibiotic not practiced or advocated in poultry farms.
- In view of the major discrepancies in both the studies published in 2014 and 2017 and its subsequent conclusion as poultry farming practice as major source of resistant bugs may not be appropriate; it needs thorough analysis with proper surveillance to draw any such conclusion.

Containment of AMR and Way Forward

Responsible use of antimicrobials in all species is certainly imperative in order to minimize the emergence, maintenance and transmission of resistant organisms. While human health remain a priority, bacterial infections affect health and welfare in both animals and humans, an appropriate and measured policy must be developed through a complete understanding of the ecology of resistance in both populations, as well as in the broader ecological web. Multi-sectoral approach is therefore essential for containment of emergence of AMR.

Though there is widespread and increasing concern of AMR, limited focus has been given on the role of environmental factors in propagating resistance. There are plausible indications that contaminated raw water, waste water and other environmental determinants etc. are playing an important role in the development and spread of AMR.

'One Health' approach appears to be the most appropriate, the concept turns to a movement now. However, there is a need to bridge the gap of collaboration of different sections- biomedical, animal health, aquaculture, agriculture, environmental science and the social science.

Indian Federation of Animal Health Companies (INFAH) fully acknowledge the concerns for responsible and prudent use of antibiotics for animal welfare and protection as well as management of infectious diseases ensuring that the foods from our animals are safe and healthy for humans. INFAH advocates to follow the best practices so the problem of antibiotic resistance is at its minimal for animals and human beings. Continuous effort is required from all stakeholders to encourage rational use of Antibiotics. There is ample scope of improvement in reduction of misuse of antibiotics through awareness, training & stringent regulation. AMR is an extremely complex problem which needs to be addressed by adopting comprehensive multi-sectoral approach collaborating human health, animal health, agriculture and environmental sectors to align policies, strategies and activities.

Annexure A

Estimated Antimicrobial usage {MT) of Animal health sector in India for the year 2021

Sr. No.	Antibiotics Antimicrobials	Livestock	Poultry		Total Consumption
	Therapeutic Purpose		Therapeutic use	MFA	
1	Aminoglycosides (Streptomycin, Gentamycin, Amikacin, Neomycin)	66	31	-	97
2	Penicillin (Natural Penicillin, Amino-penicillins)	80	16	-	96
3	Sulphonamides (Including Trimethoprim)	144	17	-	161
4	Cephalosporins	63	05	-	68
5	Fluroquinolones	125	62	-	187
6	Tetracyclines (Tetracycline, Oxytetracycline, CTC)	105	24	53	182
7	Macrolide (Tylosin, Tiamulin, Tilmicosin, Erythromycin)	05	55	52	112
8	Others (BMD, Lincosamides, Avilamycin, Streptogramins, Flavophospholipol etc.)	-	-	60	60
	Total Consumption of Antibiotics in Livestock& Poultry	588	210	165	963

Infah's Estimates Antimicrobial Usage (MT) of Animal Health Sector in India for the Year 2020

Sr. No.	Antibiotics/Antimicrobials	Livestock	Poultry		Total Consumption
	Therapeutic Purpose		Therapeutic use	MFA	
1	Aminoglycosides (Streptomycin, Gentamycin, Amikacin, Neomycin)	55	30	-	85
2	Penicillin (Natural Penicillin, Amino-penicillins)	75	15	-	90
3	Sulphonamides (Including Trimethoprim)	140	17	-	157
4	Cephalosporins	55	5	-	60
5	Fluroquinolones	120	60	-	180
6	Tetracyclines (Tetracycline, Oxytetracycline, Chlortetracycline)	100	23	52	175
7	Macrolide (Tylosin, Tiamulin, Tilmicosin, Erythromycin)	5	50	30	85
8	Others (BMD, Lincosamides, Avilamycin, Streptogramins, Flavophospholipol etc.)	-	-	80	80
	Total Consumption of Antibiotics in Livestock and Poultry	550	200	162	912

INFAH's Estimates Antimicrobial Use in Animal Healthcare in India, 2020- Methodology

AMU Estimation in Poultry

- Estimation of AMU was based on population of commercial poultry (broiler, layer, breeder separately) with respect to usage of antimicrobials.
- Antimicrobial use in broiler, layer and breeder were calculated separately.
- Antimicrobial use in therapeutic and for preventive purpose (medicated feed) were estimated separately. Also, usage in feed and water/injectable were considered separately.

I. Therapeutic use of antibiotics was estimated based upon average field usage pattern.

- Broiler- 50 grams (10 percent antibiotic formulation- 5 mg) per 1000 birds was considered
- Layer- 5 mg per kg b.wt for 3 days p.m. or 36 days p.a. was considered
- Breeder- 25 mg per kg b.wt for 5 days p.m. or 60 days p.a. was considered

A. AMU in Broilers-Therapeutic Use

(Based on average field usage pattern in brooding and treatment during rearing)

Farm use antibiotics per 1000 birds (g)- considering 50g of 10% formulation	Total annual usage in broilers - calculation	AMU in MT
5	(5X4.5X10^9) / 10^9) X 3	67.5

(5 mg X 450 m) converted to MT / 10^9 X 3 times a year

B. AMU in Layers and Breeders-Therapeutic Use

Class	Antibiotic usage	Population*	Avg BWT (in kg)	Calculation	AMU in MT
Layer	5 mg per kg b.wt for 3 days p.m. or 36 days p.a	220 million	1	1X5X220X10^6X36*	40
Parent	25 mg per kg b.wt for 5 days p.m. or 60 days p.a	30 million	2	2X25X30X 10^6X60**	90

*1 Kg b.wt X 5 mg X 220 m X 36 days p.a - conversion to MT
** 2 Kg b.wt X 25 mg X 30 m X 60 days p.a - conversion to MT

Total consumption of Antibiotics in Poultry for Therapeutic purpose = ~200 MT

C. Estimated Bifurcation of AMU- as per Antibiotic Class- Therapeutic Use

Antibiotic class	Usage in MT
Amoxycillin	15
Amikacin	9
Gentamicin	21
Flumequine	3
Enrofloxacin	35
Levofloxacin	22
Tetracycline /Oxytetracycline	23
Cephalosporins - Ceftiofur	5
Macrolide - Tylosin	15
Macrolide - Tiamulin Hydrogen Fumarate	25
Macrolide-Tilmicosin / Erthromycin	10
Sulfonamide (Including Trimethoprim)	17
Sub-Total AMU in Therapeutic Use in Poultry	**200**

II. AMU in Poultry as Medicated Feed Additive

Medicated Feed additives or Antimicrobials use in feed were calculated based on:

- The total feed production and average usage of antibiotics in feed
- Based on the field usage pattern of antimicrobials (% share of each anti-microbial) in feed, and further classification into categories was done.

A. Calculation of AMU as MFA in Poultry as per Feed production/consumption

Feed	Feed Prod. in MMT	Integration / Own prod.	Branded feed	60% Integration/ Own feed mfg. using MFA	40% Integration / Own feed mfg. Not using AGP	70% Branded Feed mfg. using Antibiotic	30% Branded Feed mfg. Not using Antibiotic	Feed prod. with MFA in MMT	Feed with MFA in MT
Broiler Feed	15.75	14.18	1.58	8.51	5.67	1.10	0.47	9.61	
Layer Feed	10.35	6.21	4.14	3.73	2.48	2.90	1.24	6.62	
Breeder Feed	1.5	0.9	0.60	0	0	0	0		
Total	27.6							**16.23**	**16231500**

Inclusion level @ 100 gm /MFA / MT of Feed- in general

Considering 10% MFA formulation of API 100g = 10 g per MT of feed= 10 g X 16231500 = 162315000 g = 162 MT

B. Bifurcation of AMU- as per Antibiotic class- MFA

MFA	Conc. of Active	Mixing ratio g/Ton of Feed	Antibiotic API in g per MT Feed	Total Active in Broiler Feed MT	Total Active in Layer Feed MT	Total Active Antibiotics as MFA in MT
Avilamycin	10%	100	10	9.61	0.00	9.61
BMD/Bacitracin	10%	150	15	36.04	0.00	36.04
Enramycin	6%	63	3.78	1.82	0.00	1.82
Flavophospholipol	4%	45	1.8	1.73	0.00	1.73
Lincomycin	11%	20	2.2	2.11	0.00	2.11
Tylosin	10%	250	25	0.00	24.83	24.83
Tiamulin	10%	250	25	0.00	24.83	24.83
Virginiamycin	50%	20	10	9.61	0.00	9.61
Oxytetracycline/CTC	15%	300	45	21.62	29.79	51.41
Total MT						161.98

AMU estimation in Livestock

- AMU estimation in livestock is based on actual consumption of antimicrobials by leading manufacturers and marketers. Collated multiple information data points separately for each category of antimicrobials. The estimated data were further extrapolated to capture consumption in uncovered/unorganized market controlled by smaller or regional companies.

Few Examples of Calculations

Antibiotic Category Wise

1) Estimated Consumption of Penicillin (Natural/Amino-penicillin)

API/Ingredient	Industry estimate – API consumption in the year 2020 in KG	Convertio-n Factor	Consumption unit (Kg)	Consumption in MT	Est. Consumption in Livestock	Est. Consumption in Poultry
Benzyl Penicillin	15000	1	15000	15	15	
Procaine Benzyl Penicillin	40000	0.57	22800	23	23	
Ampicillin	10000	1	10000	10	10	
Amoxycillin	32000	1	32000	32	17	15
Cloxacillin	10000	1	10000	10	10	
Total Penicillin (Natural/Amino-penicillin)			89800	**90**	**75**	**15**

2) Estimated consumption of Fluoroquinolones

Sl No.	API/Ingredient	Industry estimate – API consumption in the year 2020 in KG	Convertion Factor	Consumption unit (Kg)	Consumption in MT	Est. Consumptio-n in Livestock	Est. Consumption in Poultry
1	Enrofloxacin	145000	1	145000	145	110	35
2	Levofloxacin	26000	1	26000	26	5	21
3	Flumequin	3000	1	3000	3		3
4	Marbofloxacin	1000	1	1000	1	1	
5	Ciprofloxacin/ others	5000	1	5000	5	4	1
	Total Fluoroquinolones			180000	**180**	**120**	**60**

Acknowledgements

INFAH therapeutic sub-committee acknowledges the valuable contribution of our Managing Committee Members:

Dr. Vijay Makhija	:	President
Dr. D. K. Dey	:	Past President
Vijay Teng	:	Immediate Past President
Satish Pasrija	:	Past President
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Gautam Chatterjee	:	MC Member
Dr. Shirish Nigam	:	General Secretary
Dr. T. Natesan	:	MC Member

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Vision

Towards creating trust among the Veterinary Professionals and Livestock, Poultry, Aqua & Companion animal stake holders to enhance Animal Health industry's value and contribution to society, by setting high standards of competitiveness, ethical business practices, innovation and leadership among its members for sustainable Animal Health Industry in India and also ensuring significant presence across the Globe.

Mission

- Create a database on various segments of Animal Health Industry for business decisions.
- Formulate a fair marketing environment through ethical business practices.
- Contribute towards the development of regulatory framework for the new and existing animal health products.
- Contribute towards drafting National Health Policy of India with all stakeholders.
- Partnering with Global Animal Health Trade Bodies for establishing identity of Indian AH industry.

Affiliated to

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