Guidelines for Antimicrobial Standards in Livestock Healthcare

Editors

Rishendra Verma

Vijay Teng

Nitin Bhatia

Published by

Indian Association for the Advancement of Veterinary Research (IAAVR)

&

Indian Federation of Animal Health Companies (INFAH)

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COVER INSIDE PAGE

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INDEX

Guidelines for Antimicrobial Standards in Livestock Healthcare

Rishendra Verma, Vijay Teng, Nitin Bhatia

Summary

Antimicrobials are an integral part of therapeutics and contribute to reduction in burden of common infectious diseases of humans and livestock globally. Food animal produce should be safe and healthy for humans for which antimicrobials play both a beneficial as well as detrimental role. India harbors more than 10% of the Worlds food animal population and consumes 3% of the World's antibiotics for ensuring a better disease management of its farm animals. In fact, human resistance to anti-bacterials is more due to the inappropriate and non-judicious dosing in use than from the resistance transmitted from animal sources. Regulations controlling antibiotic usage especially in terms of its prescription and withholding period should be enforced in practice. Considering the economic status of our livestock farmers and per animal productivity, antibiotic are advocated only in times of its need and its only adherence to the regulatory requirements that needs consistent re-enforcement.

Indian Association for the Advancement of Veterinary Research (IAAVR)in association with**Indian Federation of Animal Health Companies (INFAH)** organized Round Table on '**Guidelines for Antimicrobial Standards in Livestock Healthcare**' during the **16th Indian Veterinary Congress, 23rdAnnual Conference of IAAVR** and National Symposium on 'Strengthening of Governance in Animal Health and Production Activities for the Benefit of Farmers and Livestock owners' atCollege of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology (OUAT), Bhubneshwar on 27-28th February' 2016.

The round table was attended by more than 120 Veterinarians associated with academic and research field and policy makers from Indian Council of Agricultural Research (ICAR) and its associated institutes, State and Central Universities with an aim to deliberate over the concerns of antibiotic usage in animal healthcare. The round table was Co-chaired by Dr Sitangsu Mohan Deb, Director, ICAR-National Research Centre on Yak; Vijay Teng, General

Secretary, INFAH and Dr Rishendra Verma, Founder Secretary, IAAVR.

Eminent speakers *viz* Dr SumanthGandra, Centre for Disease Dynamics, Economics and Policy (CDDEP, Washington); Dr G Sarath Chandra, Professor and Head, Pharmacovigilance laboratory for Animal feed and Food Security, TANUVAS; Dr S K Mody, Professor and Head, Department of Veterinary Pharmacology and Toxicology, S.D.A.U, Sadarkrushinagar;MrSomuAmbat, Access Consultancy; and Industry professionals, Dr Nitin Bhatia, Intas Animal Health and Dr D. J. Kalita, Zydus Animal Health.

The world human population is expected to reach 9.7 billion by 2050 as per FAO estimates, and to suffice the consumption requirements of this growing world populations, the world food production has to double in the next 40 years and 70% of the food must come from efficiency improving technologies. It is also postulated that the growing urban population (70% in cities) with increasing income (2.8 times the current income) will focus on higher protein sources and the consumptions are likely to double. The livestock sector currently contributes 40% of the global value of agricultural output and supports the livelihood and food security for the growing population. Animal source foods would be a major growth drivers for increased consumption of growing population and emerging middle class globally. The changes in technology has assisted double the output of livestock products from 1950 to 2000 and the potential is still being explored. Animal source foods are best sources of Vitamin A, Vitamin B_{12}, Riboflavin, Calcium, Iron, Zinc and proteins

On a worldwide basis cereals supply more than 50% of human requirements for energy and nearly 50% of the protein. Animal products viz meat, milk, eggs and animal fat supply 17% of the energy and 32% of the protein. As per estimates. Livestock and its products are estimated to make up over half of the total value of Agricultural gross outputs in the industrialized countries and about a third of the total in developing countries.

India's livestock sector is one of the largest in the world with a holding of 11.6% of world livestock population. India is home to 56.7 percent of the world's buffaloes, 12.5 percent of the world's cattle, 20.4 percent of world's small ruminant population, 1.5 percent of pigs and 3.1 percent of poultry. Currently the country is facing the 'nutritional transition' because of the growing population and incomes leading to a dramatic increase in demands for animal products. Small operations are giving way to large industrial operations, especially in the poultry farming sector. Animal husbandry is an integral component of Indian agriculture supporting livelihoods' for more than two-third of the rural population. The livestock sector in India provides employment to about 8.8% of Indian population. Economically, livestock alone contributes 25.6 percent of the agricultural output of India and 4.11% of total GDP.

Bacterial infections make up a significant proportion of animal illnesses. To mitigate farmer's losses resulting from diseases outbreaks, the Veterinarians take all possible steps to treat the infections and ensure effective treatment and prevention of the infections. Anti-bacterial' s are in use in farm animals for decades for the same reason they are used in people to treat or prevent diseases that cause inflammation and suffering. Antibiotics are often the best choice to treat sick animals or prevent animals from getting sick. The scientific deliberations highlighted that antibiotics are an essential part of therapeutic management of infectious diseases in both livestock and pet animals, insuring better animal health and life. Judicious use of antimicrobials for the management of bacterial infections assures healthy food from the animal sources.

India currently contributes 3% of the world livestock antibiotic consumption and harbor's 10% of the world food animal production. By 2030, this consumption would be 4% considering the animal population and antibiotics are a must for the healthy and secure life of our animals and ourselves and the need is to strike a balance between the benefits and risk of using antimicrobials in the food supply chain.

As per FAO report, the antibiotic usage in 2010 was 63, 151 tons in food animals with a projected increase of 67 percent by 2030 (105, 596 tons) and two third (66 percent) of the increase would be due to increase in number of animals raised for food production.

The recent report of CDDEP also highlights India advocates 22% of the world antibiotic medication to 17% of world human population and above all the highlighting fact is if we consider the dosage of antibiotics in kilograms or pounds, human physicians advocate 10 times the amount of antibiotic to humans compared to the same used in food animal production.

The discussions even highlighted that the recent CSE study highlights that concentration of antibiotics isolated from specimens are within the MRL outlined by European Union and United States. The concerns was the responsible and prudent use of antibiotics for animal welfare and protection as well as management of infectious diseases ensuring that the foods from these animals are safe and healthy for humans

The group also agreed that antibiotic usage does also lead to its excretion in milk, urine and faeces. Since milk is a product consumed by humans, it should be mandatory to have a withdrawal period and milk produced from treated animals should not be consumed till the MRL are below the described limited. Regulations for antibiotic use in food animals are in place by Central Drugs Standard Control Organization (CDSCO) and the Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare. In January' 2012, G.S.R. 28(E) the mandate of inclusion of withdrawal period in the labelling of all products meant for food animals was made into practice and need to be adhered to while procurement and supply of milk from these treated animals. Further the second Amendment of the Drugs and Cosmetics Rules (2006) contains list of drugs including antibiotics which require prescription for their use. In 2013, a new category of H_1 drugs was added in the fourth amendment to the Drugs and Cosmetic Rule (GSR 588 (E)). The Times of India reported that the regulator has proposed the introduction of a new 'Schedule H_1', in the Drugs and Cosmetics Act which will contain a list of antibiotics and anti-tuberculosis drugs currently on market."These drugs will only be sold against a prescription that the chemist *will have to retain*. The label of these drugs will have to carry a special warning. I am instructing the state drug controller generals to be ready to conduct surprise checks on compliance of retailers once H_1 is notified," the newspaper quoted the drugs regulator Dr G N Singh.

Considering that antibiotics are perquisite for a better animal health, their judicious use and adherence to regulatory requirements would ensure healthy food from these animal sources and minimal antibiotic resistance in humans

SUGGESTED LITERATURE

1. NATIONAL POLICY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE INDIA 2011 Directorate General of Health Services

Ministry of Health & Family Welfare NirmanBhawan, New Delhi [www.ncdc.gov.in/ab_policy.pdf]

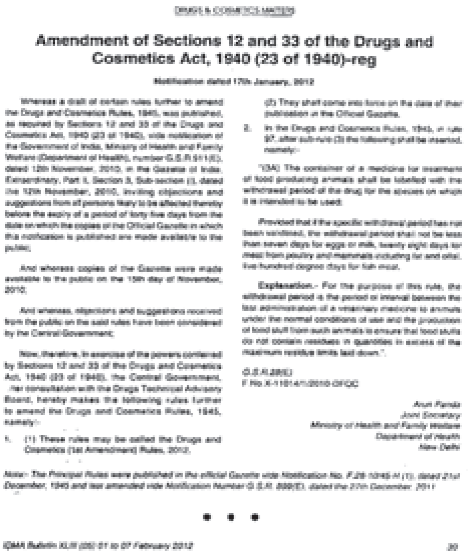
2. Rationalizing antibiotic use to limit antibiotic resistance in India+Global Antibiotic Resistance Partnership (GARP) - India Working Group *Indian J Med Res. 2011 Sep; 134(3): 281–294.

3. India Center for Disease Dynamics, Economics & Policy (CDDEP)www.cddep.org/garp/indiaSep 18, 2015 - SituationAnalysis: *Antibiotic* Use and *Resistance* in India ... Technical Support Unit, MoHFW, *Public Health Foundation of India*, New Delhi.

4. *World Health Organization. (2014). Antimicrobial resistance: global report on surveillance 2014 (p. 257).Ganguly N.K., N.K. Arora, S. J. Chandy, M.N. Fairoze, J.P.S. Gill, U. Gupta, S. Hossain, S. Joglekar, P.C. Joshi, M. Kakkar, A. Kotwani, A. Rattan, H. Sudarshan, K. Thomas, C. Wattal, A. Easton, R. Laxminarayan, "Rationalizing antibiotic use to limit antibiotic resistance in India" Indian Journal of Medical Research, 134, September, 142-55, 2011.*

5. *Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis.2013;13(12):1057–98. doi:10.1016/S1473-3099(13)70318-9.*

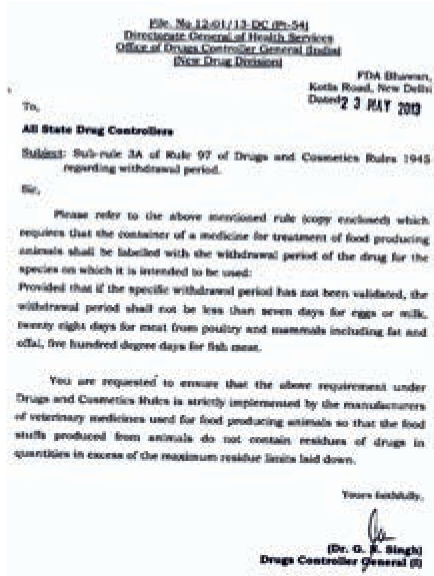
Regulation enforced under Drug and Cosmetics Rule



DRUGS & COSMETICS MATTERS

Amendment of Sections 12 and 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940)-reg

Notification dated 17th January, 2012



File. No 12-01/13-DC (Pt-54)
Directorate General of Health Services
Office of Drugs Controller General (India)
(New Drug Division)

FDA Bhawan,
Kotla Road, New Delhi
Dated 2 3 MAY 2013

To,

All State Drug Controllers

Subject: Sub-rule 3A of Rule 97 of Drugs and Cosmetics Rules 1945 regarding withdrawal period.

Sir,

Please refer to the above mentioned rule (copy enclosed) which requires that the container of a medicine for treatment of food producing animals shall be labelled with the withdrawal period of the drug for the species on which it is intended to be used:
Provided that if the specific withdrawal period has not been validated, the withdrawal period shall not be less than seven days for eggs or milk, twenty eight days for meat from poultry and mammals including fat and offal, five hundred degree days for fish meat.

You are requested to ensure that the above requirement under Drugs and Cosmetics Rules is strictly implemented by the manufacturers of veterinary medicines used for food producing animals so that the food stuffs produced from animals do not contain residues of drugs in quantities in excess of the maximum residue limits laid down.

Yours faithfully,

(Dr. G. N. Singh)
Drugs Controller General (I)

भारत का राजपत्र
The Gazette of India

MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health and Family Welfare)
NOTIFICATION

The Drugs and Cosmetics Rules, 1945 were amended vide G.S.R 28(E) dated 17.01.2012 making it andatory to mention Withdrawal Period on the label of veterinary drugs used in food producing animals to ensure that the food stuffs produced do not exceed the specified residual limits. The same is being adhered by the Indian Veterinary Pharmaceutical Industry

No. 102-74/2014-Trade
Government of India
Ministry of Agriculture
Department of Animal Husbandry, Dairying and Fisheries

Krishi Bhawan, New Delhi,
Dated, 3rd June, 2014

To,
All Directors/Commissioners (Animal Husbandry)
Of all States and UTs.

Subject: Use of antibiotics for treatment of food producing animals and in animal feeding.

Sir,

The primary use of antibiotics for animal treatment is as a schedule drugs for treatment of infectious and contagious diseases in animal. It is a well known fact that following administration of any drugs including antibiotics, there should be a withdrawal period to be given for food producing animals. In this regard, the Drug Controller General of India have issued a notification under the Drugs and Cosmetics Act, 1940 wherein the drug manufacturers has been directed that the container of a medicine for treatment of food producing animals shall be labelled with a specific withdrawal period of the drug for the species on which it is intended to be used. If the specific withdrawal period has not been validated, the withdrawal period shall not be less than seven days for eggs or milk, twenty eight days for meat from poultry and mammals including fat and offal, five hundred degree days for fish meat. The withdrawal period is the period of interval between the last administration of a veterinary medicine to animals under the normal conditions of use and production of food stuff from such animals so as to ensure that food stuffs do not contain residues in quantities in excess of the maximum permissible residue limits laid down.

2. Apart from above use, antibiotics are also used as feed premix for regular feeding in poultry and animals used for meat, milk and egg production. This kind of regular feeding of antibiotics has serious consequences on human being since residues of antibiotics may accumulate in meat, milk and eggs. Consumption of antibiotic contaminated meat, milk and eggs may develop antibiotic resistance in both human being and animals. This type of use of antibiotics should be discouraged and in this regard, the farmers/ industries and feed manufacturers should be advised/educated on not to use antibiotics for animal feeding.

3. Further, the use of hormones as growth promoters used in food producing animals should also be stopped since it has also adverse effect on human and animal life.

4. All the State Governments and Union Territories are requested to advise all the State Veterinarians, feed manufacturers and also the persons involved in treatment of animal for judicious use of antibiotics and hormones for the treatment of ailing food producing animals. An awareness programme at the consumer and farmers level may also be arranged. At the same time use of antibiotics and hormones in animal food should also be stopped.

Yours sincerely,

(S.K. Dora)
Asst. Commissioner

F. No. X-11026/64/2014-BD
Directorate of General of Health Services
Central Drugs Standard Control Organization
FDA Bhawan, Kotla Road, New Delhi
(O/o DCG (I))

Dated: 05/06/2014

To,

1. All State/UT Drugs Controllers

Sub: Use of antibiotics for treatment of food producing animals and in animal food -regarding.

Sir,

The Drugs and Cosmetics Rules were amended by the Ministry of Health and Family Welfare vide Gazette notification G.S.R. 28(E) dated 17th January 2012, to create a provision that the container of a medicine for treatment of food producing animals shall be labelled with the withdrawal period of the drug for the species on which it is intended to be used. The Ministry of Agriculture, is a nodal Ministry for matters relating to livestock production, preservation, protection and improvement of stocks, dairy development etc. The Department of Animal Husbandry, Dairying and Fisheries under that Ministry has issued a circular to all Directors/ Commissioners (Animal Husbandry) of all State and UTs vide their letter no. 102-74/2014-Trade dated 3rd June, 2014 on use of antibiotics for treatment of food producing animals and in animal feeding. A copy of the letter is enclosed.

It has been stated in the letter that the State Governments and Union Territories are requested to advise the State Veterinarians, feed manufactures and also the persons involved in treatment of animal for judicious use of antibiotics and hormones for the treatment of ailing food producing animals. An awareness programme at the consumer and farmers level may also be arranged. **At the same time use of antibiotics and hormones in animal food should also be stopped.**

In view of the above you are requested to take up the matter with the Directors/ Commissioners (Animal Husbandry) in your State/ Union Territory for the compliance of the directions issued by the Department of Animal Husbandry, Dairying and Fisheries. Arrangements may also be made to give publicity to the contents of the directions issued so as to ensure compliance by the manufacturers involved in the production of such food stuffs from animals.

Yours faithfully,

(Dr. G. N. Singh)
Drugs Controller General (India)

1. **Copy forwarded for information to**
   I. **AS & DG, (CGHS), Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi**
   II. **JS (R), Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi**
2. **Copy forwarded for information and necessary follow up to The Zonal /Subzonal offices of CDSCO.**

Introduction of Schedule H & H_1 under the Drugs and Cosmetics Rules for antibiotics

Global Antimicrobial Consumption in Food Animals

Sumanth Gandra MD,MPH
Center for Disease Dynamics, Economics & Policy
February 27, 2016

Disclaimer/Disclosures

- I am not a Veterinary physician
- I am an infectious disease physician
- No Conflicts of Interest

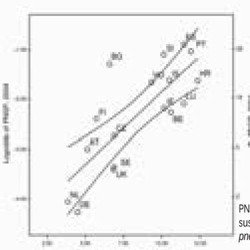
Outline of the Talk

- Relation between antimicrobial use and resistance
- Will antimicrobial consumption increase in animal sector with current regulatory scenario
- Global antimicrobial consumption in humans and food animals
- Role of antimicrobial growth promoters(AGPs) in food animals

Antimicrobial Consumption and Resistance

- Antimicrobial consumption is the major driver of antimicrobial resistance
- Variations in antibiotic resistance across countries are attributable, in part, to differential volumes and patterns of antimicrobial consumption

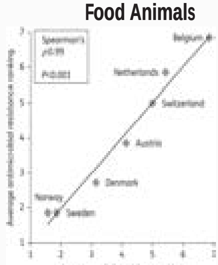
Antimicrobial Consumption and Resistance- Humans



PNSP: Penicillin Non-susceptible *Streptococcus pneumoniae*

Emerg Infect Dis. 2008 Nov; 14(11): 1722–1730.

Antimicrobial Consumption and Resistance- Food Animals

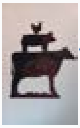


E. coli isolates from poultry, pigs, cattle and veal

Chantziaras I et al. JAC 2014;69:827-834

Resistance from food animals to humans

Food Animals

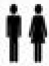


A) direct transmission of bacteria not adapted to transmission in humans
e.g: **Salmonella, Campylobacter**

B) direct transmission of organisms already adapted to transmission in humans
e.g: **VRE, MRSA (CC97)**

C) transfer of resistance genes into pathogens transmitting among humans

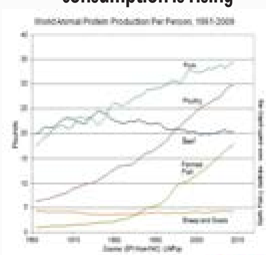
Human



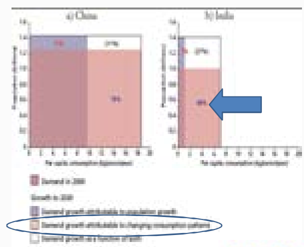
Chang Q et al. Evolutionary Applications, 2014.

Will antimicrobial consumption increase in animal sector with current regulatory scenario

Demand for animal protein for human consumption is rising



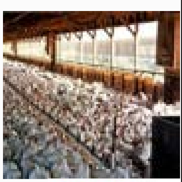
Per-capita demand for Poultry in India will increase by 577% : 2000-2030



Source: Mapping supply and demand for animal source foods to 2030, FAO

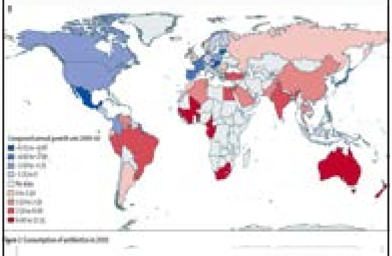
Shifting farming practices

- To meet the increasing demand a shift towards highly cost-efficient and vertically integrated **intensive livestock** production systems



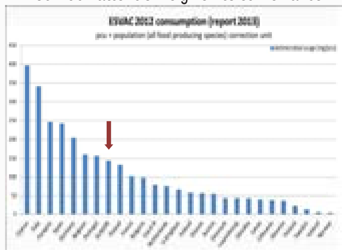
Global antimicrobial consumption in humans and food animals

Antibiotic consumption in humans



Antimicrobial use data in food animals

- Not much attention is given to surveillance

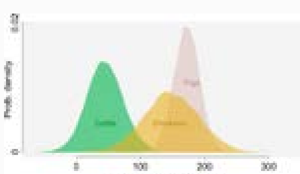


Global Antimicrobial consumption in food animals

Methodology

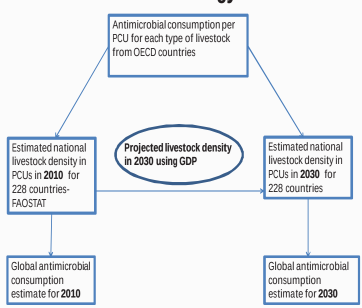
- Estimated **antimicrobial consumption per PCU** for each type of livestock from OECD countries for both **intensive** and **extensive** farming
- Population correction unit (PCU)corresponds to 1 kg of living or slaughtered animal
- For example, a herd of 10 pigs each weighting 100kg corresponds to 1000PCUs

Mean antimicrobial consumption by species



- The **mean** antimicrobial consumption for:
  - Chickens- 148mg/PCU
  - Pigs- 172mg /PCU
  - Cattle- 42mg/PCU

Methodology

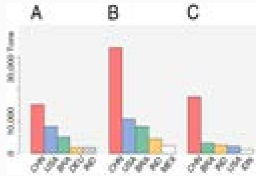


Results

- Global consumption was estimated at **63,151 tons in 2010** and is projected to rise by 67%, to **105,596 tons, by 2030**
- **Two thirds** (66%) of the global increase is due to the **growing number of animals** raised for food production
- The **remaining third** (34%) is due to a shift in farming practices, with a larger proportion of animals projected to be **raised in intensive farming systems** by 2030

CDDEP

Results

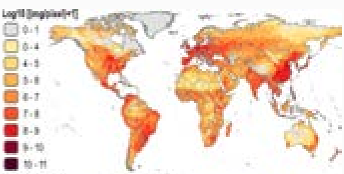


A- Largest five consumers of antimicrobials in livestock in 2010

B- Largest five consumers of antimicrobials in livestock in 2030

CDDEP

Global Antimicrobial consumption



Some Hot spots:
Southeast coast China
South coast of India, Mumbai, Delhi
Midwest & Southern USA
South of Brazil

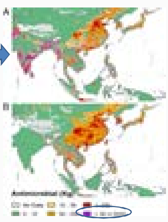
CDDEP

High antimicrobial consumption growth in India

- Areas high antimicrobial consumption **(>30kg·km⁻²)** will grow by 312% due to extreme growth in chicken antimicrobial consumption

Poultry

Pigs



In Asia, the total acreage of areas of high antimicrobial consumption (>30 kg·km−2) will grow by **4%** for **pork** and **143% for chicken**

CDDEP

E.coli resistance rates in poultry cloacal swabs from 18 farms in Punjab

Antibiotic	Broiler			Layer		
	Overall	Contracted	Independent	Overall	Contracted	Independent
Ampicillin	**51.5**	51.7	51.4	**35.7**	32.6	37.1
Chloramphenicol	**11.9**	5.3	15.1	**2.1**	0	3.0
Ciprofloxacin	**57.9**	52.5	60.5	**19.8**	13.7	22.5
Co-trimoxazole	**51.6**	57.4	48.8	**32.1**	15.4	39.3
Ceftriaxone	**6.6**	3.0	8.4	**1.2**	0.4	1.5
Gentamicin	**20.6**	19.0	21.4	**4.6**	2.6	5.5
Nitrofurantoin	**23.5**	19.4	25.5	**13.0**	7.0	15.5
Nalidixic Acid	**96.2**	93.5	97.6	**75.4**	59.0	82.4
Tetracycline	**58.8**	58.9	58.7	**34.5**	24.7	38.8

Brower C et al. unpublished

CDDEP

E.coli resistance rates in poultry cloacal swabs from 18 farms in Punjab

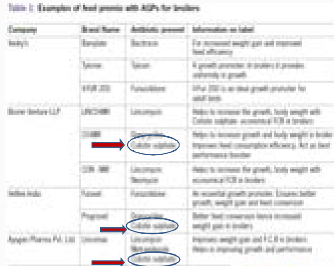
Farm	Facility	Resistance Classification		
		Singly Resistant	Moderately MDR (2-4)	Highly MDR (>4)
Broiler	Independent	**5.8**	57.9	**36.3**
	Contracted	**7.2**	60.5	**31.6**
	Overall	**6.3**	58.8	**34.8**
Layer	Independent	29.3	55.2	12.5
	Contracted	44.5	39.2	2.6
	Overall	33.9	50.4	9.5

Brower C et al. unpublished

CDDEP

Role of antimicrobial growth promoters (AGPs) in food animlas

AGPs for Broilers



Source: Centre for Science and Environment

AGP and Average Daily Growth

Species-specific relative average daily growth difference between animals raised with and without antibiotics as growth promoters

	1980s literature (%)	2000s literature (%)
Cattle	7	3
Chickens	4	0.7
Pigs	8	1

Source: OECD Report- Global Antimicrobial Use in Livestock Sector, Feb-2015

Impact of AGP Termination in Denmark- 1995-1998 & 1999-2001

Source: OECD Report- Global Antimicrobial Use in Livestock Sector, Feb-2015

Conclusion

- With no change in current laws, global antibiotic consumption in food animals will **grow by 67%** by 2030
- **One third** of the increase will be imputable to a shift toward **intensive production** systems

Conclusion

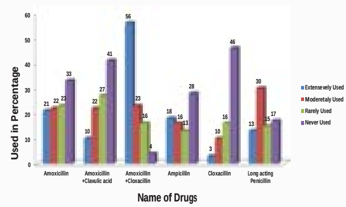
- India has high resistance rates in chicken (and in humans)
- In India, areas of high antimicrobial consumption will grow by 312% due to **extreme growth in chicken** antimicrobial consumption
- Urgent **need for a regulatory provision** in India for antimicrobial use in cattle, chicken, and pigs raised for domestic consumption

Round Table on 'Guidelines for Antimicrobial Standards in Livestock Healthcare

Antimicrobial Use in Farm Animals and its Availability in Milk and Meat products- A Pharmacological Insight

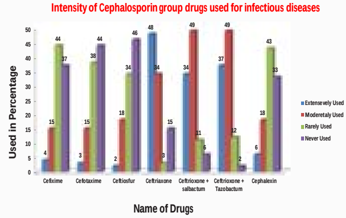
Dr.S.K.Mody
Professor and Head
Department of Pharmacology and Toxicology
College of Veterinary Science
S.D.A.U., Sardarkrushinagar-385506, Gujarat

Intensity of Penicillin group drugs used for infectious diseases



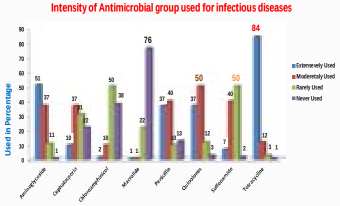
- Prescription of antimicrobial drugs in farm animals is either for curing microbial infections or as growth promoters.
- Antimicrobials have been important tools in control of infectious diseases in farm animals.
- The pharmacology of antibiotics involves both pharmacokinetic and pharmacodynamic (PD) properties. Pharmacokinetics pertains to drug concentration and time in the *host*, while pharmacodynamics describes the concentration- and time-dependent interactions of antibiotics against *pathogens* in the host.

Intensity of Cephalosporin group drugs used for infectious diseases

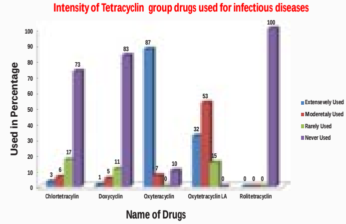


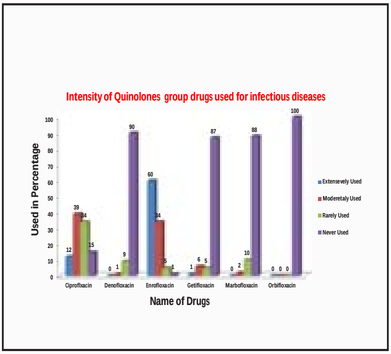
PHARMACOEPIDEMIOLOGY OF ANTIMICROBIAL DRUG USAGE IN NORTH GUARAT

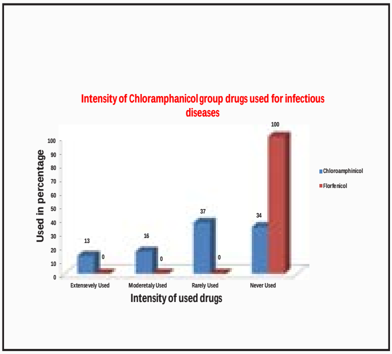
Intensity of Antimicrobial group used for infectious diseases

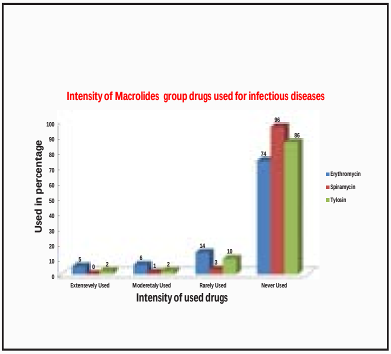


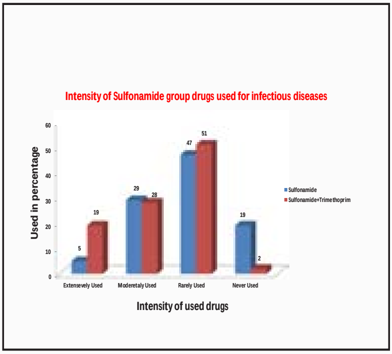
Intensity of Tetracyclin group drugs used for infectious diseases

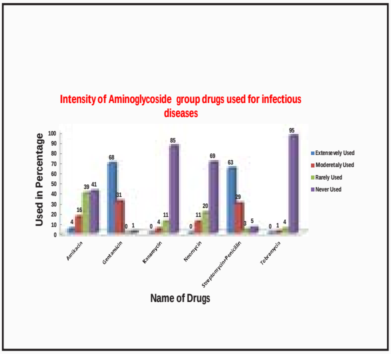


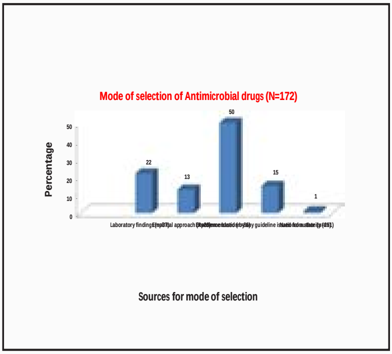

Intensity of Quinolones group drugs used for infectious diseases
Used in Percentage
Name of Drugs
Extensevely Used
Moderetaly Used
Rarely Used
Never Used
Ciprofloxacin
Denofloxacin
Enrofloxacin
Getifloxacin
Marbofloxacin
Orbifloxacin

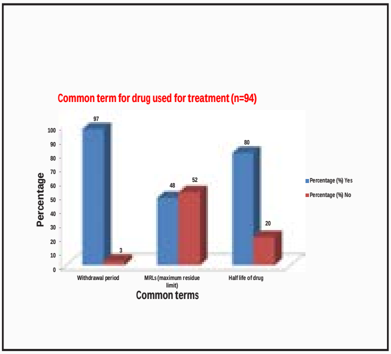

Intensity of Chloramphanicol group drugs used for infectious diseases
Used in percentage
Intensity of used drugs
Chloroamphinicol
Florfenicol
Extensevely Used
Moderetaly Used
Rarely Used
Never Used

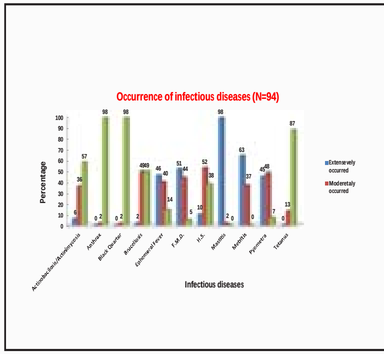

Intensity of Macrolides group drugs used for infectious diseases
Used in percentage
Intensity of used drugs
Erythromycin
Spiramycin
Tylosin
Extensevely Used
Moderetaly Used
Rarely Used
Never Used

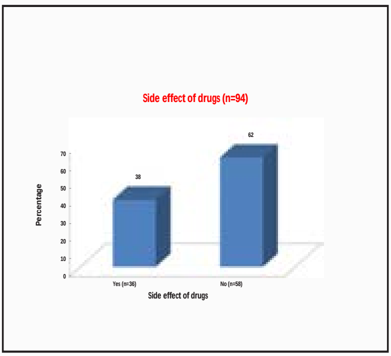

Intensity of Sulfonamide group drugs used for infectious diseases
Used in percentage
Intensity of used drugs
Sulfonamide
Sulfonamide+Trimethoprim
Extensevely Used
Moderetaly Used
Rarely Used
Never Used

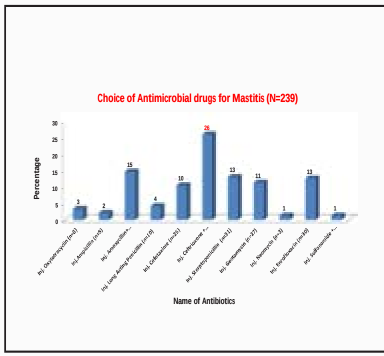

Intensity of Aminoglycoside group drugs used for infectious diseases
Used in Percentage
Name of Drugs
Extensevely Used
Moderetaly Used
Rarely Used
Never Used
Amikacin
Gentamicin
Kanamycin
Neomycin
Streptomycin+Penicillin
Tobramycin

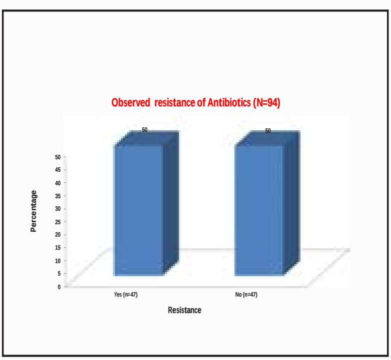

Mode of selection of Antimicrobial drugs (N=172)
Percentage
Sources for mode of selection

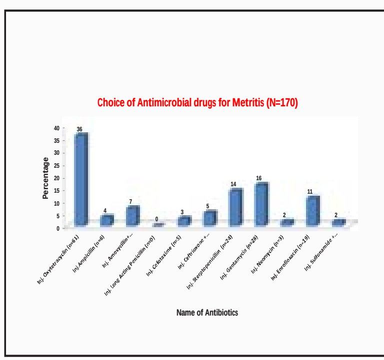

Common term for drug used for treatment (n=94)
Percentage
Percentage (%) Yes
Percentage (%) No
Withdrawal period
MRLs (maximum residue limit)
Half life of drug
Common terms


Occurrence of infectious diseases (N=94)
Percentage
Extensevely occurred
Moderetaly occurred
Actinobacilosis/Actinimycosis
Anthrax
Black Quarter
Brucelosis
Ephemeral Fever
F.M.D.
H.S.
Mastitis
Metritis
Pyometra
Tetanus
Infectious diseases

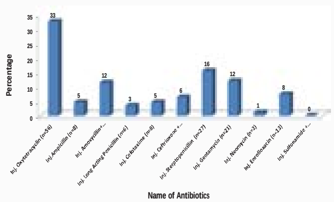

Side effect of drugs (n=94)
Percentage
Yes (n=36)
No (n=58)
Side effect of drugs


Choice of Antimicrobial drugs for Mastitis (N=239)
Percentage
Name of Antibiotics


Observed resistance of Antibiotics (N=94)
Percentage
Yes (n=47)
No (n=47)
Resistance


Choice of Antimicrobial drugs for Metritis (N=170)
Percentage
Name of Antibiotics

Choice of Antimicrobial drugs for Pyometra (N=172)



Growing concern about antimicrobial therapy

- Drug resistance problem
- Drug residue problem

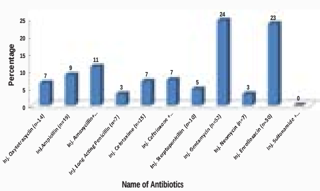
How to use ?

With proper knowledge of

PK

PD

Choice of Antimicrobial drugs for Urinary Tract Infection (N=214)



Pharmacokinetics

- Pharmacokinetics is the science of quantitating the change in drug concentration in the body over time as a function of the administered dose.
- $t_{1/2}$ = 0.693/slope or $t_{1/2}$ = ln 2 /slope
- V_d = Amount of drug in body/Serum drug concentration
- Cl = Rate of elimination / Serum drug concentration
- Withdrawal time =

  1.44 x ln (Therapeutic concentration/Tissue tolerance) x $t_{1/2}$
- *eg* -- A drug having therapeutic concentration 10 µg/ml

  and tissue tolerance 0.01 µg/ml

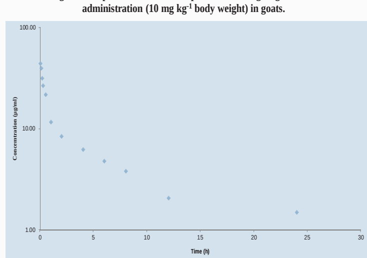
  1.44 x ln (10/0.01) x $t_{1/2}$ or 9.94 $t_{1/2}$
- This means withdrawal time of this drug 10 half lives
- If a disease process changed the half-life by either increasing V_d or decreasing clearance (Kidney disease) causing the half life changed(increased).
- This phenomenon supports the observation that seriusly ill animals with altered PK deserve increased attention to ensure complete drug withdrawal time.

Antimicrobial drug

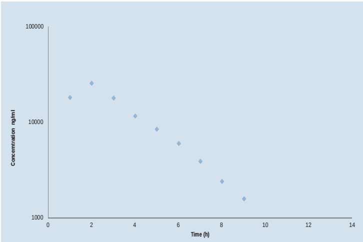
should have

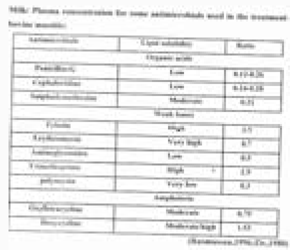
- Low MIC
- High bioavailability
- High lipophilic
- High volume of distribution
- Required Conc./MIC or AUC/MIC ratio

Semi logarithmic plot of ceftizoxime in plasma following single dose intravenous administration (10 mg kg^{-1} body weight) in goats.



Semi logarithmic plot of ceftizoxime in plasma following single dose intramuscular administration (10 mg kg-1 body weight) in goats.





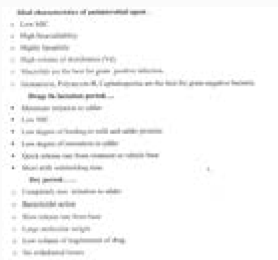
Milk: Plasma concentration for some antimicrobials used in the treatment of bovine mastitis

Antimicrobials	Lipid solubility	Ratio
Organic acids		
Penicillin G	Low	0.13-0.26
Cephalosporins	Low	0.16-0.28
Sulphonamides	Moderate	0.31
Weak bases		
Tylosin	High	3.5
Erythromycin	Very high	4.7
Aminoglycosides	Low	0.3
Trimethoprim	High	1.9
polymyxin	Very low	0.3
Amphoterics		
Oxytetracycline	Moderate	0.75
Doxycycline	Moderate/high	1.53

(… 1996; … 1988)

PK parameters of ceftizoxime in plasma after I/M administration alone @ 10mg.kg-1 b.wt.

Parameters	Unit	
β	h-1	0.09
t1/2β	h	7.41
Tmax	h	0.25
Cmax	µg/ml	30.03
AUC 0-t	µg/ml*h	148.65
AUC	µg/ml*h	152.32
AUMC	µg/ml*h^2	1447.38
MRT	h	9.48
Cl b	(mg)/(µg/ml)/h	2.02
Vd area	(l/kg)	0.70
Cl b	(l/h/kg)	0.07
Body weight	KG	31 kg
Dose @ 10 mg/kg	mg	



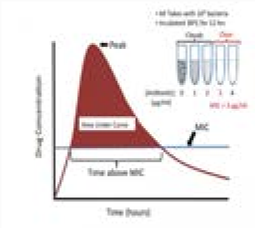
Representative body surface area to body weight ratio for various species

Species	Body weight (kg)	Surface area (m²)	Km factor	Dose equivalent (kg⁻¹)
Man adult	60	1.6	37.5	1
Man child	20	0.8	25	1.5
Mouse	0.02	0.0066	3	12.5
Rat	0.15	0.025	6	6.3
Cat	3	0.24	12.5	3
Dog	16	0.65	24.5	1.5
Sheep/goat	50	1.1	45.5	0.8
Pig	75	1.5	50	0.75
Cow	150	2.4	62.5	0.6
Cow	500	5.0	100	0.4
Pony	280	4.4	63.5	0.6
Horse	350	4.0	87.5	0.4
Horse	650	5.9	110	0.3

Pharmacodynamics ---- MIC

- The MIC is defined as the minimal concentration of antibiotic that prevents a clear suspension of 10^5 colony-forming units (CFUs) of bacteria/mL from becoming turbid after overnight incubation; turbidity usually connotes at least a 10-fold increase in bacterial density. Because clear bacterial suspensions may have bacterial densities that are 10^5 CFU/mL or less, the MIC may actually be bactericidal to some extent.
- If the minimal concentration of the antibiotic that prevented turbidity lowered the bacterial density from 10^5 to at least 10^2 CFU/mL, that is, a 99.9% (3-log_{10}) reduction in bacterial inoculum, the minimal concentration that prevented turbidity (ie, the MIC) is also the MBC.
- For bactericidal drugs, the MBC is usually the same as, and generally not more than fourfold greater than, the MIC.
- In contrast, the MBCs of bacteriostatic drugs are many-fold greater than their MICs.
- Bacteriostatic drugs include the macrolides, clindamycin, the tetracyclines, the sulfonamides, linezolid, and chloramphenicol.
- Bactericidal drugs include the beta-lactams, vancomycin, the aminoglycosides, the fluoroquinolones, daptomycin, and metronidazole.

Pharmacodynamics



MRL

- ADI = NOEL(mg/kg BW) x Standard Human Weight
  ____
  Safety factor

- Safe Concentration =

  ADI (µg/kg/day) x 60 kg
  ____
  Food Factor x 500 g/day

Drug Residue

- A chemical residue is either the parent compound or metabolite of that parent compound that may accumulate , deposit, or otherwise be stored within the cell. Tissue, organ or edible products (Milk, meat,egg)
- A feed additive is defined as a drug, chemical or other biological substance added directly to the feed to modify some asect of performance or production in food producing animals

Daily food consumption

Large animals		Poultry		Fish	
Muscle	300 gm	Muscle	300 gm	Muscle and skin in natural proportion	300 gm
Liver	100 gm	Liver	100 gm		
Kidney	50 gm	Kidney	10 gm		
Fat	50 gm	Fat	90 gm		
Total	500 gm	Egg	100 gm		
Milk	1500 gm				
Honey	20 gm				

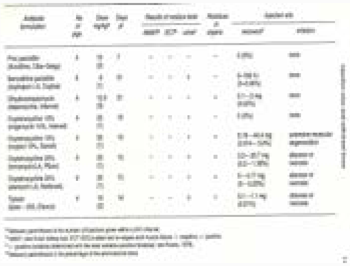
Drug withdrawal time

- Drug withdrawal time is actually determined based on experimental data
- A drug is administered to healthy animals, group of animals are slaughtered at sequential time intervals and their tissues are analyzed for drug concentrations
- The time group which contains drug below the established tolerance is the withdrawal time.
- Withdrawal time for the FDA-approved drugs for use in food animals are only valid for the specified species, dose, route, and frequency of administration.
- They are also specific to the manufacturer's products and formulations

Food factor breakdown of a 1500 gm diet

Edible product	Food factor
Cattle	
Milk	3
Muscle	1
Liver	½
Kidney	1/3
Fat	1/4
Sheep	
Muscle	1
Liver	1/5
Kidney	1/5
Fat	1/5
Poultry	
Eggs	1
Muscle	1
Liver	1/3
Fat	1/2

Persistance and detection of residues of various antimicrobial formulations post IM injection in neck region of normal pigs



3	Penicillin				
	Pharmacologically active substances	Marker residue	Animal species	MRLs	Target tissues
	Amoxicillin	Amoxycillin	All food-producing species	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 4 µg/kg	Muscle Fat Liver Kidney Milk
	Ampicillin	Ampicillin	All food-producing species	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 4 µg/kg	Muscle Fat Liver Kidney Milk
	Benzylpenicillin	Benzylpenicillin	All food- producing animals	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 4 µg/kg	Muscle Fat Liver Kidney Milk
	Cloxacillin	Cloxacillin	All food- producing animals	300 µg/kg 300 µg/kg 300 µg/kg 300 µg/kg 30 µg/kg	Muscle Fat Liver Kidney Milk
	Dicloxacillin	Dicloxacillin	All food- producing animals	300 µg/kg 300 µg/kg 300 µg/kg 300 µg/kg 30 µg/kg	Muscle Fat Liver Kidney Milk

Commission of the European committee /no. 508/1999/ 4 march, 1999

List of pharmacologically active substances for which Maximum Residue Limits have been fixed

Sir no	Pharmacologically Active substances	Marker residue	Animal species	MRLs	Target tissues
1.	All substances belonging to the sulphonamide group	Patent drug	All food-producing species Bovines, ovine, caprine	100µg/kg 100µg/kg 100µg/kg 100µg/kg 100µg/kg	Muscle Fat Liver Kidney Milk
2	Diamino pyrimidine derivatives	2	Diamino pyrimidine derivatives	2	Diamino pyrimidine derivatives
	Trimethoprim	Trimethoprim	Bovine Porcine Equidae Poultry Not for use in animals from which eggs are produced for human consumption Fin fish	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle Fat Liver Kidney Milk Muscle Skin and fat Liver Kidney Muscle Fat Liver Kidney Muscle Skin and fat Liver Kidney Muscle and skin in natural proportions

4	Cephalosporin				
	Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue
	Cefazolin	Cefazolin	Bovine, ovine and caprine	50µg/kg	Milk
	Cefquinone	Cefquinone	Bovine	50 µg/kg 50 µg/kg 100 µg/kg 200 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk

EU- MRLs (Maximum Residue Levels) of some important veterinary drugs in bovine milk (European Commission, 1999).

Sr. No.	Pharmacological active substances	Marker residues	MRLs in milk (µg/ kg)
1	All sulfonamide drugs	Same as parent drug	**100**
2	Trimethoprim	Trimethoprim	**50**
3	Amoxicillin	Same as parent drug	**4**
4	Ampicillin		
5	Benzyl penicillin		
6	Cloxacillin	Same as parent drug	**30**
7	Dicloxacillin		
8	Cefazoline	Cefazoline	**50**
9	Cefquinome	Cefquinome	**20**
10	Enrofloxacin	Sum of enrofloxacin and its metabolite ciprofloxacin	**100**
11	Tylosin	Tylosin A	**50**
12	Chlortetracycline	Sum of parent drug and its 4-epimer	**100**
13	Oxytetracycline		
14	Thiamphenicol	Thiamphenicol	**50**
15	Spiramycin	Sum of spiramycin and neospiramycin	**200**
16	Albendazole	Sum of albendazole -sulphoxide, -sulphone, and -2 aminosulphone	**100**

Quinolones

	Pharmacologically active substances	Marker residue	Animal species	MRLs	Target tissue
	Danofloxacin	Danofloxacin	Bovine (Not for use in animals from which milk is produced for human consumption) Chicken Not for use in animals from which eggs are produced for human consumption	200 µg/kg 100 µg/kg 400 µg/kg 400 µg/kg 200 µg/kg 100 µg/kg 400 µg/kg 400 µg/kg	Muscle Fat Liver Kidney Muscle Skin and fat Liver Kidney
	Difloxacin	Difloxacin	Chicken, turkey	300 µg/kg 400 µg/kg 900 µg/kg 600 µg/kg	Muscle Skin and fat Liver Kidney
	Enrofloxacin	Sum of enrofloxacin and ciprofloxacin	Bovine Rabbit Porcine Poultry (Not for use in animals from which eggs are produced for human consumption)	100 µg/kg 200 µg/kg 100 µg/kg 400 µg/kg 400 µg/kg 200 µg/kg 100 µg/kg 100 µg/kg 200 µg/kg 300 µg/kg 100 µg/kg 100 µg/kg 200 µg/kg 300 µg/kg 100 µg/kg 200 µg/kg 300 µg/kg	Muscle Fat Liver Kidney Milk Muscle Fat Liver Kidney Muscle Skin and fat Liver Kidney Muscle Skin and fat Liver kidney

Tetracycline

	Pharmacologically active substances	Marker residue	Animal species	MRLs	Target tissues
	Chlortetracycline	Sum of parent drug and its 4 epimer	All food producing species	100 µg/kg 300 µg/kg 600 µg/kg 100 µg/kg 200 µg/kg	Muscle Liver Kidney Milk Eggs
	Doxycycline	Doxycycline	Bovine (Not for use in animals from which milk is produced for human use) Porcine Poultry (Not for use in animals from which eggs are produced for human consumption)	100 µg/kg 300 µg/kg 600 µg/kg 100 µg/kg 300 µg/kg 300 µg/kg 600 µg/kg 100 µg/kg 300 µg/kg 300 µg/kg 600 µg/kg	Muscle Liver Kidney Muscle Skin and fat Liver Kidney Muscle Skin and fat Liver Kidney
	Oxytetracycline	Sum of parent drug and its 4-epimer	All food-producing species	100 µg/kg 300 µg/kg 600 µg/kg 100 µg/kg 200 µg/kg	Muscle Liver Kidney Milk Eggs
	Tetracycline	Sum of parent drug and its 4-epimer	All food producing species	100 µg/kg 300 µg/kg 600 µg/kg 100 µg/kg 200 µg/kg	Muscle Liver Kidney Milk Eggs

Conclusion

- Antimicrobial drug therapy in animals should be rationally effective with proper knowledge of PK and PD.
- Awareness should be created for food of animal origin to be antimicrobial residue free.

  (Veterinarians , academicians , pharmaceutical companies as well as regulatory authority should work together.)

Antimicrobials – ADI & MRL in Milk and Meat products

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Feed Additives -

- As ingredients or combinations of ingredients added to the basic feed mix or parts thereof to fulfill a specific need.
- Usually used in micro quantities and requires careful handling and mixing.

Type of Contaminants-Veterinary drugs

- Antibiotics
- Chloramphenicol
- Oxalonic acid
- Growth promoters
- Antibiotic feed supplements
- Furazolidone

Episodes of crisis

- NF residues in poultry and aquaculture products imported to EU from Thailand, China, Taiwan,
- India, Vietnam, Ecuador and Brazil
- Poultry and pork produced in Portugal, Italy, Greece, Romania and Bulgaria
- CAP in milkpowders (baltic states), shrimp (Asia)
- casings (China)

Animal Drug Residues

- *"Residues of veterinary drugs include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned."*

VETERINARY DRUG RESIDUES

•EU legislation on use of and monitoring for veterinary drugs Council directive 96/23/EC
• On measures to monitor certain substances and residues thereof in live animals and animal products" > National monitoring programs
• Establishment of a network of community and National reference Laboratories Commission decision 2002/657/EC
• Method performance criteria
• Introduction of Minimum Required Performance Limits (MRL)

Food and Drug Administration (FDA) Center for Veterinary Medicine/European Feed & Food Safety Authority(EFFSA)

- **Regulates use of Feed additives**
- **Clearance for testing of new feed additives requires obtaining an investigational new animal drug (INAD) to test a product.**
- **New animal drug Application(NADA) is required to market a product.**
- **Clearance is required to use feed additives.**

Delaney Clause - 1958

- Congress passed the Delaney Clause in 1958 – **Zero Tolerance.**
- **No substance can be used as a feed additive, even in minute amounts**, if it has been in any way implicated as **an inducer of cancer** in either human or beast.

FDA

- **Form 1900 required for human risk drugs.**
- **Category I – safest to use, no withdrawal period required.**
- **Category II – no residues allowed, withdrawal period required.**

Examples of Feed Additives

- Antibiotics
  - **Compound produced by microorganisms that inhibits the growth of microorganisms.**
  - Examples of claims that can be listed on label.
    - Improves performance (rate of gain).
    - Improves feed efficiency or feed conversion.
    - Increases growth rate.
    - Increases milk production.

Animal Drug Residue Tolerance Levels

Growth Promotion and Feed Efficiency

- **In general, Antibiotics are fed to reduce the incidence of Subclinical levels of bacterial infections of the digestive and respiratory tracts - thus credited with improved rate of gain and feed efficiency. Partial list.......**
  - **Chlortetracycline, Oxytetracycline, Erythromycin**
  - **Lasalocid, Monensin, Penicillin**

Summary

- Feed additives must be used according to label.
- Stiff fines for non compliance.
- For best results use as directed.
- Protect your market and livelihood.

Allergenicity: β-Lactam Antibiotics

- Anaphylactic reactions have been reported to result from consumption of beef or pork containing penicillin.

Human Health Risk Issues

- Drug residue allergy
- Cancer, reproductive, and Developmental effects
- Development of antibiotic resistant microbes
- Drug misuse

Microbiological Effects

- Disruption of normal human flora in the intestine.
  - Bacteria that usually live in the intestine act as a barrier to prevent incoming pathogenic bacteria from getting established and causing disease.
- Antibiotic residue might reduce total numbers of these bacteria or selectively kill some important species.

Tolerance: Hazard Identification

- Short term
  - Allergenicity
  - Toxicity
- Long term
  - Microbiological effects
  - Carcinogenicity
  - Reproductive effects
  - Teratogenicity

Carcinogenicity: Nitrofurans, Nitroimadazoles

- Furazolidone and its metabolites have been shown to induce cancer in animals.
- Had been labeled and approved for anti-protozoaland other uses for a wide variety of conditions in poultry and swine.
- FDA approval withdrawn 1991.
- FDCA Delaney Clause.

Dose-Response and Exposure Assessment

- Toxicological tests in laboratory animals.
  - Part of pre-clinical drug development.
- Development of NOAEL.
- Safety factors.
- Acceptable daily intake (ADI).
- Exposure assessment.
  - Food consumption.
  - Aggregate exposure.
- Use to develop Tolerance Level.

Animal Drug Withdrawal Time

- Other considerations
  - Aesthetic considerations
  - Risks perceived by public
  - Sensitive populations and issues
  - International relations and trade barriers

Withdrawal Time

- Time required for a drug or chemical concentration to fall below the Tolerance Level established in a specific target animal tissue.
- Dependent upon drug, dose, formulation, route of administration, species, target tissue and disease / management factors.
- Pharmacokinetics-toxicokinetics of the drug is the main factor.
  - Therapeutic level vs. Elimination
- PK of elimination can be different for different tissues

Extralabel (Off-Label) vs. Label Drug Use

- Higher dose than label
- Different route than label
- Different species than label
- Different disease indication than label

Animal Drug Withdrawal Time

- Experimentally determined.
- Time required that concentrations in all food animal tissues or products are below tolerance.
- Margin of safety (MOS) increased to 95% confidence interval for 99% of population.
  - MOS = LD1/ED99
- Expensive
  - Limited products
  - Healthy animals

Drug Residue Testing

- Target tissues tested
  - Milk
  - Kidneys often tested at slaughter
- STOP
  - Swab test on premises
- FAST
  - Fast antimicrobial screen test
- SOS
  - Sulfa-on-site
- CHARM II; SNAP
  - Milk residues
- Lab tests
  - HPLC/GC/Mass Spectrometry

Drugs Most Likely to be Detected in Meat

- Penicillin (including ampicillin)
- Tetracycline (including chlortetracycline and oxytetracycline)
- Sulfonamides (including sulfadimethoxine and sulfamethazine and sulfamethoxazole)
- Neomycin
- Gentamicin
- Streptomycin

Neomycin

- Neomycin is an aminoglycoside antibiotic that is used to treat intestinal, respiratory, wound infections and mastitis.

Potential Adverse Effects: Tetracyclines

– Particularly to liver, kidney, bones and teeth.
– Little metabolism of this drug in humans or animals and it was primarily excreted in the urine
• Not mutagenic, carcinogenic, or teratogenic in animal studies; some toxic effects were observed at high doses.
– NOAEL 18 mg/kg body weight/day.
• Therapeutic doses occasionally associated with discolored teeth, allergic reactions, or peripheral blood changes
• Oxytetracycline did induce antibiotic resistance in coliforms in the human intestine; JECFA used this for MRL.
– NOEL 2 mg/person/day
• There have been reports of allergic reactions but no cases that have involved exposure to residues in foods.
• JECFA estimated that if OTC residues in meat, milk and eggs were at the MRL. residues would total 260 μg.

Potential Adverse Effects: Neomycin

• Neomycin is not readily metabolized in animals or in humans.
• Not genotoxic. Like streptomycin and gentamicin, it has been reported to cause damage to the kidney and to hearing.
– Recent data indicate that people with a rare mutation in their mitochondrial DNA may be more susceptible to deafness caused by aminoglycosides and other environmental factors than the general population.
• JECFA based its recommendation for a maximum daily intake of 3.6 mg/kg bw on results on hearing loss in guinea pigs.
• JECFA calculated that the estimated dose of neomycin from veterinary drug residues was 3 mg/day, primarily from milk (2.25 mg), kidney (0.5 mg), and muscle (0.15 mg). This was 3000 times less than the recommended oral therapeutic dose of neomycin.

Potential Adverse Effects: Sulfonamides

• Metabolized by numerous pathways with the major metabolite in humans, swine and cattle being an acetyl derivative.
• Data cited by JECFA indicate that the primary mechanism of toxicity of sulfonamides is associated with the thyroid–hypothalamus
– Toxicity should be measured by parameters of thyroid and pituitary function.
• NOAEL 2.2 mg/kg bw/day.
• Hypersensitivity reactions (primarily skin rashes) to therapeutic levels of sulfonamides have been reported but there have been no cases that involved exposure to residues in foods.

Gentamicin

Potential Adverse Effects: Gentamicin

• Like streptomycin and neomycin, gentamicin has been reported to cause damage to the kidney and to hearing.
• Depleted rapidly from muscle and fat but tends to persist in kidney and liver.
• Not readily metabolized in animals or in humans.
• JECFA estimated that if residues in meat were at the recommended MRL, the maximum daily intake of gentamicin from residues would total 785 μg.
– 30 μg from muscle, 200 μg from liver, 250 μg from kidney, 5 μg from fat, 300 μg from milk

Potential Adverse Effects: Streptomycin

- Not readily absorbed from the GIT because of its high molecular mass and not metabolized significantly w/ inj.
- Oral doses of the drug are eliminated unchanged in the feces.
- Reports of allergic reactions to streptomycin
  – No cases that have involved exposure to residues in foods.
- One significant adverse effect in humans that occurred during treatment of pregnant women with TB.
- Streptomycin may also have adverse effects on kidney fn.
- No other evidence of effects on fertility or reproduction.
- It is not expected that low food residues/low abs. would affect fetal development.

Less Antibiotic Use In Food Animals Leads To Less Drug Resistance In People

- Campylobacter jejuni is a leading bacterial cause of foodborne illness in industrialized countries.
- Drug resistance can make Campylobacter infections difficult for to treat, and can result in longer bouts of and a higher risk of serious or even fatal illness.
- Australia prohibited the use of fluoroquinolones, in food animals such as poultry.
- Only 2% of the locally acquired Campylobacter isolates were resistant to ciprofloxacin, a type of fluoroquinolone (29% in countries w/o ban).
  – Sweden prohibited the use of fluoroquinolones for food animals in 1986
  – Norway has never licensed their use in food animals
- FDA proposed banning fluoroquinolones in poultry in 2000; finally enacted in September 2005.

Development of Antibiotic-Resistant Bacteria

- Bad bugs → no drugs
- A major issue of drug use in food animals as well as over-use of antibiotics in humans

Animal Drug Residue Concerns

- Consumer health risk
  – Environmental concerns
- Consumer preference
- Production loss for the producer
  – Lost milk product ($6,000 to $80,000)
  – Lost animal ($500 to $2000)
- Legal action against the producer
  – Violative (illegal) residues

Antibiotic-Resistant Bacteria Isolated From Meat

- Hypothesis was that the greater the amount of a drug used, the more likely bacteria would develop resistance to it.
- Beef:
  – Tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > cephalothin
- Pork:
  – Tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > gentamicin
- Chicken:
  – Tetracycline > sulfa > streptomycin = cephalothin > ampicillin > chloramphenicol > gentamicin
- Turkey:
  – Sulfamethoxazole > tetracycline > streptomycin > ampicillin > cephalothin > gentamicin

"MRL"-drugs

- Council regulation 2377/90
- • Annexes of CR 2377/90
- – Annex I - final MRLs
- – Annex II - no MRLs needed
- – Annex III - provisional MRLs
- – Annex IV - forbidden substances
- • Safety evaluation > ADI > MRL > withdrawal

Theoretical Maximum Daily Intake

- **The TMDI is the sum of residues present in a**
- **standard food basket (daily consumption of)** :
- 300 g muscle
- 100 g liver
- 50 g fat
- 50 g kidney TMDI ADI
- 1500 g milk
- 100 g eggs
- 20 g honey

MRL needed!

MRL”-drugs

- Safety and residue studies to be provided by the
- **Applicant**
- In practice these studies are only performed on
- major food producing species
- Major problem for minor species
- Very limited number of drugs (or none at all) available
- **for treating e.g. laying hens, fish, bees**
- **Off-label use**
- Dilemma with regard to tolerance levels

Determining the Acceptable Daily Intake (ADI)

- Adverse systemic effects
- Reproduction and developmental effects
- Mutagenic effects
- Carcinogenic effects
- Effects on human intestinal flora
- Immunologic effects
- Pharmacological properties
- Endocrine effects

Rapid Alert System for Food and Feed

- **Number of MRL violations very limited**
- **EU monitoring programs indicate ~ 0.05 – 0.1 % noncompliant**
- Import control on approved drugs is limited
- **MRLs differ throughout the world !**

Determining an MRL

- **Chemical identity and properties**
- **Uses and recommended doses in food animals**
- **Pharmacokinetic, metabolism and**
- **pharmacodynamic data**
- **Total residue (radiolabel) studies**
- **Residue depletion studies in food animals**
- **Available routine method of analysis including**
- **method performance**

Good Laboratory Practices

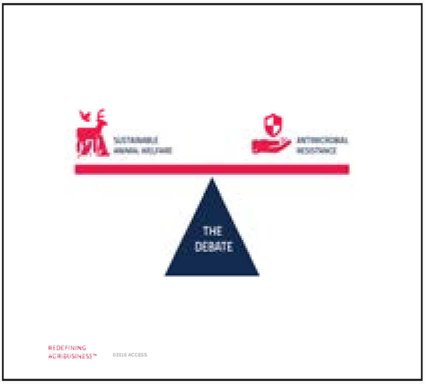
- **SOP**
- **Accreditated**
- **Approved Methodology**
- **PAM, AOAC, FAO, OIE, FDA, EPA,**
- **EC Directives**


Quality Control
Calibrated Glasswares
Glass distillation of solvents
Certified Standards
Trained personnal
ISO 9001-2000


To succeed in your mission, you must have single-minded devotion to your goal.


Validation
Repeatability
Reproducibility
Precision
Recovery
LOQ
LOD
MRPL
ISO 9001-2000


Accreditation
NABL
ISO 17025
GVP



GLOBAL ANTIMICROBIAL DEBATE IN FOOD CHAIN

IN SUPPORT OF RESPONSIBLE DRUG USE

SOMU AMBAT
somu@youraccess.co

01 The Debate

Surrounding AMR - Constraints & Complexity

Animal Welfare
Animals sick or at risk have the right to be treated

Ethical
Antibiotics are important for food security

Science Based
ABX are not all the same

Sustainable
Vaccines will not substitute ABX
Disease will always be present

Consumer Perceptions:
Emotion driven
Ag mainly responsible
Sophistication of NGOs & activists
Prevention and Growth - Negative perception
Reactive Stakeholders -differentiation

Technical:
AMR is a complex subject
Complexities for global judicious use

Regulatory framework:
Tendency toward Precautionary Principle
Geographically Inconsistent

TAKEAWAYS

01 The Debate

02 Classes of AB's
Shared; Animal Only; Human Only

03 Risk Analysis

04 Global Classification
WHO; OIE

05 Policy & Position

WHAT ARE ANTIBIOTICS

Antimicrobials
the broadest term used, refers to any type of product that has activity against a variety of microorganisms, which can include bacteria, viruses, fungi, and parasites

Antibiotics
are a type of antimicrobial. Specifically, antibiotics are, in most cases, compounds produced by a fungus or another microorganism that kill or inhibit the growth of bacteria that cause disease in humans or animals

WHY DO WE NEED ANTIBIOTICS?

ANIMAL WELFARE: Policies that eliminate all types of antibiotics from production also increase animal suffering and death from preventable and treatable illnesses.

SUSTAINABILITY: Policies that eliminate all antibiotics in chicken production versus policies that allow animal-only antibiotics result in the loss of 1 million servings of chicken annually – for every single chicken barn that adopts the policy.

FOOD SAFETY: Healthy animals are an important first step for a safe food supply.

ANTIBIOTICS 101

AO: Animal Only
Antibiotics belonging to classes not used in human medicine
Ionophores: monensin, narasin,
Orthosomycin: Avilamycin
Quinolines: Halquinol
Bambermycin: Flavomycin
Carbadox

SC: Shared Class
Antibiotics belonging to classes used too in human medicine

GP: Growth Promotion
A challenge for SC

CU: Continuous use Therapy
A challenge for SC

AW: Animal Welfare
Important reason for the use of antibiotics

Sustainability
Economically sound, socially acceptable and environmentally friendly

AMR: Anti Microbial Resistance

WHO Antibiotic Classifications:
CI: Critically important
HI: Highly important - All SC
I: Important
NC: not classified

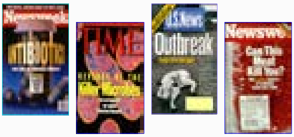
	AO	SC
Enteric Disease	☑	☑
Systemic Disease	☐	☑
Growth Indications	☑	☐
Continuous Use	☑	☐
Animal Welfare	☑	☑
Sustainability	☑	☑
Food Chain Acceptance	☑	☑☐

02 Classes of AB's

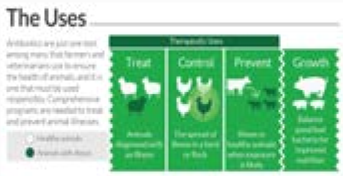
04 Risk Analysis

Resistance and Food Safety

There are public concerns that people may acquire foodborne illnesses that cannot be appropriately treated with antibiotics as a result of antibiotic-resistant bacteria that are derived from food animals that have been treated with antibiotics

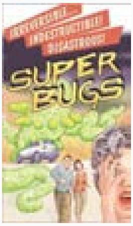


WHY ARE ANTIBIOTICS USED?

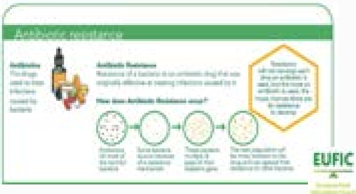


THE HUMAN HEALTH RISK

A person becomes sick with a bacterial infection that cannot be appropriately treated with antibiotics as a result of animal-derived antibiotic-resistant bacteria or genes



AMR 101



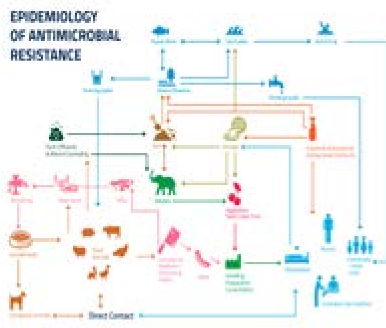
KEY QUESTIONS

0% 100%

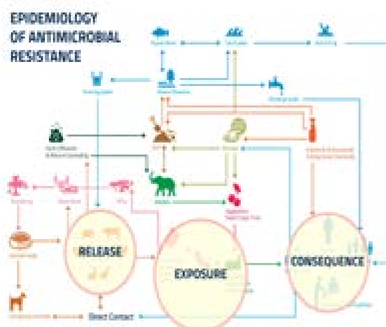
ANIMAL USE CONTRIBUTION VS. HUMAN USE CONTRIBUTION

- To what extent does the use of antibiotics in animal production contribute to bacterial antibiotic resistance already present in humans?
- To what extent should resources be directed to intervene?
- How will success be determined?

AMR 101



AMR 101



THE 3-STEP RA PROCESS

- An antibiotic must select for foodborne bacteria that acquire antibiotic-resistance in food animals during treatment
  - Release
- A person must ingest meat from a treated animal that is contaminated with those same antibiotic-resistant foodborne bacteria
  - Exposure
- The person that ingests these bacteria must become sick with a bacterial infection that cannot be appropriately treated with antibiotics as a result of those animal-derived antibiotic-resistant bacteria
  - Consequence

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WHAT IS RISK?

Risk = Hazard * Exposure
Hazard = something that can cause harm
Exposure = amount of hazard or time in presence of hazard
Foodborne Hazard Examples
- Dioxin, pesticides
- Salmonella, E. coli 0157:H7
- Antibiotic resistant Salmonella

Risk = Probability (event) * Consequence/Impact
Probability = how often?
Event = the defined hazard or adverse event
Consequence = unwanted outcome
Express as: Low, Medium or High; or 1 in 1 million

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RISK ASSESSMENT STARTS BY CONNECTING THE CAUSAL CHAIN

Adverse treatment outcomes in humans

Antibiotic use on-farm

If there is NO connection, there is NO RISK

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04 Global Classification

Critically Important Antimicrobials for Human Medicine

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RISK COMPARISON OF MARCROLIDE ANTIBIOTICS

Risk (High to Low)	Yearly Probability
Being the victim of a violent crime	1 in 200
Dying from heart disease	1 in 384
Dying from cancer	1 in 514
Dying from a stroke	1 in 1,750
Being murdered	1 in 18,000
Dying from choking	1 in 200,000
Acquiring a food-borne infection from fruit or vegetables	1 in 375,000
Being struck by lightning	1 in 550,000
Being attacked by a shark	1 in 700,000
Dying from a bee sting	1 in 6 million
Acquiring resistant *Campylobacter* from macrolide treated poultry which results in treatment failure	<1 in 14 million
Dying from a dog bite	1 in 18 million
Dying from Salmonella poisoning from an egg shell	<1 in 142 million
Acquiring resistant E. *faecium* from macrolide treated poultry which results in treatment failure	<1 in 3 billion

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LIST OF ANTIMICROBIAL AGENTS OF VETERINARY IMPORTANCE

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WHO CRITICALLY IMPORTANT LIST

GLOBAL INFLUENCE

- All countries use antibiotics in animals. Including Europe.
- Europeans still use antibiotics for therapy but had historically moved away from using antibiotics for production claims
- In the United States applying the newest FDA guidance will change the antibiotic use to closely align with current Europe regulations. Shared class antibiotics (those classes used in both humans and animals) will not be allowed for production claims but only for therapy under the oversight of a veterinarian.
- With the new FDA Guidance, and similar changes currently ongoing in Canada, Canada, US and Europe will be similarly aligned on antibiotic regulation.
- The differences;
  - Europe allows use of some antibiotics not allowed in the US,
  - Europe metrics on antibiotic use does not include ionophores
  - US and Canada will still allow use of animal-only antibiotics for production reasons

EUROPEAN CLASSIFICATION

The AMEG proposes to classify antimicrobials from the WHO CIA list in three different categories:

Category 1
as antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited,

Category 2
as antimicrobials used in veterinary medicine where the risk for public health is estimated higher and

Category 3
as antimicrobials not approved for use in veterinary medicine.

CLASSES OF ANTIMICROBIALS

HUMAN	HUMAN & ANIMAL	ANIMAL
Aminocyclitols	Aminoglycosides	Avilamycin
Carbapennems & other penems	Carbapenems	Bambermycin
Glycylcyclines	Cephalosporins (1,2,3,4 generation)	Bacitracin (polypetide)
Lipopetitides - daptopepdies	Chloramphenicol (No in U.S./Yes EU)	Carbadox
Metronidinazole	Flouroquinolones/Quinolones	Ionophores
Monobactams	Glycopeptides	
Mupirocin	Lincomsamides	
Mycobacterium anti-infectives	Macrolides	
Nitrofurantoins	Monobactams	
Nitroimidazoles	Polymixin B	
Oxazolidinones	Quinolones	
Rifamycins	Streptogramins	
Sulfones	Sulfonamides	
Tuberculosis/mycobacterial drugs	Tetracyclines	
	Pleuromutilin* (WHO not FDA152)	
Not of Concern	Used for therapy under veterinary supervision as prescribed.	Used for therapy and productivity, in animals ONLY.

US MEDICALLY IMPORTANT CLASSIFICATION

- Determined by GFI # 152 Appendix A
- Established in 2003
- FDA's plans to modify the use of shared-class antibiotics in farm animals such as cattle, pigs, chickens and others.
- FDA's stated goal is to promote judicious use of antibiotics, protect public health, and help curb the development of antimicrobial resistance.
- Guidance 209, The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, limits the use of shared-class antibiotics for animals to therapeutic purposes
- Guidance 213 advises companies on how to revise product labeling and promotion of affected products
- FDA's proposed revisions to the Veterinary Feed Directive efficiencies for allowing veterinarians to direct feed mills to mix medicated feeds for preventing, controlling and treating diseases

05 Policy & Position

Need and Purpose of an Antibiotic Policy

- Provide clear understanding of action with regard to antimicrobial product development, product marketing & use in food animal production and companion animals globally
- Platform upon which strategies and tactics, as well as business decisions should be based
- Provides direction for how we will support market access for antimicrobial products to enable trade and food security

KEY FACTORS TO BALANCE

- Science-based risk-benefit assessment vs. political decision
- Human health and food safety vs. animal health needs
  - Future animal protein availability and affordability
- Therapeutic use vs. performance use
- Veterinarian oversight vs. lay person use
- Unintended consequences vs. desired outcome
  - Risk-risk analysis
  - Risk-benefit analysis

ANTIBIOTIC POLICY: POINT BY POINT

RESPONSIBLE USE

- Preserve effectiveness of antibiotics in farm animals to protect human health and food safety, and to ensure animal health & welfare
- Voluntarily narrow the use of antibiotics approved for both humans and animals to therapeutic uses only for animals
- Move towards removing promotion of shared-class antibiotics for growth performance in animals
- Globally transition current label indications for shared-class antibiotics to therapeutic indications

POSSIBLE ACTIONS

Legislative

e.g. Prescription system i.e. access via control (feed mills, marketing channels)

Veterinary oversight

Responsible use, veterinarian network via communication and education

Regulatory review process

Resistance monitoring
Use / sales data
Risk assessments

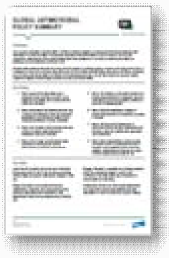
ANTIBIOTIC POLICY: POINT BY POINT

TRANSPARENCY & VALIDATION

- Support veterinarian oversight of shared-class antibiotics and the development of veterinarian infrastructures globally
- Support the development of enhanced tools that will allow veterinarians and farmers to verify and validate responsible use of antimicrobials
- Share accurate information about why antibiotics are used in animals so consumers, retailers, veterinarians and farmers can make more informed decisions about antibiotic use.

ANTIBIOTIC POLICY ELEMENTS

- Responsible Use
- Transparency & Validation of Use
- Focus on Innovation



FOOD CHAIN COMPANIES GLOBAL VISION SPECIFICS

1. Prohibit the use of antimicrobials in food animals that are by WHO definition “critically important” to human medicine, and not presently approved for veterinary use.
2. Classes of antimicrobials that are currently approved as dual use (for use in both human and veterinary medicine) for treatment or prevention of animal disease can only be used in conjunction with a veterinary-developed animal health care program.
3. Prohibit the use of any medically important antimicrobials for growth promotion in food animals, as defined by WHO.
4. Utilize animal production practices that reduce, and where possible eliminate, the need for antimicrobial therapies and adopt existing best practices and/or new practices that would result in subsequent reductions of antimicrobial use. Successful strategies will be shared broadly.

TAKEAWAYS

01 The Debate

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WHO; OIE

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CATEGORIES OF ANTIBIOTICS

SHARED CLASS

"Responsible use does not simply equate to using fewer antimicrobials."

Use the right drug in the right amount
by the right route for the right period of time"

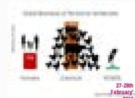
Jackie Atkinson, Director of Authorisations
Veterinary Medicines Directorate
United Kingdom
January 21, 2012

Antibiotic Use in Animal Healthcare and its Residues

Nitin Bhatia
Intas Animal Health
Intas Pharmaceuticals Limited
Ahmedabad, Gujarat- 380015 (India)

Animal Health - key for Future food

- The global biomass of animals raised for food now exceeds the global mass of humans
- In Asia, daily animal protein intake grew from 7 grams per capita per day (1960) to 25 grams per capita per day (2013)
- To meet the increasing demands, countries such as Brazil, Russia, Indi, China and South Africa (BRICS) have shifted towards highly cost effective and vertically integrated intensive livestock production systems



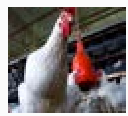
27-28th February 2016

Animal Health - Key for Future Food

27-28th February 2016

Animal Health - key for Future food

- Animal source foods provide micronutrients that are difficult to obtain in adequate quantities from plant sources alone
  - Vitamin A
  - Vitamin B_{12}
  - Riboflavin
  - Calcium
  - Iron and
  - Zinc



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Animal Health - key for Future food

- With growing times, population and income, the appetite for meat, egg and dairy products is on an increase.
- Rapid income growth in low and middle-income countries has increased demand for animal protein.
- It's the responsibility of government, regulatory bodies and industry to feed the human population with the best and safe nutrition of both; the animal and plant origin.

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Annual Per Capital Consumption

Country	Meat (kg)	Milk (kg)	Egg (kg)
USA	120.2	253.8	13.9
UK	84.2	241.5	10.5
India	4.4	68.7	2.4
Australia	111.5	230.9	7.2
China	58.2	28.7	18.5
Brazil	85.3	124.6	8.8
World-over	41.9	108	9

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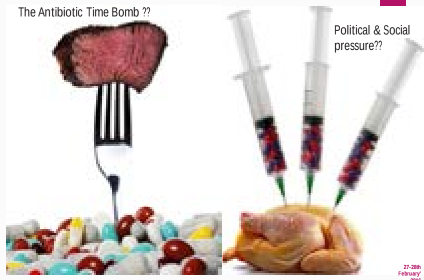
Antibiotics & its usage

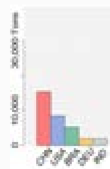


Antibiotics

- Discovery of antibiotics/antimicrobials is one of the most significant achievements of modern medicine and has substantially contributed to reduction in burden of common infectious diseases of humans and livestock globally.
- Antimicrobials are used in various applications including human and animal medicine, food production, plant agriculture and industrial applications.
- In food producing animals they are typically used for three purposes
  - therapeutic reasons (cure of diseases)
  - prophylactic reasons (prevent a disease) and
  - as growth promoters

Antibiotics Usage – Worldwide

- In 2010, countries with the largest shares of global antimicrobial consumption in food animal production were
  - China (23%)
  - United States (13%)
  - Brazil (9%)
  - India (3%) and
  - Germany (3%)



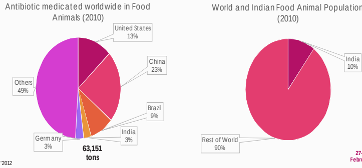
Antibiotics in Use (Veterinary)

The antibiotics/antibacterials used in Veterinary medicines belong to 6 major groups, viz.

- Beta-lactarns
- Aminoglycosides
- Tetracyclines
- Macrolides
- Quinolones and
- Sulphonamides

Antibiotic medication in Food Animal *vs* Food Animal population (2010)

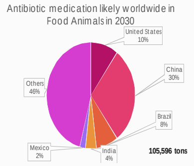
Global trends of antimicrobial use in food animals



Source: UN-FAO-STAT 2012

Antibiotic medication in Food Animals (2030)

- The projected rise is 67% by 2030
- Two third (66%) of the global increase in antimicrobial consumption is due to growing number of animals raised for food production



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Myths vs Facts

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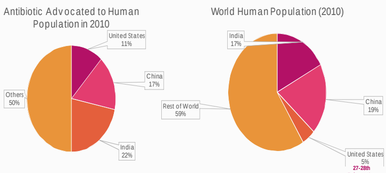
Antibiotic medication in Humans (2010)



CDDEP, Washington DC

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Myths vs Facts - 1

- **Myth #1:**

  "Antibiotics in livestock are making humans more resistant to antibiotics."

- **Fact . . .**

  Use of antibiotics by humans is the main culprit for the resistant bacteria confronting patients and human health practitioners today. The CDC confirmed this in its recent report and noted that 50 percent of antibiotics prescribed for use in human health are inappropriate."

Richard Raymond, MD, former Undersecretary for Food Safety, US Department of Agriculture (USDA)

27-28th February' 2016

Who/ What is the Cause of Concern

27-28th February' 2016

Myths vs Facts - 2

- **Myth #2:**

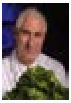
  "Antibiotic use in livestock is making our food less safe."

- **Fact . . .**

  Studies suggest that if we removed the use of antibiotics from all animals, we may have less safe food due to the fact that sick animals would be entering the food supply, carrying an increased level of bacteria with them. Therefore, striking a balance between the benefits and risks of using antimicrobials in the food supply is approved by FDA for animals

  The fact remains that. . . harmful bacteria may be found on raw meat products, kitchen surfaces, knives and other utensils – right in your kitchen.

  "Whether the harmful bacteria such as Salmonella that are sometimes found in raw meat are resistant to antibiotics or not, does not affect their sensitivity to heat and sanitizers that are used to make meat safe. Hence, following USDA recommended meat and poultry products' safe handling practices will reduce the risk of infection."



Michael Doyle, PhD, Professor of Food Microbiology and Director of the Center for Food Safety at the University of Georgia

27-28th February' 2016

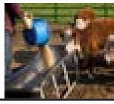
Myths vs Facts - 3

- **Myth #3:**

  "Animal Health Usage of Antibiotics is rampant and cause of resistance worldwide."

- **Fact . . .**

  "Sales does not equal use and use is not the same thing as resistance"



Ron Phillips, Spokesman for the Animal Health Institute

27-28th February' 2016

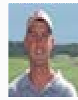
Myths vs Facts - 6

- **Myth #6:**

  "Organic producers never use antibiotics."

- **Fact . . .**

  "When antibiotics are deemed medically necessary to treat a sick animal, farmers and ranchers, both 'conventional' and 'organic,' have an ethical responsibility to treat them. To balance their responsibility to the animal's health and the requirements of organic labeling, most organic producers either market treated animals as conventionally raised or sell them to a producer who is not in the organic or similar program. Regardless, milk and meat from animals that receive antibiotic therapy can only be marketed after the appropriate withdrawal period has elapsed to ensure that the antibiotic has sufficiently cleared the animal's system, but even then, the animals cannot be labeled as organic."



Will Gilmer, dairy farmer, Gilmer Dairy Farm, Alabama, USA

27-28th February' 2016

Myths vs Facts - 4

- **Myth #4:**

  "Antibiotics are only used as growth promoters because the conditions in tightly confined feeding operations are so terrible."

- **Fact . . .**

  Farm animals would crowd together even if they had a wide open field or barn because it is their nature to do so. And, even in large spaces, animals still can and do contract illnesses requiring treatment.

  "The judicious use of antimicrobials in food animals keeps them healthy and healthy animals mean healthy food for humans. Its important for Veterinarians and producers to use good judgment to decide when and how an antimicrobial is to be used to maximize public and animal health benefits while minimizing risks.

  Strategic use of Antibiotics for disease prevention (where disease is predicted, but may not yet have been documented) and control (where disease is present in a portion of the herd or flock and will likely spread) is essential for animal health and welfare."

Katherine Waters, DVM, MPH, University of Minnesota

27-28th February' 2016

MRLs – Indicator of Antibiotic Residues in Food Animals

27-28th February' 2016

Myths vs Facts - 5

- **Myth #5:**

  "Buying organic and antibiotic-free is better for me and my family."

- **Fact . . .**

  "There is no scientific evidence to suggest a difference in nutritional content or bacterial safety between the two. For my patients, it's not always a realistic possibility due to access and cost. I recommend to many of my patients to purchase nutritious food that they can afford.

  Overall, I tend to see more problems with consumers mishandling food after it is purchased. Consumers should always practice safe food handling practices, whether organic or conventionally produced. Clean, Separate, Cook (use a meat thermometer to ensure the meat is cooked to a safe internal temperature) and Chill."

Keith Ayoob, RD, EdD, FADA – Associate Clinical Professor, Pediatrics, Albert Einstein College of Medicine

27-28th February' 2016

Antibiotics Residues

- Antibiotic residues are remnants of antibiotic drugs or their active metabolites that are present within tissues or products e.g. meat, milk and eggs from treated animals

27-28th February' 2016

Acceptable Daily Intake (ADI)

- ADI is a measure of the amount of a specific substance (originally applied for a food additive, later also for a residue of a veterinary drug or pesticide) in food or drinking water that can be ingested (orally) on a daily basis over a lifetime without an appreciable health risk. ADI is expressed in mg/kg b.wt per day.

27-28th February' 2016

Withdrawal Period

- A withdrawal period is established to safeguard human from exposure of antibiotic added food. The withdrawal time is the time required for the residue of toxicological concern to reach safe concentration as defined by tolerance. It is the interval from the time an animal is removed from medication until permitted time of slaughter. Heavy responsibility is placed on the Veterinarian and livestock producer to observe the period for a withdrawal of a drug prior to slaughter to assure that illegal concentration of drug residue in meat, milk and egg do not occur.

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Maximum Residual Limits (MRLs)

- Most countries have established tolerance or safe levels (T/SL) or MRLs
- The Codex Alimentarius Commission is the accepted international agency responsible for food safety issues and has established MRL listing for antibiotics
- MRL calculation assumes an average daily intake per person of:
  - 500 g of meat
  - 1.5 litres of milk
  - 2 eggs
  - 20 g of honey

27-28th February' 2016

Conclusion & Suggestions for Way Forward

27-28th February' 2016

Antibiotic residues in chicken meat (µg/kg) - CSE Study

Antibiotic	Muscle Detected conc	MRL (EU)	MRL (US)	Liver Detected conc	MRL (EU)	MRL (US)	Kidney Detected conc	MRL (EU)	MRL (US)
Oxytetracycline	8.45-13.60	100	200	9.13	300	600	8.25	600	1200
Chlortetracycline	10.2	100	200	ND	300	600	ND	600	1200
Doxycycline	14.61-20.66	100	--	11.94	300	--	15.73	600	--
Enrofloxacin	3.84-58.06	100	30	3.37-131.75	200	--	15.73	200	--
Ciprofloxacin	3.55-26.27	100	--	7.55-64.59	200	--	18.5	200	--

27-28th February' 2016

Conclusion

- There is no doubt that neither humans nor animals/ birds can live without antibiotics as they are the most effective control for microbials and infectious diseases. However, at the same time misuse of antibiotics may result in the human health hazards
- The effective prevention of infectious diseases and adoption of strict hygiene standards and rearing skills may reduce our need for antibiotics particularly in poultry.

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Steps to prevent Antibiotic Residues

- Dairy producers realize the importance of eliminating the possibilities of having antibiotic residues in milk and dairy beef.
- Producers can take the following steps to mitigate or lessen the chances of antibiotic residues.

1. Establish a valid Veterinarian-client-patient relationship to ensure proper diagnosis and treatment of disease.
2. Implement a preventive animal health program to reduce the incidence of disease.
3. Maintain milk quality and implement an effective mastitis management program to reduce the use of antibiotics.
4. Implement employee training and awareness of proper animal drug use.
5. Only use approved over-the-counter antibiotics, according to label instructions, and approved prescription antibiotics which have the proper label.

27-28th February' 2016

Steps to prevent Antibiotic Residues

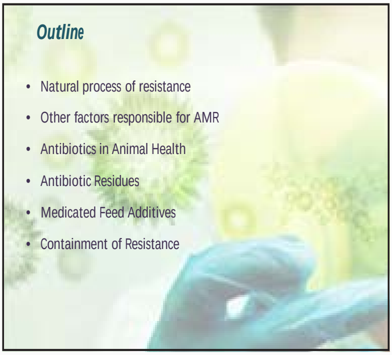
6. Keep records of antibiotic use and identify all treated animals, including treatment protocols.
7. Use drug residue screening tests specific for the drug utilized before marketing milk and/or meat from treated animals.
8. Do not use drugs that are specifically prohibited for use in milking, dry, or growing animals.
9. Segregate and milk treated animals after, or in a separate facility from, all non-treated animals to ensure that milk is not accidentally commingled.
10. If in doubt about residue status, do not market milk and/or dairy beef from treated animals.

27-28th February' 2016

“ THANK YOU ”

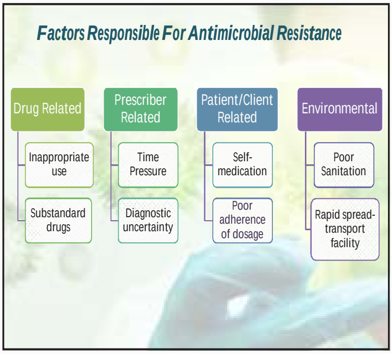
27-28th February' 2016

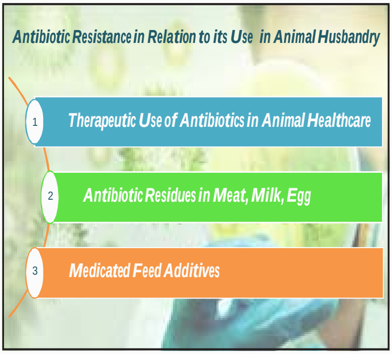

ANTIMICROBIAL RESISTANCE
Dr D J Kalita
Cadila Healthcare Ltd
Div: Zydus Animal Health
Ahmedabad


Outline
• Natural process of resistance
• Other factors responsible for AMR
• Antibiotics in Animal Health
• Antibiotic Residues
• Medicated Feed Additives
• Containment of Resistance


Every time an antibiotic is used, whether appropriately or not, in human beings or in animals...
...the probability of the development and spread of antibiotic-resistant bacteria is increased
Ref.: 1) Austin DJ et al., Proceedings of the National Academy of Sciences of the United States of America. 1999; 96 : 1152-6
2) Laxminarayan R et.al., Washington, DC; 2007 , http://www.rff.org/Publications/Pages/PublicationDetails.aspx?PublicationID=9575


Resistance is a Natural Phenomenon
➢ A natural biological unstoppable phenomenon
➢ All antimicrobial agents have the potential to select drug-resistant subpopulations of microorganisms
Mutant


Factors Responsible For Antimicrobial Resistance
Drug Related
Inappropriate use
Substandard drugs
Prescriber Related
Time Pressure
Diagnostic uncertainty
Patient/Client Related
Self-medication
Poor adherence of dosage
Environmental
Poor Sanitation
Rapid spread-transport facility


Antibiotic Resistance in Relation to its Use in Animal Husbandry
1 Therapeutic Use of Antibiotics in Animal Healthcare
2 Antibiotic Residues in Meat, Milk, Egg
3 Medicated Feed Additives

1. *Use of Antibiotics in Animal Healthcare*

- Antimicrobials are valuable tools and are essential for the continuing health and welfare of animals. In addition, they also make a significant contribution to productive and efficient livestock farming

- **Antibiotics used in veterinary are mostly conventional.**
  No advanced antibiotics are used in Veterinary, as used in humans.

- Antibiotics are being used in livestock since their introduction and are still found reliable to treat infectious bacterial diseases.

For example, Tetracycline classes of antibiotics makes up to 40% of the total veterinary antibiotic market; have limited use in humans in many countries. But, despite their use in animals since long, veterinarians have found little evidence of resistant strains causing hard to treat infections.

1. *Use of Antibiotics in Animal Healthcare*

- Critically important antibiotics are used routinely in livestock are argued for posing Threat to Human Treatment

- Veterinary Antibiotics are mostly conventional. Though "There may be overlap in the use of medically-valuable antibiotic groups 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. When used appropriately, the likelihood of fluroquinolone-use in cattle giving rise to an untreatable bacterial disease in a human patient is almost negligible.

2. *Antibiotic Residues in Meat, Milk, Egg*

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

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

The Field Vets need to educate the Farmers to adhere withdrawal periods so that there are no or negligible issues on residues

2. *Antibiotic Residues – Indian Report (Delhi), July,2014*

Antibiotic residues found in chicken meat (mcg/kg)(70 samples -Delhi and NCR)

Antibiotic	Muscle	Liver	Kidney
Oxytetracycline	8.45-13.60	9.13	8.25
Chlortetracycline	10.2	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

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

2. *Antibiotic Residues – MRL calculations*

- MRL assumptions consider an average daily intake per adult person as: (i) 500 grams of meat, (ii) 1.5 liters of milk, (iii) 2 eggs, and (iv) 20 grams of honey. Unfortunately, in our country due to varied reasons, an average daily intake of a common Indian is considerably lower than the assumptions on which MRLs are calculated.

Annual per capita consumptions of animal food

Country	Meat (kg)	Milk (L)	Egg (kg)
USA	121	253.8	13.9
UK	84.2	241.5	10.5
India	**4.4**	**68.7**	**2.4**
Australia	111.5	230.9	7.2
China	58.2	28.7	18.5
Brazil	85.3	124.6	8.8

3. *Medicated Feed Additives*

- Growth promoting feed antimicrobials, used in minute quantities are not a cure-all of rearing problems, but are most suitable for controlling microbial imbalance in the GI tract

- These drugs demonstrate measurable benefit of enhanced productivity, increased efficiency in feed conversion ratio coupled with target animal safety, residue avoidance and environmental safety

- Use of antibiotics minimizes the outbreak of diseases in animals also controls zoonotic pathogens such as Salmonella, Campylobacter, E coli and Enterococci

- The correlation between the development of antibiotic resistance in bacteria and the use of antibiotic growth promoter has never been clearly demonstrated or supported by evidence.

3. *Medicated Feed Additives*

Consequences of Ban on Antibiotics as growth promoter in Europe

- The withdrawal of MFAs in EU caused impairment of animal health & welfare (incidence of intestinal and respiratory infections has increased) despite the efforts to improve other aspects of husbandry.
- There had been steep rise in the use of therapeutic antimicrobials and decline of animal production in countries after the unilateral ban on these products, as supported by the evidence.
- The ban of MFA had an economic impact on farms, due to increased costs for veterinary prescription and therapies, lost of feed use efficiency, prolongation of the production cycle.

3. *Medicated Feed Additives*

Consequences of Ban on Antibiotics as growth promoter in Europe

- In Sweden, 20 years after their ban of growth promoters, the loss in production from pigs has not yet been fully recovered on a national basis.
- From Denmark, there are reports of increased morbidity and mortality among pigs, mostly associated with enteric infections; 11% of 'finishing' herds experienced permanent problems with increased frequency of diarrhoea or reduced weight gain.

Controversy of Ban on MFA in Europe

In Europe, banning of several antibiotic growth promoters as a precaution - against the advice of the EU's own Scientific Committee on Animal Nutrition (SCAN) -that there were insufficient data to support a ban

In the words of the National Research Council and Institute of Medicine, 'given some limited facts, authoritative opinions, and some projections on probable biological events, scenarios can be quickly woven to paint a bleak picture of the future'. The potentially adverse effects of bans are often ignored.

The Dutch-HAN report (Pieterman & Hanekamp) states that 'scientific knowledge is not used to the fullest in the review of the potential risks imposed by AGPs. On the contrary, in the EEA report shows selective scientific material that highlights the risks of the use of AGPs are referred to; a fallacy of exclusion.'

3. *Medicated Feed Additives*

The problems of developing countries like India are different from those of developed countries.

In most of the developed countries, the problem is over production and highly intense farming practices.

Whereas, in developing countries like India - the problems are poverty, malnutrition and unemployment, so here food security is the prime goal rather than food safety.

Facts surrounding Antibiotics

- **Farm animals are a Not the major source of human-resistant infections:**

While there is a definite risk that farms could contribute to human infection, "it is clear that they are not an important factor in the development of multi-drug resistant bacterial infections in people".

Scientific evidence shows many hospital patients with infections caused by antibiotic resistance contracted the disease from other people or from contaminated surfaces in the hospital environment.

"A US Centers for Disease Control (CDC) report in 2013 listed 18 strains of antibiotic-resistant bacteria which pose a threat to human health, and in only two cases did they identify that livestock could be a potential source for resistant strains of salmonella and campylobacter."

Published in Animal Pharm: 16 November 2015

UK Dept of Health and DEFRA published (Sept, 2013) the UK Five Year Antimicrobial Resistance Strategy 2013-2018. On page 8, the contribution of the animal reservoir is addressed as follows:

"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."

Facts surrounding Antibiotics

- **Resistance - Rarely Transmitted from Animals to Humans :**

Recent European studies suggested the genes causing resistance in the different species are quite distinct, meaning the resistant strains must have emerged independently. This suggests the majority of bacteria are adapted to living on a particular host species and so a strain of bacteria found in cattle or sheep is unlikely to survive in humans (Animal Pharm, Nov., 2015)

A research team using sophisticated method (whole-genome sequencing) has concluded that, "The relatively large genomic differences observed between chicken and human E. coli strains suggests that clonal transmission of ESBL-producing E. coli from chickens to humans is a rare event."

A review by B.Lazarus et al. published in 2015 in Clinical Infectious Diseases; 60(3) :439,

- **Resistance is Rarely Transmitted from Animals to Humans :**

Mather et al., in Science (Sept 27, 2013), performed a study using whole-genome sequencing of 142 human and 120 animal-S.Typhimurium DT104 isolates and concluded:

"**We demonstrate that the bacterium and its resistance genes were largely maintained within animal and human populations separately and that there was limited transmission, in either direction**"

And, "**This study challenges current views on the contribution of the animal reservoir as source for Salmonella and AMR in humans**" and points out the relevance of 'acquiring targeted genotypic data set.

The 2012 SVARM report, "Swedish Veterinary Antimicrobial Resistance Monitoring,"10 (published in 2013) concluded:

"**In conclusion, it was shown that the overlap between isolates of E.coli producing ESBL and AmpC from humans and broilers appears to be limited.**" (in Sweden)

The corresponding article is published by Börjesson S, et al. (2013, Clin Microbiol)11

Containment of Antibiotic Resistance

- Development /Discovery of New Anti-microbial agent
- Rationalize Use of Antibiotics

Judicious use of Antibiotics

- **The Animal Healthcare industry advocates for responsible and judicious use of antibiotics, advising on how they should be used and handled to limit their potential for development of resistant bacterial strains.**
- **Antibiotics should always be used according to label recommendation, under veterinary prescription, and only when necessary.**
- **Future policies and national strategies on antibiotics need to promote responsible use among veterinarians and farmers and collect antibiotic use data.**

Summary & Outlook

- The AMR campaign has been considered excessive clinical use of AB generally evenly directed at human and animal medicine, but there has been a concerted attack on the Veterinary use of antibiotics, based on the assumption that all such usage is imprudent since it might act as an important source of resistance in bacteria
- It is recognized that the biggest driver of AMR in people is the use of antimicrobials in humans or human health
- Antibiotics used in veterinary are mostly conventional. No advanced antibiotics are used in Veterinary, as used in humans.
- Theoretical hazard to human health arises from the use of growth-promoting antibiotics, an independent examination of the facts, shows that the actual risk is extremely small and may be zero in many cases
- Rationalize use of Antibiotics to maintain its effectiveness as long as possible