Journal of Animal Feed Science and Technology 6 (2018) 15-25
DOI: http://dx.doi.org/10.21088/jafst.2321.1628.6118.3

Sub-therapeutic use of antibiotics in animal feed and their potential impact on environmental and human health: a comprehensive review

Atul Kumar[1], Anil Patyal[2], A.K. Panda[3]

[1] Assistant Professor [3]Professor and Head, Department of Veterinary Public Health and Epidemiology, Dr. G. C. Negi College of Veterinary and Animal Sciences, CSK Himachal Pradesh Agricultural University, Palampur, Himachal Pradesh 176062, India.
[2]Assistant Professor, Department of Veterinary Public Health and Epidemiology, College of Veterinary Science and Animal Husbandry, Chhattisgarh Kamdhenu University, Anjora, Durg, Chhattisgarh 491001, India.

Keywords:

Antibiotics;
Animal Feed;
Animal Origin Foods;
Detection Methods;
Health Risks.

Abstract

The increasing human population and rising incomes across the globe proportionally increases the demand for food and other livelihood resources. The requirements for wholesome and nutritious food are ever-increasing and animal husbandry sector has contributed much to the needs of people. Several measures have been applied to increase the productivity of livestock which has resulted in significant increase in the milk, meat, eggs and fish production. However, animal products can potentially be contaminated with thousands of chemicals used for various purposes in routine animal husbandry practices. Among veterinary drugs, antibiotics are the most widely used ones for chemotherapeutic and prophylactic purposes as well as feed additives to promote growth and improve feed efficiency in livestock. Although, the safe and effective use of antibiotics in animals has received considerable attention in most of the countries around the globe including India. However, the indiscriminate use of antimicrobials in animal husbandry practices especially sub-therapeutic usage in animal feed as a growth promoter may have plethora of adverse impacts on human and environmental health. Therefore, the present review is an effort to address the various issues pertaining to sub-therapeutic usage of antibiotics in animal feed, methods for their detection in foods of animal origin and their potential risks to human and environmental health.

Introduction

Antibiotics are used in livestock production system to maintain health and productivity of animals. For more than four decades, Indian livestock and poultry producers have used antibiotics in animal husbandry practices and therefore; issues on safety to animals and humans and continued efficacy of antibiotics have been raised throughout the history of their usage. Usually, these drugs are administered in relatively large (therapeutic) doses to treat sick animals. However, sub-therapeutic doses of antimicrobial are also being frequently used in animal feeds to improve feed efficiency and rate of growth and to prevent or reduce the incidence of infectious diseases such as necrotic enteritis in chickens, dysentery and proliferative enteropathy in porcine etc. [1]. Generally, in management of livestock including poultry, antibiotic usage has expanded to an extent that approximately 70-80% of all animals reared for food purposes receive medication for at least once in their lives.

Antibiotics play a very crucial role in animal production for number of reasons. However, owing to their increased and non-judicious use in animal nutrition and clinical medicine; great attention from consumer's health point of view has centered on the safety of their residues in food of animal origin i.e. milk, meat, eggs, fish and even honey [2]. The contamination of otherwise usable milk, meat and eggs by residues of antibiotics and their subsequent widespread release into the environment is a frequent sequel to antibiotic usage in food producing animals [3]. Antibiotic residues in food of animal origin are also a priority for the industry because higher

Corresponding Author: Atul Kumar, Assistant Professor, Department of Veterinary Public Health and Epidemiology, Dr. G. C. Negi College of Veterinary and Animal Sciences, CSK Himachal Pradesh Agricultural University, Palampur, Himachal Pradesh 176062
E-mail: dratul9@gmail.com

© Red Flower Publication Pvt Ltd

standards of food safety assurance are being required by our society. Further, presence of residues in such animal origin food products may also prove as a barrier for export of these products due to strict food hygienic standards and residue limits established by the international community.

The indiscriminate use of antibiotics and their subsequent presence in animal origin food not only affects the industry but also poses a serious threat to human and environmental health including the emergence of antibiotic resistant microorganisms, carcinogenic and mutagenic effects, possible allergic/ hypersensitivity reactions in certain individuals and ecological disturbances. The Food and Drug Administration (FDA) considers antibiotic contaminated food as adulterated. In order to safeguard human health, the World Health Organization (WHO), Food and Agriculture Organization (FAO) together with OIE (World Organization for Animal Health) has consistently recommended restrictions on non-therapeutic uses of antibiotics in animal agriculture [4]. WHO and FAO has also set standards for acceptable daily intake (ADI) and maximum residue limits (MRLs) in animal origin food products. Discarding contaminated animal products represents a considerable economic loss in itself. However, failure to discard such food items may lead to severe penalties if antibiotics are detected in the supply submitted for sale.

Hence, there are various areas of concern over the usage of antibiotics and the threat to the human and environmental health. Therefore, the present review discusses this aspect of sub-therapeutic usage of antibiotics in animal feeds, methods of their detection in animal food products along with their impacts on human and environmental health with the objectives to create interest in pursuing answers for some of the complex issues relative to this subject.

Sub-Therapeutic Use of Antibiotics in Animals

Antibiotics are therapeutically used in food-producing animals to treat existing infections and prophylactically to prevent development or control spread of disease and, to increase daily body weight gain or the amount of growth per unit of feed eaten (i.e., feed efficiency) by administering doses lower than those required to treat or prevent disease, over extended periods of time [5]. Almost all food-producing animals are raised in groups and administering drug individually to all the animals is not only stressful to animals and handlers but is also expensive and dangerous as it contributes to spread of diseases too. Therefore, practically, addition of antibiotics to animal feed (or water) is the most common way to administer drugs to groups of animals especially in large commercial farms. Moreover, it is generally appreciated that the use of sub-therapeutic doses of antibiotics is one of the best available tool which has facilitated intensive animal farming. This practice has contributed to lowering production costs per animal, which has ultimately led to a greater availability and lower costs of animal origin foods (meat, milk and eggs) to the consumers, leading to overall improvement of animal and human health [6].

The growth promoting effects of antibiotics were first discovered in 1940s when a few farmers in USA found that pigs fed with penicillin-fermented mixture grew faster [7-9] and chickens fed by-products of tetracycline fermentation were found to grow faster than those that were not fed those by-products [10]. Since then, antibiotics are commonly added to commercial feed for improving growth especially in poultry and piggery. Numerous studies have witnessed the applicability and beneficial effects of antimicrobials in improving promoting growth, feed efficiency, reproductive performances and overall carcass quality of animals as summarized in Table 1.

Often, the amount of antibiotics given is not under the direct control of the farmers, due to premixed antibiotics contained in the feed they purchase. However, there is scarcity of data on antibiotics usage in animal husbandry practices, which could be attributed to lack of surveillance systems, unwillingness of food animal producers, animal feed producers, and veterinary pharmaceutical companies to provide comprehensive reports of antimicrobial consumption or sales [28]. But, growing demand for animal protein globally has undoubtedly expanded the usage of antibiotics in animal husbandry practices.

No published estimates of antimicrobial use in animals exist at present, and estimates of that use differ markedly. National Research Council of USA estimated that 40% of the antibiotics produced are used for feed additives with estimated allocation of 0.5 million kg to the cattle industry, 1.0 million kg to poultry, 1.4 million kg to swine, and 0.4 million kg to other animals such as companion animals [29]. More than 40% of the drugs were added in animal feed at sub-therapeutic level for improving animal production in USA during 1990s [18]. With a substantial contribution to the development of food-animal production at global level, veterinary antibiotics tend to be necessities to cope with increasing food demand for humans. In 2013, the global consumption of all antimicrobials in food animals was estimated to be 100, 812 -190, 492 tons and if the same trend is followed it is projected to

Table 1: Effect of antimicrobials on feed efficiency, growth promotion, reproductive performance, and carcass quality –Evidences

Compounds	Species	Observations	Reference
Tiamulin, Nosiheptide Salinomycin	Pigs	Improvement in carcass quality	[11-14]
Chlortetracycline	Sows	Increased conception and farrowing rates	[15]
Salinomycin	Weaning Piglets	Increased average weight gain	[16]
Antimicrobials	Pigs	Increased digestion of nitrogen and phosphorus	[17,18]
Antimicrobials	Pigs	Increased feed utilization and weight gain	[18]
Avoparcin, Bacitracin Efrotomycin, Lincomycin, Penicillin G procaine Virginiamycin	Poultry	Improvement in weight gain and feed efficiency	[19]
Roxarsone Bacitracin Virginiamycin	Poultry	Improved growth and feed conversion efficiency	[20]
Salinomycin, Avilamycin,	Poultry	Improved growth	[21]
Bacitracin	Poultry	Increased feed intake and decreased feed conversion ratio	[22]
Bacitracin zinc, Colistin sulfate, Flavomycin, Florfenicol	Fish	Improvement in feed conversion and growth	[23,24]
Tetracycline, Penicillin	Poultry	Improvement in egg production, hatchability and feed efficiency	[25]
Antibiotics in feed	-	Better quality meat with higher amount of protein and less fat	[26]
Avilamycin	Poultry	Increased weight gain	[27]

reach 150,848-297,034 tons by 2030. Further, India has been ranked as the fourth largest user of antibiotics in animal feed which is expected to increase by 82% in India by 2030 [30]. In a similar study conducted in some northern Indian states by Centre for Science and Environment, New Delhi (India) observed that that the extensive use of antibiotic supplements in the animal feed, and untreated litter has given rise to the growth of drug resistant bacteria and they are spreading out of the farms because of poor hygiene practices and improper waste management [31].

Human and Evironmental Health Risks

Human Health Risks

It is undeniable that rational use of antimicrobials plays a vital role in the production of food animals and protecting public health, while irrational and irresponsible use may cause various health problems in humans [32]. The potential effects of using antibiotics in domesticated animals have caused serious public health concern for decades. Early concerns focused mainly on the use of antibiotics in animal feed for growth promotion. In 1960, government of the United Kingdom of Great Britain and Northern Ireland (UK) established the Netherhorpe Committee to investigate whether use of antibiotics in animal feeds constituted a danger to humans. This was followed, in 1968, by the UK government-appointed Swann Committee (Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine) which concluded that administration of antibiotics to food-producing animals poses significant hazards to human and animal health because it leads to the emergence of antibiotic resistant strains of bacteria [33].

However, establishing direct causal associations between usages of antibiotics in animal husbandry practices and their potential risks to human health is often difficult. But, several studies have measured antibiotic residues in animals or animal products as a proxy for the level of antibiotic usage in animal production and management [34]. Among the different classes of antibiotics, tetracyclines and fluoroquinolone residues have been most frequently reported in animal origin food products [35-37].

Further, studies have shown a close association between the prevalence of antibiotic resistant bacteria in animals and in humans [38-40]. Numerous ecological, cross-sectional and evidence based studies has attempted to establish the link between prevalence of antimicrobial resistance bacteria and use of antibiotics in food animal production especially in contexts of cattle, pigs, and poultry. For example, in an ecological study of temporal trends in Netherland, it was observed that the introduction of vancomycin and pristinamycin in swine production was associated with increased prevalence of resistant *Enterococci* from human fecal samples [41]. Similarly, in a cross-sectional study in US, correlations among quinupristin-dalfopristin resistance in *E. faecium* isolates have been drawn between humans, farm animals, and meats [42].

Now, it is well established that all antimicrobial drugs have side effects when human and animals are exposed to them with higher doses or for prolonged period of time than recommended. The loss of effectiveness of the most widely used antibacterials (i.e., tetracyclines and penicillin) and of other antibacterials with plasmid-mediated resistances poses risks to both human and animal health. Therapeutic failure with these antibacterials would lead to large but unquantifiable morbidity and mortality in humans and animals. Therefore, the health risks from the development of bacterial resistance to antibacterial in animal feeds is cause for great concern. Currently, some unbiased, scientific data demonstrate that usage of antibiotics in food-producing animals (cattle, swine, poultry, and fish), particularly large-scale administration (e.g., in feed) of low doses over long periods of time, poses following public health threat:

Development of antimicrobial resistance (AMR) and other human health hazards

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. It is a major public health crisis, threatening the emergence and reemergence of untreatable infectious diseases worldwide on a massive scale [43-45]. Understanding the process of evolution and spread of antimicrobial resistance is of utmost importance to evaluate the contribution of animal husbandry practices in development of this grave public health issue. From fundamental biology and evolutionary perspective, the development of antimicrobial resistance in response to exposure to antibiotics is inevitable [46]. Bacterial exposure to sub-lethal concentrations of antimicrobial agents drives the selection of resistant strains. If such exposure is continued for considerable period of time then resistant strains are advantaged in terms of reproduction and spread. The other important scientific principles behind development of AMR includes genetic and regulatory changes in bacteria developing resistance to antibiotics, transfer of resistance genes from one bacterium to another and finally, the resistance may continue even after antimicrobials are no longer present as suggested by some of the findings of research works conducted by various researchers [47,48].

As per WHO, emergence of antibiotic resistant microorganism is one of the most serious global medical problems particularly in developing nations, including India, where the burden of infectious diseases is high and healthcare spending is low. The country has among the highest bacterial disease burden in the world. Antibiotics, therefore, have a critical role in limiting morbidity and mortality in the country. Medical authorities are already confronted with infections for which no antibiotic is effective because the causative bacteria have acquired resistance to all available antibiotic agents. AMR, the global spread of drug resistant bacteria, is currently responsible for approx. 0.7 million annual deaths worldwide and if the status quo is maintained then AMR could evolve into a global calamity, killing some 10 million people annually by 2050 [49]. AMR is also a threat to the livestock sector and thus to the livelihoods of millions who raise animals for subsistence [50].

One of the issues receiving close attention at the moment is the link between use of antibiotics in animals and the development of resistance in human pathogens. Antimicrobial resistant bacteria of animal origin can be transmitted to humans through the contaminated environment and food products and by direct contact with animal handlers [51-53]. There is evidence that resistance in some human enteric pathogens has arisen because of transfer of resistant bacteria or resistance genes from animals to people via the food chain [54]. Over-use and misuse of antibiotics therapeutically has driven the resistance problem in human medicine whereas it would seem that prophylactic use to some extent and growth promotant use in particular have contributed most to the emergence of resistant bacteria in animals [41]. Some of the resistance problem can be attributed to the transfer of resistant bacteria from animals to human and the transfer of resistance genes from animal pathogens and commensal bacteria to human pathogens [55]. However, for purposes of truly understanding attributable risk, it is important to determine the antibiotic residues in animal feed, milk, meat, eggs, fish, water etc. along with acquisition of information on origin of resistant infections.

Apart from development of AMR, the presence of antibiotics or their residues in food of animal origin is also associated with several other adverse human health effects. Several antibiotics are potent antigens or act as a haptens and their occupational exposure on a daily basis can lead to hypersensitivity reactions. The most of the hypersensitivity reactions have been reported against ß-lactam antibiotic residues in milk or meat. Such reactions can lead to urticaria, anaphylaxis, bronchospasm, angioedema, hemolytic anemia, thrombocytopenia, acute interstitial nephritis, serum sickness, vasculitis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis etc. [56]. The nitrofurans at higher concentrations in milk may cause carcinogenic and mutagenic effects [57]. Etminan et al. [58] reported the risk of retinal detachment in individuals upon continued exposure to fluoroquinolones. Chloramphenicol is also associated with optic neuropathy, aplastic anemia and brain abscess with varied intensities and clinical manifestations [59-62].

Environmental Risks

With the developments in analytical techniques, it has now become evident that man-made antibiotics can make their way to the environment through various routes namely, direct discharges from manufacturing units, excretion through biological matter (urine and faeces) of animals and humans after usage or through discarding unused medicines [63,64]. Such exposure routes may eventually leads to accumulation of antibiotics in the environment which may have profound effects on some ecosystems.

Effect on micro-ecosystem

One of the concerns is the potential effect of antibiotics on the ecological climax. Soil micro-organisms play a very important role in maintaining the balance in ecosystem e.g. nitrogen fixation, and antibiotics has potential to disrupt such processes. However, we still lack sufficient evidences for establishing links between antibiotic exposure and disturbed ecosystem. Likewise, waste-water treatment plants for household and industrial discharges largely depends on the functionality of complex microbial ecosystems, which could be disturbed by antibiotic exposure. However, many microbial ecosystems tend to show a large degree of resilience owing to their ability for horizontal gene transfer. Thus, even after long duration of exposures to high concentrations of antibiotics, environmental compartments appear to harbor a very diverse microbial flora. Although, the critical point is, of course, the exposure level required to affect the function of the microbial ecosystems e.g. the waste water treatment plants, receiving highly contaminated waste from pharmaceutical units manufacturing antibiotics may witness a disturbed function [65].

Effect on biogas production

A large amount of antibiotics used for intensive animal farming are excreted out in the environment through animal excreta and waste water. Those antibiotic residues in the environment may partially inhibit methanogenesis in anaerobic waste-storage facilities, commonly used at Concentrated Animal Feeding Operation (CAFOs), and thus, decrease the rate at which bacteria metabolize animal waste products [63,66]. During the anaerobic digestion of livestock waste, certain antimicrobials, including amoxicillin, aureomycin, oxytetracycline, thiamphenicol, florfenicol, sulfadimethoxine, and tylosin, had inhibitory effects on methane production [67-70]. However, in few studies, it was observed that the amount of antibiotics required for inhibiting anaerobic digestion of pig waste slurry was very high. Amin et al. [70] reported that concentrations of oxytetracycline, amoxicillin, andtylosin required for producing inhibitory effects are 8000, 9000, and 9000 mg/L, respectively. Similarly, only high concentration of thiamphenicol (160 mg/L), amoxicillin (120 mg/L), tetracycline (50 mg/L), and sulfamethoxydiazine (50 mg/L) had inhibitory effect on biogas production in the anaerobic digestion of pig waste slurry [67,69]. In reality, it is very difficult to observe such high levels of antibiotics in the excreta.

Determination of Antibiotic Residues in Foods of Animal Origin

Determination of antibiotic residues has become essential and growing concern in recent years for maintaining healthful characteristics of food stuffs and protecting public health. Moreover, the successful implementation of national regulations and monitoring/surveillance programmes depends upon availability and use of appropriate analytical techniques. Numerous techniques are available, employed and are in practice like enzyme linked immunosorbent assay (ELISA), bioassays for screening and high performance liquid chromatography (HPLC) coupled with photodiode array/UV/Fluorescence detectors/Mass spectrometry to identify and quantify the commercially used antimicrobial agents in feed and their residues in food of animal origin [2, 71].

Biosensors provide several advantages such as opportunity for automation, *in situ* analysis and development of large number of commercial detection kits. Further, they are highly specific, quick and can also detect non- polar molecules in real time [72]. But the limitations include chances of their contamination and failure to get heat sterilized [73].

ELISA is a widely used method for the detection of antibiotic residue in all kinds of food samples [74]. ELISA based techniques have the advantage of high sensitivity, broad specificity and ability to handle large number of small volume samples in short time [75]. But expensive nature and failure to detect the residues in real time are its major drawbacks [76].

HPLC coupled with selective detectors like Diode array detector (HPLC-DAD), Fluorescent detector (HPLC-FLD) or Mass Spectrometry (HPLC-MS) is another effective and sensitive system for the detection of antibiotic residue. HPLC coupled with tandem mass spectrometry techniques (HPLC-MS/MS) has been recommended by the Food safety and standard authority of India (FSSAI) for determination and quantification of most of the antibiotic residues in foods of animal origin. However, owing to its expensive nature very few laboratories in India have this facility to routinely test the food samples. Every method has its own limitations, with some lacking sensitivity and/or specificity, others are time consuming and quite expensive to execute in routine analysis.

Perplexity and Dilemma

Although a definitive link between antibiotic usage in animal feeds and their potential risks to human health is clear, but a number of data gaps still remains. For instance, antibiotic residues are also released into the environment through human waste and disposal and particularly around the sites of antibiotic production, and have been detected in ground and surface waters and soil [77,78]. In India, some of the highest levels of residues ever detected in surface waters were found in lakes and wells surrounding a wastewater processing plant that serves close to 100 pharmaceutical manufacturing plants around Hyderabad [79]. Therefore, occurrence of antibiotic residues in environmental compartments can also contribute to emergence of resistance strains. The proponents of sub-therapeutic antibiotic usage in animal feed believe and argue that such small doses of antibiotics used for this purpose are very small as compared to their therapeutic doses and it is not definitely known whether such low doses really select for resistance or not [80]. Even those, who accept that use of antibiotics as growth promoters in animal feeds may promotes emergence of antibiotic-resistant strains, believe that evidence of this possibility having a major impact on human health is either non-existent or minimal [81]. Moreover, the fact that various bacterial species showing resistant to antibiotics used in animals does not prove their origin and it is contended that humans might contract the infection from some other source and there is possibility that both animals and humans are infected with the same resistant organism from a common source. This is supported by the fact that drug resistant isolates from humans and animals were found to be genetically different in many instances [82].

The provisional supposition on transmission of resistance through food chains is also not universally accepted. Those, who accept it, recommend good hygienic practices in the kitchen and use of vaccines in the birds and animals to reduce the incidence of transmission. Therefore, the proponents believe that a ban on the sub-therapeutic use of antibiotics may lead to an overall deterioration of animal health (in terms of diarrhea, weight loss, reproductive failures and mortality). Hence, this may further lead to increased incidences of food-borne infections and intoxications in consumers; subsequently leading to more frequent use of antibiotics for therapeutic purposes in animals [83,84]. Therefore, restriction on the use of antibiotics as feed additive is considered unwarranted by some of the proponents.

However, in today's scenario, this does not justifies the inappropriate or sub-therapeutic use of antibiotics in animal agriculture. Some earlier economic analyses suggested that there is meager economic benefit from using antibiotics as feed additives, and that equivalent improvements in growth rate and feed consumption can also be achieved by improved hygiene [55]. A recent report indicated that the costs of withdrawing antimicrobial growth promoters in India would be roughly US$1.1 billion. However, widespread resistance may hold more consequence for India than for other countries because of India's high bacterial disease burden [85].

Further, Sub-therapeutic use of antibiotics in animal feeds has been questioned since the introduction of antibiotics because the infectious agents can develop resistance to the antibiotic being used and perhaps to other antibiotics as well. Emergence of antibiotic resistant pathogens appeared soon after antibiotic usage began and such resistance is known to be capable of compromising antibiotic therapy. Although, the potential human health hazards due to development of bacterial resistance to antibiotics used at sub-therapeutic levels in animal feeds is clear enough; but, only very few recorded instances of unfavorable human health effects due to antibiotic resistant bacteria have been linked directly to all usages of antibiotics in the production of many billions of animals over the past many decades [86]. It is very difficult to conduct a feasible, comprehensive epidemiological study of the effects on human health arising from the sub-therapeutic use of antibiotics in animal feeds. This is because, it is not easy to determine the antimicrobial history of the animal from which a particular piece of meat or glass of milk came, especially in large developing countries like India with 120 billion human population. Moreover, it is also very difficult to determine the antibiotic history of the humans with respect to their direct/indirect exposure to antibiotics or to organisms from other people who had been exposed directly to sub therapeutic doses of antibiotics.

Further, there are apprehensions among researchers that the economic consequences of limiting sub-therapeutic usage of antibiotics in animal feed could be significant over the short term, but most of the drugs in question could be replaced with alternative drugs already approved by FDA. Thus, the balance between immediate economic benefits and future health risks is very important. However, the lack of scientific certainty on the magnitude of both the probable health risks and the attributed increases in animal origin food production makes the formulation of a solution to this perplexity and dilemma even more cumbersome.

Strategies to Reduce Antibiotic Usage in Animal Husbandry

The following solutions can potentially reduce the antibiotic consumption globally:

1. Reduce unnecessary use of antibiotics in agriculture and their dissemination into the environment. The assumed benefits of antibiotics used as growth promoters in animal feed can be achieved by improved cleanliness of animal houses [87,88]. Improved hygiene also has a moral imperative for the welfare of domesticated animals.
2. The systems combining surveillance (Antimicrobial Resistance Monitoring System) and regulation (Hazard Analysis and Critical Control Point, HACCP), covering farm to fork should be enforced effectively. Regulations have been the principal instrument to limit antimicrobial use in animal production. A global regulation putting a cap of using 50 mg of antimicrobials/kilogram of animal product/year, could reduce total global consumption of antimicrobials by 64% [30].
3. Promote low-animal-protein diets. Recently, Republic of China has revised its dietary guidelines and recommends that the nation's 1.3 billion population should consume between 40g to 75g of meat per person each day. If followed this measure not only reduce the greenhouse gas emissions but could also have an indirect but substantial impact on the global consumption of veterinary antimicrobials [88]. According to Van Boeckel et al. [30], restricting the intake of meat to 40g/person/day could reduce global consumption of antimicrobials in food animals by 66%.
4. Charging a user fee on sales of antibiotics for non-human use from veterinary drug users can significantly dissuade non-judicious use of antibiotics [90]. This type of approach has also been supported by World Bank [91]. The revenues generated from such system can be diverted to support research on new antimicrobials, vaccines and diagnostics along with improvement in livestock rearing practices [92]. According to one estimate, imposing a user fee of 50% of the current price on veterinary antibiotics could reduce global consumption by 31% [30].

Although, all the strategies suggested here to address this issue are not exhaustive and mutually exclusive but if all these are considered in combination; they may possibly reduce the global consumption of antimicrobials in animals by up to 85%.

Conclusions

Antibiotics are indispensable tools for the treatment of various old as well as emerging infectious diseases. However, there are conclusive evidences which suggest that the indiscriminate and sub therapeutic usage of antibiotics not only in animal husbandry practices but also in human medicine has led to the emergence of antibiotic resistant pathogenic organisms. This is now considered as a major public health issue across the globe and therefore, is being addressed at every critical point of decision. The first restriction to use the antibiotics has been placed on food producing animals. The addition of antibiotics in animal feed and its direct relationship with human health hazards is somewhat misleading. But keeping in view the magnitude of problem, such stern actions has to be considered for betterment of mankind and survivability of human race. However, it might be just impossible to impose a blanket ban on the use of antibiotics in animal husbandry farms in a global scale. But close monitoring of the situation is imperative everywhere to avert or restrain emergence of resistant strains. Moreover, all antibiotic use needs to be evaluated and carefully controlled to preserve antibiotics as a healthcare tool in people and animals. Other control measures include improvements in food hygiene to reduce the spread of zoonotic bacteria to human via the food chain, ban on over the counter sale of antibiotics, development of novel opportunities to combat antimicrobial resistance and improvement in animal husbandry and managemental practices. To specifically address the issue in animal health, the livestock industries and associated professional must reduce and refine the use of antibiotics in animal production and replace antibiotics with other alternative disease control measures as much as possible. In addition, the medical profession must control misuse and overuse of antibiotics in hospitals and community practice. Although it is an inevitable consequence of the evolutionary adaptation of microbes; use and misuse of antimicrobial drugs by the humans have driven the increasingly rapid and prevalent emergence of resistance in a range of pathogenic and commensal organisms. So all in all, action plans to tackle this issue both at national and global levels stress the need for a holistic 'One Health' approach.

Reference

1. Taylor DJ. The pros and cons of antimicrobial use in animal husbandry. Bailliere'sClin Infect Dis 1999; 5:269-87.
2. Kumar A, Gill JPS, Bedi JS, Aulakh RS. Multiresidue determination of pesticides in honey using QuEChERS method and human health risks assessment. In Proceedings of 15th Annual Conference of IAVPHS and National Symposium on Intersectoral Approaches to Combat Zoonoses: Strategies & Challenge; 2017. Tirupati, India. 2017. p.274.
3. DuPont HL, Steele JH. The human health implication of the use of antimicrobial agents in animal feeds. Veterinary Quarterly 1987;9(4):309-20.
4. World Health Organization. WHO global strategy for containment of antimicrobial resistance. 2001. [cited 2018Jan 12]. Available from: http://www.who.int/csr/resources/publications/drugresist/WHO CDS CSR DRS 2001 2 EN/en/.
5. Crawford LM. The impact of residues on animal food products and Human Health. Rev Sci tech OffintEpiz 1985;4:669-85.
6. Donoghue DJ. Antibiotic residues in poultry tissues and eggs: human health concerns. Poultry Science 2003;82:618–21.
7. Wahlstrom RC, Terrill SW, Johnson BC. Effect of antibacterial agents on growth of baby pigs fed a "synthetic" diet. ProcSocExpBiol Med 1950; 75(3):710-1.
8. Hewes CG. The influence on the growth and progeny of the guinea pig resulting from oral administration of aureomycin (chloretracycline) and penicillin. J Nutr 1955;57(3):353-60.
9. Taylor JH, Gordon WS. Growth-promoting activity for pigs of inactivated penicillin. Nature 1955; 176(4476):312-3.
10. Stokestad ELR., Jukes TH, Pierce J, et al. The multiple nature of the animal protein factor. Journal of Biological Chemistry 1949;180:647-54.
11. Cromwell GL, Stahly TS, Jensen AH, Plumlee MP, Krider JL, Russett JC. Efficacy of thiopeptin as a growth promotant for growing barrows and gilts – a cooperative study. J AnimSci 1984a;59:892-5.
12. Cromwell GL, Stahly TS, Speer VC, O'Kelly R. Efficacy of nosiheptide as a growth promotant for growing-finishing swine – a cooperative study. J Anim Sci 1984b;59:1125-8.
13. Cromwell GL, Stahly TS. Efficacy of tiamulin as a growth promotant for growing swine. J AnimSci 1985;60:14-19.
14. Lindemann MD, Kornegay ET, Stahly TS, Cromwell GL, Easter RA, Kerr BJ, et al. The efficacy of salinomycin as a growth promotant for swine from 9 to 97 kg. J AnimSci 1985;61:782-8.
15. Soma JA, Speer VC. Effects of pregnant mare serum and chlortetracycline on the reproductive efficiency of sows. J AnimSci 1975;41:100-105.
16. Nagaraja TG, Taylor MB. Susceptibility and resistance of ruminal bacteria to antimicrobial feed additives. Appl Environ Microbiol 1987;53:1620-25.
17. Hardy B. A world without growth promoters. In: First Annual Turtle Lake Science Conference. 1999. Nottingham, Nottingham University Press.
18. Van Lunen TA. Growth performance of pigs fed diets with and without tylosin phosphate supplementation and reared in a biosecure all-in all-out housing system. Can Vet J 2003;44:571-6.
19. Feighner SD, Dashkevicz MP. Subtherapeutic levels of antibiotics in poultry feeds and their effects on weight gain, feed efficiency, and bacterial cholyltaurine hydrolase activity. Appl Environ Microbio 1987;53:331-6.
20. Chapman HD, Johnson ZB. Use of antibiotics and roxarsone in broiler chickens in the USA: analysis for the years 1995 to 2000. PoultSci 2002;81:356-64.
21. Knarreborg A, Lauridsen C, Engberg RM, Jensen SK. Dietary antibiotic growth promoters enhance the

bioavailability of alpha-tocopheryl acetate in broilers by altering lipid absorption. J Nutr 2004:134: 1487-92.

22. Guban J, Korver DR, Allison GE, Tannock GW. Relationship of dietary antimicrobial drug administration with broiler performance, decreased population levels of Lactobacillus salivarius, and reduced bile salt deconjugation in the ileum of broiler chickens. PoultSci 2006;85:2186-94.

23. He S, Zhou Z, Meng K, Zhao H, Yao B, Ringo E, et al. Effects of dietary antibiotic growth promoter and Saccharomyces cerevisiae fermentation product on production, intestinal bacterial community, and nonspecific immunity of hybrid tilapia (Oreochromisniloticus female x Oreochromisaureus male). J AnimSci 2011;89(1):84-92.

24. Zhou Z, He S, Liu Y, Cao Y, Meng K, Yao B, et al. Gut microbial status induced by antibiotic growth promoter alters the prebiotic effects of dietary DVAQUA(R) on Aeromonashydrophila-infected tilapia: production, intestinal bacterial community and non-specific immunity. Vet Microbiol 2011; 149:399-405.

25. Gustafson RH, Bowen RE. Antibiotic use in animal agriculture. J ApplMicrobiol 1997;83:531-41.

26. Hughes P, Heritage J. Antibiotic growth-promoters. Feed Tech 2002;6(8):20-22.

27. Costa MC, Bessegatto JA, Alfieri AA, Weese JS, Filho JAB, Oba, A. Different antibiotic growth promoters induce specific changes in the cecalmicrobiota membership of broiler chicken. PLoS ONE 2017; 12(2):e0171642.

28. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences. 2015;112(18): 5649-54.

29. NRC. National Research Council (US) Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds. Washington (DC): National Academies Press (US); 1980.

30. Van Boeckel TP, Glennon EE, Chen D, GilbertM, Robinson TP, Grenfell BT, et al. Reducing antimicrobial use in food animals. Science 2017; 357(6358):1350-52.

31. CSE Study: Antibiotic Resistance in Poultry Environment. 2017. [cited 2018April 27]. Available from: http://cdn.downtoearth.org.in/uploads/ABR-report-30Aug2017.pdf.

32. Hao H, Cheng G, Iqbal Z, Ai X, Hussain HI, Huang L, et al. Benefits and risks of antimicrobial use in food-producing animals. Frontiers in Microbiology 2014; 5:288.

33. Swann MM, Baxter KL, Field HI, Howie JW, Lucas IAM, Millar ELM et al. Report of the joint committee on the use of antibiotics in animal husbandry and veterinary medicine. London: Her Majesty's Stationery Office; 1969.

34. CDDEP. Center for Disease Dynamics, Economics & Policy report on Antibiotic Use and Resistance in Food Animals: Current Policy and Recommendations. 2016. [cited 2018May 13]. Available from:https://www.cddep.org/wp-content/uploads/2017/06/india_abx_report-2.pdf.

35. Gaurav A, Gill JPS, Aulakh RS, Bedi JS. ELISA based monitoring and analysis of tetracycline residues in cattle milk in various districts of Punjab. Veterinary World 2014;7:26-29.

36. Chowdhury S, Hassan MM, Alam M, Sattar S, Bari MS, Saifuddin AKM, Hoque MA. Antibiotic residues in milk and eggs of commercial and local farms at Chittagong, Bangladesh. Veterinary World 2015;8(4):467-71.

37. Jank L, Martins MT, Arsand JB, Motta TMC, Feij TC, Castilhos TDS et al. Liquid chromatography-tandem mass spectrometry multiclass method for 46 antibiotics residues in milk and meat: Development and Validation. Food Analytical Methods 2017;1-13.

38. Schwarz S, Kehrenberg C, Walsh TR. Use of antimicrobial agents in veterinary medicine and food animal production. Int J Antimicrob Agents 2001; 17(6):431-7.

39. Aarestrup FM. Veterinary drug usage and antimicrobial resistance in bacteria of animal origin. Basic ClinPharmacolToxicol 2005;96(4):271–81.

40. Vieira AR, Collignon P, Aarestrup FM, McEwen SA, Hendriksen RS, Hald T, Wegener HC. Association between antimicrobial resistance in Escherichia coli isolates from food animals and blood stream isolates from humans in Europe: An ecological study. Foodborne Pathog Dis 2011;8(12):1295–1301.

41. Van den Bogaard AE, Stobberingh EE. Epidemiology of resistance to antibiotics. Links between animals and humans. Int J Antimicrob Agents 2000;14:327-35.

42. Donabedian SM, Perri MB, Vager D, Hershberger E, Malani P, et al. Quinupristin-dalfopristin resistance in Enterococcus faecium isolates from humans, farm animals, and grocery store meat in the United States. J ClinMicrobiol 2006;44:3361-5.

43. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. Nat Med 2004;10:S122-9.

44. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis 2005;5:481-93.

45. Erb A, Sturmer T, Marre R, Brenner H. Prevalence of antibiotic resistance in Escherichia coli: overview of geographical, temporal, and methodological variations. Eur J ClinMicrobiol Infect Dis 2007; 26:83-90.

46. Wright GD. The antibiotic resistome: the nexus of chemical and genetic diversity. Nat Rev Microbiol. 2007;5:175-86.

47. Sorum M, Johnsen PJ, Aasnes B, Rosvoll T, Kruse H, et al. Prevalence, persistence, and molecular characterization of glycopeptide-resistant enterococci in Norwegian poultry and poultry farmers 3 to 8 years after the ban on avoparcin. Appl Environ Microbiol 2006; 72:516-21.

48. Zhang Q, Sahin O, McDermott PF, Payot S. Fitness of antimicrobial-resistant Campylobacter and Salmonella. Microbes Infect. 2006;8:1972-8.

49. O'Neill J. Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: final report and recommendations. 2016. [cited 2018 May 20]. Available from: http://bit.ly/2m3jc2E).

50. Lowder SK, Skoet J, Raney T. The number, size, and distribution of farms, smallholder farms, and family farms worldwide. World Dev 2016;87:16-29.

51. Price LB, Johnson E, Vailes R, Silbergeld E. Fluoroquinolone-resistant Campylobacter isolates from conventional and antibiotic-free chicken products. Environ Health Perspect 2005;113(5):557-560.

52. Graham JP, Evans SL, Price LB, Silbergeld EK. Fate of antimicrobial-resistant enterococci and staphylococci and resistance determinants in stored poultry litter. Environ Res 2009;109(6):682-9.

53. Smith TC, et al. Methicillin-resistant Staphylococcus aureus in pigs and farm workers on conventional and antibiotic-free swine farms in the USA. PLoS ONE. 2013;8(5):e63704.

54. Barton MD. Antibiotic use in animals feed and its impact on human health. Nut Res Rev 2000;13: 179-299.

55. Silbergeld, EK, Graham J, Price LB. Industrial food animal production, antimicrobial resistance, and human health. Annu Rev Public Health 2008;29: 151-169.

56. Granowitz EV, Brown RB. Antibiotic adverse reactions and drug interactions. Critical Care Clinics 2008;24:421-442.

57. Gutierrez G, Elez M, Clermont O, Denamur E, Matic I. Escherichia coli YafP protein modulates DNA damaging property of the nitroaromatic compounds. Nucleic Acids Research 2011;39:4192-4201.

58. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral Fluoroquinolones and the risk of retinal detachment. JAMA 2012;307(13):1414-19.

59. Babapour A, Azami L, Fartashmehr J. Overview of antibiotic residues in beef and mutton in Ardebil, North West of Iran. World ApplSci J 2012;19: 1417-22.

60. Wiest DB, Cochran JB, Tecklenburg FW. Chloramphenicol toxicity revisited: A 12-year-old patient with a brain abscess. Journal of Pediatric Pharmacology and Therapeutics 2012;17:182-8.

61. Wong SH, Silva F, Acheson JF, Plant GT. An old friend revisited: chloramphenicol optic neuropathy. Journal of the Royal Society of Medicines Short Reports 2013;4(3):20.

62. Jayalakshmi K, Paramasivam M, Sasikala M, Tamilam TV, SumithraA.Review on antibiotic residues in animal products and its impact on environments and human health. Journal of Entomology and Zoology Studies 2017;5(3):1446-1451.

63. Sarmah AK, Meyer MT, Boxall AB. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. Chemosphere 2006;65: 725-59.

64. Kummerer K. Antibiotics in the aquatic environment – a review – part II. Chemosphere 2009;75:435-41.

65. Larsson DGJ. Antibiotics in the environment. Upsala Journal of Medical Sciences 2014;9(2):108-12.

66. Loftin KA, Henny C, Adams CD, Surampali R, Mormile MR. Inhibition of microbial metabolism in anaerobic lagoons by selected sulfonamides, tetracyclines, lincomycin, and tylosin tartrate. Environ. ToxicolChem 2005;24:782-8.

67. Lallai A, Mura G, Onnis N. The effects of certain antibiotics on biogas production in the anaerobic digestion of pig waste slurry. Bioresour Technol 2002;82:205-8.

68. Sun JP, Zheng P, Hu BL. Combined effect of antibiotics on anaerobic digestion of piggery wastewater.Huan Jing KeXue. 2009;30:2619-24.

69. Shi JC, Liao XD, Wu YB, Liang JB. Effect of antibiotics on methane arising from anaerobic digestion of pig manure. Anim. Feed SciTechnol 2011;166-167: 457-63.

70. Amin MM, Hashemi H, Ebrahimi A, Ebrahimi A. Effects of oxytetracycline, tylosin, and amoxicillin antibiotics on specific methanogenic activity of anaerobic biomass. Int J Environ 2012;1:1-4.

71. Cháfer-Pericás C, Maquieira A, Puchades R. Fast screening methods to detect antibiotic residues in food samples. TrAC Trends in Analytical Chemistry 2010; 29:1038-49.

72. Koyun A, Ahlatcolu E, Koca Y. Biosensors and their principles. In: Kara S, editor. A Roadmap of Biomedical Engineers and Milestones. Rijeka: InTech; 2012.

73. Huet A, Delahaut P, FodeyT, Haughey SA, Elliott C, Weigel S. Advances in biosensor-based analysis for antimicrobial residues in foods. TrAC Trends in Analytical Chemistry 2010;29:1281-94.

74. Mungroo NA, Neethirajan S. Biosensors for the detection of antibiotics in poultry industry-A review. Biosensors 2014;4:472-93.

75. Wang S, Xu B, Zhang Y, He JX. Development of enzyme-linked immunosorbent assay (ELISA) for the detection of neomycin residues in pig muscle, chicken muscle, egg, fish, milk and kidney. Meat Science 2009; 82:53-8.

76. Petz M. Recent applications of surface plasmon resonance biosensors for analyzing residues and

contaminants in food. MonatsheftefürChemie-Chemical Monthly 2009;140:953-64.

77. Halling-Sorensen B, Nors Nielsen S, Lanzky PF, Ingerslev F, HoltenLützhoft HC, Jorgensen SE. Occurrence, fate and effects of pharmaceutical substances in the environment- A review Chemosphere 1998;36(2):357-93.

78. Daghrir R, Drogui P. Tetracycline antibiotics in the environment: a review.EnvironChemLett 2013; 11:209.

79. Fick J, Soderstrom H, Lindberg RH, Phan C, Tysklind M, Joakim Larsson DG. Contamination of surface, ground, and drinking water from pharmaceutical production. Environ ToxicolChem 2009;28(12): 2522–27.

80. Wallinga D, Burch DG. Does adding routine antibiotics to animal feed pose a serious risk to human health? BMJ 2013;347:f4214.

81. Turnidge J. Antibiotic use in animals–prejudices, perceptions and realities. J AntimicrobChemother 2004;53:26-27.

82. Phillips I, Casewell M, Cox T, De Groot B, Friis C, Jones R, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. J AntimicrobChemother 2004; 53:28-52.

83. Casewell M, Friis C, Marco E, McMullin P, Phillips I. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. J AntimicrobChemother 2003;52:159-61.

84. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotic and resistance. N Engl J Med 2013;368: 299-302.

85. Laxminarayan R, Van Boeckel TP, Teillant A. The economic costs of withdrawing antimicrobial growth promoters from the livestock sector. Paris: Organization for Economic Cooperation and Development, 2015.

86. Hays VW, Batson D, Gerrits R. Public health implications of the use of antibiotics in animal agriculture – preface. J. AnimSci 1986;62(Suppl. 3):1-4.

87. Engster HM, Marvil D, Stewart-Brown B. The effect of withdrawing growth promoting antibiotics from broiler chickens: a long-term commercial industry study. J ApplPoult Res 2002;431-36.

88. Miller GY, Algozin KA, McNamara PE, Bush EJ. Productivity and economic effects of antibiotics use for growth promotion in U.S. pork production. J AgricAppl Econ 2003;35:469-82.

89. Wang S, Lay S, Yu H, Shen S. Dietary guidelines for Chinese residents: comments and comparisons. J Zhejiang UnivSci B 2016;17(9):649-56.

90. Hollis A, Ahmed Z. Preserving antibiotics, rationally. N Engl J Med 2013;369:2474-6.

91. World Bank. Drug-resistant infections: A threat to our economic future (World Bank Group, 2016). [cited 2018 March 18]. Available from: http://pubdocs.worldbank.org/en/527731474225046104/AMRDiscussion-Draft-Sept18updated.pdf.

92. Outterson K, Pogge T, Hollis A. 2011. Combating antibiotic resistance through the health impact fund," SSRN Scholarly Paper ID 1866768 (Social Science Research Network, 2011). [cited2018March 18]. Available from: https://papers.ssrn.com/abstract=1866768.

SUBSCRIPTION FORM

I want to renew/subscribe international class journal **"Journal of Animal Feed Science and Technology"** of Red Flower Publication Pvt. Ltd.

Subscription Rates:
• Institutional: INR7800/USD609

Name and complete address (in capitals): ______________________________

____

Payment detail:
Online payment link: http://rfppl.co.in/payment.php?mid=15

Cheque/DD: Please send the US dollar check from outside India and INR check from India made payable to 'Red Flower Publication Private Limited'. Drawn on Delhi branch.

Wire transfer/NEFT/RTGS:
Complete Bank Account No. 604320110000467
Beneficiary Name: Red Flower Publication Pvt. Ltd.
Bank & Branch Name: Bank of India; Mayur Vihar
MICR Code: 110013045
Branch Code: 6043
IFSC Code: BKID0006043 (used for RTGS and NEFT transactions)
Swift Code: BKIDINBBDOS

Term and condition for supply of journals
1. Advance payment required by Demand Draft payable to Red Flower Publicaion Pvt. Ltd. payable at Delhi.
2. Cancellation not allowed except for duplicate payment.
3. Agents allowed 10% discount.
4. Claim must be made within six months from issue date.

Mail all orders to
Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-45796900, 22754205, 22756995, Cell: +91-9821671871
E-mail: sales@rfppl.co.in