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Antibiotics Usage in Food Animal Production and Their Public Health Hazards: A Review

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Abstract: Usage of antibiotics in livestock production beyond the treatment of infectious diseases in a sub-therapeutic dosage together with animal feed so as to promote growth and productivity in intensive animal farming is becoming a common practice both in developed and in developing countries. Despite the economic advantage in the increment of productivity, the risk towards the development of drug resistant bacteria which, in most cases, are zoonotically important is becoming a major problem worldwide. While much of the drug resistance observed in human medicine is attributed to inappropriate use in humans, there is increasing evidence that antimicrobial use in animals and agriculture serve as selection pressure for resistant food-borne pathogen development that may be transmitted to humans as food contaminants and become life-threatening. Research in this area has demonstrated that the manifestation and dissemination of bacterial antimicrobial resistance is the result of countless complex interactions between microorganisms, antimicrobials and the surrounding environment. Therefore there is an urgent need to implement strategies for prudent use of antibiotics in food animal production to prevent further increases in the occurrence of antimicrobial resistance in food-borne human pathogenic bacteria. Use of antibiotics in animals cannot be eliminated entirely since they are needed to treat diseased animals and, in some cases, to control the spread of infection to humans (who are in contact with animals). However, antibiotic use can be minimized through: reducing the disease burden and the spread of infection by strengthening disease prevention mechanisms, enforcing drug utilization regulations and legislation to be implemented properly and applying a ban on non-therapeutic antibiotic use which intern limit additional damages and also create opportunity for preservation of future antimicrobials in an era when their efficacy is gravely compromised.

Key words: Antibiotic resistance · Food animals · Growth promoters · Public health

INTRODUCTION

Usage of Antibiotics in livestock includes not only treatment of infections but also as growth promoter at a sub-therapeutic dose in animal feed to improve feed efficiency in contemporary intensive animal production [1].

Antibiotics when used in food animals can be dosed at low levels for growth promotion, at intermediate levels to prevent disease and at high, therapeutic levels to treat infected animals. Studies have shown that antibiotics used at low, sub-therapeutic levels improve growth rate and efficiency of feed use, reduce mortality and morbidity and improve reproductive performance [2]. Despite the economic advantages in the increment of productivity practices in usage of antibiotics, especially those in which sub-therapeutic levels are used have been the topic of much debate regarding the development of antibiotic-resistant bacteria. These resistant bacteria can contaminate foods that come from those animals and a person who consumes these foods can develop antibiotic-resistant infections [3].

In more recent years, the impact of resistant bacteria on treatment options and outcomes in human medicine has become both a national and international concern and much attention has been focused on food-producing animals as a potential source of antimicrobial-resistant bacteria in humans [4]. These efforts, however, have been

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met with continued debate and disagreement within the medical, veterinary and regulatory communities as to whether the use of antimicrobials in food animals is a significant risk factor or not for the development of antibiotic-resistant pathogens [5]. The objective of this paper was therefore to review the usage of antibiotics and common growth promoters in food animal industry and its effect in public health in line with the present Food and Drug Administration guidelines.

Antibiotics in Food Animal Production: Usage of antibiotics in farm animals is quite heavy and widespread and has been a common practice in modern intensive farms of developed world such as North America and Europe for quite some time. This practice is becoming a trend in developing world like Ethiopia where small scale dairy and poultry farms are expanding aggressively in all regions of the country in line with poorly implemented drug and medicament utilization rules and regulations. Different researchers indicated that nowadays most beef, pork and poultry consumed by humans contain small amounts of antibiotics as a result of an attempt to increase quality and quantity of output on farms, though the ultimate goal of food animal production is to deliver a safe, affordable, nutritious high-quality food product to the consumer [6].

Unlike the situation in human medicine where individual patients can be treated, food animal medicine is often practiced on a population basis for reasons of animal welfare, logistics and efficiency since it is impractical to individually treat each animal in a group that consists of hundreds to tens of thousands. Herd health medicine also relies heavily on preventive medicine strategies to control or prevent disease in high risk populations. Addition of antimicrobial agents to feedstuffs, or by water, or parenteral administration to groups of animals by injection to prevent or control disease progression is done strategically [7].

The high population density of modern intensively managed livestock operations results in sharing of both commensal flora and pathogens, which can be conducive to rapid dissemination of infectious agents to other animals and humans. As a result, livestock in these environments commonly require aggressive infection management strategies [8].

Despite the widespread adoption of antibiotic use in food animals and absence of reliable data about the quantity and patterns of use twelve classes of antimicrobials:- arsenicals, polypeptides, glycolipids, tetracycline, macrolides, lincosamides, polyethers, beta-lactams, quinoxalines, streptogramins and sulphonamides used at different times in the disease management of poultry, cattle and swine [9].

However, other classes of antimicrobials used in agriculture have not led to concerns about dissemination of resistance in humans. A distinctive class of antibiotics in ruminants alter intestinal flora to achieve increased energy and amino acid availability and improved nutrient utilization without evidence of resistance and effects in co-selection for resistance to other classes of antimicrobials [5].

Growth Promotion: The term "antibiotic growth promoter" is used to describe any medicine that destroys or inhibits bacteria and is administered at a low, sub-therapeutic dose. The use of antibiotics for growth promotion has arisen with the intensification of livestock farming. Infectious agents reduce the yield of farmed food animals and, to control these, the administration of sub-therapeutic antibiotics and antimicrobial agents has been shown to be effective [10].

Table 1: Antibiotic growth promoters used in livestock production

Drug	Effect
Bambermycin	Increase feed conversion ratio; growth promotion in poultry and cattle.
Lasalocid	Increase feed conversion ratio.
Monensin	Increase feed conversion ratio; increase weight gain in cattle and sheep.
Salinomycin	Increase feed conversion ratio; increase weight gain.
Bacitracin	Promotes growth of poultry.

Ref. [8]

Use of Antibiotic in Beef Production: Producers and veterinarians take great care to administer only the amount of antibiotics needed to bring an animal back to health. The Beef Quality Assurance (BQA) program has been trained beef producers about the safe and appropriate use of antibiotics since the 1980s. The National Cattlemen’s Beef Association Producer Guidelines for “Judicious Use of Antimicrobials” have been in place since 1987 and specifically outline the appropriate use of these products: Avoid using antibiotics that are important in human medicine, use a narrow spectrum of antimicrobials whenever possible, treat the fewest number of animals possible and antibiotic use should be limited to prevent or control disease and should not be used if the primary intent is to improve performance [5]. Beef producers use antibiotics to ensure optimum health of their animals. In order to maintain animal health, antibiotics may be used to prevent the onset of disease, halt its progression or prevent the spread of illness after it occurs. Only healthy animals grow and reproduce well. The beef community discourages feeding low levels of antibiotics to promote growth, because of concern over resistance [2].

Use of Antibiotic in Poultry Production: There is a variety of potentially useful ingredients that could be added to the feed or drinking water of a poultry flock to improve production or to reduce the spread of disease. Some of these potential ingredients have been tested in live poultry flocks; others have only been tested in a laboratory without the use of live birds. Most of the potential ingredients need to be more thoroughly tested in live birds and in real production flocks before they are be completely embraced by poultry producers [11]. With current consumer preferences tending towards purchasing products from livestock grown without antibiotics, these should be studied more thoroughly for the beneficial applications they may have in poultry production [12].

Antibiotics are widely used in modern livestock and poultry production to treat sick animals, but they are also administered in sub-therapeutic doses, usually in water or feed, to protect animals against disease and to promote growth. Sub-therapeutic antibiotics (STAs) can promote growth, by improving nutrient absorption and by depressing the growth of organisms that compete for nutrients, thereby increasing feed efficiency [13].

Use of Antibiotic in Swine Production: The major inputs in food animal production feed, labour and capital can be improved on some operations by feeding antibiotics. AGP use can enhance the growth rate and the feed conversion ratio, the rate at which animals convert feed into weight gain and it can increase labour or capital productivity by hygienic management in animal housing or transportation [14]. Using AGPs could also reduce variability in animal weights and sizes, avoiding financial penalties at markets for animals outside the range suited for mechanized processing. The effect of sub-therapeutic levels of antibiotic feed additives on growth rate and feed efficiency have been reported in cattle, swine and poultry for more than 50 years, but effect sizes vary widely among operations [15].

Many alternatives to antibiotic growth-promoters have been proposed. Due to possible restrictions on the use of sub-therapeutic antibiotics in the future, alternatives will be needed. A systematic approach involving nutrition, immunology and management will be required to determine a cost-effective method to maximize pork production without the use of antibiotic growth promoters [16].

Alternatives to Antibiotic Growth Promoters in Food Animals: Because of the seriousness of antibiotic resistance, we must consider alternative food animal production techniques. Changes to animal husbandry practices could reduce the need for antibiotics and the burden of drug-resistant bacteria [11]. Often minor changes suffice, for example: straw bedding, additional space, more frequent cleaning and better ventilation [16].

Essentially, there are many ways in which they can reduce our dependence on antibiotic use in animals. An obvious choice is the development of alternatives to antibiotics that work via similar mechanisms, promoting growth whilst enhancing the efficiency of feed conversion. Growth promoters have been shown to perform best when conditions are worst: i.e. when the animal is in poor health and the living conditions unhygienic. If their local environment is improved, with overcrowding reduced and infection control techniques introduced, then the actual need for growth promoters may be removed however, three widely used alternatives are available [17].

In-Feed Enzymes: In-feed enzymes are routinely added to pig and poultry feeds and work by helping to break down certain components of the feed, such as glucans, proteins and phytates, that the animal may have problems digesting. They are produced as fermentation products from fungi and bacteria and seem to only have a positive effect on the animal [2].

Competitive Exclusion Products: Competitive exclusion products are in-feed microbes consisting of a variety of species of bacteria that are marketed as being "Friendly". The mechanism of action is believed to be that, by allowing such bacteria to colonise the gastrointestinal tract, potential pathogens are prevented from colonising the gut and thus causing infection [2].

Probiotics: Probiotics are similar to competitive exclusion products. They are believed to improve the overall health of an animal by improving the microbial balance in its gut. The way they work has not been established, although it has been hypothesized that their action can be summarised in three ways. The first proposal is a reiteration of the competitive exclusion principle: by colonising the gut in large numbers, the probiotic bacteria exclude pathogens and thus prevent them from causing infection. The second possibility is that they act as a stimulus for the immune system. As the immune system is engaged following exposure to probiotic bacteria, any hostile bacteria are also noticed, following increased surveillance by leukocytes and thus potential pathogens are eliminated. The third suggestion proposes that probiotics have a strong, positive influence on intestinal metabolic activities, such as increased production of vitamin B12, bacteriocins and propionic acid [6]. The problem caused by the use of live bacterial products is that there may be potential dangers concerning antibiotic resistance and cryptic virulence factors [9].

Antibiotic Resistance: Antibiotic resistance is the ability of bacteria to resist the effects of an antibiotic that is, the bacteria are not killed and their growth is not stopped [18]. Resistant bacteria survive exposure to the antibiotic and continue to multiply in the body, potentially causing more harm and spreading to other animals or people. It also is a property of bacteria that confers the capacity to grow in the presence of antibiotic levels that would normally suppress growth of or kill susceptible bacteria [10]. A bacterium is said to have becomes resistant to an antibiotic when the minimum inhibitory concentration (MIC) is significantly (i.e., =four times) higher than the sensitive parent or than the range of MICs found in the same species of bacteria not previously exposed to that antibiotic [19]. In addition, it is the ability of certain bacteria to survive exposure to an antibiotic, which is normally able to destroy or limit the growth of the bacteria. This can occur from exposure to the antibiotic or through the transfer of resistance genes. Bacteria have the ability to adapt to their environment. The use of antibiotics may create an environment that favours one type of bacterium over another, allowing it to multiply. The bacteria can adapt to their environment by genetic mutation one or two mutations can allow the bacteria to become resistant to the antibiotic or they can acquire resistance genes from another organism [20].

Antibiotic resistance can occur in a number of ways: such as; Naturally occurring phenomenon, over-use and/or inappropriate use of antibiotics in human medicine, use in agro-food industries to treat specific diseases or to prevent illness and/or to promote growth, use of antibacterial cleaning products (e.g., community or household disinfectants or antiseptics) and use of cleaning and disinfection products in farm and veterinary practices [21].

Antibiotic Resistance in Livestock Production: Sub-therapeutic use of antibiotics in livestock production has always been controversial due to the risk of development of antibiotic-resistant bacteria. Intrinsic resistance is not affected by the use of antibiotics; therefore acquired antibiotic resistance is the principle concern. Researchers have observed that growth-promotion of livestock still occurs in spite of the development of antibiotic resistant bacteria. This leads to speculation that the growth-promoting effect of antibiotics is independent of the mechanism responsible for development of resistance or its transfer between species of organisms. However, the practice of administering antibiotics at continuous, low dosages has been shown to accelerate the development of resistant bacteria [5]. In a series of studies, it has also been shown that persistence of bacterial resistance in livestock is highly dependent on the duration of exposure and type of antibiotic used [22].

Antibiotic Resistant Bacteria in Humans: The greatest threat to the use of antimicrobial agents for therapy of bacterial infections is the development of resistance in pathogenic bacteria. Bacteria isolated from patients before antibiotics came into clinical use had virtually no resistance plasmids. The introduction of each new antimicrobial compound has been followed by emergence of antimicrobial resistance [20]. In some cases resistant bacteria emerged shortly after a new agent came into clinical use, whereas in other cases several years or even decades elapsed. In general the occurrence of resistance among pathogenic bacteria in different countries follows the consumption of antimicrobial agents. In human medicine it is generally agreed that the use of antimicrobial agents is the most important factor in the selection of resistance in bacteria and close association exists between the rate of resistance development and the quantities of antimicrobial agents used [23].

Association Between Antibiotic Use in Food Animal and Antibiotic Resistance in Human: Associations between antibiotic use in food animals and the prevalence of antibiotic-resistant bacteria isolated from those animals have been detected in observational studies as well as in randomized trials. Antibiotic-resistant bacteria of animal origin have been observed in the environment surrounding livestock farming operations, on meat products available for purchase in retail food stores and as the cause of clinical infections and subclinical colonization in humans [24].

Antibiotic Use in Food Animals Can Lead to Resistant Infections in Humans. Studies Have Shown That: Antibiotic use in food animals allows antibiotic-resistant bacteria to thrive while susceptible bacteria die; resistant bacteria can be transmitted from food animals to humans through contaminated food; Resistant bacteria in food can cause infections in humans and Infections with resistant bacteria can cause illnesses that are more severe and more likely to result in death as well as higher health care costs [1].

Public Health Risk of Antibiotic Use in Food Animals: Antibiotic use in farming is common but with serious effects on human health, it is time to think about responsible use in animals. Antibiotic use in both humans and animals is contributing to a reservoir of resistant bacteria resulting in increased human mortality and increased hospital stay lengths globally [25].

The World Health Organization (WHO) warns the misuse of antimicrobial medicines and new resistance mechanisms are "making the latest generation of antibiotics virtually ineffective", while at the 2013, G8-Summit, scientific ministers issued a statement calling antimicrobial resistance (AMR) "A major health security challenge of the twenty first century" [25].

Antibiotics are an integral part of industrialised livestock production. The indiscriminate use of antibiotics in animal agriculture has come under scrutiny from governments, companies and consumers concerned with preserving for as long as possible the ever-diminishing arsenal of antimicrobials that work in humans [26]. This overuse of antibiotics encourages the evolution of antibiotic-resistant bacteria strains by giving bacteria resistant to the antibiotics a better chance of survival. Because the antibiotics we feed animals are similar to those for humans, the evolution of antibiotic-resistant bacteria strains is a serious public health threat. Poultry products often carry at least one bacterial strain and it is now increasingly likely that the bacteria in the meat you buy are an antibiotic-resistant strain [7].

Tracking and Reducing the Public Health Impact: Antibiotics must be used judiciously in humans and animals because both uses contribute to the emergence, persistence and spread of resistant bacteria. Resistant bacteria in food-producing animals are of particular concern. Food animals serve as a reservoir of resistant pathogens and resistance mechanisms that can directly or indirectly result in antibiotic resistant infections in humans. Resistant bacteria may be transmitted to humans through the foods we eat and some bacteria have become resistant to more than one type of antibiotic, which makes it more difficult to treat the infections they cause. Preserving the effectiveness of antibiotic drugs is vital to protecting human and animal health. Nowadays, antibiotics are valuable tools for reducing animal disease and suffering. Use of antibiotic in food animals cannot stop. But decisions about what antibiotics to use and how to use them must be made with consideration of their potential impact on human health [19].

Minimizing Antibiotic Use in Animals: Use of antibiotics in animals cannot be eliminated entirely since they are needed to treat diseased animals and, in some cases, to control the spread of infection to humans (Who are in contact with animals). However, antibiotic use can be minimized. Concerns about the linkage of antibiotic use in food animals to the development of drug resistance in pathogens in animals and, ultimately, in humans have prompted attempts to limit the use of antibiotics in animal production whenever feasible [5]. The therapeutic applications are obvious when faced with the potential losses that can be incurred with the re-emergence of active infection and disease in a herd, flock, or school. If a goal of animal production specialists is to reduce overall use and, certainly, inappropriate use of antibiotics in food animals [22] strategies must be implemented that offset the potential for increased severity and incidence of animal infection. Reducing the use of antibiotics in food animals must benefit human and animal health in reducing the incidence and severity of disease [7]. The WHO Global Strategy for Containment of Antimicrobial Resistance addresses this challenge. It provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms through: reducing the disease burden and the spread of infection, improving access to appropriate antimicrobials, improving use of antimicrobials, strengthening health systems and their surveillance capabilities, enforcing regulations and legislation and encouraging the development of appropriate new drugs and vaccines [27].

Judicious Use of Antibiotics: Responsible antibiotic use programs specific to each animal species are in place to guide the judicious use of antibiotics within the health management programs established by veterinarians and producers [28].

Since the 1980s, the Beef Quality Assurance program has set standards and helped train farmers and ranchers about the appropriate use of antibiotics on farms and ranches. The guidelines are based on the American Veterinary Medical Association (AVMA), the American Association of Bovine Practitioners (AABP) and the Academy of Veterinary Consultant's (AVC) judicious use guidelines. The Producer Guidelines for the "Judicious Use of Antimicrobials," has been in place since 1987 and outlines: Avoidance of using antibiotics that are important to human medicine, avoid the selection of an antibiotic with a broad spectrum of activity, whenever possible, limit antibiotic use to sick or at risk animals and should be –used to prevent, treat or control disease and should not be used if the primary intent is to improve performance [29].

Infection Control Measures: The use of antimicrobials as growth promoting agents rests on their role in controlling infection in growing animals. Similarly, many of the alternatives are aimed at controlling infection. But what of direct measures used to control infection in farm animals? The Australian Pig Farming Industry pioneered the "all-in-all-out" method of pig production. This is a new system, used to replace the older technique of having a constant stream of pigs moving through the farm. Instead of having a range of ages, all the pigs weaned within a week are designated into a single cohort and are housed together in one shed."Segregated early weaning" takes note of the observation that the sow is an important source of pathogens. If piglets are weaned early, they are less likely to come into contact with pathogens from their mothers [30].

Finally, vaccination is used to offer protection against certain pathogens, such as enterotoxigenic *E. coli* and various *mycoplasma* infections. One of the major drawbacks to all these schemes are the huge cost involved [15]. Other drugs may be used for beef and poultry only under strict limits and some organizations and authorities seek to further restrict the use of some or all drugs in animals. Other authorities, such as the world organization for animal health, say that concerns for bacterial resistance in humans is overblown and restricting the availability of medicine is detrimental to animal health and the economical production of food [4].

Global Policy on Antibiotic Use in Food Animals: The use of those antibiotics belonging to classes of compounds currently approved in one or more countries worldwide for use in human medicine is prohibited when used solely for growth promotion purposes. All uses of antibiotics in food animal production should follow the Guiding Principles for Sustainable Use. Sustained reductions in the total use of antibiotics belonging to classes of compounds currently approved for use in human medicine are encouraged and will be considered a favourable factor in supply decisions [27].

New FDA Policies on Antibiotic Use in Food Animal Production: FDA defines appropriate therapeutic uses of antibiotics in food animals as the "Treatment, control and prevention of specific diseases necessary for assuring the health of food-producing animals." Ask drug companies to notify FDA of their voluntary decisions to remove growth promotion from product labels. It Clarifies that drug companies can change use claims and marketing status without submitting additional safety or effectiveness data unless they are claiming new treatment uses or changing the makeup of a drug. New drug users must have a specific dosing duration and level for an identified disease and be available only to certain animals, not an entire herd or flock [26]

Many large meat and poultry producers administer low doses of antibiotics to healthy food animals to offset the effects of overcrowding and poor sanitation and to promote faster growth, not to treat animal disease. FDA and the Centres' for Disease Control and Prevention all have testified before Congress that there is a definitive link between the routine, nontherapeutic use of antibiotics in food animal production and the crisis of antibiotic resistance in humans [31].

CONCLUSIONS

It is evident that at present, the resources devoted to study the role of antibiotic use in food animals both in terms of funding and scientific inquiry are insufficient. It is now critical that agricultural use of antibiotics is recognized as one of the major contributors to the development of resistant organisms that result in life-threatening human infections and included as part of the strategy to control the mounting public health crisis of antibiotic resistance. The misuse and overuse of antibiotics in food animals is a major source of the problem. Improved surveillance and national regulation is needed to ensure that antibiotics are used prudently and are not routinely fed to animals for nontherapeutic purposes. A ban on nontherapeutic antibiotic use not only would help to limit additional damage but also would open up an opportunity for better preservation of future antimicrobials in an era when their efficacy is gravely compromised and few new ones are in the pipeline. We will achieve these priorities by elevating the conversation through stakeholder engagement in each area of the world where we do business, seeking alignment; in principles and criteria for antibiotic use and develop specific action plans and timelines for each species.

- Avoid the selection of an antibiotic with a broad spectrum of activity, whenever possible.
- Antibiotics should not be used if the primary intent is to improve performance
- Limit antibiotic use to sick or at risk animals.
- It is better to assess the public health impacts of antibiotic use in animals and policy changes on antibiotic consumption.
- Recognize the problem of resistance and the creation of effective national inter-‑sectoral task forces.
- Policy decisions in the future regarding the use of antimicrobials in animals will be based on science and sound risk assessment and not on emotionalism.
- The producer and veterinarian should work closely when antibiotic therapy is needed in a flock and both must continue to work toward ensuring a safe food supply for consumers.

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