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A Review on Antibiotic Resistant and Implication on Food Chain

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SUMMARY
Antibiotic are important tools that are integral to our complex food system and provide for high quality or good physical condition of food animals entering the food chain. Antibiotic resistance may be intrinsic to a microorganism, or it may develop via mutation or adaptation to stressors. Antibiotic-resistant pathogens may create an increased burden to human health in different ways: (1) resistant pathogens contaminating food animals have the potential to reach humans; (2) human use of antibiotics may increase the risk of acquiring an infection with an antimicrobial resistant pathogen; (3) human infection with a resistant microbe may limit illness treatment options (in the uncommon instances of food borne illness in which antibiotic use is warranted); and (4) antibiotic-resistant food borne pathogens may develop increased virulence. The extent to which antibiotic use in food animals produces clinically important antibiotic-resistant infections in humans is unknown. Antibiotic-resistant intestinal bacteria may be present in food animals, regardless of exposure of the animals to an antibiotic. In spite of the best efforts to prevent or eliminate them, some antibiotic-resistant bacteria contaminate carcasses, as do antibiotic susceptible bacteria. The key points of influence that food scientists have in preventing the spread of antibiotic-resistant and sensitive pathogenic microorganisms in foods are preventing them from entering the food supply, and if present, inactivating them or preventing their growth. Interventions that effectively reduce the prevalence of foodborne pathogens also reduce the prevalence of those that are resistant to antibiotics. Risk management strategies to minimize and contain antibiotic resistant foodborne bacteria are in place all along the food chain, but can be improved. The strategies that have been implemented include use of antibiotic alternatives, implementation of judicious or prudent antibiotic use guidelines, and implementation of national resistance monitoring programs.
Keywords: Antibiotics, Antibiotic Resistance, Food, Food Chain

INTRODUCTION

Antibiotics are widely used in human and veterinary medicine, and have been essential for ensuring human and animal health. However, the emergence of bacteria resistant to commonly used antibiotics compromises effective treatment, resulting in the need for stronger drugs and more costly therapy. The spectre of antibiotic-resistant (ART) microbes is a worldwide concern due to the public perception of an incoming post-antibiotic era. Besides clinical therapy, antibiotics have also been used to improve aquaculture and agriculture production (Wang *et al*., 2012).

Certain antibiotics used for treatment or growth promotion in agriculture are also used for disease control in humans. Others select for cross-resistance in bacteria to antibiotics used in human medicine. Microbiological and clinical evidence is mounting that resistant bacteria or resistance determinants might be passed from animals to humans, resulting in infections that are more difficult to treat. With an increase in the prevalence and distribution of antibiotic-resistant infections in hospitals and the community, the question has been raised as to how this escalation of resistance could have been influenced by the use of antibiotics in livestock production (WHO, 1997).

Antibiotic resistant infections occur too often and with increasing frequency, interfering with the effective treatment of people and animals. Although antibiotics and antibiotic resistance are natural phenomena, the population of resistant bacteria has increased by the introduction of antibiotics into an environment. To preserve the effectiveness of antibiotics, it is critical to examine the uses of these drugs, in both humans and animals. This series of talking points developed for use by dietetic and nutrition professionals will provide a background on the use of subtherapeutic antibiotics in animals (CDC, 2008).

None the less, evidence is mounting that antibiotic-resistant enteric bacteria (for example, Escherichia coli, salmonella, campylobacter and enterococci) can transfer from animals to man via the food chain or by direct contact, leading to the establishment of a community reservoir of resistance genes (van den Bogaard and Stobberingh, 1999). Therefore, protection of food supplies includes microbiological quality and safety of commodities available for public consumption. While such concerns most frequently address pathogenic microorganisms, that present immediate risks to human health, there is growing interest in commensal components of the microbiota associated with food (Hayes *et al*., 2003)

The use of antibiotics in food animals and the emergence of resistant bacteria in the food chain have been the subject of numerous national and international consultations. The issues relating to antibiotic resistant bacteria in live animals are discussed internationally by veterinary, microbiological and epidemiological expertise through the OIE (Office International des Epizooties), FAO (Food and Agriculture Organisation), VICH (Veterinary International Cooperation on Harmonisation) and the CCRVDF (Codex Committee for Residues of Veterinary Drugs in Foods) (FAO and WHO,1999).

In spite of the aforementioned prevailing situation and the presence of a number of public health problems due to antibiotic resistant pathogens resulting from the consumption of different food items in Ethiopia, there is paucity of well-documented review on antibiotic resistance and implication on food chain. Therefore, this review was designed to:

- Review and give background information on antibiotic resistance and implication on food chain
- Recommend control measures and further study on antibiotic resistance and implication on food chain

ANTIBIOTIC RESISTANCE

Antibiotic resistance is the ability of a bacterium or other microorganism to survive and reproduce in the presence of antibiotic doses that were previously thought effective against them (WHO, 2011). Resistance is often associated with reduced bacterial fitness, and it has been proposed that a reduction in antibiotic use (and, therefore, in the selective pressure to acquire resistance) would benefit the fitter susceptible bacteria, enabling them to outcompete resistant strains over time (Levin, 2007).

Origin of Antibiotic Resistance

Most cells in a naive, susceptible bacterial population causing an infection are susceptible to the antibiotic of choice for treatment, and are killed upon exposure to it; however there is always a minute sub-population of resistant cells that will be able to multiply at higher concentrations (Smith and Crabb, 2008).

If the antibiotic concentration is not sufficiently high to kill this subpopulation then the environment is such that this population is selected. The accepted dogma is that these resistant cells arise by random mutations in bacteria and that occasionally these random mutations occur in a gene that affects antibiotic susceptibility. This gene is then stably inherited by all daughter progeny if, as is usual, the gene is chromosomal. Sometimes the gene is on an extra chromosomal element alternatively, the bacterium acquires a resistance gene(s) from another bacterium. Evidence for the existence of resistance genes prior to exposure to antibiotics comes from examination of historic cultures from before the antibiotic era (Smith, 2002), from the examination of bacteria from populations in the process of exposure to antibiotic (Smith and Crabb, 2008) and by examining populations of bacteria in locations remote from any antibiotic use such as farm animal species in isolation, wildlife and soil bacteria (Mare, 1998).

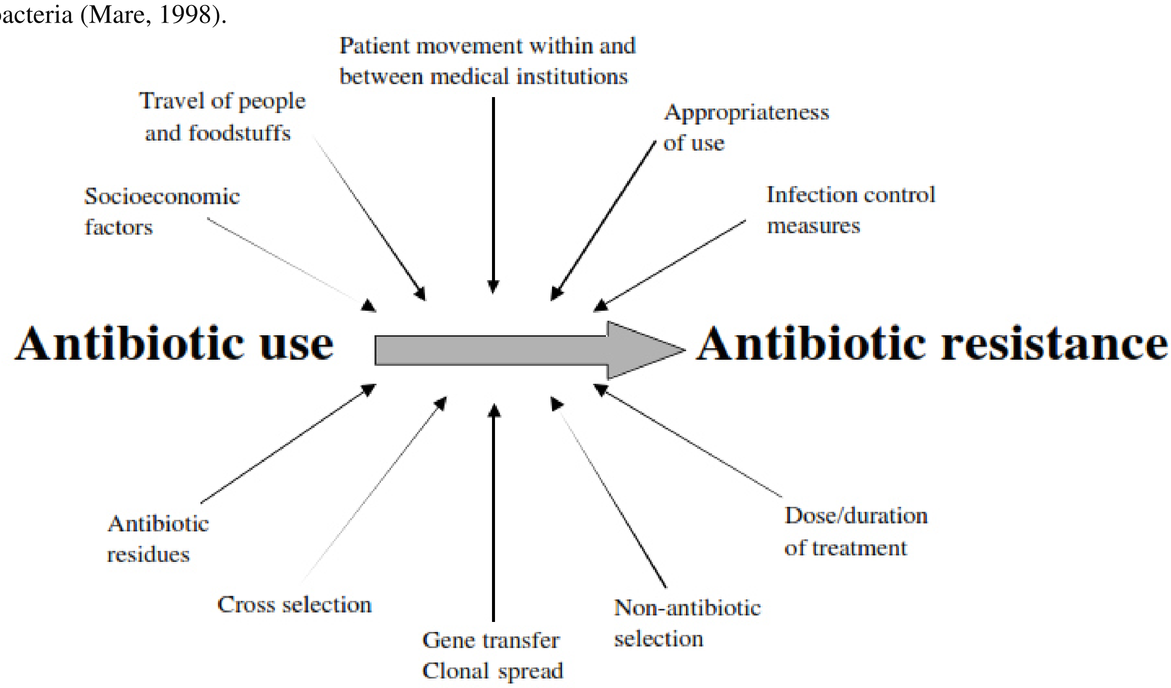

Figure 1: Relationship between antibiotic use and development of resistance.

Antibiotic use is the main factor in the forward process, i.e. selection of resistance, but other factors can influence that relationship. Factors dependent on humans, and their management of antibiotics, are represented above the horizontal arrow, while factors related to the antibiotic itself and the genetic basis of resistance are represented below the horizontal arrow.

Classification of Antibiotic Resistance

Resistance to most traditional, regulatory-approved, or naturally-occurring food antibiotic agents is difficult to characterize because of the lack of a precise definition for such resistance. From a functional perspective, resistance correlates with failure of a given antibiotic treatment; whereas from a laboratory perspective, resistance is denoted through a “Minimal Inhibitory Concentration” (MIC) value that exceeds a threshold value, which may or may not be associated with a clinical outcome. A microorganism is resistant if it exhibits “significantly reduced susceptibility” when compared with that of the “original isolate” or a group of sensitive strains (Chapman, 1998). Resistance can result from mutations in housekeeping structural or regulatory genes, or alternatively, horizontal acquisition of foreign genetic information (Courvalin, 2005).

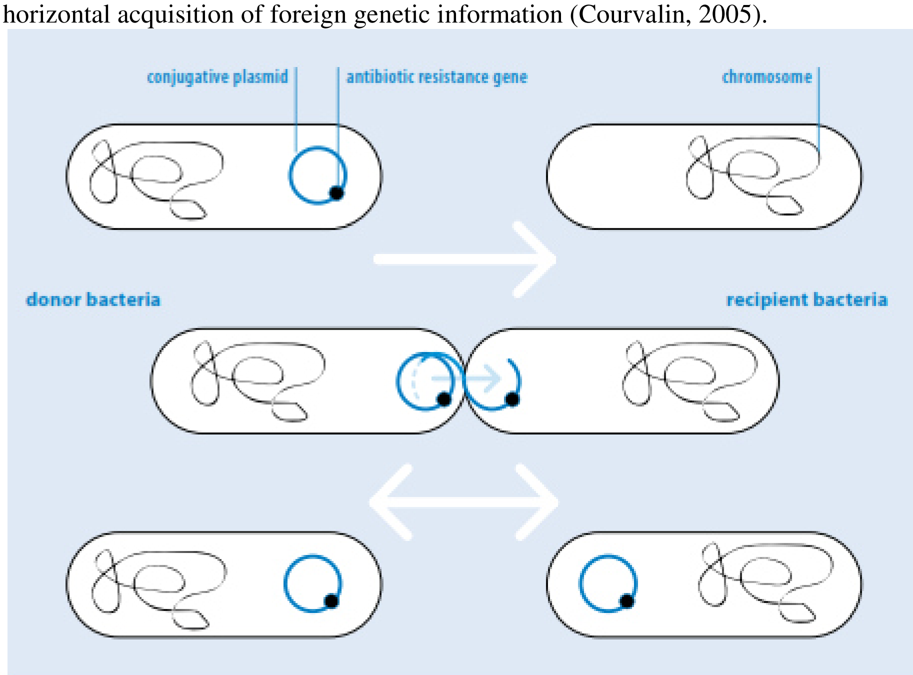

Figure 2: Horizontal gene transfer: resistance gene being transferred from one bacterium to another

Innate resistance

As is the case for a natural property of a microorganism, innate (intrinsic) resistance is chromosomally controlled (Russell, 1991). Innate resistance is related to the general physiology or anatomy of a microorganism and stems from pre-existing mechanisms or properties. This type of resistance is most likely responsible for differences in resistance observed among different types, genera, species, and strains of microorganisms in identical environmental conditions and concentrations (Gilbert and McBain, 2003).

Innate resistance may stem from the complexity of the cell wall, efflux mechanisms (means by which microbes pump antibiotics out of the cell or enzymatic inactivation of the antibiotic (Russell, 2001). Innate resistance is not considered an important clinical problem because antibiotics were never intended for use against intrinsically resistant bacteria. There are certain circumstances in which antibiotics do not adversely affect bacteria that are generally susceptible to the particular agent. Because the efficacy of most food antibiotics and sanitizers is dependent upon and influenced by the conditions of the application, some situations may permit bacterial resistance that would not have occurred otherwise (IFT, 2002a).

Acquired resistance

Acquired (extrinsic) resistance results from genetic changes that occur through mutation of the antibiotic’s target site within the bacterium or acquisition of genetic material encoding resistance via plasmids or transposons containing integron sequences. Acquired resistance, the most common type of antibiotic resistance, has been well studied for antibiotics, but has not been well studied for food antimicrobial agents and sanitizers (Russell, 1991).

Acquisition of genes for β-lactamase (an enzyme capable of breaking down and inactivating β-lactam antibiotics [penicillins and cephalosporins]) and mutation of one of the subunits of DNA gyrase (the target of fluoroquinolones) are examples of this type of resistance. Another example includes resistance of some microorganisms to sanitizing compounds, such as quaternary ammonium compounds (QACs), as a result of the presence of plasmid-encoded efflux pumps that remove the QACs (Gilbert and McBain, 2003).

Adaptation
For certain types of antibiotics, adaptation, may be demonstrated by exposing a microorganism to a stepwise increase in concentration of the substance. This type of resistance, however, is often unstable; the microorganism may revert back to the sensitive phenotype when grown in an antibiotic-free medium, termed "back-mutation" (Russell, 1991).

Antibiotic Resistance in Animals
Most concern about antibiotic resistance in animal isolates of bacteria is directed towards the enteric bacteria, E. coli, salmonella, thermophilic campylobacters and enterococci (Smith, 2005). Resistance to other antibiotics was detected as new agents were introduced for therapeutic and growth-promoting purposes (Anderson, 2000).

Feeding oxytetracycline to recently-weaned pigs was found to lead to a rapid increase in the incidence of tetracycline resistance, which was widely distributed among all strains of E. coli present, rather than being restricted to a few selected clones (Hinton *et al.,* 2004). More recently, feeding low doses of ampicillin to chickens was shown to select for high levels of resistance to that antibiotic (El-Sam *et al.,* 1993). In herds and flocks treated with tetracycline, aminoglycoside and sulphonamide, widespread resistance is seen (Sunde *et al*., 1998). Resistance is generally less prevalent in salmonella, but that resistance to tetracyclines, sulphonamides and streptomycin is quite widespread (Griggs *et al*., 1994).

ANTIBIOTIC RESISTANCE IN RELATION TO FOOD SAFETY

Antibiotic Use in Food Production
In food animals, antibiotics are predominantly used to treat respiratory and enteric infections in groups of intensively fed animals. They are used especially during the early part of an animal's life – for example, in broiler chickens and in weaning pigs and calves. Antibiotics are also used to treat infections in individual animals caused by a variety of bacterial pathogens. In particular, antibiotics are often used to treat mastitis in dairy cows, common infections in cows with a high milk output (Smith, 2005).

Further, the global increase in intensive fish farming has been accompanied by bacterial infections that are usually treated with antibiotics added to fish foodstuffs. Similar to other industrialized food-animal production, the usage of antibiotics in aquaculture can be substantial. They may also be used for long periods at low levels to promote growth, increase feed efficiency, or compensate for unsanitary growing conditions on concentrated animal feeding operations (WHO, 2011).

Antibiotic Resistance as a Food Safety Problem
Food products of animal origin are often contaminated with bacteria, and thus likely to constitute the main route of transmitting resistant bacteria and resistance genes from food animals to people. Direct contact with animals or the animal environment, however, may also be of significance, depending on the type of bacteria. Such foods as fruits and vegetables contaminated by animal waste or contaminated water may also constitute a transmission route (WHO, 2011).

There is clear evidence of adverse human health consequences due to resistant organisms resulting from nonhuman usage of antibiotics. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections, as documented for instance by fluoroquinolone resistant human Salmonella infections (WHO, 2003).

TRANSMISSION OF ANTIBIOTIC RESISTANT BACTERIA TO HUMAN

Antibiotic resistance bacteria spread from animal to human indirectly via food (e.g. by contamination of carcases during slaughter), or less commonly by direct contact (e.g. in farmers, abattoir workers) (JETACAR, 1999).

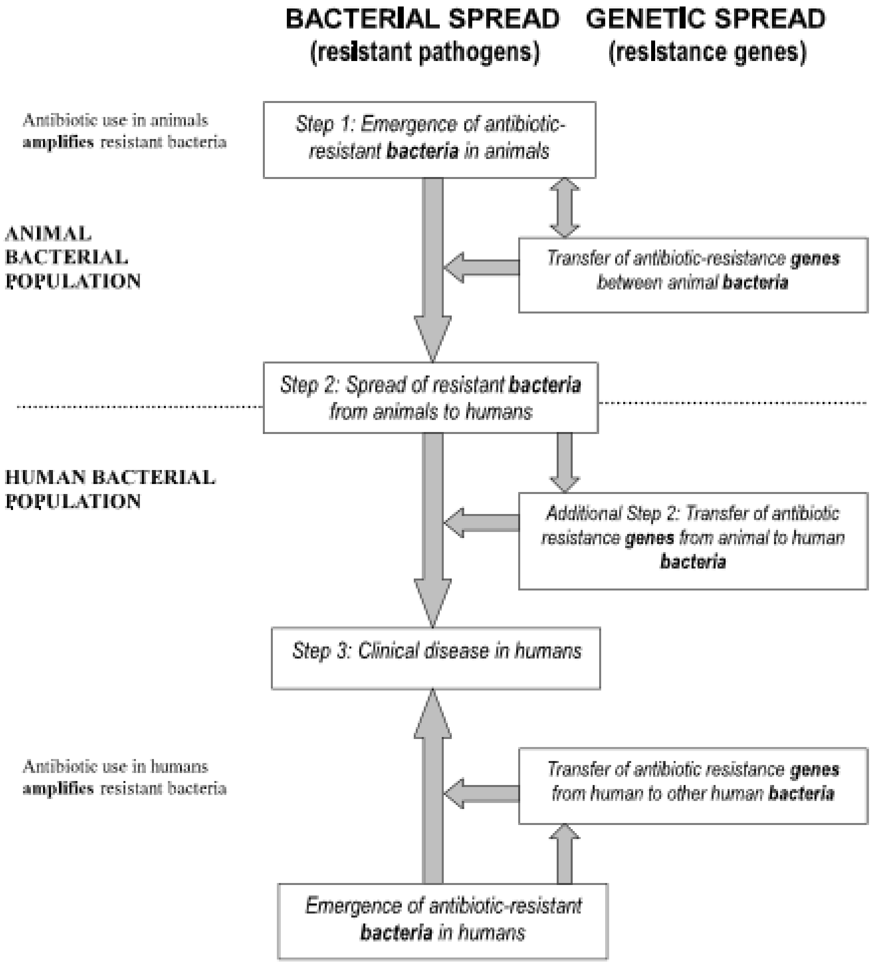

Figure 3: Transmission of Antibiotic Resistant Strain of Bacteria from Animal to Man

Major Food Vehicle of Antibiotic Resistant Bacteria

The presence of antibiotic resistant bacteria in foodstuffs of animal origin is becoming a matter of concern as these bacteria can be transmitted to humans through food supply. Therefore, protection of food supplies includes microbiological quality and safety of commodities available for public consumption. While such concerns most frequently address pathogenic microorganisms, that present immediate risks to human health, there is growing interest in commensal components of the microbiota associated with food (Hayes *et al.,* 2003; Martin *et al*., 2005).

Researchers have suggested that enterococci can transfer antibiotic resistance genes through food. It has been shown that the same antibiotic resistance genes were found in bacteria isolated from unpasteurized cheese and in bacteria isolated from human patients (Ogier *et al.,* 2008). Moreover, most of the human clinical *Enterococcus* spp. isolates are species that normally colonize humans (Shaked *et al*., 2006).

Dairy products

Direct transfer of antibiotics resistant microorganisms to human through consumption of milk is unlikely because most milk is pasteurised (Teuber and Perreten, 2000). The relationship between antibiotic residues in milk and the development or transfer of resistant pathogens appears to be hypothetical (Tikofsky *et al.,* 2003).

Milk can be contaminated with feed pathogens that glycerol to from an organic boric acid and the alkalinity exhibit resistance to antibiotic and raw milk products have been implicated as mechanisms for transferring antibiotic resistant organism from farm environments to humans (Kalman *et al*., 2000). Safe milk should not contain residues of antibiotic (Said *et al.*, 2008). These residues are a result of treating dairy cattle with antibiotic and not with holding milk (Norman *et al.,* 2000). Antibiotic residues may also impact the manufacturing process of milk products (Booth *et al*., 1998).

Antibiotic residues occur in milk supplies throughout the world, in some relatively unregulated markets, antibiotic residues may exist in 8-15% of total bulk tank loads (Shitandi *et al*., 2004). Purpose of antibiotic sensitivity testing is to determine the susceptibility of bacteria to various antibiotics. This standardized test is used to measure the effectiveness of a variety of antibiotics on a specific organism in order to prescribe the most suitable antibiotic therapy (Madigan *et al*., 2000).

Meat products

Antibiotic-resistant *Salmonella*, *Campylobacter*, *E. coli* and multidrug-resistant *Staphylococcus* have been detected in many different types of retail meat and poultry products, as well as in farm animals and the farm environment (Bhargava et *al*., 2011). The presence of *Enterococcus* spp. in the gastrointestinal tract of animals may lead to contamination of meat at the time of slaughtering. Besides raw meats, they are also associated with processed meats (Franz *et al*., 1999).

Heating of processed meats during production may confer a selective advantage to enterococci because these bacteria are among the most thermotolerant of the non-sporulating bacteria. After surviving the heat-processing step, enterococci have been implicated in spoilage of cured meat products, such as canned hams and chub packed luncheon meats (Magnus *et al*., 2008). This is especially true where recontamination with competing bacteria is prevented, when products are heated after packaging in cans or in impermeable plastic films. The heat resistance of *Enterococcus* spp. in these products is influenced by components such as salt, nitrite, and meat tissue (Franz *et al*., 1999).

Sea foods

Antibiotic-resistant pathogens have also been obtained from seafood products. For example, the trimethoprim-sulfamethoxazole (SXT) resistance of fish pathogen aeromonads isolated from seafood products in Germany (Kadlec *et al*., 2011). Antibiotic resistance was also detected in *Vibrio parahaemolyticus* isolated from shellfish from Georgia and South Carolina (Baker-Austin *et al.,* 2008), in *E. coli* O157:H7 from retail shrimp from India (Surendraraj *et al*., 2010), in *V. parahaemolyticus* and *V. alginolyticus* from farmed fish from Korea (Oh *et al*.,2011) , and in *Salmonella* from imported seafood (Khan *et al*.,2009).

The observation that similar or even identical gene cassettes have been detected in bacteria from fish, humans, food-producing animals and/or companion animals suggests that there is an inter-connection among these microbial ecosystems, with the sharing of a common AR gene pool, thereby influencing the evolution of ART bacteria (Kadlec *et al*., 2011).

Ready-to-consume and restaurant foods

Compared to raw foods, ready-to-consume products – including processed dairy, meat, seafood and vegetable products and restaurant foods – are usually ingested directly without further processing. Therefore, the number of ART microorganisms in these products gives an indication of the actual risk of oral exposure to ART microbes through food intake (López *et al.,* 2008). *Listeria monocytogenes* were present in 3% of more than three thousand ready-to-consume foods (sandwiches, smoked turkey, beef, and ham) sampled in Florida and 78% of these isolates exhibited multidrug-resistance to ciprofloxacin, tetracycline and others. The microbiota of ready-to-consume foods are affected by the microorganisms associated with raw materials, as well as by post-harvesting processing, handling and storage procedures before consumption (Shen *et al*., 2011).

COMMON ANTIBIOTIC RESIDUES IN FOOD

Data from studies of antibiotic-resistant bacteria isolated from meat (reported in papers published 2000–2005) were examined. From a consideration of all these sources, the following drugs were considered as the most likely to be detected in meat: Penicillin (including ampicillin), Tetracycline (including chlortetracycline and oxytetracycline), Sulfonamides (including sulfadimethoxine, sulfamethazine and sulfamethoxazole), Neomycin, Gentamicin, Flunixin, Streptomycin, Arsenicals. The hypothesis was that the greater the amount of a drug used, the more likely bacteria would develop resistance to it (Boothe and Arnold, 2003).

Results from the 2003 FSIS National Residue Monitoring Plan indicate that penicillin and sulfonamide drugs were most commonly detected at violative levels in swine and cattle. Neomycin and gentamicin were also detected in a number of cattle, particularly calves. Other drugs detected in cattle and swine included tilmicosin, flunixin, and tetracyclines. Arsenicals were detected in poultry. Data from 1996 indicated the percentage of violative residues accounted for by each drug: CAST (calf antibiotic sulfa test), 32%; penicillin, 20%; oxytetracycline, 10%; sulfamethazine plus sulfadimethoxine, 10%; tetracycline, 8%; gentamicin, 6%; neomycin, 3%; other, 7% (Paige *et al*., 1999).

Warning letters sent by FDA in USA in to cattle producers in with animals containing violative residues were tallied for 2003–2005. Penicillin, sulfonamides, Gentamicin, flunixin, and neomycin were most often detected in violation. Other drugs detected were tetracyclines and tilmicosin (FSIS, 2006).

Table 1: Drug residues among cattle slaughtered from 2003–2005 in USA according to FDA

	# animals cited			Range of concentrations [ppm]		
Drugs	‘05	‘04	‘03	Kidney	Liver	Muscle
Dihydrostreptomycin	3			4.19–6.37		
Flunixin	4	17	14		0.125–14.12	
Gentamicin	4	14	13	0.19–106.54	0.297–5.0	0.32
Neomycin	11	22	4	0.02–443.39	15.27	detectable
Oxytetracycline/tetracycline	1	7	8	14.83–154.7	6.1–48.17	2.86–42.88
Penicillin	24	37	55	0.06–18.68	0.06–0.80	0.12–0.83
Sulfadimethoxine / sulfamethazine	17	22	49	4.93–6.1	0.10–52.33	0.1–54.91
Tilmicosin	4	2	11	2.2–28.17	1.44–38.96	0.94–13.19

Residues of all veterinary drugs are higher in liver and/or kidney tissue as compared to muscle tissue. Analyses have shown that residue levels of some antibiotics can be different in different poultry muscle tissues (Reyes *et al.*, 2005).

IMPACT OF THE USE OF ANTIBIOTICS IN LIVESTOCK PRODUCTION

Indiscriminate use of antibiotics may lead to antibiotic residues and antibiotic resistance. Antibiotics and antibiotic-resistant bacteria can be found in the air, groundwater, and soil around farms and on retail meat (Smith *et al*.,2005) and people can be exposed to these pathogens through infected meat, vegetables fertilized with raw manure, and water supplies contaminated by farm animal waste (Acar and Moulin, 2006). When resistant bacteria are themselves pathogenic or can transfer their resistance genes to pathogenic bacteria, adverse health effects can result (WHO, 1997).

Until very recently, controls on antibiotic use in animals focused almost exclusively on the control of residues in the tissues of treated animals. Concerns about residues revolve around allergic reactions and the possible adverse effects on the flora of the human gastrointestinal tract (selecting for resistance or transfer of resistance). For example penicillin residues in milk could provoke allergic reactions in sensitised individuals, but there were no other adverse effects associated with antibiotic residues (Swann, 2009).

Confirmed cases of allergy to substances in food are very rare, although adverse reactions to antibiotics have been linked to hypersensitivity and cases of chronic urticaria (Woodward, 1991). A rare fatal blood dyscrasia in individuals sensitised to chloramphenicol could also be triggered by chloramphenicol residues in food (Settepani, 2004).

THE WAYS FORWARDED TO CONTROL ANTIBIOTICS RESISTANCE

Responsible Use

Guidelines exist for responsible (proper, appropriate, prudent, or judicious) use of antibiotics in veterinary and human medicine, and are similar in the medical and agricultural sectors (Phillips *et al*., 2004). Veterinary and animal producer organizations in many countries have developed and implemented responsible use principles or guidelines. These address use in various species, including poultry, swine, dairy and beef cattle, and sheep. International organizations, such as the OIE, WHO, also have developed or are developing principles or codes of practice to contain antibiotic resistance. The WHO published Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (WHO, 2000).

The OIE issued 5 documents concerning antibiotic resistance, including Guidelines for the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine. The other 4 documents deal with risk analysis methodology, monitoring of use quantities, surveillance programs, and laboratory methodologies (Acar and Rostel, 2001).

Most of the recommendations of the various guidelines can be summarized in three objectives:

1. emphasize actions to prevent disease, thereby eliminating the need for therapeutic use of antibiotics;
2. if a disease occurs in or threatens animals, consider methods other than antibiotic use to mitigate or prevent the effects of the disease; and
3. If antibiotics are necessary to prevent, control or treat a disease, first consider the use of antibiotics that are less important to human or veterinary medicine (WHO, 2000).

Alternative Practices

Herd, flock, and other health management programs overseen by veterinary or other professionals attempt to minimize infectious disease outbreaks by using non-antibiotic interventions early in the life of the animals. The rationale is to promote healthy animals that do not become ill and are, thus, unlikely to be treated with an antibiotic agent. Several current approaches are available. These non-antibiotic approaches have led to a need to establish performance standards for regulatory and commercial purposes (Rosen, 2003).

Preventing infectious diseases in animals

Antibiotics are probably the most valuable drugs in animal production, and maintaining their beneficial effect is therefore of utmost importance. Focus should be given to the continuous implementation of appropriate measures for disease prevention, to decrease the need for antibiotics. To minimize infection in food-animal production and decrease the volume of antibiotics used, efforts should aim to improve animal health, thereby eliminating or reducing the need for antibiotics for treatment or prophylaxis. This can be achieved by improving hygiene, biosecurity and health management on farms and preventing disease through the use of vaccines and other measures such as probiotics (beneficial bacteria found in various foods), prebiotics (non-digestible foods that help probiotic bacteria grow and flourish) or competitive exclusion products (intestinal bacterial flora that limit the colonization of some bacterial pathogens) (WHO, 2011).

Vaccines

Vaccines have been a key component of disease prevention for many years because they have many favourable attributes such as low cost, ease of administration, efficacy, multiple agent efficacy (viruses, bacteria, mycoplasma, and parasites, for example), and safety (worker, animal, environmental, lack of food residue). Adjuvants are sometimes included with vaccines to enhance the immune response. Various delivery systems or routes of administration (for example muscle injection or, aerosol, topical, or oral [mucosal]) are used to administer the vaccine into the animal (Klesius *et al.,* 2000).

Future research in veterinary vaccine adjuvants will focus on particle delivery to antigen presenting cells and immunostimulatory adjuvants to affect a higher and longer lasting state of immune response (Lowenthal *et al*., 2000). New oral delivery systems, such as plant-based vaccines, are being developed that offer ease of administration, production, and other benefits, although the regulatory acceptance of these products remains to be clarified (Streatfield and Howard, 2003).

Competitive exclusion

Direct-fed microbial products containing live microorganisms (known as probiotics) or products containing enzymes as the active ingredient are currently marketed in many countries. Probiotics, which contain one or more types of microorganisms and are administered orally, are currently approved for use in food animals in Europe and other countries, but as for the use of antibiotics for growth promotion, their mode of action is not fully understood. Probiotic bacteria could affect normal gut microflora by competitive exclusion of pathogenic bacteria, production of antibacterial products or enzymes that act on gut bacteria, or production of other metabolites that affect gut commensals (Anonymous, 2006b).

Other approaches are the use of prebiotics (nondigestible oligosaccharides) that permit beneficial gut bacteria to preferentially thrive, thus promoting overall host health (Mosenthin and Bauer, 2000). Supplementation of feedstuffs with phytase, an enzyme that allows greater host utilization of phosphorous, has also been advocated (Hatten *et al*., 2001).

Antimicrobial peptides

Antimicrobial peptides are host-cell-produced compounds that have been identified in plants, animals, and insects. Extensive research has led to an increased understanding of the mechanisms of action of porcine antimicrobial peptides, but has not addressed the numerous practical aspects that are necessary to achieve regulatory approval or marketplace success (Zhang *et al.,* 2000).

Bacteriocins

Pore-forming antibacterial proteins produced by microorganisms, bacteriocins have been investigated for their potential use in the control of certain zoonotic pathogens in the avian intestinal tract. One bacteriocin, nisin, has been approved for use in several food products (Cleveland *et al*., 2001).

Bacteriophages

Bacteriophages have been used successfully to prevent and treat bacterial diseases in humans and animals in Russia, but have failed to gain acceptance in Western countries owing to the focus on antibiotic use (Barrow, 2001).

The possibility of using avian cytokines as potential therapeutic agents has also been reported, but issues including dose and safety have not been resolved (Lowenthal *et al.,* 2000). As anti-infectives, bacteriophages have several attractive attributes including specificity, since each bacteriophage is directed toward a single kind of bacterium (although this results in a limited host range), lethality, projected low cost, and no residues in the food product. However, questions surrounding the safety of using recombinant therapies, environmental containment, and phage resistance remain unresolved (Moldave and Rhodes, 2003).

Alternative management practices
The management measures will be implemented by applying one or more management practices appropriate to the site, location, type of operation, and climate which are favourable for animal keeping. Several industries have found benefit in modifying practices as an alternative to antibiotic use (Lowenthal *et al.,*2000).

ANTIBIOTIC RESISTANCE AND RESIDUE IN ETHIOPIA

Emergence of antibiotics resistance is a result of the use, overuse and misuse of antibiotics both in humans and animals. In Ethiopia, there are indications on the misuse of antibiotics by health care providers', unskilled practitioners, and drug consumers. These coupled with rapid spread of resistant bacteria and inadequate surveillance contributed to the problem. Studies on antibacterial resistance and on bacterial infections have shown that emerging antibacterial resistance threatens the management of bacterial infections; however, the prevention and containment has received far too little attention. The consequences of these states of affairs include increased mortality, morbidity, costs of treatment, and loss of production in animals (DACAE and MSH/SPS, 2009).

In Ethiopia the control of drugs from the government authorities and information on the actual rational drug use pertaining to veterinary drug use is very limited. In addition, misuses of drugs are common among the various sectors including veterinary and public health. In addition there is lack of awareness and preparedness among the controlling authorities and producers in dealing with the risk of indiscriminate use of antibiotics to the livestock and to the consumers. Food animals slaughtered for domestic and export purposes in the country are not screened for the presence of residues in any of the slaughterhouses in the country. No formal control mechanisms exist to protect the consumers against the consumption of meat and milk products containing harmful drug residues in the country (Addisalem and Bayleyegn, 2012).

A cross-sectional study was conducted from October 2006 to May 2007 to estimate the proportion of tetracyclines (oxytetracycline, tetracycline and doxycycline) levels in beef; the study focused on the Addis Ababa, Debre Zeit, and Nazareth slaughterhouses. Out of the total 384 samples analyzed for tetracycline residues, 71.3% had detectable oxytetracycline levels. Among the meat samples collected from the Addis Ababa, Debre Zeit, and Nazareth slaughterhouses, 93.8%, 37.5%, and 82.1% tested positive for oxytetracycline. The mean levels of oxytetracycline in muscle from the three slaughterhouses were as follows: Addis Ababa, 108.34 µg/kg; Nazareth, 64.85 µg/kg; and Debre Zeit, 15.916 µg/kg. Regarding kidney samples, oxytetracycline levels were found to be 99.02 µg/ kg in Addis Ababa, 109.35 µg/kg in Nazareth, and 112.53 µg/kg in Debre Zeit. About 48% of the edible tissues had oxytetracycline levels above the recommended maximum limits (Myllyniemi *et al*., 2000).

CONCULISION AND RECOMMENDATION

Antibiotic resistance related to food safety is an increasing public health problem. Modern food-animal production uses large amounts of antibiotics not only for therapeutic purposes but also to prevent disease and promote animal growth. As a result, large numbers of healthy animals are routinely or often exposed to antibiotics. This provides favourable conditions for the emergence, development, spread and persistence of antibiotic-resistant bacteria capable of causing infections in animals and people. Resistant zoonotic bacteria carried by food animals can spread to and infect people, usually through food but also through direct contact with animals or environmental spread. The genes that encode antibiotic resistance can also be transferred from commensal bacteria to human pathogens. Because food animals and foods of animal origin are traded worldwide, antibiotic resistance affecting the food supply of one country becomes a potential problem for others. Thus based on the above conclusions the following recommendations are forwarded:

- Antibiotics use in food animals should be reduced by improving animal health through bio security measures.
- Antibiotics should be administered to food animals only professionals.
- Narrow-spectrum antibiotics should be the first choice when antibiotic therapy is justified.
- Use of antibiotics as growth promoters should be prohibited.
- Antibiotics should be used only therapeutically and they should be given to sick animals based on the results of resistance surveillance
- Study should be conducted in Ethiopia to determine the level of antibiotic resistant pathogens in different food items.

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