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Animal Health: Global Antibiotic Issues

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Glossary

Antibiotic resistance A form of drug resistance in which certain microorganisms could survive after exposure to one or more antibiotic treatment.

Foodborne illness Any disease resulting from the consumption of food contaminated by pathogens, viruses, parasites, or toxins.

Prebiotics Nondigestible food ingredients that stimulate the growth or activity of bacteria (probiotics) in the digestive system and eventually benefit the host.

Probiotics Live bacteria that could have health benefits on the host.

Withdrawal periods Time required after administration of antibiotics in agricultural animals needed to ensure that antibiotic residues in meat, egg, or milk products is below the determined maximum residue limit.

Zoonotic pathogen Pathogenic bacteria that could cause an infectious disease that is transmitted between species from animals other than humans to humans, or from humans to other animals.

Introduction

Antibiotics are antimicrobial compounds that can inhibit and even destroy bacterial and fungal growth. Some compounds, such as aminoglycosides and penicillins, are isolated from living organisms, whereas others, such as oxazolidinones, quinolones, and sulfonamides, are produced by chemical synthesis. Accordingly, antibiotics can be classified based on their origin as natural origin, semisynthetic origin, or synthetic origin. Most of the common antibiotics used today are semi-synthetic modifications of a variety of natural compounds. These antibiotics are used in both human medicine and animal agriculture to reduce incidences of diseases. They are usually administered by injection or orally via feed and water.

Antibiotics used for growth promotion in livestock and poultry not only allow the growth of healthier and more productive farm animals through improved weight gain and feed conversion efficiency, but they are also effective against animal diseases (Dibner and Richards, 2005). However, low-dose or specific employment of antibiotic as growth promoters that may involve bacterial antibiotic resistance and the replacement of these antibiotics with some natural products are under pressure.

Antibiotics widely administered in preharvest farm animals also help to reduce foodborne pathogens and prevent foodborne illness, which causes high morbidity and mortality rates worldwide. Currently, broad-spectrum antibiotics are commonly employed as feed additives for the preslaughter inhibition of foodborne pathogens. Owing to difficulties in determining specific agents targeting specific pathogen at the farm animal level, antibiotics have been shown to lower foodborne illness, and thus reduce morbidity and mortality, in humans (Callaway *et al.*, 2003). Other nonantibiotic antimicrobials are also used in foodborne pathogen prevention. These strategies include vaccination and the use of bacteriocins, bacteriophages, enzymes, probiotics, prebiotics, and organic acids.

As an essential strategy for controlling animal diseases, antibiotics have been employed in agricultural farming for therapeutic purposes. Multiple antibiotics have been approved

for use against livestock diseases, including respiratory disease, enteric disease, and mastitis (Radostits *et al.*, 2007), as well as necrotic enteritis, chronic respiratory diseases, gangrenous dermatitis, fowl cholera, and avian influenza commonly seen in poultry (Pattison, 2008), as will be elaborated in this article.

Based on Page and Gautier's most recent study, commonly used classes of antibiotics in farm animals all over the world are summarized in Table 1 (Page and Gautier, 2012).

Although the employment of antimicrobial agents has multiple significant benefits in animal agriculture, the appropriate use of these agents, including how to select the right ones, how to administrate them, and how to assess their risks, is a highly complex issue and continues to be a challenge for most growers and farmers. Knowledge and understanding of the common infectious diseases in multiple farm animals and guidelines for antimicrobial use in animal and animal products are crucial (Radostits *et al.*, 2007).

Some important topics addressed in this article include the patterns of antimicrobial use, preharvest and postharvest, therapeutic and subtherapeutic, nutritional, and for treatment. In addition, alternative antimicrobials and their appropriate employment in farm animals will also be discussed.

Antibiotics Used as Growth Promoters

Since the 1950s, antibiotics have been used as growth promoters in agricultural animal production in the United States, Australia, and several European countries (Dibner and Richards, 2005). Generally, 'growth promoter' refers to products that help to grow an animal faster for the same unit amount of feed consumed in a given period of time. Several researchers have shown that low-concentration (usually 2.5–50 mg kg⁻¹) addition of antibiotics to animal feed results in an accelerated growth rate and improved feed conversion efficiency in agricultural animals such as cattle, pigs, sheep, and poultry (Amy *et al.*, 2007). The improvement in average growth rate was estimated to be between 4% and 8%, and feed utilization was improved from 2% to 5% in 1994 (Ewing and Cole, 1999); a majority of recent studies have shown larger

Table 1 The most commonly employed antibiotics in farm animals worldwide

Country	Year	Livestock	Poultry
Australia	2006	Macrolides, penicillins, sulphonamides, and tetracyclines	–
Belgium	2009	Colistin, macrolides, penicillins, and tetracyclines	Macrolides and penicillins
Canada	2008	Lincosamides, macrolides, penicillins, and tetracyclines	–
Denmark	2010	Cephalosporin, macrolides, penicillins, penicillin-aminoglycoside, pleuromutilins, and tetracyclines	Macrolides, penicillins, and tetracyclines
Finland	2009	Aminoglycosides, beta-lactams, cloxacillin, fluoroquinolones, penicillin, and tetracyclines for all terrestrial species	
France	2010	Macrolides, penicillins, polymyxins, and tetracyclines	Penicillins, polymyxins, and tetracyclines
Germany	2005	Beta-lactams, sulphonamides, and tetracyclines for all species	
Japan	2004	Aminoglycosides, cephalosporins, macrolides, penicillins, sulphonamides, and tetracyclines	Aminoglycosides, macrolides, and tetracyclines
Kenya	2004	Aminoglycosides and penicillins for all farm species	
Netherlands	2009	Aminoglycosides, cephalosporins, colistin, neomycin, penicillins, penicillin-aminoglycoside, and tetracyclines	Colistin, fluoroquinolones, neomycin, penicillins, and tetracyclines
New Zealand	2009	Aminoglycosides, cephalosporins, macrolides, penicillins, penicillins, sulphonamides, and tetracyclines	Bacitracin
Norway	2010	Aminoglycosides, penicillins, and sulphonamides for all terrestrial species	
South Africa	2004	Macrolides, penicillins, sulphonamides, and tetracyclines for food-producing species	
Sweden	2010	Macrolides, penicillins, pleuromutilins, and tetracyclines	Penicillins
Switzerland	2005	Aminoglycosides, penicillins, polymyxins, sulphonamides, and tetracyclines	Aminoglycosides, penicillins, sulphonamides, and tetracyclines
USA	2010	Macrolides, penicillins, sulphonamides, and tetracyclines for food-producing species	
UK	2010	Penicillins and tetracyclines for food-producing species	

benefits, up to 10% gain in both weight and feed conversion efficiency (JETACAR, 1999).

The exact mechanisms of growth promotion by antibiotics are still speculative. But, based on recent *in vivo* animal experiments, the antibactericidal effect of antibiotics is the most likely explanation for growth promotion. Antibiotics may help concentrate nutrients by reducing the amount of several intestinal bacteria that are able to divert nutrition away from an animal's body. In addition, antibiotics could also inhibit release of toxins in the gut by intestinal bacteria. Antimicrobial growth promoters could also help increase the availability and absorption of nutrients and energy by maintaining the composition of gut microflora, thus thinning the barrier in small intestine and at the same time assisting the digestion of grain-based high-energy diets.

Current Use of Antibiotic Growth Promoters

In the United States, beta-lactam antibiotics, especially penicillins and lincosamides, as well as macrolides, especially erythromycin and tetracyclines, are commonly used as growth promoters in pigs (Peter and John, 2004). Multiple other antimicrobial compounds are also used in US swine production to stimulate growth. These include arsenical compounds, bacitracin, flavophospholipol, pleuromutilins, quinoxalines, and virginiamycin (Peter and John, 2004). In Australia, similar antibiotics are employed in animal agriculture. Such growth promoters include arsenical compounds,

flavophospholipol, macrolides (especially kitasamycin and tylosin), olaquinox, and streptogramin (especially virginiamycin) (JETACAR, 1999). Compared to the United States and Australia, the application of antibiotics in growth promotion in the European countries is relatively limited. In pig production, avilamycin, flavophospholipol, and ionophores, especially monensin and salinomycin, are among the few approved growth promoters in use in Europe (Angulo, 2004).

In the cattle industry, major antibiotics including flavophospholipol, monensin, and virginiamycin are commonly used as growth promoters in the United States (Peter and John, 2004). Owing to the high energy requirements of cattle, growth promoters may play an important role by stimulating muscle formation and improving milk productivity (Peter and John, 2004). However, the use of growth promoters can have several side effects in cattle. The most common harmful effect is lactic acidosis, which both impairs milk production and debilitates cattle. To counteract this side effect and maintain a balance between benefit and harm, administration of lasalocid and monensin are probably the safest and most effective antibiotic growth promoters due to their activity in inhibiting most of the lactate-producing bacterial species without harming the major lactate fermenters. Australian cattle farmers also employ flavophospholipol, lasalocid, and monensin (JETACAR, 1999). Other cattle growth promoters used in Australia include narasin, oleandomycin, and salinomycin. The use of glycopeptide avoparcin was no longer permitted after 2000. In the European Union, the same types of ionophores – monensin and salinomycin – are used in cattle. However, the use of

pristinamicin and quinupristin has been banned since 2000 (Dibner and Richards, 2005).

For the poultry meat and egg industries, specific growth promoters such as flavophospholipol and virginiamycin are employed in the United States (Peter and John, 2004). In Australia, poultry producers use arsenical compounds, flavophospholipol, bacitracin, and virginiamycin (JETACAR, 1999). Growth promoters are not allowed to be used in layer farms in Australia. In Europe, major growth promoters used in the poultry industry include avilamycin, avoparcin, bacitracin, and virginiamycin. According to several recent studies, a 10 mg per kg dose of avoparcin is able to improve feed conversion efficiency by 2.96%, increase the growth rate of meat chickens by 2.37%, and increase 1.33 net cents per kg liveweight; 17.6 mg per kg dose of virginiamycin, similarly, is able to increase these three values by 3.48%, 3.19%, and 1.48%, respectively (Mehdi *et al.*, 2011).

The Future of Antibiotic Growth Promoters

In 2000, the World Health Organization (WHO) recommended several global principles, including rapidly phasing out all antibiotic growth promoters from agricultural animal production, specifically those that are used in the treatment of human diseases (World Health Organization, 2000). Four years later, WHO also recommended for assessment of risk and surveillance of antibiotic growth promoters used in agricultural animals and the pattern of antimicrobial resistance in various animal and human bacterial pathogens (World Health Organization, 2004).

Though the relationship between application of antibiotics in farm animal production and the trend of antimicrobial resistance in human bacterial pathogens is still under debate, the idea of antibiotic-free animal production is based on an emotional level instead of a legislative level. In fact, from the point of view of many consumers, the use of antibiotics as growth promoters has negative effects on public health, and a certain percentage of consumers want to reduce or control the use of antibiotics in food animals, regardless of their practical advantages. The use of antibiotics as growth promoters is being curtailed under consumer pressure. The replacement of these antibiotics/antimicrobials with some consumer-friendly and natural organic bioactive components is a potential area of research interest worldwide.

The Potential Alternatives to Antibiotics for Growth Promotion

In light of the declining demand for antibiotic growth promoters, more and more research has been focused on developing alternatives to growth stimulation and improving feed utilization and efficiency. Since the benefits of growth promotion may result from the alteration of gut microflora, alternatives to antibiotic growth promoters may be required to improve animal intestinal gut flora through natural and organic bioactive and functional feed supplements. Therefore, research interest has concentrated on following the five approaches: in-feed enzymes, probiotics, prebiotics, organic acids, bioactive phytochemicals, and competitive exclusion of

pathogens by-products being administered via water or feed. So far, none have been proved to replace the use of antibiotics in growth stimulation thoroughly and successfully, and thus further research is needed. The possibilities of using these potential alternatives to synthetic antibiotics are explored below.

In-feed enzymes

Feed enzymes have been employed extensively in both livestock and poultry feed for more than 15 years, especially in wheat- or barley-based diets (Choct, 2002). In-feed enzymes are usually produced by fermentation of fungi and bacteria, after which these are used to stimulate growth as additives in animal feeds. Several studies have investigated the effectiveness of in-feed enzymes as a substitute for antibiotic growth promoters for improving nutrient absorption and digestibility, gaining body weight, and animal performance. Based on recent studies, it was demonstrated that in-feed enzymes often have activities in promoting digestion of feed components that are normally poorly digested or totally undigested in agricultural animals (Hedemann *et al.*, 2009). The mechanism by which in-feed enzymes promote digestion of feed components is believed to involve the breakdown of those hard-to-digest chemical components in the grains and meals such as non-starch polysaccharides, especially arabinoxylans and beta-glucans, phytates, and proteins (Gerard *et al.*, 2011). Added routinely to the feed of livestock and poultry, these enzymes are efficient at maximizing feed conversion efficiency, and more importantly they have no or very few side effects. As a consequence, numerous researchers are now focusing on improving the quality of existing enzymes, intending to broaden the range of feed ingredients in which they could be used as alternative growth promoters.

Competitive exclusion products

Owing to the increasing concerns about the role of chemical antibiotics in bacterial resistance in both agricultural animals and humans, and following Darwin's competitive exclusion principle, many researchers are seeking biological alternatives to replace antibiotic growth promoters with competitive exclusion products. Competitive exclusion products are usually processed from and composed of various species of undefined or partially defined bacteria isolated from the gastrointestinal tracts of agricultural animals. Products such as BroilactTM, AvigardTM, and PreemptTM are often administered to newborn animals, especially poultry, and have shown their effectiveness in animal growth promotion, gut health maintenance, and even the control of pathogenic infection (Alaeldein, 2013). Several studies have found that a significant improvement of animal feed conversion ratio using Avigard treatment results from the reduction in feed intake and also the prevention of pathogenic colonization such as *Salmonella* and *Campylobacter* from the gut (Gerard *et al.*, 2011). At the same time, multiple competitive exclusion products can also help reduce diarrhea and mortality levels, but the mechanisms remain unclear.

Probiotics

Similar to competitive exclusion products, probiotics are defined as directly fed mono- or mixed cultures of living microorganisms that can compete with undesired microbes

and benefit the host by improving the properties of the indigenous microbiota (Fuller, 1992). Available probiotics can be divided into two main categories. One category is colonizing species such as *Lactobacillus*, *Lactococci*, and *Enterococcus*; the other is free-flowing noncolonizing species, which include both *Bacillus* and *Saccharomyces cerevisiae*. These beneficial microbes are able to ameliorate the overall health of animal by improving the gut microbial balance; however, their exact mechanism is still under investigation. One major hypothesis for their actions could involve their influence on intestinal metabolic activities, including the improvement of bacteriocins, propionic acid, and vitamin B12 production, and increasing the villous length and nutrient absorption (Christina *et al.*, 2009). Other possible mechanisms include competitive exclusion of pathogenic microorganisms and their immunostimulatory activities.

Probiotics are also effective in helping boost weight gain and feed conversion rates in newborn animals. However, several questions about the active strains, the maximum dosage, the effective delivery system, and the potential risks remain unanswered and need to be further investigated. One more potential danger of using live probiotics refers to their antibiotic resistance. A report from the Scientific Committee on Animal Nutrition (2001) concerning the safety of probiotic products found that *Lactobacillus plantarum* and *Pediococcus acidilactici* were tetracycline-resistant. As a consequence, the use of probiotics could possibly put the whole food chain and the environment at risk. Moreover, the permanent establishment of probiotics in animal gastrointestinal tracts is difficult. Several studies have indicated that gut microflora are active and efficient in preventing new organisms from colonizing and becoming established (Jonsson and Conway, 1992). Finally, the high cost and high dosage of administration required for probiotics for growth promotion might also be a serious drawback to their widespread application in animal agriculture.

Prebiotics

Prebiotics are nondigestible feed ingredients that are able to provide selective stimulatory effects on both the growth and metabolic activity of certain gut microflora, including the probiotics mentioned above. Their effects are based on the nature of the compound, but essentially they could exert the same or similar actions as probiotics. Unlike probiotics, which are foreign microorganisms introduced into the gut competing with colonic communities which have already become established, the chief advantage of employing prebiotics in improving gut function is that their target bacteria are already commensal with the large intestine (Macfarlane *et al.*, 2008). However, prebiotics cannot be effective if the targeted beneficial bacteria are not in the gut due to, for example, antibiotic therapy or intestinal diseases. One potential area of future research would be examining the combined effect of both probiotics and prebiotics, known as 'synbiotics,' for the replacement of antibiotic growth promotants (Louise, 2009).

Organic acids

Some evidence has shown that in the presence of organic acids, mainly short-chain fatty acids such as acetic, butyric, and propionic acids, there is significant increased growth of gut

mucosa. Butyric acid, the metabolic product of *Lactobacillus*, is one of the representatives of organic acids that could potentially be used as alternative growth promoters. Butyric acid exerts multiple effects on the intestinal function of both animals and humans, including acting as a vital energy source for intestinal cells, stimulating epithelial cell proliferation and differentiation (Dalmasso *et al.*, 2008), and inducing anti-inflammatory effects (Hodin, 2000). In addition, by stimulating the expression of tight junction proteins and the production of antimicrobial peptides in mucosa, butyric acids are also able to strengthen the gut mucosal barrier (Schauber *et al.*, 2003; Bordin *et al.*, 2004; Peng *et al.*, 2007).

Bioactive phytochemicals

A variety of plant-derived agents are employed worldwide as feed additives in farm animals. As a substitute for antibiotics, these plant-derived compounds also exert production-enhancing effects, including the improvement of dairy weight gain, enhancement of feed conversion efficiency, and increasing milk and egg production (Halldor, 2012). As the secondary metabolites of flowering plants, essential oils have been used as nonantibiotic antimicrobials as animal feed additives for the purpose of both growth stimulation and bacterial inhibition (Hammer and Carson, 2011). Para-thymol, an isomeride of thymol, with higher antibacterial activity and lower volatility, has been found to be safer and exerts even better growth-promoting effects than thymol and carvacrol (Peng *et al.*, 2011). Other bioactive phytochemicals patented worldwide include isoflavone, produced by *Fabaceae* family, diaryheptanoid from the bark of the Japanese shrub alder *Alnus pendula*, *Curcuma aromatica* Salisb extracted from ginger, saponin extracted from yucca, alkaloids from plume poppy, and lignocellulose obtained from *Magnolia*, all of which have been claimed to effectively modulate gut microflora, improve immune function, and promote both absorption and digestion of nutrients by livestock and poultry (Halldor, 2012).

Antimicrobials for Pre-harvest Foodborne Pathogens Reduction in Food Animals

According to the Centers for Disease Control and Prevention (CDC), an estimated 48 million illnesses, 128 000 hospitalizations, and 3000 deaths are caused by foodborne pathogens annually (Centers for Disease Control and Prevention, 2012). Zoonotic pathogens colonized in the gastrointestinal tract of food animals can be shed in feces. Fecal contents play a significant role in carcass cross-contamination and are likely to reach consumers and food processors. In addition, fecal content is a direct source for pathogens in water, soil, vectors, and crops. As a consequence, it remains a major public health concern to reduce the foodborne pathogenic bacteria populations at the farm level. A broad range of preharvest intervention strategies have been employed, and some are still under development. Owing to increased worldwide concern about the transmission of antibiotic resistance from farm animals to humans, the preharvest use of antibiotics has been limited and even gradually prohibited. Though the reduced preslaughter use of antibiotics to reduce foodborne pathogens in farm animals has been partially offset by an increased use of

prescribed antibiotics for therapeutic purposes, the direct use of several common antibiotics and alternative natural antimicrobial agents as a substitute for antibiotics is urgently needed. Major potential natural strategies include using bacteriocin, vaccination, introducing bacteriophages, adding enzymes or organic acids as feed supplements, and the enhancement of competition by introducing substrate-adapted competitive products such as probiotics and prebiotics. Parallel and simultaneous application of more than one preharvest strategy could be a promising strategy to synergistically lower the incidence of foodborne illness.

Selected Antibiotics Registered for Preslaughter Use in Agricultural Animals

Foodborne illness is a significant factor contributing to mortality and morbidity not only in the United States but throughout the world. Various agents such as viruses, bacteria, fungi, and parasites are responsible for more than 200 known foodborne diseases. Among the numerous and various threats, *Salmonella*, *Escherichia coli* O157:H7 (EHEC), *Campylobacter*, and *Listeria* are the leading causes of meat products-related illness and deaths in the United States. Most of these foodborne pathogens are able to live on the skin or in the gastrointestinal tract of food animals such as cattle, swine, sheep, and poultry, especially chickens and turkeys, and in the farm environment where the soil is fertilized with composted animal manure (D'Aoust *et al.*, 2008; Meng *et al.*, 2008; Nachamkin, 2008; Swaminathan *et al.*, 2008). Thus, antibiotics have been widely employed in preharvest use in farm animals and in humans to reduce foodborne pathogens and to prevent foodborne illness. In spite of the widespread use of antibiotics in animals, it is often difficult to choose a specific antibiotic which could target specific pathogens because the microbes usually fall into diverse groups. As a result, broad-spectrum antibiotics are usually employed in preharvest animals. Based on recent research, antibiotic treatment for controlling gastrointestinal pathogens has been found to disrupt the gut microbial ecosystem and thus impair animal health, meat or milk production, and even food safety. Despite the potential shortcomings of antibiotic preharvest treatment, recent research at the farm animal level has shown that antibiotics do have the potential to kill foodborne pathogens inside the body and thus improve food safety.

Most of the antibiotics are routinely administered through animal diets to exert their antimicrobial activities. For example, monensin, one antibiotic in the ionophore class, which might not induce or increase antibiotic resistance and is also not therapeutically used in humans, is approved for use in food animals in the preharvest reduction of foodborne pathogenic bacterial populations.

Poultry

Antibiotics have been put into widespread use in poultry farms for disease prevention and treatment since the 1940s. Campylobacteriosis in humans is frequently acquired via the consumption of undercooked poultry meat contaminated with *Campylobacter jejuni*, identified and isolated from multiple farm animals but most commonly in poultry meat products

(Vugia *et al.*, 2007). Effective antibiotics such as erythromycin can be administered in feed or drinking water. Because fluoroquinolones and erythromycins belong to the classes of antimicrobials, these are also used in human campylobacteriosis treatment. The preharvest use of these two antibiotics in poultry needs to be carefully evaluated. Some researchers have pointed out that *Campylobacter* is resistant to macrolides and fluoroquinolones due to the inappropriate use of these antibiotics (Nachamkin, 2008).

Human listeriosis is caused by infections of the bacterium *Listeria monocytogenes*, which result from the consumption of contaminated poultry or ready-to-eat poultry products. Its resistance to many commonly used antibiotics makes treatment of *L. monocytogenes* more difficult. However, a study has found that pediocin and enterocin were more active against *L. monocytogenes* than nisin (Cintas *et al.*, 1998).

Colonization by *Salmonella enterica* serovars Enteritidis and Typhimurium in poultry is relatively common and a major public health concern. Transmission of enteric salmonellosis to humans usually occurs through consumption of contaminated poultry and poultry products, specifically eggs. Owing to the presence of multiple antibiotic-resistant strains of *Salmonella*, antibiotic treatment against this pathogen has been compromised at least to some extent. One major concern is the strain of *Salmonella enterica* serovar Typhimurium (DT104) commonly found in poultry and eggs. DT104 is demonstrated to be resistant to at least five antibiotics – ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. Preharvest control of DT104 continues to be a significant challenge due to its increased virulence by alterations of inherent pathogenic characteristics and treatment failures resulting from the inappropriate use of antibiotics (Besser *et al.*, 2000). However, combined use of trimethoprim and sulfonamide at the preharvest level might be effective in reducing *Salmonella* in chicken gut. Other possible choices include fluoroquinolones and the third-generation cephalosporins (D'Aoust *et al.*, 2008); Table 2 shows the preslaughter FDA-approved antibiotics commonly used in the poultry industry (Teshome *et al.*, 2007).

Cattle

EHEC causes infection and various diseases, especially hemorrhagic colitis, in humans with a relatively low infectious dose (Lee and Greig, 2010). EHEC is mainly harbored in the gastrointestinal tracts of healthy cattle and is shed in their feces. The major source of EHEC was traced to ruminant manure, but undeniably, EHEC was also identified in some nonruminant farm animals including swine and fowl due to the cross-contamination spread by ruminant manure. But, since bovine manure is the major source of EHEC contamination in the farm environment and animal meat products, effective preharvest control targeting reduced prevalence and quantity of fecal EHEC excretion by live cattle is crucial. EHEC does not typically exhibit the drug resistance to the use of multiple antibiotics which is frequently found in enteropathogenic *E. coli* and other foodborne pathogens like *Campylobacter* and *Salmonella*, though the use of ionophores does not show significant influence on the prevalence of EHEC (Edrington *et al.*, 2003; LeJeune and Kauffman, 2006). However, it has been shown that almost all EHEC isolates are

Table 2 FDA-approved antibiotics for preharvest subtherapeutic purpose in poultry

Antibiotics	Dosage in feed (mg head ⁻¹ day ⁻¹)	Main treatment purpose	Withdrawal time (days)
Arsanilic acid	75–120	Feed efficiency and growth	5
Avilamycin	5–10	Feed efficiency and growth	None
Avoparcin	7.5–15	Feed efficiency and growth	None
Bacitracin	4–50	Feed efficiency and growth	None
Bambermycins	1–20	Feed efficiency and growth	None
Chlortetracycline	10–100	Disease control	None
Lincomycin	2–4	Feed efficiency and growth	None
Oxytetracycline	5–50	Disease control	0–3
Penicillin	2–50	Feed efficiency and growth	None
Roxarsone	23–46	Feed efficiency and growth	None
Spiramycin	5–20	Feed efficiency and growth	None
Avoparcin	7.5–15	Feed efficiency and growth	None
Tylosin	10–110	Feed efficiency, growth, and disease control	None
Virginiamycin	> 25	Disease control	None

Table 3 FDA-approved antibiotics for preharvest subtherapeutic use in cattle

Antibiotics	Dosage in feed (mg head ⁻¹ day ⁻¹)	Main treatment purpose	Withdrawal time (days)
Bacitracin zinc	35–70	Feed efficiency and growth	None
Bambermycins	1–5	Growth	None
Chlortetracycline	350	Disease control	2
Laidlomycin	5–10	Feed efficiency and growth	None
Lasalocid	10–30	Feed efficiency and growth	None
Monensin	5–30	Growth and Disease control	None
Oxytetracycline	75	Disease control	None
Tylosin	8–10	Disease control	None
Virginiamycin	10–25	Disease control	None

susceptible to neomycin sulfate (Mora *et al.*, 2005). Neomycin sulfate is an approved antibiotic used in cattle, where it has been demonstrated to significantly decrease the fecal excretion of EHEC (Elder *et al.*, 2002; Woerner *et al.*, 2006). Given appropriate use and quick withdrawal, neomycin appears to be a promising candidate for preharvest use in the cattle industry. Table 3 shows the commonly used FDA-approved preslaughter antibiotics in the cattle industry (Teshome *et al.*, 2007).

Swine

Antibiotics and other antimicrobial agents have been widely used as preharvest feed additives in the swine industry since the early 1950s. In addition to effectively stimulating swine growth rates and improving reproductive performance, preharvest use of antibiotics is also able to reduce the populations of foodborne pathogens including *Campylobacter*, EHEC, *Listeria*, and *Salmonella*. Currently, preslaughter use of carbadox, cephalosporins, lincosamides, macrolides, penicillins, pleuromutilins, polypeptides, quinolones, sulfonamides, and tetracyclines is cleared by the Food and Drug Administration in swine feed (Morrison, 2001). Among these approved antibiotics, the feeding of chlortetracycline and tylosin decreased fecal shedding in swine artificially infected with EHEC, and the feeding of spectinomycin in pigs under 4 weeks old and weighing less than 15 lb effectively controlled the infectious

bacterial enteritis caused by *E. coli* and salmonella (Friendship, 2006). However, bacitracin did not exert significant antimicrobial effects on EHEC (Irwin *et al.*, 2003). Table 4 shows the commonly used FDA-approved preslaughter antibiotics in the swine industry (Teshome *et al.*, 2007).

Nonantibiotic Antimicrobials Used in Preharvest Reduction of Foodborne Pathogens in Farm Animals

Because of the increased concern among consumers about antibiotic resistance, several nonantibiotic antimicrobials have been developed and introduced for use by farmers to inhibit preharvest foodborne pathogens. The major potential agents include bacteriocin, bacteriophages, chlorate, vaccines, organic acids, and other plant- or animal-derived products. Some of their advantages and disadvantages will be discussed in this part.

Bacteriocins

Bacteriocins are proteins or peptides with antimicrobial activities produced by certain bacteria for the purpose of inhibiting the growth of their competitive bacterial strains in the environment. Such antimicrobial proteins are able to inhibit the growth of several major foodborne pathogens including EHEC, *Salmonella*, and *Listeria* (Stahl *et al.*, 2004; Patton *et al.*,

Table 4 FDA-approved antibiotics for preharvest subtherapeutic use in swine

Antibiotics	Dosage in feed (mg head ⁻¹ day ⁻¹)	Main treatment purpose	Withdrawal time (days)
Apramycin	150	Disease control	28
Arsanilic acid	45–90	Feed efficiency and growth	5
Bacitracin methylene disalicylate	10–30	Feed efficiency and growth	None
Bacitracin zinc	20–40	Feed efficiency	None
Bambermycins	2–4	Growth	None
Carbadox	50	Disease control	42
Chlortetracycline	>50	Disease control	None
Lincomycin	40–200	Disease control	None
Oxytetracycline	22	Disease control	5
Penicillin	10–50	Feed efficiency and growth	None
Roxarsone	182	Disease control	5
Tiamulin hydrogen fumarate	35–200	Disease control	2–7
Tilmicosin	181–363	Disease control	7
Tylosin	10–110	Feed efficiency, growth, and disease control	None
Virginiamycin	>25	Disease control	None

2007). The application of bacteriocin isolated from *Lactobacillus salivarius* and *Paenibacillus polymyxa* in chicken intestinal tracts has been shown to induce a dramatic reduction in broiler chicken cecal *Campylobacter* colonization (Svetoch and Stern, 2010). Nisin has already been found to be effective in spoilage bacteria reduction in meat and milk, and encapsulated nisin is able to inhibit the growth of *L. monocytogenes* (da Silva Malheiros *et al.*, 2010), although nisin's preharvest application is still under research. However, under the basic principle of bacteriocin, by protecting bacteriocins from ruminal or gastric degradation, once reaching the lower gut, bacteriocins exert their antimicrobial activities by disrupting the cell membranes of target foodborne pathogens. Owing to their nontoxic characteristics on eukaryotic host cells, bacteriocins are considered safe for consumption of meat and meat products.

Bacteriophages

Because they are highly specific in recognizing and injecting 'disrupting DNA' into a host bacterium, bacteriophages can be active against specific bacterial strains. Specificity allows bacteriophages to be used against targeted foodborne pathogens in a mixed population without disturbing the composition of normal gut microflora. In 2007, a phage spray produced by Omnilytics (Salt Lake City, UT), specifically against EHEC in preharvest live cattle, was approved by the FDA. Other studies have also tested the short-term reduction of *Salmonella* colonization in poultry and swine (Callaway *et al.*, 2008). Several researchers have also tested the oral consumption of large doses of bacteriophages and found it to be harmless to animals. Owing to their rapid replication and high level of specificity, bacteriophages can serve as a potential preharvest strategy against foodborne pathogens in agricultural animals. However, the efficacy of bacteriophages against infecting bacteria should be tested in the lab before application. The specificity of bacteriophages is also a disadvantage when a need to target multiple pathogens or causative agents of disease is not confirmed (Inal, 2003). In addition, compared to antibiotics, bacteriophages are more complex organisms that are able to transfer genes between bacteria and induce pathogenic

mutation. Only by careful selection of strictly lytic bacteriophages and sequencing their hereditary materials can cross-gene transfer be prevented (Inal, 2003). In comparison with antibiotics, the administration of bacteriophages requires trained personnel, which makes the application of bacteriophages much more difficult for farmers.

Chlorate

Chlorate is the analog of nitrate reductase, both of which can catalyze the conversion from nitrate to nitrite for the anaerobic respiration of *Salmonella* and *E. coli*. The accumulation of chlorite, degraded from chlorate, in the cytoplasm is able to kill bacteria (Stewart, 1988). Some studies have demonstrated that chlorate administered in drinking water significantly reduces EHEC populations in both cattle and sheep in the rumen, intestine, cecum, and feces (Callaway *et al.*, 2003). In addition, preliminary studies examining the use of chlorate in broilers and in turkeys have also yielded promising results (Byrd *et al.*, 2003; Moore *et al.*, 2006). Addition of chlorate to swine diets reduced experimentally inoculated *Salmonella* and EHEC fecal and intestinal populations (Anderson *et al.*, 2001a, b). Currently, chlorate has been licensed as a product but needs evaluation in its application.

Vaccination

Vaccination is the method of inhibiting pathogens by inducing the defense mechanisms of animals' own immune systems. Some specific vaccination has already shown great efficacy in reducing the levels of foodborne pathogens in agricultural farm animals. Vaccines against *Salmonella* strains have been developed for use in swine and dairy cattle (House *et al.*, 2001). More recently, a vaccine designed to inhibit fecal EHEC in cattle has also been developed (Fox *et al.*, 2009). Based on these research efforts, the use of vaccination in preslaughter reduction of foodborne pathogens seems to hold promise. Vaccines made from any one bacteria serovar cannot confer cross-protection against another serovar, no matter how much antigenic similarity there is between them, but more than 2500 serovars of *Salmonella* are found in animals and humans. *Campylobacter jejuni*, *Campylobacter hyointestinalis*, *Campylobacter*

upsaliensis, *Campylobacter lari*, and *Campylobacter fetus* are also found in farm animals (Singh, 2009). As a consequence, super-high specificity and additional costs prevent vaccination from being commonly used in agriculture.

Other natural antimicrobial agents as feed supplements

Organic acids are gradually being employed in animal nutrition for both their nutritional value and their antimicrobial effects. Organic acids produced by the anaerobic microflora of the large intestine include acetate, lactate, malate, and propionate. Some of them have been shown to exhibit antimicrobial activity against gram-negative bacteria such as EHEC, *Salmonella*, and *Campylobacter* (Huyghebaert *et al.*, 2011).

Various plant products can also serve as antimicrobial agents. For example, pasteurized blueberry juices have been shown to have antimicrobial effects on multiple major foodborne pathogens such as *Salmonella* Typhimurium, *C. jejuni*, *L. monocytogenes*, and EHEC (Biswas *et al.*, 2012). Other organics such as cocoa, peanut skin, and the pomace of blueberry and blackberry have also shown antimicrobial activity but need further study. Multiple fruits and vegetables contain phenolic compounds, such as lignins and tannins, both of which are able to affect the gastrointestinal tract via antimicrobial activity (Cueva *et al.*, 2010). Tannins have been found to significantly reduce the population of EHEC in cattle (Wang *et al.*, 2009). Another study showed that highly lignified forages could reduce the shedding period of EHEC (Wells *et al.*, 2005). In addition, most of the essential oils such as citrus oil usually exert their antimicrobial effects by disrupting the cell membrane of bacteria (Turgis *et al.*, 2009). As a result, both organic acids and bioactive phytochemicals have been proposed as potential preharvest agents against foodborne pathogens in farm animals.

Multiple animal-derived products have also been documented as being effective in foodborne-pathogen inhibition. Chitosan, isolated from the exoskeletons of crustaceans and arthropods (insects, spiders, millipedes, and centipedes), has been shown to inhibit the growth and reduce trans-shell penetration of mold and several foodborne pathogens including *S. Enteritidis*, *E. coli*, and *L. monocytogenes* (Leleu *et al.*, 2011). A heat-stable and salt-tolerant peptide, pleurocidin, could be isolated from myeloid cells and mucosal tissue of both vertebrates and invertebrates, whose inhibitory effect against different foodborne pathogens such as *L. monocytogenes* and EHEC has already been documented (Jung *et al.*, 2007). Other products such as defensin, lactoferrin, lactoperoxidase, lysozyme, and ovotransferrin have all shown their potential in meat or the preservation of milk products and in reducing multiple foodborne pathogens, but their application in preharvest control of foodborne pathogens in farm animals needs to be studied further.

Antibiotics Used as Veterinary Medicine

The therapeutic treatment of individual sick animals with antibiotics or other effective antimicrobials is essential and is employed all over the world. In 2007, global sales of animal health products included: Western Europe (US\$110 million), North America (US\$725 million), the Far East (US\$435

million), Latin America (US\$275 million), Eastern Europe (US\$150 million), and the rest of world (US\$80 million) (Evans *et al.*, 2008). Antibiotics used for veterinary therapy are often administered orally through feed and water, or by injection, in order to relieve animals' suffering and reduce production losses. However, if certain livestock or poultry are sick, the whole herd or flock needs to be treated to prevent the spread of disease. In these cases, antibiotic treatment is usually given in high doses, intermittently within a relatively short period of time. Broad-spectrum or combinations of antibiotics are commonly used in such situations when the specific pathogens of concern are unidentified or in doubt. Worldwide estimated sales of antibiotic products in 2007 include macrolides (US\$629 million, 22.7%), penicillins (US\$550 million, 19.8%), tetracyclines (US\$533 million, 19.2%), quinolones (US\$531 million, 19.1%), and sulphonamides (US\$118 million, 4.3%), with the leading products being oxytetracycline (US\$272 million), enrofloxacin (US\$259 million), chlortetracycline (US\$257 million), ceftiofur (US\$200 million), florfenicol (US\$114 million), and tulathromycin (US\$90 million) (Evans *et al.*, 2008). However, a narrow-spectrum antibiotic able to target a specific pathogen involved in animal disease should be the first choice and could also lower the risk level of antibiotic resistance. The major animal diseases requiring therapeutic use of antibiotics are respiratory and enteric diseases in calves and pigs, necrotic enteritis in poultry, and mastitis in dairy cattle.

Approved Antibiotics against Livestock Diseases

Antibiotics are commonly used therapeutically against a broad range of infectious diseases in livestock, including cattle, pigs, sheep, and horses, but currently treatment using antibiotics is becoming more pathogen-specific under the supervision of veterinarians. There are three major therapeutic patterns of antibiotic use in livestock: prophylaxis, which targets exposed healthy animals before onset of risk diseases; metaphylaxis, which is the mass treatment of animal populations currently suffering from diseases before the onset of blatant illness; and treatment for animals experiencing acute clinical diseases. The dose regimen for these three therapeutic uses of antibiotics relies on the expected minimum inhibitory concentration of the target pathogens expected to be implicated.

Three of the most prevalent infectious diseases in livestock are respiratory disease, enteric disease, and mastitis (Giguère *et al.*, 2006; Radostits *et al.*, 2007; Zimmerman *et al.*, 2012).

Mannheimia, *Pasteurella*, and *Haemophilus* are three major pathogens responsible for respiratory disease in cattle, and they constitute one of the biggest health challenges for dairy cattle (Barrett, 2000; Rerat *et al.*, 2012). Tetracyclines, especially chlortetracycline and oxytetracycline, are commonly added to feed and water to treat cattle respiratory disease (Apley and Coetzee, 2006). Other approved antibiotics for bovine respiratory disease treatment include aminoglycosides, especially spectinomycin and neomycin, macrolides in the form of tilmicosin and erythromycin, tylosin, penicillins (amoxicillin and ampicillin), cephalosporin especially ceftiofur, and sulfonamides (sulfamethazine and sulfadimethoxine). Besides

these, florfenicol and enrofloxacin are also approved by the FDA (Apley, 2001).

Apart from respiratory disease, enteric disease involving *E. coli* and *Salmonella* is also common in livestock. Neomycin, in the aminoglycoside class, is commonly used as a water additive against these enteric disease. Chlortetracycline and oxytetracycline under the tetracycline class are also approved by the FDA for the treatment of these enteric bacterial pathogens (Apley, 2001). Infectious agents include rotavirus, coronavirus, and cryptosporidium, for which antimicrobials are still under research.

Mastitis is a major problem in dairy cattle and can impair normal lactation. Pathogens including *Pseudomonas*, *Staphylococcus*, *Mycoplasma*, *Pasteurella*, *E. coli*, and *Streptococcus* cause mastitis (Kandasamy *et al.*, 2011). Novobiocin, pirlimycin, and streptomycin are FDA-approved therapeutics for treatment of mastitis. Any of these antibiotics can be used alone or in combination with penicillin (Wagner and Erskine, 2006). Other approved intramammary antibiotics against mastitis are amoxicillin, cephalirin, cloxacillin, hetaicillin, and lincomycin (Wagner and Erskine, 2006). Erythromycin is also approved by the FDA in the form of an injectable antibiotic. In addition to these, beta-lactams, cephalosporins, neomycin, and tetracyclines are also recommended.

In addition to these three major livestock diseases, footrot, metritis, pleuropneumonia, and colitis are also common in farm animals. In the case of footrot (infectious pododermatitis), ceftiofur, injectable oxytetracyclines, tylosin, erythromycin, and trimethoprim-sulfonamide combinations are FDA-approved antibiotics. Metritis is also a common disease in dairy cows. Tylosin and injectable oxytetracycline are the only two products approved by the FDA for the treatment of metritis. Procaine penicillin, amoxicillin, tetracyclines, trimethoprim, and tilmicosin are usually used for treatment of pleuropneumonia in swine (Constable *et al.*, 2008). For colitis, caused by *Serpulina*, dimetridazole, tiamulin, and lincomycin are three common antibiotics being used currently (Friendship, 2006; Burch *et al.*, 2008). For effective control of lactic acidosis in the lambs, virginiamycin is used as a feed additive, though therapeutic use of antibiotics is relatively rare in sheep or goat production due to the high cost. For horses, gentamicin is injected routinely for foal sepsis, whereas virginiamycin is given in feed against laminitis (Apley, 2001).

Approved Antibiotics against Poultry Diseases

Since the 1940s, antibiotics have also been used in poultry farming for both therapeutic and prophylactic purposes. But due to recent improvements in husbandry, hygiene conditions, and farm management, bacterial diseases in poultry have been better controlled with less reliance on antibiotics. However, antibiotic therapy is still useful and required when alternative disease control methods such as vaccination fail. Important and common poultry diseases include necrotic enteritis, chronic respiratory diseases, gangrenous dermatitis, fowl cholera, and avian influenza (Pattison, 2008; Saif *et al.*, 2008). Antibiotic treatments for these diseases are predominantly done through supplementation in either water or feed. Most of

the effective and common antibiotics are being used as therapeutic intervention in poultry diseases (Hofacre, 2006).

Necrotic enteritis is the most common infectious disease in modern poultry farms and can result in huge financial losses. *Clostridium perfringens* is the major causative bacteria of necrotic enteritis. However, the occurrence of this disease is always associated with the outbreak coccidial infection, which induces the gut to be more susceptible to *C. perfringens* (Dahiya *et al.*, 2006). Tetracycline, streptomycin, neomycin, bacitracin, and avilamycin in feed are the four most common antibiotics targeting necrotic enteritis (Wages, 2001). Control of *C. perfringens* infection together with prevention of coccidiosis could be accomplished by adding antibiotics such as virginiamycin (20 g ton⁻¹), bacitracin (50 g ton⁻¹), and lincomycin (2 g ton⁻¹) to feed (Wages, 2001). The ionophore classes of anticoccidial compounds are also effective in preventing coccidial infections. In addition, probiotics administration is also used as an effective method to both prevent and treat clinical necrotic enteritis.

Controlling respiratory disease in poultry is important to ensure maximum economic profits. Respiratory disease in poultry is induced by several complex factors including viral presence, stress, and dietary changes, but *Mycoplasma gallisepticum* infection is responsible for most respiratory diseases in poultry (Animal Health National Program, 2007). A variety of antibiotics such as tylosin, tiamulin, tilmicosin, aivlosin, tetracyclines (mainly doxycycline, chlortetracycline, and oxytetracycline), spiramycin, erythromycin, gentamicin and ketasamycin, neomycin, and colistin are used, both alone and in various combinations, to control and cure respiratory disease in poultry (Loehren *et al.*, 2008). But fluoroquinolones (enrofloxacin, danofloxacin, norfloxacin, flumequin, etc.) are used in the withdrawal phase.

Gangrenous dermatitis is caused by contamination of more than one type of bacteria including *Clostridium septicum*, *Staphylococcus aureus*, and *E. coli* (Li *et al.*, 2010). Owing to the involvement of various bacterial pathogens in gangrenous dermatitis, broader-spectrum antibiotics are needed for the treatment and control of this disease. Preferred effective antibiotics include erythromycin, penicillin, and tetracycline, especially oxytetracycline (Wages, 2001).

Pasteurella multocida is the causal agent of fowl cholera (Siti and Robert, 2000). This contagious bacterial disease usually results in high morbidity and mortality rates. Sulfonamides are commonly used for early treatment (Wages, 2001). Sulfaquinoxaline sodium, together with sulfamethazine and sulfadimethoxine in feed or water, is commonly used to control fowl cholera in poultry (Loehren *et al.*, 2008). Tetracycline and norfloxacin administered via feed and water or administered parenterally are also helpful in controlling fowl cholera. And combination streptomycin-dihydrostreptomycin injection is effective in ducks.

Other useful antibiotics include lincomycin, virginiamycin, spectinomycin, tylosin, and erythromycin, which are mainly used as gram-positive antimicrobials. In addition, gentamicin and ceftiofur are the most commonly used in *in ovo* injectable antibiotics (Loehren *et al.*, 2008). In the case of protozoan diseases, which include coccidiosis caused by *Eimeria* and histomoniasis caused by *Histomonas meleagridis*, coccidiostats and histomonostats in the form of feed additives are used as effective antimicrobials (Wages, 2001).

Limitations of Antibiotic Use in Animals

Antibiotics employed for infectious disease prevention and treatment in large groups of farm animals such as cattle, swine, and chicken are usually administered orally in drinking water or as feed additives, and sometimes also via intramammary infusions. These antibiotics are likely to result in residue in edible tissues such as milk and eggs. Multiple antibiotic residues are harmful during the development of human organs, as well as the nervous and reproductive systems. As a result, infants and young children are most susceptible to these residue compounds because of their weak body protection. By establishing preslaughter withdrawal periods, restricting certain antibiotics used in laying hens, and discarding milk produced after intramammary infusions of antibiotics in lactating animals, these harmful antibiotic residues could be reduced or even eliminated (Page and Gautier, 2012).

Public Health Concerns about Antibiotic Resistance

The use of antibiotics, first introduced in the mid-twentieth century, was considered the single most effective medical strategy for dramatically reducing morbidity and mortality in both humans and animals (Andersson and Hughes, 2010). However, the overuse of antibiotics has caused increased antibiotic resistance among multiple human pathogens. Whether or not the pool of resistance genes generated by use of antibiotics in farm animals has induced the prevalence of failures in therapy for human infectious diseases is compounded by the widespread use of antibiotics in livestock and poultry is still controversial. So far, judging from numerous journal articles, reviews, conference reports, newspapers, and TV reports, the inappropriate use of antibiotic in farm animals and its potential risk to human health have become the greatest public health concern among both consumers and scientists. Governments worldwide have already sought regulatory and legal authority in order to restrict or even abolish the nontherapeutic use of antibiotics (Page and Gautier, 2012).

Conclusion

Antimicrobial substances, especially antibacterial agents, are commonly employed worldwide to improve the performance, health, and production of livestock, dairy cattle, and poultry. These agents are used to protect against illness, help reduce significant agricultural losses, and prevent foodborne infections in humans. For the subtherapeutic use of antimicrobials, preharvest treatment for both promotion of animal growth and inhibition of colonization and cross-contamination of foodborne pathogens have drawn great attention because of the urgency of the situation as well as the effectiveness of antibiotics in human disease treatment. However, some agents used in animal agriculture belong to classes also employed in human medicine, such as macrolides, penicillins, sulphonamides, and tetracyclines. This dual use of antibiotics and the common concern of multiple antibiotic resistance in human pathogens and the potential impact of antibiotic residues in food on public health are controversial

and have raised concerns. As a result, efforts to develop alternatives such as plant-derived antimicrobial agents and bio-preservatives are underway. Although the thoughtful and measured therapeutic use of antibiotics or other effective antimicrobials is essential to livestock producers, regulatory bodies, and consumers, narrow-spectrum antibiotics remain the first choice, and a comprehensive understanding of the use of narrow-spectrum antibiotics in preharvest-level farm animal production, along with proper guidance from the veterinary profession, are vital to solving this complex issue.

See also: Food Safety: Emerging Pathogens. Food Security: Postharvest Losses. Poultry and Avian Diseases. Vaccines and Vaccination Practices: Key to Sustainable Animal Production

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