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Current status and prospects for in-feed antibiotics in the different stages of pork production — A review

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Abstract: Antibiotics have long been of great benefit for people, both in the medical treatment of human disease and in animal food where they improve the growth performance and feed utilization during animal production. Antibiotics as in-feed supplements affect all stages of pork production, including the gestation, nursing, growing, and finishing stages, although the effects show stage-dependent differences. However, the use of antibiotics in animal feed has become a worldwide concern. This review describes why sub-therapeutic levels of antibiotic additives in animal feed have become an integral part of animal feeding programs for more than 70 years, particularly in pork production. It also discusses the threat of the long-term use of sub-therapeutic levels of antibiotics in pork production. In recent years, the effectiveness of in-feed antibiotics has tended to decrease. This review analyzes this change from various perspectives. First, the equipment used at pig farms has improved dramatically and is more sanitary. Worldwide, more pig farms use pig farrowing crates, gestation crates, piglet nursery crates, flooring devices, piggery ventilation and cooler systems, automatic pig feeders, piggery heating equipment, and artificial insemination systems. In addition, scientists have replaced the use of antibiotics with organic acids, fermented mash, probiotics, prebiotics, minerals, oligosaccharides, enzymes, herbs/flavors, and protein/amino acids, and have improved management and husbandry techniques. In addition, animal welfare legislation has been aimed at improving the quality of the floors and living space, ensuring that animals have permanent access to fresh water, and setting a minimum weaning age. Finally, the prospects and the possibility of replacing antibiotics in pork production are described, in line with recent research results.

Keywords: Pork Production; Antibiotic Resistance; In-feed Additives; Weaning; Food Conversion Rate; Diarrhea

INTRODUCTION

Antibiotics are agents that either kill or inhibit the growth of microorganisms, including substances produced by microorganisms and synthetic antibacterial compounds. The first antibiotic, penicillin, was discovered by the Scottish scientist, Alexander Fleming, in 1928, for which he shared the Nobel Prize in 1945 [1]. Antibiotics then became the first treatment for life-threatening infections caused by bacteria in humans. Severe protein feed shortages plagued American farmers from the early part of the twentieth century until the end of World War II, and low growth rates and feed efficiency led to meat shortfalls and high prices. In 1950, American farmers rejoiced at news from a New York laboratory: a team of scientists had discovered that adding antibiotic to livestock feed accelerated the animals' growth and cost less than conventional feed supplements [2]. However, different antibacterial agents had different stimulating effects on pig gain rates. Especially, the effect of antibiotics on growth rate and intestinal flora were different in swine [3]. Since then, antibiotics have become an integral part of animal feeding programs, particularly in the pork and poultry industries. More than 1,000 experiments were conducted in the US between 1950 and

1985. Summarizing the results, they found that antibiotics were the most effective agents for improving growth and feed efficiency in young pigs, as well as the entire growing-finishing period, and reducing mortality and morbidity, particularly in young pigs. The mortality rate can be twofold higher under farm conditions than in a research station environment where the facilities are generally cleaner, the disease load is lower, and the environment is less stressful [4].

The natural weaning process of piglets is gradual and occurs at about 2 to 3 months of age. Weaning represents a shift from the piglet's reliance on the sow's milk to other food sources. However, in most developed countries and some developing countries, weaning is abruptly terminated early in life at 19 to 25 days of age. Early weaned piglets have to be reared artificially. Early weaning has been adopted to increase the reproductive efficiency of the sows, particularly with regard to maximizing the sows' litter size at birth and maximizing the number of sows that deliver each year, followed by the successful rearing of early weaned piglets. However, early weaning occurs at a time when there are marked changes in the piglets' intestinal structure and function, such as villous atrophy and crypt hyperplasia, which are generally associated with poor performance, as they are thought to cause a temporary decrease in the digestive and absorptive capacity of the small intestine [5]. Weaned piglets must rapidly adapt to dramatic changes in the social and physical environments, separation from maternal littermates, mixing with unfamiliar piglets, abrupt changes in diet from suckling the dam to ingesting solid feed from a feeder, and establishing a social hierarchy. Consequently, early weaning is very stressful for piglets. Studies have shown that the weaning process has deleterious effects on intestinal mucosal health, highlighted by increased intestinal permeability and agonist-stimulated secretory responses. Diarrhea is the nemesis of the early weaned piglet. Enteropathogens infect the small intestine, which results in secretory or malabsorptive diarrhea. High death losses from diarrhea have dampened the enthusiasm for early weaning of artificially reared piglets. Usually, the nursing piglet is protected from enteropathogens by antibodies bathing the gut from the dam's colostrum and milk. Artificially reared early weaned piglets are protected from enteropathogens by feeding them diets containing additives, such as antibiotics. In addition, adding an antibiotic to the feed results in significant growth performance and improves food conversion rate. Antibiotic trials conducted by the Agricultural Research Council of Britain [1] indicated that Aureomycin and penicillin improve the growth performance and food efficiency of pigs by 10%. Most countries have begun to regulate finisher feeds containing antimicrobial agents because of residual antibiotics.

However, after more than 70 years of using antibiotics as supplements, there is worldwide concern that antimicrobial resistance has made drugs used to treat human disease less effective. Statistics indicate that between 1970 and 2000, the majority of pig diets (70% to 80% of starters, 70% to 80% of growers, and 50% to 60% of finisher feeds) contained antimicrobial agents [6]. About 13,000 tons of antibiotics were administered to animals in 2010 to promote growth of livestock in the USA [7]. In Japan, 175 tons of antibiotics were administered to promote growth of livestock in 2001. In 2007, China produced 210,000 tons of antibiotics and administered 97,000 tons to animals for promoting growth. Zhu et al assessed the type and concentrations of antibiotic resistance genes (*ARGs*) at three stages of manure processing in land disposal at three large-scale (10,000 animals per year) commercial swine farms in China [8]. In-feed or therapeutic antibiotics used on these farms included all major classes of antibiotics except vancomycin. They detected 149 unique ARGs among all of the farm samples; the top 63 ARGs were enriched 192-fold (median) to 28,000-fold (maximum) compared with their respective antibiotic-free manure or soil controls. This review will discuss the advantages and disadvantages of antibiotic feed additives with regard to pork production and possible substitutes as an alternative to antibiotics in pork production.

Efficacy of antibiotic supplements for sows

Antibiotics added to the diet can improve a sow's reproductive performance, conception rate, litter size, and farrowing rate. As early as 1954, Stewart et al reported no significant effects of Chloromycetin on reproductive performance; however, the greater percentage of ova shed, represented by normal embryos in lots receiving Chloromycetin, suggested that the antibiotic has favorable effect on embryo survival [9]. Hays et al reported similar results. The conception rate (68.5% vs 75.6%), farrowing rate (60.9% vs 70%), and number of live pigs per litter (9.8 vs 10.0) tended to be higher for antibiotic-fed sows; however, the differences were not significant [10]. A later experiment on the use of chlortetracycline in sow breeding rations resulted in a significant increase in farrowing rate from 62% to 79% by feeding 1 g of chlortetracycline per sow daily during the pre-breeding and breeding periods. Farrowing rate also increased from 74% to 86% by feeding 0.5 g of chlortetracycline per sow daily during the pre-breeding and breeding periods. Adding 1.0 g chlortetracycline daily from weaning to 15 days post-mating improved the breeding, conception, and farrowing rates [11]. Antibiotic-treated gilts farrow significantly more pigs per litter (including pigs born dead) than did control gilts. More pigs were farrowed alive in the antibiotic-treated group than in the control group. However, no treatment differences due to antibiotics were observed on the weight of pigs farrowed alive, number of pigs weaned, or weaning weight [12]. Bacteriological studies of the vaginal flora before breeding revealed that the treatments did not significantly change the bacterial population. Nevertheless, adding antibiotics to the sow's feed improved the conception rate, litter size, and farrowing rate [13].

Efficacy of antibiotic supplements for early weaned piglets

Weaning a pig is a gradual process that occurs at about 3 months of age and represents the shift from piglet reliance on sow's milk to other food sources. However, in most developed countries' pig production systems, weaning is an abrupt process occurring early in life, at 19 to 25 days of age. It is often associated with development of intestinal malfunction and diarrhea. Rearing early-weaned piglets artificially, to maximize sow reproductive performance, is an attractive management concept in the pig industry. The sow's milk when the piglets are 19 to 25 days of age does not satisfy their growing capacity. Thus, the piglet food source shifts from the sow's milk to other food sources as soon as possible. However, an early-weaned piglet does not secrete sufficient quantities of hydrochloric acid into the stomach to cause optimal activation of enzymes and efficient digestion of a diet based on plant protein [14,15]. Insufficient acid secretion, together with stress, such as the need to rapidly adapt to dramatic changes in the social and physical environments and weaning, may disturb the balance of intestinal flora and allow the proliferation of coliforms, resulting in scours and poor performance [16]. The intestinal mucosa is a unique interface between the microbial and chemical environments that protects the internal milieu from potentially hostile pathogens. Previous studies have demonstrated that when weaning occurs at an earlier age it triggers the breakdown of intestinal barrier function. The villi in pigs with post-weaning diarrhea and mortality were significantly shorter than in pigs of those herds without deaths [17]. Pigs taken from herds with a long history of postweaning diarrhea had in general significantly shorter villi and deeper crypts than their counterparts from a specific pathogen-free herd [18]. Diarrhea is the nemesis of the early-weaned piglet. The weaning of piglets at 14 days is too early and 21 days is more suitable in terms of nutrition, gene expression, immune response, and pathology [19], although the immune system cannot protect a 19 to 25 day-old piglet from pathogens. The enteropathogens infect the small intestine where they produce a secretory or malabsorptive diarrhea. A naturally-nursing piglet is protected from the enteropathogens by antibodies bathing the gut. The source of the antibodies is the dam's colostrum and milk. Thus, feeding piglet diets containing antibodies protects them from enteropathogens. The properties of antimicrobials have been researched extensively. The administration of streptomycin daily to piglets from birth until 4 weeks of age results in a live weight gain of 8% over that of untreated piglets at 8 weeks, the time of weaning. The best average daily gain was obtained in litters with a poor birth weight and piglets affected with diarrhea [20]. *Escherichia coli* (*E. coli*) comprises the majority of the intestinal flora, and almost all strains isolated are hemolytic [21]. Saunders et al reported a syndrome that was consistently associated with certain serotypes of *E. coli* and presented evidence suggesting that they were of primary importance in its etiology [22]. Pigs treated with antimicrobials show no signs of gut malfunction at any time, whereas untreated weaned controls develop clinical diarrhea [23]. The antimicrobial treatment resulted in a higher daily weight gain compared with weaned controls. Commercial application in the US is substantial, particularly in weanling and starter pigs [24].

Efficacy of antibiotic supplements for growing pigs

There is no doubt that in-feed antibiotics improve the growth performance and feed efficiency of growing pigs. In 1949, McGinnis et al reported that a crude protein supplement prepared from Aureomycin (chlortetracycline) mash promoted the growth of turkeys [25]. Turkeys fed Aureomycin at comparatively low levels in the diet showed a growth response. However, little or no response was observed in turkeys fed vitamin B_{12} [26]. It was also confirmed that Aureomycin produces significant growth performance when added to pigs' diet. Aureomycin and penicillin improved the growth of fatting pigs by 10% and Terramycin (oxytetracycline) was as effective as Aureomycin at promoting growth [27]. Antibiotics also improve food conversion but have no effect on carcass quality. The beneficial effects of antibiotics on body weight gain were accompanied by increased feed utilization efficiency, improved appetite, and a superior general appearance of the hair coat and skin. Thus, antibiotics have been used as a feed additive worldwide for several decades. The magnitude of the improvement in growth rate depends on the type of antibiotic, feed level, farm environment, and pig conditions. Adding 225 mg streptomycin per pound of acorn-soybean ration resulted in a 40% increase in growth over the control group. However, the 10 mg streptomycin per pound feed had no significant effect [28]. This result is consistent with the findings of Cuff et al, who also reported that Terramycin was effective for increasing growth performance [29]. In a comparison of the growth-promoting effects of low-level Aureomycin, penicillin, and neomycin, adding 10 mg Aureomycin per pound of feed was very effective for increasing average daily gain. Furthermore, adding procaine penicillin at levels of 1 and 5 mg per pound of feed resulted in a significant growth response. Interestingly, 10 mg neomycin per pound of feed had a deleterious effect on growth [28]. Becker et al compared other antibiotics for stimulating gain rate in pigs. The results showed that 5 mg Aureomycin and Terramycin per pound of diet were the most effective and had equal activity for stimulating rate of gain in swine. Streptomycin at 5 mg per pound of diet or 0.00375% 3-nitro-4-hydroxy phenylarsonic acid failed to yield a significant gain response in healthy pigs [30]. In a comparison of the value of adding Terramycin, chloromycin, bacitracin, and an arsenic acid derivative to a corn-peanut meal basal ration, Aureomycin and Terramycin produced significant growth responses. This result agrees with that of Luecke et al [28].

The problem with feeding antibiotics to livestock

The problem is antibiotic resistance. Much scientific evidence indicates a relationship between feed medication and pathogenic resistance in humans. Antimicrobial resistance is the ability of a microbe to resist the effects of medication previously used to treat them. Antibiotics should only be used when needed, as prescribed by health professionals [1]. Antibiotic consumption in the livestock industry contributes to the overall problem of antibiotic resistance. Antimicrobial resistance threatens effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi [31]. Antibiotic resistance arises as a result of natural selection and is an inherent consequence of exposure to antibiotic compounds. Due to normal genetic variation in bacterial populations, individual organisms carry mutations that render antibiotics ineffective, conveying a survival advantage to the mutated strain [32]. If large numbers of bacteria are resistant to an antibiotic, it becomes more difficult and more expensive to treat human bacterial infections. When antibiotics fail, the consequences include extra visits to the doctor, hospitalization or extended hospital stays, a need for more expensive antibiotics to replace the older ineffective ones, lost workdays and, sometimes, death [32]. As early as late spring 1944, Delamater et al reported the first example of a sulfadiazine-resistant hemolytic *Streptococcus* causing disease that occurred at Keesler Field, Mississippi, a large Army Air Forces training center. Enzo et al confirmed that multiple classes of antimicrobial compounds (commonly at concentrations >100 μg/L) were detected in swine waste storage lagoons [33]. In addition, multiple classes of antimicrobial compounds were detected in surface and groundwater samples collected proximal to the swine and poultry farms. These observations indicate that animal waste used as fertilizer for crops may serve as a source of antimicrobial residues in the environment [34]. Cotta et al indicated that tetracycline and erythromycin/tylosin resistant bacteria were isolated in numbers ranging from 10% to 30% of total recoverable bacteria from swine feces and stored manure [35]. Whitehead and Cotta detected 10 different resistance genes in the fecal and manure pit samples by polymerase chain reaction) [36]. Moreover, Kumarasamy et al reported that multidrug resistant Gram-negative bacteria pose the greatest risk to public health. Not only is the increase in resistance of Gram-negative bacteria faster than that in Gram-positive bacteria but also there are fewer new antibiotics active against Gram-negative bacteria, and drug development programs have appeared insufficient with regard to providing therapeutic cover over the last 10 to 20 years [37]. Two nosocomial outbreaks of sepsis caused by *Serratia marcescens* (*S. marcescens*) occurred in July 1999 and January 2002, in Tokyo, Japan. In July 1999, 10 inpatients developed sudden onset high fever, disseminated intravascular coagulation, and acute renal failure, and five died. Twenty-one strains of *S. marcescens* were isolated from patients' blood and urine. In January 2002, 24 inpatients developed sudden onset high fever and seven died. *S. marcescens* was isolated from a towel, environmental samples, and the inpatients [38].

DISCUSSION AND FUTURE DIRECTIONS

The above discussion shows that antibiotics are the most effective at improving the growth and efficiency of young pigs. In 1950, American farmers rejoiced at the news that scientists had discovered that adding antibiotics to livestock feed accelerated animal growth and cost less than conventional feed supplements [2]. Since that time, antibiotics have provided great benefits to pork producers for several decades. However, warnings about bacterial resistance have overshadowed the benefits. The consumption of antibiotics in the pig industry will increase dramatically as the human population increases. This means that more antibiotic resistant bacteria will arise and spread among animals and the environment and cause more human disease.

The mechanism used by antibiotics to promote growth involves the ability to suppress or inhibit the growth of certain microorganisms. The direct effects of antibiotics in promoting growth can be explained by decreased competition for nutrients and reduced microbial metabolites that depress growth [39,40]. Bassaganya et al reported that poor health status associated with the dirty environment results in suppressed growth; pigs in a clean room had a greater cumulative average daily gain and average daily food intake than pigs in a dirty room [41]. Cromwell summarized data collected in the US between 1950 and 1985, indicating that responses to antibiotics under farm conditions may be twice as great as in a research station environment where the facilities are generally cleaner, the disease load is less, and the environment is less stressful. This was confirmed by Emborg et al, who analyzed data from 6,815 flocks collected from 1995 to 1999 and concluded that kg broilers produced per m^2 and percent dead broilers in total were not affected by the discontinued use of antibiotics where the facilities were recognized as cleaner [42]. However, the feed-conversion ratio increased marginally [43]. Similar results were also reported by Lain et al, who found that the level of antimicrobial use for treating diarrhea after weaning (and the incidence of diarrhea in weaned piglets) did not increase significantly after withdrawal of an antibiotic growth promoter from weaner feeds according to the farmer's evaluations [44]. As early as 1955, Coates et al demonstrated that oral antibiotics do not have growth-promoting effects in germ-free animals [45]. Coates et al indicated that antibiotics reduce gut size and cause thinning of intestinal villi and the total gut wall. Many studies have found that antibiotic additives are more efficient in unsanitary conditions. Overall, scientists have demonstrated that the feeding environment significantly affects the antibiotic response. Antibiotics have less of an effect on rate of growth and feed efficiency in a clean feeding environment. Pigsty facilities have improved dramatically over the past several decades with animal welfare legislation aimed at improving the quality of the floors, living space, permanent access to fresh water, and setting a minimum weaning age. Meanwhile, research has focused on replacing antibiotics with organic acids, fermented mash, probiotics, prebiotics, minerals, oligosaccharides, enzymes, herbs/flavors, protein/amino acids, and management and husbandry techniques [46]. Pigs fed antibiotics or 0.5% ACTIVATE Starter DA was a dry organic acid blend composed of calcium salt of 2-hydroxy-4-[methylthio] butanoic acid, fumaric acid, benzoic acid, and carrier with 31% L-met activity) showed the same improvements in weight gain and feed efficiency as those fed a control diet [47]. The survival rate of coliforms is strongly influenced by pH (regeneration cycle of 70 min at pH 5, and 25 min at pH 7), regardless of the digesta origin. The following killing potency order was established for coliform bacteria: propionic<formic<butyric<lactic<fumaric<formic<propionic<lactic<sorbic<benzoic [48]. Adding some amino acids to the diet during the weaning period not only improves intestinal structure but also elevates the immunocompetence of the piglets. Diet formulation techniques can help the pig counteract some of the normal gut changes that occur at weaning. Low-protein, amino-acid fortified diets limit the amount of fermentable protein present in the gut and help reduce post-weaning diarrhea. In these cases, proper amino acid fortification and ratios relative to lysine are essential so as not to limit pig growth [49]. In recent years, pig toys, such as 'porky play', have gained popularity on European pig farms as a way of preventing stress, as pigs that play with simple toys have fewer chances of developing harmful behavior like ear and tail biting. Porky play distinguishes itself from other toys as it is made of biodegradable material with imidazolium oligomers with an antibacterial function. Riduan developed a series of imidazolium oligomers with a range of terminal alkyl groups that kills *E. coli* within 30 seconds [50].

In May 2015, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance, which calls on all countries to adopt national strategies within 2 years [51]. The European Commission decided to phase out and ban the marketing and use of antibiotics as growth promoters in animal feed on 1 January, 2006. Since then, the use of antibiotics is only allowed with a veterinary prescription for direct applications or as medicated feed [52]. In the US, the National Action Plan for Combating Antibiotic-Resistant Bacteria [53] stressed the need to slow the spread of antibiotic resistance through stewardship at all levels. Southeast Asian WHO countries committed to address the issue in the Jaipur Declaration [54]. The process is also under way in South Africa, started by the work of the global antibiotics resistance partnership and continued through a broad coalition of government and private sector leaders [55].

SUMMARY

In line with recent research results, the effects of organic acids, fermented mash, probiotics, prebiotics, minerals, oligosaccharides, enzymes, herbs/flavors, protein/amino acids and improved management and husbandry techniques, especially clean and hygienic conditions, can completely replace antibiotics in all stages of the pork industry.

CONFLICT OF INTEREST

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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