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Antibiotic Use in Poultry: A Driving Force for Organic Poultry Production

ABSTRACT

Antibiotics are used in poultry production not only for therapeutic purposes; some producers also administer sub-therapeutic dosages for growth promoting purposes, and residues can be detected in eggs and poultry meat if proper withdrawal protocols are not followed. Furthermore, zoonotic bacteria may acquire resistance to antibiotics as a result of administration of sub-therapeutic dosages. Consumers perceive organic meat as a more healthful food because the birds are not raised with antibiotics, and this is a primary reason why consumers purchase organic poultry products, driving sales of organic poultry meat and eggs, which increased 151% over a 1-year period (1999 to 2000) and which have continued to increase since 2000. In response to this consumer demand, large conventional poultry-producing companies have launched "raised-without-antibiotics" lines of products. This review aims to discuss organic poultry-production and the impact of antibiotic use in conventional production systems on consumer perception and purchase of organic poultry products.

INTRODUCTION

Since the 1950s, the poultry industry in the United States has used antibiotic growth promoters at sub-therapeutic levels as feed additives to improve performance in terms of feed conversion and weight gain. In 1965, a rearing period of 112 days would produce a 2.5-lb chicken with a 4.7 feed conversion ratio (weight / feed intake). Currently, the rearing period for a 6-lb chicken is only 42 days and the feed conversion ratio is only 1.8 *(37)*. The improvement in production rate and efficiency is partly due to the use of antibiotic growth promoters. Currently, one difficulty in meeting market demand is consumer opposition to antibiotic growth promoters as feed additives in poultry diets.

Because of consumer opposition and concerns over antibiotic-resistant bacteria, many countries all over the world have banned or restricted the inclusion of antibiotics in animal diets for growth promotion purposes. The U.S. currently restricts the use of some antibiotics in poultry for either

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therapeutic or sub-therapeutic purposes. However, a number of antibiotics are still allowed for use at sub-therapeutic purposes. The use of antibiotics in poultry production has resulted in emergence of a niche market consisting of "antibiotic-free", "organic" or "all natural" labeled products. The aim of this review is to present the background and literature that describe the history, scenarios and science behind the development of the organic poultry market as a function of the use of antibiotics in poultry production.

Poultry production history

After World War II, the broiler industry began to grow as one of the most integrated agricultural industries in the United States. Before World War II, most of the chickens that were used for meat were hens that had outlived their fertility or young roosters. During World War II, consumption of chicken increased because, unlike red meat, poultry was not rationed. Despite the heavy loss of poultry to diseases and poor feed quality, broiler production nearly tripled between 1940 and 1945 *(34, 54)*.

As the growth of the broiler industry grew, the demands for feed increased and the technology for production improved. Large feed companies developed production contracts with growers because they realized the potential for growth of the poultry industry *(36)*. Furthermore, during this time, the cotton industry was in decline, which eventually encouraged expansion of the broiler industry in the south *(15)*. Alabama, Mississippi, Georgia, North Carolina and Arkansas produced 27 percent of the United States broilers in the 1950s. Within 15 years, they became the top five states for broiler production, producing more than 60 percent of the broilers in the nation *(34)*.

In 1957, the Poultry Products Inspection Act (PPIA) was passed, which regulated commerce across state lines, including inspection of poultry by the USDA. Before the act, the USDA offered producers the opportunity for voluntary inspections of broilers *(20)*. The purpose of the PPIA was to protect against practices harmful to health, because of a rise in human deaths from bacterial diseases that could be traced to contaminated poultry meat. The PPIA was also established to instill confidence in consumers to purchase poultry meat. Following implementation of the act, processors built new plants to meet the inspection requirements, and the inspection of broilers increased from 25 percent to 75 percent in 1 year *(36)*. In 1991 the USDA and FSIS implemented mandatory requirements for refrigeration and labeling with the passage of the Egg Products Inspection Act (EPIA 9 CFR part 590) *(25)*. The first egg safety regulation for prevention of *Salmonella* Enteritidis in egg shells was proposed in 2004 but was not approved until 2009 (21 CFR&AC Parts 16 and 118). This FDA regulation is aimed at reducing bacterial contamination of eggs on farms and further growth of bacteria during storage and transportation *(21)*.

The continuous improvement in production and the establishment of government regulations has led to a staggering increase in poultry consumption. To supply this consistently growing consumer demand, selective breeding methods have been applied to obtain producing hens rapidly and fast growing meat chickens with low feed conversion ratios (FCR) measured in terms of mass gained vs. feed consumed. The meat chicken market weight, rearing length and FCR have all significantly improved as a result of this selective breeding. Similarly, the egg production system changed in the late '50s from small-scale farmers into an organized industry, which uses selective breeds for reduced FCR and longer production cycles. However, antibiotic growth promoters have also received credit for these improvements in production performance.

Antibiotic use in veterinary medicine and poultry production

Antibiotics are chemical compounds produced by a variety of microorganisms (bacteria, fungi, etc.) or synthesized in laboratories. Antibiotics differ in physical, chemical and pharmacological properties, as well as in their mechanism of action and antimicrobial spectrum *(Table 1)*. Bactericidal mechanisms include inhibition of (1) protein synthesis; (2) cell wall synthesis; (3) DNA coiling (4) DNA synthesis; or (5) cytoplasmic membrane synthesis.

Growth promoting antibiotic (GPA) use is loosely defined as the practice of providing antibiotics to healthy animals at concentrations below 200 grams per ton of feed for more than 14 days *(18)*. This sub-therapeutic concentration increases animal production by stabilizing the bacterial population, which allows the bird to obtain more nutrients from the diet *(31)*. However, concerns over foodborne pathogens developing antibiotic resistance has driven research for alternatives to antibiotic growth promoters *(40)*. These concerns exist worldwide in areas where antibiotics are used for growth promoting purposes; the EU nations, however, banned the use of antibiotics at sub-therapeutic levels in 2006 *(16)*.

In recent years, production of new antibiotics has decreased considerably because of the costs associated with development and the low profits from antibiotics relative to other drugs. The emergence of resistant bacteria, fungi and protozoa has increased, and these microorganisms have developed defensive mechanisms to evade the destructive action of antibiotics *(17)*. Emerging bacterial resistance has stimulated research on human health and animal production as well as putting increased pressure on the worldwide antibiotic market *(26)*.

The rules for organic poultry are very clear with regard to use of antibiotics. The National Organic Program (NOP) states that in the case of disease and when preventive methods did not work, medical treatment must be provided, but always with the aim of maintaining the organic status.

Table 1. Classes of antibiotics and their mechanisms of action, spectrum of activity and some specific characteristics of these antibiotic classes

Antibiotic Class	Synthesis	Mechanism bacterial inhibition	Spectrum of activity	Characteristics
Aminoglycosides	*Streptomyces* spp.	Protein synthesis	Gram-negative	Exhibit a post-antibiotic effect in which there is no or very little drug level detectable in blood, but still inhibits bacterial re-growth due to strong, irreversible binding to the ribosome.
Bambermycins	*Streptomyces bambergiensis*	Cell wall synthesis	Gram-positive bacteria with the exceptions of *Lactobacillus* and *Bifidobacterium*	Used as a feed additive for growth promoting effects.
Beta-Lactams	Fungal product	Cell wall synthesis	Gram-negative and some Gram-positive	Unstable in acidic conditions. Many bacteria produce lactamases that break the cyclic bond in the chemical structure.
Cephalosporins	Acremonium fungi	Cell wall synthesis	Gram-negative/ some Gram-positive	Less suscpetible to penicillinases than Beta-Lactams. Stable in acidic conditions.
Glycopeptides	Chemically synthesized	Peptidoglycan synthesis	Gram-positive enterococci	In 1997, The FDA Center issued an order placing severe restrictions on the use of all glycopeptides in food animals.
Ionophores	Chemically synthesized	Leakage of cell membrane	*Parasitic coccidia*	Some coccidiostats are converted by bacteria present in the litter into inorganic arsenic.
Lincosamides	*Streptomyces lincolnensis*	Protein synthesis	Gram-positive cocci	Can diffuse to tissues, so are useful for treatment of bone and joint infections and also effective in treating *Necrotic* Enteritis.
Macrolides	Produced by a variety of bacteria	Protein synthesis	Gram-positive	Effective against *Mycoplasma.*
Polypeptides	Fungi, bacteria, plants and eukaroytic cells	Interference with cytoplasmic membrane	Bacilli, including *E. coli* and *Pasturella*	Includes Bacitracin, which is no longer approved for use at sub-therapeutic dosages.
Quinolones	Chemically synthesized	DNA coiling	Gram-positive Gram-negative	Were used prophylactically. FDA banned use in poultry in 2005.
Sulfonamides	Chemically synthesized	DNA and RNA synthesis	Gram-positive Gram-negative	Used for the treatment of Fowl Typhoid and Pullorum disease.
Streptogramins	*Streptomyces* spp.	Cell wall and protein synthesis	Anerobic bacteria	Virginiamycin belongs to this class of antibiotics and is commonly used at growth promoting concentrations in the feed.
Tetracyclines	*Streptomyces* spp.	Protein synthesis	Gram-positive Gram-negative	Resistance is usually plasmid-mediated with acquisition of an efflux pump or protection from ribosomal protein interference. Tetracyclines can be used to treat disease caused by Vancomycin-resistant bacteria.

In general, antibiotics, growth promotants and synthetic pesticides are not allowed. If the animals are treated with prohibited substances, then their products can no longer be labeled and sold as organic *(9)*. In accordance with those restrictions, the National Organic Standard Board listed under the section 205.603 the synthetic substances allowed for use in organic livestock *(38)*.

Antibiotics and growth promotion

In addition to selective breeding, the discovery of the growth promoting effects of antibiotics in poultry in 1946 by Moore and co-workers *(35)* also significantly affected production. The group was studying the nutritional impact of feeding chicks sulfonamides. Specifically, they were concerned that vitamin availability could be decreased by antibiotic inhibition of certain bacterial groups, with subsequent decrease in growth of the bird. To their surprise, an increase in growth rate was observed for chicks receiving a combination or single doses of sulfasuxadine or streptomycin along with folic acid. They hypothesized that the antibiotics were inhibiting bacteria that produced toxins, such that inhibition of these bacteria lead to an increased growth rate.

The discovery of the growth promoting effects of antibiotics eventually led to their use as a common practice in most food animals, without veterinary prescriptions. Some of the antibiotics were used solely as growth promoters in food animals, including bambermycin, avilamycin, efrotomycin and ionophores (monesin, avilamycin, varasin and lasalocid) *(5)*.

The first reports of antibiotic resistant bacteria followed shortly after the discovery of the growth promoting effects of antibiotics *(50)*. Concerns were not only for resistant zoonotic bacteria and veterinary pathogens, but also for residues that could be present in the raw meat and eggs. Shortly after the appearance of the first cases of antibiotic resistant bacterial diseases in humans, recommendations were made for banning the use of antibiotics as growth promoters, included penicillins, tetracyclines, tylosin and sulfonamides *(53)*. Yet nearly four decades passed before the FDA began enacting antibiotic regulations. In 2005, fluoroquinolones at sub-therapeutic levels were prohibited in poultry production *(19)*. In 2012, severe limitations were placed on the use of cephalosporins in food animals *(22)*. Since then, concern about the increase of multi-drug resistant bacteria through the animal production chain has created much debate, promoting development of the organic market. Even before these federal rulings were enacted, the organic poultry niche had developed, partly driven by concerns over antibiotic use in food animals.

Use of antibiotics in poultry and its impact on consumers

Antibiotic resistance. Antibiotic resistance begins with the exposure of bacteria to an antibiotic agent, leading to the elimination of sensitive bacteria and selecting for resistant populations. However, the dissemination and selection of resistance is a complex matter that causes a serious public health problem. Recent metagenomic studies revealed that although antibiotic resistance has always been present in nature and did not emerge as a consequence of antibiotic usage, antibiotic pressure facilitated rapid and widespread emergence of resistance, including emergence of drug-resistant pathogenic bacteria *(11)*. In the late 1950s, resistance to multiple drugs (MDR) was first detected among enteric bacteria, including *Escherichia coli, Shigella* and *Salmonella.* These zoonotic bacteria can be quite prevalent in poultry, and diseases caused by MDR strains are typically more difficult to treat than those caused by bacteria that are resistant to only one antibiotic *(3, 6)*. The most common pathway for bacteria to acquire resistance is through mobile genetic elements, including bacteriophages, plasmids, naked DNA or transposons. Plasmid-mediated gene transference facilitates the flow of resistant genes between bacteria, accelerating the acquisition of antibiotic resistance *(10)*. Resistance can also be acquired through sequential mutations in the chromosome, as is the case for fluoroquinolone resistance. When antibiotics are administered for more than 10 days, bacteria may become resistant to that antibiotic as well as other antibiotics. As an example, 2 days after the administration of tetracycline to chickens, tetracycline-resistant *E. coli* can be isolated from fecal samples, and within 2 weeks, *E. coli* becomes resistant not only to tetracycline but also to multiple other drugs *(28)*.

Therapeutic levels of antibiotics are typically delivered in the water because even when animals reduce feed intake, they continue to drink. However, sub-therapeutic doses are almost always delivered in the feed. This difference in delivery can also have an impact on resistance. When birds are given therapeutic doses of tylosin (0.53 g/L), *Campylobacter* populations are significantly decreased, but this dosage does not select for resistant mutants *(30)*. However, at growth promoting levels (0.05g/Kg), resistance does emerge *(30)*.

Once the administration of antibiotics ceases, the loss of resistance is a slow process *(49)*. Even after the antibiotic is removed from the environment, some bacteria populations can retain their antibiotic resistance for extended periods of time *(33)*. Although fluoroquinolone usage was banned in poultry production in 2005, resistant *Campylobacter* can still be isolated today, because fluoroquinolone resistance confers a fitness advantage to this pathogen in the absence of antibiotic pressure *(33)*. However, the opposite is true for resistance to macrolides *(32)*. It appears that the gene mutation that confers resistance to macrolides may reduce growth ability, although it is not fully understood how the *gyr*A mutation resulting in fluoroquinolone resistance gives *Campylobacter* a competitive advantage. What is known is that the multidrug efflux pump works synergistically with *gyr*A mutations, reducing the concentration of fluoroquinolones within the cell *(29, 42)*. *In vivo* studies in poultry models have demonstrated how fluoroquinolone-resistant *Campylobacter* strains are able to persist in the natural host even in the absence of antibiotic pressure *(33)*.

One of the impacts of usage of antimicrobials is modulation of microbial populations, which can be beneficial or can have harmful consequences. It is known that indigenous microbiota provide barriers against pathogenic bacteria and infection *(43)*. Antimicrobials can disrupt the microbial barrier, favoring the colonization of harmful bacteria and reducing the recovery time of indigenous microflora. Since sub-therapeutic doses tend to stabilize the gut microflora, disruptions of the flora are more likely at higher therapeutic doses. Like pathogenic bacteria, the normal microflora may also develop antibiotic resistance. Since many of the genes conferring resistance are on mobile genetic elements, the normal microflora can be a source of antibiotic resistance genes for pathogenic bacteria *(48)*.

Antibiotic residues in retail products. The use of antibiotics therapeutically and sub-therapeutically varies by country, as do regulation of antibiotic usage and the level of enforcement. In those countries with regulations, a withdrawal period is typically required prior to slaughter, because antibiotics can accumulate in the tissues and thus expose consumers to these chemicals *(13)*. The variation in regulation and enforcement of the regulation by countries is apparent when studies are conducted evaluating residue concentrations in poultry meat. A Venezuelan investigation revealed that of 20 samples, 50% were positive for residues at concentrations that exceeded the maximum limit of residues allowed in poultry meat *(45)*. The Iran Veterinary Organization, conducting research in the Teheran Province, reported that of 270 samples, 24 (8.8%) were positive for residues *(44)*. In Saudi Arabia, 35% of the samples of broiler meat were positive for residues *(1)*. A study conducted in the Dominican Republic found 6.6% of broiler meat samples and nearly half of the eggs sampled were positive for residues *(46)*. In the U.S., regulations are strongly enforced and meats are continuously monitored and tested for antibiotic residues. In 2010, the USDA Food Safety Inspection Service reported that no residues were detected in 319 samples of chicken meat *(56)*.

Regulations concerning broilers and layers differ depending on the drug. Ionophores, for example, can be used in broilers but not in layers. Some drugs, including Enrofloxacin, are not approved for use in layers or broilers. Enrofloxacin, a commonly used quinolone, is de-ethylated to ciprofloxacin *in vivo*. Ciprofloxacin is used in human medicine because it is active against several zoonotic pathogens, including *Salmonella, Campylobacter* and *Shigella*; therefore, administration of Ciprofloxacin can begin prior to precise diagnosis *(41)*. However, *Campylobacter* and *Salmonella* frequently colonize poultry, and administration of Enrofloxacin to poultry has led to selection for resistant strains of pathogens, jeopardizing human treatment with Ciprofloxacin *(60)*.

In the U.S., antibiotics must be withdrawn prior to slaughter for a specific amount of time (28 days for poultry meat) in order to eliminate residues from the meat. For eggs, any eggs laid while antibiotics are administered, as well as eggs laid after withdrawal for a specific amount of time (7 days for eggs laying hens), cannot be used as food. Several studies have demonstrated contamination of poultry tissues, liver, egg breast, with antibiotic residues at harmful concentrations leading to allergic hypersensitivity reactions or toxic effects. Penicillin residues are the most frequently cited causes of allergic reaction in persons who consume animal products containing residues *(14)*. Other antibiotics, including tetracyclines, sulphonamides and aminoglycosides, can also cause allergic reactions *(51)*. Aminoglycosides (e.g., streptomycin) can cause varying degree of nephrotoxicity and ototoxicity as well as muscular paralysis that may affect respiratory muscles.

Organic production

Van Loo and co-workers *(58)* conducted a consumer survey and reported that the main motivating factor for buying organic chicken is the perception that organic chicken has fewer residues (pesticides, hormones, antibiotics), is safer, and is a healthier food than conventionally produced chicken. In this survey, nearly all the consumers that only purchased organic chicken were opposed to the use of antibiotics in production. Similarly, Demeritt and co-workers *(12)* reported that 54% of consumers of organic foods purchased organic eggs for similar reasons. This notion has driven significant growth in the production of organic poultry and eggs.

Organic chicken is the most widely available organic meat. In 2008, more than 9.0 million certified organic broilers and more than 5.5 million certified organic layer hens *(55)* were produced. In that same year, 398.5 thousand certified organic turkeys were produced. Sales of organic meat and poultry grew from $33 million in 2002 to an estimated $121 million in 2004, and this growth trend has continued. Similarly, organic egg sales in 2004 were $140 million, increasing in 2005 to $161 million, with an estimated annual growth ranging from 8 to 13% *(39)*.

However, consumers of organic meat and eggs pay a premium for these products. Organic broiler prices ranged from $2.21 to $2.48 per pound in 2008, versus $0.74 to $0.85 per pound for conventional broilers. Similarly, prices for organic eggs ranged from $2.37 to $2.78 per dozen while prices for conventional eggs ranged from $0.98 to $1.55 per dozen *(55)*.

Certified organic poultry products are regulated by the National Organic Program/USDA *(38)*. Rearing organic birds requires that the birds (1) are not exposed to antibiotic or chemicals; (2) have access to outdoors; and (3) are fed certified organic feed. To become organically certified, a USDA certifying agent reviews the written organic system plan and inspects the farm. The USDA's Agricultural Marketing Service proposed free-range as another label standard, which must not be confused with certified organic. The label free-range is defined as any chicken raised with access to outdoors, not necesarilly under the organic program *(38, 57)*.

To provide birds with access to outdoors, different housing systems can be used. A permanent structure that is similar to conventional housing can be used, but it must have a door for outdoor access. Free-range types of systems may use a small housing structure in which the birds are not restricted by a fence and the house provides shelter at night and from inclement weather. Portable houses, another option, are usually lightweight and enclosed but are moved to fresh grass periodically *(38)*.

Advantages and disadvantages of poultry organic production. Organic animal systems require animal housing, management and feeding that will promote animal health and keep the level of disease low *(2)*. In spite of preventive treatments, health problems are present, and some are more common in organic than in conventional farms. Poultry and laying hens raised under organic conditions are more likely to be exposed to potential zoonotic pathogens such as *Salmonella* and *Campylobacter* and therefore to increased chances of egg and meat contamination. In addition, infections caused by ubiquitous pathogens, including *Mycoplasma* spp., can increase mortality and economic losses in organic production *(7)*. Since antibiotics are not permitted in organic production, other preventive methods must be used. Organic regulation permits the use of vaccines as preventative measures *(4)*. Other alternative treatments, including herbs, homeopathic drugs and probiotics, are available, although their effectiveness is slight. Beyond the health problems, other problems, such as behavioral disorders, can appear because of the access to outdoors and exposure of poultry and layers to potential predators *(59)*. Some studies report a higher incidence of cannibalism and feather pecking, mainly in layers, because beak trimming is not allowed in organic systems *(27, 47)*.

The higher mortality rates and the long rearing period in organic systems (81 days vs 42 days) are factors that increase the price on the market. But in general the higher production cost of organic poultry than of poultry raised by conventional systems is mainly attributed to the prices of the organic cereals and soybeans that are 50–100% more expensive than conventional feed *(55)*. However, many consumers are willing to pay the higher prices. In 2007, the American Meat Institute and the Food Marketing Institute surveyed organic consumers and reported that better health, more nutritive benefits, better animal welfare and better taste are the main reasons that drive them to purchase organic products *(24)*. In general, the term "organic" can be confusing for many consumers, who assume that organic products are safer because consumers perceive that the rearing system is more natural *(40, 52)*. However, for poultry producers, the increasing demand for organic products and their high price in the market make switching to organic production more appealing. Few studies have compared the profitability of organic vs. conventional rearing systems. However, Cobanoglu and coworkers *(8)* conducted a one-year study in Turkey in which they observed that even with high production costs, organic meat production was more profitable than conventional, with a net income and gross margin of 230% and 180%, respectively for organic and conventional.

Conclusions and future considerations

Large producers in the U.S. have noticed the growth of the organic poultry market and were aware that subtherapeutic antibiotic usage was a large driving force for the organic market growth. For this reason, large companies began launching lines of chicken products raised without antibiotics. Large restaurant chains, also aware of consumer preferences, are purchasing or implementing plans to acquire only chicken that has been raised without antibiotics.

Regardless of consumer preferences, the public health threats that have arisen from antibiotic usage in food animals drove the EU to ban sub-therapeutic antibiotic practices. Likewise, the FDA has also issued guidelines to reduce and eventually phase out the use of antibiotics as growth promoters in animal production *(23)*. Although antibiotic usage in conventional production does partially drive organic sales, consumers also have additional reasons for organic poultry purchases *(9)*. Thus, how or if the cessation of use of antibiotics for growth promotion in conventional poultry will affect sales of organic poultry is not known.

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