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Growth promoter in broiler and pig production

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Abstract. The pressure for reducing the use of antibiotic growth promoters (AGP) in livestock is an irreversible process, and several countries are adhering to the restrictions on AGP usage. Sweden was the first country that changed laws of AGP usage, and the USA is not only limiting AGP use but also moving towards a significant reduction of general antibiotics usage. The increasing pressure to prohibit the use of these additives is based on the possibility of allergic reactions and induction of cross-resistance of pathogenic bacterial strains in people. In broiler and pig production the AGP is used with the objective of obtaining better results of weight gain and feed conversion. However, considerable variability in performance response to AGP has been observed, contingent on genetic potential, phase of rearing, as well as hygiene and management practices. It is clear that AGP restrictions in the production of animal food are a growing process and therefore its consequences must be evaluated, including its effect on animal performance and the economic results of such restriction. Noting these considerations, the purpose of this review is to disseminate relevant information about the use of antibiotic growth promoters in broiler and pig production.

Keywords: additive, biosafety, feed conversion, nutrition, performance

Promotor de crescimento na produção de frangos e suínos

Resumo. A pressão para reduzir o uso de antibióticos promotores de crescimento (AGP) na pecuária é um processo irreversível, e vários países estão aderindo às restrições ao uso de AGP. A Suécia foi o primeiro país que mudou as leis de uso de AGP, e os EUA não estão apenas limitando o uso de AGP, mas também caminhando para uma redução significativa no uso geral de antibióticos. A crescente pressão para proibir o uso desses aditivos baseia-se na possibilidade de reações alérgicas e indução de resistência cruzada de cepas bacterianas patogênicas em pessoas. Na produção de frangos e suínos, o AGP é utilizado com o objetivo de obter melhores resultados de ganho de peso e conversão alimentar. No entanto, foi observada uma variabilidade considerável na resposta do desempenho ao AGP, dependente do potencial genético, da fase de criação e das práticas de higiene e manejo. É perceptível que as restrições de AGP na produção de alimentos para animais são um processo crescente e, portanto, suas consequências devem ser avaliadas, incluindo seu efeito no desempenho animal e os resultados econômicos. Observando essas considerações, o objetivo desta revisão é disseminar informações relevantes sobre o uso de antibióticos promotores de crescimento na produção de frangos e suínos.

Palavras chave: aditivo, biossegurança, conversão alimentar, nutrição, desempenho

Promotor del crecimiento en la producción de pollos de y cerdos

Resumen. La presión para reducir el uso de antibióticos que promueven el crecimiento (AGP) es un proceso irreversible, y varios países se están adhiriendo a las restricciones sobre el uso de AGP. Suecia fue el primer país en cambiar las leyes de uso de AGP, y Estados Unidos no solo está limitando el uso de AGP, sino que también está reduciendo significativamente el uso general de antibióticos. La creciente presión para prohibir el uso de estos aditivos se basa en la posibilidad de reacciones alérgicas e induce resistencia cruzada de cepas bacterianas patógenas en las personas. En la producción de pollos y cerdos, se usa AGP para obtener mejores resultados de aumento de peso y conversión alimenticia. Sin embargo, se observó una variabilidad considerable en la respuesta de desempeño al AGP, dependiendo del potencial genético, la fase de reproducción y las prácticas de higiene y manipulación. Es notable que las restricciones AGP en la producción de alimentos para animales es un proceso creciente y, por lo tanto, sus consecuencias deben ser evaluadas, incluido su efecto sobre el rendimiento animal y los resultados económicos. Observando estas consideraciones, el propósito de esta revisión es difundir información relevante sobre el uso de antibióticos que promueven el crecimiento en la producción de pollos y cerdos.

Palabras clave: aditivo, bioseguridad, conversión alimenticia, nutrición, rendimiento

Introduction

Antimicrobial additives have been used since the 1950s and are an important alternative to allow adequate productivity for animals raised under increasingly intensive conditions. As a consequence of the widespread use and results of AGP in livestock production, there is interest in the study of these additives by meet industry and the academic community. A total of 68.200 publications are presented as results when using the words “broiler” and “antibiotic” in a database search. And the result is 175.000 when the words "swine" and "antibiotic" are used. As seen, the number of publications on the subject is extensive, but studies are conducted with variations in location, management, environmental conditions, nutrition, active principle of the AGP, etc., which variations may be connected to the contradictory results found in performance of broilers and pigs. Many studies have shown no difference in weight gain among animals receiving or not receiving AGP, but results reporting the effectiveness of the antibiotic as a growth promoter are also reported, with positive effects on weight gain. Contradictory results are also observed in the feed intake and feed conversion variables (Albino et al., 2006; Aristides et al., 2012; Attia et al., 2011).

On the other hand, it seems to be unequivocal the efficiency of AGP in improving feed conversion (Baurhoo et al., 2007; Cho et al., 2013) and weight gain (Cravens et al., 2013) when there is a health challenge. The effect observed by the addition of AGP in pig feed is similar to the effect observed in broilers for the variables weight gain, feed intake and feed conversion. Pigs that are not exposed to sanitary challenge and receive AGP have weight gain similar to or greater than those that do not receive AGP (Santana et al., 2015; Valchev et al., 2009; Yoon et al., 2014). Currently, antibiotic growth promoter (AGP) is the main feed additive used in animal production and are linked to improvements in animal performance.

The animal feed industry has undergone significant changes to adapt to new market demands. Consumers want chickens and pigs to be raised without the use of chemical additives in feed, and AGP is a pressured class by public opinion. The increasing pressure to ban the use of these additives as growth promoters in animal feed is based on the possibility of allergic reactions and cross-resistance induction of pathogenic bacterial strains in humans (Roca et al., 2015). Countries such as the European Union have specified laws that prohibit the use of antibiotics as growth promoting additives (USDA, 2010). Tetracyclines, penicillins, chloramphenicol, systemic sulfonamides, furazolidone, nitrofurazone and avorpacin were banned as feed additives in Brazil (MAPA, 2018). Recently, in 2016, the Ministry of Agriculture, Livestock and Food Supply of Brazil regulated the prohibition of the use of colistin sulfate as a growth promoter for poultry, swine and cattle.

Antibiotic growth promoter and antibiotics: a brief history

Antibiotic is defined by the World Health Organization as any substance of natural, synthetic or semi-synthetic origin, which in low concentrations destroys or inhibits the growth of microorganisms, causing little or no damage to the host organism. Antibiotic growth promoter is defined as antibiotic agents used to increase daily weight gain or feed efficiency in food-producing animals (WHO, 2003). The history of antibiotics begins with synthetic sulfonamides in 1935 when Gerhard Domagk announced in a brief publication about Prontosil (sulfochrysoidine) (Lesch, 2007). In 1948, sulfaquinoxaline was the first antibiotic to be officially licensed for inclusion in poultry feed against coccidiosis. In the mid-1950s, new uses of antibiotics were widespread; Streptomycin sprays and solutions were used to treat and prevent bacterial infections, while tetracycline preservatives retarded spoilage in animal foods in the United States (Kirchhelle, 2018).

Investigating antibiotic fermentation residues as an alternative source of vitamin B12-rich dietary supplements, researchers found that antibiotic residues would be able to increase animal weight gain, and it was believed that eating low-dose antibiotics would protect against bacterial diseases (Finlay & Marcus, 2016). The AGP was officially licensed in 1951 and rapidly introduced into animal production. Feeds with growth-promoting antibiotics were adopted in the poultry sector, and large-scale integrated production facilities have been developed, facilitated by the routine use of antibiotics and AGP (Tessari & Godley, 2014). Pig farmers were more resistant to the use of AGP because the rearing structures were smaller and the management more varied. However, the situation changed over the years, and by 1958 it was estimated that up to 50% of pigs in Europe received AGP and that most weaners had access to feed containing tetracycline. The German Minister of Agriculture estimated that 80% of the feed for young pigs, calves, and poultry contained AGP (Kirchhelle, 2016).

Following US development policy, antibiotics were taken to cattle ranching in Africa, South America, and Southeast Asia, where governments were willing to modernize agriculture to leverage the economy. This spread of antibiotics first raised little concern, and during the 1940s and 1950s, Americans and Soviets considered agricultural antibiotics as an effective way to increase animal productivity (Kirchhelle, 2018). In Brazil, the growth of grain production promoted an increase in intensive farming, combined with the use of antibiotics. Between 1968 and 1998, chicken production increased 20-fold and became increasingly intensive. Until 2010, 90% of birds in Brazil were produced in confined environments. Pig production has also intensified and, as a consequence, in 2010, Brazil accounted for 9% of world consumption of agricultural antibiotics. In the same year, China became the world's largest consumer of agricultural antibiotics, consuming about 23% of the world's antibiotics (Van Boeckel et al., 2015).

The idea of antibiotic and AGP use has slowly and fragmentarily changed with increasing concern about antibiotic residues and bacterial resistance (Kirchhelle, 2018). Under intense pressure, the US Food and Drug Administration (FDA) introduced the first national milk penicillin residue monitoring program in 1960 (Smith-Howard, 2017). Six years later, public concerns and waste detections resulted in the first national meat antibiotic monitoring program. Also, in 1960, Britain's Public Health Laboratory Service issued data on increased bacterial resistance in agricultural environments and led to the creation of the so-called Netherthorpe Committee. The committee report in 1962 suggested maintaining the use of existing antibiotics but recommended restrictions on new antibiotics (Kirchhelle, 2018).

With the discovery of bacterial resistance transfer forms, the British commissioned a comprehensive review of antibiotics in 1968. In November 1969, the Swann Committee recommended a series of reforms, and the restriction of antibiotics of medical relevance and veterinary prescription was the most severe and significant (Martin, 2007). Restrictions on certain AGP, such as penicillin and tetracyclines, were later adopted by Great Britain (1971), member states of the European Community (1976) and Switzerland (1973) (Castanon, 2017; Kirchhelle, 2018). In Sweden, AGP restrictions had been introduced in 1977 and, in contrast to other countries, Swedish farmers proactively reacted and called for a total ban on the use of AGP, which occurred in 1986 (Andersen, 2018). Sweden campaigned for a complete ban on AGP, and following the mad cow disease crisis, EU Member States established the European Antibiotic Resistance Surveillance System in 1998, and AGP was banned in 2006 (Kahn, 2017; Kirchhelle, 2016). In Japan, regulators reacted to EU reforms by banning avoparcin and orienticin additives in 1997 and recently announced that they will ban general antibiotic use by 2020 (Kirchhelle, 2018). The use of agricultural antibiotics in the US has recently declined (FDA, 2017), but the therapeutic and prophylactic use of antibiotics in animal production remains legal.

The episode of resistance conferred by the mcr^{-1} gene in 2015 resulted in a ban on colistin in Brazil and China (Cardoso, 2019; Walsh & Wu, 2016). Vietnam has announced that it will ban the use of AGP by 2020 (USDA, 2016). India has also developed an action plan for antibiotic reductions and introduced withdrawal times for livestock production (Kahn, 2017; Kirchhelle, 2018). And in response to initiatives from the World Health Organization, Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste are introducing policies to reduce the use of AGP and to combat antibiotic resistance, including surveillance, training of professionals and farmers, and the establishment of independent national drug regulatory authorities (Goutard et al., 2017).

Supply chain regulation and the reduction of antibiotic and PCA consumption will require global solutions with medium- and long-term, flexible and transparent assessment measures (Kirchhelle, 2018). Recent WHO plans for bacterial resistance control and increased surveillance of antibiotic use are an important step but require global dissemination and adherence (FAO, 2016) and the One Health approach will facilitate the development of global actions across sectors (Dar et al., 2016).

Possible mode of action of antibiotic growth promoter

It is clearly noticeable that the restriction on the use of AGP in animal production is expanding and it is necessary to understand the mode of action of these additives to search for alternatives as potential substitutes. Rosen (1995) reviewed a total of 12,153 studies conducted on AGP-fed animals and concluded that 72% of AGP generated a positive response to animal performance. The magnitude of the responses was related to animal management, farm disinfection procedures, age of farm structures and feed quality.

Two types of direct action of antibiotics on sensitive bacteria and/or fungi are expected: agent death or growth arrest. In theory, it would be possible to obtain a bactericidal effect of any antibiotic on a sensitive microorganism when its concentration is increased (Kohanski et al., 2007). For an antibiotic to have a growth-promoting effect, the AGP must be incorporated as an ingredient into the feed at dosages below the minimum inhibitory concentration, and capable of effectively improving zootechnical indexes (Jensen et al., 2004; Lorençon et al., 2007).

Although the direct action on microorganisms is elucidated, the effect of AGP on *in vivo* chickens and swine is not fully understood. The mechanisms of action of AGP are complex and act in different ways. Four main mechanisms have been proposed as an explanation for the auxiliary effect on animal growth: inhibition of subclinical infections; reduction of microbiological metabolites that reduce animal growth; reduced nutrient use by unwanted microbiological organisms, and increased absorption and nutrient use by an animal with a thinner-walled gut (Dibner & Richards, 2005; Gaskins et al., 2002).

The control of subclinical diseases is widely accepted, but difficult to prove. The AGP act on bacteria that depress animal growth, but do not cause diagnosable disease. Possibly, chronic stimulation of the immune system, responding to disease, results in the production of reactive intermediates of oxygen, nitric oxide, lysozymes, and free radicals. The generated molecules are harmful to body cells, generating oxidative stress, increasing the demand for nutrients from the diet and not allowing the animal to fully express its genetic potential for growth (Raqib & Cravioto, 2009). Some metabolic, physiological and nutritional responses are reported in Table 1.

The effect of AGP coincides with decreased activity of the bile salt hydrolase (BSH) enzyme (Guban et al., 2006; Knarreborg et al., 2004; Smith et al., 2014). BSH produced by intestinal bacteria catalyzes the conjugation of conjugated bile acids (CBA) in the gut (Begley et al., 2006). CBAs are made up of a hydrophobic steroid nucleus that is conjugated to glycine or taurine. Thus, CBA is amphipathic and acts as a more efficient detergent than deconjugated bile acids to emulsify and solubilize lipids for fat digestion (Begley et al., 2006). Consequently, BSH activity has a significant impact on animal nutrition by modifying CBA-mediated fat metabolism and endocrine functions (Begley et al., 2006; Jones et al., 2008). Guban et al. (2006) correlated AGP dietary supplementation with fat digestibility in broilers, decreased population levels of *Lactobacillus salivarius*, and a reduced pool of deconjugated bile salts. Based on these results, the APC mechanism of action to promote weight gain and improve feed conversion is associated with reduced BSH activity and improved lipid metabolism.

The non-antibiotic anti-inflammatory mechanism of AGP, the theory developed by Niewold, (2007), is the first theory that explains performance observations without the apparent contradictions and inconsistencies associated with other proposed theories. It is well established that many antibiotics have physiological side effects, many of which are specific to the chemical class of the compound. However, what antibiotics have in common is that it can accumulate in inflammatory cells (Labro, 2000; Labro, 1998). Most accumulated antibiotics increase the intracellular death of bacteria and it can inhibit the innate immune response.

Table 1. Metabolic, physiological and nutritional responses associated with antibiotic growth promoter.

Physiologic	Nutricional	Metabolic
Increase		
Nutrient absorption	Energy retention	Liver protein synthesis
Feed intake	Nitrogen retention	Alkaline phosphatase
	Vitamin absorption	
	Trace elements absorption	
	Fatty acid absorption	
	Glucose absorption	
	Calcium absorption	
Decrease		
Intestinal transit time	Loss of energy through the intestine	Ammonia production
Intestinal wall diameter	Vitamin synthesis	Toxica mines production
Intestinal wall lenght		Aromatic phenols
Intestine weight		Fatty acid oxidation
Mucosa cell turnover		Excreted fat
		Microbiota urease

Adapted from Gaskins et al. (2002).

One consequence of intestinal inflammation is increased macromolecular intestinal permeability, which would increase local penetration of low molecular weight antibiotics. Phagocytic cells may accumulate antibiotics, in some cases 10 to 100 times the ambient concentration (Table 2). The relevant effect of this accumulation of many antibiotics on phagocytic inflammatory cells would be attenuation of the inflammatory response. As a consequence, proinflammatory cytokine levels would be lower than those of untreated animals, which would result in less catabolic stimulation (Niewold, 2007).

Antibiotics have been shown to inhibit one or more of several different inflammatory cell functions (Table 2), chemotaxis, production of reactive oxygen species, and production of proinflammatory cytokines. For animal production, cytokine release may be a determining factor, because after cytokine release there is an acute phase response. In addition to a shift in liver protein production to acute-phase protein, muscle tissue catabolism and loss of appetite occur (Gruys et al., 2006).

Table 2. Intra-phagocytic accumulation of antibiotics that may lead to inhibition of phagocytic function.

Antibiotic	Intracellular accumulation (intra: extra cellular ratio)	Inhibition of phagocytic function
Chloramphenicol	4	No
Beta Lactam	<1	Limited
Cyclins	2	Yes
Quinolones	5	No
Macrolids	100	Yes
Streptogramin	40	Yes

Adapted from Niewold (2007).

Intestinal inflammation usually causes the accumulation of inflammatory cells in the mucosa, leading to a thinner intestinal wall. The thinner intestinal wall observed using AGP is consistent with reduced inflammation due to reduced influx and accumulation of inflammatory cells (Larsson et al., 2006). This explains why the effect of AGP is absent from germ-free animals, and why the effects of AGP are greatest when animals are under higher infectious pressure, such as occurs at certain ages, under certain rearing conditions and in certain regions (Page, 2006). And the different microbial compositions using AGP are, in this perspective, a consequence of an altered immune state rather than a direct effect of AGP on the microbiota (Niewold, 2007).

Antibiotic growth promoter in the diet of broilers and pigs

Growth promoters are administered at relatively low concentrations, ranging from 2.5 mg / kg to 125 mg/kg (ppm), depending on drug type and animal species (WHO, 2003). It was estimated that the global average annual antimicrobial consumption per kilogram of animal produced was 148 mg / kg - 1 and 172 mg/kg^{-1} for chickens and swine, respectively (Van Boeckel et al., 2015). Data obtained from 25 pig production systems showed that the average consumption of antimicrobials is 358 mg/kg of pigs produced. The same study estimated that pigs were exposed, on average, 66.3% of their shelf life to antimicrobials in these systems (Dutra, 2017). Antibiotics used as growth promoters in chicken and pig diets are listed in Table 3.

Table 3. Antibiotics used as growth promoters in broiler and pig diets.

Antibiotic	Specie
Avilamycin	Broiler; Pigs
Bacitracin	Broiler; Pigs
Enramycin	Broiler; Pigs
Flavomycin	Broiler; Pigs
Halquinol	Broiler; Pigs
Lincomycin	Broiler; Pigs
Narasin	Pigs
Salinomycin	Pigs
Tiamulin	Pigs
Tylosin	Broiler; Pigs
Virginiamycin	Broiler; Pigs

Adapted from: Bresslau (2017).

The greatest effect of AGP has attributed to improved feed conversion and this response is highest in genetically improved animals, fast-growing animals and animals reared in intensive production systems. Other effects observed with the use of AGP are faster growth rate, reduced mortality, high resistance to disease challenge, increased reproductive performance, and better stool and litter quality.

Broiler chickens at 42 days of age that were not exposed to health challenges presented contradictory weight gain results regarding the removal of APC from the diet. In this situation, many studies have shown no difference in weight gain between animals receiving or not APC. However, results reporting the effectiveness of the antibiotic as a growth promoter were also found, demonstrating positive effects on weight gain (Figure 1). Contradictory results are also observed in the feed intake and feed conversion variables (Peng et al., 2016; Silva et al., 2018; Tayeri et al., 2018). On the other hand, when there is some health challenge, it seems to be unequivocal the efficiency of AGP in improving feed conversion (Baurhoo et al., 2007; Cho et al., 2013) and weight gain (Cravens et al., 2013; Mallet et al., 2005). Using a meta-analysis containing 183 experiments, Cardinal et al. (2019) demonstrated that feed intake showed a better result for broilers receiving AGP in the initial phase, but no effects of AGP were observed in the final and total phases. The weight gain and feed conversion presented better results when broilers were fed AGP diet in the initial and total phases, but no difference between broilers receiving or not AGP was observed in the final phase of rearing.

The effect observed by the addition of AGP in the pig feed is similar to the effect observed on broilers for the variables weight gain, feed intake and feed conversion. Pigs that are not exposed to sanitary challenge and receive AGP presented weight gain equal to or greater than pigs that do not receive AGP (Santana et al., 2015; Valchev et al., 2009; Yoon et al., 2014). When piglets were exposed to health challenge the presence of AGP in the diet resulted in better weight gain and feed conversion (Li et al., 2017; Long et al., 2018). In a meta-analysis, compiling 81 experiments without health challenge, Cardinal et al. (2019) reports that pigs show weight gain rates higher when AGP is present in diets in post-weaning and in overall performance, but no such effect was detected during the growing-finishing phase. And the feed conversion is better in pigs fed AGP diets when compared with diets without AGP in all rearing phases. In Figure 2 it is possible to observe studies demonstrating the weight gain of piglets in the post-weaning period receiving or not AGP in the diet:

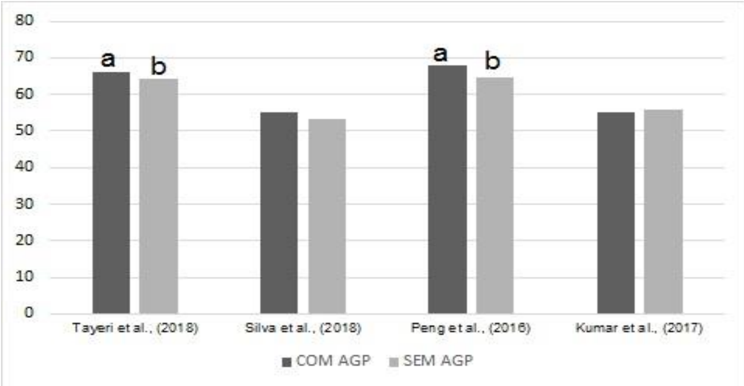

Figure 1. Weight gain of broiler receiving or not antibiotic growth promoter - without health challenge. Com AGP:With AGP; Sem AGP: Without AGP.

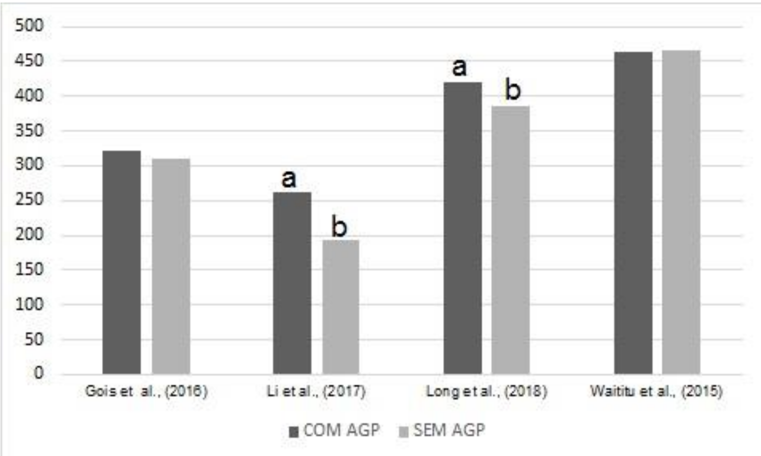

Figure 2. Weight gain of post-weaning piglets with or without antibiotic growth promoter - without health challenge. Com AGP:With AGP; Sem AGP: Without AGP.

Economic impact of withdrawal of antibiotic growth promoter from broilers and pig diets

There are several techniques that can be used to analyze the economic implications of antibiotics on the production system. The choice of technique will depend on many factors, such as the nature of the problem, data availability, and the amount of resources available to perform the analysis (Ryan, 2019).

Some studies estimated the potential economic impact of banning AGP on the US pig industry, and when compared there are large differences in estimates of increased cost per pig: USD 0.59/pig (Miller et al., 2003), US $ 1.37pig (Miller et al., 2005), $ 2.33/pig and $ 4.50/pig (Hayes & Jensen, 2003). This large variation was also observed in studies conducted in Denmark, even estimating the increase of EUR $ 1.04 per pig produced (WHO, 2003). Performing an economic impact estimate using performance data and dietary changes in swine without exposure to health challenges, Cardinal et al. (2019) conclude that the increase in production cost will be a minimum of $ 1.83 in the total creation period.

For chicken production, the National Research Council published an industry impact estimate and concluded that banning the AGP would lead to a 1.76% increase in production costs, resulting in a cost increase for consumers of US $ 2.20 per capita per year (NRC, 1994). Graham et al. (2007) estimated that the net effect of AGP use resulted in an expense of $ 0.0093 per chicken. From these results, the authors found no basis for the claim that the use of AGP reduces the cost of production. However, this study did not include changes in veterinary costs, nor did it consider changes in performance associated with APG removal. In contrast, Cardinal et al. (2019) concluded that the AGP withdrawal in the initial phase and total period, rearing broilers without health challenge, will increase the production cost in $ 0.01 and $ 0.03 per animal.

The results of the economic impact of banning AGP found in the studies may not be applicable in all countries or all farms within a country. As described by some authors, the ban on AGP would affect producers in different ways, changing impact results according to location, property size, contractual arrangements and production practices (MacDonald & Wang, 2011; McBride et al., 2008). Similarly, different management variables and health and sanitation practices were highlighted in studies that described the ban on AGP in 1986 in Sweden (Wierup, 2001).

Farms that produce APC chickens in the US tend to be farms with older structures with less modern equipment and are less likely to follow a security risk management plan (MacDonald & Wang, 2011; McBride et al., 2008). Laanen et al. (2014) demonstrated that improved biosecurity in swine herds can help reduce the amount of prophylactically used antimicrobials and is positively associated with daily weight gain. However, as far as we know, there are no publications of production impact estimates for investing in biosecurity measures and production systems with optimal hygiene conditions.

Conclusions and considerations

Banning the use of antibiotics as growth promoters within animal production has become a key issue, discussed in the consumer market, meat producers and exporters worldwide, and the scientific community. The global trend is to allow the use of antibiotics only for the treatment of animal diseases, abolishing their use as growth promoters. However, the issue of banishment is not easy to solve. Growth promoters are associated with improved feed conversion and reduced mortality, increasing productivity gains. With the immediate rise in production costs, the elimination of AGP from the diet faces resistance from producers and industry. To ban AGP without higher production costs, it is necessary to adopt new strategies within animal production, using programs that involve different management strategies, nutrition, health, as well as biosecurity programs, with efficient management and professional training.

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