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RETIRADA DE ANTIBIÓTICOS PROMOTORES DE CRESCIMENTO DA ALIMENTAÇÃO DE FRANGOS DE CORTE E SUÍNOS E SUA IMPLICAÇÃO NA PRODUÇÃO ANIMAL

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“Quem estará nas trincheiras ao teu lado?
- E isso importa?
- Mais do que a própria guerra.”
Ernest Hemingway

Muito obrigada!

RETIRADA DE ANTIBIÓTICOS PROMOTORES DE CRESCIMENTO DA ALIMENTAÇÃO DE FRANGOS DE CORTE E SUÍNOS E SUA IMPLICAÇÃO NA PRODUÇÃO ANIMAL[1]

Autora: Kátia Maria Cardinal

Orientador: Andréa Machado Leal Ribeiro

Resumo: Este trabalho foi realizado com o objetivo de estimar o impacto produtivo e econômico causado pela retirada dos antibióticos promotores de crescimento (AGP) da dieta de frangos de corte e suínos por meio de uma meta-análise. Foram selecionadas publicações indexadas contendo dados referentes à utilização de AGP (AGP+) ou não (AGP-), em dietas para frangos de corte e suínos. Os resultados de desempenho zootécnico (consumo de ração, ganho de peso e/ou conversão/eficiência alimentar) foram considerados. A metodologia para construção, codificação e análise das bases de dados seguiu as recomendações da literatura específica. Duas meta-análises foram realizadas pelas análises sequenciais: abordagem gráfica (para observar a coerência dos dados biológicos), correlação (para identificar fatores relacionados) e variância-covariância (para comparar grupos). O número anual de frangos e suínos abatidos no Brasil, ganho de peso alvo e conversão alimentar para cada fase, a variação na conversão alimentar, custo de alimentação e custos de AGP foram usados para construir um modelo para estimar os efeitos da retirada AGP sobre os custos de alimentação. Para complementar a análise econômica, uma análise de sensibilidade foi realizada utilizando o preço da ração contendo AGP e a diferença na conversão alimentar entre os tratamentos AGP+ e AGP-. A base de dados de frangos foi composto por 174 artigos científicos contendo 183 experimentos, totalizando 121.643 frangos de corte, sendo a maioria Ross (52% dos estudos). Os AGP mais freqüentes no banco de dados foram avilamicina (41% dos tratamentos AGP +) e flavomicina (19%). Maior consumo de ração, ganho de peso e menor conversão alimentar foram atribuídos ($P < 0,05$) às dietas AGP + na fase inicial (1-21 dias). Na fase final (22-42 dias) não foram observadas diferenças nas variáveis de desempenho ($P > 0,05$). Os tratamentos AGP + apresentaram maior ganho de peso e melhor conversão alimentar no período total (1-42 dias). Os resultados da conversão alimentar foram melhorados ($P < 0,05$) com avilamicina e flavomicina; a virginiamicina melhorou o ganho de peso

e a conversão alimentar. No período total, o impacto econômico foi de US $ 0,03 por animal e um total de US $ 183.560.232 por ano. A base de dados de suínos continha 81 artigos científicos contendo 103 experimentos totalizando 42.923 suínos, a maioria dos quais estavam na fase pós-desmame (70% dos estudos). Os AGP mais freqüentes no banco de dados foram avilamicina (24,7% dos tratamentos AGP +) e Colistina (15,4%). Maior ganho de peso (P < 0,05) foi observado nas dietas AGP + pós desmame e no período total. No entanto, nenhum efeito da AGP sobre o ganho de peso de suínos em crescimento/ terminação foi observado (P > 0,05). Melhor (P < 0,05) conversão alimentar em suínos alimentados com dietas AGP + foi observada no período total de criação. Ganho de peso e conversão alimentar melhoraram (P < 0,05) com a adição de avilamicina, bacitracina e tilosina. O impacto econômico com a retirada do AGP foi de US $ 1,83 por animal e US $ 79 258.694 por ano para a indústria suína brasileira. Concluiu-se que os frangos e suínos alimentados com dietas AGP + apresentam melhor desempenho que aqueles alimentados com dietas AGP -, e que a retirada do AGP aumenta os custos de produção.
Palavras-chave: aditivo, conversão alimentar, custo, análise de sensibilidade

[1] Tese de Doutorado em Zootecnia - Produção Animal, Faculdade de Agronomia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brasil. (103 p.) Março, 2020.

WITHDRAWAL OF ANTIBIOTIC GROWTH PROMOTERS FROM BROILER AND PIG DIETS AND ITS IMPLICATION IN ANIMAL PRODUCTION[1]

Author: Kátia Maria Cardinal

Supervisor: Andréa Machado Leal Ribeiro

Abstract: This work was designed to stimate the productive and economic impact caused by the withdrawal of antibiotic growth promoter (AGP) from the diet of broilers and pigs through a meta-analysis. Indexed publications containing data regarding the use of AGP (AGP+) or not (AGP-) in diets for broilers and pigs were selected. The results of performance (feed intake, weight gain and / or conversion / feed efficiency) were considered. The methodology for building, coding and analyzing the databases followed the recommendations of the specific literature. Two meta-analyzes were performed by sequential analysis: graphical approach (to observe the coherence of biological data), correlation (to identify related factors) and variance-covariance (to compare groups). The annual number of broilers and pigs slaughtered in Brazil, target weight gain and feed conversion for each stage, variation in feed conversion, feed cost and AGP costs were used to build a model to estimate the effects of AGP withdrawal on feeding costs. To complement the economic analysis, a sensitivity analysis was performed using the price of the feed containing AGP and the difference in feed conversion between the AGP+ and AGP- treatments. The broiler database consisted of 174 scientific articles containing 183 experiments, totaling 121,643 broilers, the majority being Ross (52% of the studies). The most frequent AGP in the database were Avilamycin (41% of AGP+ treatments) and Flavomycin (19%). Higher feed intake, weight gain and lower feed conversion were attributed ($P < 0.05$) to AGP+ diets in the initial phase (1-21 days). In the final phase (22-42 days), there were no differences in performance variables ($P > 0.05$). The AGP+ treatments showed greater weight gain and better feed conversion in the Total period (1-42 days). The results of feed conversion were improved ($P < 0.05$) with Avilamycin and Flavomycin; Virginiamycin improved weight gain and feed conversion. In the total period, the economic impact was US $ 0.03 per animal and a total of US $ 183,560,232 per year. The pig database contained 81 scientific articles containing 103 experiments totaling 42,923 pigs, most of which were in the post-weaning phase (70% of the studies). The most frequent AGP in the database were Avilamycin (24.7% of AGP+ treatments) and Colistin (15.4%). Greater

weight gain ($P < 0.05$) was observed in the AGP+ diets after weaning and in the total period. However, no effect of AGP on the weight gain of growing / finishing pigs was observed ($P > 0.05$). Better ($P < 0.05$) feed conversion in pigs fed AGP+ diets was observed in the total rearing period. Weight gain and feed conversion improved ($P < 0.05$) with the addition of Avilamycin, Bacitracin and Tylosin. The economic impact with the withdrawal of AGP was US $ 1.83 per animal and US $ 79 258,694 per year for the Brazilian pig industry. It was concluded that broilers and pigs fed with AGP+ diets perform better than those fed with AGP- diets, and that the withdrawal of AGP increases production costs.
Key Words: additive, feed conversion, productive cost, sensitivity analysis

[1]Doctoral thesis in Animal Science – Animal Production, Faculdade de Agronomia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil. (103 p.) March, 2020.

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LISTA DE ABREVIATURAS E SIMBOLOS

$	Dólar
%	Porcento
AGP	*Antibiotic Growth Promoter*
APC	Antibiótico Promotor de Crescimento
BSH	Enzima sal biliar hidrolase
BWG	Ganho de peso corporal
CBA	Ácidos biliares conjugados
d	Dia
DFVA	"Danish Veterinary and Food Administration"
FCR	Conversão alimentar
FDA	"Food and Drug Administration"
FI	Consumo de ração
g	Grama
GLM	Modelo linear generalizado
IBGE	Instituto Brasileiro de Geografia e Estatística
kg	Quilograma
MAPA	Ministério da agricultura, pecuária e abastecimento
mg	Miligrama
n	Número de observações de cada média
OMS	Organização Mundial da Saúde
P	Probabilidade
R^2	Coeficiente de determinação do modelo
RSE	Erro residual padrão
USD$	Dólar americano

CAPÍTULO I

INTRODUÇÃO

Aditivos antimicrobianos vêm sendo utilizados desde a década de 50, sendo uma alternativa importante para permitir uma produtividade adequada a animais criados sob condições cada vez mais intensivas. Atualmente os antibióticos promotores de crescimento (APC) são os principais aditivos usados na alimentação animal e estão conectados a melhorias na produtividade animal (Brown et al., 2016).

Quando é realizada uma busca no Google® acadêmico com as palavras “broiler” e “antibiotic” são apresentados como resultados 68.200 publicações e quando são utilizas as palavras “swine” e “antibiotic” o resultado é de 175.000. Como visto, o número de publicações sobre o tema é extenso, porém os estudos são realizados com variações em local, manejo, condições de ambiência, nutrição, princípio ativo do APC, etc, variações essas que podem estar ligadas aos resultados contraditórios encontrados para variáveis de desempenho de frangos e suínos. Muitos estudos demonstraram não ocorrer diferença no ganho de peso entre animais recebendo ou não APC, porém também foram encontrados resultados relatando a eficiência do antibiótico como promotor de crescimento, com efeitos positivos no ganho de peso. Resultados contraditórios também são observados nas variáveis de consumo de ração e conversão alimentar (Albino et al., 2006; Attia et al., 2011; Aristides et al., 2012). Por outro lado, com ocorrência de desafio sanitário parece ser inequívoca a eficiência dos APC na melhoria da conversão alimentar (Baurhoo et al., 2007, Cho et al., 2014) e do ganho de peso (Cravens et al., 2013). Para suínos o efeito observado pela adição de APC na ração para as variáveis ganho de peso, consumo de ração e conversão alimentar é similar ao efeito observado em frangos. Os suínos que não são expostos a desafio sanitário e recebem APC apresentam ganho de peso igual ou superior aos que não recebem APC (Valchev et al., 2009; Yoon et al., 2014; Santana et al., 2014).

A indústria de alimentação animal tem passado por mudanças significativas, no sentido de adequar-se às novas exigências do mercado. Por parte dos consumidores há o desejo que frangos e suínos sejam criados sem o uso de aditivos nas rações, e a classe mais pressionada pela opinião pública é a dos APC (Santana, 2011). A crescente pressão para proibir o uso destes aditivos como promotores de crescimento em rações animais é baseada na possibilidade de reações alérgicas e indução de resistência cruzada de cepas bacterianas patogênicas ao homem (Baurhoo et al., 2009).

Países como os da União Européia especificaram legislações que proíbem o uso de antibióticos como aditivos promotores de crescimento (DFVA, 2010). No Brasil, as tetraciclinas, penicilinas, cloranfenicol, sulfonamidas sistêmicas, furazolidona, nitrofurazona e avorpacina já foram proibidas como aditivos de ração (Nunes, 2008). Recentemente, em 2016, o Ministério da Agricultura Pecuária e Abastecimento normatizou a proibição do uso do sulfato de colistina como promotor de crescimento para aves, suínos e bovinos.

O banimento do uso de APC na produção de frangos e suínos possui consequências que devem ser consideradas, como a sanidade do rebanho e perdas produtivas. Sendo que há um número extenso de trabalhos já publicados sobre o tema com resultados contraditórios, a análise sistemática das publicações permitirá otimizar as informações já disponíveis na literatura, respondendo questões específicas sem despender recursos com estudos adicionais com animais. A meta-análise aumentará a acurácia das estimativas de efeito, especialmente pela diversidade nos protocolos de pesquisas, gerando conclusões com maior precisão analítica e ajustada à diversidade experimental. A aplicação das metodologias de bioinformática permitirá a investigação das perdas produtivas e a estimação empírica da eficiência de utilização de nutrientes de suínos e frangos de corte. Desta forma, os objetivos deste estudo são: quantificar as diferenças de desempenho em frangos de corte e suínos recebendo dietas com e sem APC por meio de uma meta-análise e estimar o impacto econômico consequente da retirada do APC da alimentação.

REVISÃO DE LITERATURA

Antibióticos e antibióticos promotores de crescimento: um breve histórico

Antibiótico é definido pela Organização Mundial de Saúde como toda substância de origem natural, sintética ou semissintética, que em baixas concentrações destrói ou inibe o crescimento de microrganismos, causando pequeno ou nenhum dano ao organismo hospedeiro. Já os antibióticos promotores de crescimento (APC) são definidos como agentes antibióticos utilizados com o propósito de aumentar o ganho de peso diário ou a eficiência alimentar em animais produtores de alimentos (WHO, 2000).

A história dos antibióticos agrícolas começa com as sulfonamidas sintéticas em 1935, quando um farmacêutico alemão comercializou Prontosil (sulfochrysoidine) (Lesch, 2007). Em 1948, a sulfaquinoxalina foi o primeiro antibiótico a ser oficialmente licenciado para inclusão em rações para aves contra a coccidiose. Em meados da década de 50, novos usos dos antibióticos foram disseminados; sprays e soluções de estreptomicina foram usados para tratar e prevenir infecções bacterianas, enquanto os conservantes de tetraciclina retardavam a deterioração em alimentos de origem animal nos Estados Unidos (Kirchhelle, 2019).

Investigando os resíduos de fermentação antibiótica como uma fonte alternativa de suplementos alimentares ricos em vitamina B12, pesquisadores descobriram que os resíduos antibióticos seriam capazes de aumentar o ganho de peso de animais, e acreditava-se que a alimentação com baixas doses de antibióticos protegesse contra doenças bacterianas (Finlay e Marcus, 2016). Os APC foram oficialmente licenciados em 1951 e inseridos rapidamente na produção animal. Rações com APC foram adotadas no setor avícola e houve o desenvolvimento de instalações de produção integrada em larga escala, facilitada pelo uso rotineiro dos antibióticos e APC (Thoms, 2012; Tessari e Godley, 2014). Os produtores de suínos foram mais resistentes ao uso de APC, pois as estruturas de criação eram menores e os manejos de criação mais variados. Porém, a situação foi sendo alterada ao longo dos anos e em 1958 estimava-se que até 50% dos suínos da Europa recebiam APC e que a maioria dos leitões desmamados tinham acesso a alimentos contendo tetraciclinas.

Poucos anos mais tarde, o Ministro da Agricultura da Alemanha estimou que 80% dos alimentos para suínos jovens, bezerros e aves continham APC (Kirchhelle, 2016).

Seguindo a política de desenvolvimento dos EUA, os antibióticos foram levados para a pecuária da África, América do Sul e Sudeste da Ásia, onde os governos estavam dispostos a modernizar a agricultura com o objetivo de alavancar a economia. Essa grande disseminação dos antibióticos provocou poucas preocupações inicialmente, e durante as décadas de 1940 e 1950, americanos e soviéticos consideravam os antibióticos agrícolas como uma maneira eficaz de aumentar a produtividade animal (Kirchhelle, 2019). No Brasil, o crescimento da produção de grãos promoveu um aumento da criação intensiva, aliada ao uso de antibióticos. Entre 1968 e 1998, a produção de frango aumentou 20 vezes e se tornou cada vez mais intensiva. Até 2010, 90% das aves no Brasil eram produzidas em ambientes confinado (Silbergeld, 2016). A produção de suínos também se intensificou e, como consequência, em 2010, o Brasil foi responsável por 9% do consumo mundial de antibióticos agrícolas (Van Boeckel et al., 2015). No mesmo ano, a China se tornou o maior consumidor mundial de antibióticos agrícolas, consumindo uma parcela aproximada de 23% dos antibióticos mundiais.

A ideia quanto ao uso de antibióticos e APC mudou, de forma lenta e fragmentada, com a crescente preocupação com resíduos de antibióticos e com a resistência bacteriana (Kirchhelle, 2019). Sob intensa pressão, a instituição americana para administração de Alimentos e Medicamentos (FDA) introduziu o primeiro programa nacional de monitoramento de resíduos de penicilina no leite em 1960 (Smith-Howard, 2010). Seis anos depois, preocupações públicas e detecções de resíduos resultaram no primeiro programa nacional de monitoramento de antibióticos na carne. Também em 1960, o Serviço de Laboratório de Saúde Pública da Grã-Bretanha emitiu dados sobre aumento da resistência bacteriana em ambientes agrícolas e levaram à criação do chamado Comitê de Netherthorpe. O relatório do comitê, em 1962, sugeriu a manutenção do uso de antibióticos existentes, porém recomendou restrições sobre os novos antibióticos (Kirchhelle, 2019).

Com o descobrimento das formas de transferência de resistência bacteriana, os britânicos encomendaram uma vasta revisão sobre antibióticos em 1968. Em novembro de 1969, o Comitê Swann recomendou uma série de reformas, das quais a restrição de antibióticos de relevância médica e de prescrição veterinária foi a mais significativa (Bud, 2009; Swann, 1969). Restrições a certos APC, como a penicilina e as tetraciclinas, foram posteriormente adotadas pela Grã-Bretanha (1971), estados membros da Comunidade Européia (1976) e Suíça (1973) (Lebek e Gubelmann, 1979; Castanon, 2007). Na Suécia, as restrições APC haviam sido introduzidas em 1977 e, em contraste com outros países, os agricultores suecos reagiram de forma proativa e pediram a proibição total do uso dos APC, que aconteceu em 1986 (Andersen, 2018; Kahn, 2016). A Suécia fez campanhas para proibição ampla dos APC e, após a crise da doença vaca louca, os Estados-membros da União Europeia estabeleceram o Sistema Europeu de Vigilância da Resistência aos Antibióticos em 1998, e os APC foram banidos em 2006 (Kirchhelle, 2016; Kahn, 2016). No Japão, os reguladores reagiram às reformas da UE banindo os aditivos avoparcina e orienticina em 1997, e anunciando recentemente que banirão o uso geral de antibióticos até 2020 (Milanov et al., 2016; Anon., 2017). O uso de antibióticos agrícolas nos EUA diminuiu recentemente (FDA, 2017), porém o uso terapêutico e profilático de antibióticos na produção animal permanece legal.

O episódio de resistência conferido pelo gene mcr-1 em 2015 resultou na proibição da colistina no Brasil e na China (Walsh e Wu, 2017; Davies e Walsh, 2018). Já o Vietnã anunciou que reduzirá o número de antibióticos para 15 e proibirá o uso de APC até 2020 (USDA, 2016). A Índia também desenvolveu um plano de ação para reduções de antibióticos e introduziu tempos de retirada de medicamentos para a produção de gado (Kahn, 2016). E como reação das iniciativas da Organização Mundial da Saúde, Bangladesh, Butão, Indonésia, Mianmar, Nepal, Sri Lanka e Tailândia também anunciaram restrições aos antibióticos agrícolas (Goutard, 2017).

A regulamentação das cadeias de suprimento e a redução do consumo de antibióticos e APC exigirão soluções de nível global com medidas de médio a longo prazo, flexíveis e sujeitas a avaliação transparente (Kirchhelle, 2019). Planos recentes da OMS para controle da resistência bacteriana e a vigilância no uso de antibióticos são um passo importante, mas que requerem divulgação e adesão global (OMS, 2017).

Possíveis mecanismos de ação dos antibióticos promotores de crescimento

É claramente perceptível que a restrição ao uso de APC na produção de animais está se expandindo e é necessário compreender os mecanismos de ação desses aditivos para buscarmos alternativas como potenciais substitutos. Rosen (1995) revisou um total de 12.153 estudos conduzidos em animais alimentados com APC e concluiu que 72% dos APC geraram resposta positiva no desempenho animal. A magnitude das respostas foi relacionada ao tipo de manejo animal, aos procedimentos de desinfecção, à idade das estruturas da fazenda e à qualidade da ração.

Dois tipos de ação direta dos antibióticos sobre as bactérias e/ou fungos sensíveis são esperados: a morte do agente ou a parada do seu crescimento. Em teoria, seria possível obter efeito bactericida de qualquer antibiótico sobre um micro-organismo sensível quando a sua concentração é aumentada (Tavares, 1990; Mellor et al., 2000). Para um antibiótico funcionar como promotor de crescimento, este deve ser incorporado como ingrediente à ração em dosagens abaixo da concentração inibitória mínima, capazes de melhorar de forma efetiva os índices zootécnicos (Lorençon et al., 2007).

Apesar da ação direta sobre os micro-organismos estar esclarecida, o efeito dos APC *in vivo* em frangos e suínos ainda não está completamente esclarecido. Os mecanismos de ação dos APC são complexos e atuam de diferentes maneiras. Quatro principais mecanismos de ação foram propostos como explicação para o efeito de auxiliar no crescimento animal: inibição de infecções subclínicas; redução de metabólitos microbiológicos que prejudicam o crescimento; redução do uso de nutrientes por organismos microbiológicos indesejados, e o aumento da absorção e do uso de nutrientes por um animal que possui intestino com paredes mais finas (Gaskins et al., 2002; Dibner e Richards, 2005; Page, 2006).

O controle de infecções subclínicas é bastante aceito, porém de difícil comprovação. Os APC agem sobre bactérias que provocam doenças não diagnosticáveis, mas que de alguma maneira deprimem o crescimento do animal. Possivelmente, a estimulação crônica do sistema imunológico, respondendo a doenças, tem como consequência a produção de intermediários reativos do oxigênio, óxido nítrico, lisozimas e radicais livres. As moléculas geradas são nocivas às células corporais, gerando estresse oxidativo, aumentando a demanda de nutrientes provenientes da dieta e, dessa maneira, não permitindo que o animal expresse de maneira total o seu potencial genético para crescimento (Raqib & Cravioto, 2009). Algumas respostas metabólicas, fisiológicas e nutricionais estão reportadas na Tabela 1.

Tabela 1- Respostas metabólicas, fisiológicas e nutricionais associadas aos antibióticos promotores de crescimento

Fisiológico	Nutricional	Metabólico
Aumenta		
Absorção de nutrientes	Retenção de energia	Síntese proteica no fígado
Consumo de ração	Retenção de nitrogênio	Fosfatase alcalina
	Absorção de vitaminas	
	Absorção de elementos traço	
	Absorção de ácidos graxos	
	Absorção de glicose	
	Absorção de cálcio	
Reduz		
Tempo de trânsito intestinal	Perda de energia pelo intestino	Produção de amônia
Espessura da parede intestinal	Síntese de vitaminas	Produção de aminas tóxicas
Comprimento da parede intestinal		Fenóis aromáticos
Peso de intestino		Oxidação de ácidos graxos
Turnover das células da mucosa		Gordura excretada
		Urease da microbiota

Adaptado de Gaskins *et al*., (2006)

Tem sido demonstrado que o efeito dos APC coincide com a diminuição da atividade da enzima sal biliar hidrolase (BSH) (Knarreborg et al., 2004; Guban et al., 2006; Smith et al., 2014). O BSH produzido pelas bactérias intestinais catalisa a desconjugação de ácidos biliares conjugados (CBA) no intestino (Begley et al., 2006). Os CBA são constituídos de um núcleo esteroide hidrofóbico que é conjugado com uma glicina ou taurina. Desta forma, os CBA são anfipáticos e funcionam como um detergente mais eficiente do que os ácidos biliares não conjugados para emulsionar e solubilizar lipídios para digestão de gordura (Begley et al., 2006). Consequentemente, a atividade da BSH tem um impacto significativo na nutrição do animal, modificando o metabolismo da gordura mediada pela CBA e as funções endócrinas (Begley et al., 2006; Jones et al., 2008).

Guban et al. (2006) correlacionaram a suplementação dietética de APC para melhorar o ganho de peso com a digestibilidade da gordura em frangos de corte, os níveis populacionais diminuídos de *Lactobacillus salivarius* e um pool reduzido de sais biliares desconjugados. Com base nesses resultados, o mecanismo de ação do APC para promover o ganho de peso e melhorar a conversão alimentar está associado à redução da atividade da BSH e à melhora do metabolismo lipídico.

O mecanismo anti-inflamatório não antibiótico dos APC, teoria desenvolvida por Niewold (2007), é a primeira teoria que explica as observações de desempenho sem as aparentes contradições e inconsistências associadas às outras teorias propostas. Está bem estabelecido que muitos antibióticos têm efeitos colaterais fisiológicos, muitos dos quais são específicos da classe química do composto. No entanto, o que os antibióticos têm em comum é que eles se acumulam nas células inflamatórias (Labro, 1998, 2000). A maioria dos antibióticos acumulados aumenta a morte intracelular de bactérias e eles podem inibir a resposta imune inata.

Uma das consequências da inflamação intestinal é o aumento da permeabilidade intestinal macromolecular, o que aumentaria a penetração local de antibióticos de baixo peso molecular. As células fagocíticas podem acumular antibióticos, em alguns casos 10 a 100 vezes a concentração ambiente (Tabela 2). O efeito relevante desta acumulação de muitos antibióticos em células inflamatórias fagocíticas seria atenuação da resposta inflamatória. Como consequência, os níveis de citocinas pró-inflamatórias seriam menores que os dos animais não tratados, o que resultaria em um menor estímulo catabólico.

Os antibióticos mostraram inibir uma ou mais das várias funções diferentes das células inflamatórias (Tabela 2), quimiotaxia, produção de espécies reativas de oxigênio e produção de citocinas pró-inflamatórias. Para a produção animal, a liberação de citocinas pode ser um fator determinante, sendo que após a liberação das citocinas ocorre uma resposta de fase aguda. Além de uma mudança na produção de proteínas hepáticas para proteínas de fase aguda, ocorre catabolismo do tecido muscular e perda de apetite (Gruys et al., 2006).

Tabela 2- Acúmulo intra fagocitário de antibióticos que podem levar a inibição da função fagocitária

Antibiótico	**Acúmulo intracelular (relação intra:extra celular)**	**Inibição da função fagocitária**
Cloranfenicol	4	Não
Beta lactâmicos	<1	Alguma/Limitada
Ciclinas	2	Sim
Quinolonas	5	Não
Macrólidos	100	Sim
Estreptogramina	40	Sim

Adaptado de Newold (2007).

A inflamação intestinal geralmente leva ao acúmulo de células inflamatórias na mucosa, levando a uma parede intestinal mais espessa. A parede intestinal mais fina observada usando APC é consistente com a inflamação reduzida devido ao influxo reduzido e ao acúmulo de células inflamatórias (Larsson et al., 2006). Isso explica por que o efeito do APC está ausente de animais livres de germes, e por que os efeitos dos APC são maiores quando os animais estão sob maior pressão infecciosa, como ocorre em certas idades, em certas condições de criação e em certas regiões (Page, 2006). E as diferentes composições microbianas ao usar APC são, nesta perspectiva, uma consequência de um estado imunológico alterado em vez de um efeito direto do APC sob a microbiota (Niewold, 2007).

Antibióticos promotores de crescimento na dieta de frangos e suínos

Os promotores de crescimento são administrados em concentrações relativamente baixas, variando de 2,5 mg/kg a 125 mg/kg (ppm), dependendo do tipo de droga e da espécie animal (WHO, 2003). Foi estimado que o consumo anual médio global de antimicrobianos por quilograma de animal produzido foi de 148 mg/kg − 1 e 172 mg/kg – 1, O que esse 1 quer dizer? 1mg/kg para frangos e suínos, respectivamente (Boeckel et al., 2015). Dados obtidos de 25 sistemas de produção de suínos mostraram que o consumo médio de antimicrobianos é de 358 mg/kg de suínos produzidos. O mesmo estudo estimou que os suínos foram expostos, em média, 66,3% de sua vida útil a antimicrobianos nesses sistemas (Dutra, 2017). Os antibióticos utilizados como promotores de crescimento nas dietas de frangos e suínos estão listados na Tabela 3.

Tabela 3 - Antibióticos utilizados como promotores de crescimento nas dietas de frangos e suínos

Antibiótico	**Espécie**
Avilamicina	Frango; Suíno
Bacitracina	Frango; Suíno
Enramicina	Frango; Suíno
Flavomicina	Frango; Suíno
Halquinol	Frango; Suíno
Lincomicina	Frango; Suíno
Narasina	Suíno
Salinomicina	Suíno
Tiamulina	Suíno
Tilosina	Frango; Suíno
Virginiamicina	Frango; Suíno

Adaptado de Bresslau (2017)

O maior efeito dos APC é atribuído à melhoria da conversão alimentar, e essa resposta é a mais alta em animais geneticamente melhorados, de crescimento rápido e criados em sistemas de produção intensiva. Outros efeitos observados com o uso do APC são taxa de crescimento mais rápida, redução da mortalidade, alta resistência ao desafio promovido por doenças, melhor desempenho reprodutivo e melhor qualidade das fezes e da cama.

Frangos de corte aos 42 dias de idade que não foram expostos a desafios sanitários apresentam resultados de ganho de peso contraditórios quanto à retirada de APC da dieta. Nessa situação muitos estudos demonstraram não ocorrer diferença no ganho de peso entre animais recebendo ou não APC, porém também foram encontrados resultados relatando a eficiência do antibiótico como promotor de crescimento, com efeitos positivos no ganho de peso (Figura 1). Resultados contraditórios também são observados nas variáveis de consumo de ração e conversão alimentar (Peng et al., 2016; Silva et al., 2018 e Tayeri et al., 2018). Por outro lado, quando há algum tipo de desafio parece ser inequívoca a eficiência dos APC na melhoria da conversão alimentar (Baurhoo et al., 2007, Cho et al., 2014) e do ganho de peso (Mallet et al., 2005; Cravens et al., 2013).

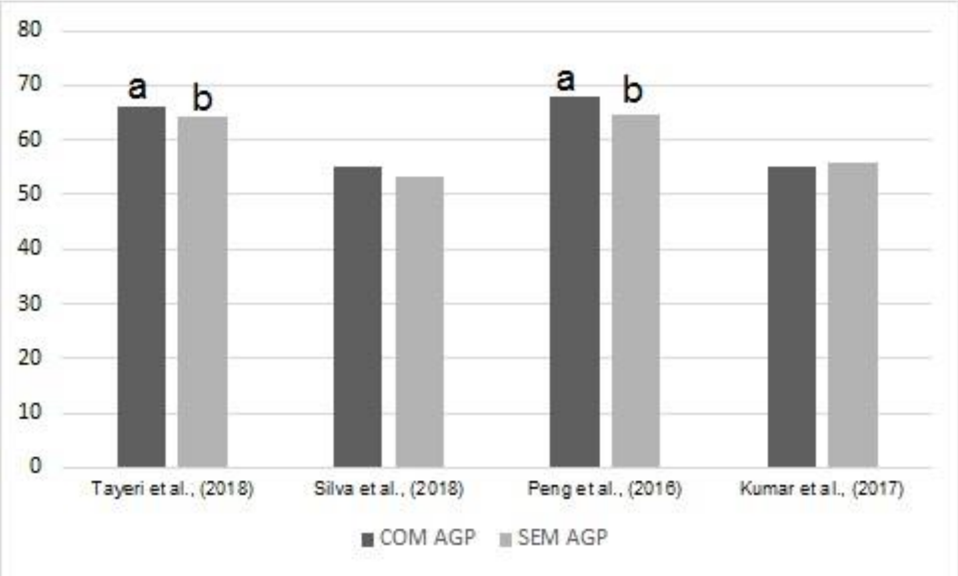

Figura 1- Ganho de peso de frangos de corte(g/dia) recebendo ou não antibiótico promotor de crescimento, sem desafio sanitário

Para suínos o efeito observado pela adição de APC na ração para as variáveis ganho de peso, consumo de ração e conversão alimentar é similar ao efeito observado em frangos. Os suínos que não são expostos a desafio sanitário e recebem APC apresentam ganho de peso igual ou superior aos suínos que não recebem APC (Valchev et al., 2009; Yoon et al., 2014; Santana et al., 2014). Quando leitões foram expostos a desafio sanitário a presença de APC na dieta resultou em melhor ganho de peso e conversão alimentar (Li et al., 2017 e Long et al., 2018). Na Figura 2 é possível observar estudos demostrando o ganho de peso de leitões em período pós desmame recebendo ou não APC na dieta:

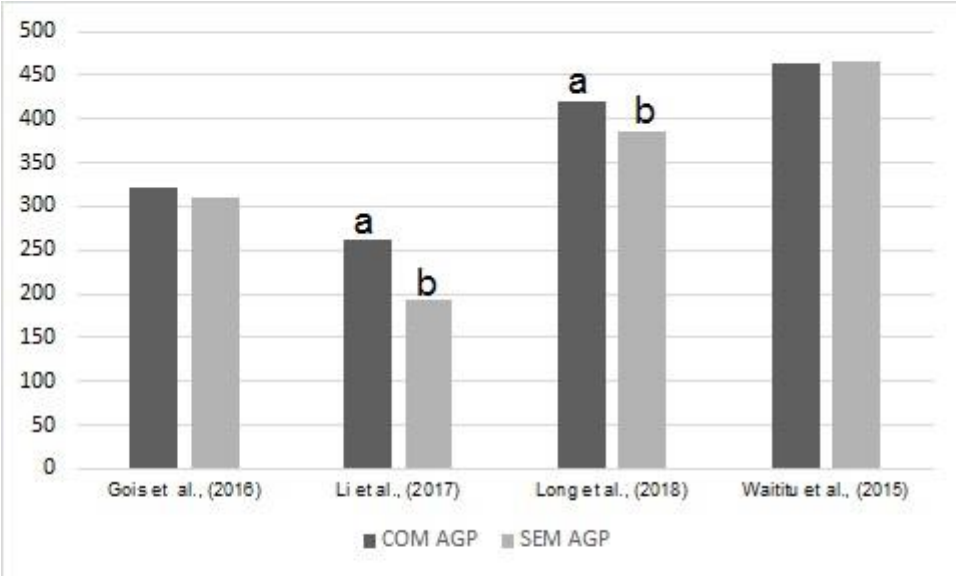

Figura 2 – Ganho de peso de leitões pós desmame (g/dia) recebendo ou não antibiótico promotor de crescimento, sem desafio sanitário

Meta-análise

A demanda por novas ferramentas analíticas é grande em áreas regidas por questões éticas, como a pesquisa com animais. Nesse contexto, as técnicas de bioinformática podem ser importantes aliadas, visto que permitem reduzir o uso de animais nos estudos e, ao mesmo tempo, obter respostas novas a partir de dados já disponíveis na literatura científica (Rodrigues et al., 2010). A meta-análise é uma técnica desenvolvida para integrar os resultados de diversos estudos em um mesmo tema de pesquisa e extrair informações adicionais destes dados (Lovatto et al., 2007). O termo também se refere a um conjunto de procedimentos para estimar a direção e a magnitude dos efeitos (Sauvant et al., 2008).

Na área animal, o emprego da meta-análise para reunir informações distintas e oriundas de diferentes condições experimentais está aumentando. Quando é realizada uma busca no Google acadêmico com as palavras “broiler” e “antibiotic” são apresentados como resultados 68.000 publicações e quando são utilizas as palavras “swine” e “antibiotic” o resultado é de 175.000. Este crescente volume de publicações científicas gerado pelo desenvolvimento das pesquisas e conclusões obtidas em diferentes trabalhos pesquisando sobre o mesmo tema é um outro fator que tem motivado os pesquisadores a compilar informações publicadas (Lovatto & Sauvant, 2002; Hauptli et al., 2007), na busca por resutados mais conclusivos que um único experimento poderia dar.

No Brasil as meta-análises ganharam destaque pelo uso na suinocultura, introduzida por Lovatto et al. (2006) que ensina as premissas básicas para realização desse estudo. Andretta et al. (2010) utilizaram meta-análise para avaliar o efeito do ácido linoleico conjugado no desempenho de leitões, assim como Lehnen et al. (2011) utilizaram esta metodologia para avaliar a digestibilidade ileal de aminoácidos e minerais de suínos recebendo diferentes enzimas. A meta-análise também se mostra presente em pesquisas com aves. Nascimento et al. (2011) realizaram equações de predição de energia metabolizável para alimentos energéticos, e Averós et al. (2018) avaliaram como as características dos sistemas intensivos afetam simultaneamente o desempenho e o bem-estar de frangos de corte. Todos os autores extraíram conclusões que não poderiam ser obtidas com a realização de um único experimento, confirmando a meta-análise como uma metodologia eficiente.

Sauvant et al. (2008) relacionaram as etapas que devem ser seguidas para realização de uma meta-análise: (1) determinação do tema a ser estudado, (2) seleção das publicações a serem utilizadas na construção da base de dados, (3) avaliação criteriosa da literatura disponível para que a mesma contenha os parâmetros definidos como essenciais para a tabulação, (4) tabulação dos dados em base eletrônica, (5) análise gráfica para obter visão global e identificação das relações específicas a serem investigadas, (6) aplicação de técnicas estatísticas e (7) interpretação dos resultados.

Em estudos meta-analíticos fundamentados em experimentos realizados de forma independente é necessário o uso de ponderações, para que sejam eliminados os efeitos das diferenças entre os estudos (ambiente, gênero, idade do animal, etc.), eliminando o efeito individual dos estudos para aumentar a inferência da sistematização científica, visando integrar o conhecimento disponível para criar modelos funcionais capazes de simular de forma satisfatória a realidade (Oviedo-Rondón et al., 2007; Velho et al., 2009).

Em meta-análises são utilizados dois tipos de modelos: modelos de efeito fixo e modelos de efeito aleatório. O modelo de efeito fixo é adequado quando se acredita que o efeito do tratamento é idêntico entre os estudos, quando o objetivo for estimar um efeito de tratamento para uma população específica. O modelo de efeito aleatório pode ser utilizado quando o pesquisador combina vários estudos que tem o mesmo objetivo, mas que não foram conduzidos da mesma maneira. Neste caso, é possível extrapolar o resultado para outras populações, o que torna a análise mais abrangente (Rodrigues & Ziegelmann, 2010).

Impacto econômico da retirada dos antibióticos promotores de crescimento da dieta de frangos e suínos

Existem diversas técnicas que podem ser usadas para analisar as implicações econômicas dos antibióticos no sistema de produção. A escolha da técnica dependerá de vários fatores, como a natureza do problema, disponibilidade de dados, bem como a quantidade de recursos disponíveis para realizar a análise (Ryan, 2019).

Alguns estudos estimaram o impacto econômico potencial da proibição dos APC na indústria de suínos dos EUA, e, quando comparados, existem grandes diferenças nas estimativas de aumento de custos por suíno: USD 0,59 / suíno, (Miller, 2003), US $ 1,37 / suíno (Miller et al., 2005), US $ 2,33 / suíno e USD $ 4,50 / suíno (Hayes e Jensen, 2003). Essa grande variação também foi observada nos estudos conduzidos na Dinamarca, chegando a estimar o aumento de EUR $1,04 por suíno produzido (WHO, 2002). Para a produção de frangos, o National Research Council publicou uma estimativa de impacto feita pela indústria e concluiu que o banimento dos APC geraria um aumento de 1,76% nos custos de produção, resultando em um aumento no custo para os consumidores de US$ 2,20 per capita por ano (NRC, 1999). Graham et al. (2007) estimou que o efeito líquido do uso de APC resultou num gasto de US$ 0,0093 por frango. A partir desses resultados, os autores não encontraram base para a alegação de que o uso de APC reduz o custo de produção. Porém, este estudo não incluiu mudanças nos custos veterinários, assim como não considerou as mudanças no desempenho associadas à remoção dos APC.

Os resultados do impacto econômico do banimento dos APC podem não ser aplicáveis em todos os países ou em todas as granjas dentro de um país. Como descrito por alguns autores, a proibição dos APC afetaria os produtores de maneiras diferentes, alterando os resultados do impacto de acordo com a localização, tamanho da propriedade, modalidades contratuais e práticas de produção (McBride, 2008, MacDonald e Wang, 2011). Da mesma forma, diferentes variáveis de gestão e práticas de saúde e saneamento foram destacadas em estudos que descreveram a proibição dos APC, em 1986 na Suécia (Wierup, 2001).

Foi demonstrado que granjas que produzem frangos com APC nos EUA, tendem a ser granjas com estruturas mais antigas, com equipamentos menos modernos, e são menos propensas a seguir um plano de gerenciamento de riscos de segurança (MacDonald e Wang, 2011). Laanen et al. (2013) demonstraram que a melhoria da biossegurança em rebanhos de suínos pode ajudar a reduzir a quantidade de antimicrobianos usados profilaticamente e está positivamente associada ao ganho de peso diário. Porém, até onde sabemos, não há publicações de estimativas de impacto produtivo em relação a investir em medidas de biossegurança e sistemas de produção com condições de higiene otimizadas.

HIPÓTESES E OBJETIVOS

A retirada dos antibióticos promotores de crescimento da ração de frangos e suínos piora os índices zootécnicos e, como consequência, aumenta o custo de produção destas espécies.

Os objetivos deste estudo são:

- Quantificar a relação entre o uso ou não dos antibióticos promotores de crescimento das dietas de frangos e suínos e as respostas de desempenho produtivo.
- Estimar o impacto econômico da retirada dos APCS em diferentes senários produtivos para frangos e suínos.

CAPÍTULO II

Withdrawal of antibiotic growth promoters from broiler diets: performance indexes and economic impact

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Withdrawal of antibiotic growth promoters from broiler diets: performance indexes and economic impact

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Scientific section for the paper: Management and Production

[¶]

ABSTRACT

This study aimed to estimate the productive and economic impacts caused by the withdrawal of antibiotic growth promoters **(AGP)** from broilers diet. Indexed publications that compared diets with or without AGP (AGP+/ AGP-) for broilers (from initial to final phase) were collected and results of the feed intake, weight gain and feed conversion were compiled in a database. A meta-analysis was performed following sequential analyses: graphical approach (to observe biological data coherence), correlation (to identify related factors), and variance-covariance (to compare groups). The annual number of broiler slaughtered in Brazil, target weight gain and feed conversion for each phase, the variation in feed conversion, feed cost, and AGP costs were used to build a model to estimate the effects of the AGP withdrawal on feeding costs. The database comprised 174 scientific articles containing 183 experiments, totaling 121,643 broilers, most of which were Ross (52% of the studies). The most frequent AGP sources/forms in the database were Avilamycin (41% of the AGP+ treatments), Flavomycin (19%), Virginiamycin (16%) and Bacitracin (14%). Higher feed intake, weight gain and lower feed conversion were attributed (P<0.05) to AGP+ diets during Initial phase (1-21 days). In Final phase (22-42 days) no differences were observed in performance variables. Treatments AGP+ presented higher weight gain and better feed conversion in the Total period (1-42 days). The results of feed conversion were improved (P<0.05) with Avilamycin and Flavomycin; Virginiamycin improved weight gain and feed conversion. In the Total period, the economic impact was $ 0.03 per animal and a total of $ 183,560,232 per year. It was concluded that broilers fed AGP+ diets have higher weight gain and better feed conversion than those fed AGP- diets, and withdrawing AGP increases production costs.

Key words: feed conversion, productive cost, sensitivity analysis, weight gain

INTRODUCTION

The pressure for reducing the use of antibiotic growth promoters (**AGP**) in livestock is a growing and irreversible process, and several countries are adhering to the restrictions and ban on AGP usage. Sweden was the first country which changed laws of AGP usage and, in 2006, the EU imposed a complete ban of all AGP. The USA is not only limiting AGP use but also moving towards a significant reduction of general antibiotics usage in industrial food animal production (Salim et al., 2018). The most recent effort toward AGP restriction in Brazil and China was banning the use of Colistin in 2016 (Walsh and Wu, 2017; Davies and Walsh, 2018). In the same year, Vietnam announced the ban AGP by 2020 (USDA, 2016). India has introduced drug withdrawal time for livestock production (Kahn, 2017) and Bangladesh, Bhutan, Indonesia, Myanmar, Nepal, Sri Lanka, and Thailand have announced AGP restrictions (Goutard, 2017). The increasing pressure to prohibit the use of these additives is based on the possibility of induction of cross-resistance of pathogenic bacterial strains in people (Baurhoo et al., 2009; Tang et al., 2017).

In broiler production, there is an estimated annual use of 148 $mg.kg^{-1}$ of AGP (Van Boeckel et al., 2015) 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. Many studies have shown no weight gain difference in broilers fed an AGP diet in the absence of health problems (Denev et al., 2006; Baurhoo et al., 2007; El-Faham et al., 2015; Naveenkumar et al., 2017). However, other studies have reported the efficiency of AGP, with positive effects on broilers weight gain and feed conversion (Zhang et al., 2005; Peng et al., 2016; Wu et al., 2018).

It is clear that AGP restrictions in the production of animal food are expanding and therefore its consequences must be studied, including its effect on broiler performance and the expected economic results of such restriction. The objective of this study was to quantify the performance differences in broilers receiving diets with and without AGP and to estimate the economic impact of this withdrawal through the meta-analysis technique.

MATERIAL AND METHODS

Search and Data Filtering

Scientific literature presenting experimental results of broiler performance with AGP was searched in different online data sources (Google Scholar, ScienceDirect, Scopus, Scielo, and PubMed) using the keywords: “antibiotic growth promoter” and “performance” in addition to the terms “broiler” or “chicken”. The search terms were tested in English, Spanish, and Portuguese. References in the final publication list were also reviewed to identify any additional relevant articles. This diversity of scientific databases was intended to prevent potential publication bias. Following identification, the studies were critically evaluated according to relevance and quality in relation to the meta-analysis objectives. Abstracts were examined by two researchers, and a record was only removed from the database following agreement. At this stage, a set of information about each selected study was examined against a previously prepared checklist, and critically evaluated for eventual methodological errors. For the exclusion of pre-selected manuscripts, the following factors were considered: presence of sanitary challenge, slow-growing breeds, absence of control treatment, inconsistent methodological data, error of statistical design, and gross errors in result data. The criteria for publication selection were: (1) in vivo experimental evaluation of diets with AGP (AGP+) and without AGP (AGP-); (2) antibiotics dosage within the recommended range for growth promoters; (3) AGPs permitted in the Brazilian standard legislation of 2016 (MAPA, 2016); (4) initial, final and/or total period results expressed; (5) rates of feed intake, weight gain, and feed conversion or feed efficiency stated; (6) year of publication from 1990 until 2018.

Data Systematization and Coding

The methodology used for database construction and for data encoding followed the methods described in the literature (Sauvant et al., 2005; Lovatto et al., 2007). The data were entered in an electronic spreadsheet, which consisted of rows representing the treatments and columns representing the exploratory and descriptive variables. Relevant information to the objective of this study (body weight, feed intake, weight gain, and feed conversion) and other variables (genetic strain, age, sex, dietary nutritional composition, and duration of experimental period) were included to allow for a descriptive analysis of the studies. Some codes were used to create grouping criteria in the analytical models; the main codes were applied for the presence (AGP+) or absence (AGP-) of AGP and for each antibiotic, such as "A" for Avilamycin and "B" for Bacitracin. Other codes were used as moderating variables to represent the variability of the compiled trials (e.g.: effect of study or trial).

Statistical Analysis

A series of graphical analyses were used to analyze the data distribution and to obtain a general view of their consistency and variance heterogeneity. Based on these analyses, correlation hypotheses were formulated to define the statistical models (Lovatto et al., 2007). During this step, the data distribution per year and the presence or absence of AGP were evaluated. The performance data of AGP- treatments were relativized according to their respective AGP+, in order to estimate the impact (percentage variation) of AGP withdrawal. Additionally, the relationships between and within studies were evaluated.

Variance-covariance analyses were conducted using the GLM procedure in the Minitab 18 statistical package (Minitab Inc., State College, PA); the effects of gender, type of facilities and year of publication were tested. However, the factors were not significant (P > 0.05) and consequently, all three factors were removed from the model. A mixed model was applied, considering treatments as fixed effect, while inter-study codes and mean body weight were random effects (P < 0.05). The analyses were performed considering treatments, the inter-study codes, and body weight. The variables analyzed were feed intake, weight gain, and feed conversion. The analyses were grouped by the rearing phase: Initial (1 to 21 d), Final (22 to 42 d), and Total phase (1 to 42 d). The Total phase analysis was carried out considering the entire database, including both rearing phases. Individual analyses were also performed for the main AGP in the database. Residual analysis was performed, and it was observed that the residuals were normally distributed.

Economic Impact

The parameters obtained by meta-analysis were used to build a model that estimates the withdrawal of AGP on the production costs, particularly feeding costs in Brazilian scenario. Brazil was chosen for this simulation as it is a large producer and exporter of broiler meat. Moreover, AGP withdrawal is an important and current debate in Brazilian meat industry. The simulation (Table 1) considered the annual slaughtering rate, reported at 5,840,000,000 broilers in 2017 (IBGE, 2017), the target weight gain and feed conversion for each phase (AGP+), the variation in feed conversion (obtained from the meta-analysis), as well as feed and AGP costs (information provided by a local feed factory).

Equations for economic impact simulation:

Cost of feeding per animal = $\alpha \times \left(\frac{\beta}{1000}\right)$ (1)

Where: α: feed intake of the phase (kg/day), and β: cost of feed ($/ton).

Feed intake of the phase = $\tau \times FCR$ (2)

Where: τ: weight gain of the phase (kg) and FCR: feed conversion (kg/kg).

Cost of feed: $\mu + ɣ$ (3)

Where: μ: price of feed ($/ton) and ɣ: price of AGP ($/ton).

Cost of feeding herd/year: $\left(\alpha \times \left(\frac{\beta}{1000}\right)\right) \times Ɲ$ (4)

Where: Ɲ: number of slaughters in the year (head).

The performance data of animals that received and did not receive AGP was used in the equations, and the difference between the results was calculated to estimate the economic impact.

The currency conversion rate used for the calculation of production costs in USD was: $1.00 = R$ 3.75.

A sensitivity analysis was performed using the key variables “feed conversion” and “AGP price.” It indicates whether one or more variables can have an impact on the economic results of a production system and influence its profitability (Saltelli et al., 2000). To define the scenarios in which the withdrawal of AGP would have a negative economic impact, the range between feed conversion in AGP+ and AGP- treatments was increased from 0.0% to 5.0%, and the price of AGP was halved and increased up to five times. When the value of the economic impact was greater than zero, AGP withdrawal was judged as an economically sound strategy, and when the impact value was less than zero, AGP use was judged as a better economic decision to avoid financial loss. The price of feed used to evaluate the Total phase was utilized in the sensitivity analysis. In this study, only the feed cost was considered; therefore, other factors such as management and sanitary costs were not included in the economic impact model.

RESULTS

Composition of Database

The database consisted of 174 articles (listed in Supplementary Table 1) containing 183 experiments. The majority of selected papers (98%) were published between 1998 and 2018 (Figure 1), and studies were developed in Brazil (14%), Korea (12%), Canada (9%), USA (9%) and other countries (56%), such Africa, Egypt, China, France, Israel, among others. The total number of broilers used in all trials was 121,640, with the initial and final body weight of 0.45 and 2.3 kg, respectively. The most used strains were Ross (52% of the treatments), Cobb (28%) and Arbor Acres (10%). Groups with mixed sexes were used in 20% of the database studies, while treatments with males and females separated, represented 60% and 2% of the total, respectively. The sex of the animals was not described in 18% of the studies. The Initial phase was described in 16% of the studies, and the Final phase and Total in 7% and 22%, respectively. The majority of the studies (55%) described the performance per week of production. The most frequent antibiotics in the database were Avilamycin (41% of the AGP+), Flavomycin (19%), Virginiamycin (16%) and Bacitracin (14%). Pens and battery housing systems were used in 75% and 15% of the database studies, respectively. A summary of the manuscripts is available in Supplementary Table 2.

Performance

The AGP + presented a positive impact on broiler performance. A negative variation in weight gain was observed in 76% of comparisons between AGP + / AGP- treatments in the database (Figure 1). Likewise, better feed conversion was observed in 84% of individual comparisons among treatments. However, it is important to point out that some of these variations were not statistically significant in the original studies.

In the meta-analyze, feed intake showed better result (P < 0.05) to AGP+ in the Initial phase (1 to 21 days), but no effects (P > 0.05) were observed in the Final phase (22 to 42 days) and Total phases (1 to 42 days) (Table 2). The weight gain presented a grather result (P < 0.05) when AGP+ diets were used in the Initial and Total phases, but no difference was observed in the Final phase (P > 0.05), with 2.79 and 3.84% differences between AGP+ and AGP-. Feed conversion had better results (P < 0.05) in AGP+ in Initial and Total phases, and no difference was observed in Final phase. The biggest difference between AGP+ and AGP- was 3.48% in Total phase, followed by Initial with 2.64%.

Analyzing each AGP individually (Table 3), feed intake was not influenced by the treatments (P > 0.05), regardless of the AGP analyzed. The addition of Avilamycin and Flavomycin did not result in any detectable difference between AGP + and AGP - (P > 0.05) in weight gain. Virginiamycin showed positive effect on weight gain (P < 0.05) in AGP + compared to AGP-. Avilamycin, Flavomycin, and Virginiamycin showed better results (P < 0.05) of feed conversion in AGP+.

Economic Impact

AGP withdrawal in Initial phase and Total period increased the production cost in $ 0.01 and $ 0.03 per animal, totalizing an amount of $ 38 950 725 and $ 183 560 232 per year in Brazil (Table 4).

In the sensitivity analysis (Figure 2), "AVOID" indicates when it is possible not to use AGP without having a negative economic impact and "USE" indicates when the use of AGP usage is important to avoid economic losses. There is little elasticity between the variables not to use the AGP without economic losses. If the price of AGP increases five times compared to the current price, and the variation between the feed conversion of AGP+ and AGP- is at a maximum of 0.5%, there will be no economic losses taking out AGP. If the price of AGP is half of the current price with zero variation in feed conversion, there will be no negative economic impact. However, in the situation of the half of current price, a variation in feed conversion higher than 0.15% indicates the use of the additive. With the current AGP price and the results of feed conversion found in the meta-analysis (2.64% in Initial, 1.50% in the Final phase and 3.48% in Total period), there will be economic losses withdrawing AGP.

DISCUSSION

A reduction in the effectiveness of AGP in the last 30 years was suggested by Laxminarayan et al. (2015), which may be linked to optimization of production conditions, increasing in the baseline weight gain of animals, increasing level of resistance, and potential switch in the type of molecules used. In contrast, the "year" effect was not significant in the current meta-analysis. This result may be associated to the fact that the studies selected to compose the database did not have any type of sanitary challenge.

Our results showed a clear connection between AGP feed supplementation and broiler performance, which was particularly evident in feed conversion and weight gain in Initial (1 - 21 d) and Total (1 - 42 d) phases and feed intake in the Initial phase. Instead, no relation between AGP usage and growth was found in the Final (22 - 42 d) phase. A multitude of factors can influence the performance results, including the environment, stress and diet characteristics. Different mechanisms of action have been proposed and several studies have been carried out to explain AGP function: a growth-promoting effect may be associated to modification of some intestinal characteristics in the first week of life of chickens, as deeper crypts in the ileum, indicating faster tissue development (Miles et al., 2006). In addition, the studies show the ability of AGP to reduce normal early microbial proliferation, and hence competition for nutrients during the gut maturation, which takes approximately 6 to 9 days in chicks (Geyra et al., 2001). These alterations may be related to better nutrient absorption, resulting in lower feed intake and greater weight gain when compared to chickens that do not receive AGP in the Initial phase. Nutrient absorption is not the intestines' sole function, as they perform an immunological role as well (Round et al., 2010). The close and intermittent contact of the gastrointestinal mucosa with the enteric microbiota results in a constant state of inflammation (Biancone et al., 2002) and can influence macromolecular intestinal permeability (MacDonald and Monteleone, 2005). AGP accumulates in inflammatory cells and enhance the intracellular killing of bacteria, inhibiting the innate immune response (Labro, 1998, 2000). Therefore, the use of AGP decreases the catabolic costs of maintaining an immune response by allowing more resources to be dedicated to anabolic processes (Niewold, 2007). The first days of life of a chicken can be considered stressful, since it happens the vaccination management, transportation, setting in new place and microbial exposures resulting from living on litter, as well as the introduction of a diet with anti-nutritional factors (Yassin et al., 2009; Willis et al., 2008). Considering the hypothesis of a non-antibiotic action of AGP, which results in a reduced intestinal inflammatory response (Niewold, 2007), this may be an explanation why AGP results in positive effects on the Initial phase. On the other hand, broilers in Final phase are much more able to cope with stressors, because the first contact with microorganisms has already occurred and it results in a lower level of immune response (Koutsos and Klasing, 2014), and there is a reduction on total stress, since the adaptation of the animal to the environment already occurred.

Also (who?) has been proposed that AGP growth-promoting effect does coincide with a decrease in bile salt hydrolase (**BSH**) activity in the gut (Knarreborg et al., 2002, 2004, Guban et al., 2006, Lin et al., 2014). The lactobacilli are present in the crop and in the digestive tract (Lu et al., 2003, Hilmi et al., 2007), and this genus is responsible for BSH production, active in the small intestine (Moser and Savage, 2001), impairing the emulsification and absorption of dietary lipid. Other authors affirm that AGP is the most common dietary intervention to modulate the gut microbiota (Dibner and Richards, 2005) and the activity of the intestinal microbiota, including both pathogenic and commensal bacteria (Lin et al., 2013). Some differences in the spectrum of activities, differing gut microbiota effects could be expected between different AGP, and this has been demonstrated in some studies (Neumann and Suen, 2015; Costa et al., 2017). As an example, Zinc bacitracin increased the diversity of the cecal microbiota of Cobb broilers, with increases in *Faecalibacterium* and *Ruminococcus torques* phylotype, and reductions in *Lactobacillus salivarius phylotype* and *Eubacterium* (Crisol-Martínez et al., 2017). All these mechanisms acting as interrelated multi factors may explain the best results observed in the Total period of rearing.

When AGP was analyzed individually, there is variation in performance responses. However, there is an improvement in feed conversion regardless of the AGP used. Avilamycin is an oligosaccharide classified as an orthosomysin. The Virginiamycin is a streptogramin combination that is a fermentation product of *Streptomyces virginiae* and Flavomycin is a polypeptide obtained from *Streptomyces bambergiensis* and *Streptomyces ghanaensis* (Giguère, 2013). The different results may be associated with the effectiveness of AGP in different mechanisms of action in the organism and the rearing phase of the animal. Niewold (2007) reported that AGP compounds can essentially be divided into groups based on their interaction with inflammatory cells, as non-accumulating, accumulating without inhibition of function, and accumulating with inhibition of function; for example, cyclines, macrolides (Tylosin) and peptides (Bacitracin) showed phagocyte-inhibition function (Labro, 2000). In another proposed mode of action, tetracycline antibiotics were consistently potent inhibitors of BSH. Both Roxarsone and Oxytetracycline inhibited BSH activity by over 95%. The β-lactam and lincosamide displayed a relatively lower inhibitory effect on BSH activity, and macrolide and peptides had a weak effect on BSH (Smith et al., 2014). In another point of view, there are different metabolites changes by dietary supplementation with AGP. Many long chain fatty acids in the intestine of bacitracin-supplemented were increased, but not in virginiamycin-supplemented chicks. At the same time, levels of amino acid metabolites (lysine and tryptophan) were substantially altered by dietary supplementation with virginiamycin or bacitracin (Gadde et al., 2018). The mechanisms of action of AGP are not yet completely clear, so it is not possible to attribute which one of them is linked to the differences in results.

The productive impact considered in this study was focused on the broilers feeding, and this can become part of a more complete economic impact analysis, taking in account aspects such as sanity, productive structure, labor, housing period, among others. Although it is based in a very simple approach, the model may provide relevant information for nutritionists and producers while facilitating the decision-making process. Some costs associated with the production system are difficult to measure and have not been included in the economic calculations (Kjeldsen et al., 2006). Different authors report that the economic impact will affect producers differently, since there is a variation in the factors considered in the characterization of the productive scenario, such as farm size, contracting arrangements, and production practices (McBride et al., 2008; McDonald and Wang, 2011). On the other hand cost of feed is estimated to be more than 70% of the total production cost.

To better understand our findings in relation to production costs, it is safe to consider that the sum of feed and AGP cost increases total feeding costs, which conversely reduces feed cost by improving feed conversion ratio. The meta-analysis highlighted a reduction in broiler performance when fed AGP- diets, which may lead to an increase in production costs. Considering the current situation (AGP prices and 3.48 % of better feed conversion using AGP), the results from Total performance showed an increase of 0.8% in the cost of production per animal with the withdrawal of AGP. However, if techniques to reduce close to zero the difference in feed conversion between AGP+ and AGP- are used, it will be possible to raise broilers without AGP, as can be observed in the sensitivity analysis. To reduce the variation in feed conversion it is necessary to implement new management, using the biosecurity as a tool to reduce diseases (Gelaude et al., 2014) and vaccination to improve the overall health status, reducing the risk of secondary infections (M'Sadeq et al., 2015). As coccidiosis is considered a great risk factor to broilers reared without AGP, it is of foremost importance to understand *Eimeria* spp. cycle and the immunization process in flocks to benefit intestinal health (Parent et al., 2018). Also, the optimization of the climate and housing conditions and nutritional strategies are necessary to reduce the variation between AGP+ and AGP-. Various feed additives such as essential oils, copper sulfate, zinc oxide, probiotics, and prebiotics have been studied (Huyghebaert et al., 2011; Ali et al., 2017; Moraes et al., 2019) aimed to replace AGP. The use of organic acids in broiler diet can have a beneficial effect on the performance by decreasing pathogenic bacteria, like *Salmonella, Campylobacter* and *Escherichia coli* (Naseri et al. 2012). Polycarpo et al. (2017) observed a significant interaction between organic acids and microbiological challenge on FCR. Under experimental conditions carried out without microorganism inoculation, the organic acids improved broilers' FCR and presented similar results to antibiotics. Adding organic acid to the drinking water helps to regulate gut microbiota and to increase the digestion of feed (Açıkgöz et al., 2011; Hamed and Hassan, 2013). Although it is possible to reduce the variation in feed conversion between AGP+ and AGP-, there is still a long way. It is necessary to evaluate strategies to improve productivity without the use of AGP and analyze other factors that directly interfere in the production cost besides the feeding.

CONCLUSION

Broilers fed diets with AGP show better performance in the total period of rearing, mainly because of its effect on the initial phase. The AGP withdrawal from broiler diet presents different results of performance in total phase according to the AGP used. The worse performance of broilers with withdrawal of AGP becomes a significant increase in production costs.

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Table 1. Inputs for estimating the economic impact caused by the withdrawal of antibiotic growth promoters (AGP) from broiler diets

Inputs	**Initial phase (1-21 days)**	**Total Period (1-42 days)**
Annual slaughterings, heads	5.840.000.000	5.840.000.000
Weight gain, kg	0.80	2.50
Feed conversion target (AGP+), kg/kg	1.47	1.66
Feed conversion variation[1], %	2.64	3.48
Feed cost, $/ton	232.00	230.00

[1]Feed conversion variation: Variation between diets with and without AGP obtained by the meta-analysis.

Table 2. Performance -obtained by meta-analysis- of broilers fed diets with (AGP+) or without antibiotic growth promoters (AGP-)

Variable	Treatments		P	RSE	R^2	%
	AGP+	AGP-				
Initial (1-21 days)						
Feed intake, g/d	55	56	0.005	1.059	99.15	1.78
	(n:86)	(n:75)				
Weight gain, g/d	38	37	< 0.001	1.043	98.29	2.70
	(n:87)	(n:76)				
Feed conversion, g/g	1.47	1.51	< 0.001	0.049	92.66	2.64
	(n:86)	(n:75)				
Final (22-42 days)						
Feed intake, g/d	161	162	0.111	2.952	98.21	0.61
	(n:37)	(n:34)				
Weight gain, g/d	82	82	0.561	1.841	97.70	0.00
	(n: 39)	(n:36)				
Feed conversion, g/g	1.96	1.99	0.128	0.056	96.01	1.50
	(n:37)	(n:34)				
Total (1-42 days)						
Feed intake, g/d	90	91	0.127	15.707	87.85	1.09
	(n:476)	(n:452)				
Weight gain, g/d	54	52	0.040	8.886	82.62	3.84
	(n:513)	(n:489)				
Feed conversion, g/g	1.66	1.72	< 0.001	0.157	74.61	3.48
	(n:482)	(n:458)				

P: Probability of treatment effect. The models included the study effect (P < 0.001).

RSE: Residual standard error.

R^2: Coefficient of determination of the model.

%: Percentage change between AGP+ and AGP-.

n: Number of studies observations in each mean.

Table 3. Total performance* -obtained by meta-analysis- of broilers fed diets containing specifics antibiotic growth promoters (AGP+) or not (AGP -)

Variable	Treatments		P	RSE	R^2
	AGP+	AGP-			
Avilamycin					
Feed intake, g/d	91	93	0.108	15.786	87.51
	(n:200)	(n:199)			
Weight gain, g/d	54	53	0.248	8.952	82.47
	(n:219)	(n:218)			
Feed conversion, g/g	1.63	1.71	< 0.001	0.118	82.17
	(n:206)	(n:205)			
Flavomycin					
Feed intake, g/d	90	91	0.743	24.082	78.41
	(n:102)	(n:93)			
Weight gain, g/d	51	51	0.622	9.921	78.13
	(n:104)	(n:95)			
Feed conversion, g/g	1.72	1.76	0.037	0.312	67.39
	(n:102)	(n:93)			
Virginiamycin					
Feed intake, g/d	83	85	0.566	14.406	88.45
	(n:65)	(n:64)			
Weight gain, g/d	49	47	0.042	9.117	78.77
	(n:70)	(n:69)			
Feed conversion, g/g	1.68	1.75	0.015	0.165	76.63
	(n:65)	(n:64)			

*The model considered the effect of the study (P <0.001) and the mean weight of animals as adjusted variable (P <0.001).

P: Probability of treatment effect. The models included the study effect (P <0.001).

RSE: Residual standard error.

R^2: Coefficient of determination of the model.

%: Percentage change between AGP+ and AGP-.

n: Number of studies observations in each mean.

Table 4. Simulation of the economic impact of the antibiotic growth promoter Withdrawal from broiler diets containing antibiotic growth promoters (AGP+) or not (AGP -)

	Treatments		
	AGP+	**AGP-**	**Variation**
Initial (1-21 days)			
Feed conversion, g/g	1.47	1.51	2.64
Feed intake, g/animal	1155	1176	1.78
Feeding cost, $/animal	0.27	0.28	0.01
Feeding cost[1], $/year	1,596,452,300	1,635,403,026	38,950,725
Total (1-42 days)			
Feed conversion, g/g	1.66	1.72	3.48
Feed intake, g/animal	4.150	4.290	0.14
Feeding cost, $/animal	0.96	0.99	0.03
Feeding cost, $/year	5,601,424,320	5,784,984,552	183,560,232

[1]Feeding cost: considering 5.840.000.000, slaughtered broilers/year (IBGE, 2017).

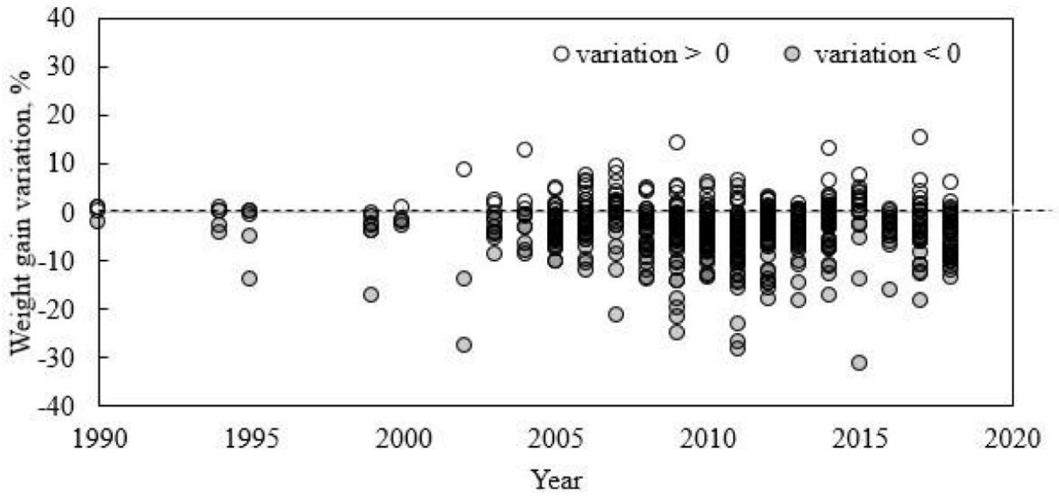

Figure 1. Percentage change calculated for each treatment containing antibiotic growth promoter (AGP) in relation to its respective treatment without AGP in studies included in the database according to year of publication.

Variation between feed conversion (AGP+ and AGP-; %)	Variation in price of AGP					
	X/2	X[1]	2X	3X	4X	5X
0.00	AVOID[2]	AVOID	AVOID	AVOID	AVOID	AVOID
0.15	USE[3]	AVOID	AVOID	AVOID	AVOID	AVOID
0.30	USE	USE	AVOID	AVOID	AVOID	AVOID
0.50	USE	USE	USE	AVOID	AVOID	AVOID
1.00	USE	USE	USE	USE	AVOID	AVOID
2.00	USE	USE	USE	USE	USE	USE
3.00	USE	USE	USE	USE	USE	USE
4.00	USE	USE	USE	USE	USE	USE
5.00	USE	USE	USE	USE	USE	USE

Figure 2. Sensitivity analysis of antibiotic growth promoter (AGP) withdrawal of broiler diets according to the variation of the additive price and variation between feed conversion rate with or without AGP.

[1]X: current price of antibiotic growth promoter.

[2]AVOID: the situation where it is possible to raise broilers without AGP with no economic losses.

[3]USE: the situation where it is indicated the use of AGP to have no economic losses.

CAPÍTULO III

Withdrawal of antibiotic growth promoters from pig diets: performance indexes and economic impact – A meta-analysis

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WITHDRAWAL OF ANTIBIOTIC GROWTH PROMOTERS FROM PIG DIETS: PERFORMANCE INDEXES AND ECONOMIC IMPACT – A META-ANALYSIS

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Abstract

This study aimed to estimate the productive and impact on feeding costs caused by the elimination of antibiotic growth promoters (AGP) from pig diet. Indexed publications that compared diets with AGP (AGP+) or without AGP (AGP-) for pigs (from weaning to finishing phases) were collected, and the performance results (feed intake, weight gain, and/or feed conversion/efficiency) were compiled in a database. A meta-analysis was performed following sequential analyses: graphical approach (to observe biological data coherence), correlation (to identify related factors), and variance-covariance (to compare groups). The target weight gain and feed conversion, the variation in feed conversion, feed cost, and AGP cost were used to build a model which estimates the effects of AGP withdrawal on feed cost. The database comprised 81 scientific articles containing 103 experiments totaling at 42,923 pigs, most of which were in the post-weaning phase (70% of the studies). The most frequent AGP in the database were Avilamycin (24.7% of the AGP+ treatments), Colistin (15.4%), Tiamulin (11.7%), Tylosin (8.0%), Lincomycin (9.4%), and Bacitracin (5.4%). Higher weight gain ($P < 0.05$) was observed in AGP+ diets post weaning (6.57%), as well as during the overall period (from post-weaning to finishing phases) (4.41%). However, no effect of AGP on the weight gain of growing-finishing pigs was observed. Better ($P < 0.05$) feed conversion in pigs fed AGP+ diets was observed in all rearing phases. Weight gain and feed conversion improved ($P < 0.05$) with the addition of Avilamycin, Bacitracin, and Tylosin. The AGP withdrawal in the post-weaning phase increased the impact on feeding costs by USD $0.86 per animal and in the growing-finishing phase the increase was USD $ 3.11. It was concluded that pigs fed AGP+ diets have higher performance than

those fed AGP- diets, and that the withdrawal of AGP increases the feeding costs.

Introduction

Antimicrobial additives have been used in animal feed since the 1950s, and the consumption of antibiotics and antibiotic growth promoters (AGP) is expected to increase by 67% between 2010 and 2030. This prediction is related to the shifting production practices in middle-income countries, where large scale intensive farming routinely uses AGP to address sanitary pressure and hazardous management practices [1]. This result can be an overestimation, taking in account the compliance of many countries with the restrictions on AGP use, and in some cases, the complete ban of AGP use in animal production. Sweden was the first country in the EU to impose such a ban of all AGP in 2006; the USA is not only limiting AGP use, but is also moving toward a significant reduction of general antibiotic usage in industrial food animal production [2]. The most recent effort toward AGP restriction in Brazil and China was banning the use of colistin in 2016 [3,4]. In the same year, Vietnam announced the ban of AGP by 2020 [5]. India [6], Bangladesh, Bhutan, Indonesia, Myanmar, Nepal, Sri Lanka, and Thailand [7] have also imposed AGP restrictions. 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 humans [8,9].

In industrial pig production, AGP are used to improve intestinal function, thereby helping to reduce the incidence of diarrhea in post-weaning animals [10,11]. There is considerable variability in the performance responses to AGP, contingent on genetic potential, age, as well as hygiene and management practices. Many studies have shown no weight gain difference in animals fed an AGP diet in the absence of health problems [12,13,14,15]. However, other studies have reported positive effects of AGP on pig weight gain and feed conversion [16,17,18,19], mainly during the growing and finishing stages of production [20].

It is clear that AGP use restriction in the production of food animals is expanding and therefore its consequences must be studied, including its effect on pig production performance and the expected economic results on feeding cost of such restriction. The objective of this study was to quantify the performance differences in pigs receiving diets with and without AGP, and to estimate the impact on feeding costs of AGP withdrawal.

Material and methods

Search, Data Filtering and Coding

Scientific literature presenting experimental results of pig performance with antibiotic growth promoters (AGP) were searched for in different online data sources (Google Scholar, ScienceDirect, Scopus, Scielo, and PubMed) using the keywords: “antibiotic growth promoter” and “performance” in addition to the terms “swine” or “pig”. As strategy, "AND", "OR" and "*" were used to aid in the search, aiming to find as many studies as possible. The search terms were tested in English, Spanish, and Portuguese. References cited in the resulting publication list were also reviewed to identify any additional relevant articles. This diversity of scientific databases was intended to prevent potential publication bias. Following identification, abstracts were examined by two researchers, and a record was only removed from the database following agreement. At this stage, the studies were critically evaluated according to relevance and quality in relation to the meta-analysis objectives. A set of information about each selected study was examined against a previously prepared checklist, and critically evaluated for eventual methodological errors. For the exclusion of pre-selected manuscripts, the following factors present in the checklist (S1) were considered: presence of sanitary challenge, slow-growing breeds, absence of control treatment, inconsistent methodological data, error of statistical design such as factorial design analyzed as simple difference in means, and gross errors in result data. The criteria for publication selection were: (1) *in vivo* experimental evaluation of diets with AGP (AGP+) or without AGP (AGP-); (2) antibiotics dosage was within the recommended range for growth promoters; (3) the AGP used was permitted in the Brazilian standard legislation of 2016; (4) the experimental pigs were in post-weaning, growing, or finishing phases; (5) the rates of feed intake, weight gain, and feed conversion or feed efficiency were stated; (6) year of publication was 1990 until 2018.

The methodology used for database construction and data encoding followed the methods described in the literature [21,22]. The data were entered in an electronic spreadsheet, which consisted of rows representing the treatments and columns representing the exploratory and descriptive variables. Information relevant to the objective of the study (body weight, feed intake, weight gain, and feed conversion) and other variables (genetic strain, age, sex, dietary nutritional composition, and duration of the experimental period) were included to allow for a descriptive analysis of the studies. Some codes were used to create grouping criteria in the analytical models; the main codes were applied for the presence (AGP+) or absence (AGP-) of AGP and for each antibiotic, such as "A" for

Avilamycin and "B" for Bacitracin. Other codes were used as moderating variables to represent the variability of the compiled trials (e.g.: effect of study or trial).

Composition of the database

The database consisted of 81 articles containing 103 experiments (S2). The majority of the selected papers (97%) were published between 1998 and 2018 (Fig 1), and studies were developed in China (20%), Brazil (16%), USA (16%), Canada (9%), and other countries (31%), such Greece, Spain, Poland, and Korea. The total number of pigs used in all trials combined was 42,932, with 17.3 and 30.4 kg as the average of the initial and final body weights, respectively. Weaned pigs were used in 70% of the studies (average age at weaning: 23 days, minimum: 14 days, maximum: 35 days), and the performance of pigs in the growing-finishing phase was evaluated in 20% of the articles, while the last 10% did not include a description of the production phase. The average duration of the experiments was 29 days (maximum: 134 days). The most frequent antibiotics in the database were Avilamycin (24.7% of AGP+ treatments), Colistin (15.4%), Tiamulin (11.7%), Tylosin (8.0%), Lincomycin (9.4%), and Bacitracin (5.4%). Mixed-sex groups were used in 47% of the reviewed studies, and treatments with male-only or female-only groups represented 7% and 2% of the total, respectively. The gender of the pigs was not stated in the remaining 44% of the studies.

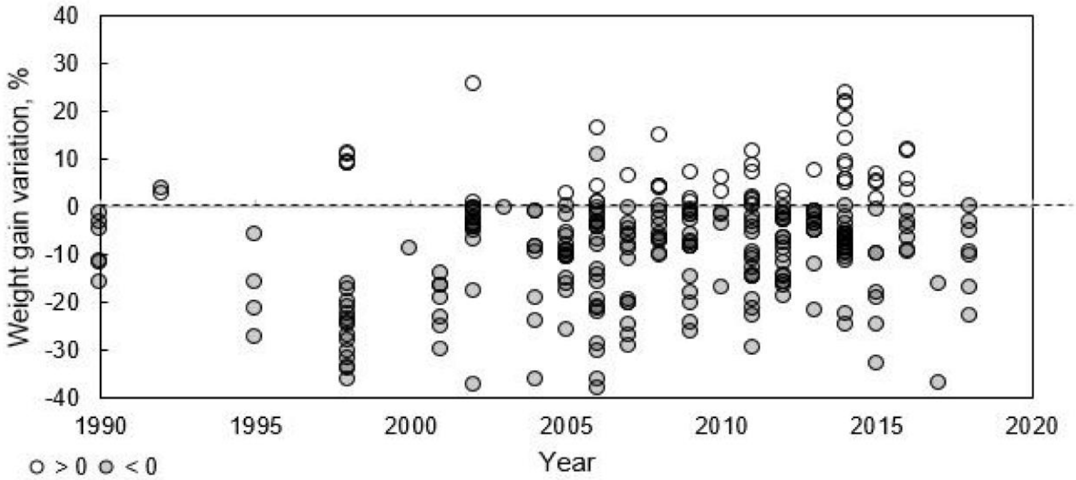

Fig 1. Percentage variation calculated for each treatment containing antibiotic growth promoter (AGP+) in relation to the opposite treatment without it (AGP-). Data collected from the studies included in the database, according to year of publication.

Statistical analysis

Series of graphical analyses were used to analyze the data distribution and to obtain a general view of their consistency and variance heterogeneity. Based on these analyses, correlation hypotheses were formulated to define the statistical models [22]. During this step, the data distribution per year, country, and for the presence or absence of AGP were evaluated. The performance data of the AGP- treatments were relativized according to their respective AGP+, in order to estimate the impact (percentage variation) of AGP withdrawal. Additionally, the relationships between and within studies were evaluated.

Variance-covariance analyses were conducted using the GLM procedure in the Minitab 18 statistical package (Minitab Inc., State College, PA); the effects of gender of the animals, type of facilities and year of publication were tested.

However, the factors were not significant (P > 0.05) and consequently, all three factors were removed from the model. A mixed model was applied, considering treatments as fixed effect, while inter-study codes and mean body weight were random effects (P < 0.05). Variables analyzed were feed and lysine intake, weight gain, and feed conversion. The analyses were grouped by rearing phase (post weaning and growth-to-finishing), when the information about the phase of rearing was provided in the original publication. In addition, an overall performance analysis was carried out considering the entire database, including the studies with both rearing phases and also the studies without phase identification (information not provided in the publication). Individual analyses were also performed for the main AGP in the database. A residual analysis was performed, and it was observed that the residuals were normally distributed.

Impact on feeding costs

The parameters obtained by the meta-analysis were used to construct a model that estimates the effects of AGP elimination on the production costs, particularly feeding costs in the Brazilian scenario. Brazil was chosen for this simulation as it is a large producer and exporter of pork. Moreover, AGP withdrawal is an important and current debate in the Brazilian meat industry. The simulation (Equation 1 to 4 and Table 1) considered the target weight gain and feed conversion for each phase (in AGP+ diets), the variation in feed conversion (obtained from the meta-analysis), as well as feed and AGP costs (information provided by a local feed factory).

Cost of feeding per animal = $\alpha \times \left(\frac{\beta}{1000}\right)$ (1)

Where: α: feed intake of the phase (kg/day) and β: cost of feed ($/ton).

Feed intake of the phase = $\tau \times FCR$ (2)

Where: T: weight gain of the phase (kg) and FCR: feed conversion (kg/kg).

Cost of feed: $\mu + y$ (3)

Where: μ: price of feed ($/ton) and ý: price of AGP ($/ton).

The performance data of animals that received and did not receive AGP was used in the equations, and the difference between the results was calculated to estimate the impact on feeding costs

The currency conversion rate used for the calculation of impact on feeding costs in USD was: $1.00 = R$ 3.75.

Table 1. Inputs for estimating the economic impact caused by the withdrawal of antibiotic growth promoters (AGP) from pig diets

Inputs	**Post-Weaning**	**Growing-Finishing**	**Overall performance[1]**
Weight gain, kg	20	90	110
Feed conversion target (AGP+), kg/kg	1.64	2.56	1.80
Feed conversion change[2], %	3.59	5.51	3.92
Feed cost, USD $/ton	747	253	248

[1]Overall performance: The analysis considered the entire database.

[2]Feed conversion change: the difference between diets with and without AGP obtained by the meta-analysis.

A sensitivity analysis was performed using the key variables "feed conversion" and "AGP price." A sensitivity analysis indicates whether one or more variables can have an impact on the economic results of a production system and influence its profitability [24]. The equations developed to calculate the impact on feeding costs were used to perform the sensitivity analysis. Feed conversion data were simulated to obtain 0.0, 1.0, 2.0, 3.0, 4.0, and 5.0% of difference between AGP+/AGP-. The AGP price was reduced in half or increased 1.0, 2.0, 3.0, 4.0, and 5.0 times compared to the current price. When the value of the impact on feeding costs was greater than zero, AGP withdrawal was judged as an economically sound strategy, and when the impact value was less than zero, AGP use was judged as the better economic decision to avoid financial loss. The price of the feed used to evaluate the overall performance was utilized in the sensitivity analysis. The analysis was performed using Microsoft Excel 2016.

In this study, only the feed cost was considered; therefore, other factors such as management and sanitary costs were not included in the economic impact model.

Results

Performance

The use of AGP+ diets presented an overall positive impact on pig performance. A negative variation in weight gain was observed in 83% of comparisons between AGP+ and AGP- diet-fed pigs in the database (Fig 1). Likewise, better feed conversion was observed in 77% of the intra-study comparisons among treatments. However, it is important to point out that some of these changes were not statistically significant in the original studies.

In the meta-analysis, the feed and lysine intake did not differ ($P>0.05$) between the AGP + and AGP- treatments in all the examined production phases. Weight gain rates were higher ($P < 0.05$; Table 2) when AGP+ diets were used in post-weaning and in overall performance, but no such effect was detected during the growing-finishing phase (P > 0.05). AGP+ diet resulted in 6.57% and 4.41% weight gain in the post-weaning and overall performance phases, respectively. The effect on feed conversion even more pronounced (P < 0.05) in pigs fed AGP+ diet, in all rearing phases; The highest effect was 5.51% in the growing-finishing phase, followed by the overall performance with 3.92%, and finally the post-weaning phase with 3.59%.

Table 2. Performance (obtained by meta-analysis) of pigs fed diets with antibiotic growth promoters (AGP+) or without antibiotic growth promoters (AGP-)

Variable	**Treatments**		**P**	**RSE**	**R^2**	**%**
	AGP+	**AGP-**				
Post weaned						
Feed intake, kg/d	0.609 (N:197)	0.592 (N:190)	0.508	0.251	58.33	2.79
Weight gain, kg/d	0.365 (N:202)	0.341 (N:195)	0.039	0.115	56.85	6.57
Feed conversion, g/g	1.642 (N:194)	1.701 (N:187)	0.008	0.213	62.24	3.59
Lysine intake, kg/d	0.763 (N:151)	0.737 (N:148)	0.412	0.267	55.53	3.40
Growing/ finishing						
Feed intake, kg/d	2.095 (N:69)	2.080 (N:46)	0.855	0.317	65.79	0.71
Weight gain, kg/d	0.805 (N:70)	0.769 (N:47)	0.078	0.101	68.65	4.47
Feed conversion, g/g	2.565 (N:69)	2.704 (N:46)	0.038	0.232	54.49	5.51

Lysine intake, kg/d	2.053 (N:48)	2.016 (N:32)	0.735	0.244	60.99	1.80
Overall performance*						
Feed intake, kg/d	0.884 (N:208)	0.882 (N:198)	0.907	0.158	95.10	0.22
Weight gain, kg/d	0.443 (N:217)	0.423 (N:207)	0.028	0.094	84.05	4.51
Feed conversion, g/g	1.809 (N:208)	1.880 (N:198)	<0.001	0.195	85.76	3.92
Lysine intake, kg/d	0.923 (N:151)	0.907 (N:150)	0.575	0.247	82.79	1.73

*Overall performance: The analysis considered the entire database. The model considered the effect of the study (P<0.001) and the body weight of animals (P<0.001).

P: Probability of treatment effect. The models included the study effect (P<0.001).

RSE: Residual standard error.

R^2: Coefficient of determination of the model.

%: Percentage of difference between AGP+ and AGP-.

N: Number of observations in each means.

Analyzing each AGP treatment individually (Table 3), AGP- diet influenced feed intake (P > 0.05). The addition of Colistin, Tiamulin, and Lincomycin did not result in any detectable difference in weight gain between AGP+ and AGP- diets (P > 0.05), while the addition of Avilamycin, Bacitracin, and Tylosin showed a positive effect on weight gain, as well as feed conversion (P < 0.05).

Table 3. Overall performance* (obtained by meta-analysis) of pigs fed diets containing specific antibiotic growth promoters (AGP+) or without it (AGP-)

Variable	Treatments	P	RSE	R^2

	AGP+	AGP-			
Colistin					
Feed intake, kg/d	0.690 (N:42)	0.674 (N:42)	0.526	0.117	96.98
Weight gain. kg/d	0.388 (N:45)	0.374 (N:45)	0.439	0.083	87.96
Feed conversion. g/g	1.645 (N:42)	1.641 (N:42)	0.917	0.160	79.67
Avilamycin					
Feed intake, kg/d	0.759 (N:60)	0.755 (N:57)	0.838	0.123	95.86
Weight gain, kg/d	0.403 (N:61)	0.371 (N:58)	0.039	0.091	81.04
Feed conversion, g/g	1.714 (N:60)	1.806 (N:57)	0.008	0.183	87.27
Bacitracin					
Feed intake, kg/d	0.675 (N:10)	0.750 (N:10)	0.253	0.132	97.14
Weight gain, kg/d	0.289 (N:12)	0.221 (N:12)	0.049	0.108	59.11
Feed conversion, g/g	1.802 (N:10)	1.915 (N:10)	0.048	0.126	96.49
Tylosin					
Feed intake, kg/d	1.497 (N:22)	1.490 (N:22)	0.898	0.192	95.90
Weight gain, kg/d	0.607 (N:22)	0.541 (N:22)	0.036	0.119	86.54

Feed conversion, g/g	2.005 (N:22)	2.172 (N:22)	0.045	0.195	86.08
Tiamulin					
Feed intake, kg/d	0.647 (N:13)	0.689 (N:13)	0.177	0.075	98.18
Weight gain, kg/d	0.334 (N:13)	0.322 (N:13)	0.391	0.036	94.10
Feed conversion, g/g	1.554 (N:13)	1.675 (N:13)	0.080	0.165	89.02
Lincomycin					
Feed intake, kg/d	0.468 (N:13)	0.479 (N:13)	0.678	0.065	97.06
Weight gain, kg/d	0.210 (N:13)	0.195 (N:13)	0.514	0.055	91.03
Feed conversion, g/g	1.673 (N:13)	1.7818 (N:13)	0.098	0.157	60.75

*Overall performance: The analysis considered the entire database. The model considered the effect of the study (P <0.001) and the mean weight of animals as adjusted variable (P <0.001).

P: Probability of treatment effect. The models included the study effect (P <0.001).

RSE: Residual standard error.

R^2: Coefficient of determination of the model.

%: Percentage of difference between AGP+ and AGP-.

N: Number of observations in each mean.

Impact on feeding costs

AGP withdrawal in the post-weaning phase increased the impact on feeding costs by USD $0.86 per animal. In the growing-finishing phase, the increase was more pronounced, with a rate of USD $ 3.11 per animal and using the overall performance, the impact on feeding costs is expected to be USD $ 1.83 per animal (Table 4).

Table 4. Simulation of the economic impact of eliminating antibiotic growth promoters

	Treatments		
	AGP+	**AGP-**	**Change, %**
Post-Weaning			
Feed conversion, kg/kg	1.64	1.70	3.59
Feed intake, kg/animal	32.80	33.98	3.47
Feeding cost, USD $/animal	24.50	25.37	3.42
Growing-Finishing			
Feed conversion, kg/kg	2.56	2.70	5.51
Feed intake, kg/animal	230.40	243.10	5.22
Feeding cost, USD $/animal	58.47	61.58	5.05
Overall performance[1]			
Feed conversion, kg/kg	1.80	1.87	3.92
Feed intake, kg/animal	198.00	205.76	7.77
Feeding cost, USD $/animal	49.19	51.02	3.58

Data from pig diets containing antibiotic growth promoters (AGP+) or without it (AGP-)

[1] Overall performance: The analysis considered the entire database.

In the sensitivity analysis (Fig 2), "AVOID" indicates a scenario where the elimination of AGP has no negative impact on feeding costs, and "USE" indicates one where the use of AGP is necessary for avoiding economic losses. The model has a measure of change within each variable (by defining them as ranges) to enable AGP withdrawal without incurring an economic loss in feeding. For example, if the difference in feed conversion between the AGP+ and AGP- diets does not exceed 0.5%, and AGP price increases five times over the current price, AGP can be eliminated with no impact on feeding costs. However, considering the current AGP price and the difference in feed conversion ratio between the two diets (5.51% in the growing-finishing phase; 3.92% in overall performance, and 3.59% in the post-weaning phase), an impact on feeding costs is expected. If AGP price was halved, with zero variation in feed conversion, AGP withdrawal will have no negative impact on feeding costs. However, in the situation of half of the current price, even a variation in feed conversion less than 0.15% would require AGP use to maintain profitability.

Variation between feed conversion (AGP+ and AGP-	Variation in price of AGP					
	X/2	X[1]	2X	3X	4X	5X
0.00	AVOID[2]	AVOID	AVOID	AVOID	AVOID	AVOID
0.15	USE	AVOID	AVOID	AVOID	AVOID	AVOID
0.30	USE	USE	AVOID	AVOID	AVOID	AVOID
0.50	USE	USE	USE	AVOID	AVOID	AVOID
1.00	USE	USE	USE	USE	USE	USE
2.00	USE	USE	USE	USE	USE	USE
3.00	USE	USE	USE	USE	USE	USE
4.00	USE	USE	USE	USE	USE	USE
5.00	USE	USE	USE	USE	USE	USE

Fig 2. Sensitivity analysis for antibiotic growth promoter (AGP) elimination from pig diets according to the change in the additive price and the change between feed conversion rates with and without AGP.

[1]X: current price of antibiotic growth promoter.

[2]AVOID: the scenario rearing pigs without AGP incurs no impact on feeding costs.

[3]USE: the scenario where the use of AGP is expected to incur no impact on feeding costs.

Discussion

Our results showed a clear connection between AGP feed supplementation and pig growth, which was particularly evident in feed conversion and weight gain. Contrarily, no relation was found between AGP supplementation and feed intake. Laxminarayan et al. [25] suggest that there has been a reduction in the effectiveness of AGP in the last 30 years, which may be linked to optimization of production conditions, increasing in the baseline weight gain of animals, increasing level of resistance, and potential switch in the type of molecules used. In contrast, the "year" effect was not significant in the current meta-analysis. This result may be associated to the fact that the studies selected to compose the database did not have any type of sanitary challenge.

The mechanism by which AGP act is not entirely understood to date, and a multitude of factors will influence the performance results: including the rearing environment, stress, and diet characteristics. Different mechanisms of action have been proposed and several studies have been carried out to explain AGP function; a growth-promoting effect coincides with the decreased activity in bile salt hydrolase (BSH) in the gut [26,27]. Conjugated bile acids play a critical role in lipid solubilization and micelle formation, and are the target substrates of BSH. De-conjugation of bile acids by BSH compromises lipid metabolism and results in an attenuated energy harvest [27]. Other authors confirmed the use of AGP to be the most common dietary intervention to modulate the composition of gut microbiota [28,29] and their activity, including both pathogenic and commensal bacteria [30]. The gut bacterial population influences a variety of immunological, physiological, nutritional, and protective processes of the gastro-intestinal tract, and exerts effects on the overall health and performance of non-ruminant animals [28]. Although the composition of gut microbiota varies among pigs, it is possible to verify the reduction of *L. johnsonii*, *Clostridiales*, and *Turicibacter* along with the increase of *L. amylovorus* in the ileum when the animals were fed a diet containing AGP [29]. Another hypothesis is that AGP can, directly or indirectly, affect the intestinal physiology of the pig. Nutrient absorption is not the intestines' sole function, as they perform an immunological role as well [31]. The close and intermittent contact of the gastro-intestinal mucosa with the enteric microbiota results in a constant state of inflammation [32], and can increase macromolecular intestinal permeability [33]. AGP accumulate in the inflammatory cells and enhance the intracellular killing of bacteria, inhibiting the innate immune response [34,35]. In addition, some AGP, such as Avilamycin, decreased NFκB expression in mesenteric lymph nodes, ileum, colon, and liver, suggesting a decrease in those tissue´s inflammatory response [36]. Therefore, the use of AGP decreases the catabolic costs of maintaining an immune response by allowing more resources to be dedicated to anabolic processes [37].

The weaning phase is an extremely stressful phase in industrial pig production, and is caused by multi-factorial stressors, including social, environmental, nutritional, and psychological conditions [38,39]. During this period, the piglets experience breast milk withdrawal and must adapt to a new plant-based and less digestible diet with some anti-nutritional properties. Considering the hypothesis of a non-antibiotic action of AGP, which results in a reduced intestinal inflammatory response [36,37], this may be an explanation of the positive correlation between AGP and piglet weight gain in post-weaning. On the other hand, pigs in the finishing phases are much more able to cope with stressors due to their increased ability to synthesize immunoglobulins [40], and that can limit the response to dietary AGP in this phase.

When AGP were analyzed individually, the higher variation in performance responses were found in the peptides (Bacitracin), macrolide (Tylosin) and orthosomycin (Avilamycin), and the lower responses were those of macrolides Tiamulin and Lincomycin, along with polymyxins (Colistin). Even some AGP belonging to the same general classification had different effects, and this behavior could be reflected in the roles AGP play in different action mechanisms in the organism, which result in rearing-phase-specific action. Niewold [37] reported that AGP compounds can essentially be divided into groups based on their interaction with inflammatory cells, as non-accumulating, accumulating without inhibition of function, and accumulating with inhibition of function; for example, cyclines, macrolides (Tylosin) and peptides (Bacitracin) showed phagocyte-inhibition function [35]. In another proposed method of action, tetracycline antibiotics were consistently potent inhibitors of BSH, while both Roxarsone and Oxytetracycline inhibited BSH activity by over 95%. β-lactam and lincosamide (Lincomycin) displayed relatively lower inhibitory effects on BSH activity, whereas macrolides (Tylosin and Erithromycin) and peptides (Bacitracin) had a weak effect on BSH activity [27]. Antibiotics growth promoters have an impact on the intestinal microbiota, but there are still doubts about the mode of action. Experiments using chickens as model indicate that the use of tylosin, a macrolide that inhibits growth of gram-positive and a limited number of gram-negative bacteria, can reduce levels of gram-positive pathogens (*Clostridium* *perfringens*) [41]. Other author related that tylosin rather accelerated the shift in microbiota that normally occurs over time as the host grows [42]. The tiamulin, another macrolide, can reduced ileal microbiota diversity and promoted the establishment of Firmicutes such as *L. amylovorus*–like bacteria in the ileum of weaned piglets [43].

Several studies have estimated the economic impact caused by the withdrawal of AGP from the pig industry. In our study, the impact on feeding costs of Overall Performance resulted in a loss of $ 1.83 per pig; Miller et al. [44] and Brorsen [45] suggest $ 1.37 and $ 2.33 per pig, respectively. The large differences in the results may be linked to the factors considered to generate the economic models. Some costs associated with the production system are difficult to measure and have not been included in the economic calculations [46]. Different authors report that the economic impact will affect producers differently, since there is a variation in the factors considered in the characterization of the productive scenario, such as farm size, contracting arrangements, and production practices [47, 48]. The productive impact considered this study was focused on the feeding of pigs, and this can become part of a more complete economic impact analysis, taking into account aspects such as sanity, productive structure, labor, housing period, among others. Although it is based in a very simple approach, the model may provide relevant information for nutritionists and producers while facilitating the decision making process. The equations were to estimate the economic impact in the Brazilian scenario because the country is one of the largest producers and exporters of pork. However, the equations are easy to understand and updated productive data from different countries/scenarios can be simulated, even with economic and production scenarios different from Brazil.

To better understand our findings in relation to the impact on feeding costs, it is safe to consider that the increased feed costs are a result of AGP use, which conversely reduces feed cost by improving feed conversion ratio. The result of the impact on feeding costs for Overall Performance is not the simple summation of the post-weaning and growing-finishing phases. The Overall Performance feed cost is the weighted average of the period that the animals receive the feed, and the performance data was obtained by the meta-analysis with a large number of studies.

The meta-analysis highlighted a reduction in pig performance when fed AGP- diets, which may lead to an increase in the feeding costs. Considering the current situation (AGP prices and a 3.92% better feed conversion using AGP), the results of the overall performance showed an increase of 3.6% in the feeding costs per animal with AGP withdrawal. However, if the difference in feed conversion between AGP+ and AGP- diets is brought down to zero, there will be no increase in feed costs, and AGP could be eliminated from animal feed as exhibited by the results of the sensitivity analysis. To reduce the difference in feed conversion it is necessary to implement new management strategies, mainly using biosecurity as a tool to reduce diseases [49], and vaccination to improve the overall health status, reducing the risk of secondary infections [50,51]. The optimization of the climate and housing conditions can improve performance and reduce the usage of AGP.

Nutritional strategies are also necessary for such reduction; various feed additives as organic acids, essential oils, copper sulphate, zinc oxide, probiotics, and prebiotics have been studied to elucidate their effects [52]. Probiotics improved gut health [52,53] and demonstrated an ability to affect the presence of pro-inflammatory cytokines and chemokines in vitro or in the pigs' gut microbiota [54]. Although it is possible to reduce the difference in feed conversion between animals fed AGP+ and AGP- diets, there is still a long way to eliminate such difference entirely. It is necessary to evaluate different strategies to improve productivity without the use of AGP, and to analyze any factors that directly interfere in production costs in addition to feed.

Conclusions

The use of AGP improves weight gain and feed conversion in post-weaning piglets. Grather ratios of feed conversion were also shown in the growth-finishing pigs fed AGP+ diets. The inferior performance of the animals fed AGP- diets resulted in an increase in feeding costs.

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Supporting information

S1 file. **Inclusion and exclusion criteria check list**

S1 file. **Articles included in the database**

CAPÍTULO IV

Considerações finais

O banimento do uso de antibióticos como promotores de crescimento (APC) dentro da produção animal se tornou uma questão fundamental, discutida no mercado consumidor, nas empresas produtoras e exportadoras de carnes em todo o mundo e na comunidade científica. A tendência global é de permitir o uso de antibióticos apenas para o tratamento de enfermidades dos animais, abolindo o seu uso como promotores de crescimento. Porém, a questão do banimento não é fácil de ser resolvida. Os promotores de crescimento são associados à melhora na conversão alimentar dos animais e redução no índice de mortalidade, elevando os ganhos de produtividade. Com o aumento imediato nos custos produtivos, a eliminação dos APC da dieta enfrenta resistência dos produtores e da indústria. Para o banimento dos APC sem maiores custos produtivos, é necessária a adoção de novas estratégias dentro da produção animal, utilizando programas que envolvam diferentes estratégias de manejo, nutrição, sanidade, assim como programas de biosseguridade, com gestão eficiente e treinamento dos profissionais envolvidos. Dentro das estratégias nutricionais, há o crescente avanço nas tecnologias de substituição aos APC, com foco no uso de combinações de soluções, como os probióticos, prebióticos, ácidos orgânicos e óleos essenciais, que modificam de uma maneira menos agressiva o microbioma intestinal, porém que promovem o equilíbrio deste e, como consequência, melhoram a saúde e desenvolvimento dos animais. Para o banimento completo do uso dos APC, faz-se necessário o desenvolvimento de soluções de nível global com medidas de médio a longo prazo, flexíveis e com avaliações transparentes. Planos recentes da OMS para controle da resistência bacteriana e a vigilância no uso de antibióticos são um passo importante. E no Brasil, para acompanhar o alinhamento mundial contra a resistência bacteriana, o Ministério da Agricultura (Mapa) criou o Programa Nacional de Prevenção e Controle de Resistência a Antimicrobianos na Agropecuária (AgroPrevine), auxiliando no controle efetivo do uso de antibióticos.

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