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PREVALENCE OF ANTIMICROBIAL-RESISTANT *ENTEROCOCCUS FAECIUM* IN COMMERCIAL CATTLE: A SYSTEMATIC REVIEW AND META-ANALYSIS

PREVALÊNCIA DE *ENTEROCOCCUS FAECIUM* RESISTENTE A ANTIMICROBIANOS NA BOVINOCULTURA COMERCIAL: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

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SUMMARY

The use of antimicrobials in animals is broader compared to humans, which can influence the increase in microbial resistance. This study was a systematic review which determined the prevalence of resistant *Enterococcus faecium* in commercial cattle. Eighteen studies were included, mainly carried out in European countries (n= 9) and in the production (n= 11) and retail (n= 7) environments. The main material used in the detection of the microorganism was milk. The mean prevalence of resistant *E. faecium* in cattle was 4.3% (95% CI= 2.8–5.0%), but the prevalence in Asia was higher [25.4% (95% CI= 20.5-30.6%)]. There was a higher prevalence in samples from retail (13.7%; 95% CI= 11.5-16.1%) and collected mainly from equipment surfaces (12.5%; 95% CI= 5.5-26.1%) than in the others tested samples. Antibiotics frequently tested were vancomycin, tetracycline, ciprofloxacin, and erythromycin, with resistance percentages of 50%, 59%, 79%, and 94%, respectively. These results reinforce the need to plan interventions to reduce antimicrobials in food-producing animals.

KEY-WORDS: Microbial resistance. Rational use of antimicrobials. Bovines. Cattle.

RESUMO

O uso de antimicrobianos em animais é mais frequente quando comparado aos humanos, e isso pode influenciar no desenvolvimento da resistência microbiana. O presente estudo teve como objetivo realizar uma revisão sistemática cujo desfecho de interesse foi a prevalência de *E. faecium* resistente a antimicrobianos na bovinocultura comercial. Foram incluídos 18 estudos, realizados principalmente em países europeus (n=9), em ambientes de produção (n=11) e destinados ao varejo (n=7). O principal material utilizado na detecção do microrganismo foi o leite. A prevalência de *E. faecium* resistente em bovinos foi de 4,3% (IC 95%=2,8-5,0%), mas a prevalência na Ásia foi maior [25,4% (IC 95%=20,5-30,6%)]. Houve maior prevalência em amostras do varejo (13,7%; IC 95%=11,5-16,1%) e coletadas principalmente de superfícies de equipamentos (12,5%; IC 95%=5,5-26,1%). Os antibióticos frequentemente testados foram vancomicina, tetraciclina, ciprofloxacino, e eritromicina, com percentuais de resistência de 50%, 59%, 79%, e 94%, respectivamente. Estes resultados reforçam a necessidade de intervenções planejadas para reduzir a utilização de antimicrobianos nos animais criados para produção de alimentos.

PALAVRAS-CHAVE: Resistência microbiana. Uso racional de antimicrobianos. Bovinos. Gado.

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INTRODUCTION

Antimicrobials are widely used in human and veterinary medicine to treat and prevent some infectious diseases and promote growth in food animals. Selective pressure due to its constant and sometimes inappropriate use of these drugs has resulted in multi-resistant bacteria that no longer respond to traditional therapies.

Enterococci are opportunistic bacteria from the gastrointestinal tract in humans and animals that can be found in the environment; hospital-acquired infections (Gilmore et al., 2013); contaminating food (food-related material or during their manufacture, storage or commercialization) (Franz et al., 2003).

Over the past three decades, *Enterococcus faecium* has become a prominent cause of human and animal infections characterized by high-level resistance to multiple antibiotics (Munita et al., 2012; Tyson et al., 2018), because of their mobile genetic configuration, chromosomal exchange, or mutation resulting in a selective advantage and clonal expansion of their lineages (Hegstad et al., 2010).

The World Health Organization (WHO) considers drug resistance a global public health concern, since the potential to transfer antimicrobial resistance genes from enteric bacteria in animals to humans can influence human health and the environment (de Jong et al., 2019). The use of antimicrobials in intensive animal breeding is one of the leading causes of the emergence of multidrug-resistant strains (Kimera et al., 2020). Determination of antimicrobial susceptibility of *Enterococcus* in cattle and swine fecal samples showed high level of resistance to erythromycin and tetracycline, in both species, and to streptomycin and kanamycin only in swines samples (Aasmäe et al., 2019).

The antimicrobial resistance of some bacteria has an important impact on the country's economy and animal and public health (Prestinaci et al., 2015). Increases in mortality and morbidity in animals due to resistant bacteria direct impact food production resulting in elevated prices of milk, eggs, and meat (Dadgostar, 2019).

Given the global concern about the growing trend of resistance to antimicrobials and the lack of studies that synthesized these findings in food-producing animals, this systematic review aimed to determine the prevalence of *Enterococcus faecium* resistance in commercial cattle, to describe the geographic distribution and the time course of resistance trends, as well as to map the antimicrobials associated with this resistance.

MATERIAL AND METHODS

This systematic review was performed according to the recommendations specified in the Cochrane Handbook for Systematic Reviews of Interventions (HIGGINS & THOMAS, 2021) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (MOHER et al., 2009). The registration of the review protocol is in the International Prospective Register of Systematic Reviews (PROSPERO), protocol number (CRD42020160160), accessible in https://www.crd. york.ac.uk/prospero/.

Eligibility criteria

The included studies addressed information about resistant Enterococcus faecium in food-producing cattle and their products; and in environments such as slaughterhouses, sales outlets (retail, supermarket, butchers), distributors, transport, storage tanks and in the processing industry.

Studies with incomplete data, data obtained from simulated laboratory conditions, therapeutic guides, guidelines, abstracts, books, book chapters, and methodological studies were excluded.

Information sources

The searches were carried out in the following electronic databases: SCOPUS, Web of Science, MEDLINE and EMBASE, without restriction to language. It was considered the studies published from the last ten years (from 2009 until 2019) and this restriction is justified due to the dynamics of resistance that may vary significantly over time.

Search strategy

The descriptors explored in the search combined Medical Subject Headings (MeSH) terms and their entry terms being them: (Cattle OR (Bos indicus) OR zebu OR zebus OR (Bos taurus) OR (Domestic Cow) OR (Domestic Cows) OR (Bos grunniens) OR Yak OR Yaks) AND ((Drug Resistance) OR (Microbial Drug Resistance) OR (Antimicrobial Drug Resistance) OR (Antimicrobial Drug Resistances) OR (Antibiotic Resistance) AND (*Enterococcus faecium*) OR (*Streptococcus faecium*)).

Selection process

Following a calibration exercise, the reviewers (ALB, FBA, JMS, RLSS and SVS), independently and in pairs, evaluated the titles and the abstracts according to the eligibility criteria. After a second calibration exercise, the same teams of reviewers, in pairs and independently, applied the eligibility criteria to the full text, to confirm potentially eligible studies. The differences were resolved by consensus among the reviewers. When necessary, a third reviewer was used to resolve disagreements.

Data extraction

A standardized and pre-tested data extraction form with instructions was used. The same reviewers, in pairs and independently, were calibrated by extracting at least 3 articles and then coming to a consensus. This procedure should occur until the reviewers are able to extract the data. For articles published only in summary or that whose important information is missing, we contacted the authors to obtain complete information about the methods and results. The following data were extracted: continent and country where the study was conducted, year of collection, type of antibiotic, material analyzed (nasal discharge, feces, carcass, meat, milk and equipment, etc.), environment (retail and production), number of samples, number of positive strains of *Enterococcus faecium* in cattle and prevalence of resistant *Enterococcus faecium*.

Risk of bias assessment

The risk of bias was assessed by reviewers, in pairs and independently, using the adaptation instrument evaluation of cross-sectional studies (MACLEOD et al., 2015). The items investigated were: i) Was some lottery/randomization procedure used to collect the samples? ii) Did the study describe how the resistance of *Enterococcus faecium* was determined? iii) Did the study describe how the total number of samples or animals was determined/calculated? iv) Did the study describe whether researchers adhered to animal welfare regulation rules or if the project was approved by an animal use ethics committee? v) Did the authors mention any conflicts of interest? vi) Was the study published in a journal with an editorial peer-review policy? The results were recorded as yes, no, not reported or not applicable. The disagreements were resolved by a third reviewer, when necessary.

Statistical analysis

Meta-analyzes were performed by grouping prevalence using the DerSimonian and Laird random model and double arcosene transformation proposed by Freeman-Tukey to stabilize variances (BARENDREGT et al., 2013). The temporal trend was investigated by meta-regression of the prevalence identified in double arcosene, in the model of moment's method with the maximum restricted likelihood with the modification of the variance of the coefficients suggested by Knapp & Hartung (2003).

Subgroup analysis was carried out with information by region, environment and material used in the sample. In all analyzes, 95% confidence intervals (95% CI) were considered. The analyzes were performed using the statistical software STATA® version 14.2.

RESULTS AND DISCUSSION

Overall, 3,201 records, 18 studies presented resistance data of *E. faecium* specific in cattle (Figure 1). Studies on resistant *E. faecium* in dairy and meat cattle were performed in different continents. Europe countries seem to have a greater number of research (n= 9; 50%) and the main material infected by the microorganism was milk (n= 10; 55%) (Table 1).

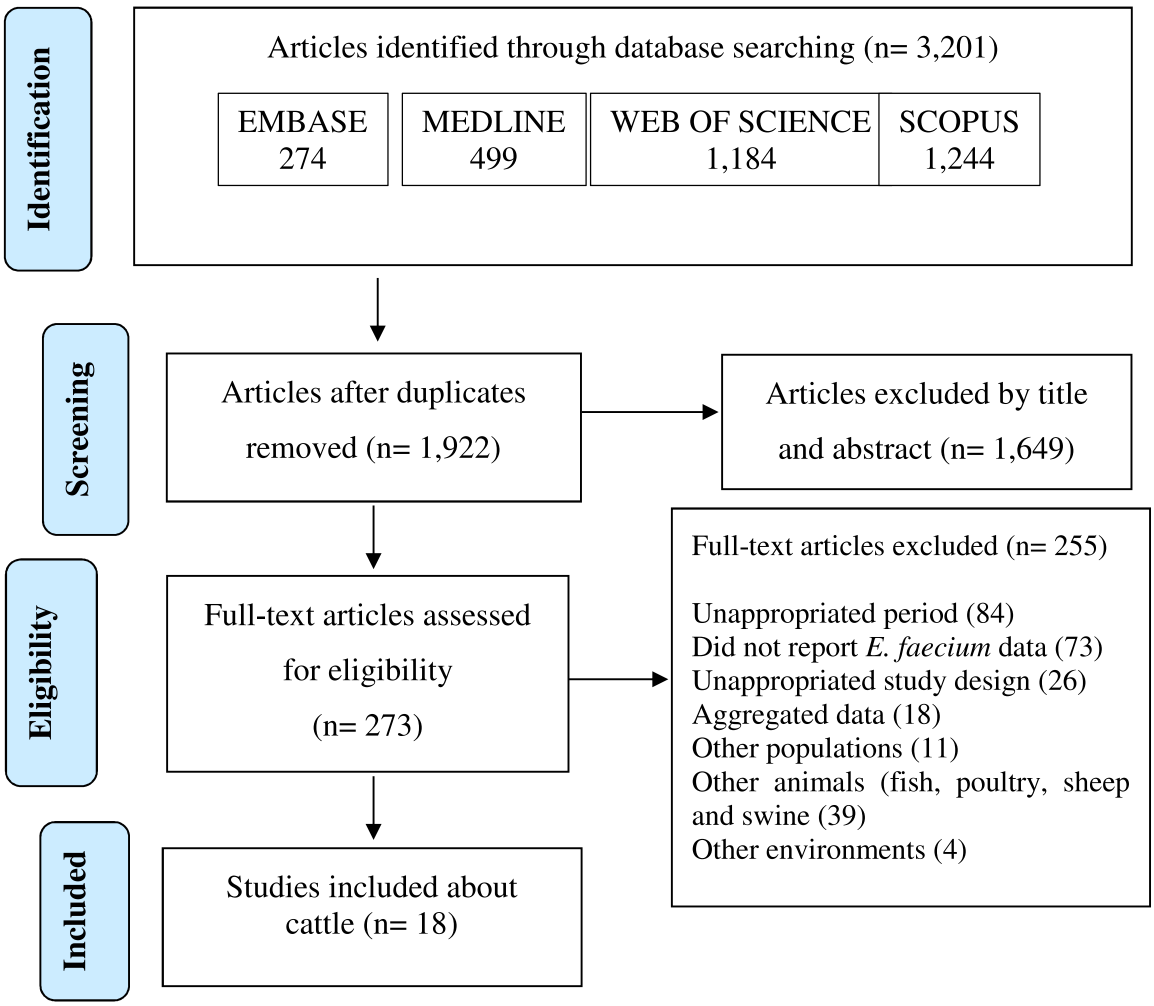

Figure 1 - Flowchart of the study selection process.

Table 1 - Characteristics of the included studies (n= 18 studies).

Author (year)	Continent	Country	Conduct study year	Sample environment	Source of samples
CAMARGO et al., 2014	South America	Brazil	2009	Retail	Milk and dairy products
DE JONG et al., 2019	Europe	European Union	2013	Production	Feces, rectal swab or intestinal contents
EDRINGTON et al., 2011	North America	United States	2009	Production	Feces, rectal swab or intestinal contents
GAGLIO et al., 2016	Europe	Italy	NR	Production	Equipment surfaces
GOUSIA et al., 2016	Europe	Greece	2010	Retail	Meat and meat products
GUERRERO-RAMOS et al., 2016	Europe	Spain	NR	Retail	Meat and meat products
KATEETE et al., 2013	Africa	Uganda	2010	Production	Milk and dairy products
KUREKCI et al., 2016	Asia	Turkey	2014	Retail	Milk and dairy products
MUS et al., 2019	Asia	Turkey	2011	Other location	Meat and meat products
MUS et al., 2019	Asia	Turkey	2011	Other location	Milk and dairy products
NGBEDE et al., 2017	Africa	Nigeria	2014	Production	Feces, rectal swab or intestinal contents
PESAVENTO et al., 2014	Europe	Italy	2012	Retail	Meat and meat products
PESAVENTO et al., 2014	Europe	Italy	2012	Retail	Milk and dairy products
RÓZAŃSKA et al., 2019	Europe	Poland	2014	Production	Milk and dairy products
SOARES-SANTOS et al., 2015	Europe	Portugal	2011	Production	Milk and dairy products
TANIH et al., 2017	Africa	South Africa	2014	Production	Feces, rectal swab or intestinal contents
TERENTJEVA et al., 2019	Europe	Latvia	2016	Production	Feces, rectal swab or intestinal contents
WERNER et al., 2012	Europe	Germany	2010	Production	Milk and dairy products
WU et al., 2016	Asia	China	2011	Production	Milk and dairy products
YOGURTCU & TUNCER, 2013	Asia	Turkey	2010	Retail	Milk and dairy products

The prevalence of resistant *E. faecium* was 4.3% (95% CI= 3.8% to 5%) (Figure 2). The meta-regression showed a slight decrease in the prevalence of resistance over the years ($p > 0.05$) (Figure 3). In subgroups analysis, Asia was the most prevalent continent to resistant *E. faecium*. Regarding the origin, there was a higher prevalence of resistance in samples from retail locations and in samples collected from equipment surfaces (Table 2). Comparing the results of samples obtained from large-scale animal husbandry farms with other smaller properties or animals in slaughter places can influence the results. At the sale sites, the high prevalence of *E. faecium* may be a consequence of most samples being of Asian origin, the continent with the highest prevalence of resistance to this microorganism. The heterogeneity in sampling techniques, the differences in reporting the use of antimicrobial in food animals and the differences of antimicrobials commerce policies worldwide can contribute to the increase of antimicrobial resistance and its impact on the environment, animals, and human health (POKHAREL et al., 2020).

It should be noted that results from different antibiotics of human interest were grouped, which increases the applicability of the findings. The most tested antibiotics were vancomycin (9 of 18 studies - 50%), tetracycline (10 of 17 - 59%), ciprofloxacin (11 of 14 - 79%), and erythromycin (15 of 16 - 94%). Among the studies, 9 of them (50%) found resistance to most tested antibiotics (Table 3). Studies in African countries observed that among *Enterococcus* spp. isolated from livestock (cattle, pigs and chickens); 86.4% (766 isolates) were resistant to clindamycin, 73.3% (650 isolates) to penicillin, 67.9% (1,099 isolates) to erythromycin, 45.8% (824 isolates) to vancomycin and 36.8% (303 isolates) to tetracycline (SEKYERE & MENSAH, 2020). In the present study, similar data of resistant *E. faecium* was observed to erythromycin and vancomycin. Vancomycin-resistant enterococci cause one-third of all healthcare-associated infections in the United States and one-fifth of them in some European countries (HIDRON et al., 2008).

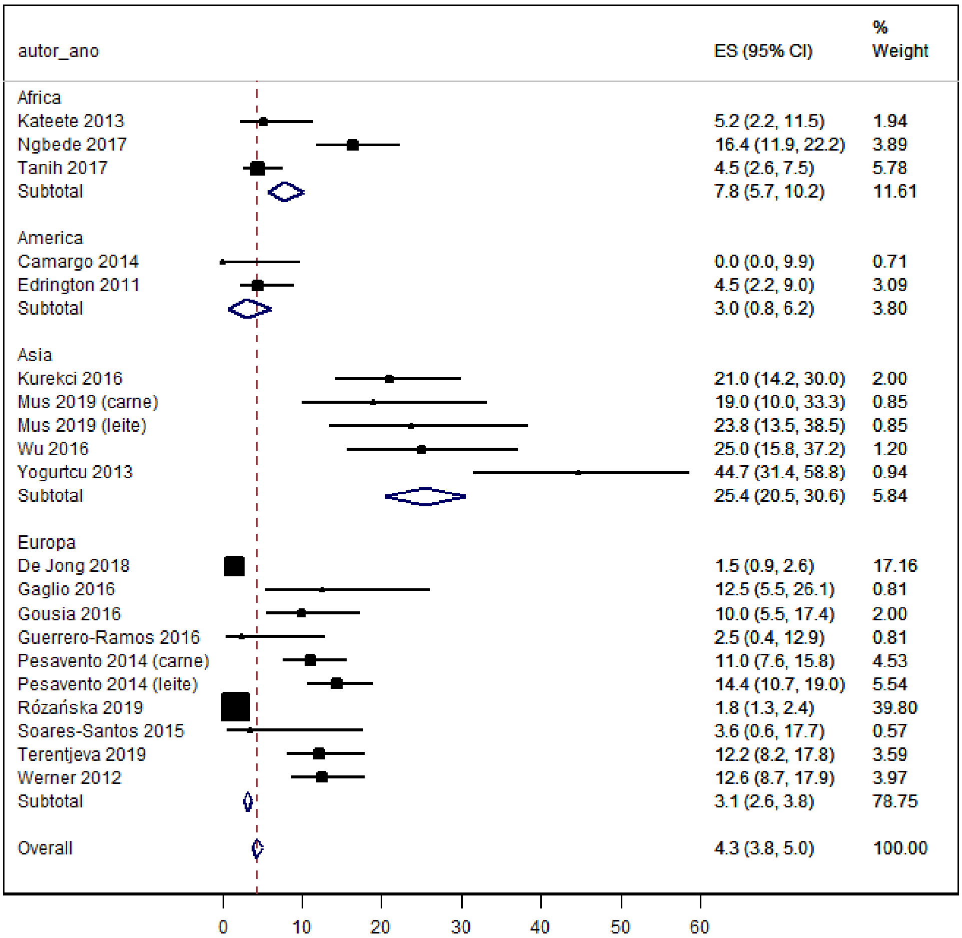

Figure 2 - Meta-analysis of the prevalence of resistant *Enterococcus faecium* in cattle, by continent

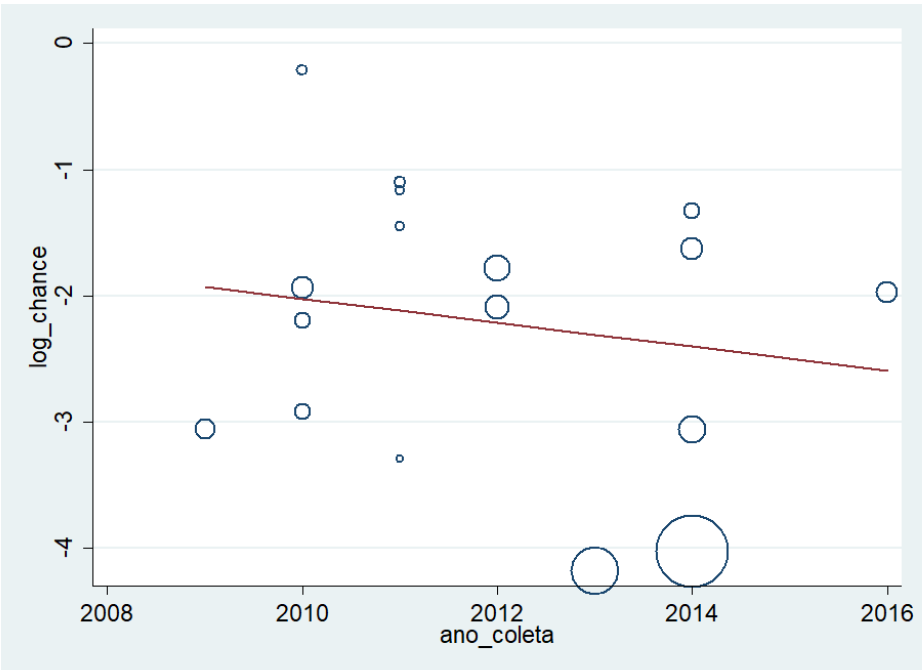

Figure 3 - Meta-regression of the prevalence of resistant *Enterococcus faecium* in cattle, according to the year of sampling

Table 2 - Meta-analysis of the prevalence of resistant *Enterococcus faecium* in cattle on selected subgroups.

Subgroups (number of studies)	% (95% CI)
Continent	
Africa (n= 3)	7.8 (5.7 to 10.2)
America (n= 2)	3.0 (0.8 to 6.2)
Asia (n= 4)	25.4 (20.5 to 30.6)
Europe (n= 9)	3.1 (2.6 to 3.8)
Environment	
Production (n= 11)	3.0 (2.5 to 3.6)
Retail (n= 7)	13.7 (11.5 to 16.1)
***Collected materials**	
Equipment surfaces (n= 1)	12.5 (5.5 to 16.1)
Faeces (n= 5)	4.1 (3.2 to 5.1)
Meat and meat products (n= 4)	10.2 (7.4 to 13.6)
Milk and dairy products (n= 10)	3.8 (3.1 to 4.6)

95% CI: 95% Confidence Interval. * The study may have used more than one type of material.

Table 3 - Susceptibility and resistance of *Enterococcus faecium* to antibiotics in commercial cattle.

Antibiotic / Study	1	2	3	4	5	6	7	8	9a	9b	10	11a	11b	12	13	14	15	16	17	18	R/N	% R
Amoxicillin	-	-	-	-	-	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1	100
Amoxicillin + clavulanate	-	-	-	-	-	-	-	-	-	-	-	S	S	-	-	-	-	-	-	-	0/2	0
Ampicillin	-	R	-	S	R	S	-	S	-	-	R	R	R	-	-	-	S	R	R	S	7/12	58
Chloramphenicol	-	-	S	S	R	S	-	S	-	-	R	R	R	R	S	R	-	S	-	S	6/13	46
Ciprofloxacin	-	-	R	R	R	S	S	I	-	-	R	R	R	R	-	R	R	S	R	-	11/14	79
Daptomycin	-	R	-	-	-	-	R	-	-	-	-	-	-	S	-	-	R	S	-	-	3/5	60
Erythromycin	-	R	R	R	R	S	R	I	-	-	R	R	R	R	R	R	R	R	-	I	15/16	94
Gentamycin	S	R	S	S	-	S	-	I	-	-	R	R	R	R	-	-	S	S	R	S	6/13	46
Kanamycin	-	-	-	-	-	S	-	R	-	-	-	-	-	R	-	-	-	-	-	-	2/3	67
Levofloxacin	-	-	-	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/1	0
Linezolid	-	S	-	S	S	-	-	S	-	-	-	S	S	R	-	R	S	-	-	-	2/9	22
Nitrofurantoin	-	-	-	-	-	-	-	-	-	-	-	-	-	R	-	S	-	-	-	-	1/2	50
Norfloxacin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	S	0/2	0
Penicillin G	-	-	R	S	R	-	-	S	-	-	-	R	R	R	S	R	-	-	R	S	7/11	64
Quinupristin + dalfopristin	-	-	R	S	S	S	-	S	-	-	S	-	-	R	S	R	R	-	-	-	4/10	40
Rifampicin	-	-	-	-	-	-	-	-	-	-	R	-	-	-	R	-	-	R	-	-	3/3	100
Streptomycin	S	-	R	S	-	S	-	S	-	-	R	-	-	R	S	-	-	R	R	R	7/11	64
Sulfamethoxazole + trimethoprim	-	-	-	-	-	-	-	-	-	-	-	-	-	-	R	-	-	-	-	S	1/2	50
Teicoplanin	-	-	-	-	R	S	S	S	-	-	-	R	R	-	-	-	S	S	-	-	3/8	37
Tetracycline	-	R	R	S	S	S	S	S	-	-	R	R	S	R	S	R	R	R	R	R	10/17	59
Tigecycline	-	R	-	-	-	-	-	-	-	-	-	-	-	S	-	-	S	-	-	-	1/3	33
Tylosin	-	-	R	-	-	-	-	-	-	-	-	-	-	R	-	-	-	-	-	-	2/2	100
Vancomycin	S	R	-	S	R	-	S	S	R	R	S	R	R	R	S	R	S	S	R	S	9/18	50

1.Camargo et al., 2014; 2. De Jong et al., 2018; 3. Edrington et al., 2011; 4. Gaglio et al., 2016; 5. Gousia et al., 2016; 6. Guerrero-Ramos et al., 2016; 7. Kateete et al., 2013; 8. Kurekci et al., 2016; 9a. Must et al., 2019 **(meat)**; 9b. Must et al., 2019 **(milk);** 10. Ngbede et al., 2017; 11a. Pesavento et al., 2014 **(meat)**; 11b. Pesavento et al., 2014 **(milk)**; 12. Rózańska et al., 2019; 13. Soares-Santos; Barreto; Semedo-Lemsaddek, 2015; 14. Tanih et al., 2017; 15. Terentjeva et al., 2019; 16. Werner et al., 2012; 17. Wu et al., 2016; 18. Yogurtcu; Tunci, 2013. **N: number of studies. R: resistance. S: sensitive. I: intermediary.**

The main risk of bias found in the studies was the absence of sampling and sample size data. Besides that, half of the studies did not describe potential conflicts of interest (Table 4). The literature review has described that the genes encoding vancomycin, quinupristin, or gentamicin resistance are similar to isolates of *E. faecium* from humans and animals/their meat. The same genes in different hosts indicate the transfer of resistance genes in *E. faecium* isolated from animals to isolates of human origin (HAMMERUM, 2012). As long as animal production expands and the global population increases, the use of antimicrobials in animals for food is expected to increase by 67% (from 63,000 tons in 2010 to 105,000 tons in 2030) (VAN BOECKEL et al., 2019). Efforts to reduce the use of antimicrobials in animals are expanding, with at least 53% of member countries of the Animal Health Organization banning antimicrobials from promoting growth (TIMOTHY et al., 2012).

CONCLUSION

The prevalence of *Enterococcus faecium* resistant in commercial cattle was higher in Asia and observed mainly in retail environments. There was no significant variation in the prevalence of microbial resistance over time. The higher percentage of resistance was observed with erythromycin and ciprofloxacin, antibiotics also routinely used in human medicine. These results reinforce the need to plan interventions that can reduce the use of antimicrobials in food producing animals.

Ethics approval: Not applicable

Conflict of interest: The authors declare no conflict of interest.

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