A systematic review of tetracycline resistance genes in animals and derived products in Latin America and the Caribbean

Uma revisão sistemática dos genes de resistência à tetraciclina em animais e produtos derivados na América Latina e Caribe

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ABSTRACT
We aimed to systematize and assess scientific information on tetracycline (TET) resistance genes in animals, products, and by-products in the Latin America and the Caribbean (LAC) region. PRISMA guidelines were followed. Only original articles published in peer-reviewed journals were considered. Sixty articles published between 2003 and 2023 met the inclusion criteria. The geographical areas of study were Brazil, Mexico, Chile, and Costa Rica, and, to a lesser extent, Colombia, Bolivia, Cuba, Jamaica, Puerto Rico, and Uruguay. The studies were related to livestock, wild animals, and pets. The most common isolated bacteria were *Escherichia coli* and *Salmonella* spp. The *tet* genes found in higher frequency in the samples or isolates evaluated were *tet*A, *tet*B, *tet*M, *tet*L, *tet*K, *tet*C, *tet*O, *tet*D, *tet*G, *tet*W, *tet*S, *tet*Q, *tet*E, *tet*H, *tet*f, *tet*Z, and *tet*Y. Studies evaluating the presence of *tet* genes in animals in LAC are limited despite TET being antibiotics widely used in animals. It is necessary to establish cross-border public policies that allow the constant training of medical and related personnel regarding the responsible use of antibiotics in animals and the effective monitoring of the phenomenon in the region.


RESUMO


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Introduction

The growth of the world population has boosted animal production to meet the high demand for food (Food and Agriculture Organization, 2009). The high animal population densities on a global scale increase the risk of infectious disease outbreaks, leading in turn to increased use of antibiotics both therapeutically and as a growth promoter (Santamaría et al., 2011). Similarly, pet ownership has become more common among families and has increased the global companion animal population, especially dogs and cats, leading to a more frequent presentation of infectious diseases. It has also favored the close contact between humans and animals, depicting a massive challenge for public health (Gomez et al., 2007). In addition, due to current climate changes and global warming, a shift in the distribution of vectors (such as ticks) and the incidence of diseases transmitted by them has been noticed over the last few years (Freitas et al., 2018).

Tetracyclines (TET) are bacteriostatic antibiotics that inhibit protein synthesis. They have become the first option for treating a wide range of infections in human and veterinary medicine, given their broad spectrum (Shutter & Akhondi, 2022). However, their efficacy has declined over time due to the emergence of antibiotic resistance derived from high utilization in the agriculture sector. The most common mechanism of TET resistance is the expression of efflux pumps and ribosomal protection. These two mechanisms are usually mediated by tet genes, primarily transferred horizontally through mobile genetics elements (Roberts & Schwarz, 2016).

The emergence of TET resistance genes represents a threat to the success of bacterial infection treatments, Chopra & Roberts (2001), as this group of antibiotics has been established as an alternative option to treat patients with drug-resistant bacteria such as methicillin-resistant Staphylococcus aureus and extended-spectrum β-lactamase-producing bacteria (LaPlante et al., 2022).

Animals could become spreaders of resistance genes through direct contact with humans or the food chain. This is important to understand the phenomenon and to articulate and strengthen antimicrobial surveillance worldwide. Therefore, this systematic review aimed to systematize and assess scientific publications on TET resistance genes in animals, products, and by-products in the Latin America and the Caribbean (LAC) region.

Materials and Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). Identifying relevant articles considered a specific research question: What are the TET resistance genes and the carrying bacteria found in animals, their products, and by-products in South America and the Caribbean?

Search strategy

The search procedure was performed on March 31, 2023. Four online databases were used to perform the search given the quantity and comprehensive coverage of the available literature (i.e., Web of Science®, PubMed®, Redalyc®, OVID®/MEDLINE). No previous standardized, systematic review on the topic has been published. The research question was separated into components, and different synonyms were established per word.

Eligibility criteria

The inclusion criteria only considered articles published in peer-reviewed journals. Findings were not limited by year or country of publication, not by language.

The systematic article selection process

The selection of citations was done through a stepwise process. The first step was selecting the articles according to the information in the title. Subsequently, the eligible sources were screened by abstract. Lastly, each full text of selected articles was reviewed with particular attention to the materials, methods, and results sections to answer the research question. Articles were considered not eligible using the following non-inclusion criteria: i) irrelevant topics (e.g., COVID, plant-based compounds, ELISA, mecA, CTX-M, plasmid coding, bla-related genes); ii) species other than the ones of interest/environment (e.g., human, soil, water treatment plant,
sediment); iii) not the country/region of interest (e.g., United States, Canada, Mexico, European Union, China, Australia); iv) not an original article (e.g., review, book). Finally, two authors hand-searched the reference lists of relevant articles identified by the full-text screening for additional published primary articles (snowballing).

Data extraction and descriptive statistics

The recovered literature was exported into Excel for sorting and filtering. After all relevant articles were compiled, data extraction was performed considering bibliographic information and specific information to answer the research question. A description of the step-by-step review protocol and the selection of relevant articles is presented in Figure 1.

Results

Sixty articles published between 2003 and 2023 met the inclusion criteria. The reports were mainly from Brazil (37/60; 61.6%), followed by México (8/60; 13.3%), Chile (4/60; 6.6%), Costa Rica (3/60; 5.0%), and to a lesser extent, Colombia (two reports), and Bolivia, Cuba, Jamaica, Puerto Rico, and Uruguay (one report each). One of the studies compiled samples from Argentina, Mexico, Brazil, and Chile.

The bacteria reported by the relevant studies (considering combined results for one of the reports) were *Escherichia coli* and *Salmonella* spp. (14/60; 23.3% each one), *Enterococcus* spp. (6/60; 10%), *Staphylococcus* spp. (5/60; 8.3%), *Streptococcus* spp. (4/60; 6.6%), *Klebsiella pneumonia* (3/60; 5%) and other minor bacteria. In four of the studies, no bacteria were reported or specified.

The results presented below include combined results. The studies mainly were related to livestock animals such as cattle (n=25), poultry (n=16), pigs (n=9), and fish (n=6), among others. In addition, there were 12 reports on wild animals and four studies on horses, dogs, and cats.

The analyzed matrices were feces (n=29) (including intestinal content, cloacal/rectal swab, fecal samples), tissues (n=18) (including lymph nodes, organs, skin swabs, meat), milk (n=9), carcasses (n=9), and other fluids such as urine, ruminal content, and nasal secretions (n=5), among different minor matrices.

The *tet* genes most reported were *tet* A and *tet* B (n=32 each), *tet* M (n=26), *tet* L (n=17), *tet* K (n=14), *tet* C and *tet* O (n=13 each), *tet* D and *tet* G (n=8 each), *tet* W (n=7), *tet* S (n=6), *tet* Q (n=4), and *tet* E (n=3), among other minor findings.

Figure 1 – Flowchart of selection of relevant articles according to the PRISMA guidelines (Page et al., 2021), describing the progress of the citations through the systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *Some citations contain more than one non-inclusion criterion.
Although a TET-antibiotic susceptibility profile was not found in five studies, tet genes were detected. For these cases, the antibiotics for which resistance was reported were erythromycin, rifampicin, carbenicillin, amoxicillin–clavulanic acid, chloramphenicol, enrofloxacin, streptomycin, and streptomycin.

Detailed data on molecular testing, antibiotics susceptibility tests, and other relevant information extracted from the relevant articles is presented (Table 1). The geographical distribution of tet genes in the studies carried out in the relevant papers by country and animal species is shown (Figure 2).

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<td>Escherichia coli</td>
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<td>Carcass</td>
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<td>Bac teroides spp., Prevotella spp., Clostridium spp.</td>
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<td>Abscess materials (meta-tarsal, soft tissues, ear, prostate), tissue samples (lung, liver, tongue, brain, spleen, kidney), fluid samples (pleura, joint, blood, endometrium, udder, pericardium)</td>
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<td>tetL, tetM, tetW</td>
<td>Mayorga et al. (2015)</td>
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NR = Not Reported; AMC = Amoxicillin-Clavulanic acid; AMX = Amikacin; AMP = Ampicillin; AMX = Amoxicillin; ATM = Aztreonam; AZM = Azithromycin; CB = Carbenicillin; CEC = Cefaclor; CEF = Cephalothin; CEP = Cephalaxin; CXM = Cefuroxime; CFM = cefixime; CHL = Chloramphenicol; CFZ = Cefazolin; CIP = Ciprofloxacin; CLI = Clindamycin; CRO = Ceftriaxone; CTF = Cefotiofur; CTX = Cefotaxime; CTZ = Cefazidime; DOX = Doxycycline; ENR = Enrofloxacin; ERY = Erythromycin; ESPI = Spectomycin; ETP = Ertapenem; FEP = Cefepime; FLF = Florfenicol; FOX = Cefoxitin; GEN = Gentamicin; KAN = Kanamycin; LOM = Lomefloxacin; LYN = Levofloxacin; MER = Meropenem; MIN = Minocycline; NAL = Nalidixic acid; NOR = Norfloxacin; NIT = Nitrofurantoin; OFX = Ofloxacin; OTC = Oxacecloracycline; OXA = Oxacillin; PEN = Streptomycin; RIF = Rifampicin; SAM = Ampicillin-Sulbactam; SF = Sulfanilamide; STR = Streptomycin; STX = Trimethoprim/Sulfamethoxazole; SUL = Sulfadiazine; TET = Tetracycline; TMP = Trimethoprim; TOB = Tobramycin; AD = Agar dilution; DD = Disc diffusion; BM = Broth microdilution; ACS = Antibiotic concentrations strips; MDM = Microplate dilution method; MM = Microdilution method.

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NR = Not Reported; AMC = Amoxicillin-Clavulanic acid; AMK = Amoxicillin; AMX = Amoxicillin; ATM = Aztreonam; AZM = Azithromycin; CB = Carbenicillin; CEC = Cefaclor; CEF = Cefadroxil; CEM = Cefazolin; CFM = Cefoxitin; CMX = Cefoxitin; CHL = Chloramphenicol; CFZ = Cefazolin; CIP = Ciprofloxacin; CLI = Clindamycin; CRO = Ceftriaxone; CTB = Cefotaxim; CTX = Ceftriaxone; DOX = Doxycycline; ENR = Enrofloxacin; ERY = Erythromycin; ESP = Spectomycin; ETP = Ertapenem; FEP = Cefepime; FLF = Flufenicol; FOX = Cefotaxin; GEN = Gentamicin; KAN = Kanamycin; LOM = Lomefloxacin; LVA = Levofloxacin; MRF = Meropenem; MIN = Minocycline; NAL = Nalidixic acid; NOR = Norfloxacin; NF = Nitrofurantoin; OXF = Ofloxacin; OTC = Oxytetracycline; OXZ = Oxacinil; PEN = Penicillin; RIF = Rifampicin; SAM = Amoxicillin/Sulbactam; SF = Sulfamethoxazole; ST = Streptomycin; STR = Streptomycin; SUL = Sulfadiazine; TET = Tetracycline; TMP = Trimethoprim; TOB = Tobramycin; AD = Agar dilution; DD = Disc diffusion; BM = Broth microdilution; ACS = Antibiotic concentrations strips; MDM = Microplate dilution method; MM = Microdilution method.
Table 1 – Continued...

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<td>Cloaca swabs, tissues, carcasses</td>
<td>TET, NAL, CIP (DD and BM)</td>
<td>tetA, tetO</td>
<td>Kleining et al. (2021)</td>
</tr>
<tr>
<td>Mexico</td>
<td>Escherichia coli</td>
<td>Cattle</td>
<td>Feces, carcasses</td>
<td>TET, AMP, CEF (DD)</td>
<td>tetB, tetA, tetB + tetB</td>
<td>Martínez-Vázquez et al. (2021)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Klebsiella pneumoniae</td>
<td>Cattle</td>
<td>Feces, skin swabs, milk</td>
<td>NR (DD)</td>
<td>tetA, tetB, tetC, tetD, tetG</td>
<td>Nobrega et al. (2021)</td>
</tr>
<tr>
<td>Mexico</td>
<td>Escherichia coli</td>
<td>Poultry</td>
<td>Cloacal samples</td>
<td>TET, CB (DD)</td>
<td>tetA, tetB</td>
<td>Rojas-Jiménez et al. (2022)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Salmonella Heidelberg</td>
<td>Poultry</td>
<td>Carcass</td>
<td>CTF, NAL, ERY, DOX, AZM, TET, SF (DD)</td>
<td>tetA</td>
<td>Nuncio et al. (2022)</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Escherichia coli</td>
<td>Tapir</td>
<td>Feces</td>
<td>TET, CTX, FEP, AMP, SAM (BM)</td>
<td>tetB</td>
<td>Silva et al. (2022)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Salmonella enterica</td>
<td>Poultry</td>
<td>Feces</td>
<td>NR (NR)</td>
<td>tetA</td>
<td>Alikhan et al. (2022)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Enterococcus spp.</td>
<td>Cattle, poultry</td>
<td>Meat, cheese</td>
<td>ERY, RIF (DD)</td>
<td>tetL, tetM</td>
<td>Costa et al. (2022)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Enterococcus faecalis, Streptococcusagalactiae, Enterococcus faecium, Escherichia coli, Acinetobacter baumannii, Streptococcus hyovaginalis, Micrococcus luteus</td>
<td>Cattle</td>
<td>Milk</td>
<td>TET, AMP, FOX, ENR, PEN, OXA (DD)</td>
<td>tetL, tetM</td>
<td>Oliveira et al. (2022)</td>
</tr>
</tbody>
</table>

NR = Not Reported; AMC = Amoxicillin-Clavulanic acid; AMK = Amikacin; AMP = Ampicillin; AMX = Amoxicillin; ATM = Aztreonam; AZM= Azithromycin; CB = Carbenicillin; CEC = Cefacor; CEF = Cephalothin; CEP= Cephalaxin; CXM= Cefuroxime; CFM= Cefixime; CHL = Chloramphenicol; CFZ = Cefazolin; CIP = Ciprofloxacin; CLI = Clindamycin; CRO = Ceftriaxone; CTF = Cefotaxime; CTX = Cefotaxime; CTZ = Cefazidime; DOX = Doxycycline; ERY = Erythromycin; ESP = Spectomycin; ETP = etrapenem; FEP = Cefepime; FLF = Florfenicol; FOX = Cefoxitin; GEN = Gentamicin; KAN = Kanamycin; LOM = Lomeflaxoxin; LVX = Levofloxoxin; MER= Meropenem; MIN = Minocycline; NAL = Nalidixic acid; NOR = Norfloxacin; NIT= Nitrofurantoin; OFX = Ofloxacin; OTC = Oxytetracycline; OXA = Oxacillin; PEN = Streptomycin; RIF = Rifampicin; SAM= Ampicillin/Sublactam; SF = Sulfonamid; STR = Streptomycin; STX = Trimethoprim/Sulfamethoxazole; SUL = Sulfadiazine; TET = Tetracycline; TMP = Trimethoprim; TOB = Tobramycin; AD = Agar dilution; DD = Disc diffusion; BM = Broth microdilution; ACS = Antibiotic concentrations strips; MDM = Microplate dilution method; MM = Microdilution method.

Figure 2 – Geographical distribution of the tet genes and the related animal species by country found in the studies carried out in the Latin America and the Caribbean region (2003-2023). The color scale among countries obeys the reporting frequency, with the lightest color being the lowest frequency and the darkest, the highest, comparatively.
Discussion

This systematic review provides a comprehensive overview of the distribution of TET resistance genes in animals, products, and by-products in the LAC region. Based on our results and the nature of the information compiled herein, animal-related TET resistance in the region of interest cannot be defined as a critical, significant, high, or negligible fact. What is clear is the need to explore the phenomenon and understand its multi-causal and multi-stage trend, where human medicine, veterinary medicine (livestock, pets, wildlife), and environmental sciences converge. Therefore, AR monitoring and its implications should follow a One Health approach (Collignon & McEwen, 2019).

Antibiotics contribute to treating millions of infections in both animals and humans. Nevertheless, the increase in AR is now a central menace to worldwide public health (Murray et al., 2022; World Organisation for Animal Health, 2021). Such an emerging phenomenon is incontrovertible, related to the unrestrained use of antibiotics in the agricultural segment and human and veterinary medicine (O’Neill, 2016; Wall et al., 2016). Therefore, the World Health Organization (WHO) compiled a list of Critically Important Antimicrobials (CIA), requiring surveillance to reduce the AR spread and reserve drugs of importance for human medicine, which includes antibiotics that should be of restricted use in veterinary medicine (World Health Organization, 2018). According to the WHO’s list, TET class antimicrobials are considered highly important in human medicine, given the limited therapy for infections and diseases caused by 1) bacteria that can be transmitted to humans from non-human sources or 2) bacteria that can acquire resistance genes from non-human sources such as Brucella spp., Chlamydia spp., and Rickettsia spp. (World Health Organization, 2019). Similarly, the World Organisation for Animal Health (2021) established the TET group as a critically crucial antimicrobial agent in the veterinary sector for animals intended for food production, given the wide range of applications, the nature of the diseases treated, and the lack of antimicrobial alternatives.

The role of animals as links of epidemiological importance — that is, as vectors and reservoirs of antimicrobial resistance is an increasingly global issue (Murray et al., 2022). It is well known that TET has been widely used in livestock not only for treating infectious diseases but also as growth promoters and as a prophylactic therapy option (Santamaria et al., 2011). Therefore, the current and future scenario of the TET resistance phenomenon is incredibly predictable.

The relevant articles on tet genes in animals, products, and by-products over the last two decades suggest a growing interest in AR and its impacts on animal and human health in the study area. This can be due to the increasing importance of the region as one of the world’s leading producers and food suppliers (Kalinowski, 2021) and its relevant livestock population (i.e., beef and dairy cattle, pigs, poultry, sheep), which justifies the potential research resources allocation in this field to protect public health and prevent economic losses related to animal diseases.

The studies compiled herein mainly concerned livestock animals (e.g., cattle, poultry, pigs, fish). It is well known that using antimicrobials in livestock represents an intolerable risk to public health and the environment since it promotes AR via its distribution within food-associated microbiota or the introduction of resistant ones to soil and water (Arnold et al., 2016). Therefore, a greater frequency of regional studies focused on these animal species is unsurprising given their already recognized importance.

A significant proportion of the related research has been focused on dairy cattle. The most assessed by-product matrix has been milk. This can be explained as bovines have been the most important meat and milk production species in LAC, with Brazil being the world’s second-largest dairy herd producer (Williams & Anderson, 2019).

Notably, despite the remarkable productive potential of some countries in the region, AR-related studies for such a massively used family of antibiotics, namely TET, are still scarce for animal species of economic interest. For example, fishing and aquaculture are major economic activities in Chile (Food and Agriculture Organization, 2021), and oxytetracycline is commonly used in the Chilean aquaculture industry (Cartes et al., 2017). Nevertheless, only two studies have been carried out on bacteria in trout species. Piscirickettsia salmonis is a Rickettsiaceae of great importance due to the fatal effects it has generated in the immense productions of salmon and rainbow trout in countries with such productive potential, such as Chile, where it causes approximately 90% of all deaths that affect farmed salmonid species (Chile, 2016; Figueroa et al., 2019). Likewise, Epilithonimonas spp., a genus of the Flavobacteriaceae family, is also recognized as an essential disease-causing pathogen in fish farms and responsible for significant economic losses. For both, the preferred treatment continues to be TET despite multiple reports of resistance during the last 10 years (Cartes et al., 2017; Figueroa et al., 2019; Henriquez et al., 2016). Therefore, there is a possibility that these bacteria can serve as a reservoir of tet resistance genes.
The presence of these genes in the aquatic systems could hurt the ecosystem health. It could be a potential risk to public health, given the possible entrance of bacteria carrying AR genes to the food chain or through direct contact by handling sick fish (Gazal et al., 2020). An exemplary situation that draws attention is the report of tetX in fish in LAC (Concha et al., 2021) since its mechanisms confer resistance to human tigecycline —a spearhead TTC-class antibacterial agent developed for the treatment of polymicrobial multidrug-resistant infections (Cabello et al., 2013; Tasina et al., 2011). Consequently, tet genes monitoring could represent a valuable tool for surveillance of the status of TET resistance in aquaculture to predict the outcome of the established treatments, analyze the management of each fish farm, and ensure the implementation of better practices if needed.

Another example is Argentina, the second-largest beef producer in the region and a vital sheep meat producer (Williams & Anderson, 2019). No studies have been carried out on the topic so far. In the same way, Brazil, Colombia, Peru, and Argentina are the largest chicken producers (Kalinowski, 2021), and for these last three, there are no studies on the subject to date either.

Surprisingly, wild animals were in second place regarding the frequency of reporting tet genes in the region. The diversity of the tet genes identified in such animal species leads to the belief that the widespread use of antibiotics in the livestock and agriculture industry impacts different ecosystems and promotes a selective pressure in the wildlife microbiota, which drives antimicrobial resistance determinants (Sacristán et al., 2020). Considering that America is the continent that has the most megadiverse countries (i.e., Brazil, Colombia, Ecuador, Mexico, Peru, Venezuela, and the United States) (United Nations Environment Programme, 2023), the evaluation of the degree of anthropogenic impact through the presence of these genes is of great importance in terms of conservation.

On the other hand, few studies linked to companion animals were identified, even when the bond between people and their pets is increasingly recognized, and many owners consider their pets family members (World Small Animal Veterinary Association, 2020). This close contact can promote the exchange of resistant pathogens via saliva, urine, feces, aerosols, and skin, thus amplifying AR in humans and pets. Enterobacteriaceae have recently gained more attention as clinically significant pathogens for small-animal medicine since human-pet bonds (Ljungquist et al., 2016). Consequently, expanding research on pets is a priority. With this knowledge, veterinarians can then make recommendations to protect the health of both their patients and owners.

Enterobacteriaceae includes important pathogens that usually cause community-acquired infections as well as healthcare-associated infections such as enterotoxemia and enterobacteria, catheter-associated urinary tract infections, and surgical-related and nosocomial infections in humans (Ljungquist et al., 2016). Similarly, several of the major foodborne bacterial pathogens are members of this family (Bintsis, 2017). It is one of the dissemination pathways that has received the most attention from the One Health approach (Institute of Medicine, 2012). Salmonella spp. and E. coli were found to be the more frequent enterobacteria of the report with the same number of articles. These bacteria have a crucial impact on human and animal health (Farmer et al., 2010). Listeria monocytogenes —a microorganism capable of causing abortion, encephalitis, meningitis, and septicemia in both animals and humans (Matle et al., 2020), is considered highly susceptible to antimicrobials. It is well known that it can acquire genes of AR from conjugative plasmids and transposons that are usually associated primarily with tetM and other tet genes from various organisms (Baquero et al., 2020).

Staphylococcus spp. was the third most frequently reported bacteria in the present review. This genus has gained interest due to its increased detection of infections in humans and animals. Transmission of Staphylococcus spp. generally occurs through direct contact (e.g., contact with a wound, medical equipment, clothing) (Snyder et al., 2008) or contact with any symptomatic carrier (including animals). Since Staphylococcal bacteria can colonize the human skin and nares, transmission can occur through the hands during milking (Cuny et al., 2010; Gordon & Lowy, 2008).

Enterococci is a large genus of over 50 different species usually found in the gastrointestinal and genitourinary tracts of humans and animals but considered an opportunistic pathogen causing severe infections, such as endocarditis and urinary and bloodstream infections (Said et al., 2022). This was the fourth genus of the TET-resistance report herein.

As previously reported (Roberts, 2005), most of the genes identified were efflux pump-type, where the tetA and tetB genes were reported in samples from most of the assessed animals, which corroborates that this gene has the most extensive host range among these genes (Chopra & Roberts, 2001). Likewise, tetA has a broad host range and is often carried by various environmental genera (Hedayatianfard et al., 2014).

The tetM was the ribosomal protection-type gene more frequently found, which confirms the wide distribution of this gene, probably due to its association with conjugative chromosomal elements (Di Franceso et al., 2021).
High levels of \textit{tetB}, \textit{tetM}, \textit{tetO}, and \textit{tetW} have also been reported in wastewater lagoons at cattle feedlots in the United States (Peak et al., 2007) and other animal productions worldwide (Gargano et al., 2021). The \textit{tetL} gene was initially found in Gram-positive genera (Roberts and Schwarz). However, the studies related herein found it in Gram-negative species (Martini et al., 2017; Silva et al., 2013). This may be because they are in small transmissible plasmids (Gargano et al., 2021). The \textit{tetO} gene has been reported in a high proportion in manure samples, mainly from cattle, and has been found on plasmids and in association with conjugative transposons (Wang et al., 2016).

On the other hand, most of the TET-resistant bacteria reported in this review showed the co-presence of two or more \textit{tet} genes. It is unclear whether a synergistic effect exists following this trend in the same strain (Nobrega et al., 2021).

Most isolates reported herein were also resistant to other-than-TET antibiotics such as quinolones and fluoroquinolones, \(\beta\)-lactams, sulphonamides, and macrolides, possibly because \textit{tet} genes are often contained in mobile genetic elements (Askari Rizvi, 2018). Therefore, other antimicrobial resistance genes are also possible (Jara, 2010).

It is worth noting, however, that the presence of these genes was reported in isolates with phenotypic sensitivity to TET, which means that the inappropriate use of the antibiotic (e.g., subinhibitory concentrations) could induce the expression of the genes.

A different scenario and not contemplated from the methodology of this review would be that some isolates with phenotypic resistance to TET would not display resistance genes. This can be explained given that more than 38 genes are coding for TET resistance reported to date by Roberts & Schwarz (2016), and many of them are not species-specific. Thus, they may be mediated by another not yet considered. An intrinsic resistant mechanism is also possible. These are mutations affecting the expression and function of one or more elements (e.g., repression/activation systems, pumps, porin) that can impact the susceptibility to TET and other antibiotics in a simultaneous way (Grossman, 2016).

Most studies did not specify why some \textit{tet} genes were selected, and others were not. Among those who did, some studies reported that \textit{tet} genes were chosen because they represented the majority of \textit{tet} genes currently characterized or because they have recently been described in other bacteria in animals (Miranda et al., 2003).

This systematic review has strengths and limitations. As strengths, a clearly stated and delimited research question-based protocol was observed, and the eligibility of relevant studies was based on a pre-established and precise inclusion/exclusion criterion. Two authors independently followed selection principles, and results from each search step were always by consensus, reporting agreement measures throughout the process. Lastly, data extracted from the relevant studies were demarcated, and all the authors constructed, filled, and revised a matrix of findings. As limitations, grey literature —papers, reports, technical notes, unpublished theses, dissertations, or governmental or academic documents indexed by commercial publishers, was not fully considered since many of these documents are difficult to locate and obtain. We tried to control this by snowballing, leading to a maximum yield of relevant articles.

Antimicrobial resistance is a global crisis that endangers society’s ability to successfully treat bacterial infections since most antimicrobials used to treat bacterial infections in humans are also used in animals. Given the close human-animal relationship, its interaction and direct dependence on the environment, and its consequent effect of resistance to antimicrobials, it is logical and essential to adopt the One-Health approach when addressing this problem.

Studies evaluating the presence of \textit{tet} genes in animals in LAC are limited despite TET being antibiotics widely used in animals. It is necessary to establish cross-border public policies that allow the constant training of medical and related personnel regarding the responsible use of antibiotics in animals and the effective monitoring of the phenomenon in the region.

Among other limitations, reports continue to focus on the World Health Organization-published Global Priority Pathogens (GPP) List, World Health Organization (2017). This one-family and 11-species bacterial catalog was drawn up to guide and promote research and development of new antibiotics, given the significant threat to human health that those bacteria pose. The above could mask the reality of a more remarkable emergence of other equally essential resistance determinants.

In the same way, reports from clinical samples are still limited, and they are essential for establishing an antimicrobial stewardship program that promotes the appropriate use of these drugs in sick animals, improving the patients’ outcomes. In addition, as the resistance to TET is mainly related to the acquisition of mobile genetic elements —such as plasmids and transposons, and the dissemination through conjugation (Jara, 2010), it would also be essential to assess the genetic mobile aspects in which these genes are contained and to investigate their roles and dissemination.

Countries must concentrate efforts on identifying the dynamics of AR, including resistance to TET, through molecular techniques that can facilitate understanding the epidemiology of this problem, which affects both animal and human health.

**Conflict of Interest**

None declared.
Ethics Statement

Given the desk-based nature of the research, no ethical requirement was needed.

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