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An analysis of investigations into the use of tulathromycin in cattle

Larissa da Costa Rodrigues Bartolomeu[1], Fábio Luiz Bim Cavalieri[2], Marcia Aparecida Andreazzi[2], Sidnei do Amaral Freire[1]

[1]Postgraduate Program in Clean Technologies / ICETI / Unicesumar University, Maringá, Paraná, Brazil
[2]Veterinary Medicine course and the Postgraduate Program in Clean Technologies / ICETI/ Unicesumar University, Maringá, Paraná, Brazil

Correspondence Author: Márcia Aparecida Andreazzi, Veterinary Medicine course and the Postgraduate Program in Clean Technologies, Unicesumar University, Avenue Guedner, 1610, 87050-900, Maringá, Paraná, Brazil.
Cesumar Institute of Science, Technology and Innovation - ICETI, Maringá, PR, Brazil
E-mail: marcia.andreazzi@unicesumar.edu.br

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ABSTRACT: The use of antibiotics is an important tool for animal production, especially for raising cattle. Therefore, considering the concern with the use of antibiotics in animal production, there is a need to analyze and know the situation of publications regarding the antibiotic tulathromycin, a drug of current relevance with promising use in animal production chains, especially for the chain bovine production. Thus, the aim of this study was to perform an analysis of publications on the antibiotic tulathromycin, with emphasis on its use in cattle. A scientometric study was carried out, based on a survey of journals indexed in the Web of Science and SciELO databases, using the descriptors: Tulathromycin, Draxxin, Tulaxx, Tulissin and Treoxin. After refinement and analysis regarding duplicity and adherence to the scope of the research, the search resulted in 158 articles, published between the years 2004 to 2021, from which information was collected: year of publication, central theme of the research, animal species and data on the purpose of its use in cattle breeding. Data were tabulated and organized in a electronic spreadsheet and descriptive analysis was used. The results showed that the number of publications on the antibiotic tulathromycin increased over the years and the articles discussed various topics, however, the use of antibiotics as a way of treating various animal diseases stood out, especially research on Respiratory Disease in beef cattle, and the main *agents associated with Bovine Respiratory Disease were Mannheimia haemolytica (12.25%) and Mycoplasma* bovis (10.20 %).

Keywords: animal production; antibiotics; scientometrics.

INTRODUCTION

To ensure productivity and competitiveness in animal production, using drugs for therapeutic and prophylaxis purposes is a widespread practice and among the medications used, antibiotics are the most prescribed (Regitano; Leal, 2010).

In Brazil, there are basically four therapeutic approaches for the use of antimicrobials in production animals that differ in terms of use, dose and duration of treatment. Being a growth promoter, whose function is modulating the intestinal microbiota, results in performance gains. ; as a prophylactic use, which seeks prevention, individually or in groups, before the disease occurs; such as metaphylactic use, which results from the treatment of animals at risk and prevents the spread of the infectious agent in a group as soon as some animals become ill, and therapeutic use, which is the individual or group treatment of sick animals (Dias et al., 2011).

The pharmaceutical industry currently provides many antimicrobials that are administered in different ways and that play a significant role in promoting and maintaining the health of herds in health control programs (Ema, 2022; Zoetis, 2022). However, there is a worldwide tendency to restrict the use of antibiotics in production animals due to several factors. First, the use of medicines in animal production systems must be done carefully, with veterinary prescriptions, respecting the dosages and

indications for the different diseases according to the manufacturer, the grace period, which has mandatory registration with the Ministry of Livestock Agriculture and Supply and that care is taken in terms of conservation and application (Dias et al., 2011).

Second, in addition to these points, there is a growing global concern about antimicrobial resistance. Thus, the use of antibiotics in livestock must be carried out judiciously and effectively (Lekagul et al., 2020), as antimicrobial resistance represents a global threat to human and animal health (Slizovskiy et al., 2020). Antibiotics are often used as first-line agents for the therapeutic treatment of infections caused by different bacterial agents, and the main classes of antibiotics used worldwide are macrolides, tetracyclines, fluoroquinolones and aminoglycosides (Yatoo et al., 2019). Among the antibiotics of the macrolide class, we highlight tulathromycin, a relatively new semi-synthetic antibiotic, a member of the triamide subclass, approved mainly for treating respiratory diseases in cattle and swine (Maletic et al., 2015). Tulathromycin is a molecule for exclusive use in animal production, with concentrated action on lung tissue, eliminating sensitive pathogenic respiratory bacterial agents (Zoetis, 2022). In addition, it has the advantage of being a single-dose, injectable and extra-long-acting antibiotic (Ema, 2022; Farmabase, 2022; Zoetis, 2022). These characteristics result in prolonged antimicrobial action and reduced animal handling and stress. Thus, the objective of this study was to analyze, in the scientific literature, publications about the antibiotic tulathromycin and to carry out a qualitative and quantitative analysis of these publications, seeking to highlight the different directions of investigations, understanding the scientific behaviour of studies with this antibiotic, especially related to the use in cattle.

MATERIALS AND METHODS

The study consisted of a scientometric analysis, a quantitative method that allows evaluation the current state of science (VANTI, 2002). In August 2022, a survey of scientific production published in journals indexed in the Web of Science databases (https://www-webofscience.ez188.periodicos.capes.gov.br) and Scientific Electronic Library Online was carried out (SciELO) (http://www.scielo.org), following the methodological recommendations of Schubert, Glanzel and Braun (1989) for scientometric studies.

Descriptors were used with the name of the antibiotic: Tulathromycin and the commercial names of the products containing the antibiotic for veterinary use: Draxxin (Zoetis®), Tulissin (Virbac®), Treoxin (Farmabase®) and Tulaxx (Ourofino®). After refinement and analysis regarding duplicity and adherence to the scope of the research, the survey resulted in 158 scientific articles published between the years 2004 to 2021. Then, the analysis of scientific production was carried out using a quantitative approach, for through the reading of titles and abstracts, the following information was identified and collected: year of publication of the scientific article, which allowed the elaboration of a historical analysis of the publications, central thematic axis of the research, differentiating, the animal species and the objectives of the study with the antibiotic, stratifying those related to cattle. Data were tabulated and organized in an electronic spreadsheet (*Microsoft Excel* 2016) and descriptive analysis was used.

RESULTS

The analysis of the number of articles published on the antibiotic tulathromycin showed growth over the years, emphasising the last six years, which concentrated 61.39 % of the publications (Table 1).

Table 1. Number (N) and percentage (P) of scientific articles published on the antibiotic tulathromycin every 6 years between 2004 and 2021.

Year	N	P (%)
2004 a 2009	13	8,23
2010 a 2015	48	30,38
2016 a 2021	97	61,39
Total	158	100,00

Table 2. Number (N) and percentage (P) of scientific articles published on the antibiotic tulathromycin in animals, according to animal species, between the years 2004 and 2021 (n:140).

Animal species	N	P (%)
Cattle	75	53,58
Swine	34	24,28
Horses	10	7,14
Goats as sheep	5	3,58
Others animal species	16	11,42
Total	140	100,00

Regarding the thematic axis of the publications, it was verified that most of the studies discussed the evaluation of the use of the antibiotic tulathromycin in different animal species (n = 140; 88.61%), followed by studies on the evaluation of techniques of detection of residues in products of animal origin (n = 10; 6.33%) and review of literature and forms of application (n = 8; 4.0%).

Due to the higher percentages of publications referring to the use of antibiotics in animals, the studies were categorized according to the animal species evaluated. Thus, it was possible to observe that the studies carried out with bovine and swine

species stood out (Table 2). On the other hand, the result on tulathromycin in cattle, as a function of aptitude, beef or milk, showed a reduced number of publications involving dairy cattle (Table 3).

Table 3. Number (N) and percentage (P) of scientific articles published on the antibiotic tulathromycin in cattle, according to aptitude, between the years 2004 and 2021 (n:75).

Animal	N	P (%)
Beef cattle	61	81,34
Dairy cattle	14	18,66
Total	75	100,00

The survey showed that, of the total number of articles published on the antibiotic tulathromycin in cattle, most associated its use with BRD, and of the total number of articles that discussed BRD, studies on the relationship between tulathromycin and *Mannheimia haemolytica* stood out and *Mycoplasma bovis* (Table 4).

Table 4. Number (N) and percentage (P) of scientific articles published on the antibiotic tulathromycin in cattle according to the disease between 2004 and 2021 (n:75).

Animal	N	P (%)
Bovine Respiratory Disease (BRD)	49	65,34
Other diseases	26	34,66
Total	75	100,00
BRD and *Mannheimia haemolytica*	6	12,25
BRD and *Mycoplasma bovis*	5	10,20
BRD and other agents	38	77,55
Total	49	100,00

DISCUSSION

It is believed that the increase in the number of publications in the last six years is because some Tulathromycin-based products only obtained registration for preventive use in Europe in 2007. In addition, the increasing restrictions on the use of medicines via feed. Therefore, increased the use of this drug each year, partially justifying this increase in publications. On the thematic axes of the publications, it appears that tulathromycin, a relatively new drug on the market, is a macrolide antibiotic of the subclass of triamylides, being the first antibiotic in a single injectable dose of extra-long action, indicated for the treatment of some animal diseases, such as bovine respiratory disease (BRD) (Crosby et al., 2018; Mzyk et al., 2019), treatment of bovine keratoconjunctivitis (Angelos; Ball; Byrne, 2011) and necrobacillosis interdigital (TOREHANOV et al., 2021). In the case of pigs, it is also used for the treatment of Swine Respiratory Complex (SRC) (Jong et al., 2021) and in the case of sheep, as a treatment for pneumonia in newborn sheep and goats (Lianou; Fthenakis, 2022), among other diseases.

Regarding the studies that evaluated the detection in products originating from animals that were treated with tulathromycin, it was found that many discussed, for example, the type of technique to be used, seeking the best detection sensitivity in plasma and in milk of lactating goats (Lin et al., 2016), in beef, pork, equine and milk (Song et al., 2016) and in bovine synovial fluid (Jones et al., 2015). Regarding the studies that evaluated the form of application (Coetzee et al., 2018; Hairgrove et al., 2021), it is known that, in fact, the administration of this drug requires caution, so much so that the manufacturers themselves advise that the administration of the drug product, either by subcutaneous or intramuscular injection, as in the case of cattle and swine, respectively, the dose must be divided so that large volumes are not injected in the same place (Zoetis, 2022). The result of the higher percentage of studies involving cattle and pigs shows that tulathromycin is, in fact, frequently indicated for the therapeutic treatment of BRD (Ema, 2022; Zoetis, 2022) and Swine Respiratory Complex (SRC) (Ema; 2022; Farmabase, 2022). The antibiotic is also indicated for the treatment of bovine keratoconjunctivitis associated with *Moraxella bovis*, *Neisseria spp* and interdigital necrobacillosis (foot-rot) caused by *Fusobacterium necrophorum*, *Bacteroides melaninogenicus* and *B. nodosus* (Ema, 2022; Zoetis, 2022).

Indeed, tulathromycin has been used for the therapeutic and metaphylactic treatment of the SRC associated with several bacterial pathogens. Brazil has a high potential for growth in meat production, standing out on the world stage. However, to meet this growing demand, it is necessary to combat diseases that compromise production performance and, among them, respiratory challenges are among the main causes of health-related economic losses within a swine production unit (MARTÍNEZ et al., 2007). Thus, due to the different agents involved and found in the respiratory challenges in swine, it became known as the SRC, with different etiology (Morés et al., 2015).

In the case of swine, tulathromycin is indicated for the treatment of SRC associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Glaesserella (Haemophilus) parasuis*, *Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae*, as well as for the metaphylactic treatment of SRC in animals at high risk of contracting disease (Farmabase, 2022; Zoetis, 2022). The result of the lower number of publications on the use of tulathromycin in dairy cows may be due to the necessary precautions. Since some manufacturers point out that the product should not be applied to cows producing milk for human consumption, as

well as not the product should be used in pregnant cows or heifers intended for the production of milk for human consumption within two months before the expected date of calving (Ema, 2022; Zoetis, 2022). In the case of beef cattle, manufacturers claim that after 18 days of treatment, the beef can be released for human consumption (Zoetis, 2022).

Research has shown that most published articles on the antibiotic tulathromycin in cattle were associated with RBD. The general term "Bovine Respiratory Disease" (RBD) refers to a series of respiratory disorders which have a high frequency and economic impact on livestock worldwide and are of concern due to the high rate of morbidity and mortality in animals (Crosby et al., 2018). RBD, also defined as a "respiratory complex", is multifactorial. Therefore, the constant exposure of the respiratory system to potentially pathogenic microorganisms is associated with the anatomical characteristics of the bovine respiratory system, which predispose these animals to lung diseases, low immunity and unfavourable environmental conditions. Are predisposing factors for its occurrence (Radostits et al., 2021). In addition, other risk factors that may precede and contribute to infection are weaning stress and changes in diet and environmental temperature and humidity. Thus, this disease, which is caused by several factors acting alone or together, can affect the lower respiratory tract, that is, the lungs (pneumonia) and/or the upper respiratory tract (rhinitis, tracheitis, bronchitis) (Zoestis, 2022).

A variety of pathogens can cause RBD, of viral origin (*Bovine Respiratory Syncytial Virus* - BRSV, *ParaInfluenza* 3 - PI3, *Adenovirus*, *Bovine Viral Diarrhea Virus* - BVDV, *Bovine Herpervirus* - BHV-1), bacterial (*Mannheimia hemolytica*, *Pasteurella multocida*, *Mycoplasma bovis*, *Histophilus somni*), parasitic (*pulmonary Strongyl*) or fungal (*Aspergillus*). These agents interact with each other or together, culminating in an inflammatory process or allergic reaction that triggers the disease (Zoetis, 2022). The bacteria can cause an acute syndrome by invading the airways of animals that were already weakened by viral infections. Among the pathogenic bacteria, *Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, Haemophilus somnus* and *Mycoplasma bovis* stand out (Radostits et al., 2021). Thus, studies on the relationship between tulathromycin and Mannheimia haemolytica stood out of the total number of articles that discussed BRD. *Mannheimia haemolytica* is the bacterial pathogen most frequently isolated from cattle with BRD, and the prevalence of antimicrobial resistance in this organism has increased in recent years (Crosby et al., 2018).

Mannheimia (M.) haemolytica is one of the main respiratory pathogens of domestic ruminants and this bacterium causes pneumonia in cattle, sheep, and goats, septicemia in lambs, and mastitis in sheep (Kirkan, Kaya 2005). *M. haemolytica* is a commensal bacterium of the upper respiratory mucosa and nasopharynx of healthy cattle and one of the main bacterial agents of the respiratory disease complex in cattle, also known as transport fever. In calves, M. haemolytica can cause pneumonia after some stressful process, associated or not with viral infections (Mahu et al., 2015); the disease can also be associated with the stress caused by weaning (Hanzlicek et al., 2010). In cattle, the clinical presentation of the disease is characterized by respiratory disorders with runny nose, fever, cough and weight loss (Batista et al., 2018). Studies that associated BRD with *Mycoplasma bovis* were also identified, such as the study that evaluated *Mycoplasma bovis* associated with BRD and pneumonia syndrome and chronic polyarthritis in confined cattle (Kinnear et al., 2020). Among the several potential agents responsible for developing RbD in calves, heifers, and confined dairy cows *M. bovis* is frequently associated with this respiratory distress syndrome (AEBI et al., 2015). Clinical signs are non-specific and include fever, tachypnea, dyspnea, and decreased appetite, with or without nasal discharge and cough (Gagea et al., 2006). Cases of otitis media may accompany mycoplasma pneumonia, arthritis or both, in the same animal or other animals of the herd (Maunsell; Donovan, 2009).

CONCLUSIONS

Based on the results obtained in this study, there was a reduced number of publications on the antibiotic tulathromycin. However, in the last six years, there has been significant growth in the number of articles published, which dealt with different axes, and the use of the antibiotic in the treatment of varying animal diseases was the most relevant and, among the animal species studied, cattle stood out, especially beef cattle, in which studies related the species with Bovine Respiratory Disease, associated, mainly with *Mannheimia haemolytica* and *Mycoplasma bovis.*

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Author's Contributions:

The authors confirm contribution to the paper as follows: study conception and design: Larissa da Costa Rodrigues Bartolomeu, Fábio Luiz Bim Cavalieri, Marcia Aparecida Andreazzi and Sidnei do Amaral Freire; data collection: Larissa da Costa Rodrigues Bartolomeu and Marcia Aparecida Andreazzi; analysis and interpretation of results: Larissa da Costa Rodrigues Bartolomeu, Fábio Luiz Bim Cavalieri and Marcia Aparecida Andreazzi; draft manuscript preparation: Larissa da Costa Rodrigues Bartolomeu, Marcia Aparecida Andreazzi and Sidnei do Amaral Freire. All authors reviewed the results and approved the final version of the manuscript.

Conflict Of Interest

The authors declare no conflict of interest

Software/Data Availability

Electronic spreadsheet (*Microsoft Excel* 2016)

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