A SYSTEMATIC REVIEW OF THE USE OF TULATHROMYCIN IN VETERINARY MEDICINE

Moldovan (Pop) Carmen[1], Dreancă Alexandra[1]*, Rotar Oana[1], Madru Mihai[2], Ioan Mărcuș [1]

[1]University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Cluj-Napoca, Romania; [*]Corresponding author: alexandra.dreanca@usamvcluj.ro
[2]S.C. ProfesionalVet S.R.L., Apahida, Cluj, Romania

Abstract The study's findings can help animal health professionals explore alternative treatments for respiratory diseases in sheep and improve their overall health. The review aims to synthesize current research on the use of tulathromycin in veterinary medicine. Key studies demonstrate that tulathromycin is effective in treating bacterial pathogens responsible for respiratory disease, including Mannheimia haemolytica and Pasteurella multocida. The pharmacokinetic properties of tulathromycin, characterized by rapid absorption, extensive tissue distribution, and prolonged elimination half-life, contribute to its therapeutic advantages. Additionally, the review examines the dosage regimens, administration routes, and potential side effects reported in clinical trials. Data regarding antimicrobial resistance to tulathromycin is discrepant due to several sources that display negative results regarding the sole use of this macrolide and its off-label use. Although limitations exist, a consolidated further research on the application of tulathromycin in sheep, highlighting its benefits and addressing potential challenges in its use is needed.

Keywords: tulathromycin, Draxxin, sheep pathology, ovine medicine

Abbreviations

AMU – Antimicrobial use
BRD – Bovine Respiratory Disease
BRSV – Bovine Respiratory Syncytial Virus
BVD – Bovine Viral Diarheea
CXCL-8 – Interleukine 8
ELDU – Extra-label drug use
FARAD – Food Animal Residue Avoidance Databank
FDA – Food and Drug Administration
FFC – Floramfenicol
IBR – Infectious Bovine Rhinotracheitis
LAOTC – Long-Acting Oxytetracycline
MIC90 – Minimal inhibitory concentration required to inhibit 90% of isolates
PI-3 – Parainfluenza-3 Virus
PRDC – Porcine Respiratory Disease Complex
PRRSV – Porcine Reproductive and Respiratory Syndrome
TUL – Tulathromycin
US – United States
WDIs – Milk and meat withdrawal intervals

INTRODUCTION

Tulathromycin is a noteworthy macrolide recognized as the inaugural member of a fresh subclass within this class. Comprised of a blend of two distinct types of azalides – a 3-membered ring azalide and a 15-membered ring azalide – this molecule boasts three nitrogen/amino functional groups (Mladenov et al., 2023). The molecule presents valuable properties including pKa values ranging from 8.6 to 9.6. This unique attribute facilitates the unhindered migration of its uncharged component from the bloodstream to the body's tissues, where it assembles in acidic conditions. This occurrence is known as ion trapping, and slow release from cells may account for the long-term retention of the drug in the lungs and other tissues (Mladenov et al., 2023; Villarino et al., 2013).

As an antimicrobial property, it binds to the 50S subunit of bacterial ribizomes, thus inhibiting direct protein synthesis, provoking lack of division, ATP and subsequent cellular death (Fig. 1) (Mladenov et al., 2023). Besides inducing apoptosis in leukocytes, according to the latest studies, tulathromycin possesses properties related to NF-κβ inhibition, therefore underexpressing the secretion of CXCL-8 and the production of leukotriene B_4, prostaglandin E_2, and lipoxin A_4 (De Lamache et al., 2019a; Fischer et al., 2011, 2013).This medication touches the activity of all the mechanisms that were previously mentioned, thus having antimicrobial, anti-inflammatory and immunomodulatory properties (Bigelow et al., 2023).

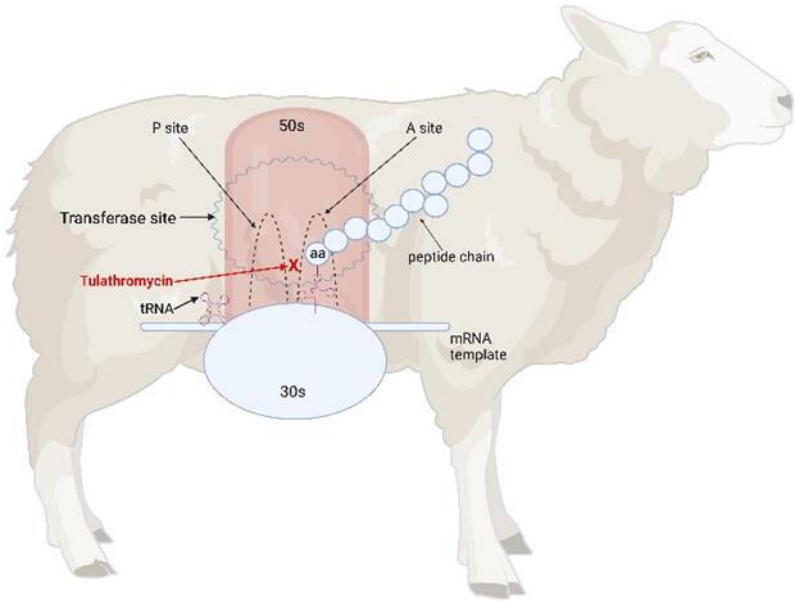

Fig.1. Tulathromycin mechanism of action at a molecular level, in ovine species

After administering a single dose of 2.5 mg/kg intramuscularly in sheep, the maximum plasma concentration of tulathromycin was 1.19 µg/mL, which was achieved in about 15 minutes. The elimination half-life (t1/2) was observed to be 69.7

hours. The bioavailability of tulathromycin in sheep after intramuscular administration is 100%. (Mladenov et al., 2023).

It is reported that pregnant ewes present an average maximum plasma concentration of 4.9 μg/ml (±2.2), compared to 3.6 μg/ml (±2.3) in non-pregnant ewes. Non-pregnant ewes were studied to have a maximum concentration time of 1.6 hours, while pregnant ewes presented a mean of 4 hours ± 2. The average elimination half-life was 110.8 hours (±20.9) in pregnant ewes and 118 hours (±66) in non-pregnant ewes. The results suggest that pregnancy does not significantly alter pharmacokinetics in ewes (MacKay et al., 2019; Washburn et al., 2015).

The research aims to gather and analyze existing literature on the topic to provide a comprehensive overview of the effectiveness of tulathromycin in veterinary medicine. The study specifically focuses on the potential of tulathromycin in treating respiratory pathologies in sheep.

MATERIALS AND METHODS

Data Analysis

This paper is organized into 2 sections. The first section gives a brief overview of the general use of tulathromycin, in multiple species approved by the drug organisms. The second section examines the literature by trying to find studies from the last 10 to 20 years in which tulathromycin was considered off-use in respiratory pathologies for ovine species. Before any literature investigation, the following research question had been formulated: „If it is researched, why tulathromycin is not accepted as an antimicrobial for ovine respiratory pathologies?" It was brought to light that this medication is already used off-label for metaphylaxis and in the treatment of respiratory pathologies encountered in ovine. Therefore, why is it not approved if it is used and researched?

PubMed and Google Scholar were the electronic databases used for this review and different keyword combinations were tested: tulathromycin in sheep, Draxxin, tulathromycin mechanism of action, and tulathromycin in respiratory pathologies. Three authors carefully read each article's abstract to determine whether or not the article should be included in the study. Once the articles were chosen, their full text was investigated.

RESULTS AND DISCUSSIONS

General information about the use of tulathromycin

Given the small number of articles referring only to the administration of tulathromycin in sheep, it was decided that the scope should be extended to also explain its general use in cattle and swine.

Tulathromycin is used in the treatment of respiratory infections in cattle and swine species and pododermatitis in sheep. This drug has been studied many times *in vitro* against pathogens such as *Streptococcus pneumoniae, Streptococcus pyrogens, Haemophilus influenzae, Pasteurella multocida,* and *Mycoplasma bovis,* having initially relevant results but in the last period, some studies started to present this medicine as developing antibacterial resistance, mainly because of the irresponsible use (Soliman & Mahmoud, 2021).

As we talk about commercial products, in Romania, tulathromycin is presented under Draxxin. This product is a highly effective veterinary medication that comprises a 100mg/ml solution of tulathromycin (The Prospect of Draxxin). The broad-spectrum antibiotic is widely used in veterinary medicine to tackle respiratory diseases in various livestock species. Its proven efficacy, safety, and convenience make it an invaluable resource in the fight against respiratory infections in ovine populations (Politis et al., 2019). Common pathogens targeted include *Mannheimia haemolytica, Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma spp*.

Tulathromycin use in cattle

When discussing the feeding lot cattle, it is important to note that the bovine respiratory disease complex is the most significant pathology (BRD). This is an infection caused by a virus or bacteria that can lead to fatal pneumonia in calves. The aetiology is represented by stress, a pre-existing viral infection, and a new bacterial infection. BRD mostly affects calves within four weeks of weaning and is commonly referred to as "shipping fever." It's a "multi-factorial syndrome" dependent on several factors, including secondary bacterial or viral infections. *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* are the most common bacterial agents associated with BRD, while BVD, IBR, BRSV, and PI-3 are common viral agents. For this reason, prophylactic vaccination is world widely accepted and practised (Bagley, 1997; Larson & Step, 2012).

Especially when talking about heifers, the sensitivity to climate conditions, must be acknowledged. These individuals present to be at the highest risk when it comes to drastic climate conditions. For this reason, metaphylaxis is essential in the attempt to avoid economic loss. This medical procedure is conditioned by multiple in-vitro and in-vivo studies that evaluate tulathromycin's antimicrobial activity and prophylactic effect against respiratory diseases in dairy heifers under cold stress (Stanton et al., 2010). Besides the prophylactic effect which is worldwide accepted, there are a few studies that recognise the potential of tulathromycin as a single-use molecule in the treatment of BRD in North America, also stating again its immunomodulatory effect and the lack of retreatment in 50% of bovine population (Wellman & O'Connor, 2007).

Tulathromycin has shown promising results in both *in-vitro* studies and *in-vivo* studies. Previously, it demonstrated a 100% killing rate for pathogens such *as Staphylococcus pneumoniae*, *Staphylococcus pyogenes*, *Haemophilus influenzae*, *Pasteurella multocida*, and *Escherichia coli*. From a clinical perspective, none of the treated subjects exhibited any symptoms of climate stress. Although the study involves dairy cattle, its findings may provide insights into the potential application of tulathromycin in sheep facing similar environmental challenges (Soliman & Mahmoud, 2021). These findings suggest that research regarding tulathromycin presents the molecule as a treatment for respiratory pathologies during various in vitro studies, while in vivo studies focus mainly on methaphylaxis and stress-related pathologies.

Tulathromycin use in swine

When it comes to swine pathology, more precisely infectious disease, the porcine respiratory disease complex (PRDC) causes significant economic losses in the swine industry. PRDC is a multifactorial disease caused by a combination of bacterial and viral pathogens, environmental factors, and host factors such as stress, genetics, and age. The disease primarily affects the respiratory tract of pigs, leading to clinical

signs such as coughing, sneezing, and difficulty breathing. PRDC can also cause secondary infections and lead to death in severe cases (Yao et al., 2022). The management of PRDC in swine populations requires comprehensive and effective strategies such as vaccination, biosecurity measures, and antibiotic treatment to prevent and control the disease. In regards to bacterial agents, the most encountered pathogens are represented by *Actinobacillus plueropneumoniae* and *Pasteurella multocida*. The two are identified as being highly susceptible to tulathromycin, presenting no temporal variability in the minimum inhibitory concentration (Vilaró et al., 2023). Moreover, in the latest study, the immunomodulatory effect of tulathromycin has been presented. At the standard dose of 2.5 mg/kg, tulathromycin prevents morphological alterations in blood monocyte-derived macrophages, it inhibits PRRSV-induced CXCL-8 secretion, along with the intracellular production of reactive oxygen species (De Lamache et al., 2019). This draws our attention to the use of tulathromycin as a real antimicrobial molecule in respiratory pathologies with better efficacy in swine species.

Tulathromycin use in ovine

Sheep farmers worldwide are all too familiar with the devastating impact of respiratory diseases on their flocks. These illnesses can cause significant suffering and even death among sheep, leading to significant losses for farmers. Farmers must take proactive measures to prevent and manage these diseases to protect their flocks and their livelihoods. Sadly in countries like Romania, actions regarding metaphylaxis and prophylactic measures are taken into action by the farmer himself without the consent of a veterinarian, thus off-label use and antibacterial resistance are rapidly encountered. As previously mentioned, *Pasteurella multocida* has a significant impact on the livestock industry. This pathogen not only affects cattle but also swine and ovine species. It is one of the most feared causes of disease due to its widespread antibiotic resistance, which includes ampicillin, oxytetracycline, tilmicosin, tiamulin, lincosamides, and sulphonamides. However, tulathromycin is known to be one of the few molecules that remain effective against this pathogen, with little to zero antibiotic resistance. Therefore, it is an essential treatment option for animals infected with *Pasteurella multocida* (Abate & Fentie Kassa, 2023; Cid et al., 2019; Khalili et al., 2016; Marru et al., 2013).

Alongside *Pasteurella multocida*, another two pathogens that are encountered in bronchopneumonia in sheep, are represented by *Mannheimia haemolytica* and *Mycoplasma ovipneumoniae*. Tulathromycin presents itself with a great systemic distribution and does not cause the same adverse effect, as the molecule of tilmicosin that is included in the same class of antibiotics. Tilmicosin is reported to produce cardiotoxicity, while the only side effect reported after the administration of tulathromycin is a reaction at the injecting site (Politis et al., 2019). Following our previous study in which tulathromycin's toxicity was tested, the dose of 2.5 mg/kg is completely safe, whereas only a dosage of 12.5mg/kg induces hepatic and cardiac toxicity in ovine species (Moldovan et al, 2023).

When discussing economic factors, it's important to consider other pathogens such as *Campylobacter spp*, *Chlamydophila abortus*, *Coxiella burnetti*, and *Toxoplasma gondi*. These illnesses have a significant impact on human health, with the latter three being zoonotic diseases. *Campylobacter spp* presents in the form of a helicoidal, gram-negative bacillus which affects more commonly the digestive tract,

but in this species, it is known to affect the reproductive system. Once again, tulathromycin shows promising results (Yaeger et al., 2020).

A total of 19 articles were found relevant when investigating the potential of tulathromycin in respiratory pathogens involving small ruminants. Out of the 19 studies, 12 were furthermore selected, containing specific data regarding the effectiveness, pharmacokinetics and microbial resistance in ovine species. The most relevant were highlighted in Table 1, describing the research questions and the main objective of the research.

Table 1.

Most relevat studies highlighting the use of tulathromycin in ovine species

Nr. Crt.	Authors, Year, Title, Journal	Main point
1	Politis A.P., Vasileiou N.G.C., Ioannidi K.S., Mavrogianni V.S., 2019, Treatment of bacterial respiratory infections in lambs, Small Ruminant Research	This paper discusses the treatment of bacterial respiratory infections in lambs. Immediate action is necessary to control clinical signs and limit lung lesions. Administering antimicrobial agents effective against the causal bacteria, such as fluoroquinolones, tilmicosin, **tulathromycin**, chlortetracycline, doxycycline, and oxytetracycline, is recommended. Identification of affected lambs is crucial for correct treatment. Non-steroid anti-inflammatory drugs are to be given concurrently, and metaphylactic treatment for healthy lambs within affected flocks should be considered. Management changes in the flock should be implemented to prevent the disease.
2	Haimanot D Marru, Takele T Anijajo and Adem A Hassen, 2013, A study on Ovine pneumonic pasteurellosis: Isolation and Identification of *Pasteurellae* and their antibiogram susceptibility pattern in Haramaya District, Eastern Hararghe, Ethiopia, BMC Veterinary Research	Sheep are a major livestock component in Ethiopia, but health issues, poor management, and feed shortages hinder their potential. In the remote Haramaya district, information on livestock disease is lacking. A study was conducted to identify the causative agents and antimicrobial susceptibility of bacterial Pasteurella isolates among pneumonic sheep in the district. Of 256 samples, 25% contained *Pasteurella*, with most isolates being *Mannheimia haemolytica*. Age and body temperature were associated with Pasteurella isolates. The isolates consistently responded to various antibiotics, with chloramphenicol being the most effective, followed by **tulathromycin**. Both species were resistant to gentamycin and vancomycin.
3	Khalili I, Ghadimipour R, Ghaderi R, Shokri GH, Jabbari AR, Razmaraii N, Ebrahimi M, 2016, Isolation, identification, and monitoring of antibiotic resistance in *Pasteurella multocida* and	The study aimed to identify and assess the susceptibility of the microorganisms causing pneumonic pasteurellosis in sheep in East Azerbaijan province, Iran. Among 320 cases of pneumonia, *Pasteurella multocida* was isolated from 1.87% of lung samples, while *Mannheimia haemolytica* was not found. *P. multocida* was determined as the main cause of the disease, with outbreak frequency varying throughout the year. The bacteria were identified using cultural, morphological, biochemical, and PCR

	Mannheimia haemolytica isolated from sheep in East Azerbaijan province, Iran, Archives of Razi Institute	techniques. Antimicrobial susceptibility testing revealed resistance to amoxicillin and relative susceptibility to ceftiofur and **tulathromycin.**
4	Van Nguyen P, Le C, Ho X, Truong P, Van Loi B, Nguyen K., 2023, First Report of Antimicrobial Resistance of *Mannheimia haemolytica* from Phan Rang Sheep in Vietnam, Pakistan Veterinary Journal	*Mannheimia haemolytica*, a Gram-negative bacteria associated with respiratory diseases, is found to be prevalent in Phan Rang sheep in Vietnam. The study found that these isolates were more susceptible to ofloxacin, ciprofloxacin, enrofloxacin, and chloramphenicol, but resistant to oxytetracycline, **tulathromycin**, erythromycin, penicillin, and ampicillin. Over 74% of *M. haemolytica* isolates exhibited multidrug resistance, with a good correlation between genotype and resistance phenotype for oxytetracycline.
5	Champour Mohsen, Taghipour Alinaghi, 2015, Comparative efficacy of tulathromycin versus a combination of florfenicol-oxytetracycline in the treatment of undifferentiated respiratory disease in large numbers of sheep, *Journal of Advanced Veterinary and Animal Research* Vol 2, no.3	The study compared the efficacy of **tulathromycin** (TUL) with a combination of florfenicol (FFC) and long-acting oxytetracycline (LAOTC) in treating undifferentiated respiratory diseases in sheep. Results showed that TUL was more effective than FFC and LAOTC combined treatment. The first group of sheep was cured, while the second group needed further treatment. This field trial demonstrates that TUL can effectively treat undifferentiated respiratory diseases in sheep.
6	Moon Catherine S., Berke Olaf, Brent P. Avery, Mcewen A. Scott, Reid-Smith J. Richard, Scott Lisa, Menzies Paula, 2011, Rates and determinants of antimicrobial use, including extra-label, on Ontario sheep farms, Canadian Journal of Veterinary Research Vol 75, no.1	A study on 49 Ontario sheep farms found that antimicrobial use (AMU) and extra-label drug use (ELDU) are prevalent. High exposure rates were found for chlortetracycline, penicillins, and oxytetracycline. The study suggests that public health concerns about antimicrobial use in Ontario sheep may be warranted and could help create drug use and licensure strategies for the Canadian sheep industry. In the farms included in this study, **tulathromycin** did not show any remanence.
7	Abate Fentahun Mitku, Kassa Tsegaw Fentie, 2023, Isolation and identification of Mannheimia haemolytica and	This study aimed to isolate and identify *M. haemolytica* and *P. multocida* from sheep in Ethiopia, assessing antibiotic susceptibility patterns. Results showed M. haeimolytica was the predominant isolate, and most antibiotics, including **tulathromycin**, were not fully effective against it. Treatment and vaccination of ovine

	Pasteurella multocida from symptomatic and asymptomatic sheep and their antibiotic susceptibility patterns in three selected districts of north Gondar zone, Gondar Ethiopia, *Veterinary Medicine and Science* Vol 9, no.4	pneumonic pasteurellosis should be emphasized using effective drugs and appropriate herd management practices.
8	Washburn K, Fajt V, Coetz, 2015, Pharmacokinetics of tulathromycin in nonpregnant adult ewes, Journal of Veterinary Pharmacology and Therapeutics Vol 38, no.4	The study analyzed plasma concentrations and pharmacokinetic parameters of **tulathromycin** in sheep, comparing it to cattle and goats. Results suggest similar dosing (2.5 mg/kg SC) for sheep, assuming similar inhibitory concentrations.
9	MacKay Evelyn E., Washburn Kevin, Padgett Ashley L., Fajt Virginia R., Lo Chih-Ping, Mays Travis P., Washburn Shannon E., 2019, Pharmacokinetics of tulathromycin in fetal sheep and pregnant ewes, *Journal of Veterinary Pharmacology and Therapeutics* Vol 42, no.4	Macrolides, used in medicine for pregnant women and livestock, may control infectious ovine abortion. A study found **tulathromycin** in fetal plasma and amniotic fluid, but - 84 -t stime-course in the fetus differed, raising questions about its transport and elimination.
10	Martin Krysta L., Clampham Maakie O., Davis Jennifer L., Bayenes Ronald E., Lin Zhoumeng, Vickroy Thomas W., Riviere Jim E., Tell Lisa A., 2018, Extra label drug use in small ruminants, *Journal of the American Veterinary Medical Association* Vol 253, no.8	The FARAD Digest reviews common medications used to treat small ruminants in the US and FARAD-recommended WDIs following ELDU in small ruminants. The digest focuses on sheep and goats, as they are considered minor species by the FDA. Despite a decline in sheep and goat production, FARAD has seen an increase in requests for information on WDIs following ELDU in small ruminants since 2007. It seems that **tulathromycin** is often given to sheep and goats at the cattle dosage (2.5 mg/kg, SC, once).
11	Cid Dolores, Fernández-Garayzábal José, Pinto Chris, Domínguez Lucas, Vela Ana Isabel, 2019, Antimicrobial	*Pasteurella multocida* causes diseases in sheep and pigs, and antimicrobial susceptibility studies are crucial for effective therapy. A study found low resistance rates to various antimicrobials in both sheep and pig isolates. However, sheep isolates showed lower percentages of

	susceptibility of Pasteurella multocida isolated from sheep and pigs in Spain – Short communication, *Acta Veterinaria Hungarica* Vol 67, no.4	resistance and MIC90 values compared to pig isolates. However, **tulathromycin** was not found to exibit antimicrobial resistance in both species. The differences in susceptibility patterns may be influenced by the lower use of antimicrobials in the small ruminant industry compared to the pig farming industry.
12	Van Nguyen P., Le C., Ho X., Truong P., Van Loi B., Nguyen K., 2023, First Report of Antimicrobial Resistance of Mannheimia haemolytica from Phan Rang Sheep in Vietnam, Pakistan Veterinary Journal Vol 43, no.1	Mannheimia haemolytica, a Gram-negative bacteria associated with respiratory diseases, is found to be prevalent in Phan Rang sheep, in Vietnam. The study found that these isolates were more susceptible to ofloxacin, ciprofloxacin, enrofloxacin, and chloramphenicol, but resistant to oxytetracycline, **tulathromycin**, erythromycin, penicillin, and ampicillin. Over 74% of *M. haemolytica* isolates exhibited multidrug resistance, with a good correlation between genotype and resistance phenotype for oxytetracycline.

Numerous studies in previous research talk about the efficacity of tulathromycin highlighting its use, especially for *Pasteurella multocida* induced pulmonary disease in ovine species. Interestingly, a conspicuous observation to emerge from the data comparison was the fact that the latest studies already showed resistance to tulathromycin. This resistance is associated with both *Pasteurella spp* and *Mannheimia spp*. Nowadays, it seems that combinations of tulathromycin and another antimicrobial such as florfenicol or oxytetracycline are tested as therapeutic agents in respiratory pathologies in ovine, suggesting chemical potentialization between these molecules, providing antimicrobial and immunomodulatory effects. Complementary to our subject, is the antibioresistance for multiple antibiotics in random different parts of the world, from America to Ethiopia, *Mannhemia haemolytica* being the most incriminated bacteria, presenting antimicrobial resistance. Remarkably, there are few studies in which the use of tulathromycin offers potential for controlling resistant bacterial strains, although several studies have determined its increasing bacterial resistance.

It is worth investigating if chloramphenicol, being the least resistant antimicrobial for respiratory pathogens, could be used alongside tulathromycin for potentisation and a greater effect, thus treating and preventing respiratory pathologies and their systemic complications. Our previous study (Moldovan et al, 2023), highlights the extra-label drug use of tulathromycin in small ruminants and acknowledges the dosage of 2.5 mg/kg sc, once as a treatment often used by farmers. Therefore, it is important to search for more studies that can quantify the patterns of antibiotic usage in ovine species.

It is also necessary to establish all the potential and relevant uses of tulathromycin, not only for respiratory bacterial strains, but also for agents causing abortion, septicaemia, gastro-intestinal pathologies with bacterial enteritis, or hepatic abscesses, and to determine if in the area of use, tulathromycin is still relevant to be used as an antimicrobial agent or livestock animals have already developed antibioresistance. Since multiple studies have tested and proven the efficacy of

tulathromycin in small ruminants, the off-label use should be replaced by a prescription-based treatment, based on data support from previous antibiograms.

We are aware that our study may have two limitations, the first being a low number of articles targeting the use of tulathromycin in specific ovine pathologies. The second one is represented by numerous in vitro studies and the lack of in vivo studies for the use of tulathromycin as a metaphylactic agent and as a specific treatment for respiratory pathologies in small ruminants. These limitation reveal the difficulty of collecting data on ovine species, the vast body of literature being concentrated on cattle and swine species. Data regarding antimicrobial resistance to tulathromycin is discrepant due to several sources that display negative results regarding the sole use of this macrolide and its off label use. Although limitations exist, consolidated further research on the administration of tulathromycin in sheep, highlighting its benefits and addressing potential challenges in its use is needed.

CONCLUSIONS

In conclusion, the reviewed studies collectively highlight the diverse aspects of tulathromycin use in sheep, from its efficacy in treating respiratory diseases to considerations of antimicrobial resistance and pharmacokinetics. While these studies provide valuable insights, ongoing research is essential to further elucidate the nuances of tulathromycin's role in sheep health and to guide responsible antimicrobial use in the livestock industry.

Tulathromycin has great potential for future European Medicines Agency approval for its antimicrobial effect in sheep medicine. This study provides new perspectives for the use of tulathromycin in dermatitis, mastitis, bacterial pneumonia, infectious abortions in the sheep population due to its good sensibility against the bacterial strains described above. The study's findings can help veterinarians and animal health professionals explore alternative treatments for respiratory diseases in sheep and improve their overall health and well-being.

REFERENCES

1. Abate, F. M., & Fentie Kassa, T. (2023). Isolation and identification of Mannheimia haemolytica and Pasteurella multocida from symptomatic and asymptomatic sheep and their antibiotic susceptibility patterns in three selected districts of north Gondar zone, Gondar Ethiopia. Veterinary Medicine and Science, 9(4), 1803–1811. https://doi.org/10.1002/vms3.1166
2. Bagley, C. V. (1997). Animal Health Fact Sheet BOVINE RESPIRATORY DISEASE DISEASE CONDITIONS (OR SYNDROMES).
3. Bigelow, R. A., Richeson, J. T., McClurg, M., Valeris-Chacin, R., Morley, P. S., Funk, J. L., & Scott, M. A. (2023). Characterizing the influence of various antimicrobials used for metaphylaxis against bovine respiratory disease on host transcriptome responses. Frontiers in Veterinary Science, 10. https://doi.org/10.3389/fvets.2023.1272940
4. Cid, D., Fernández-Garayzábal, J. F., Pinto, C., Domínguez, L., & Vela, A. I. (2019). Antimicrobial susceptibility of Pasteurella multocida isolated from sheep and pigs in Spain – Short communication. Acta Veterinaria Hungarica, 67(4), 489–498. https://doi.org/10.1556/004.2019.048

5. De Lamache, D. D., Moges, R., Siddiq, A., Allain, T., Feener, T. D., Muench, G. P., McKenna, N., Yates, R. M., & Buret, A. G. (2019a). Immuno-modulating properties of Tulathromycin in porcine monocyte-derived macrophages infected with porcine reproductive and respiratory syndrome virus. PLoS ONE, 14(8). https://doi.org/10.1371/journal.pone.0221560
6. De Lamache, D. D., Moges, R., Siddiq, A., Allain, T., Feener, T. D., Muench, G. P., McKenna, N., Yates, R. M., & Buret, A. G. (2019b). Immuno-modulating properties of Tulathromycin in porcine monocyte-derived macrophages infected with porcine reproductive and respiratory syndrome virus. PLoS ONE, 14(8). https://doi.org/10.1371/journal.pone.0221560
7. Fischer, C. D., Beatty, J. K., Duquette, S. C., Morck, D. W., Lucas, M. J., & Buret, A. G. (2013). Direct and Indirect anti-inflammatory effects of tulathromycin in bovine macrophages: Inhibition of CXCL-8 secretion, induction of apoptosis, and promotion of efferocytosis. Antimicrobial Agents and Chemotherapy, 57(3), 1385–1393. https://doi.org/10.1128/AAC.01598-12
8. Fischer, C. D., Beatty, J. K., Zvaigzne, C. G., Morck, D. W., Lucas, M. J., & Buret, A. G. (2011). Anti-inflammatory benefits of antibiotic-induced neutrophil apoptosis: Tulathromycin induces caspase-3-dependent neutrophil programmed cell death and inhibits NF-κB signaling and CXCL8 transcription. Antimicrobial Agents and Chemotherapy, 55(1), 338–348. https://doi.org/10.1128/AAC.01052-10
9. Khalili, I., Ghadimipour, R., Ghaderi, R., Shokri, G. H., Jabbari, A. R., Razmaraii, N., & Ebrahimi, M. (2016). Isolation, identification, and monitoring of antibiotic resistance in Pasteurella multocida and Mannheimia haemolytica isolated from sheep in East Azerbaijan province, Iran. Archives of Razi Institute, 71(3), 153–160. https://doi.org/10.22034/ari.2016.106920
10. Larson, R. L., & Step, D. L. (2012). Evidence-Based Effectiveness of Vaccination Against Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in Feedlot Cattle for Mitigating the Incidence and Effect of Bovine Respiratory Disease Complex. Veterinary Clinics of North America: Food Animal Practice, 28(1), 97-106.e7. https://doi.org/10.1016/J.CVFA.2011.12.005
11. MacKay, E. E., Washburn, K. E., Padgett, A. L., Fajt, V. R., Lo, C. P., Mays, T. P., & Washburn, S. E. (2019). Pharmacokinetics of tulathromycin in fetal sheep and pregnant ewes. Journal of Veterinary Pharmacology and Therapeutics, 42(4), 373–379. https://doi.org/10.1111/jvp.12744
12. Marru, H. D., Anijajo, T. T., & Hassen, A. A. (2013). A study on Ovine pneumonic pasteurellosis: Isolation and Identification of Pasteurellae and their antibiogram susceptibility pattern in Haramaya District, Eastern Hararghe, Ethiopia. http://www.biomedcentral.com/1746-6148/9/239
13. Mladenov, D., Yordanov, S., & Dimitrova, A. (2023). TULATHROMYCIN – A SEMI-SYNTHETIC MACROLIDE ANTIBIOTIC. I. CHARACTERISTICS AND ANTIBACTERIAL ACTIVITY. In Bulgarian Journal of Veterinary Medicine (Vol. 26, Issue 1, pp. 1–9). Trakia University. https://doi.org/10.15547/bjvm.2325
14. Moldovan C., Dreanca A., Madru M., Muresan C. & Marcus I. (2023). A preliminary study of the biological and toxicological effects of tulathromycin in sheep, RRMV, 33(4), 89-96.
15. Politis, A. P., Vasileiou, N. G. C., Ioannidi, K. S., & Mavrogianni, V. S. (2019). Treatment of bacterial respiratory infections in lambs. Small Ruminant Research, 176, 70–75. https://doi.org/10.1016/j.smallrumres.2019.05.005
16. Soliman, E. S., & Mahmoud, A. E. (2021a). In-vitro Antimicrobial Activity and In-vivo Prophylactic Influence of Tulathromycin against Respiratory Diseases in Dairy Heifers Exposed to Cold Stress. Advances in Animal and Veterinary Sciences, 9(8), 1211–1222. https://doi.org/10.17582/journal.aavs/2021/9.8.1211.1222

17. Soliman, E. S., & Mahmoud, A. E. (2021b). In-vitro Antimicrobial Activity and In-vivo Prophylactic Influence of Tulathromycin against Respiratory Diseases in Dairy Heifers Exposed to Cold Stress. Advances in Animal and Veterinary Sciences, 9(8), 1211–1222. https://doi.org/10.17582/journal.aavs/2021/9.8.1211.1222
18. Stanton, A. L., Kelton, D. F., LeBlanc, S. J., Millman, S. T., Wormuth, J., Dingwell, R. T., & Leslie, K. E. (2010). The effect of treatment with long-acting antibiotic at postweaning movement on respiratory disease and on growth in commercial dairy calves. Journal of Dairy Science, 93(2), 574–581. https://doi.org/10.3168/jds.2009-2414
19. The prospect of Draxxin
https://www.vmd.defra.gov.uk/ProductInformationDatabase/current/starts-with-d?page=9
20. Vilaró, A., Novell, E., Enrique-Tarancon, V., Baliellas, J., & Fraile, L. (2023). Susceptibility trends of swine respiratory pathogens from 2019 to 2022 to antimicrobials commonly used in Spain. Porcine Health Management, 9(1). https://doi.org/10.1186/s40813-023-00341-x
21. Villarino, N., Brown, S. A., & Martín-Jiménez, T. (2013). The role of the macrolide tulathromycin in veterinary medicine. In Veterinary Journal (Vol. 198, Issue 2, pp. 352–357). https://doi.org/10.1016/j.tvjl.2013.07.032
22. Washburn, K., Fajt, V. R., Coetzee, J. F., Rice, S., Wulf, L. W., & Washburn, S. (2015). Pharmacokinetics of tulathromycin in nonpregnant adult ewes. Journal of Veterinary Pharmacology and Therapeutics, 38(4), 414–416. https://doi.org/10.1111/jvp.12196
23. Wellman, N. G., & O'Connor, A. M. (2007). Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. Journal of Veterinary Pharmacology and Therapeutics, 30(3), 234–241. https://doi.org/10.1111/j.1365-2885.2007.00846.x
24. Yaeger, M. J., Wu, Z., Plummer, P. J., Meral, M., Phd, O., Beyi, A. F., Xu, C., Zhang, Q., & Griffith, R. W. (2020). Experimental evaluation of tulathromycin as a treatment for Campylobacter jejuni abortion in pregnant ewes Orhan Sahin dvm, phd (Vol. 81, Issue 3).
25. Yao, L., Yang, L., Ling, Y., Wei, Y., Shen, X., & Ding, H. (2022). Pharmacokinetic/Pharmacodynamic Relationships of Tulathromycin Against Actinobacillus pleuropneumoniae in a Porcine Tissue Cage Infection Model. Frontiers in Veterinary Science, 9. https://doi.org/10.3389/fvets.2022.822432