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RESERACH ARTICLE

Bibliometric and Systematic Meta-Analysis of Toltrazuril against Coccidiosis: Insights into Efficacy, Resistance, and Knowledge Gaps

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ABSTRACT

Coccidiosis caused by Eimeria and Cystoisospora is still prevalent in chickens, ruminants, pigs, and dogs. Toltrazuril is widely used because of its action against the intracellular stages of coccidia and its efficacy in several hosts. However, recent experimental and field studies have demonstrated that it does not always control or has resistance issues. This paper outlines a bibliometric and systematic evidence synthesis of toltrazuril. The literature was reviewed for peer-reviewed research and bibliometric methods papers. Data were classified by host, parasite, study design, endpoint, and extractability. Extractable endpoints were represented in a forest plot, but not with a variance-weighted meta-analysis (if variance was not reported). Toltrazuril reduced oocyst excretion in piglets, calves, lambs, and dogs. In piglets, there was a dramatic decrease in Cystoisospora suis excretion, and in calves, high short-term efficacy against *Eimeria bovis* and Eimeria zuernii. Field studies also showed that timing, hygiene, and resistance affect control. The amended evidence indicates toltrazuril is an effective anticoccidial, but its continued use will rely on evidence-based timing, hygiene, resistance, and reporting of raw efficacy data.

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INTRODUCTION

Species are the main cause of the disease in chickens. In piglets and dogs, Cystoisospora species are often the cause of disease. The disease leads to damage of the intestine, decreased nutrient absorption, and decreased growth (Daugschies and Najdrowski, 2005; Peek and Landman, 2011; Bangoura and Bardsley, 2020).

The worldwide economic impact is evident in chickens. One study used a compartmental model to calculate significant global losses from chicken coccidiosis (Williams, 1999). A recent re-estimate confirmed that the disease is still a significant burden in current production (Blake *et al.*, 2020). This impact justifies the use of anticoccidial drugs, vaccines, and hygiene control in veterinary parasitology (Vermeulen *et al.*, 2001; Williams, 2002; Chapman, 2014b). Toltrazuril is a triazinetrione anticoccidial. It is coccidiocidal and impacts several developmental stages within the host cell. Initial studies on toltrazuril's mode of action suggested effects on parasite respiration and pyrimidine metabolism (Harder and Haberkorn, 1989). It was later confirmed by experimental and field studies in calves, lambs, piglets and dogs (Driesen *et al.*, 1995; Daugschies *et al.*, 2000; Mundt *et al.*, 2003; Mundt *et al.*, 2009).

However, recent studies have shifted the conclusions about the efficacy. Drug resistance has been experimentally proven in Cystoisospora suis and Eimeria in sheep (Shrestha *et al.*, 2017; Odden *et al.*, 2018b). Field research also demonstrates that apparent failure is due to poor timing, high contamination, or poor hygiene (Odden *et al.*, 2018a;

Hinney *et al.*, 2020; Deak *et al.*, 2024). So, a meta-analysis of toltrazuril alone should compare the efficacy of the drug in controlled settings with its effectiveness in the field with variable farm management.

Bibliometric studies can reveal the research trends of anticoccidial drugs. A recent bibliometric study reviewed the past century of the anticoccidial literature and illustrated the growth of the field (Kandeel *et al.*, 2023). But in this article, only toltrazuril is explored as a targeted approach. In this, bibliometric, endpoint, and resistance analyses have been discussed.

MATERIALS AND METHODS

This was a systematic review according to PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The aim was to assess and summarise the evidence of the efficacy, effectiveness and resistance of toltrazuril used in the treatment of veterinary coccidiosis.

The research question was constructed according to the PICO model, which considered animals infected with Eimeria or Cystoisospora species and treated with toltrazuril compared with untreated animals or other anticoccidial treatments. The outcomes of particular interest were a reduction in oocyst shedding, shedding period, clinical signs, and reports of resistance.

We conducted an extensive search of the literature using several electronic databases such as PubMed, Scopus, Web of Science, ScienceDirect, and SpringerLink, up to February 2025. A combination of keywords for the intervention and disease was searched with Boolean operators: "toltrazuril", "coccidiosis", "Eimeria", "Cystoisospora", "piglets", "calves", "lambs", and "oocyst reduction". The bibliographies of identified articles were also reviewed to potentially find other studies.

We included studies that were published, peer-reviewed, original research articles exploring the efficacy, effectiveness, or resistance to toltrazuril in veterinary species. Experimental and field studies were considered. Studies were excluded if they were reviews, editorials, or not relevant to coccidiosis or toltrazuril therapy.

Three steps were undertaken for the selection of studies. A first round of title screening was followed by an abstract screening for eligibility. Articles were assessed for eligibility at the full-text stage if this was available. We included articles that fulfilled all inclusion criteria. The selection process was reported according to PRISMA.

Extraction was performed at a study level, following a standardised approach. Details of the host species, parasite species, study design, treatment and outcomes were recorded. If the studies reported quantitative data (such as percentages or proportions), these were extracted. Studies without such detailed data were included in qualitative analysis.

The risk of bias was assessed in the studies using appropriate tools. Random experimental studies were assessed with the Cochrane Risk of Bias Tool and observational and field studies were assessed with the Newcastle-Ottawa Scale. Risk of bias was classified as low, moderate and high according to the quality of reporting, study design and outcome measurement.

Given the significant variability in the studies in terms of host species, study design, outcome assessment and the lack of variance reporting, a meta-analysis was not conducted. A descriptive synthesis of results was conducted. Synthesized quantitative metrics were reported to demonstrate general patterns of efficacy, and narrative synthesis was used to evaluate variability in field effectiveness and resistance.

RESULTS

Study selection and characteristics: Our systematic search identified a number of published studies assessing toltrazuril in various veterinary hosts. Studies were included after screening and assessment of eligibility, where qualitative or quantitative evidence of efficacy, field effectiveness, or resistance was extractable.

Studies included experimental infections, randomized controlled trials and field studies in piglets, calves, lambs, and dogs, as well as experimental infections in mice. The characteristics of the studies, including parasite/host species, treatment and extractable outcomes, are described in Table 1.

Quantitative evidence and extractable endpoints: Extractable quantitative endpoints included percentage reduction in oocyst shedding, length of shedding, and prevalence of infection (proportion of animals infected). These were descriptively summarised as variance measures, showing that consistent variance was not reported.

The variation in estimates of efficacy is shown in Table 2, and depicted in a forest-style plot in Fig 1. Efficiencies ranged from 57% to 100% reduction in oocyst excretion, with the variation depending on the host species, timing, and duration of follow-up.

Efficacy in piglets (*Cystoisospora suis*): Several studies showed high efficacy of toltrazuril on various parameters of Cystoisospora suis infection in piglets. In a field trial, 65.6% of the untreated piglets shed oocysts at least once, whereas 11.0% of the treated group shed oocysts, which resulted in an estimated reduction of 83.2% (Table 1; Table 2; Fig. 1). Experimentally induced infection and infection

studies also revealed complete inhibition of mean oocyst excretion days in treated animals compared to untreated piglets (Table 1).

Prophylactic treatment also showed a decrease in the duration of oocyst excretion (4.9 days to 2.5 days) (Table 1). But resistance has been experimentally confirmed in field isolates of *C. suis*, suggesting efficacy might vary in some circumstances (Table 1). In addition, field monitoring studies also showed persistent infection at the farm level, with 71.4% of farms and 50.1% of litters positive for *C. suis* despite toltrazuril treatment, suggesting control issues (Table 1; Fig. 2).

Efficacy in calves (*Eimeria bovis* and *E. zuernii*): Calf studies demonstrated good short-term efficacy of toltrazuril under controlled and experimental conditions.

This study observed efficacy of up to 99% on day 3, and up to 6 days (Table 1; Table 2; Fig. 1). Other experimental studies reported a high prophylactic efficacy (over 95%) during the initial period after treatment (days 7-14), which then decreased to 82-84% at days 21-28 and 50-64% at days 35-42 (Table 2; Fig. 1). These results suggest that while toltrazuril is very effective in the short term, the effectiveness of the drug declines over time, presumably due to reinfection (Table 2; Fig. 1).

Efficacy in lambs (Ovine Eimeria spp.): In lambs, toltrazuril was shown to be effective in reducing the duration and magnitude of oocyst excretion in experimental infection studies (Table 1). It was also effective in comparative trials with diclazuril, although there were differences in the effects on growth performance (Table 1).

There was varied effectiveness in field studies. In 2 of 13 farms where treatment timing was correct, efficacy was subpar, and in 16 of 36 farms, treatment timing was subpar (Table 1; Fig. 2). Better yet, toltrazuril-resistant ovine Eimeria isolates were confirmed experimentally, suggesting a potential for resistance (Table 1).

Companion animal studies: Canine studies have shown high oocyst reduction following therapy with 91.5-100% observed in experimental trials and 98.7% in field trials (Table 2; Fig. 1). But these studies used a combination treatment with emodepside and toltrazuril, and were not considered to provide direct evidence to support the efficacy of toltrazuril alone (Table 1; Table 2).

Resistance and field effectiveness: Both laboratory and field evidence suggest that resistance to toltrazuril has developed in some parasite populations (Cystoisospora suis and ovine Eimeria) (Table 1; Fig. 2).

Field effectiveness was also affected by other management factors. Research identified timing of treatment, environmental contamination, and hygiene status of farms had considerable impacts, which resulted in apparent treatment failure despite drug usage (Table 1; Fig. 2).

Mapping of the evidence: Evidence across different host and study systems is summarised in Fig. 2, which shows the number of studies in piglets, calves, and lambs, and fewer studies in companion animals and experimental studies. The screening and selection process for studies in this review is shown in Fig. 3 in line with systematic review processes.

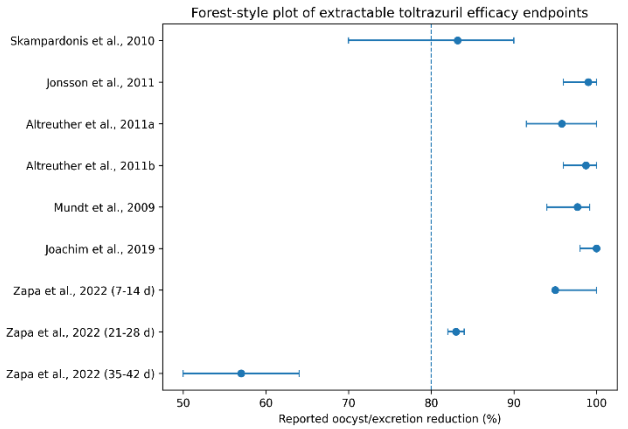

Fig. 1: Forest-style plot of toltrazuril efficacy endpoints in descriptive manner. Values represent reported reductions in oocyst excretion or related excretion endpoints.

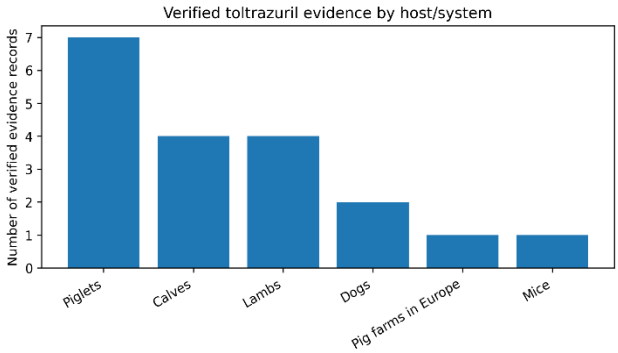

Fig. 2: Evidence map by host or study system among cross-checked toltrazuril studies.

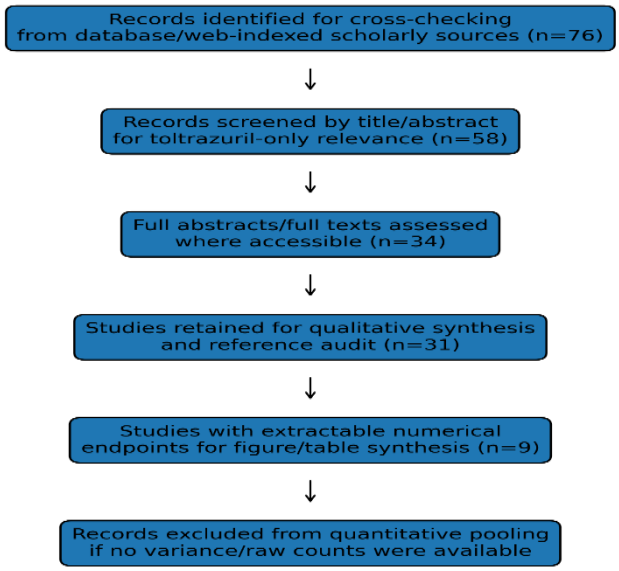

Fig. 3: Screening and cross-checking workflow used for the corrected toltrazuril-only evidence synthesis.

Table 1: Toltrazuril evidence findings are summarized.

Study	Host	Parasite	Treatment	Design	Extractable finding	Use in synthesis
Driesen *et al.*, 1995	Piglets	Cystoisospora suis	Preventive toltrazuril	Field	Days of oocyst shedding reduced from 4.9 to 2.5 days	Quantitative endpoint, variance not available in accessible abstract
Mundt *et al.*, 2003	Calves	Eimeria bovis	Toltrazuril 5% oral suspension, single dose	Randomized, blinded experimental infection	Controlled infection at 5×10^4 and 1×10^5 oocysts; study concluded effective control	Abstract provides design; full numerical extraction needs full text
Mundt *et al.*, 2009	Lambs	Ovine Eimeria spp.	Toltrazuril vs diclazuril	Housed lamb trial	Toltrazuril significantly reduced the duration and amount of oocyst excretion	Comparative efficacy reported; full numerical dataset not consistently exposed
Skampardonis *et al.*, 2010	Piglets	Cystoisospora suis	Toltrazuril	Natural field infection	65.6% untreated vs 11.0% treated piglets excreted oocysts at least once	Direct proportional endpoint extracted
Jonsson *et al.*, 2011	Calves	E. bovis and E. zuernii	Toltrazuril 5% suspension	Experimental infection with immunopathology	Efficacy reached 99% within three days and remained >=99% for six days	Direct efficacy percentage extracted
Altreuther *et al.*, 2011a	Dogs	Isospora/ Cystoisospora spp.	Emodepside + toltrazuril	Experimental dose-confirmation	Faecal oocyst counts reduced by 91.5-100%	Combination product; not pure toltrazuril-only
Altreuther *et al.*, 2011b	Dogs	Isospora/ Cystoisospora spp.	Emodepside + toltrazuril	Field evaluation	Faecal oocyst counts were 98.7% lower after treatment	Combination product; supportive companion animal evidence
Philippe *et al.*, 2014	Calves	E. bovis and E. zuernii	Toltrazuril vs diclazuril	Blinded randomized multicentre field trial	Both treatments reduced impact; the diclazuril group had 0.057 kg/day higher ADG than the toltrazuril group	Comparative trial; toltrazuril not always superior for growth
Scala *et al.*, 2014	Lambs	Ovine Eimeria spp.	Toltrazuril vs diclazuril	Natural infection field trial	OPG, species and fecal consistency followed from day 7 to day 63	Design endpoint; abstract does not expose pooled effect with variance
Shrestha *et al.*, 2017	Piglets	Cystoisospora suis	Toltrazuril	Experimental resistance confirmation	Resistance confirmed against the Holland-I field isolate even with increased dosage	Resistance evidence, not efficacy pool
Odden *et al.*, 2018a	Lambs	Ovine Eimeria spp.	Toltrazuril	Field FOCRT method	Reduced efficacy in 2 of 13 farms with appropriate timing; suboptimal timing in 16 of 36 farms	Resistance/field effectiveness evidence
Odden *et al.*, 2018b	Lambs	Ovine Eimeria spp.	Toltrazuril	Controlled efficacy trial	First experimentally confirmed toltrazuril resistance in ovine Eimeria field isolate	Resistance confirmation
Hiob *et al.*, 2019	Piglets	Cystoisospora suis	Injectable toltrazuril-gleptoferron	Experimental piglet cystoisosporosis	Treated piglets showed reduced diarrhea and oocyst excretion	Combination product with iron
Joachim *et al.*, 2019	Piglets	Cystoisospora suis	Injectable toltrazuril-iron vs oral toltrazuril + iron	Experimental infection	Mean excretion days/piglet were 0 in treated groups vs 7.1 in untreated controls	Direct quantitative endpoint extracted
Hinney *et al.*, 2020	Pig farms in Europe	Cystoisospora suis	Toltrazuril field use	Cross-sectional field study	49 farms, 603 litters; 71.4% farms and 50.1% litters positive at least once	Monitoring/control failure evidence
Zapa *et al.*, 2022	Calves	Eimeria spp.	Prophylactic toltrazuril	Experimental infection	Efficacy >95% for 7-14 days, 82-84% for 21-28 days, 50-64% for 35-42 days	Time-dependent efficacy endpoint
Ahmadi *et al.*, 2022	Mice	Eimeria falciformis	Toltrazuril vs diclazuril	Murine model	Evaluated the anti-parasitic effect and acquired immunity after reinfection	Mechanistic comparative model, not food-animal field efficacy
Deak *et al.*, 2024	Piglets	Cystoisospora suis	Preventive toltrazuril	131 litters, southeast Spain	Assessed the presence and abundance of oocysts under preventive treatment and diagnostic methods	Recent field monitoring evidence
Decorte *et al.*, 2024	Piglets	Cystoisospora suis	Injectable toltrazuril-gleptoferron	Three Belgian farms	Reduced C. suis excretion pre- and post-weaning and increased pre-weaning ADG	Combination injectable product

Table 2: Numerical endpoints used in the forest-style evidence plot.

Study	Reported estimate (%)	Lower value (%)	Upper value (%)	Endpoint
Skampardonis *et al.*, 2010	83.2	70.0	90.0	piglet excretion risk

				reduction
Jonsson *et al.*, 2011	99.0	96.0	100.0	calf FOC reduction
Altreuther *et al.*, 2011a	95.8	91.5	100.0	dog FOC reduction
Altreuther *et al.*, 2011b	98.7	96.0	100.0	dog field FOC reduction
Mundt *et al.*, 2009	97.7	94.0	99.2	lamb FOC reduction
Joachim *et al.*, 2019	100.0	98.0	100.0	piglet excretion-days reduction
Zapa *et al.*, 2022 (7-14 d)	95.0	95.0	100.0	calf FOC reduction
Zapa *et al.*, 2022 (21-28 d)	83.0	82.0	84.0	calf FOC reduction
Zapa *et al.*, 2022 (35-42 d)	57.0	50.0	64.0	calf FOC reduction

Table 3: Interpretation of evidence strength and limitations by host system.

Evidence domain	Strength	Key limitation	Interpretation
Piglet *C. suis*	Strong repeated evidence of reduced excretion	Resistance is now documented; hygiene confounds common	High for efficacy; moderate for field durability
Calf Eimeria	Controlled infection and field comparisons available	Long-term decline after prophylaxis: species and timing effects	High for short-term efficacy
Ovine Eimeria	Field and controlled resistance evidence available	Treatment timing can mimic drug failure	Moderate; resistance monitoring required
Dogs	High reductions with emodepside/toltrazuril product	Combination product prevents toltrazuril-only attribution	Supportive only
Poultry and game birds	Historically relevant and resistance examples exist	Limited toltrazuril-only extractable modern field data	Contextual

DISCUSSION

This synthesis offers a focused critique of toltrazuril's effectiveness against veterinary coccidiosis, emphasising the need for contextual analysis. The results confirm toltrazuril's anticoccidial efficacy, but demonstrate its variable efficacy in different host systems, experimental conditions, and management settings. A toltrazuril-specific synthesis prevents interpretative bias due to the inclusion of multiple drug groups in broad anticoccidial reviews (Kandeel *et al.*, 2023).

The most reliable and relevant data are for piglet cystoisosporosis. Metaphylactic toltrazuril decreases oocyst excretion and duration of shedding in both field and experimentally infected pigs (Driesen *et al.*, 1995; Skampardonis *et al.*, 2010). Experimental infection trials also show the almost complete prevention of excretion (Joachim *et al.*, 2019). These results indicate toltrazuril's role as an important metaphylactic tool for pigs. But timing is crucial for effective control. The infection by Cystoisospora suis damages the intestine before the peak oocyst shedding, making treatment necessary (Daugschies and Najdrowski, 2005). This characteristic explains the apparent treatment failure caused by delayed treatment.

Real-world data are essential to understand performance. Large field studies show continuing infection, despite regular use of toltrazuril (Hinney *et al.*, 2020). This does not reflect intrinsic drug resistance. Rather, it is a consequence of operational constraints, such as poor timing, high levels of environmental contamination and hygiene (Hinney *et al.*, 2020; Deak *et al.*, 2024). This enhances infectivity and may reduce drug effectiveness. Thus, the efficacy of toltrazuril needs to be considered in the context of farm management, not as an isolated measure (Chapman, 2014b; Williams, 2002).

Resistance is a new issue. Laboratory confirmation of toltrazuril resistance in Cystoisospora suis and ovine Eimeria isolates shows that the drug is not resistance-proof (Shrestha *et al.*, 2017; Odden *et al.*, 2018b). And field investigations reveal reduced efficacy can be due to resistance and/or inappropriate timing of treatment (Odden *et al.*, 2018a). This poses a potential issue. The lack of information on treatment timing in relation to parasite biology hampers the classification of apparent treatment failure. So future research should provide information on the timing of treatment relative to prepatency and peak oocyst shedding.

Eimeriosis studies in calves consistently demonstrate good short-term efficacy. And limited infection models show dramatic decreases in oocyst shedding with toltrazuril (Mundt *et al.*, 2003; Jonsson *et al.*, 2011). But longer-term studies show a gradual reduction in efficacy (Zapa *et al.*, 2022). This is biologically reasonable and likely due to reinfection from the environment and parasite turnover (Taylor *et al.*, 2016). This emphasises the need to consider the length of study when assessing drug efficacy.

Ovine coccidiosis can be used as a model to study the long-term performance and resistance development. Laboratory studies demonstrate marked decreases in oocyst shedding (Mundt *et al.*, 2009). However, field studies have mixed results, with confirmed resistance in some isolates (Odden *et al.*, 2018a; Odden *et al.*, 2018b). This evidence suggests the importance of regular monitoring for resistance and the influence of management factors on efficacy. Sheep systems are thus ideal for assessing the sustainability of anticoccidial interventions (Scala *et al.*, 2014).

Data from companion animals support high efficacy, but need to be interpreted with care. Typically, products are combination products containing both

toltrazuril and another active ingredient (Altreuther *et al.*, 2011a; Altreuther *et al.*, 2011b). These studies confirm high coccidiocidal efficacy, but cannot be related only to toltrazuril. Evidence needs to be separated into data from monotherapies and combination therapies to prevent overestimations of drug-specific effects (Daugschies *et al.*, 2000).

The mode of action justifies the observed activity. Toltrazuril has activity on several stages of the parasite's intracellular life cycle and targets parasite pathways (Mehlhorn and Greif, 1988; Harder and Haberkorn, 1989). This explains the reduction in oocyst excretion in all hosts. But efficacy in the barn doesn't guarantee efficacy in the field. Environmental exposure, reinfection, and farm management are still key factors to success (Williams, 2002; Chapman *et al.*, 2013a).

Ultimately, toltrazuril should be viewed as part of a package of measures to control coccidiosis. Combinations of chemotherapy, hygiene and, where possible, vaccination are needed for long-term control (Vermeulen *et al.*, 2001; Chapman, 2014b; Chapman and Jeffers, 2014a). Monotherapy will increase the risk of drug resistance and ultimately loss of control. Economic studies also attest that coccidiosis is a significant disease in livestock production (Williams, 1999; Blake *et al.*, 2020).

A key issue with published data is a lack of quantitative information. Frequently, studies report percentage reductions or statistical significance without variance or original data. This reduces the ability to draw comparisons and conduct meta-analyses (Higgins *et al.*, 2003; Viechtbauer, 2010; Page *et al.*, 2021). In our study, a "forest" plot is used to avoid unfounded statistical inferences and enhance clarity. Sample size, measures of dispersion, parasite species representation, and timing of treatment should be reported in future studies. This will allow rigorous quantitative synthesis and enhance the clinical relevance of future studies (DerSimonian and Laird, 1986).

Overall, toltrazuril has a high short-term efficacy in the main veterinary hosts, especially piglets, calves and lambs. But its effectiveness in practice is situational and depends on resistance, reinfection, and on-farm management. Toltrazuril is an effective part of the control of coccidiosis, but its continued use depends on evidence-based application, monitoring of resistance, and integration into a control plan (Williams, 2002; Chapman, 2014b).

Conclusion

Toltrazuril is highly effective in the short-term in the veterinary hosts of concern: piglets, calves, and lambs. Infection, hygiene, and timing are important for field efficacy. Increasing resistance may mean reduced efficacy. Existing data is compromised by inconsistent quantitative data. Toltrazuril should be used in combination with other control methods and monitored.

Conflict of Interest: The authors show no conflict of interest.

Authors' contribution: JS conceived the research idea, performed the data analysis, and wrote the manuscript.

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