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# Validation of efficacy of rabbit anticoccidial drugs commonly used in Kenya

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## ABSTRACT
The objective of this study was to determine the efficacy of three most commonly used off label (poultry based) anticoccidials in treatment of rabbit coccidiosis by smallholder rabbit farmers in Kenya. The test drugs as independently identified by farmers and agro-veterinary suppliers in a baseline survey were sulphachloropyrazine, amprolium and trimethoprim-sulphamethoxazole and were benchmarked against diclazuril (diclosol 1%) as the standard drug in experimental and natural coccidial infections. Sixty weaner rabbits of New Zealand white and California white breeds were randomly allocated to six treatment groups (A, B, C, D, E and F) each with 10 rabbits in a controlled laboratory trial. Groups B, C, D, E and F were experimentally infected with mixed *Eimeria* species while group A served as uninfected-untreated (negative) control group. Four of the infected groups were respectively treated with sulphachloropyrazine (E), amprolium hydrochloride 20% (B), trimethoprim-sulphamethoxazole combination (F) and diclazuril (diclosol 1%) (D) at dosages recommended by the manufacturers (poultry reference dosages). Group C was the infected untreated (positive) control group. Field efficacy trials in naturally infected rabbits were then conducted to validate the laboratory results. Results revealed high efficacy of suphachloropyrazine and diclazuril manifested by reduced oocysts counts, faecal and lesion scores in the controlled laboratory trial approaching those of the negative control group. Similarly, sulphachloropyrazine and diclazuril recorded high efficacies against natural coccidiosis in the field trials which was manifested by significant reduction of oocysts shed. Trimethoprim-sulphamethoxazole recorded moderate to satisfactory efficacy in the field trial but was not efficacious in the laboratory trial. Amprolium was not able to control coccidiosis in both laboratory and field trials at the recommended poultry reference dosages. This study recommends prudent use of available efficacious anticoccidial drugs in the country to prevent development of resistance.

Key words: Amprolium, diclazuril, *Eimeria*, Kenya, oocyst, rabbit coccidiosis, sulphachloropyrazine

## RÉSUMÉ
L'objectif de cette étude était de déterminer l'efficacité des trois anticoccidiens les plus couramment utilisés sans étiquette (à base de volaille) dans le traitement de la coccidiose du lapin par les petits éleveurs de lapins au Kenya. Les médicaments d'essai identifiés indépendamment par les agriculteurs et les fournisseurs agro-vétérinaires dans une enquête de référence étaient la sulphachloropyrazine, l'amprolium et le trimethoprim-sulphaméthoxazole et étaient comparés au diclazuril (diclosol 1%) comme médicament standard dans les infections coccidiennes expérimentales et naturelles. Soixante (60)

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lapins sevrés de race blanche de Nouvelle-Zélande et de race blanche de Californie ont été répartis au hasard dans six groupes de traitement (A, B, C, D, E et F), chacun avec 10 lapins dans un essai contrôlé au laboratoire. Les groupes B, C, D, E et F ont été expérimentalement infectés avec des espèces mixtes d'*Eimeria* tandis que le groupe A a servi de groupe témoin non infecté-non traité (négatif). Quatre des groupes infectés ont été traités respectivement par la sulphachloropyrazine (E), le chlorhydrate d'amprolium 20% (B), l'association triméthoprime-sulphaméthoxazole (F) et le diclazuril (diclosol 1%) (D) aux doses recommandées par les fabricants (doses de référence pour la volaille). Le groupe C était le groupe témoin infecté (positif) non traité. Des essais d'efficacité sur terrain des lapins naturellement infectés ont ensuite été menés pour valider les résultats de laboratoire. Les résultats ont révélé une efficacité élevée de la suphachloropyrazine et du diclazuril manifestée par une diminution du nombre d'oocystes, des scores fécaux et de lésions dans l'essai de laboratoire contrôlé approchant ceux du groupe témoin négatif. De même, la sulfachloropyrazine et le diclazuril ont enregistré des efficacités élevées contre la coccidiose naturelle dans les essais sur le terrain qui se sont manifestées par une réduction significative de la perte d'oocystes. Le triméthoprime-sulphaméthoxazole a enregistré une efficacité modérée à satisfaisante dans l'essai sur le terrain mais n'a pas été efficace dans l'essai en laboratoire. Amprolium n'a pas été en mesure de contrôler la coccidiose dans les essais en laboratoire et sur le terrain pour les doses de référence de volaille recommandées. Cette étude recommande l'utilisation prudente des médicaments anticoccidiens efficaces disponibles dans le pays afin d'empêcher le développement d'une résistance.

Mots-clés: Amprolium, diclazuril, *Eimeria*, Kenya, oocyste, coccidiose de lapin, suphachloropyrazine

## INTRODUCTION

Farmers in Kenya spend significant amount of money to control rabbit diseases (Okumu *et al.,* 2014). The most common and devastating of these diseases is coccidiosis which results in huge economic losses (Bhat *et al.*, 1996). Rabbit coccidiosis mainly affect weanlings resulting in high mortality and morbidity. It presents with clinical signs of dehydration, diarrhoea, rough hair coat, inappetence, poor performance, and reduced productivity (Jithendran, 2010). Two forms of coccidiosis occur in rabbits and is caused by 11 different species of *Eimeria* (Pakandl, 2009). One form is intestinal coccidiosis where *Eimeria* spp. invade the intestines resulting in varied pathogenicity (Sivajothi *et al.,* 2014). The other form is hepatic coccidiosis caused by *E. stiedae* that invades the biliary epithelial cells (Bhat *et al.,* 1996). Mixed infection by both forms are common in Kenya (Okumu *et al.,* 2014). Transmission of both forms occur through feco-oral route and is exacerbated by poor hygiene (Pakandl, 2009). Several control strategies are used to control coccidiosis. These include strict biosecurity and hygiene (Pakandl, 2009), use of vaccines (Drouet-Viard *et al.*, 1997), and natural extracts from plants, fungus and microorganisms (Quiroz-Castañeda and Dantán-González, 2015). However, the use of synthetic chemical anticoccidials labelled for poultry remain the most commonly used prevention and treatment method against rabbit coccidiosis in Kenya. To date there are no specific rabbit anticoccidials in Kenya and farmers use poultry anticoccidials to treat rabbit coccidiosis. This, they do using the poultry dosages with little or no knowledge of their safety and efficacy against rabbit coccidian parasites. No literature exist in Kenya on the efficacies of these drugs against rabbit *Eimeria* spp. The purpose of this study was to determine the efficacy of most commonly used poultry based anticoccidial drugs by rabbit farmers in Kenya benchmarked against a standard drug (Diclosol 1%) that have proven efficacy

elsewhere and have not been used in Kenya, under experimental and/or field conditions.

## MATERIALS AND METHODS

**Description of the study.** The three most commonly used anticoccidials by rabbit farmers were determined through an already published baseline survey (Ogolla *et al.,* 2017) as suphachloropyrazine, trimethoprim-sulphamethoxazole and amprolium. A total of 60 rabbits were randomly allocated into six groups each consisting of 10 rabbits (A, B, C, D, E, and F). Groups A and C served as uninfected untreated (negative control) and infected untreated (positive control), respectively. Rabbits in groups B, C, D, E and F were challenged with 120,000 mixed *Eimeria* sporulated oocysts administered orally using a syringe. Treatments were commenced either when oocyst per gram o.p.g counts reached at least 500,000 o.p.g and/or when clinical signs of coccidiosis were observed. Group B was treated with amprolium administered at 1g/liter for 7 consecutive days. Group D was treated with diclazuril (Diclosol 1%) at 10 ppm for 48 hours. Group E was treated with sulphachloropyrazine 30% for six days as follows: 1$^{st}$, 2$^{nd}$, 3$^{rd}$, 5$^{th}$, 7$^{th}$, and 9$^{th}$ day. Group F was treated with trimethoprim-sulphachloropyrazine combination administered at 1g/litre for 7 consecutive days. All the treatments were administered according to the manufacturer's instructions in fresh drinking water changed on a daily basis. Fecal samples were collected from the 2$^{nd}$ day to day 30 post infection. The number of oocysts per gram of feces of each group was determined using modified McMaster technique (MAFF, 1986). Daily number of dead rabbits was recorded and mean weight gain for each group determined at the end of the experiment. In order to assess the lesion score, three rabbits from each group were picked randomly for necropsy examination at the end of the experiment, in addition to those that died during the trial. Lesion scores were determined through macroscopic examination of the duodenum, jejunum, ileum, caecum, colon and the liver of each rabbit. The lesions were scored as 0 when no evident lesion was seen while a score of 3 was assigned to the severely infected rabbits as described by Elbahy *et al.* (2006). Feces voided were observed and scored from day 1 post infection to day 20 post treatment according to Ramadan *et al.* (1997). Field trials were then conducted in 10 farms to validate the laboratory results.

**Field trials**. Any rabbit with oocyst counts 500,000; or <500,000 oocysts but presenting with clinical signs of coccidiosis such us diarrhea, inappearence and dehydration met the inclusion criteria. The rabbits were randomly assigned to four treatment groups: FA, FB, FC and FD. Each treatment group had 90 sick rabbits. Each treatment group was further subdivided into 18 sub-treatment groups each containing five rabbits giving 18 replications distributed randomly on a prorate basis in all the ten farms. Group FA received diclazuril (diclosol 1%) at 10ppm for 48 hours while group FB were given sulphachloropyrazine at 2g per liter on days 1, 2, 3, 5, 7 and 9. Group FC received trimethoprim-sulphachloropyrazine combination at 1g per liter administered daily for 7 days and finally, group FD was put under amprolium hydrochloride (20%) treatment at 1g per liter (1000ppm) for 7 consecutive days. Oocyst counts were pooled for each sub-treatment group and mean oocyst counts determined after every two days up to day 20 post treatment.

**Assessment of drug efficacies**. Efficacy of the drugs was assessed through fecal oocyst counts, fecal scores, lesion scores, mortality and survival rates and mean weight gains of various treatment groups. The effectiveness of the test drugs was determined by comparing the above parameters for the treated groups with those for positive and negative control groups.

**Data analysis.** Analysis of variance was performed by one or two way ANOVA as described by GenStat. Significant differences of

the means of the various treatment groups were assessed by Bonferroni multiple comparison test to control overall significance levels as described in Genstat statistical analysis program (GenStat 15th Edition). The resulting data were presented as mean ± SEM and significance levels stated at $p<0.05$.

## RESULTS AND DISCUSSIONS

**Mean fecal scores and standard error of means (SEM)**. Diclazuril (diclosol 10ppm) and sulphachloropyrazine 1.5g/ liter showed satisfactory results 9 days after treatment in alleviating diarrhea and promoting production of normal fecal pellets as shown in Table 1. Additionally, diclazuril and sulphachloropyrazine treatment groups revealed a significant ($p<0.05$) reduction in fecal score 1.17±0.17 and 1.33±0.21, respectively, compared to positive control group (3.0±0.32). This was in agreement with previous studies that also demonstrated the superior efficacy of curative diclazuril against coccidiosis in rabbits (Vereecken *et al.,* 2012) and avian coccidiosis (El-Banna *et al.,* 2005). There was no significant difference ($p>0.05$) in fecal scores between amprolium and trimethoprim-sulphamethoxazole treatment groups with that of the positive control group as presented in Table 1.

**Oocysts sheding.** Sulphachloropyrazine and diclazuril caused a significant ($p<0.05$) reduction in mean oocyst shed by the 7th day post treatment at 0.83±0.401 x $10^4$/g and 0.122±0.0958 x $10^4$/g, respectively compared to the infected untreated group 170.20±68.921 x $10^4$/g. By day 13 post treatment, diclazuril group recorded 0.00±0.00 oocyst count impressively better than even that of negative control group 0.173±0.068 x $10^4$/g while sulphachloropyrazine group recorded an oocyst counts of 2.03±0.829 x $10^4$/g. On day 20 post treatment when the experiment was terminated, the mean number of oocysts shed remained extremely low in the diclazuril group 0.002±0.00167 x 104/g and sulphachloropyrazine group 3.31±0.857 x $10^4$/g compared to the infected untreated group, amprolium group and trimethoprim-sulphamethoxazole group as presented in Table 2. The efficacy of sulphachloropyrazine in reduction of oocysts shed has also been elaborated in poultry anticoccidial trials (Das *et al.,* 2017). Likewise, the superior efficacy of diclazuril in elimination of oocysts shed has been reported by several studies on rabbit coccidiosis (Vanparijs *et al.,* 1989; Vereecken *et al.,* 2012) and poultry coccidiosis (El-Banna *et al.,*2005). Trimethoprim-sulphachloropyrazine group had a higher reduction in oocysts shed on day 7 post treatment 61.17±10.603 x 104/g relative to amprolium and infected untreated groups. However, the mean number of oocysts shed by the trimethoprim-sulphamethoxazole group started to rise again from day 13 post treatment and by 20 days post treatment had reached 231.67±51.43 x$10^4$/g. Nevertheless, this was still significantly lower ($p<0.05$) compared with the infected untreated group 737.50±213.478 x $10^4$/g. On the other hand, the number of oocysts shed by the amprolium group 7 days post treatment was higher 357.67±123.451 x $10^4$/g compared to that of infected untreated group 170.20±68.921 x $10^4$/g though not significantly different ($p<0.05$). In this study, amprolium had the least efficacy compared to the other test drugs. These results agree with earlier studies by Laha *et al.* (1999), Hunduma and Kebede (2016), Das *et al.* (2017), and deviates from results reported by others (Laha e*t al.,* 2015; El-Ghoneimy and El-Shahawy, 2017).

**Clinical presentation and gross lesions**. The clinically sick rabbits in the various treatment groups presented with distended abdomen, matted perineal region, loss of weight and varying degree of dehydration. Few rabbits from positive control (1 rabbit) and amprolium (1 rabbit) treatment groups had jaundice. No significant clinical findings were observed in

**Table 1. Fecal scores from day of treatment to day 20 post treatment in a drug efficacy trial on rabbit coccidiosis in Kenya**

| Groups | Treatment day 0 | 5 days after treatment | 9 days after treatment | 13 days after treatment | 17 days after treatment | 20 days after treatment |
|---|---|---|---|---|---|---|
| Negative control (A) | 1.33±0.21[a] | 1.0±0.0[a] | 1.33±0.21[a] | 1.33±0.24[a] | 1.17±0.19[a] | 1.17±0.18[a] |
| Amprolium (B) | 3.0±0.26[b] | 3.17±0.31[c] | 3.17±0.40[b] | 3.0±0.24[bc] | 2.50±0.24[b] | 2.25±0.23[b] |
| Positive control (C) | 3.17±0.31[b] | 3.0±0.32[c] | 3.0±0.32[b] | 3.20±0.26[c] | 2.75±0.24[b] | 3.0±0.00[b] |
| Diclazuril (D) | 2.67±0.2[1b] | 2.17±0.40[bc] | 1.17±0.17[a] | 1.33±0.24[a] | 1.17±0.19[a] | 1.0±0.18[a] |
| Sulphachloropyrazine (E) | 2.67±0.21[b] | 1.83±0.31[ab] | 1.33±0.21[a] | 1.17±0.24[a] | 1.20±0.21[a] | 1.0±0.20[a] |
| Trimethoprim-sulphamethoxazole (F) | 2.83±0.3[1b] | 2.33±0.42[bc] | 2.0±0.37[ab] | 2.0±0.24[ab] | 2.67±0.19[b] | 2.33±0.18[b] |
| SD | 0.838 | 1.051 | 1.043 | 0.985 | 0.860 | 0.844 |
| p-value | <0.001 | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Values within a column without common superscript are significantly different at p 0.05

Fecal score was done according to Ramadan *et al.* (1997) with 1 indicating normal well-formed fecal pellets through 5 indicating severe diarrhea with/out profuse amount of blood.

**Table 2. Oocyst counts from day 1 to day 20 post treatment in the laboratory trial**

| Group | Mean oocyst shed per treatment group x $10^4$/gram of feces | | | | | |
|---|---|---|---|---|---|---|
| | Day 1 before treatment | Day 3 post treatment | Day 7 post treatment | Day 13 post treatment | Day 17 post treatment | Day 20 post treatment |
| Negative control (A) | 0.059±0.023[a] | 0.093±0.022[a] | 0.090±0.0304[a] | 0.173±0.0679[a] | 0.141±0.0396[a] | 0.138±0.0383[a] |
| Amprolium (B) | 19.01±9.567[a] | 351.00±127.691[b] | 357.67±123.451[b] | 416.83±129.864[a] | 429.60±129.847[ab] | 430.00±62.450[ab] |
| Positive control (C) | 34.93±16.280[a] | 151.67±52.180[ab] | 170.20±68.921[ab] | 432.40±142.793[a] | 642.40±177.504[b] | 590.02±96.128[b] |
| Diclazuril (D) | 59.700±12.351[a] | 14.198±9.178[a] | 0.122±0.095[8a] | 0.00±0.00[a] | 0.00±0.00[a] | 0.002±0.00167[a] |
| Sulphachloropyrazine (E) | 149.00±110.392[a] | 61.91±37.202[a] | 0.83±0.401[a] | 2.03±0.829[a] | 2.03±0.698[a] | 3.31±0.857[a] |
| Trimethoprim-sulphamethoxazole (F) | 197.17±92.657[a] | 95.08±35.184[ab] | 61.17±10.603[a] | 230.50±154.302[a] | 358.00±163.169[ab] | 231.67±51.43[a] |
| p-value | 0.154 | 0.004 | <0.001 | 0.008 | <0.001 | <0.001 |

Values within a column without common superscript are significantly different at p 0.05

rabbits treated with diclazuril while only one rabbit from the sulphachloropyrazine group had rough hair coat and slight dehydration, other rabbits from the group appeared normal. At necropsy, moderate to severe hepatic and intestinal gross lesions were observed in rabbits in the amprolium, trimethoprim-sulphamethoxazole and positive control groups. Lesions observed were marked congestion of caecum (Fig. 1), ileum and duodenum, greyish to dark luminal contents, few with blood stains (Fig.1), necrotic spots in the caecum (Fig.1), serosal surfaces had hyperemia and echymotic haemorrhages, discoloration of epithelial mucosa of ileum, jejunum and duodenum with haemorrhagic areas, and ballooning of sections of the ileum and caecum. Rabbits from diclazuril and sulphachloropyrazine treatment groups had few to no gross intestinal and hepatic lesions, appearing almost similar to those from negative control group. Conversely, amprolium and trimethoprim-sulphamethoxazole were not effective in reversing intestinal and hepatic gross lesions. Liver of rabbits from amprolium and trimethoprim-sulphamethoxazole presented with hepatic gross lesions of congestion, hepatomegaly, raised multinodular lesions on the liver surface that sometimes coalesced to form larger nodules (Fig. 2), distended bile ducts and entire biliriary tree, discoloured and firm consistency, enlarged gallbladder with thick to solid yellowish-white contents (Fig. 2 and 3), as also observed in liver organs of rabbits from positive control group. These lesions were mild in the sulphachloropyrazine and almost non-existent in diclazuril treatment groups (Fig 4) which did not have any significant lesions and appeared as those of negative control groups.

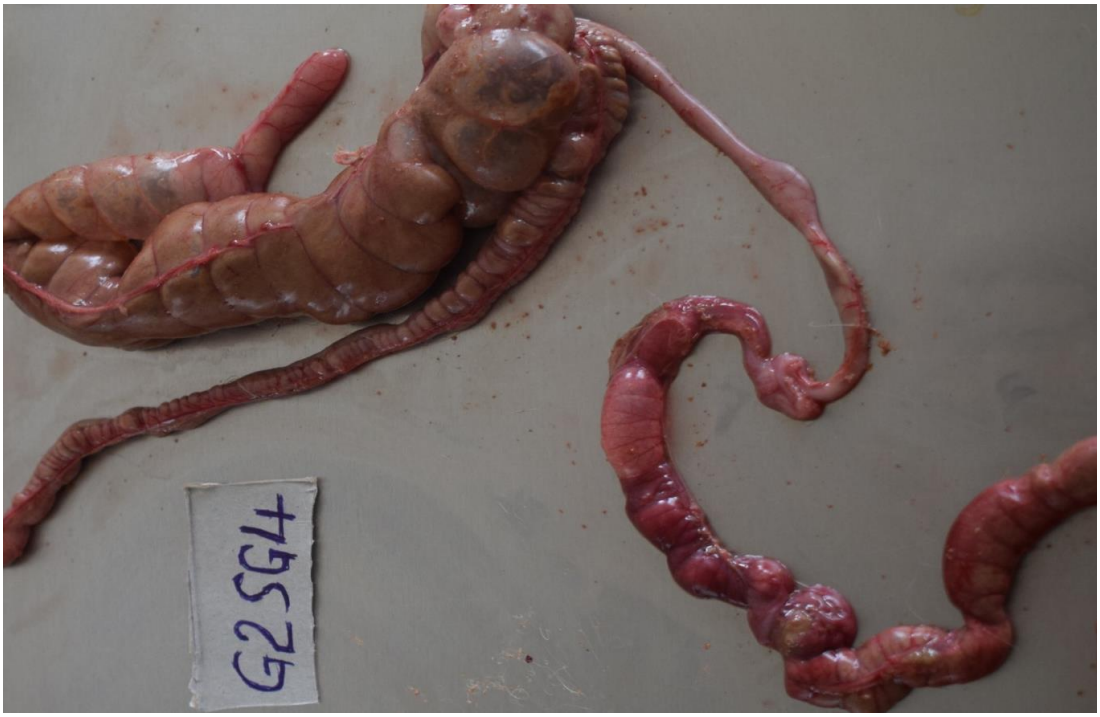


**Figure 1. Gross intestinal lesions from amprolium treatment group (B) showing areas of extensive congestion and hyperemia (white arrow), ballooned sections of caecum and intestine (white arrow heads) and necrotic foci (black arrow)**

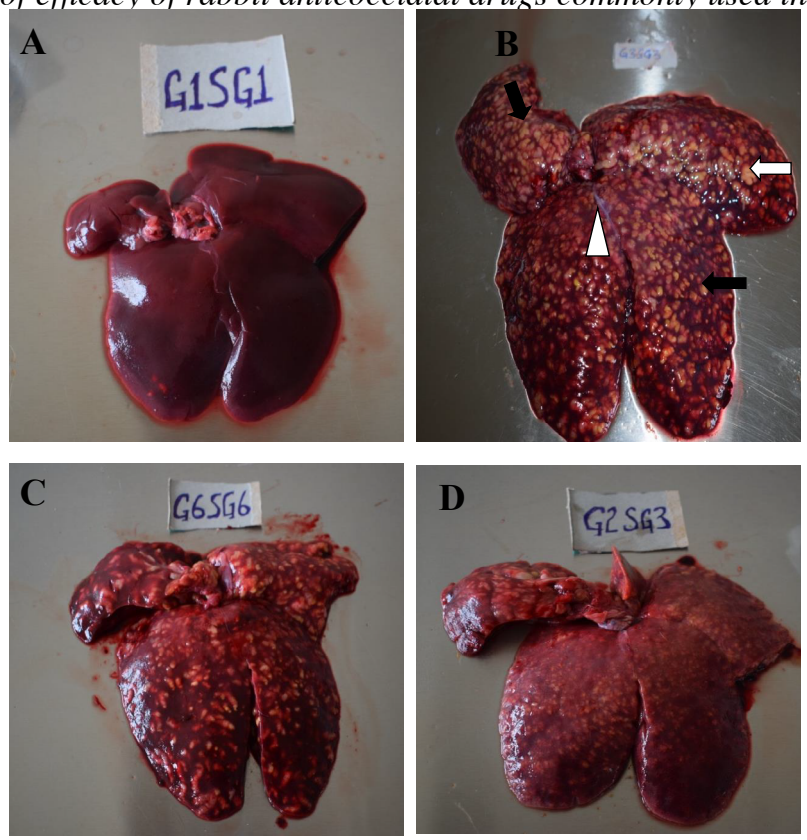


**Figure 2. Gross lesions on liver organs at termination of the experiment: A-normal liver from the negative control group, B- Enlarged liver (hepatomegaly) from positive control group with multinodular yellowish-white lesions (black arrow) that sometimes coalesced to form larger nodules (white arrow) and fibrinous strands (white arrow head), C and D- enlarged livers from trimethoprim-sulphamethoxazole and amprolium treatment groups, respectively with multinodular lesions affecting entire hepatic parenchyma.**

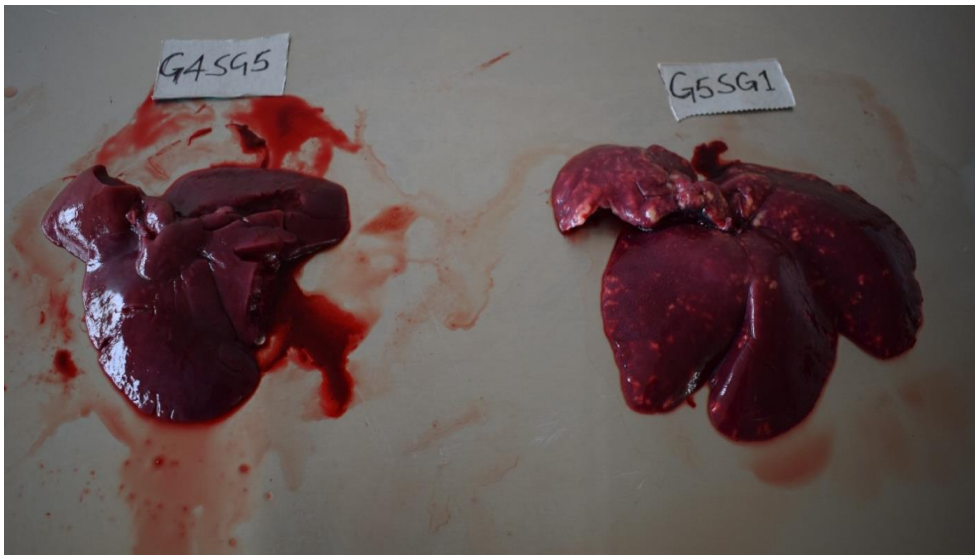


**Figure 3. Rabbit livers from diclazuril (E) group appearing normal with no visible gross lesions and sulphachloropyrazine group (F) presenting with few non-raised gross lesions (arrows) at termination of the experiment**

**Table 3. Oocysts shed from day of treatment to day 20 post treatment in the field trial**

| Group | Oocysts shed per treatment group x 103/gram of feces | | | | | |
|---|---|---|---|---|---|---|
| | 1st day of treatment | Day 2 of treatment | Day 6 of treatment | D ay 10 after treatment | Day 16 after treatment | Day 20 after treatment |
| Diclazuril FA | 473.44±176.01[a] | 506.44±187.63[a] | 1.13±0.73[a] | 0.13±0.10[a] | 0.04±0.03[a] | 0.00±0.00[a] |
| Sulphachloropyrazine FB | 280.33±44.67[a] | 300.50±52.94[a] | 15.54±3.96[a] | 1.07±0.22[a] | 0.59±0.14[a] | 0.44±0.14[a] |
| Trimethoprim/ sulphamethoxazole FC | 266.78±37.03[a] | 235.72±31.68[a] | 40.34±9.80[a] | 1.36±0.31[a] | 0.75±0.11[a] | 0.91±0.11[a] |
| Amprolium hydrochloride FD | 454.06±93.93[a] | 513.50±115.82[a] | 318.43±72.94[b] | 188.31±45.86[b] | 232.47±61.97[b] | 258.92±70.15[b] |
| p-value | 0.345 | 0.212 | <0.001 | <0.001 | <0.001 | <0.001 |

Values within a column without common superscript are significantly different at p<0.05

**Field trial.** In the field trial, diclazuril and sulphachloropyrazine were efficacious against coccidiosis as indicated by decreased oocysts shed of 0.00±0.00 x 103 and 0.44±0.14 x 103 o.p.g, respectively. Trimethoprim-sulphamethoxazole combination had moderate to satisfactory efficacy while amprolium hydrochloride was not able to control clinical coccidiosis in the field. Response to treatment in natural cases validated the laboratory results, with respect to oocyst shedding as shown in Table 3.

## CONCLUSION

The present study has demonstrated the efficacy of diclazuril and sulphachloropyrazine in treatment of clinical coccidiosis of rabbits at the recommended poultry dosages. Insofar as timing of treatment is concerned, better results are achieved when treatment is commenced at onset of the disease when clinical signs are still mild or non-existent. These drugs should be used judiciously in treatment of clinical cases of rabbit coccidiosis in combination with strict biosecurity and sanitation to prevent development of drug resistance. On the other hand, therapeutic use of trimethoprim-sulphachloropyrazine and amprolium were not efficacious at the recommended poultry dosages against clinical rabbit coccidiosis. This study recommends their use strictly as prophylactics against rabbit coccidiosis.

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## STATEMENT OF NO CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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