Veterinary Parasitology 291 (2021) 109387

Contents lists available at ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Network meta-analysis comparing the effectiveness of anticoccidial drugs and anticoccidial vaccination in broiler chickens

Jordan Eckert[a], Miranda Carrisosa[b], Rüdiger Hauck[b,c,*]

[a] Department of Mathematics & Statistics, Auburn University, Auburn, AL 36849, United States
[b] Department of Poultry Science, Auburn University, Auburn, AL 36849, United States
[c] Department of Pathobiology, Auburn University, Auburn, AL 36849, United States

ARTICLE INFO

Keywords:
Coccidiosis
Necrotic enteritis
Prevention
Prophylaxis

ABSTRACT

With the trend to organic production and concerns about using antibiotic feed additives, the control of infections with *Eimeria* spp. in broiler flocks has become more difficult. Vaccination against coccidia is an alternative, but there are concerns that the live vaccines used might have negative effects on production parameters and intestinal health. Reports of experiments directly comparing anticoccidial drugs and anticoccidial vaccines are rare. This network meta-analysis (NMA) identified and analyzed 61 articles reporting 63 experiments testing anticoccidial drugs and anticoccidial vaccines under conditions resembling commercial broiler production. The effect sizes were mean differences in body weight/body weight gain (BW/BWG) and feed conversion rate (FCR) between the 175 included groups. The results show that groups vaccinated against coccidia have a similar BW/BWG and FCR at processing age compared to groups given anticoccidial drugs. However, the results tended to be more favorable for anticoccidial drugs than for vaccines. The analysis of eight subsets, containing only groups (1) groups that had not received an AGP in addition to an anticoccidial drug, (2) groups that had not received ionophores, (3) groups that had not received chemicals, (4) groups that had not received an attenuated vaccine, (5) groups that had not received a fully virulent vaccine, (6) groups that were not additionally challenged with bacteria or not challenged, (7) groups that had received a severe challenge as defined by a total infection dose of more than 100,000 oocysts or were not challenged, (8) groups that were challenged on day 15 or earlier or not challenged brought similar results and confirmed the robustness of the NMA. In addition, the analysis exposes unnecessary, as well as inherent, problems with data quality, which every researcher working with coccidia should carefully consider, and identifies under-researched areas that should be addressed in future research.

1. Introduction

At least seven recognized *Eimeria* spp. can infect chickens causing coccidiosis. Depending on the *Eimeria* spp., the infection dose and the immune status of the host, coccidiosis can impair body weight (BW) or body weight gain (BWG) and feed conversion rate (FCR) and cause clinical disease and mild to severe gross lesions (Cervantes et al., 2020). In addition, *Eimeria maxima* predisposes chickens to Necrotic Enteritis (NE) caused by some strains of *Clostridium perfringens*. Coccidiosis and NE are considered the first and second most important diseases of broilers (USAHA Committee, 2019).

Without antibacterial growth promoters (AGPs), on which poultry growers have relied for decades to improve intestinal health and weight gains, and with the trend to organic production and concerns about using antibiotic feed additives, the control of coccidiosis has become more difficult. Vaccination against coccidia is an alternative, but there are concerns that the live vaccines used might have negative effects on BWG, FCR and intestinal health and predispose the vaccinated birds to NE (Prescott et al., 2016). This is more of a concern with first-generation, fully virulent vaccines, but even second-generation, attenuated vaccines can have negative side effects (Shojadoost et al., 2013). In addition, attenuated vaccines are not available in all countries.

Williams (Williams, 2002) reviewed literature and information on vaccination of broilers against *Eimeria* spp. in 2002. Summarizing

Abbreviations: AGP, antibacterial growth promotor; BW, body weight; BWG, body weight gain; CV, coefficient of variation; FCR, feed conversion rate; NE, necrotic enteritis; NMA, network meta-analysis; SD, standard deviation; SE, standard error.

* Corresponding author at: Department of Poultry Science, 260 Lem Morrison Dr, Auburn, AL 36849, United States.
E-mail address: ruediger.hauck@auburn.edu (R. Hauck).

https://doi.org/10.1016/j.vetpar.2021.109387
Received 8 January 2021; Received in revised form 4 February 2021; Accepted 5 February 2021
Available online 15 February 2021
0304-4017/

reports comparing the performances of broilers, either vaccinated or treated with anticoccidial drugs, he concluded that there were few consistent differences. However, concerns persist, and reliable information is now even more necessary than 18 years ago, while reports of experiments directly comparing anticoccidial drugs and anticoccidial vaccines are rare.

Network meta-analysis (NMA) is a method used to compare the effects of multiple treatments on a health outcome. It allows for a quantitative synthesis of the network by combining direct evidence from comparisons of treatments within experiments and indirect evidence experiments on the basis of a common comparator (Lu and Ades, 2004; Lumley, 2002; Tonin et al., 2017). The aim of the NMA was to compare how anticoccidial drugs and anticoccidial vaccines influenced final body weight (BW) and FCR in broilers, either unchallenged or challenged with *Eimeria* spp.

2. Materials and methods

2.1. Literature search, inclusion criteria and study selection

Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) recommendations (Moher et al., 2009) were followed for literature search, study selection and data extraction. All steps were done independently by two reviewers, and discrepancies were decided by the senior author after revisiting the articles.

Pubmed and Web of Science were searched on February 06, 2020 using the term "(Coccidia OR Eimeria) AND (broiler OR broilers)" for articles published from 2000 to 2019. Additional articles were identified by the reference list of Kipper et al. (Kipper et al., 2013), a previous meta-analysis about experimental infections of chickens with *Eimeria* spp. No language restrictions were set. After removal of duplicates, the list included 1073 articles. In the first step, title and abstract of all articles were screened, and in the second step, full texts were evaluated to determine whether experiments met the inclusion criteria for experiments and groups (supplemental document 1).

Inclusion criteria for experiments were:

- Use of commercial broilers, no layer-type chickens or traditional breeds
- Floor-pen experiments on litter, no experiments in cages or field studies
- Duration of at least 40 days
- BW/BWG or FCR for days 1 through days 40–50, the common marketing age in many countries, reported
- At least two groups meeting the inclusion criterion for groups

The inclusion criterion for groups was that the birds were either left untreated, given a commercial anticoccidial drug or a single dose of a commercial vaccine against coccidia; birds given multiple doses were regarded as challenged, not vaccinated. Birds had not received any experimental treatment like plant extracts or probiotics; groups receiving a commercial antibacterial growth promoter were included because this was not considered an experimental treatment but a treatment representing production practices.

Acceptance for publication was taken as criterion for the methodological quality of the experiments.

2.2. Data extraction and data preparation

The following variables were extracted from the selected articles:

- Year published
- Continent on which the experiment was conducted
- Number of replicate pens per group
- Sex of birds
- Treatment of groups: untreated, given an anticoccidial drug or vaccinated and challenged with coccidia or unchallenged
- Challenge with coccidia for challenged groups:
  - Route of infection
  - Age at challenge
  - Challenge species and doses
  - Additional challenge with bacteria
- Anticoccidial drug or anticoccidial drug combination and dose for groups given an anticoccidial drug
- If a fully virulent or an attenuated vaccine was used
- Duration of experiment in days; if birds were grown for more than 50 days, but BW/BWG and FCR were determined on any day between day 40 and 50, this day was regarded as the end of the experiment.
- BW/BWG from day 1 to the end of the experiment; BW and BWG were not differentiated for the analysis because of the small difference. If both were given, BWG was used for the analysis, removing potential differences in the starting weight of the groups of one experiment.
- FCR from day 1 to the end of the experiment; In some cases, FCR was missing but could be calculated from BW/BWG and feed intake.
- Standard error (SE), standard deviation (SD) or coefficient of variation (CV). SD or CV were converted into SE assuming that the birds were weighed by pen unless stated otherwise in the article. In one case, SD was estimated from the interquartile range by multiplying the difference with 1.35 (Higgins and Green, 2011). If BW/BWG or FCR were given only for partial periods but not for the full duration of the experiment, but total BW/BWG and FCR could be calculated, the measure of variance for the last period was used as approximation. If only pooled SE, SD or CV were reported, these were used as approximation for all groups.

If necessary, data were extracted from graphs using ImageJ (Schneider et al., 2012). When an article gave the results of several independent experiments with differing designs, each experiment was included individually. If an article gave the results of several experiments with identical design, the means of each group with the same treatment were calculated and used in the analysis to avoid pseudo replication.

2.3. Imputation of SE of BW/BWG and FCR

SE of BW/BWG and FCR were imputed for groups for which no measure of variation was given. It is reasonable to assume the missing values were missing completely at random as they were independent studies with different experimental designs and authors. Imputation was done in R version 3.6.3 using the *missForest()* package. A random forest was trained on complete mixed type data to impute missing values nonparametrically (Stekhoven and Bühlmann, 2012). Bootstrap sampling was performed when building the training set between iterations. Imputation was done separately for FCR and BW/BWG.

2.4. Statistical analyses

The NMA was conducted using GeMTC version 0.8–4 and R 3.6.0 using a random-effects model in a Bayesian framework (R Core Team, 2019; Valkenhoef et al., 2012). The consistency of the NMA was tested by node-splitting (van Valkenhoef et al., 2016). The code is given in supplemental document 2.

The NMA was conducted for body weight BW/BWG and FCR for a near-complete set of groups excluding groups for which no measure of variation was given and for all groups using the imputed SEs. Because NMA does not allow inclusion of more than one group with the same treatment per experiment, groups had to be excluded from some experiments for the "complete" analysis. This applied only to groups treated with anticoccidial drugs. Preferentially, groups receiving less than the recommended dose of an anticoccidial drug as well as groups receiving ionophores or combinations of anticoccidial drugs were excluded (supplemental document 3).

Additionally, eight subsets were analyzed, namely (1) groups that had not received an AGP in addition to an anticoccidial drug, (2) groups that had not received ionophores, (3) groups that had not received chemicals, (4) groups that had not received an attenuated vaccine, (5) groups that had not received a fully virulent vaccine, (6) groups that were not additionally challenged with bacteria or not challenged, (7) groups that had received a severe challenge as defined by a total infection dose of more than 100,000 oocysts or were not challenged, (8) groups that were challenged on day 15 or earlier or not challenged (Table 1).

3. Results

3.1. Descriptive analysis

Sixty-one articles describing experiments fulfilling the inclusion criteria were identified. Forty-four of these were published after 2010, and 14 in 2019 alone. Nineteen were from North America, 17 from South America, 15 from Asia, nine from Europe and one from Africa. Sixty-nine experiments were described; after combining identical experiments, 64 experiments were analyzed.

The numbers of replicate pens per group ranged between 1 and 12 in individual experiments with a mean of 5.4 and a median of 5. Thirty-one experiments used male birds and 33 experiments birds of mixed sex, either unsexed or equal numbers of male and female birds. In 57 experiments, one or more groups were infected with *Eimeria* spp. Individual infection by gavage into the crop was the most common route of infection with 33 experiments, followed by using contaminated litter in 11 experiments, contaminating feed with oocysts in seven experiments, and giving a ten-fold dose of a commercial vaccine by spray in one experiment. In five experiments, birds were infected by natural introduction or presence of *Eimeria* spp. in the broiler houses without the authors knowing or describing their introduction but reporting their presence later in the experiment. Individual challenge or infection via feed was mostly done between 10 and 20 days of age, with seven experiments challenging birds older than that and one experiment individually dosing one-day-old chicks. In two experiments, birds were challenged multiple times. Birds were placed on contaminated litter when one day old in 8 experiments, or when 14 days old in three experiments. Overall, median and mode of age at challenge were 14 days.

In eight experiments, birds were challenged with a single *Eimeria* sp., namely *E. maxima* in four experiments, *E. tenella* in three and *E. acervulina* in one experiment. In 39 experiments, birds were infected with a combination of *Eimeria* spp.; these included *E. acervulina* in all experiments, *E. maxima* in 38 experiments and *E. tenella* in 37 experiments. Other *Eimeria* spp. in addition to the three mentioned species were used in 12 or less experiments each. Infection doses were given for 26 experiments. For *E. acervulina*, they ranged between 8000 and 540,000 oocysts per bird, for *E. maxima* between 1000 and 80,000 oocysts per bird and for *E. tenella* between 1000 and 100,000 oocysts per bird. In seven experiments, birds were additionally infected with *C. perfringens* and in one with *Escherichia coli*.

For 63 experiments, BW or BWG were reported; FCR was not given and could not be calculated for six experiments. For 33 experiments, only the pooled SE was reported and for four experiments only the pooled CV, for one experiment both values were given and for two experiments pooled and individual SEs for each group were reported. SEs of each group were given for nine experiments and SDs for each group for five experiments; for one of these the SDs were given only for BW, but median and interquartile range for FCR. For four experiments values for each group were given without specifying if these were SE, SD or CV; based on their value, it was deemed most plausible that they were SEs. For one experiment, CV and one other measure of variation, presumably the SE, were given for each group and for five experiments no measure of variation was given.

In 17 experiments, vaccinated groups were included. In nine of these a fully virulent vaccine was used, in seven an attenuated vaccine and in one case (Alfaro et al., 2007) the name of the used vaccine was not given.

The experiments included 175 groups (supplemental document 3). Fifty-one infected and 14 uninfected groups were given anticoccidial drugs. Forty groups received only ionophores, fifteen only chemicals, four a mixture of chemical and ionophore and five groups an ionophore and a chemical in different feeding phases. For one group, the article (Hady and Zaki, 2012) failed to mention which anticoccidial drug was

Table 1
Group sets tested by network meta-analysis (NMA) and number of groups included in each subset.

Subset	Number of groups included						
	Unchallenged			Challenged			Total
	Untreated	Anticoccidial drug	Vaccinated	Untreated	Anticoccidial drug	Vaccinated	
Complete – all groups[1]	35/32[2]	9/9	6/6	49/44	37/33	11/9	147/133
No AGP – exclusion[3] of groups treated with an antibacterial growth promotor (APG) in addition to the anticoccidial drug	34	7	6	46	32	11	136
No ionophore – exclusion[3] of groups treated with an ionophore	34	1	6	35	7	8	91
No chemical – exclusion[3] of groups treated with a chemical	35	7	6	43	26	11	128
No attenuated vaccine – exclusion[3] of groups given an attenuated or unknown vaccine	32	9	2	49	37	7	136
No fully virulent vaccine– exclusion[3] of groups given a fully virulent or unknown vaccine	35	9	3	48	34	4	133
No bacteria – exclusion[3] of groups challenged with *C. perfringens* or *E. coli* in addition to the coccidia.	28	9	5	42	37	10	131
Severe challenge – exclusion[3] of groups challenged with a total of less than 100,000 oocysts or with an unknown infection dose	17	9	5	14	12	5	62
Early challenge – exclusion[3] of groups challenged on day 16 of age or later or at an unknown age	26	9	6	33	25	8	107

[1] NMA does not allow inclusion of more than one group with the same treatment per experiment. Therefore, groups had to be excluded from some experiments for the "complete" analysis, see supplemental document 3.

[2] Number of groups included in the analysis of body weight/body weight gain and number of groups included in the analysis of FCR; in the subsets only body weight/body weight gain was analyzed.

[3] All groups included in NMA have to be from experiments with at least two treatments. Therefore, in most cases exclusion of one group resulted in the exclusion of the whole experiment.

given to the birds.

3.2. Meta-analysis results of complete set

A preliminary comparison showed that there were no substantial differences between the analysis of the data set excluding groups for which no measure of variation was available and analysis of the data using imputed SEs for these groups (results not shown). The following analyses were all conducted with data sets excluding groups for which no measure of variation was available.

Analysis of the complete set was based on 124 pairwise comparisons for BW/BWG and 114 pairwise comparisons for FCR (Fig. 1). Direct, indirect and network analysis differences in effect size were generally in good agreement with each other and between analysis of BW/BWG and FCR (Fig. 2). I^2 statistics as measure of heterogeneity was 4% for analysis of BW/BWG and 6% for analysis of FCR.

Compared to unchallenged/untreated groups, challenged/untreated groups had a significantly lower mean difference in BW/BWG and higher mean difference in FCR. In addition, challenged/vaccinated groups had a significantly higher mean difference in FCR. Other groups' mean differences in BW/BWG and FCR were not significantly different from the unchallenged/untreated groups (Fig. 3). For BW/BWG, unchallenged/treated with anticoccidial drugs was ranked as the best treatment, followed by unchallenged/untreated, unchallenged/vaccinated, challenged/treated with anticoccidial drugs, challenged/vaccinated, and lastly challenged/untreated. The probable ranking order for FCR differed in that challenged/treated with anticoccidial drugs was ranked better than unchallenged/vaccinated (Table 2).

3.3. Analysis of further sets

I^2 as measure of heterogeneity were between 3% and 5% for all subsets. Compared to unchallenged/untreated groups, challenged/untreated groups had a significantly lower mean difference in BW/BWG in all subsets. In addition, challenged groups treated with an anticoccidial drug also had a significantly lower mean difference in BW/BWG compared the unchallenged/untreated groups in the no chemicals subset, the no bacterial challenge subset and the severe challenge subset. Interestingly, there was also a non-significant trend for the unchallenged groups given an anticoccidial drug having a higher body weight than the untreated/unchallenged groups, except in the no-ionophore subset (Fig. 4).

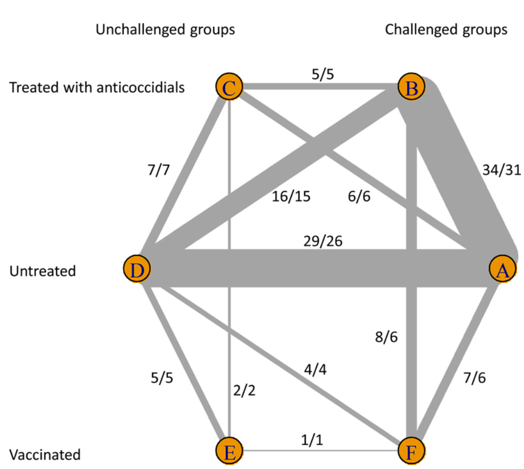

Fig. 1. Geometry of the analyzed network. Nodes represent the treatments (A – challenged/untreated; B – challenged/anticoccidial drug; C – unchallenged/anticoccidial drug; D – unchallenged/untreated; E – unchallenged/vaccinated; F – challenged/vaccinated). Numbers are counts of pairwise comparison of the analysis of the complete set for body weight or body weight gain / feed conversion rate.

4. Discussion

The aim of the NMA was to compare how anticoccidial drugs and anticoccidial vaccines influenced BW/BWG and FCR in broilers. The analyzed experiments were mainly conducted in North America, South America and Asia, and to a lesser extent in Europe. Because broilers are reared commercially for a shorter period in Europe than on other continents, several experiments from European researchers ended after 35 days and had to be excluded from this analysis. However, a larger age interval, e.g. 30–50 days, would have introduced more heterogeneity because the time after challenge has a major impact on the result, allowing for more or less compensatory growth (Henken et al., 1994; Voeten et al., 1988). The Americas, Asia and Europe cover most of the worldwide commercial broiler production. Furthermore, a similar number of experiments used attenuated and non-attenuated vaccines, so the findings of this analysis will be widely applicable. A disproportionately high number of articles was from more recent years, demonstrating the increasing interest in this topic and the timeliness of the NMA, but making the analysis also more current.

In contrast to a previous meta-analysis investigating the performance variation of broilers experimentally infected with *Eimeria* spp. (Kipper et al., 2013), the inclusion criteria for experiments were chosen to closely resemble field conditions, including that commercial broilers had to be reared in floor pens and for 40–50 days. In their meta-analysis, Kipper at al. (Kipper et al., 2013) found that the magnitude of decreased BWG after experimental infection with coccidia varied with *Eimeria* species as well as age, sex, and genetic line of the birds. Of these factors, the genetic line of birds in a broad sense, i.e. commercial broilers, was one of the inclusion criteria. Additionally, age at the end of the experiment was one of the inclusion criteria. However, age at infection and time between infection and end of the experiment is likely to be more relevant than age at the end of the experiment, because birds can show compensatory growth (Henken et al., 1994; Voeten et al., 1988). Almost all challenged groups were infected when younger than 20 days, which also reflects field conditions, where birds are commonly infected at a young age by coccidia in litter. Analysis of the early-challenge subset did not alter the results. Sex was not an inclusion criterion, but because no experiment had used exclusively female birds, there was limited variability of this parameter. What varied widely were the challenge models, even though in most experiments, birds were infected with *E. acervulina*, *E. maxima* and *E. tenella*. However, despite the different challenge models and likely due to the stringent inclusion criteria and other similarities mentioned, heterogeneity was low, indicating a good agreement between all included experiments.

Analysis of BW/BWG showed that as expected challenged/untreated groups did worse than unchallenged/untreated groups. In contrast all other treatments were not significantly different from the unchallenged/untreated groups. However, the 95% confidence intervals of BW/BWG of the vaccinated groups overlapped with the 95% confidence intervals of the untreated/challenged groups, which was partially attributable to a larger 95% confidence interval of the vaccinated groups. This was not only observed in the complete set, but also in the two subsets containing only one type of vaccine. Another potential reason of the variability beyond the different vaccine types might be different application methods. Just using different vaccine diluents for spray vaccination in the hatchery resulted in vaccine takes between 15%–75% percent of birds (Albanese et al., 2018), and further application routes including drinking water and crop gavage were used in the analyzed experiments. Knowing the reasons for the higher variability would help to use vaccines more efficiently with more consistent results.

Analysis of FCR brought similar results. However, challenged/vaccinated groups had a worse FCR than the unchallenged/untreated groups. Taken together, the results show that anticoccidial drugs and vaccines were almost equally effective in preventing reduced BW/BWG and increased FCR with a slight advantage for the anticoccidial drugs. This was confirmed by the ranking probabilities, which ranked

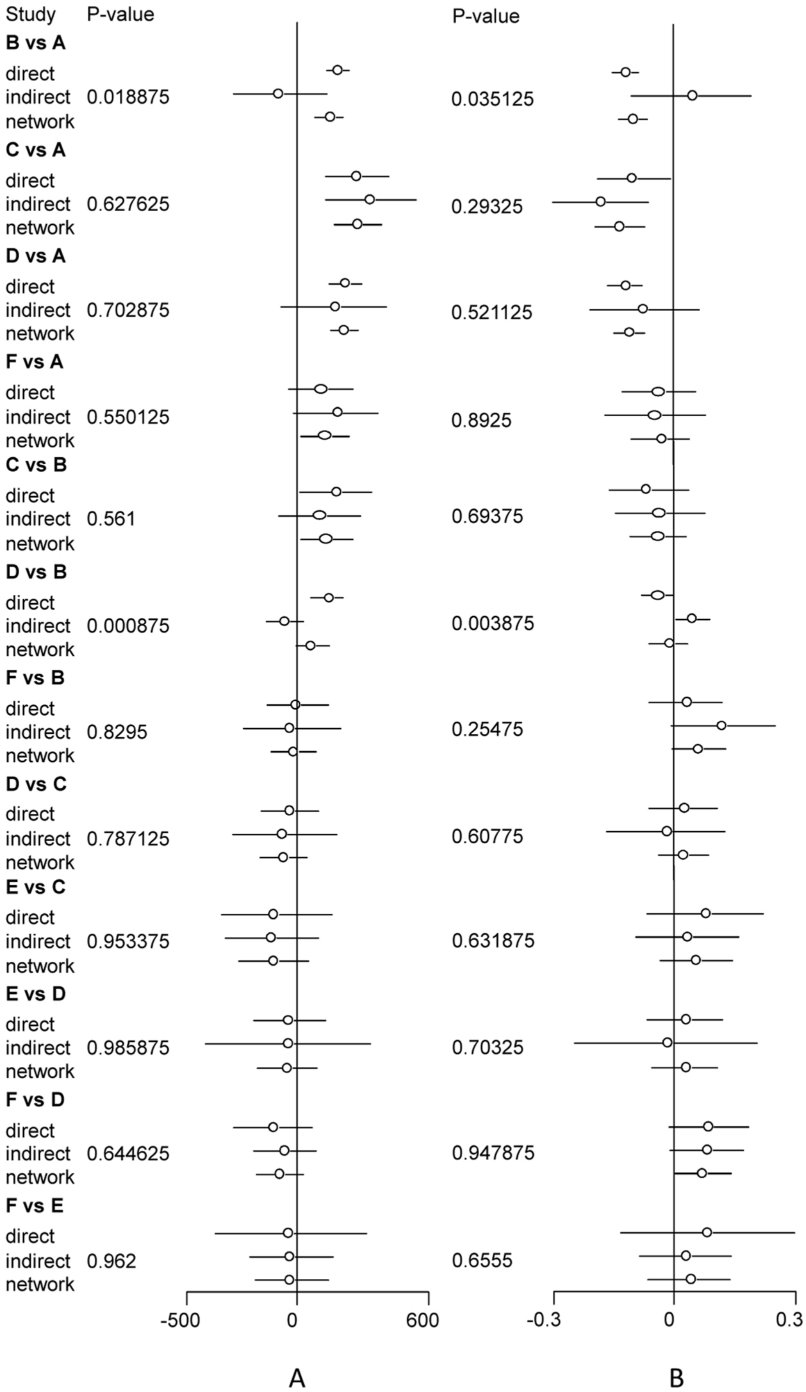

Fig. 2. Direct, indirect, and network analysis of differences in effect size of all pairwise comparisons for body weight/body weight gain (A) and feed conversion rate (B) for the complete set. Bars indicate mean differences and 95% confidence intervals. Note that for body weight, a positive difference indicates a better outcome and for feed conversion rate, a negative difference indicates a better outcome. Treatments are A – challenged/untreated; B – challenged/anticoccidial drug; C – unchallenged/anticoccidial drug; D – unchallenged/untreated; E – unchallenged/vaccinated; F – challenged/vaccinated.

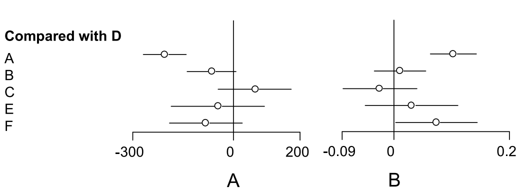

Fig. 3. Forest plots comparing body weight (A) and feed conversion rate (B) of unchallenged, untreated groups (treatment D) against the other treatments for the complete set (A – challenged/untreated; B – challenged/anticoccidial drug; C – unchallenged/anticoccidial drug; E – unchallenged/vaccinated; F – challenged/vaccinated). Bars indicate mean difference and 95% confidence interval. Note that for body weight, a positive difference indicates a better outcome and for feed conversion rate, a negative difference indicates a better outcome.

treatment with anticoccidial drugs higher than vaccination. These results are plausible, because anticoccidial vaccines are live vaccines and thus do cause a low level of damage to intestinal health, regardless if they are attenuated or fully virulent (Williams, 2002).

Similar results in all sets confirmed the robustness of the analysis. One notable difference between subsets was that in the no-chemical subset the challenged groups given anticoccidial drugs, i.e. only ionophores, had a lower BW/BWG than the unchallenged/untreated groups, while in the no-ionophore subset the challenged groups given anticoccidial drugs, i.e. only chemicals, did not do worse than the unchallenged/untreated groups. Ionophores only reduce but do not fully prevent replication of coccidia, in contrast to chemicals, most of which are coccidiocidal (Conway and McKenzie, 2007a). However, even though not significant, there was an opposite trend in unchallenged

Table 2
Ranking probability for analysis of body weight/body weight gain (BW/BWG) and feed conversion rate (FCR). Highest probabilities for each rank are highlighted.

	BW/BWG						FCR					
Rank	1	2	3	4	5	6	1	2	3	4	5	6
Unchallenged/anticoccidial drug	0.824	0.126	0.039	0.009	0.003	0.000	0.689	0.167	0.101	0.037	0.006	0.000
Unchallenged/untreated	0.094	0.610	0.257	0.034	0.004	0.000	0.149	0.444	0.323	0.080	0.004	0.000
Unchallenged/vaccinated	0.070	0.187	0.280	0.199	0.247	0.018	0.081	0.128	0.149	0.447	0.154	0.040
Challenged/anticoccidial drug	0.002	0.028	0.273	0.455	0.242	0.000	0.077	0.252	0.405	0.250	0.016	0.000
Challenged/vaccinated	0.010	0.050	0.151	0.303	0.476	0.011	0.004	0.008	0.023	0.170	0.604	0.191
Challenged/untreated	0.000	0.000	0.000	0.001	0.028	0.971	0.000	0.000	0.000	0.015	0.216	0.768

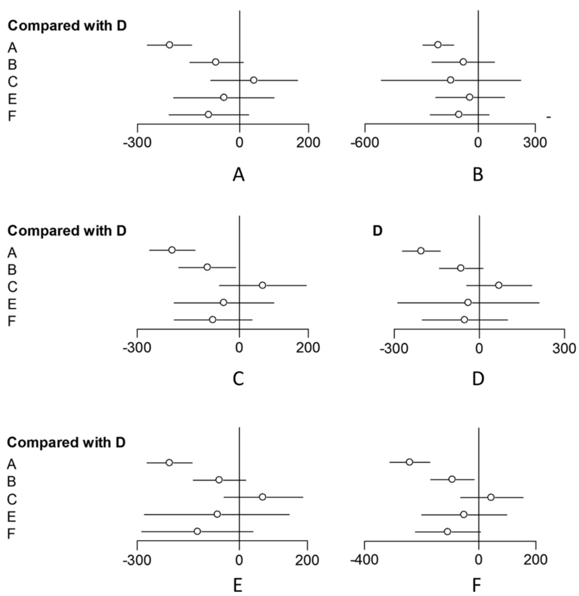

Fig. 4. Forest plots comparing body weight/body weight gain of unchallenged, untreated groups (treatment D) against the other treatments (A – challenged/untreated; B – challenged/anticoccidial drug; C – unchallenged/anticoccidial drug; E – unchallenged/vaccinated; F – challenged/vaccinated). Bars indicate mean difference and 95% confidence interval. A: no AGP subset; B: no ionophore subset; C: no chemicals subset; D: no attenuated vaccine subset; E: no fully virulent vaccine subset; F: no bacterial challenge subset; G: severe challenge subset; H: early challenge subset.

birds with treatment with chemicals numerically decreasing BW/BWG and treatment with ionophore numerically increasing it, indicating the growth-promoting activity of ionophore antibiotics, which results from their broader action against Gram-positive bacteria (Butaye et al., 2003).

The results of any analysis can only be as good as the data being analyzed, and the underlying data of the present analyses are not perfect. The imperfection of the data falls into three broad categories. The first category is lacking information in articles that should have been given, the second category is inherent to this type of experiment and the third category is under-researched areas.

Crass examples of lacking information that should have been given are failing to state which anticoccidial drug was used (Hady and Zaki, 2012) or mentioning the challenge of birds only in the abstract but not in the Materials and Methods section (Koli et al., 2018). Six articles failed to give a measure of variation, and three articles reported measures of variation without saying which they were. In contrast to these sporadic failings, it is common practice to report only pooled SE or CV. Thirty-seven articles did this. The pooled values had to be used as an approximation for the SE of individual groups but using the values for individual groups would have resulted in more accurate results of the present analysis. Some articles failed to provide information if birds had been weighed individually or pen-wise, making the conversion from SD or CV to SE unreliable. Reporting guidelines supported by professional organizations similar to the protocols by Conway and Mckenzie (Conway and McKenzie, 2007b, p. 200) should be published and then followed by authors and enforced by reviewers.

Inherent to this type of experiment is that the FCR can only be calculated on a per-pen basis and pens need a certain number of birds to simulate commercial conditions. Thus, and in spite of the numerically large number of birds, the number of replicates in these studies is low; in the analyzed dataset, the median was 5. Weighing birds individually can increase power for the analysis of bodyweights, only slightly reduced by them being pseudoreplicates. Additionally, for some infection models, it is not possible to provide an infection dose, most notably when birds are infected using contaminated litter, a method which otherwise has the advantage to most closely simulate natural infection. However, not knowing the infection dose makes comparisons across different experiments difficult.

The NMA also exposed under-researched areas. There was a relative shortage of experiments investigating the effect of anticoccidial vaccines, especially in unchallenged birds, even though the use of vaccine in antibiotic-free and organic broiler production is likely to become more common in the future. Surprisingly, there was also a shortage of experiments including treatment with chemicals. One likely reason is that these are very time-honored treatments, and a review of older literature might have provided more information. However, this NMA was restricted to the last 19 years as to best reflect contemporary management practices and bird genetics. As chemicals might increase in their importance because they are not antibiotics, research investigating aspects of their use under current management practices would be timely.

In conclusion, the results of this NMA show that vaccination against coccidia gives results that are comparable to the use of anticoccidial drugs. In addition, the analysis exposes unnecessary, as well as inherent, problems with data quality, which every researcher working with coccidia should be careful to address and identifies under-researched areas that should be addressed in future research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank Dr. Ash Abebe (Department of Mathematics & Statistics, Auburn University) for useful discussions. We especially thank Dr. Alan E. Wilson (School of Fisheries, Aquaculture, and Aquatic Sciences, Auburn University) for the guidance he provided to us in his Metanalysis class.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.vetpar.2021.109387.

References

Albanese, G.A., Tensa, L.R., Aston, E.J., Hilt, D.A., Jordan, B.J., 2018. Evaluation of a coccidia vaccine using spray and gel applications. Poult. Sci. 97, 1544–1553. https://doi.org/10.3382/ps/pey011.

Alfaro, D.M., Silva, A.V.F., Borges, S.A., Maiorka, F.A., Vargas, S., Santin, E., 2007. Use of *Yucca schidigera* extract in broiler diets and its effects on performance results obtained with different coccidiosis control methods. J. Appl. Poult. Res. 16, 248–254. https://doi.org/10.1093/japr/16.2.248.

Butaye, P., Devriese, L.A., Haesebrouck, F., 2003. Antimicrobial growth promoters used in animal feed: effects of less well known antibiotics on gram-positive bacteria. Clin. Microbiol. Rev. 16, 175–188. https://doi.org/10.1128/CMR.16.2.175-188.2003.

Cervantes, H.M., McDougald, L.R., Jenkins, M.C., 2020. Coccidiosis. In: Swayne, D.E., Boulianne, M., Logue, C.M., McDougald, L.R., Nair, V., Suarez, D.L. (Eds.), Diseases of Poultry. Wiley-Blackwell, Hoboken, NJ, USA, pp. 1193–1217.

Conway, D.P., McKenzie, M.E., 2007a. Anticoccidial Drugs and Vaccines, in: Poultry Coccidiosis. Blackwell Publishing Professional, Ames, Iowa, pp. 77–164.

Conway, D.P., McKenzie, M.E., 2007b. Basic procedures and example protocols for testing anticoccidial drugs. Poultry Coccidiosis. Blackwell Publishing Professional, pp. 49–64.

Hady, M.M., Zaki, M.M., 2012. Efficacy of some herbal feed additives on performance and control of cecal coccidiosis in broilers. In: Dan, Y. (Ed.), 2nd International Conference on Asia Agriculture and Animal (Icaaa 2012), pp. 163–168.

Henken, A.M., Ploeger, H.W., Graat, Ea.M., Carpenter, T.E., 1994. Description of a simulation model for the population dynamics of *Eimeria acervulina* infection in broilers. Parasitology 108, 503–512. https://doi.org/10.1017/S0031182000077362.

Higgins, J.P.T., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons.

Kipper, M., Andretta, I., Lehnen, C.R., Lovatto, P.A., Monteiro, S.G., 2013. Meta-analysis of the performance variation in broilers experimentally challenged by Eimeria spp. Vet. Parasitol. 196, 77–84. https://doi.org/10.1016/j.vetpar.2013.01.013.

Koli, D., Kadam, M., Gole, M., Patil, A., Hajare, S., Yeskal, A., Kolte, S., Kurkure, N., 2018. Efficacy of *Bacillus subtilis* (GalliPro) supplementation in *Clostridium perfringens* challenged necrotic enteritis of broiler chicken. Ind. J. Anim. Res. 52, 619–622. https://doi.org/10.18805/ijar.B-3253.

Lu, G., Ades, A.E., 2004. Combination of direct and indirect evidence in mixed treatment comparisons. Stat. Med. 23, 3105–3124. https://doi.org/10.1002/sim.1875.

Lumley, T., 2002. Network meta-analysis for indirect treatment comparisons. Stat. Med. 21, 2313–2324. https://doi.org/10.1002/sim.1201.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339. https://doi.org/10.1136/bmj.b2535.

Prescott, J.F., Smyth, J.A., Shojadoost, B., Vince, A., 2016. Experimental reproduction of necrotic enteritis in chickens: a review. Avian Pathol. 45, 317–322. https://doi.org/10.1080/03079457.2016.1141345.

R Core Team, 2019. R: a Language and Environment for Tatistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Schneider, C.A., Rasband, W.S., Eliceiri, K.W., 2012. NIH Image to ImageJ: 25 years of image analysis. Nat. Methods 9, 671–675. https://doi.org/10.1038/nmeth.2089.

Shojadoost, B., Peighambari, S.M., Nikpiran, H., 2013. Effects of virginiamycin against experimentally induced necrotic enteritis in broiler chickens vaccinated or not with an attenuated coccidial vaccine. J. Appl. Poult. Res. 22, 160–167. https://doi.org/10.3382/japr.2012-00541.

Stekhoven, D.J., Bühlmann, P., 2012. MissForest – non-parametric missing value imputation for mixed-type data. Bioinformatics 28, 112–118. https://doi.org/10.1093/bioinformatics/btr597.

Tonin, F.S., Rotta, I., Mendes, A.M., Pontarolo, R., 2017. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. Pharm. Pract. (Granada) 15. https://doi.org/10.18549/PharmPract.2017.01.943.

USAHA Committee, 2019. Report of the USAHA Committee on Poultry and Other Avian Species.

Valkenhoef, Gvan, Lu, G., Brock, Bde, Hillege, H., Ades, A.E., Welton, N.J., 2012. Automating network meta-analysis. Res. Synth. Methods 3, 285–299. https://doi.org/10.1002/jrsm.1054.

van Valkenhoef, G., Dias, S., Ades, A.E., Welton, N.J., 2016. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res. Synth. Methods 7, 80–93. https://doi.org/10.1002/jrsm.1167.

Voeten, A.C., Braunius, W.W., Orthel, F.W., van Rijen, M.A., 1988. Influence of coccidiosis on growth rate and feed conversion in broilers after experimental infections with *Eimeria acervulina* and *Eimeria maxima*. Vet. Q. 10, 256–264. https://doi.org/10.1080/01652176.1988.9694182.

Williams, R.B., 2002. Anticoccidial vaccines for broiler chickens: pathways to success. Avian Pathol. 31, 317–353. https://doi.org/10.1080/03079450220148988.

Further reading

Abdelrahman, W., Mohnl, M., Teichmann, K., Doupovec, B., Schatzmayr, G., Lumpkins, B., Mathis, G., 2014. Comparative evaluation of probiotic and salinomycin effects on performance and coccidiosis control in broiler chickens. Poult. Sci. 93, 3002–3008. https://doi.org/10.3382/ps.2014-04212.

Almeida, G.F.D., Thamsborg, S.M., Madeira, A.M.B.N., Ferreira, J.F.S., Magalhães, P.M., Demattê Filho, L.C., Horsted, K., Hermansen, J.E., 2014. The effects of combining *Artemisia annua* and *Curcuma longa* ethanolic extracts in broilers challenged with infective oocysts of *Eimeria acervulina* and *E. maxima*. Parasitology 141, 347–355. https://doi.org/10.1017/S0031182013001443.

Alp, M., Midilli, M., Kocabagli, N., Yilmaz, H., Turan, N., Gargili, A., Acar, N., 2012. The effects of dietary oregano essential oil on live performance, carcass yield, serum immunoglobulin G level, and oocyst count in broilers. J. Appl. Poult. Res. 21, 630–636. https://doi.org/10.3382/japr.2012-00551.

Araujo, R.G.A.C., Polycarpo, G., Barbieri, A., Silva, K.M., Ventura, G., Polycarpo, V.C.C., 2019. Performance and economic viability of broiler chickens fed with probiotic and organic acids in an attempt to replace growth-promoting antibiotics. Braz. J. Poult. Sci. 21 https://doi.org/10.1590/1806-9061-2018-0912 eRBCA-2018-0912.

Arczewska-Wlosek, A., Swiatkiewicz, S., 2015. The efficacy of selected feed additives in the prevention of broiler chicken coccidiosis under natural exposure to *Eimeria* spp. Ann. Anim. Sci. 15, 725–735. https://doi.org/10.1515/aoas-2015-0026.

Arczewska-Wlosek, A., Swiatkiewicz, S., Kowal, J., Jozefiak, D., Dlugosz, J., 2017. The effect of increased crude protein level and/or dietary supplementation with herbal extract blend on the performance of chickens vaccinated against coccidiosis. Anim. Feed Sci. Tech. 229, 65–72. https://doi.org/10.1016/j.anifeedsci.2017.04.021.

Bafundo, K.W., Cervantes, H.M., Mathis, G.F., 2008. Sensitivity of *Eimeria* field isolates in the United States: responses of nicarbazin-containing anticoccidials. Poult. Sci. 87, 1760–1767. https://doi.org/10.3382/ps.2008-00129.

Bahadoran, S., Hassanpour, H., Kheirabadi, K.P., Shekarchian, S., 2014. Effect of clopidol and amprolium/ethopabate on performance and intestinal morphology of chickens with experimental coccidiosis. Kafkas Univ. Vet. Fak. Derg. 20, 571–576. https://doi.org/10.9775/kvfd.2013.10638.

Behnamifar, A.R., Rahimi, Sh., Kiaei, M.M., Fayazi, H., 2019. Comparison of the effect of probiotic, prebiotic, salinomycin and vaccine in control of coccidiosis in broiler chickens. Iran. J. Vet. Res. 20, 51–54.

Bortoluzzi, C., Menten, J.F.M., Pereira, R., Fagundes, N.S., Napty, G.S., Pedroso, A.A., Bigaton, A.D., Andreote, F.D., 2015. Hops beta-acids and zinc bacitracin affect the performance and intestinal microbiota of broilers challenged with *Eimeria acervulina* and *Eimeria tenella*. Anim. Feed Sci. Tech. 207, 181–189. https://doi.org/10.1016/j.anifeedsci.2015.06.006.

Bortoluzzi, C., Vieira, B.S., Hofacre, C., Applegate, T.J., 2019. Effect of different challenge models to induce necrotic enteritis on the growth performance and intestinal microbiota of broiler chickens. Poult. Sci. 98, 2800–2812. https://doi.org/10.3382/ps/pez084.

Bozkurt, M., Aysul, N., Küçükyilmaz, K., Aypak, S., Ege, G., Çatli, A.U., Akşit, H., Çöven, F., Seyrek, K., Çınar, M., 2014. Efficacy of in-feed preparations of an anticoccidial, multienzyme, prebiotic, probiotic, and herbal essential oil mixture in healthy and Eimeria spp.-infected broilers. Poult. Sci. 93, 389–399. https://doi.org/10.3382/ps.2013-03368.

Bozkurt, M., Ege, G., Aysul, N., Akşit, H., Tüzün, A.E., Küçükyılmaz, K., Borum, A.E., Uygun, M., Akşit, D., Aypak, S., Şimşek, E., Seyrek, K., Koçer, B., Bintaş, E., Orojpour, A., 2016. Effect of anticoccidial monensin with oregano essential oil on broilers experimentally challenged with mixed *Eimeria* spp. Poult. Sci. 95, 1858–1868. https://doi.org/10.3382/ps/pew077.

Bozkurt, M., Selek, N., Kucukyilmaz, K., Eren, H., Guven, E., Catli, A.U., Cinar, M., 2012. Effects of dietary supplementation with a herbal extract on the performance of broilers infected with a mixture of *Eimeria* species. Br. Poult. Sci. 53, 325–332. https://doi.org/10.1080/00071668.2012.699673.

Calik, A., Omara, I.I., White, M.B., Li, W., Dalloul, R.A., 2019. Effects of dietary direct fed microbial supplementation on performance, intestinal morphology and immune response of broiler chickens challenged with coccidiosis. Front. Vet. Sci. 6, 463. https://doi.org/10.3389/fvets.2019.00463.

Cardenas, C., Zhai, W., Wamsley, K.G.S., 2017. Effects of various feed additive strategies on broilers given 10x live coccidiosis vaccine. J. Appl. Poult. Res. 26, 99–110. https://doi.org/10.3382/japr/pfw050.

Chasser, K.M., Wilson, K.M., Briggs, W.N., Duff, A.F., Bielke, L.R., 2019. Comparison of multiple methods for induction of necrotic enteritis in broilers: II. Impact on the growth curve. Poult. Sci. 98, 5488–5496. https://doi.org/10.3382/ps/pez405.

Conway, D.P., Mathis, G.F., Johnson, J., Schwartz, M., Baldwin, C., 2001. Efficacy of diclazuril in comparison with chemical and ionophorous anticoccidials against *Eimeria* spp. in broiler chickens in floor pens. Poult. Sci. 80, 426–430. https://doi.org/10.1093/ps/80.4.426.

Conway, D.P., Mathis, G.F., Lang, M., 2002. The use of diclazuril in extended withdrawal anticoccidial programs: 1. Efficacy against *Eimeria* spp. in broiler chickens in floor pens. Poult. Sci. 81, 349–352. https://doi.org/10.1093/ps/81.3.349.

Costa, C.A.F., Guidoni, A.L., Paiva, D.P., Avila, V.S., 2000. Coccidiosis and performance in broilers with anticoccidial medicated feed starting at different ages. Arq. Bras. Med. Vet. Zoot. 52, 144–149. https://doi.org/10.1590/S0102-09352000000200010.

Diniz, G.S., Borsoi, A., Lopes, J.M., Garcia, J.L., Guimaraes, J., da, S., 2009. Salinomycin and semduramicin in different concentrations on the broilers eimeriosis control. Rev. Bras. Parasitol. Vet. 18, 53–58. https://doi.org/10.4322/rbpv.01804010.

Duffy, C.F., Mathis, G.F., Power, R.F., 2005. Effects of Natustat supplementation on performance, feed efficiency and intestinal lesion scores in broiler chickens challenged with *Eimeria acervulina*, *Eimeria maxima* and *Eimeria tenella*. Vet. Parasitol. 130, 185–190. https://doi.org/10.1016/j.vetpar.2005.03.041.

Galli, G.M., Gerbet, R.R., Griss, L.G., Fortuoso, B.F., Petrolli, T.G., Boiago, M.M., Souza, C.F., Baldissera, M.D., Mesadri, J., Wagner, R., da Rosa, G., Mendes, R.E., Gris, A., Da Silva, A.S., 2019. Combination of herbal components (curcumin, carvacrol, thymol, cinnamaldehyde) in broiler chicken feed: impacts on response parameters, performance, fatty acid profiles, meat quality and control of coccidia and bacteria. Microb. Pathog. 139, 103916 https://doi.org/10.1016/j.micpath.2019.103916.

Gawel, A., Mazurkiewicz, M., Jurowski, J., 2005. Efficiency of immucox in preventing coccidiosis in hens. Med. Weter. 61, 548–552.
Giannenas, I., Papadopoulos, E., Tsalie, E., Triantafillou, E., Henikl, S., Teichmann, K., Tontis, D., 2012. Assessment of dietary supplementation with probiotics on performance, intestinal morphology and microflora of chickens infected with *Eimeria tenella*. Vet. Parasitol. 188, 31–40. https://doi.org/10.1016/j.vetpar.2012.02.017.
Giannenas, I., Tsalie, E., Triantafillou, E., Hessenberger, S., Teichmann, K., Mohnl, M., Tontis, D., 2014. Assessment of probiotics supplementation via feed or water on the growth performance, intestinal morphology and microflora of chickens after experimental infection with *Eimeria acervulina*, *Eimeria maxima* and *Eimeria tenella*. Avian Pathol. 43, 209–216. https://doi.org/10.1080/03079457.2014.899430.
Giannenas, I.A., Florou-Paneri, P., Botsoglou, N.A., Christaki, E., Spais, A.B., 2005. Effect of supplementing feed with oregano and/or alpha-tocopheryl acetate on growth of broiler chickens and oxidative stability of meat. J. Anim. Feed Sci. 14, 521–535. https://doi.org/10.22358/jafs/67120/2005.
Gomez-Verduzco, G., Cortes-Cuevas, A., Lopez-Coello, C., Avila-Gonzalez, E., Nava, G. M., 2009. Dietary supplementation of mannan-oligosaccharide enhances neonatal immune responses in chickens during natural exposure to Eimeria spp. Acta Vet. Scand. 51, 11. https://doi.org/10.1186/1751-0147-51-11.
Gottardo, E.T., Prokoski, K., Horn, D., Viott, A.D., Santos, T.C., Fernandes, J.I.M., 2016. Regeneration of the intestinal mucosa in *Eimeria* and *E. coli* challenged broilers supplemented with amino acids. Poult. Sci. 95, 1056–1065. https://doi.org/10.3382/ps/pev356.
Haq, I.-U., Pasha, T.N., Khalique, A., 2011. Comparative efficacy of herbal and allopathy drugs against coccidiosis in poultry. It. J. Anim. Sci 10, 14–16. https://doi.org/10.4081/ijas.2011.e3.
Karpeggiane de Oliveira, M.J., Sakomura, N.K., Dorigam, J.Cde P., Doranalli, K., Soares, L., Viana, G., da, S., 2019. *Bacillus amyloliquefaciens* CECT 5940 alone or in combination with antibiotic growth promoters improves performance in broilers under enteric pathogen challenge. Poult. Sci. 98, 4391–4400. https://doi.org/10.3382/ps/pez223.
Kheirabadi, K.P., Katadj, J.K., Bahadoran, S., da Silva, J.A.T., Samani, A.D., Bashi, M.C., 2014. Comparison of the anticoccidial effect of granulated extract of *Artemisia sieberi* with monensin in experimental coccidiosis in broiler chickens. Exp. Parasitol. 141, 129–133. https://doi.org/10.1016/j.exppara.2014.03.022.
Kucukyilmaz, K., Bozkurt, M., Selek, N., Guven, E., Eren, H., Atasever, A., Bintas, E., Catli, A.U., Cinar, M., 2012. Effects of vaccination against coccidiosis, with and without a specific herbal essential oil blend, on performance, oocyst excretion and serum IBD titers of broilers reared on litter. Ital. J. Anim. Sci. 11, e1. https://doi.org/10.4081/ijas.2012.e1.
Kurkure, N.V., Kolte, S.W., Bhandarkar, A.G., Kalorey, D.R., 2006. Evaluation of herbal coccidiostat "Coxynil" in broiler. Indian J. Exp. Biol. 44, 740–744.
Laika, M., Jahanian, R., 2017. Increase in dietary arginine level could ameliorate detrimental impacts of coccidial infection in broiler chickens. Livest. Sci. 195, 38–44. https://doi.org/10.1016/j.livsci.2016.11.002.
Lee, J.T., Broussard, C., Fitz-Coy, S., Burke, P., Eckert, N.H., Stevens, S.M., Anderson, P. N., Anderson, S.M., Caldwell, D.J., 2009. Evaluation of live oocyst vaccination or salinomycin for control of field-strain *Eimeria* challenge in broilers on two different feeding programs. J. Appl. Poult. Res. 18, 458–464. https://doi.org/10.3382/japr.2008-00093.
Lee, K.-W., Ho Hong, Y., Lee, S.-H., Jang, S.I., Park, M.-S., Bautista, D.A., Ritter, G.D., Jeong, W., Jeoung, H.-Y., An, D.-J., Lillehoj, E.P., Lillehoj, H.S., 2012. Effects of anticoccidial and antibiotic growth promoter programs on broiler performance and immune status. Res. Vet. Sci. 93, 721–728. https://doi.org/10.1016/j.rvsc.2012.01.001.
Lee, K.-W., Lillehoj, H.-S., Jang, S.-I., Lee, S.-H., Bautista, D.A., Donald Ritter, G., Lillehoj, E.P., Siragusa, G.R., 2013. Comparison of live *Eimeria* vaccination with in-feed salinomycin on growth and immune status in broiler chickens. Res. Vet. Sci. 95, 110–114. https://doi.org/10.1016/j.rvsc.2013.02.005.
Lu, H., Adedokun, S.A., Adeola, L., Ajuwon, K.M., 2014. Anti-inflammatory effects of non-antibiotic alternatives in coccidia challenged broiler chickens. J. Poult. Sci. 51, 14–21. https://doi.org/10.2141/jpsa.0120176.
Mathis, G.F., Froyman, R., Irion, T., Kennedy, T., 2003. Coccidiosis control with toltrazuril in conjunction with anticoccidial medicated or nonmedicated feed. Avian Dis. 47, 463–470. https://doi.org/10.1637/0005-2086(2003)047[0463:CCWTIC]2.0.CO;2.
Mohiti-Asli, M., Ghanaatparast-Rashti, M., 2015. Dietary oregano essential oil alleviates experimentally induced coccidiosis in broilers. Prev. Vet. Med. 120, 195–202. https://doi.org/10.1016/j.prevetmed.2015.03.014.
Moraes, P.O., Cardinal, K.M., Gouvea, F.L., Schroeder, B., Ceron, M.S., Lunedo, R., Frazzon, A.P.G., Frazzon, J., Ribeiro, A.M.L., 2019. Comparison between a commercial blend of functional oils and monensin on the performance and microbiota of coccidiosis-challenged broilers. Poult. Sci. 98, 5456–5464. https://doi.org/10.3382/ps/pez345.
Muro, E.M., Pelicia, V.C., Vercese, F., Goncalves Pereira de Souza, I.M., Mendes Pimenta, G.E., de Souza Gomes Oliveira, R.S., Sartori, J.R., 2015. Phytogenic additives and glutamine plus glutamic acid in diet of broilers challenged with coccidiosis. Agrarian 8, 304–311.
Nollet, L., Huyghebaert, G., Spring, P., 2007. Effect of dietary mannan oligosaccharide (Bio-mos) on live performance of broiler chickens given an anticoccidial vaccine (Paracox) followed by a mild coccidial challenge. J. Appl. Poult. Res. 16, 397–403. https://doi.org/10.1093/japr/16.3.397.
Oviedo-Rondon, E.O., Clemente-Hernandez, S., Williams, P., Losa, R., 2005. Responses of coccidia-vaccinated broilers to essential oil blends supplementation up to forty-nine days of age. J. Appl. Poult. Res. 14, 657–664. https://doi.org/10.1093/japr/14.4.657.
Pajic, M., Aleksic, N., Vejnovic, B., Polacek, V., Novakov, N., Andric, D.O., Stanimirovic, Z., 2019. Influence of anticoccidials on oxidative stress, production performance and faecal oocyst counts in broiler chickens infected with *Eimeria* species. Kafkas Univ. Vet. Fak. Derg. 25, 379–385. https://doi.org/10.9775/kvfd.2018.21021.
Perin, G., Baldissera, M.D., Fernandes, M., Barreta, M., Casagrande, R.A., Griss, L.G., Fortuoso, B.F., Volpato, A., Stefani, L.M., Boiago, M.M., de Cristo, T.G., Santiani, F., da Silva, A.S., 2019. Effects of tannin-containing diets on performance, gut disease control and health in broiler chicks. Anim. Prod. Sci. 59, 1847–1857. https://doi.org/10.1071/AN18393.
Ritzi, M.M., Abdelrahman, W., Mohnl, M., Dalloul, R.A., 2014. Effects of probiotics and application methods on performance and response of broiler chickens to an *Eimeria* challenge. Poult. Sci. 93, 2772–2778. https://doi.org/10.3382/ps.2014-04207.
Ritzi, M.M., Abdelrahman, W., van-Heerden, K., Mohnl, M., Barrett, N.W., Dalloul, R.A., 2016. Combination of probiotics and coccidiosis vaccine enhances protection against an *Eimeria* challenge. Vet. Res. 47, 111. https://doi.org/10.1186/s13567-016-0397-y.
Rodriguez, I., Honorio, C., Ramirez, J., Leon, Z., Alarcon, W., 2019. Effect of a natural anticoccidial based on saponins of *Yucca schidigera* and *Trigonella foenum-graecum* on the control of coccidiosis in broilers. Rev. Investig. Vet. Peru 30, 1196–1206. https://doi.org/10.15381/rivep.v30i3.16597.
Sakamoto, M., Faria, D.E., Nakagi, V.S., Murakami, A.E., 2014. Sources of trophic action on performance and intestinal morphometry of broiler chickens vaccinated against coccidiosis. Braz. J. Poult. Sci 16, 389–396. https://doi.org/10.1590/1516-635x1604389-396.
Scapini, L.B., de Cristo, A.B., Schmidt, J.M., Buzim, R., Nogueira, L.K., Palma, S.C., Fernandes, J.I.M., 2019. Effect of beta-mannanase supplementation in conventional diets on the performance, immune competence and intestinal quality of broilers challenged with *Eimeria* sp. J. Appl. Poult. Res. 28, 1048–1057. https://doi.org/10.3382/japr/pfz066.
Stanley, V.G., Gray, C., Daley, M., Krueger, W.F., Sefton, A.E., 2004. An alternative to antibiotic-based drugs in feed for enhancing performance of broilers grown on *Eimeria* spp.-infected litter. Poult. Sci. 83, 39–44. https://doi.org/10.1093/ps/83.1.39.
Stefanello, C., Rosa, D.P., Dalmoro, Y.K., Segatto, A.L., Vieira, M.S., Moraes, M.L., Santin, E., 2019. Protected blend of organic acids and essential oils improves growth performance, nutrient digestibility, and intestinal health of broiler chickens undergoing an intestinal challenge. Front. Vet. Sci. 6, 491. https://doi.org/10.3389/fvets.2019.00491.
Sultan, R., Aslam, A., Tipu, M.Y., Rehman, H.U., Anjum, A., Krull, W., Kumosani, T., Shaib, H., Barbour, E.K., 2019. Appraisal of a new patented method for control of chicken coccidiosis. J. Appl. Anim. Res. 47, 573–581. https://doi.org/10.1080/09712119.2019.1694028.
Tian, X., Shao, Y., Wang, Z., Guo, Y., 2016. Effects of dietary yeast beta-glucans supplementation on growth performance, gut morphology, intestinal Clostridium perfringens population and immune response of broiler chickens challenged with necrotic enteritis. Anim. Feed Sci. Tech. 215, 144–155. https://doi.org/10.1016/j.anifeedsci.2016.03.009.
Waldenstedt, L., 2003. Effect of vaccination against coccidiosis in combination with an antibacterial oregano (*Origanum vulgare*) compound in organic broiler production. Act. Ag. Scand. Sect. A -Anim. Sci. 53, 101–109. https://doi.org/10.1080/09064700310007977.
Zavala, D., Icochea, D., Cribillero, C., Molina, D., 2018. The salinomycin/nicarbazin combination as anticoccidial in broilers. Rev. Investig. Vet. Peru 29, 942–949. https://doi.org/10.15381/rivep.v29i3.14759.