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The efficacy of antibiotics to prevent collibacilosis in broiler poultry: A protocol for a systematic review and network meta-analysis.

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Abstract

Antibiotics are used in broiler poultry production both for the prevention and treatment of infectious diseases. However, antibiotic use is a driver of antibiotic resistance. The World Health Organization has published numerous reports urging all stakeholders concerned with both food-producing animals and humans to establish recommended steps to enhance the prudent use of antimicrobials (WHO, 2015). Similarly, the World Animal Health Organization has also published recommendations and position statements regarding prudent use and risk management related to antimicrobial use in animals (OIE, 2017).

Colibacillosis is an important bacterial pathogen of poultry, and a costly disease for the industry resulting in multimillion dollar losses annually through morbidity, mortality or carcass condemnation at slaughter. Colibacillosis refers to any localized or systemic infection caused entirely or partly by the organism avian pathogenic Escherichia coli (APEC). These bacteria may be isolated as the sole pathogen or contribute to a disease complex with mixed viral and bacterial infections (Guabirara and Schouler, 2015). Two main disease processes important in the broiler industry are early mortality and cellulitis. Early mortality is defined by chicks under a week of age experiencing a higher than normal percentage of deaths in a flock. Early mortality can be caused by many things, for example chilling, overheating, or dehydration, however E.coli infection, or colibacillosis, is one of the main culprits. Colibacillosis can present with omphalitis, yolk sacculitis, enteritis, pasty vents, pericarditis, perihepatitis, polyserositis, congested lungs, splenomegaly and darkened proventriculus or any these combinations (Guabiraba and Schouler, 2015; Geetha and Palanivel, 2018). Many chicks succumb to an early and severe infection or are culled due to excessive morbidity. Antibiotics are typically used to reduce early mortality (Chauvin et al., 2005; Dziva and Stevens, 2008). Those with severe infection are unlikely to survive, however appropriate treatment reduces transmission between birds and improves the suitability of those with a mild infection. Not every labelled drug for E.coli is efficacious, resistance is common (Kabir, 2010) and effectiveness can vary from flock to flock, even within a flock, with more than one strain and more than one treatment.

Understanding the efficacy of antibiotics used to prevent colibacillosis in broiler chickens is essential to optimizing their use; ineffective antibiotics should not be used for prevention or, if there are multiple efficacious antibiotics, their importance to human medicine should be considered when making decisions on antibiotic use. Systematic reviews of randomized controlled trials, and network meta-analysis to provide input on relative antibiotic efficacy, will yield the highest level of evidence for efficacy of treatments under field conditions (Sargeant and O'Connor, 2014).

Disciplines

Poultry or Avian Science | Veterinary Infectious Diseases | Veterinary Pathology and Pathobiology

Authors

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Title: The efficacy of antibiotics to prevent collibacilosis in broiler poultry: A protocol for a systematic review and network meta-analysis.

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Author contributions:
All authors contributed to the development of the review question and the methodology described in this proposal. JMS drafted the protocol, with input and final approval of all co-authors.

Registration:
This protocol is archived in the University of Guelph's institutional repository (The Atrium; https://atrium.lib.uoguelph.ca/xmlui/handle/10214/10046) and published online with Systematic Reviews for Animals and Food (SYREAF) available at: http://www.syreaf.org/. The systematic review will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Liberati et al., 2009). This protocol is reporting using the items (headings) recommended in the PRISMA-P guidelines (Moher et al., 2015).

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Introduction.

Rationale:

Antibiotics are used in broiler poultry production both for the prevention and treatment of infectious diseases. However, antibiotic use is a driver of antibiotic resistance. The World Health Organization has published numerous reports urging all stakeholders concerned with both food-producing animals and humans to establish recommended steps to enhance the prudent use of antimicrobials (WHO, 2015). Similarly, the World Animal Health Organization has also published recommendations and position statements regarding prudent use and risk management related to antimicrobial use in animals (OIE, 2017).

Colibacillosis is an important bacterial pathogen of poultry, and a costly disease for the industry resulting in multimillion dollar losses annually through morbidity, mortality or carcass condemnation at slaughter. Colibacillosis refers to any localized or systemic infection caused entirely or partly by the organism avian pathogenic *Escherichia coli* (APEC). These bacteria may be isolated as the sole pathogen or contribute to a disease complex with mixed viral and bacterial infections (Guabirara and Schouler, 2015). Two main disease processes important in the broiler industry are early mortality and cellulitis. Early mortality is defined by chicks under a week of age experiencing a higher than normal percentage of deaths in a flock. Early mortality can be caused by many things, for example chilling, overheating, or dehydration, however *E.coli* infection, or colibacillosis, is one of the main culprits. Colibacillosis can present with omphalitis, yolk sacculitis, enteritis, pasty vents, pericarditis, perihepatitis, polyserositis, congested lungs, splenomegaly and darkened proventriculus or any these combinations (Guabiraba and Schouler, 2015; Geetha and Palanivel, 2018). Many chicks succumb to an early and severe infection or are culled due to excessive morbidity. Antibiotics are typically used to reduce early mortality (Chauvin et al., 2005; Dziva and Stevens, 2008). Those with severe infection are unlikely to survive, however appropriate treatment reduces transmission between birds and improves the suitability of those with a mild infection. Not every labelled drug for *E.coli* is efficacious, resistance is common (Kabir, 2010) and effectiveness can vary from flock to flock, even within a flock, with more than one strain and more than one treatment.

Understanding the efficacy of antibiotics used to prevent colibacillosis in broiler chickens is essential to optimizing their use; ineffective antibiotics should not be used for prevention or, if there are multiple efficacious antibiotics, their importance to human medicine should be considered when making decisions on antibiotic use. Systematic reviews of randomized controlled trials, and network meta-analysis to provide input on relative antibiotic efficacy, will yield the highest level of evidence for efficacy of treatments under field conditions (Sargeant and O'Connor, 2014).

Objectives: The objective of this protocol is to describe the methods for a systematic review – network meta-analyses to address the question: "What is the efficacy of antibiotics to prevent colibacillosis in broiler chickens?"

The specific PICO elements, which will define the eligibility criteria, are as follows:

i. *Population:* Broiler poultry.
ii. *Intervention:* Antibiotics licensed for use in chickens *in ovo*, by injection, in feed, or in the water at doses consistent with therapeutic or prophylactic use. Eligible antibiotics include any antibiotic for use in treating or preventing colibacillosis in poultry included in the OIE list of antimicrobial agents of veterinary importance[1] (see also appendix 1).
iii. *Comparator:* Placebo, untreated control group, or an alternative antibiotic treatment.
iv. *Outcomes:* The outcomes of interest are mortality, Feed Conversion Ratio (FCR), condemnations due to colibacillosis, and total antibiotic use.

[1] OIE list of antimicrobial agents of veterinary importance (May 2015) available at: http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf

Methods

Eligibility criteria: In addition to eligibility criteria inherent in the PICO elements described above, eligibility includes publication in English. Both journal articles and other forms of research reports are eligible, provided they report the results of a primary research study with a concurrent comparison group using an eligible study design and with a full text of more than 500 words.

Study designs eligible: Controlled trials with natural disease exposure (individual or cluster allocated) will be eligible for inclusion, although we will document the number of controlled trials with deliberate disease challenge and analytical observational studies at full text screening and also will identify the antibiotic interventions (i.e. licensed antibiotics used at labelled doses) and whether any of the outcomes of interest were assessed for studies of these designs.

Information sources:

We will conduct the literature search in a range of relevant bibliographic databases and other information sources containing both published and unpublished literature. Table 1 presents the resources to be searched.

Table 1: Databases and information sources to be searched

Database / information source	Interface / URL
MEDLINE	PubMed
CAB Abstracts	CAB Interface
Science Citation Index	Web of Science
Conference Proceedings Citation Index – Science	Web of Science
Agricola	Proquest

Most of the key poultry conferences provide short abstracts (<500 words) in their conference proceedings, which do not provide the detail necessary to include in a systematic review. However, the Western Poultry Disease Conference provides full papers. Therefore, one reviewer will hand-search title / abstracts for potentially relevant study reports. Any articles thus identified will be entered into DistillerSR for level 2 screening by 2 reviewers.

A single reviewer will also search the USDA FDA FOI requests for antibiotics registered for prophylactic use for collibacillosis in broilers in the USA. A single reviewer will hand-search the reference lists of all included studies for any eligible studies that may have been missed by the database searches.

Search strategy:

A Science Citation Index (Web of Science) search strategy designed to identify studies of antibiotic use to prevent collibacillosis in broilers is presented in Table 2. The search strategy employs a multi-stranded approach to maximize sensitivity. The conceptual structure is as follows:

- Broilers;

AND

- Antibiotics;

AND

- Collibacillosis

AND

- Disease prevention (as opposed to treatment)

Table 2: Search strategy to identify studies of antibiotics for the prevention of collibacillosis in broilers using Science Citation Index (Web of Science)

#1 TS = (Chicken* OR Poultry* OR flock* OR gallus* OR broiler*) 193,683

#2 TS = (medicat* OR antimicrobial* OR "anti-microbial*" OR antibiotic* OR "anti-biotic*" OR antibacterial* OR "anti-bacterial*" OR antiinfect* OR "anti-infect*" OR bacteriocid* OR bactericid* OR microbicid* OR "anti-mycobacteri*" OR antimycobacteri*) 796,347

#3 TS = (apramycin OR amoxicillin OR Avilamycin OR enrofloxacin OR Neomycin OR Neomicin OR salinomycin OR salinomicin OR spectinomycin OR Sulfaquinoxaline OR ceftiofur OR gentamycin OR gentamicin OR lincomycin OR oxytetracycline OR Bacitracin OR Sulfadimethoxine OR Sulfaquinoxaline OR Virginiamycin OR Chlortetracycline OR Tylosin OR Tetracycline OR Trimethoprim OR Virginiamycin OR Sulfamethoxazole) 108,922

#4 TS = (Apralan OR Baytril OR paracillin OR Garasol OR Lincosol OR Lincomix OR Coban OR Monteban OR Neo-chlor OR neo-tetramed OR NeoMed OR Neotet OR oxy OR oxysol OR sacox OR posistac OR coxistac OR Sulforal OR Sulfadived OR di-methox OR Onycin OR tetra OR tetramed OR Stafac OR “Super Booster” OR Uniprim OR Tylan) 59,298

#5 TS = (collibacillosis OR coli OR Escherichia OR coliform OR colisepticaemia OR colisepticemia OR coligranuloma OR Hjarre’s OR “air sac disease” OR cellulitis OR peritonitis OR osteomyelitis OR “brittle bone disease” OR peritonitis OR salpingitis OR synovitis OR omphalitis OR enteritis OR “hemorrhagic septicemia” OR “chronic respiratory disease” OR “swollen head syndrome” OR “venereal colibacillosis” OR “coliform cellulitis” OR “yolk sac infection”) 582,217

#6 TS = (prophyla* OR metaphyla* OR "meta-phyla*" OR “mass treatment” or “mass medication” or “blanket medication” or “blanket treatment” OR prevent* OR “in feed” OR “in-feed” OR “in-water” OR “in water” OR “medicated” OR “in ovo”) 1,827,320

#1 AND (#2 OR #3 OR #4) AND #5 AND #6 619

The search strategies will not be limited by date, language, or publication type.

We will conduct searches using each database listed in the protocol, translating the strategy appropriately to reflect the differences in database interfaces and functionality.

Study records:

Data management: We will download the results of searches in a tagged format, load them into bibliographic software (EndNote) and de-duplicate the citations. The de-duplicated search results will be uploaded into online systematic review software (DistillerSR®, Ottawa, ON, Canada), and de-duplication will be repeated in DistillerSR using an internal program. Reviewers will have training in epidemiology and in systematic review methods. Prior to both abstract and full-text screenings, data extraction, and risk of bias assessment, the reviewers assigned to each step will undergo training to ensure consistent data collection using the forms created in DistillerSR®.

Selection process: In the first round of screening, abstracts and titles will be screened for eligibility. Two reviewers will independently evaluate each citation for relevance using the following questions:

1) Is this a primary study evaluating the use of one or more antibiotics to prevent colibacillosis in broilers?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
2) Is there a concurrent comparison group? (i.e. controlled trial with natural or deliberate disease exposure or analytical observational study)?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
3) Is the full text available in English? [language of publication can be included as a field in DistillerSR]
   YES (include for full text screening), NO (EXCLUDE), UNCLEAR (include for full text screening)

Citations will be excluded if both reviewers responded “no” to any of the questions. Any disagreements will be resolved by consensus. If consensus cannot be reached, the article will be marked as “unclear” and will advance to full text screening. A pre-test will be conducted by all reviewers on the first 250 abstracts to ensure clarify of questions and consistency of understanding of the questions.

Following title/abstract screening, eligibility will be assessed through full-text screening, using the questions included below. Two reviewers will independently evaluate the full text articles, with any disagreements resolved by consensus. If consensus cannot be reached, a third reviewer will be used. A pre-test will be conducted by all reviewers on the first 10 full texts to ensure clarify of questions and consistency of understanding of the questions.

1) Is the full text available with > 500 words?
   YES (neutral response), NO (EXCLUDE)
2) Is the full text available in English?
   YES (neutral response), NO (EXCLUDE)
3) Eligible population: Does the study evaluate broilers?
   YES (neutral response), NO (EXCLUDE)
4) Eligible intervention: Does the study assess the use of one or more of the antibiotics of interest for the PREVENTION of collibacillosis in broilers?
   YES (neutral response), NO (EXCLUDE)
5) Are at least one of the following outcomes described: mortality, FCR, condemnations due to colibacillosis, or total antibiotic use.
   YES (neutral response), NO (EXCLUDE
6) Is there a concurrent comparison group? (i.e. controlled trial with natural or deliberate disease exposure or analytical observational study)?
   YES (neutral response), NO (EXCLUDE)
7) Eligible study design: Is the study a controlled trial with natural disease exposure?
   Yes (moves to data extraction stage),
   No, the study is a controlled trial with deliberate disease induction (indicate the antibiotic(s) evaluated, but exclude from data extraction)
   No, the study is an observational study (indicate the antibiotic(s) evaluated but exclude, from data extraction)

Data collection process: Data will be extracted by two reviewers working independently. Any disagreements will be resolved by consensus or, if consensus cannot be reached, a third reviewer will be used. Authors will not be contacted to request missing data or to clarify published results. A form for data extraction will be created for this review in DistillerSR® and pre-tested on 4 full text articles to ensure question clarity.

Data items:

Study level data to be extracted include:

- Country where trial was conducted (if not stated, use country affiliation of corresponding author)
- Commercial versus research flocks
- Number of flocks enrolled in study
- Year(s) the study was conducted

- Months of data collection
- Stage of production where intervention was applied
- Stage of production where outcome was evaluated

Arm level data collected:

- Antibiotic name(s)
- Dose / route / frequency of administration
- Unit of allocation (e.g. room, flock)
- Description of comparison group
- Number of birds enrolled
- Number of pens / rooms / flocks enrolled
- Number of animals / pens / rooms / flocks lost to follow up
- Number of animals / pens/ rooms / flocks analyzed
- Any additional concurrent treatments given to both intervention groups.
- The approach used in the analysis to account for non-independent observations (not applicable, not reported, random effects, GEE, other)

Outcomes and prioritization:

- Mortality,
- FCR,
- Condemnations at slaughter due to collibacillosis,
- Total antibiotic use.

These outcomes were prioritized based on their impact on animal health and welfare and their economic importance. Formal evaluation of these criteria for prioritization was not undertaken.

Outcome data to be collected:

1) Mortality
    a. Level at which outcome data were measured (animal / room / flock)
    b. Time period for assessing outcome

2) Feed Conversion Ratio
    a. Age / weight at slaughter
    b. Level at which the outcomes data were measured (animal / room / flock)

3) Condemnation due to collibacillosis
    a. Case definition
    b. Age / weight at slaughter

4) Total antibiotic use

a. Measure used to define outcome
b. Time period for assessing outcome
c. Antibiotic(s) used

For each outcome, we will extract the possible metrics in the following order:

- 1st priority: Adjusted summary effect size ($_{adjusted}$ risk ratio or $_{adjusted}$ odds ratio, mean differences for continuous outcomes) and variables included in adjustment and corresponding precision estimate
- 2nd priority: Unadjusted summary effect size
- 3rd priority: Arm level risk of the outcome, or arm level mean of the outcome (continuous outcomes)
- Variance components.

Risk of bias in individual studies: Risk of bias will only be assessed for controlled trials with natural disease exposure. Risk of bias assessment will be performed at the outcome level for each outcome using the Cochrane risk of bias instrument (Higgins et all, 2016), with the signaling questions modified as necessary for the specific review question. The ROB-2.0 for clustered RCTs and individual RCTs will be used depending on the study design (Higgins et al., 2016). These tools are available at https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool.

Data synthesis:

Network meta-analysis. Network meta-analysis (aka mixed treatment comparison meta-analysis) will be conducted for each outcome. Network meta-analysis will use the approach described by NICE Decision Support Unit technical document (Dias et al., 2014; O'Connor et al., 2013; O'Connor et al., 2016). The approach to reporting will use the PRISMA- NMA (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx). Planned a priori sub-group analyses will be conducted for randomized versus non-randomized trials.

Meta-bias(es): Small study effects ("publication bias") will be assessed for all antibiotic-comparator combinations where there are at least 10 studies in the meta-analysis. If feasible, we will use approaches to assessing publication bias in the network of evidence using previously proposed approaches (Mavridis et al., 2013; Mavridis et al., 2014).

Confidence in cumulative evidence: The quality of evidence for each outcome will be assessed using the approach proposed by GRADE (GRADE, 2015, Puhan et al., 2014), while also considering the nature of the network meta-analysis (Jansen et al., 2011). If feasible, we will use the framework from the CINeMA platform for conveying the impact of risk of bias on the network performance.

Discussion:

This systematic review will provide a synthesis of the current evidence regarding the efficacy of antibiotics used to prevent collibacillosis in poultry. Results will be helpful for veterinarians and poultry producers when making evidence-informed decisions regarding treatment options to reduce disease and mortality, and potentially reduce the need to use antibiotics to treat collibacillosis. The results also will be helpful for identifying specific gaps in knowledge related to the efficacy of prophylactic antibiotics for collibacillosis to target additional research.

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Appendix 1: Antibiotics approved for use for collibacillosis in poultry, with trade names and labelling information.

Antibiotic (AVIAN)	Market name	Dose
Amoxicillin	Paracillin® SP (Pr) (Merck Animal Health), Amoxicillin SP (Pr) (Bio Agri Mix)	10-20 mg (8-16 mg amoxicillin trihydrate)/kg b.w. daily, for 3-5 consecutive days.
Avilamycin	Paracillin® SP (Pr) (Merck Animal Health), Amoxicillin SP (Pr) (Bio Agri Mix)	0.15-0.3 kg/1,000 kg feed (15-30 ppm avilamycin). Feed as sole ration for 21d during risk period
Bacitracin	Paracillin® SP (Pr) (Merck Animal Health),Amoxicillin SP (Pr) (Bio Agri Mix)	Broilers: 0.5 kg/999.5 kg complete feed (55 mg/kg). Feed continuously to market weight.
Ceftiofur (sodium)	Paracillin® SP (Pr) (Merck Animal Health),Amoxicillin SP (Pr) (Bio Agri Mix)	Day-old chicks: 0.08-0.2 mg ceftiofur/chick in the neck. One mL of 50 mg/mL reconstituted solution will treat ~250-625 day-old chicks.
Chlortetracycline	Paracillin® SP (Pr) (Merck Animal Health),Amoxicillin SP (Pr) (Bio Agri Mix)	Broiler, layer and replacement chickens: Add 1 kg/tonne [110 mg/kg (0.011%)] of complete feed. Feed continuously as sole ration from onset of symptoms for at least one month or until a few days after symptoms disappear.
Gentamicin	Garasol® Injection (100 mg/mL) (Intervet/Merck Animal Health) Coccivac®-B52 (Intervet/Merck Animal Health)	Each day-old chick: Inject S.C. in neck with 0.2 mg gentamicin in a 0.2 mL dose (diluted with saline solution). Healthy birds 1d of age: Spray cabinet: Dilute 1,000 dose vial with 210 mL distilled water. Each box of 100 chicks receives 21 mL of vaccine solution.

Lincomycin (hyrdrochloride)	Lincomycin Hydrochloride Soluble Powder (Rx) (Huvepharma)	Broilers: 64 mg lincomycin/gal drinking water for 7d.
	Lincosol Soluble Powder (Rx) (Med-Pharmex)	Broilers: 64 mg lincomycin/gal drinking water for 7d.
	Lincomycin Soluble Powder (Bio Agri Mix)	1 jar/2,000 L drinking water (16 mg antibiotic activity/L).
	Lincomix® Soluble Powder (Zoetis)	At first sign of disease, administer at following dosage as sole source of drinking water for 7 consecutive days.80 g soluble powder will medicate 2,000 L water or 1 level scoop (4.7 g)/120 L water (16 mg antibiotic activity/L).Stock solution: 80 g/8 L (1 level scoop/470 mL) water in a clean glass or plastic container, mix, and dispense 1 L stock solution/250 L drinking water.
Neomycin (sulfate)	Neomycin 325 (Pr) (Vetoquinol)	Flock treatment: As soon as symptoms are observed, give for 3-5d. Day-old to 2 weeks: 20 g powder/225 L water OR 100 g powder (1 pouch)/1,125 L water. 2 weeks to adulthood: 40 g powder/225 L water OR 200 g powder (2 pouches)/1,125 L

		water.
	Neo-Chlor® (Pr) (Vetoquinol),	100 g, 10 kg sizes: Dissolve 100-200 g (1-2 pouches) powder/225 L water for 3-5d. 400 g: Dissolve 400-800 g (1-2 pouches)/900 L water for 3-5d. Automatic proportioner: Set to distribute 30 mL/4 L water (1 oz/gal). Prepare stock solution by dissolving 400-800 g (1-2 pouches)/6.75 L water to medicate 900 L water.
	Neo-Tetramed (Medprodex)	Dissolve 400-800 g (1-2 pouches)/900 L water for 3-5d.
	NeoMed 325 (Medprodex)	Day-old to 2 weeks: 20 g/225 L of water OR 100 g/1,125 L of water. 2 weeks to adulthood: 40 g/225 L of water OR 200 g/1,125 L of water.
	Neotet Soluble Concentrate (Dominion)	100 g in 200-400 L of drinking water for 3d.
Oxytetracycline	Oxy 250 (Medprodex)	1 g/5 L water OR 100 g/500 L drinking water for 3-5d.
	Oxysol-62.5 (Pr) (Vetoquinol)	Dissolve 4 g powder/5 L water OR 400 g (1 pouch) powder/500 L drinking water and give for 3-5d.
Oxytetracycline HCl	Oxytetracycline HCl Soluble Powder 1000 (Bio Agri Mix)	100 g/1,350 L drinking water for 3-4d.
Salinomycin (sodium)	Sacox® 60 (Huvepharma), Bio-Cox® 60 Granular (Huvepharma)	Broiler, roaster and replacement (breeder and layer) chickens: 40-60 g/ton (0.0044-0.0066%). Feed continuously as sole ration.

	Salinomycin 60 Premix (Bio Agri Mix), Posistac® 6% Premix (Phibro), Coxistac® 6% Premix (Phibro) Coxistac® 12% Granular (Phibro), Sacox® 120 (Huvepharma AD)	Thoroughly mix 1000 g (1.0 kg) Salinomycin 60 Premix with 999 kg complete feed to obtain a finished feed containing 60 mg/kg (60 ppm) salinomycin sodium. Feed continuously as sole ration up until slaughter. Broiler chickens: Thoroughly mix 500 g Coxistac 12% Granular with 1,000 kg complete feed to obtain a medicated feed with a salinomycin sodium concentration of 0.0060% (60 mg/kg). Can be prepared in the form of meal or pellets. Feed continuously as sole ration up to marketing.
Sulfadimethoxine	Sulfadimethoxine Concentrated Solution 12.5% (Rx) (VetOne), Sulforal (Rx) (Med-Pharmex), Sulfadived™ 12.5% Solution (Rx) (Vedco), Di-Methox® Concentrated Solution 12.5% (Rx) (AgriLabs)	Use 0.05% concentration. Add 1 oz (30 mL) to 2 gal water or 25 oz/50 gal water. Treat for 6 consecutive days.
	Sulfadimethoxine 107g Powder (Rx) (VetOne), Di-Methox® Soluble Powder (Rx) (AgriLabs), Sulfasol (Rx) (Med-Pharmex), Sulfasol (Rx) (Med-Pharmex)	Use 0.05% concentration. Add 1 packet/50 gal water. Treat for 6 consecutive days. Stock solution: Add 5 packets/2 gal water.
Sulfaquinoxaline	Sulfaquinoxaline 19.2% Liquid Concentrate (Dominion)	https://cdmv.cvpservice.com/product/view/1181072?key=dosage
Tetracycline	Onycin 1000 (Pr) (Vetoquinol), Tetra 1000 (Dominion), Tetramed 250 and 1000 (Medprodex), Oxy 250 (Medprodex)	1 g/20 L of water OR 100 g/2000 L of drinking water, for 3-5d. For automatic proportioner: Set to distribute 30 mL/4 L drinking water (1 oz/gal U.S.). Prepare stock solution by dissolving 25 g powder/4 L water. This will medicate 500 L drinking water.
	Oxytetracycline HCl Soluble Powder 1000 (Bio Agri Mix)	100 g/1,350 L drinking water for 3-4d.

	Tetracycline 250 (Vetoquinol)	400 g: Dissolve 1 g/5 L or 400 g (1 pouch)/2,000 L drinking water, for 3-5d. 10 kg: Dissolve 1 g/5 L or 100 g/500 L drinking water, for 3-5d.
	Oxysol-62.5 (Pr) (Vetoquinol)	Dissolve 4 g powder/5 L water OR 400 g (1 pouch) powder/500 L drinking water and give for 3-5d
Tylosin (tartrate)	Tylan® Soluble (Rx) (Elanco)	broiler chickens: 851-1,419 mg/gal (225-375 ppm) in drinking water. Administer medicated drinking water for a single 5d period. Broiler chickens: 100-150 mg/L, depending on severity of infection.
	Tylosin Soluble Powder (Bio Agri Mix)	Mix 0.4-0.6g/4L water, Treat 5d
	Tylan™ Soluble (Pr) (Elanco (Novartis))	Broiler chickens (drinking water): Treat for 5d at not <100 mg/L (0.4 g/4 L) and not more than 150 mg/L (0.6 g/4 L) depending on severity of outbreak.
Tylosin (Phosphate)	Tylosin 40 (Bio Agri Mix)	125 kg/tonne complete diet (11 g tylosin).
	Tylan™ 100 Premix (Pr) (Elanco (Novartis))	Broiler chickens: 0.91 kg (200 g tylosin)/tonne complete feed.

Virginiamycin	Virginiamycin 44 Premix (Bio Agri Mix), Stafac® 44 (Phibro)	Broilers: Mix 0.5 kg (22 g virginiamycin)/tonne complete feed to provide 1 mg/kg b.w./day. Feed continuously as sole ration from weaning to market weight.
	Stafac® 22 (Phibro)	Broilers: Mix 1 kg (22 g virginiamycin)/tonne complete feed to provide 1 mg/kg b.w./day. Feed continuously as sole ration from day 1 to market weight.
	Stafac® 500 (Phibro)	Mix 44 g/tonne (22 g virginiamycin) complete feed. This will provide 1 mg/kg b.w./day.