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Effectiveness of Antimicrobials in the Treatment of Neonatal Diarrhea in Calves: A protocol for a Systematic Review and Meta-analysis. Authors: Bernal Cordoba, Erik Davis Fausak, N. Silva del Rio

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Fausak, Erik Davis
Silva-del-Rio, Noelia

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Supplemental Material

https://escholarship.org/uc/item/0nw528h4#supplemental

Data Availability

The data associated with this publication are in the supplemental files.

Effectiveness of Antimicrobials in the Treatment of Neonatal Diarrhea in Calves: A protocol for a Systematic Review and Meta-analysis:

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Author Contributions:
NSDR and CBC – Assist to develop search protocol and literature search. Identification of relevant studies, data extraction, data presentation and manuscript preparation.
EDF – Develop search protocol and literature search.
Contributions from other authors TBD

Abstract:
Background: Neonatal diarrhea affects nearly 25% of pre-weaned calves. Prevention through management practices is the preferable approach to control diarrhea. Once calves experience diarrhea, fluids, electrolytes and acid-base balance need to be restored. Severe cases of diarrhea should be treated with antimicrobials but the need of antimicrobials in mild and moderate clinical cases it is still under debate.
Objectives: The objective of this study is to evaluate the efficacy of antimicrobial treatments or the comparative efficacy of antimicrobials treatments in calves with mild, moderate and severe diarrhea.
Design: The search strategy will be based on population (calves with diarrhea), and intervention (antimicrobial therapy). The following data bases will be used: Medline, CAB abstracts, Scopus, and Biosis. The outcomes of interest will be the occurrence and persistence of clinical signs of diarrhea, rate of growth, weight gain, feed efficiency or mortality.
Registration: The protocol has been submitted to SYREAF 12.7.19, and eScholarship, University of California (https://escholarship.org/) 12.7.19.
Amendments from Original Protocol: N/A.

Introduction
Rationale
Neonatal diarrhea affects nearly 25% of pre-weaned calves. Prevention through management practices is the preferable approach to control diarrhea. Calves undergoing diarrhea may require treatment. The veterinary community agrees that fluids, electrolytes and acid-base balance should be

restored in diarrheic calves. However, the need of antimicrobials to treat and prevent diarrhea in calves is still under debate for moderate and mild cases. Information about the efficacy of antimicrobials should be obtained from randomized controlled studies. At the present multiple antimicrobial drugs and regimes are used to treat diarrhea in calves.

The efficacy of antimicrobial treatment regimens will be evaluated to aid veterinarians and dairy producers in their decision making. A systematic review will be conducted to identify relevant literature. Network meta-analysis will be used to combine information from multiple studies and compare treatments.

Objectives

The objective of this study is to evaluate the efficacy of antimicrobial treatments or the comparative efficacy of antimicrobials in calf diarrhea treatments. Only antimicrobials labeled to be use in calf diarrhea in the US will be included in the meta-analysis.

Methods

Eligibility Criteria:

Studies will be eligible if they are primary research articles with either a negative control (placebo, no treatment) or an active comparator (other antimicrobial, a non-antimicrobial treatment). The study population of interest are calves less than 6 months of age.

The outcome of interest is clinical cure risk after treatment (or treatment failure). The definition of cure (or failure) will be based on the authors' definition and may include mortality, specific signs of disease (i.e. fecal consistency, fever), unspecific signs of health disorder (i.e. appetite, demeanor), or performance (i.e. growth, weight gain, feed efficiency). Studies failing to report random treatment allocation will remain in the study; however, this will be included as a source of bias and assessed as a source of heterogeneity.

Clinical question

Are antimicrobial treatments effective at reducing the persistence (cure) of clinical signs of diarrhea compared to absence of antimicrobial treatment or alternative non-antimicrobial treatments or other antimicrobial treatments?

Information Sources:

The information sources used will include:

Database	Interface
Medline	Pubmed
CAB Abstracts	CAB Direct
Scopus	Scopus
Biosis	Web of Science

The research will be restricted to peer-review manuscripts written in English language. Publication date will not be limited.

Search Strategy:
The search strategy will be based on population (calves with scours/diarrhea <6 months of age) and intervention (oral or injectable antimicrobials).
PRISMA-S Template (based on v1.0 retrieved from https://osf.io/2ybwn/)

Search Strategy for *Effectiveness of Antimicrobials in the Treatment of Neonatal Diarrhea in Calves: A protocol for a Systematic Review and Meta-analysis* Protocol submission in SYREAF (http://www.syreaf.org/contact/)

Databases and Interfaces Searched:

Database	Interface	Date Coverage	Date Searched
Medline	Pubmed	1966 to Present	1 July 2019
CAB Abstracts	CAB Direct	1972 - Current	1 July 2019
Scopus	Scopus	1970 - Current	2 July 2019
Biosis	Web of Science	1926 - Current	2 July 2019

Citation Searching And Text Analysis:

Article Citation:
Howarth, J. A., D. R. Cordy, and J. Bittle. "Salmonella bredeney infection of calves and prophylaxis with chloromycetin and streptomycin." *Journal of the American Veterinary Medical Association* 124.922 (1954): 43-46.
Constable PD. Antimicrobial use in the treatment of calf diarrhea. Journal of veterinary internal medicine. 2004 Jan;18(1):8-17.
Mylrea, P. J. (1968). Passage of antibiotics through the digestive tract of normal and scouring calves and their effect upon the bacterial flora. *Research in veterinary science*, *9*(1), 5-13.
McLean, D. M., & Bailey, L. F. (1972). The effectiveness of three treatments for scouring in calves. *Australian Veterinary Journal*, *48*(6), 336–338.
Glantz, P. J., Kradel, D. C., & Seward, S. A. (1974). Escherichia coli & Salmonella newport in calves: efficacy of prophylactic and therapeutic treatment. *Veterinary Medicine, Small Animal Clinician : VM, SAC*, *69*(1), 77-82 passim.
Bywater, R. J. (1977). Evaluation of an oral glucose-glycine-electrolyte formulation and amoxicillin for treatment of diarrhea in calves. *American journal of veterinary research*, *38*(12), 1983.

Daniels, L B, D Fineberg, J M Cockrill, Q Hornsby, H P Peterson, and L Stratton
1977 Use of trimethoprim-sulfadiazine in controlling calf scours. *Veterinary medicine, small animal clinician : VM, SAC* 72(1):93–95.

Palmer, G H, R J Bywater, and M E Francis
1977 Amoxycillin: distribution and clinical efficacy in calves. *The Veterinary record* 100(23):487–491.

Gupta, A. K., & Baxi, K. K. (1978). Study on the efficacy of antibiotics and furazolidone in the treatment of clinical cases of colibacillosis in calves [India]. *Indian Veterinary Journal (India)*.

White, G., Piercy, D. W. T., & Gibbs, H. A. (1981). Use of a calf salmonellosis model to evaluate the therapeutic properties of trimethoprim and sulphadiazine and their mutual potentiation in vivo. *Research in veterinary science*, *31*(1), 27-31.

VanDamme, D. (1982). Sulfachlorpyridazine in the treatment of colibacillosis in neonatal calves. *Bovine Practice*, *3*(2), 26,28-30.

Rollin, R. E., Mero, K. N., Kozisek, P. B., & Phillips, R. W. (1986). Diarrhea and malabsorption in calves associated with therapeutic doses of antibiotics: absorptive and clinical changes. *American Journal of Veterinary Research*, *47*(5), 987–991.

Process: Key articles were identified by Principal Investigator and keywords were mined by finding references in PubMed, CAB Direct, Scopus, and Biosis. Keywords were collected and compared with keywords already utilized. Yale MeSH analyzer was also utilized to compare common Medical Subject Headings across articles. Content expert, Noelia Silva Del Rio, was consulted for identification of key pathogens and antibiotics currently used in calves.

Limits and Restrictions

Date and Time Period: Based on database coverage.

Language: English

Publication status: Published content only.

Species Included: bovine, neonatal (calves)

Study Design: Any prospective trial.

Search Filters:

Database	Interface	Search Filters Applied
Medline	Pubmed	English
CAB Abstracts	CAB Direct	English
Scopus	Scopus	English
Biosis	Web of Science	English

Full Search Strategy:

Search Database : Pubmed

Search ID	Terms (copy and paste)	Results
#1 (disease)	("Diarrhea"[Mesh] OR "Gastroenteritis/veterinary"[Mesh] OR "Escherichia coli Infections/drug therapy"[Mesh] OR "Escherichia coli Infections/veterinary"[Mesh] OR "Salmonella"[Mesh] OR "Salmonella Infections, Animal/drug therapy"[Mesh] OR "Coronavirus, Bovine"[Mesh] OR "Rotavirus Infections/veterinary"[Mesh] OR "Cryptosporidiosis"[Mesh] OR "Malabsorption Syndromes/veterinary"[Mesh] OR "enterobacter"[Mesh] OR "scours"[tiab] OR "scouring"[tiab] OR "scour"[tiab] OR Cryptosporidiosis[tiab] OR Cryptosporidioses[tiab] OR Cryptosporidium[tiab] OR "Escherichia"[tiab] OR "diarrhea"[tiab] OR "Salmonella"[tiab] OR "starvation"[tiab] OR "perfringens"[tiab] OR "rotavirus"[tiab] OR "coronavirus"[tiab] OR "Enterobacter"[tiab] OR "clostridiales"[tiab] OR "clostridiaceae"[tiab] OR "clostridia"[tiab] OR "protozoal"[tiab] OR "protozoa infection"[tiab] OR "protozoa infections"[tiab] OR "protozoan infection"[tiab] OR "protozoan infections"[tiab] OR protozoiasis[tiab] OR "protozoon infection"[tiab] OR "protozoon infections"[tiab] OR "malabsorption"[tiab])	507,737
#2 (Patient)	"Calf"[tiab] OR "calves"[tiab]	62,249

| #3 (treatment) | "oxytetracycline"[tiab] OR "terramycin"[tiab] OR "hydrotetracycline"[tiab] OR "oxyterracin"[tiab] OR "bisolvomycin"[tiab] OR "sulfachlorpyridazine"[tiab] OR "sulphachlorpyridazine"[tiab] OR "sulfanomides"[tiab] OR "pyridazines"[tiab] OR "antibiotics"[tiab] OR "antimicrobials"[tiab] OR "antiinfective"[tiab] OR "anti-infective"[tiab] "therapy"[tiab] OR "amoxicillin"[tiab] OR "ampicillin"[tiab] OR "penicillin"[tiab] OR "clavulanic"[tiab] OR "clavulanate"[tiab] OR "clavulin"[tiab] OR "amox-clav"[tiab] OR "clav"[tiab] OR "amoxiclav"[tiab] OR "chlortetracycline"[tiab] OR "aureomycin"[tiab] OR "aureomycine"[tiab] OR "biomycin"[tiab] OR "streptomycin"[tiab] OR "streptomycine"[tiab] OR "aminoglycoside"[tiab] OR "estreptomicina"[tiab] OR "strepto-hefa"[tiab] OR "sulphamethylphenasole"[tiab] OR "sulfadimidine"[tiab] OR "sulphadimidine"[tiab] OR "sulfamethazine"[tiab] OR "sulfachloropyridiazine"[tiab] OR "sulphamezathine"[tiab] OR "tetracycline"[tiab] OR "sustamycin"[tiab] OR "achromycin"[tiab] OR "tetrabid"[tiab] OR "cephamycin"[tiab] OR "cephalosporins"[tiab] OR "procaine"[tiab] OR "neomycin"[tiab] OR "fradiomycin"[tiab] OR "chloramphenicol"[tiab] OR "cloranfenicol"[tiab] OR "chloromycetin"[tiab] OR "florfenicol"[tiab] OR "florphenicol"[tiab] OR "trihydrate"[tiab] OR "aminobenzylpenicillin"[tiab] OR "ks-r1"[tiab] OR "sultamicillin"[tiab] OR "sulbactam"[tiab] OR "unasyn"[tiab] OR "ceftiofur"[tiab] OR "naxcel"[tiab] OR "trimethoprim"[tiab] OR "sulfadiazine"[tiab] OR "ditrim"[tiab] OR "tribrissen"[tiab] OR "prophylactic"[tiab] OR "sulphamethylphenasole"[tiab] OR "Gentamicin"[tiab] OR "gentavet"[tiab] OR "genticin"[tiab] OR "gentamycin"[tiab] OR "furazolidone"[tiab] OR "nifurazolidone"[tiab] OR "apramycin"[tiab] OR "fluoroquinolone"[tiab] OR "enrofloxacin"[tiab] OR "baytril"[tiab] OR "endrofloxacin"[tiab] OR "marbofloxacin"[tiab] OR "zeniquin"[tiab] OR "danofloxacin"[tiab] OR "advocin"[tiab] OR "Administration, Oral"[Mesh] OR "Neomycin"[Mesh] OR "Oxytetracycline"[Mesh] OR "Sulfachlorpyridazine"[Mesh] OR "Amoxicillin"[Mesh] OR "Amoxicillin-Potassium Clavulanate Combination"[Mesh] OR "Chlortetracycline"[Mesh] OR "Streptomycin/veterinary"[Mesh] OR "Sulfamethazine"[Mesh] OR "Tetracycline"[Mesh] OR "Penicillin V"[Mesh] OR "Procaine"[Mesh] OR "Cephamycins"[Mesh] OR "L 640876" [Supplementary Concept] OR "Chloramphenicol"[Mesh] OR "florfenicol" [Supplementary Concept] OR "sultamicillin" [Supplementary Concept] OR "ceftiofur" [Supplementary Concept] OR "sulfadiazine, trimethoprim drug combination" [Supplementary Concept] OR "Gentamicins"[Mesh] OR "Sulfonamides"[Mesh] OR "Furazolidone"[Mesh] OR "apramycin" [Supplementary Concept] OR "Enrofloxacin"[Mesh] OR "marbofloxacin" [Supplementary Concept] OR "danofloxacin" [Supplementary Concept] OR "Anti-Infective Agents/veterinary"[Mesh] OR "Electrolytes/therapeutic use"[Mesh] | **638448** |

| #4 | #1 AND #2 AND #3 Filter: English | 578 |

Search Database: CAB Direct

Search ID	Terms (copy and paste)	Results
#1 (disease)	Ti:(diarrh* OR scour* OR escherich* OR salmonell* OR enterobact* OR clostrid* OR Escherichia OR Salmonella OR Coronavirus OR Rotavirus OR Cryptosporidiosis OR Malabsorption OR scours OR scouring OR diarrh* OR starvation OR perfringens OR gastroenteritis OR coronavirus OR Enterobacter OR clostridiales OR clostridiaceae OR clostridia OR protozoal) or od:("Escherichia%20coli" OR "Clostridium" OR "Salmonella" or "Clostridium%20perfringens" OR "Enterobacteriaceae" OR "Enterobacteriales" OR "prokaryotes" OR "calf diarrhoea rotavirus" OR "betacoronavirus" OR "norovirus" OR "Eimeria") OR de: ("salmonellosis" OR "diarrhoea" OR "Escherichia%20infections" OR "cryptosporidiosis" OR "Intestinal%20diseases")	282,615
#2 (population)	Ti:(calf OR calves) OR de: ("calves" or "calf diseases")	66,381

#3 (therapy)	Ti:(oxytetracycline OR tetracycline OR antibiotic* OR antimicrobial* OR antiinfective OR therapy OR sulfachlorpyridazine OR sulphachlorpyridazine OR sulfanomide* OR strepto-hefa OR sulphamethylphenasole OR sulfadimidine OR sulphadimidine OR sulfamethazine OR sulfachloropyridiazine OR sulphamezathine OR clav* OR gentamycin* OR cephamycin OR cephalosporins OR fluoroquinolone OR enrofloxacin OR marbofloxacin OR amox* OR Penicillin OR Ampicillin OR trimethoprim* OR probiotic OR hydrotetracycline OR oxyterracin OR bisolvomycin OR pyridazines OR antibiotic* OR antimicrobial* OR antiinfective OR anti-infective OR amox* OR ampicillin OR penicillin OR clavul* OR chlortetracycline OR aureomycin* OR biomycin OR streptomycin* OR aminoglycoside* OR estreptomicina OR OR sulphamethylphenasole OR sulfadimidine OR tetracycline OR sustamycin OR achromycin OR tetrabid OR procaine OR neomycin OR fradiomycin OR chloramphenicol OR cloranfenicol OR kloramfenikol OR chloromycetin OR kloramfenikol OR florfenicol OR florphenicol OR trihydrate OR aminobenzylpenicillin OR ks-r1 OR sultamicillin OR sulbactam OR unasyn OR ceftiofur OR naxcel OR U-24769 OR trimethoprim OR ditrim OR tribrissen OR prophylactic OR sulphamethylphenasole OR Gentam* OR furazolidone OR nifurazolidone OR apramycin OR fluoroquinolone OR enrofloxacin OR baytril OR endrofloxacin OR marbofloxacin OR zeniquin OR danofloxacin OR advocin OR Neomycin OR L640876 OR ceftiofur OR Furazolidone OR "milk replacer") OR de:("animal%20feeding" or "antibiotics" or "dihydrostreptomycin" OR "spectinomycin" OR "antibiotics" OR "oral administration" OR "prophylaxis" OR "streptomycin" OR "aminoglycoside" OR "amoxicillin" OR "ampicillin" OR "antiinfective%20agents" OR "beta-lactam%20antibiotics" OR "ceftiofur" OR "cephalosporins" OR "clavulanic acid" OR "penicillins" OR "tetracyclines" OR "chlortetracycline" OR "milk%20substitutes" OR "treatment" OR "substitutes" OR "electrolytes" OR "sulfadiazine" OR "trimethoprim" OR "Drug therapy" OR "Antibacterial%20agents" OR "fluoroquinolone%20antibiotics" OR "metronidazole" OR "drug%20combinations" OR "furazolidone" OR "Chloramphenicol" OR "Neomycin" OR "sulfadiazine" OR "Sulfonamides" OR "trimethoprim" OR "beta-lactam%20antibiotics" OR "aminoglycoside%20antibiotics" OR "Tetracyclines" OR "antibacterial%20agents" OR "therapeutic%20agents" OR "therapeutic%20diets")	622,664
#4	La: English	8,146,590
#5	#1 AND #2 AND #3 AND #4	1,717

Search Database: Scopus

Search ID	Terms (copy and paste)	Results
#1	(TITL-ABS-KEY (diarrh* OR scour* OR gastroenteritis OR escherich* OR salmonell* OR enterobact* OR clostrid* OR Escherichia OR Salmonella OR Coronavirus OR Rotavirus OR Cryptosporidiosis OR Malabsorption OR starvation OR perfringens OR coronavirus OR Enterobacter OR clostridiales OR protozoal))	1,097,488
#2	(Title(Calf OR Calves))	30,691

#3	(TITL-ABS-KEY(oxytetracycline OR tetracycline OR antibiotic* OR antimicrobial* OR antiinfective OR therapy OR sulphamethylphenasole OR sulfadimidine OR sulphamethylphenasole OR sulfadimidine OR sulfanomide* OR strepto-hefa OR sulphamethylphenasole OR sulfadimidine OR sulphadimidine OR sulfamethazine OR sulfachloropyridiazine OR sulphamezathine OR clav* OR gentamycin* OR cephamycin OR cephalosporin* OR fluoroquinolone OR enrofloxacin OR marbofloxacin OR amox* OR Penicillin* OR Ampicillin* OR trim* OR therapy OR probiotic OR hydrotetracycline OR oxyterracin OR bisolvomycin OR pyridazines OR anti-infective OR chlortetracycline OR aureomycin* OR biomycin OR streptomycin* OR aminoglycoside* OR estreptomicina OR sustamycin OR achromycin OR tetrabid OR procaine OR neomycin OR fradiomycin OR chloramphenicol OR cloranfenicol OR kloramfenikol OR chloromycetin OR kloramfenikol OR florfenicol OR florphenicol OR trihydrate OR aminobenzylpenicillin OR ks-r1 OR sultamicillin OR sulbactam OR unasyn OR ceftiofur OR naxcel OR U-24769 OR trimethoprim OR ditrim OR tribrissen OR prophylactic OR sulphamethylphenasole OR Gentam* OR furazolidone OR nifurazolidone OR apramycin OR fluoroquinolone OR baytril OR endrofloxacin OR zeniquin OR danofloxacin OR advocin OR Neomycin OR L640876 OR ceftiofur OR Furazolidone OR {milk replacer})	5,659,887
#4	Language (English)	64,418,516
#1 AND #2 AND #3 AND #4		992

Search Database: BIOSIS

Search ID	Terms (copy and paste)	Results

#1	(Ti=(diarrh* OR scour* OR escherich* OR salmonell* OR enterobact* OR clostrid* OR gastroenteritis OR Escherichia OR Salmonella OR Coronavirus OR Rotavirus OR Cryptosporidiosis OR Malabsorption OR starvation OR perfringens OR gastroenteritis OR coronavirus OR Enterobacter OR clostridiales OR protozoal) *AND* **LANGUAGE:** (English)	251,111
#2	Ti=calves OR calf *AND* **LANGUAGE:** (English)	33,207
#3	Ti=(oxytetracycline OR tetracycline OR antibiotic* OR antimicrobial* OR antiinfective OR therapy OR sulpha* OR sulfa* OR clav* OR gent* OR cepha* OR fluoroquinolone OR enrofloxacin OR marbofloxacin OR amox* OR Pen* OR Amp* OR trim* OR therapy OR probiotic OR hydrotetracycline OR oxyterracin OR bisolvomycin OR pyridazines OR anti-infective OR chlortetracycline OR aureo* OR biomycin OR streptomycin* OR aminoglycoside* OR estreptomicina OR sustamycin OR achromycin OR tetrabid OR procaine OR neomycin OR fradiomycin OR chlor* OR clor* OR kloramfenikol OR florfenicol OR florphenicol OR trihydrate OR aminobenzylpenicillin OR ks-r1 OR sultamicillin OR sulbactam OR unasyn OR ceftiofur OR naxcel OR U-24769 OR trimethoprim OR ditrim OR tribrissen OR prophylactic OR sulphamethylphenasole OR Gentam* OR furazolidone OR nifurazolidone OR apramycin OR fluoroquinolone OR baytril OR endrofloxacin OR zeniquin OR danofloxacin OR advocin OR Neomycin OR L640876 OR ceftiofur OR Furazolidone OR "milk replacer") *AND* **LANGUAGE:** (English)	1,225,576
#4	#1 AND #2 AND #3	221

Search Designers:
Erik Fausak was the librarian who designed the search strategy with input and reference citation list from content expert, Dr. Noelia Silva Del Rio .

Peer Review:
Two peer reviewers examined CAB and Pubmed search strategy, gave input that was applied to search strategy. Deanna Johnson and Megan Van Noord.

Total Records	Total Records after deduplication	Deduplication software/methodology
3,868	2,707	Mendeley, matches across fields and gives confidence. All suggested merges were approved.

Study Records:
Studies will be exported from Mendeley (Mendeley Ltd.) into a systematic review management software (DistillerSR, Evidence Partners Inc.; Ottawa, ON, Canada). Duplicates will be deleted.

Selection Process:
The process to select relevant records will include the following steps:
Title screening:
    a. Does the title describe the use of an antimicrobial treatment?
    b. Does the title indicate cattle as the subject of study?

Abstract screening:
    c. Does the study describe a controlled trial?
    d. Does the abstract describe a study of diarrhea in calves?
    e. Does the study describe one or more intervention groups of an antimicrobial treatment regimen?
    f. Are antimicrobial treatments given after the diagnosis of diarrhea?
    g. Does the study describe an outcome related to clinical cure or performance (i.e. growth)?

If the answers above are yes then, full manuscripts will be evaluated. A record will only need one reviewer to indicate it is relevant to be forwarded to the full-text relevance screening. Excluded records will be evaluated by two reviewers. If there is no consensus between the two reviewers, a third reviewer will be consulted.

Data Collection Process:
Citation searches will be collected using a citation management software (Mendely Ltd.). Eligible publications after title/abstract screening will be acquired as full manuscripts with the assistance of the UC Davis librarian. Relevant data will be extracted into a spreadsheet form (Excel 2010, Microsoft Corp., Redmond, WA).

The spreadsheet form will capture the following information:
- Population: location, year, calves age, weight, and breed.
- Eligibility criteria based on author's definition (i.e. scours, fever, unspecific signs of health disorder).
- Individuals evaluating clinical signs of health disorder prior to enrollment (researcher / owner / veterinarian / other).
- Individuals applying treatments (researcher / owner / veterinarian / other)
- Individuals evaluating clinical signs of health disorder after treatment (researcher / owner / veterinarian / other).
- Description of treatment protocol implemented (drug type, dose, route, frequency).
- Definition of treatment effectiveness (cure) based on author's definition (i.e. fecal score, fever).
- Time when outcomes were measured relative to treatment onset.
- Intervention of interest and the comparator group(s) (i.e. type of drug, route, dose, frequency).
- Results of binary (i.e. mortality and clinical cure) and continuous (i.e. time to cure, growth, intake and feed efficiency) outcomes will be extracted including: sample sizes, raw data or relative measure (RR,OR), effect size, variation of effect size, other variables controlled in the analysis such as age, breed, season or other.

The possible metrics will be extracted following the order below:
1. Adjusted summary effect size.
2. Unadjusted summary effect size.
3. Arm level risk of the outcome or mean of the outcome.
4. Variance components.

Risk of bias in Individual Studies:
Cochrane ROB 2.0 tool will be modified to evaluate the risk of bias (Higgins et al., 2016). https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool.

1. Randomization process: It is expected that some studies will not report randomization. Thus, randomization without describing the allocation approach will not be considered a risk of bias.
2. Deviations from intended interventions: Reasons for trial exclusion after intervention will be evaluated.
3. Missing outcome data: Bias due to loss to follow-up data will be evaluated, but it might not be relevant in randomized calf trials.
4. Measurement of the outcome: The outcome assessors might not be blinded to interventions but if the outcome is unlikely to be biased (i.e. temperature-fever) it will be listed as a low risk of bias.

5. Bias in selection of the reported results: Time to event (clinical cure), and differences in proportions of calves across studies.

Data Synthesis:

Network meta-analysis. Based on the approach described by NICE Decision Support Unit, a generalized linear modeling framework with a logit link will be use for the binary outcomes (clinical cure and mortality; Dias et al., 2014). The software of choice to perform the data analysis with be Stata (Statacorp LP; College Station, TX).

Meta-bias(es): Publication bias in the network of evidence will be carried out as described by Mavridis et al. (2014) and presented as a funnel plot.

Confidence in Cumulative Evidence: The quality of evidence for each outcome will be assessed using GRADE (GRADE, 2015, Puhan et al., 2014), while considering the nature of the network meta-analysis (Jansen et al., 2011). If feasible, we will use the CINeMA (Confidence In Network Meta-Analysis) web-based application platform, to evaluate the impact of risk of bias on study results.

Discussion:

The proposed systematic review and network meta-analysis will summarize the current evidence regarding the efficacy of antimicrobials used for the treatment of diarrhea in calves. It is anticipated that results will assist producers and veterinarians to make evidence-based decisions when treating calves. Lastly, the proposed systematic review will assist researchers to identify current gaps in knowledge related to the efficacy of antimicrobials to treat diarrhea in calves.

References:

Dias, S., N.J. Welton, A.J. Sutton, and A.E. Ades. 2014. NICE DSU technical support document 2: A generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Decision Support Unit. https://www.ncbi.nlm.nih.gov/books/NBK310366/pdf/Bookshelf_NBK310366.pdf

Higgins, J.P.T., A.C. Sterne, J. Savovic, M. J. Page, A. Hróbjartsson, I. Boutron, B. Reeves and S. Eldridge. 2016. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database of Systematic Reviews*, *10* (Suppl 1), 29-31 dx.doi.org/10.1002/14651858.CD201601

Jansen J.P., R. Fleurence, B. Devine, R. Itzler, A. Barrett, N. Hawkins, K. Lee, C. Boersma, L. Annemans, and J.C. Cappelleri. 2011. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect

Treatment Comparisons Good Research Practices: part 1. Value in health. 14:417-428. doi: 10.1016/j.jval.2011.04.002.

Puhan M.A., H.J. Schunemann, M.H. Murad, T. Li, R. Brignardello-Petersen, J.A. Singh, A.G. Kessels, G.H. Guyatt and G.W. Group. 2014. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 349: 5630. doi: https://doi.org/10.1136/bmj.g5630

Mavridis D., N.J. Welton, A. Sutton and G. Salanti. 2014. A selection model for accounting for publication bias in a full network meta-analysis. Stat Med. 2014 Dec 30;33(30):5399-5412. doi: 10.1002/sim.6321. Epub 2014 Oct 15.