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What is the efficacy of metaphylaxis using antibiotics for the prevention of Bovine Respiratory Disease in beef cattle?

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What is the efficacy of metaphylaxis using antibiotics for the prevention of Bovine Respiratory Disease in beef cattle?

Abstract
Bovine respiratory disease complex is the most economically significant disease of feedlot cattle. Putative causal organisms include Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis, bovine herpesvirus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza type 3 virus. Although vaccination against the putative causal organisms is a frequently used approach to aid in the prevention of BRD, it is also common and legal for antibiotics to be used for metaphylaxis at the arrival of beef cattle at feedlots. With a more significant concern for prudent antibiotic use in the beef industry, it is essential for decision making with regards BRDC management to understand the efficacy of metaphylaxis as a preventive management practice for BRDC. Systematic reviews of randomized controlled trials yield the highest level of evidence for the efficacy of treatment under field conditions, and comparative efficacy can be examined using network meta-analysis for multiple comparisons. Establishing the efficacy of metaphylaxis for the prevention of BRDC will serve to improve decision makers' ability to engage in effective stewardship of antibiotics.

Disciplines
Large or Food Animal and Equine Medicine | Veterinary Pathology and Pathobiology | Veterinary Preventive Medicine, Epidemiology, and Public Health

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PRISMA-P ITEM 1 Title

What is the efficacy of metaphylaxis using antibiotics for the prevention of Bovine Respiratory Disease in beef cattle?

PRISMA-P ITEM 2 Registration

This protocol is archived in the Iowa State University institutional repository 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 [1, 2]. This protocol is reporting using the items (headings) recommended in the PRISMA-P guidelines [3, 4].

PRISMA-P ITEM 3 Authors and contributions

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All authors contributed to the development of the review question and the methodology described in this proposal. HW and JG developed the search strategy. AOC drafted the protocol, with input and final approval of all co-authors.

PRISMA-P ITEM 4 Amendments:

None to report: 10th June 2018

PRISMA-P ITEM 5 Support: source, Sponsor, and role of funder

Funding support for this project, including the development of the protocol, was provided by The Pew Charitable Trusts. Pew will be provided versions of the protocol and drafts of the reviews for comment. The Parties agree that Work Product under this Project Agreement shall remain the property of the Subcontractors and/or Provider and be deemed Work Licensed to Pew, as such term is defined in Section 5.5 of the Terms and Conditions. The Parties agree further that Pew shall not modify any of the Work Product during the course of this Project Agreement, prior to its publication.

1 Introduction.

PRISMA-P ITEM 6 Rational:

Bovine respiratory disease complex is the most economically significant disease of feedlot cattle. Putative causal organisms include *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*, bovine herpesvirus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza type 3 virus. Although vaccination against the putative causal organisms is a frequently used approach to aid in the prevention of BRD, it is also common and legal for antibiotics to be used for metaphylaxis at the arrival of beef cattle at feedlots. With a more significant concern for prudent antibiotic use in the beef industry, it is essential for decision making with regards BRDC management to understand the efficacy of metaphylaxis as a preventive management practice for BRDC. Systematic reviews of randomized controlled trials yield the highest level of evidence for the efficacy of treatment under field conditions, and comparative efficacy can be examined using network meta-analysis for multiple comparisons. Establishing the efficacy of metaphylaxis for the prevention of BRDC will serve to improve decision makers' ability to engage in effective stewardship of antibiotics.

PRISMA-P ITEM 7 Objectives:

The objective of this protocol is to describe a systematic review to address the efficacy of metaphylaxis with antibiotics for the prevention of BRDC in feedlot cattle. The specific review questions to be addressed in this protocol are as follows:

What is the efficacy of metaphylaxis using antibiotics for the prevention of Bovine Respiratory Disease in beef cattle? The specific PICO elements, which will define the eligibility criteria, are as follows:

- *Population:* Weaned cattle raised for meat in intensive systems at risk of BRDC, i.e., feedlot cattle. Calves explicitly described as veal or dairy calves are excluded from consideration.

- *Intervention:* Parentally metaphylactic use of antibiotics at the feedlot with 48 hours of arrival. Metaphylactic use is defined as "medicating a group of animals to prevent the occurrence of disease when a disease outbreak is expected". We consider the distinction between prophylactic and metaphylactic uses to be of mainly of academic interest. We are interested in approaches to medicating animals before they show clinical signs of BRD when it expected that are at risk of BRD.

- *Comparator:* No antibiotics at arrival or an alternative antibiotics metaphylaxis.

- *Outcomes:* Critical outcomes will be the cumulative incidence of first-treatment for BRDC in the first 45 days of the feedlot period. Secondary outcomes will be the cumulative incidence of first-treatment rate BRDC in the entire feedlot period and BRDC mortality in the entire feed period.

2 Methods

PRISMA-P ITEM 8 Eligibility criteria:

In addition to eligibility criteria as described in the PICO elements described above, eligibility criteria will include publication in English. Both published and unpublished (grey literature) studies are eligible, provided they report a primary research study with a concurrent comparison group using an eligible study design. Eligible designs will be trials with a concurrent control group conducted in feedlot settings, i.e., groups of penned cattle receiving rations rather than grazing on pasture. Studies must describe a trial where the investigator selected the allocation. Cluster–randomized controlled trials (C-RCT) or individually – randomized controlled trials (I-RCT) are eligible, although we anticipate all will be C-RCT.

PRISMA-P ITEM 9 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®, MEDLINE In-Process and MEDLINE® Daily Epub Ahead of Print	Ovid SP
CAB Abstracts	(via Web of Science)
Science Citation Index	(via Web of Science)
Conference Proceedings Citation Index – Science	(via Web of Science)
Agricola	Proquest

We will also hand-search the table of contents of the following relevant conferences from 1997 to 2018:

- Proceedings of the American Association of Bovine Practitioners;
- World Association for Buiatrics;
- USDA FDA FOI requests for antibiotics registered for metaphylaxis use in the USA

We will also check the reference lists of any included studies for any eligible studies that may have been missed by the database searches.

PRISMA-P ITEM 10 Search strategy:

A Science Citation Index (Web of Science) search strategy designed to identify studies on the efficacy of metaphylaxis using antibiotics for the prevention of BRD in beef cattle is presented in Table 2

The search strategy employs three concepts:

- Beef cattle

AND

- BRD

AND

Metaphylaxis

Table 2:Search strategy to identify studies the efficacy of metaphylaxis using antibiotics for the prevention of BRD in beef cattle in Science Citation Index (Web of Science)

# 10	#9 AND #2 AND #1	338

# 9	#8 OR #7 OR #6 OR #5 OR #4 OR #3	291,929
# 8	TS=((arrival* OR arrive* OR "arriving" OR "entry" OR enter*) NEAR/5 (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* OR "amoxicillin" OR "amoxycillin" OR "ampicillin" OR "erythromycin" OR "ceftiofur" OR "cloxacillin" OR "danofloxacin" OR "enrofloxacin" OR "florfenicol" OR "gentamycin" OR "gentamicin" OR "lincomycin" OR "oxytetracycline" OR "penicillin" OR "spectinomycin" OR "sulfamethoxazole" OR "tilmicosin" OR "trimethoprim" OR "tulathromycin" OR "tylosin" OR "gamithromycin" OR "tildipirosin"))	8,411
# 7	TS=(("mass" OR "blanket" OR prevent*) NEAR/5 ("amoxicillin" OR "amoxycillin" OR "ampicillin" OR "erythromycin" OR "ceftiofur" OR "cloxacillin" OR "danofloxacin" OR "enrofloxacin" OR "florfenicol" OR "gentamycin" OR "gentamicin" OR "lincomycin" OR "oxytetracycline" OR "penicillin" OR "spectinomycin" OR "sulfamethoxazole" OR "tilmicosin" OR "trimethoprim" OR "tulathromycin" OR "tylosin" OR "gamithromycin" OR "tildipirosin"))	1,241
# 6	TS=(("mass" OR "blanket") NEAR/5 (medicat* OR "dosing" OR "administration"))	3,091
# 5	TS=(("population wide" OR "whole population*") NEAR/5 (treatment* OR therap* 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*))	106
# 4	TS=(("mass" OR "blanket" OR prevent*) NEAR/5 (treatment* OR therap* 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*))	148,469
# 3	TS=(prophyla* OR metaphyla* OR "meta-phyla*")	141,094
# 2	TS=("respiratory disease*" OR "respiratory tract disease*" OR "respiratory virus*" OR "respiratory tract virus*" OR "shipping fever" OR "undifferentiated fever" OR "BRD" OR "BRDC" OR "pasteurellosis" OR "pasteurella multocida" OR "p multocida" OR "mycoplasma" OR pneumonia* OR pleuropneumonia* OR "pneumonitis" OR "pneumonitides")	217,568
# 1	TS=("cow" OR "cows" OR "cattle" OR heifer* OR "steer" OR "steers" OR "bull" OR "bulls" OR "calf" OR "calves" OR "youngstock*" OR "young-stock*" OR "beef" OR "veal" OR "bovine" OR "bovinae" OR buiatric*)	524,340

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 agreed strategy appropriately to reflect the differences in database interfaces and functionality.

We will document all search strategies and search results, and we will provide this in the final report to meet standard requirements for clear and formal reporting of the search process. We will conduct the literature search in a range of relevant bibliographic databases and other information sources containing both published and unpublished literature.

PRISMA-P ITEM 11 Study records:

Data management: We will download the results of searches in a tagged format and load them into bibliographic software (EndNote). The results will be deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required. We will save results from resources that do not allow export in a format compatible with EndNote in Word or Excel documents as appropriate and manually de-duplicate. The de-duplicated search results from EndNote will be uploaded into online systematic review software (DistillerSR®, Ottawa, ON, Canada). Reviewers will have training in epidemiology and systematic review methods. Before 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 inclusion. Two reviewers will independently evaluate each citation for relevance using the following questions:

1) Does the study involve assessment of a metaphylaxtic use of antibiotics for the prevention/control of bovine respiratory disease in feedlot cattle?

- Yes/Unclear- next question
- No –exclude

2) Is there a concurrent comparison group? (i.e., controlled trial with natural or deliberate disease exposure or analytical observational study)?

- Yes/Unclear- include for full-text assessment
- No –exclude

Citations will be excluded if both reviewers respond “no” to any of the questions. If one reviewer says "yes", the citation will move to full-text assessment. A pre-test will be conducted by all reviewers on the first 100 abstracts to ensure clarity of questions and consistency of understanding of the questions. Following title/abstract screening, eligibility will be assessed through full-text screening. The same questions will be used as for the title / abstract screening for citations with the full-text available in English. 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 consulted.

1) Correct population: Is the study population, weaned cattle in a non-grazing situation that are at risk of developing BRDC naturally, i.e., feedlot cattle?

- Yes- next question
- No –exclude

2) Correct Interventions and Comparator: Does the study assess the use of antibiotics, at a registered dose for metaphylaxis for prevention/control of BRDC in feedlot cattle?

- Yes- next question
- No –exclude

3) Correct outcome: Does the study report the risk of BRDC in the study groups?

- Yes- next question -
- No- exclude

4) Correct study design: Is the study a field trial, where an investigator is allocating animals to the intervention group- randomized or non-randomized?

- Yes- include in data extraction
- No –challenge study (indicate the antibiotic(s) studied)
- No - observational study (the investigator did not allocate to the group – allocation was chosen by producers or owner)

Data collection process: Data will be extracted by two reviewers working independently. Consensus will resolve any disagreements or, if consensus cannot be reached, a third reviewer will be consulted. 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.

PRISMA-P ITEM 12 Data items:

Study-level data collected:

- Country
- Location
- Year of conduct
- Breed
- Age (entire group or control group data if provided)
- Weight (entire group or control group data if provided)
- Definition of BRDC
- No of animals eligible for the study
- Unit of allocation (Cluster (pen) or individual)
- Approach to allocation
- The endpoint for cumulative incidence estimate

Arm-level data collected:

- Antibiotic label dose regime –As with the prior review, data will be aggregated between treatment arms within a trial if the difference between those treatment arms was due to a difference in the post-metaphylactic interval or route of antimicrobial administration or a comparison of doses on the same label
-
- Trade name as reported by investigators
- The timing of administration compared to the arrival
- Number of animals enrolled
- Number of animals lost to follow up
- Number of animals analyzed
- Number of clusters for C-RCT
- For C-RCT, the approach to the analysis of non-independent observations i.e., not reported, "multilevel model", a "variance components analysis" or may use "generalized estimating equations" (GEEs), among other techniques.

For non-randomized studies, the only information extracted will be the antibiotic label dose regime and trade names used for the study. This information will be most useful when deciding what, if any important , studies had been conducted using a non-randomized trial.

PRISMA-P ITEM 13 Outcomes and prioritization:

For the primary outcome of interest, the risk of BRDC in the first 45 days. When multiple dates are available, we will select the one closest to 28 days. We will extract the possible metrics for BRDC risk in the following order.

For C-RCT and I-RCT (few/non expected)

- 1st priority: Adjusted summary effect size ($_{adjusted}$ risk ratio or $_{adjusted}$ odds ratio), variables included in adjustment, precision estimate and variance components estimates.
- 2nd priority: Unadjusted summary effect size and corresponding precision estimate
- 3rd priority: Arm-level risk of BRDC

Prioritization means we will not collected the additional metrics if the prioritized metric is reported. The rationale for the prioritzation is that the meta-analysis should use an adjusted summary effect, as most relevant (all) studies are cluster randomized trials, and therefore the other metrics will require conversion to the summary effect.

The secondary outcomes are first-treatment rate of BRDC in the entire feedlot period and second-treatment rate for BRDC, and we will prioritize the same metrics.

PRISMA-P ITEM 14 Risk of bias in individual studies:

Risk of bias will be assessed for controlled trials with natural disease exposure. Risk-of-bias assessment will be performed at the outcome level for each of the critical outcomes using the Cochrane risk of bias instrument (Higgins et al., 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 upon the study design [5]. These tools are available at https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool.

PRISMA-P ITEM 15 Data synthesis:

Network meta-analysis. Network meta-analysis (aka mixed treatment comparison meta-analysis) will use the approach described by NICE Decision Support Unit technical document [6-9]. The approach to reporting will use the PRISMA- NMA (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx). For cluster-randomized trials, it will be necessary to verify that the potential for a unit-of-analysis error did not bias the estimate of precision. When the unit of analysis was not adjusted, we will use the approach previously proposed to adjust for non-independent observations [10]. If network meta-anlaysis can not be preformed, we will conduct pairwise meta-analyses.

PRISMA-P ITEM 16 Meta-bias(es):

Small-study effects ("publication bias") will be assessed using funnel plots for all vaccine-comparator combinations where there are at least ten studies in the meta-analysis. If feasible, we will use approaches to assessing publication bias in the network of evidence using previously proposed approaches [11, 12].

PRISMA-P ITEM 17 Confidence in cumulative evidence:

The quality of evidence for each critical outcome will be assessed using the approach proposed by GRADE [13, 14], while also considering the nature of the network meta-analysis [15, 16].

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