PRISMA-P ITEM 1 Title:

What is the efficacy of viral and bacterial vaccines in feedlot cattle to reduce bovine respiratory disease (BRD) and subsequent antibiotic use?

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]. This protocol is reporting using the items (headings) recommended in the PRISMA-P guidelines[2, 3].

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 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 Rationale"

Bovine respiratory disease complex is the most economically significant disease of feedlot cattle[4]. 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[5].

Vaccination against the putative causal organisms is a frequently used approach to aid in the prevention of BRD. With a more significant concern for prudent antibiotic use in the beef industry, it is vital that decision making with regards BRDC management be based on an understanding of the efficacy of vaccination programs and management factors that might modify the efficacy of the preventive management practice[6, 7]. 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 monovalent and polyvalent vaccinations for the prevention of BRDC in feedlot cattle 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 vaccination against putative organisms for BRDC. The specific review questions to be addressed in this protocol are as follows:

What is the efficacy of bacterial and viral vaccines (alone or in combination) administered at arrival to prevent BRDC in feedlot 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
- *Intervention:* Commercially available in any country viral and/or bacterial vaccines used alone or in combination
- *Comparator:* placebo, different vaccination regime, or no treatment.
- *Outcomes:* Critical outcomes will be the cumulative incidence of first-treatment rate 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 second-treatment rate for BRDC

2 Methods

PRISMA-P ITEM 8 Eligibility criteria:

In addition to eligibility criteria as described in the PICO elements above, eligibility criteria will include publication in English. Both published and non-published (grey literature) studies are eligible, provided they report a primary research study with a concurrent comparison group using an eligible study design. Controlled trials (i.e., with a concurrent control group) conducted in feedlot settings (groups of cattle penned receiving rations, i.e., not grazing), cluster–randomized controlled trials (C-RCT), or individually randomized controlled trials (I-RCT) are eligible.

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. **Error! Reference source not found.**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;

PRISMA-P ITEM 10 Search strategy:

A Science Citation Index (Web of Science) search strategy designed to identify studies on the efficacy of viral and bacterial vaccines in feedlot cattle to reduce bovine respiratory disease (BRD) is presented in Table 2

The search strategy employs three concepts:

- Beef cattle

AND

- BRD, or the viruses and bacteria known to cause BRD

AND

Vaccination

The search is structured so that the searches for viral vaccines are performed separately to those for bacteria vaccines within a single strategy. This is because an existing 2015 systematic review assessed the efficacy of commercially available viral vaccines for mitigation of the effects of bovine respiratory disease complex.[6] A conceptual breakdown of

beef cattle AND (BRD OR BRD viruses) AND vaccination

is therefore limited to studies published from 2014 to current in order to update this review (Figure 1, line 11).

Bacterial vaccines are captured with the following conceptual breakdown that is unlimited by date (Figure 1, line 16).

beef cattle AND BRD bacteria AND vaccination

The results of both the viral and bacterial searches are combined in line 17 to give a total number of records for all vaccines.

Table 2: Search strategy to identify studies on the efficacy of viral and bacterial vaccines in feedlot cattle to reduce bovine respiratory disease (BRD) in Science Citation Index (Web of Science) All search except #11 are Indexes=SCI-EXPANDED Timespan=All years

# 17	#16 OR #11	1,177
# 16	#15 AND #9 AND #1	724
# 15	#14 OR #13 OR #12	27,864
# 14	TS=("pasteurella multocida" OR "p multocida" OR "mycoplasma")	25,456
# 13	TS=("haemophilus somn*" OR "hemophilus somn*" OR "histophilus somn*" OR "h somnus" OR "h somni")	606
# 12	TS=("mannheimia haemolytica" OR "mannheimia hemolytica" OR "m haemolytica" OR "m hemolytica" OR "pasteurella haemolytica" OR "pasteurella hemolytica" OR "p haemolytica" OR "p hemolytica" OR mannheimios*)	2,525
# 11	#10 (Indexes=SCI-EXPANDED Timespan=2014-2018)	563
# 10	#9 AND #8 AND #1	3,219
# 9	TS=(vaccin* OR immunis* OR immuniz* OR innoculat*)	351,581
# 8	#7 OR #6 OR #5 OR #4 OR #3 OR #2	284,032
# 7	TS=("parainfluenza3" OR "influenza3" OR "parainfluenza 3" OR "influenza 3" OR "parainfluenza three" OR "influenza three" OR "parainfluenza type 3" OR "influenza type 3" OR "parainfluenza type three" OR "influenza type three" OR "PI-3" OR "PI3")	17,417
# 6	TS=("respiratory syncytial virus*" OR "BRSV" OR "RSV")	19,370
# 5	TS=("BVD" OR "BVDV" OR "BVDV1" OR "BVDV2" OR "pestivirus" OR "coronavirus" OR "BCV")	15,842
# 4	TS=(("viral" OR "virus" OR "viruses") NEAR/3 (diarrhoea* OR diarrhea*))	6,386
# 3	TS=(herpesvirus* OR "herpes virus*" OR herpesviridae* OR "herpes viridae*" OR "BoHV-1" OR "BoHV1" OR "BHV-1" OR "BHV1" OR "BHV" OR "BoHV" OR "rhinotracheitis" OR "rhinotracheitides" OR "IBRV" OR "IBR")	37,021
# 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 pneumonia* OR pleuropneumonia* OR "pneumonitis" OR "pneumonitides")	201,492
# 1	TS=("cow" OR "cows" OR "cattle" OR heifer* OR "steer" OR "steers" OR "bull" OR "bulls" OR "calf" OR "calves" OR	524,340

	"youngstock*" OR "young-stock*" OR "beef" OR "veal" OR "bovine" OR "bovinae" OR buiatric*)	

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

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 deduplicate. 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 vaccines for the prevention 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 responded “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. 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.

1) Correct population: Is the study population, weaned calves in a non-grazing situation with naturally occurring BRDC, i.e., feedlot cattle?

- Yes- Next question

- No –exclude

2) Correct Interventions and Comparator: Does the study assess the use of a commercially available monovalent or polyvalent vaccine for one of the following organisms (*Mannheimia haemolytica*, *Pasteurella heamolytica*, *Pasteurella multocida*, *Histophilus somni* or *Mycoplasma bovis*, bovine herpesvirus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza type 3 virus)?

- 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 group) with naturally occurring BRDC?

- Yes- include in data extraction study
- No –Challenge study (indicate the organism(s) studied)
- No - Observational study (the investigator did not allocate to the group – allocation was chosen by producers or owner, indicate the organism studies)

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 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.

PRISMA-P ITEM 12 Data items:

Study-level data to be 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 study

- Unit of allocation (Cluster (pen) or individual)
- Approach to allocation

Arm-level data to be collected:

- Vaccine name – as reported by investigators
- Target organism(s)
- Dose/ Route/ Frequency of administration
- Timing of vaccination compared to 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 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, risk of BRDC in the first 60 days, we will extract in the following order of possible metrics:

For C-RCT and I-RCT

- 1st priority: Adjusted summary effect size ($_{adjusted}$ risk ratio or $_{adjusted}$ odds ratio), variables included in adjustment, precision estimate and variance components estimatesf for C-RCTs.
- 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 of reported. The rationale for the prioritzation is that the meta-analysis should use an adjusted summary effect for most of these studies. Although we expect that many will be I-RCTand 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 only 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, with the signaling questions modified as necessary for the specific review question. The ROB 2.0 for clustered –RCT and individual RCTs will be used depending upon the study design [8]. 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 The approach to reporting will use the PRISMA- NMA (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx)[9-14]. 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. If network meta-analysis can not be conducted due to spare data we will conduct pairwise meta-analyses.

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

Small-study effects ("publication bias") will be assessed for all vaccine-comparator combinations, where there are at least ten studies in the meta-analysis, using funnel plots[15, 16]. If feasible, we will use approaches to assessing publication bias in the network of evidence using previously proposed approaches .

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 [17, 18]while also considering the nature of the network meta-analysis.

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