PRISMA-P ITEM 1 Title

A Protocol for a Systematic Review and Meta-Analysis of Efficacy of Infectious Bovine Keratoconjunctivitis and assessment of comprehensiveness of reporting

PRISMA-P ITEM 2 Registration

This protocol will be archived in the Iowa State University Digital 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 [2, 3].

PRISMA-P ITEM 3 Authors

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Contributions

O. Weaver drafted the protocol. All authors helped develop the selection criteria, the risk of bias assessment strategy and data extraction criteria. O. Weaver developed the search strategy. A.M O'Connor provided statistical expertise. A.M O'Connor provided expertise on infectious bovine keratoconjunctivitis. All authors read, provided feedback and approved the final manuscript.

PRISMA-P ITEM 4 Amendments

N/A

PRISMA-P ITEM 5 Support

This systematic review and meta-analysis, including the development of the protocol, was not supported by any external funding.

Introduction

PRISMA-P ITEM 6 Rationale

Infectious bovine keratoconjunctivitis, commonly known as pinkeye, limits production and weight gain in pre-weaned calves, resulting in significant economic loss each year. IBK is one of the most common diseases in pre-weaned calves which leads to clinical signs from mild conjunctivitis to severe ulceration, corneal perforation, and blindness [4]. Due to large economic losses and limits in production and weaning weight, use of effective vaccines to prevent IBK is imperative.

Moraxella bovis is the primary causal organism of IBK [4, 5]. However, available evidence does not suggest that vaccination is effective for preventing naturally occurring IBK. Although individual studies and a prior review conducted over a decade ago [4, 6, 7] suggested that autogenous and commercial IBK vaccines are not effective, a systematic review of vaccine efficacy has not been conducted recently. Further, the review conducted by Burns and O'Connor (7), was conducted using an approach not consistent with current systematic review quality standards, therefore it is of interest to know if the results of that review are repeatable. In particular, that review found strong evidence of

small study effects, and an association failure to report randomization and blinded outcome assessment and vaccine effect size. However, the study did not evaluate the effect of challenge studies, another cause of small study effects The AMSTAR standards [8] is a frequently used metric for assessing the quality of systematic reviews and the Burns and O'Connor (7) review, of which one of us was the lead author, fails to meet many of those standards.

PRISMA-P ITEM 7 Objectives

The primary purpose of this review is to summarize the efficacy of IBK vaccines using current approaches to research synthesis [9]. The secondary outcome, we will seek to assess the impact of sources of heterogeneity on the effect size. The methodological sources of heterogeneity of interest are: failure to randomize to treatment group, and blind outcome assessment, are associated with the effect size. The contextual sources of heterogeneity are the vaccine type: autogenous (farm specific vaccine), experimental, commercially available (has a "brand name"). The third outcome is to assess if reporting of the IBK vaccine trials had improved since the publication of the Burns review [7].

Methods

PRISMA-P ITEM 8 Eligibility criteria

Population: The eligible population consists of beef and dairy calves less than one year old at risk of developing naturally occurring IBK or experimentally induced IBK. Studies of vaccine efficacy in adult cattle will be excluded. The country of IBK occurrence will not be used as an exclusion factor.

Interventions and comparator: Eligible interventions and comparators include any vaccination that is not banned for use in cattle and non-active placebos. The review is not specifically limited to products registered for prevention of IBK.

Outcome: The primary outcome of interest is the number of cattle with IBK compared to the unvaccinated. This is a binary outcome. If investigators use an ordinal score this will be converted to a binary outcome: IBK or no IBK based on the description provided by the investigators.

Study designs: Eligible studies consist of trials where the investigator had the opportunity to randomize animals to group. The comparison must occur concurrently. Studies will not be limited by publication year and studies published in languages other than English will be noted but not included.

PRISMA-P ITEM 9 Information sources

All available years will be searched in MEDLINE through Web of Science and the Center for Biosciences and Agriculture International (CABI) databases. Reference lists of relevant manuscripts and the table of contents from the last 20 years of the proceedings of the American Association of Bovine Practitioners (AABP) and World Buiatrics Association will be reviewed. Recent review manuscripts of IBK will be examined for additional reports potentially missed by our database search.

PRISMA-P ITEM 10 Search strategy

The goal of the search is to find all relevant studies that would give information to support our research question. Therefore, the database search strategy included "population" AND "intervention" AND "outcome". The proposed search strategy for CABI is listed in Table 1.

PRISMA-P ITEM 11 Study records

Data management

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 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, two reviewers will independently screen abstracts and titles obtained from the search. The reviewers evaluate each citation for relevance using the following questions:

1) Does the title or abstract indicate primary research?

    a) Yes- next question

    b) No- exclude

2) Does the title or abstract describe a trial (field or challenge) for vaccine efficacy in IBK or pinkeye in cattle?

    a) Yes- next level for full text assessment

    b) No- exclude

Citations will be excluded if both reviewers responded "no" to either of the questions. Full manuscripts will be acquired if one reviewer identifies the title and/or abstract potentially relevant. The citations will be further assessed for relevance using the following questions:

1) Is the full text available in English?

    a) If no, please indicate the language

2) Correct Population: Does the study population have naturally occurring or experimentally included IBK or pinkeye?

    a) Yes- next question

    b) No- exclude

3) Correct Population: Is the study population composed of healthy beef or dairy cattle likely to be younger than one year of age (no immune compromised disease models)?

    a) Yes- next question

    b) No- exclude

4) Does the study assess a vaccine for preventing IBK?

    a) Yes- next question

    b) No- exclude

5) Does the study have a concurrent comparison group?

    a) Yes- next question

    b) No- exclude

6) Does the study report the incidence (risk/proportion) of cases of IBK in both the intervention and control groups or a score that could be converted to a proportion?

a) Yes- study eligible for data extraction

b) No- exclude

Data collection process

Data extraction will be done independently by two reviewers using DistillerSR. The data extraction process will be piloted and refined to extract and confirm relevant information is obtained in one phase rather than re-visiting each paper multiple times. This process will increase validity and efficiency.

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 IBK provided by the investigators
- Number of animals eligible for study
- Approach to allocation
- Duration of observations for IBK
- Approach to allocation used by the researchers
    - Random
    - Systematic allocation
    - Other
    - Not described

Arm level data collected

- Vaccine name – as listed by investigators
- Target organism(s)
- Type of vaccine – autogenous (commercially made), commercial registered, experimental
- Dose/ Route/ Frequency of administration
- Timing of vaccination compared to arrival

- Number of animals enrolled in the group
- Number of animals lost to follow up

PRISMA-P ITEM 13 Outcomes and prioritization

The primary outcome of interest is the risk of IBK, more specifically, the proportion of cattle diagnosed with pink eye that received the vaccine compared to those with pink eye but without the vaccine. For the primary outcome of interest, risk of IBK, we will extract in the following order of possible metrics

- Adjusted summary effect size (RR or OR) and variables included in adjustment
- Unadjusted summary effect size summary measures
- Arm level risk of BRDC

PRISMA-P ITEM 14 Risk of bias in individual studies

The risk of bias (ROB - https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool) assessment tools proposed by Cochrane ROB 2 will be used for individual trials.

PRISMA-P ITEM 15 Data synthesis

As the vaccine antigens are varied it is not reasonable to expect that all are measuring the same thing, therefore, we will conduct a pairwise analysis on the following sub groups 1) An autogenous vaccine intended for use on farm to prevent IBK (perhaps made by a company or described by the investigator as such) compared to no vaccines, 2) commercially available *M. bovis* vaccine compared to no vaccines 3) commercially available *M. bovoculi* vaccines compared to no vaccines. We will assess heterogeneity using standard methods for pairwise meta-analysis and subgroups of interest will be randomized allocation or blinded outcome assessment.

The 2nd analysis will look at the association between the three design elements, (randomized allocation or blinded outcome assessment and challenge study) and estimate of vaccine effect for all studies – autogenous, commercial and experimental vaccine. The 2nd analysis will also look at the association between the 5 ROB domains and estimate of vaccine effect, again for all studies - autogenous, commercial and experimental vaccine. We will assess the association between magnitude of comprehensive reported and vaccine effect.

PRISMA-P ITEM 16 Meta-bias(es)

Factors associated with small study effects (“publication bias”) will be assessed for all vaccine-comparator combinations regardless of type of vaccines. The goal here is to evaluate if the association between effect size and study size reported by Burns and O'Connor (7) was robust, further we will evaluate if the type of study design (challenge, autogenous, and commercial) was associated with small study effects.

PRISMA-P ITEM 17 Confidence in cumulative evidence

We will interpret the results of the pairwise meta-analysis based on standard interpretation. We will assess the impact of bias, reporting and design elements on the effect size using standard interpretation.

References:

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8. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ-British Medical Journal. 2017;358. doi: ARTN j4008

10.1136/bmj.j4008. PubMed PMID: WOS:000411858600004.
9. Sargeant JM, O'Connor AM. "One-Stop Shopping' for Information on Conducting Systematic Reviews and Meta-Analysis in Animal Agriculture and Veterinary Medicine. Zoonoses Public Hlth. 2014;61:2-. doi: 10.1111/zph.12130. PubMed PMID: WOS:000337585400002.

Table 1: Literature review search terms for the Centre for Biosciences and Agriculture International (CABI) databases.

Population	Hits
TS=(**cow, OR cows, OR** cattle, **OR** calves, OR calf, **OR heifer*,** OR **steer, OR steers, OR bull, OR bulls, OR youngstock*, OR "young-stock", OR** bovine, OR beef, **OR dairy**, OR **bovinae, OR buiatric***)	639,313
Intervention	
TS=(vaccin*, OR immuniz***, OR immunis*, OR innoculat*)**	371,156
Outcome	
TS=(**"kerato-conjunctivitis", OR conjunctivitis, OR** keratoconjunctivitis, OR IBK, OR pinkeye, OR 'pink eye', OR pink-eye OR Moraxella OR "New Forest eye")	14,645
Population AND Intervention AND Outcome	
#1 AND #2 AND #3	109