**Title**

# A protocol for an update of the systematic review of antibiotic treatment options for naturally occurring infectious bovine keratoconjunctivitis in cattle

**Registration**

NA

**Authors**

J.N. Cullen[1], jncullen@iastate.edu; J.F. Coetzee[1], hcoetzee@iastate.edu; C. Wang[1], chwang@iastate.edu; A.M. O'Connor[1,3], oconnor@iastate.edu

[1] Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA, USA

[2] Department of Statistics, Iowa State University, Ames, IA, USA

[3] Corresponding Author

Contributions:

A. O'Connor contributed the question and the development of all parts of the protocol. J. Cullen contributed to assessing the updating the search, redesign of the screening tools and design of data extraction tools. J. Coetzee assessed the adequacy of the terms for identifying relevant antibiotics. C Wang assess the adequacy of the proposed meta-analysis methods.

**Amendments**

NA

**Support**

NA

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## Introduction

**Rationale**

Infectious bovine keratoconjunctivitis (IBK), commonly referred to as pinkeye, is one of the most important production-limiting diseases of pre-weaned calves. IBK produces a range of

ocular clinical signs including lacrimation, photophobia, corneal edema, ocular pain, corneal ulceration, and potential loss of vision(Brown et al., 1998). The disease also has an impact on production. Weaning weight is decreased by 15lb to 30lb in IBK affected calves and differences in the weight between affected and unaffected animals have been observed out to 15 months of age(Thrift and Overfield, 1974; Funk et al., 2009; O'Connor et al., 2011; Funk et al., 2014). *Moraxella bovis* is a causal pathogen associated with IBK. Evidence would suggest that prevention of IBK with commercially available vaccines or farm-of-origin *Moraxella bovis* or *Moxaella bovoculi* based autogenous vaccines is of limited or no effect (Funk et al., 2009; O'Connor et al., 2011). To date, no randomized controlled trial reporting the efficacy of *M. bovis* based vaccines are publically available. A review of IBK vaccines in 2008 observed decreased vaccine efficacy when sources of bias were minimized i.e. randomization and outcome assessor blinding(Burns and O'Connor, 2008). Without further research supporting an effective vaccine program, antibiotic therapy is potentially the best method for limiting the impact of IBK. Using a systematic review strategy for a literature search identified only nine high quality randomized clinical trials for the treatment of IBK with antibiotics in 2006(O'Connor et al., 2006). While the studies generally reported favorable treatment results, very few conducted active-to-active treatment designs in favor of placebo or non-medicated control arms.(O'Connor et al., 2006) Furthermore no antibiotic regime was employed more than once precluding a pairwise meta-analysis approach for any drug comparison(O'Connor et al., 2006). In the subsequent 10 years, it is likely additional trials have been published including active-to-active designs and the statistical methods of network meta-analysis for comparing multiple treatment options have become available. Therefore the purpose of this project is to update the prior review and if feasible to conduct a mixed treatment comparison meta-analysis. This analysis will enable

clinicians and producers to make more informed decisions regarding the best antibiotic treatment strategy using a network of publically available information.

**Objectives**

The objective of the study is to use a mixed treatment comparison (MTC) meta-analysis of controlled trials to compare antibiotic treatment efficacy for IBK in beef or dairy animals. The review question is "What is the comparative efficacy of antibiotics for the treatment of IBK in beef and dairy animals?" Efficacy will mainly be measured as cure risk based on the authors definition of corneal lesion resolution. Secondary outcomes of interest include any weight related production outcomes

# Methods

**Eligibility criteria**

The eligible population consists of beef and dairy animals diagnosed with naturally occurring IBK associated with *Moraxella* spp., *Neisseria* spp., and *Branhamella catarrhalis* (reclassified as *Moraxella catarrhalis)* OR as defined as pinkeye or IBK by the authors of the original paper where bacterial isolation was not attempted. Age of the enrolled animal will not be used as an exclusion factor. Country of IBK occurrence will not be used as an exclusion factor.

Eligible interventions and comparators include any antibiotic treatment that is not banned for use in cattle (Group 1 and Group 2 on the FARAD list on day accessed – 3rd Sept 2015, (http://www.farad.org/eldu/prohibit.asp)) and non-active placebos. Non-antibiotic treatments or multidrug interventions such as antibiotics with anti-inflammatory or antibiotic combined with antibiotics will not be eligible. The rationale for not including these therapies is that unless factorial designs are used it will not be possible to attribute the effect to a component of the treatment. The review is not specifically limited to products registered for treatment of IBK.

The primary outcome of interest is the number of unhealed corneal ulcers at 21 days post treatment or time frame closest where applicable. A secondary outcome of interest is data on production outcomes that reflect weight gain, which is total weight gain or average daily gain (ADG).

Eligible studies will be controlled randomized trials that allocate individual animals to treatment arms. Eligible reports will be in English from all years indexed within the searched databases (see “Information sources” below). Only studies conducted in the field using naturally occurring disease are considered relevant to the review.

**Information sources**

All available years will be searched in MEDLINE and the Centre 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. The Food and Drug Administration (FDA) Freedom of Information (FOI) Summaries database will also be searched for approved cattle antibiotics. Recent review manuscripts of IBK will be examined for additional reports potentially missed by our database search.

**Search strategy**

The database search strategy will be "population" AND "disease" AND "intervention". For MEDLINE, "Drug Therapy", "Injections", and "Anti-Bacterial Agents" will be searched as Medical Subject Headings (MeSH). For CABI, "drug therapy", "injection", and "antibacterial agents" will also be searched as Descriptors (DE). The search strategy for CABI is listed in Table 1.

**Study records**

*Data management*

An online systematic review software will be used to manage literature records and data.

*Selection process*

At least two reviewers will independently read all abstracts/summaries identified from the search. Full reports will be acquired if one reviewer identifies the abstract as potentially relevant. The full manuscripts will be further assessed for relevance by at least two reviewers and if again deemed relevant, all data will be extracted. Assessment of relevance forms were pilot tested by the reviewers using ~20 reports.

The 1st level (abstract/ title) screening questions:

1. Does the title or abstract indicate primary research describing a trial for the antibiotic treatment of IBK or pinkeye in dairy or beef cattle?

The 2nd level (full text) screening questions:

1. Is the full text available in English?
2. Is the study population made up of beef or dairy cattle of any age or weight?
3. Does the study population have naturally occurring IBK or pinkeye as defined by the authors or conjunctivitis associated with Moraxella spp., Neisseria spp., or Branhamella spp. infection / recovery ?
4. Does the study assess antibiotic treatment(s) alone, without other components (e.g. antibiotic with an anti-inflammatory)?
5. Does the study have a comparison group that is either a placebo or active comparison?
6. Does the study report the incidence (risk/proportion) of unhealed corneal ulcers as defined by the authors as the outcome of interest?
7. Does the study describe random allocation to group?
8. Does the study report the arm level mean production outcomes?

9. Is the unit of allocation and outcome assessment at the individual level?

*Data collection process*

Data extraction will be completed independently by at least two reviewers. We pilot tested the data extraction process and refined the forms until suitable for the review with two reports. Data will be extracted independently by at least two reviewers from all eligible manuscripts. In the event the same study is obtained from multiple sources (i.e. conference proceedings and a manuscript from MEDLINE), the different sources will be combined to obtain the most complete trial description.

**Data items**

The study is the unit of concern for data extraction and studies will be extracted separately for manuscripts with more than one study. Extracted data will include study level and group level information.

*Study level information*

Country of conduct, year of conduct, age, weight, gender, breed of cattle involved, duration of study observation period, concurrent vaccinations, production system (dairy/beef/not described), summary effect measure for IBK cure if reported, mean difference in weight gain or ADG if reported, standard error of the mean, or 95% confidence interval (CI) of mean difference.

*Arm level information*

Interventions used in each arm (drug, dose, route, duration) total number of cattle in trial arm, number of events (unhealed corneal lesions) in trial arm at the end of study period, mean production outcome per trial arm, SD of mean production outcome per trial arm, pharmaceutical sponsorship of treatment, description of blinding of outcome assessment included (yes/no), description of use of randomization to group (yes/no), use of systematic allocation to treatment

arm (yes/no), and use of allocation restrictions (blocking by time, blocking by weight, stratification by severity, stratification by sex).

**Outcomes and prioritization**

The primary outcome of interest is the number cattle experiencing unhealed corneal lesions at approximately 21 days post treatment. The secondary outcome of interest will be production measures that indicate weight such as total weight or average daily gain (ADG).

**Risk of bias in individual studies**

The Cochrane Risk of Bias Scale for intervention studies will be used to assess bias at the outcome and study level(Higgins et al., 2011). The bias domains include selection bias (sequence generation and allocation concealment), detection bias (outcome assessor blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias. Two reviewers will independently assess all sources of bias as "high risk", "low risk", or "unclear". This information will be used as a source of heterogeneity in the meta-analysis.

**Data synthesis**

We propose to conduct a MTC meta-analysis using a Bayesian random-effects model(Dias et al., 2010a; Dias et al., 2010b). The suitability of the dataset for this method will be determined when data has been extracted in consultation with a statistician.

The Bayesian random-effects model for MTC will be used to produce the log odds of the outcome (unhealed corneal ulcer) for the treatment arms, risk ratios and credibility intervals for all possible pairwise comparisons, a ranking distribution for each treatment arm, and a "worst" treatment estimate. Unit of analysis issues will be handled by exclusion as all studies must have the individual as the unit of allocation Studies with missing data will be excluded from the meta-analysis and identified as such in the results. The consistency assumption will be assessed using

the residual deviance which is the difference between the posterior predicted mean values and observed mean value for each direct comparison.

Subgroup analyses will include assessment of factors associated with methodological and clinical heterogeneity. The methodological factors (sponsorship and blinding) will be used to assess the systematic bias between studies where the null hypothesis is the beta estimates of the trial factors equal zero. We expect the potential sources of clinical heterogeneity to be the severity of IBK and age of animal. We will assess this including these factors as indicator variables in the model where the null hypothesis is the beta estimates of the trial factors equal zero.

If quantitative synthesis is determined to be unfeasible, a systematic narrative synthesis paired with descriptive pairwise forest plots will be produced explaining the characteristics and findings within and between included studies.

**Meta-bias(es)**

In order to assess publication bias, we will attempt use a selection model based on study size, study design, estimated effect size, and sponsorship to determine estimates of propensity for publication (Mavridis et al., 2014). Based on previous reviews, it is unclear how many different study designs (e.g. active-to-active, placebo-controlled trials, three arm trials) will be observed and thus publication bias will be difficult to ascertain. It is unclear if enough studies will be available to conduct this analysis. The final decision will be made in consultation with a statistician when the number of studies and treatment arms are known.

**Confidence in cumulative estimate**

We will not use a GRADE panel that includes external stakeholders for summarizing the findings, however the authors will evidence profiles and evidence tables to summarize the evidence and our assessment of the GRADE categories. (Salanti et al., 2014)

# References


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Salanti, G., Del Giovane, C., Chaimani, A., Caldwell, D.M., Higgins, J.P., 2014. Evaluating the quality of evidence from a network meta-analysis. PLoS One 9, e99682.

Thrift, F.A., Overfield, J.R., 1974. Impact of pinkeye (infectious bovine kerato-conjunctivitis) on weaning and postweaning performance of Hereford calves. Journal of Animal Science 38, 1179-1184.

Table 1. Literature review search terms for the Centre for Biosciences and Agriculture International (CABI) and MEDLINE databases. Descriptors (DE) will be included for the CABI search and Medical Subject Headings (MH) for MEDLINE.

| Population AND | Disease AND | Intervention |
|---|---|---|
| TS=(beef OR bovine OR calf OR calves OR cattle OR cow OR dairy OR angus OR hereford OR holstein OR ruminant OR steer) | TS= (keratoconjunctivitis OR conjunctivitis OR pink eye OR pinkeye OR IBK OR Branhamella OR Moraxella OR Mycoplasma bovoculi OR Neisseria) | TS = (antibiotic OR antimicrobial OR amoxicillin OR ampicillin OR ceftiofur OR chlortetracycline OR cloxacillin OR danofloxacin OR enrofloxacin OR erythromycin OR florfenicol OR gamithromycin OR gentamicin OR lincomycin OR oxytetracycline OR penicillin OR spectinomycin OR sulfadimethoxine OR sulfamethoxazole OR tetracycline OR tildipirosin OR tilmicosin OR trimethoprim OR tulathromycin OR tylosin) OR DE = (drug therapy OR injection OR antibacterial agents) |

NB: for Medline MH = (Drug Therapy OR Injections OR Anti-Bacterial Agents) was substituted for DE = (drug therapy OR injection OR antibacterial agents)

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification | 1a ✓ | Identify the report as a protocol of a systematic review |
| Update | 1b ✓ | If the protocol is for an update of a previous systematic review, identify as such |
| Registration | 2 ✓ | If registered, provide the name of the registry (such as PROSPERO) and registration number |
| Authors: | | |
| Contact | 3a ✓ | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author |
| Contributions | 3b ✓ | Describe contributions of protocol authors and identify the guarantor of the review |
| Amendments | 4 ✓ | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments |
| Support: | | |
| Sources | 5a ✓ | Indicate sources of financial or other support for the review |
| Sponsor | 5b ✓ | Provide name for the review funder and/or sponsor |
| Role of sponsor or funder | 5c ✓ | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |
| **INTRODUCTION** | | |
| Rationale | 6 ✓ | Describe the rationale for the review in the context of what is already known |
| Objectives | 7 ✓ | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) |
| **METHODS** | | |
| Eligibility criteria | 8 ✓ | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review |
| Information sources | 9 ✓ | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage |
| Search strategy | 10 ✓ | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated |
| Study records: | | |
| Data management | 11a ✓ | Describe the mechanism(s) that will be used to manage records and data throughout the review |

| | | |
|---|---|---|
| Selection process | 11b ✓ | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) |
| Data collection process | 11c ✓ | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators |
| Data items | 12 ✓ | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications |
| Outcomes and prioritization | 13 ✓ | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale |
| Risk of bias in individual studies | 14 ✓ | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis |
| Data synthesis | 15a ✓ | Describe criteria under which study data will be quantitatively synthesised |
| | 15b ✓ | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) |
| | 15c ✓ | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) |
| | 15d ✓ | If quantitative synthesis is not appropriate, describe the type of summary planned |
| Meta-bias(es) | 16 ✓ | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) |
| Confidence in cumulative evidence | 17 ✓ | Describe how the strength of the body of evidence will be assessed (such as GRADE) |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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