Investigating antimicrobial and non-antimicrobial interventions used to reduce morbidity, mortality and overall antimicrobial use in male and female dairy calves: a scoping review protocol
T. E. von Konigslow¹, D. F. Kelton¹, D. L. Renaud¹, T. F. Duffield¹, K. Beattie¹ and C. B. Winder¹

¹Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1

INTRODUCTION

Rationale
Young calves are most susceptibility to infection early in life during the period in which their immune and other physiological systems are maturing (Marcato et al., 2018). In veal facilities, morbidity and mortality is highest early in the production cycle (Bährler et al., 2012; Winder et al., 2016; Renaud et al., 2018). In these calf rearing environments, group metaphylaxis is commonly provided in the first week post arrival due to the stress of transportation, co-mingling, variable periods of fasting, new housing, and feed to which these calves are exposed (Marcato et al., 2018).

Widespread antimicrobial use (AMU) can exert pressures that lead to the development of antimicrobial resistance (AMR) in pathogens, affecting both calves and the people that care for them (Bos et al., 2013; Catry et al., 2016). In response to the development of AMR, focus is being directed to judicious antimicrobial stewardship practices that include efforts to reduce AMU without sacrificing animal health and welfare. A scoping review in this context is needed to identify and describe the existing literature on various interventions with regard to their impact on the health of male and female dairy calves, to identify gaps in knowledge, and to determine the feasibility of conducting one or more systematic reviews to address specific questions about relative efficacy of interventions to reduce morbidity/mortality in these young calves. This information will be used to help direct the focus of future research and inform best practices for reducing AMU where possible in the management of young dairy calves. This scoping review will be conducted based on guidance from Arksey and O’Malley (2005) and will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018).

Objectives
There are three main objectives of this scoping review:
1. To identify and describe the existing literature which evaluates preventative and/or metaphylactic use of antimicrobial and non-antimicrobial interventions in male and female dairy calves under 3 weeks of age where outcome measures include at least one of: morbidity, mortality or overall antimicrobial use
   a. To identify, list and describe the types of interventions started in the first week of life or first week after arrival
   b. To identify and describe how researchers measure the outcomes of morbidity, mortality, and antibiotic use;
2. To assess the feasibility of conducting a systematic review assessing the relative efficacy of an intervention or group of interventions; and,
3. To identify gaps in the published research literature.

METHODS

Protocol and registration
This protocol will be time stamped, archived and available online with Systematic Reviews for Animals and Food (SYREAF; www.syref.org) and the University of Guelph Atrium [https://atrium.lib.uoguelph.ca/xmlui/handle/10214/10046]. Protocol deviations will be described and explained in the final manuscript.

Eligibility criteria
Eligibility will be restricted to English-language, and controlled trials that involve natural and purposive disease exposure (i.e. challenge trials). Eligible study populations are male and female dairy calves between 0 and 3 weeks of age, or young calves (i.e. preweaned) of unknown age upon arrival to veal, dairy beef or calf rearing facilities. Trials must examine an antimicrobial or non-antimicrobial intervention administered for disease prevention or metaphylaxis within the first week of life, or first week after arrival, and be compared to a placebo, a non-treated control, or an alternative treatment. Trials must include at least one of the following outcomes, measured within the first three weeks of life, or the first three weeks post arrival to the calf rearing facilities: morbidity, mortality, or antimicrobial use.

Information sources
The literature search will be conducted using the following electronic databases, accessed through the University of Guelph:

- Science Citation Index-Expanded (via Web of Science);
- Conference Proceedings Citation Index-Science (via Web of Science);
- CAB Abstracts (via CAB Direct);
- AGRICOLA (via ProQuest);
- Medline (via Pubmed)

One reviewer will hand search of the table of contents for relevant conference proceeding of:

- Proceedings of the American Association of Bovine Practitioners (1997 – 2018);

One reviewer will also hand search the Food and Drug Administration’s (FDA) Freedom of Information New Animal Drug Approval (NADA) summaries for relevant publications.

Search
A selection of 15 relevant analytical observational, experimental, or challenge studies identified during a broad test search conducted in Google Scholar using the population terms “veal calves” or “dairy calves” or “dairy beef” or “calves” were used to help validate the population and outcome search terms identified (Appendix 1). A full search using a set of population and outcome search terms listed in Table 1 was conducted in the Science Citation Index-Expanded
(SCI-EXPANDED) and Conference Proceedings Citation Index- Science (CPCI-S) (via Web of Science). Search terms within a set were combined using the Boolean operator “OR”. The results of each complete set of search terms were combined using the Boolean operator ‘AND’. There will be no publication date restraints applied to the databases queried.

Table 1. Test search conducted April 29, 2019 in Science Citation Index-Expanded and Conference Proceedings Citation Index-Science (via Web of Science).

<table>
<thead>
<tr>
<th>Set</th>
<th>Search Terms</th>
<th>Results (# publications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Population search terms)</td>
<td>TS=(“dairy calf” OR “dairy calves” OR “Holstein calf” OR “Holstein calves” OR “Jersey calf” OR “Jersey calves” OR “veal calf” OR “veal calves” OR “bull calf” OR “bull calves” OR “male calf” OR “male calves” OR “female calf” OR “female calves” OR “calf ranch” OR “calf ranches” OR “veal barn” OR “veal barns” OR “veal farm” OR “veal farms” OR “*weaned calves” OR “*weaned calf” OR “neonatal calf” OR “neonatal calves” OR “bob calf” OR “bob calves” OR “bob veal” OR “young calf” OR “young calves”)</td>
<td>10 651</td>
</tr>
<tr>
<td>2 (Outcome search terms)</td>
<td>TS=(morbidity OR mortality OR illness OR sickness OR disease OR “calf loss” OR death OR “antibiotic use” OR AMU OR “antimicrobial use” OR BRD OR pneumonia OR “bovine respiratory disease” OR diarrhea OR scour)</td>
<td>5 125 338</td>
</tr>
<tr>
<td>3</td>
<td>Set 1 AND Set 2</td>
<td>3 085</td>
</tr>
</tbody>
</table>

Selection of sources of evidence
Screening of title and abstract will be conducted independently in duplicate by two reviewers. Disagreements between reviewers will be resolved by consensus or discussion with mediation.
by another co-author when needed. Pre-testing of screening questions will be done on the first 100 records to ensure consistency of application of the screening questions. Agreement between reviewers will be determined at the level of the form.

1. Is the title and abstract of the publication available in English?
   a. Yes (Neutral)
   b. Unclear (Neutral)
   c. No (Exclude the publication and submit the form)

2. Do the title and abstract describe an analytic observational study or controlled trial?
   a. Yes (Neutral)
   b. Unclear (Neutral)
   c. No (Exclude the publication and submit the form)

3. Does the study investigate the population of interest (young male or female dairy calves 0-3 weeks of age or of unknown age on arrival to a veal, dairy beef, or heifer raising facility)?
   a. Yes (Include publication in the next level of screening)
   b. Unclear (Include publication in the next level of screening)
   c. No (Exclude the publication and submit the form)

Screening of the full text document will be conducted independently in duplicate as described above. Pre-testing of this form will be conducted on the first 50 records. Agreement between reviewers will be determined at the level of the answers in the screening form, and reasons for exclusion documented.

1. Is the full text document of the publication available for retrieval?
   a. Yes (Neutral)
   b. No (Exclude the publication and submit the form)

2. Is the full text document of the publication available in English?
   a. Yes (Neutral)
   b. No (Exclude the publication and submit the form)

3. Is the full text document of the publication greater than 500 words?
   a. Yes (Neutral)
   b. No (Exclude the publication and submit the form)

4. Does the study investigate the population of interest (young male or female dairy calves 0-3 weeks of age or of unknown age on arrival to a veal, dairy beef, or heifer raising facility)?
   a. Yes (Neutral)
   b. No (Exclude the publication and submit the form)

5. Does the study investigate one or more relevant interventions started within the first week of life or first week after arrival to a calf rearing facility?
   a. Yes (Neutral)
   b. No (Exclude the publication and submit the form)

6. Does the study measure at least one of the outcomes of interest (morbidity, mortality or antimicrobial use) within the first 3 weeks of life or arrival to a veal, dairy beef, or heifer raising facility?
   a. Yes (Neutral)
b. No (Exclude the publication and submit the form)

7. What is the study design?
   a. Controlled trial – natural disease exposure (neutral)
   b. Controlled trial – challenge (neutral)
   c. Cross-sectional study (exclude and submit the form)
   d. Cohort study (exclude and submit the form)
   e. Case-control study (exclude and submit the form)
   f. Other (exclude and submit the form)

**Data charting process**

**Data Management**
The results of the database searches will be imported into EndNote (Clarivate Analytics, Philadelphia, PA, USA) reference management software. Screening and data extraction for this scoping review will be performed using the web-based software DistillerSR (Evidence Partners, Ottawa, Canada). An initial scan and removal of duplicate citations will be conducted in EndNote before exporting the documents to DistillerSR where a second scan for duplication will be conducted prior to the commencement of testing, screening and data extraction.

**Data Extraction**
Data extraction on the full text documents will be conducted by the same reviewers independently and in duplicate using forms in DistillerSR. Testing of the data extraction tool will be conducted on the first 10 publications. Disagreements between reviewers will be resolved by consensus or discussion with another co-author if necessary.

**Data items**
Primary data characterization will be done for all references included after full text screening.

**Primary data characterization:**
- Outcome(s) described in the study:
  - Mortality
  - Morbidity
  - Antimicrobial use
- Intervention categories:
  - Antimicrobial
    - Antibiotic
    - Anthelmintic
  - Non-antimicrobial parenteral (not vaccine)
  - Vaccine
  - Non-antimicrobial feed or water additive / supplement
  - Diet (nutritional plane or components that are not additives or supplements)
  - Management practices (other than vaccine or diet)
  - Immune stimulant
  - Other (describe)
It is anticipated that a large number of interventions will be studied in the literature. Further data characterization is planned for all studies examining antimicrobial interventions, but other categories of interventions may also be included for further characterization based on prevalence in the literature, and resources of the review team. Further data characterization will include:

**Study characteristics:**
- Type of experimental design
- Country/countries in which the trial was conducted
- Year in which the study was conducted
- Type of citation

**Population characteristics:**
- Production system type
- Facility type (commercial, research, other)

**Intervention characteristics:**
- Number of arms in the study
- Description of each arm
  - Dose, route, and frequency of administration
  - Level at which the intervention was applied

**Outcome characteristics:**
- Period at risk
- Case definition
- Unit of measurement

**Funding:**
- Source(s) of funding

**Synthesis of results**
The results of each level of the screening and eligibility process will be reported in a flow diagram in agreement with the PRISMA-ScR guideline (Tricco et al., 2018; Item 17).

Primary data characterization will be reported in a table describing the number of eligible studies and frequency of outcome(s) reported for each intervention category. This information will be used to inform the selection of intervention types eligible for further data characterization.

Study characteristic results will include a frequency map to illustrate global foci for research on different intervention categories. A figure will be used to illustrate trends in the volume of research generate over time. Descriptive statistics of the type of experimental design and type of citation available will be reported in the text.
Population characteristics will be reported as descriptive statistics in text. Intervention characteristics will include a frequency table reporting interventions by category. The proportion of studies that investigate products applied at the group or individual level will be reported. A complete table describing each intervention in detail including dose, route and frequency of administration will be included. Outcomes characteristics will be summarized in a table by intervention type. A narrative description of case definitions, measurements and any standardized protocols will be discussed in detail.

Discussion
Main findings will be summarized, linked to the review question, and relevance to industry and researchers considered. Limitations at the study and review level will be discussed.

This work will determine the feasibility of conducting a systematic review targeting an intervention or group of interventions and will identify gaps in the literature.

Funding
This review was funded by the Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA, Guelph, ON, Canada), the Ontario Veterinary College (University of Guelph, ON, Canada), and the Veal Farmers of Ontario (Guelph, Ontario, Canada).

REFERENCES


Appendix 1 – Studies used to develop the search terms used in the review


