Protocol for a systematic review of disease control strategies used to prevent infectious mortality and morbidity in pre-weaned beef calves

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Authors' contributions

V. Margarita Sanguinetti: protocol/search strategy development, review of manuscripts and data extraction, manuscript preparation/revision

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M. Claire Windeyer: project/student supervision, acquisition of funding, project administration, protocol and search strategy development, third reviewer for resolving conflicts, and manuscript editing/revision.

Registration

This protocol will be archived in PRISM: University of Calgary Digital Repository (https://prism.ucalgary.ca) and published online with Systematic Reviews for Animals and Food (http://www.syreaf.org/). The protocol will be reported using the recommended PRISMA-P guidelines (1).

Support

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Amendments

In case any amendments are made to this protocol after its registration, they will be adequately documented in the systematic review as Protocol Deviations.

INTRODUCTION

Rationale

It is essential to optimize the production of calves in order to maximize economic returns to producers and the availability of feeder cattle and replacement stock for the industry. Morbidity and mortality in beef calves have negative impacts on beef operations and are associated with considerable economic damage (2,3). By implementing effective disease control strategies, morbidity and mortality caused by Bovine Respiratory Disease (BRD) and Neonatal Calf Diarrhea (NCD) may be reduced. Studies have shown that failed transfer of passive immunity (3–7), season of birth (8), herd size (2,3), assistance at calving (3,9), and purchasing adult cattle and using community pastures (10) are risk factors for morbidity and mortality in calves. Disease control strategies are an essential component of the health management of beef herds (11) and some preventive practices have shown financial benefits (12). Herd demographics and management practices alter the epidemiology of disease within the herd (13), with various strategies aiming to improve the animal environment, boost the immune system (14), and diminish animal exposure to potential pathogens (15). Risk factors associated with the multifactorial syndromes of BRD and NCD have been explored mainly in dairy calves (5–8), but there are a limited number of studies related to beef calves (16) and no efforts to summarize the available literature have been reported.

A systematic review of the current scientific literature will be conducted focusing on colostrum management, vaccination strategies, biosecurity, biocontainment, metaphylactic use of antibiotics, and other strategies used to prevent mortality and morbidity caused by BRD and NCD in pre-weaned beef calves. To the best of our knowledge, there is no published systematic review on disease control strategies used in beef calves during the preweaning stage.

Objectives

This protocol describes the methodology that will be used for a systematic review that will evaluate the scientific evidence related to the question: Do disease control strategy interventions reduce morbidity and mortality caused by BRD and NCD in pre-weaned beef calves compared to those not receiving the interventions? The objective of this systematic review is to evaluate critically the quality of evidence about disease control strategies that reduce morbidity and mortality in pre-weaned beef calves. The methodology follows the PRISMA-P guidelines (1).

METHODS

The review team will include four members including experts in infectious calfhood diseases (VMS, SP, CW), epidemiological methods (CW, VMS), and database and indexing (HG).

Eligibility criteria

The eligibility criteria will be based on the PICOS format framework (17):

Population (P)	Intervention or exposure population: pregnant dams or pre-weaned beef calves Outcome population of interest: pre-weaned beef calves (24h after birth until weaning)
Intervention (I)/ Exposure (E)	Disease control strategies: Colostrum management - dose, timing, route, source Vaccination - antigen, dose, timing, route of administration Biosecurity - practice, timing, duration, production group Biocontainment - practice, timing, duration, production group Metaphylactic antibiotic treatment - active ingredient, dose, timing
Comparator (C)	For randomized control trials (RCT): placebo, standard therapy, no treatment For observational studies: no exposure, non-cases
Outcome (O)	Mortality, morbidity caused by BRD and NCD in beef calves from 24 h after birth until weaning
Study designs (S)	Randomized clinical trials and observational studies

Primary research studies of RCT and observational design will be retained. Case reports and case series will be excluded. Only naturally occurring BRD or NCD studies will be included.

Information sources

The following electronic databases will be searched with no language nor time restrictions: CAB Abstracts, MEDLINE on the Ovid platform, Web of Science, and ProQuest Dissertations. The search strategy that will be used is shown below. The searches across databases will be carried out on the same day, before starting the systematic review.

Search strategy

The search strategy will gather all possibly related research to have high sensitivity. Not all PICOS/PECOS components will be included in the search strategy; in

particular, interventions (I) and exposures (E) will not be included so as to not limit the potential disease control strategies to be assessed (17).

1. CAB Abstracts

#	Query
S1	(DE "calf diarrhoea rotavirus") OR (DE"diarrhoea" OR DE "Bovine viral diarrhea virus 2" OR DE "Bovine viral diarrhea virus 1")
S2	(DE "Bovine respiratory syncytial virus") OR(DE "pneumonia" OR DE "bacterialpneumonia" OR DE "pleuropneumonia")
S3	DE "Bovine coronavirus"
S4	DE "Cryptosporidium parvum
S5	DE "Escherichia coli" OR DE "Escherichia coli infections"
S6	DE "Salmonella Typhimurium" OR DE "Salmonella Dublin" OR DE "Salmonella enterica"
S7	DE "Bovine herpesvirus 1" OR DE "Bovine herpesvirus 5
S8	DE "Bovine torovirus"
S9	DE "Mannheimia haemolytica"
S10	DE "Pasteurella multocida" OR DE "Pasteurella multocida subsp. gallicida" OR DE "Pasteurella multocida subsp. multocida" OR DE "Pasteurella multocida subsp. septica"
S11	DE "Bovine parainfluenza virus 3"
S12	(DE "morbidity") OR (DE "mortality")
S13	TI (BRD OR BVD OR NCD OR "cryptosporidium parvum" OR "bovine coronavirus" OR "E. coli" OR "Escherichia coli" OR rotavirus OR "salmonella typhimurium" OR "salmonella dublin" OR "salmonella enterica" OR "bovine rhinotracheitis" OR "bovine respiratory disease" OR "bovine herpes*" OR "bovine respiratory syncytial virus" OR BRSV OR "mannheimia haemolytica" OR "parainfluenza 3" OR "parainfluenza virus 3" OR torovirus OR "Pasteurella multocida" OR diarrh#ea OR pneumonia OR scours OR morbidity OR mortality) OR AB (BRD OR BVD OR NCD OR "cryptosporidium parvum" OR "bovine coronavirus" OR "E. coli" OR "Escherichia coli" OR rotavirus OR "salmonella typhimurium" OR "salmonella dublin" OR "salmonella enterica" OR "bovine rhinotracheitis" OR "bovine respiratory disease" OR "bovine herpes*" OR "bovine respiratory syncytial virus" OR BRSV OR "mannheimia haemolytica" OR "parainfluenza 3" OR "parainfluenza virus 3"

	OR torovirus OR "Pasteurella multocida" OR diarrh#ea OR pneumonia OR scours OR morbidity OR mortality)
S14	(DE "beef cattle") OR (DE "suckler herds")
S15	TI (beef OR suckler*) OR AB (beef OR suckler*)
S16	DE "calves" OR DE "calf diseases"
S17	TI (calf OR calves) OR AB (calf OR calves)

2. MEDLINE

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations

Search Strategy:

#	Searches
1	exp Bovine Respiratory Disease Complex/ or exp Diarrhea Viruses, Bovine Viral/
2	exp Coronavirus, Bovine/
3	exp Cryptosporidium parvum/
4	exp Escherichia coli/
5	exp Salmonella/
6	exp Herpesvirus 1, Bovine/
7	exp Torovirus Infections/ or exp Torovirus/
8	exp Mannheimia haemolytica/
9	exp Pasteurella multocida/
10	exp Parainfluenza Virus 3, Bovine/
11	exp Morbidity/

12	exp Mortality/
13	(BRD or BVD or NCD or cryptosporidium parvum or bovine coronavirus or E* coli or Escherichia coli or rotavirus or salmonella typhimurium or salmonella dublin or salmonella enterica or bovine rhinotracheitis or bovine respiratory disease or bovine herpes* or bovine respiratory syncytial virus or BRSV or mannheimia haemolytica or parainfluenza 3 or parainfluenza virus 3 or torovirus or Pasteurella multocida or diarrh?ea or pneumonia or scours or morbidity or mortality).kf,tw.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	(beef or suckler*).kf,tw.
16	(calf or calves).kf,tw.
17	14 and 15 and 16

3. Web of Science Search

TOPIC: (BRD OR BVD OR NCD OR "cryptosporidium parvum" OR "bovine coronavirus" OR "E. coli" OR "Escherichia coli" OR rotavirus OR "salmonella typhimurium" OR "salmonella dublin" OR "salmonella enterica" OR "bovine rhinotracheitis" OR "bovine respiratory disease" OR "bovine herpes*" OR "bovine respiratory syncytial virus" OR BRSV OR "mannheimia haemolytica" OR "parainfluenza 3"OR "parainfluenza virus 3" OR torovirus OR "Pasteurella multocida" OR diarrh?ea OR pneumonia OR scours OR morbidity OR mortality) AND TOPIC: (beef OR suckler*) AND TOPIC: (calf OR calves)

Timespan: 1900-2021. Indexes: SCI-EXPANDED, CPCI-S, ESCI.

4. ProQuest Dissertations

noft(BRD OR BVD OR NCD OR "cryptosporidium parvum" OR "bovine coronavirus" OR "E. coli" OR "Escherichia coli" OR rotavirus OR "salmonella typhimurium" OR "salmonella dublin" OR "salmonella enterica" OR "bovine rhinotracheitis" OR "bovine respiratory disease" OR "bovine herpes*" OR "bovine respiratory syncytial virus" OR BRSV OR "mannheimia haemolytica" OR "parainfluenza 3" OR "parainfluenza virus 3" OR torovirus OR "Pasteurella multocida" OR diarrh?ea OR pneumonia OR scours OR morbidity OR mortality) AND noft(beef OR suckler*) AND noft(calf OR calves)

Study Records

Data management

Database records of the articles recovered will be imported into Covidence (Veritas Health Innovation, Melbourne, Australia) and duplicates will be deleted by the same software. Abstract and full screening will be recorded in Covidence. Data extraction and risk of bias assessment will be documented in Microsoft Excel (Microsoft Corporation, Redmond, WA). If statistical analysis is performed, it will be done in STATA 16.1 software (StataCorp LP, College Station, Texas).

Selection process

The citations will be screened in two independent stages. The first stage of the selection process will consist of titles and abstract screening. Two independent reviewers (VMS and SP) will carry out this task using Covidence. Conflict will be resolved with a third reviewer (CW). The studies that meet inclusion criteria will pass to the next phase. The concordance among the reviewers will be evaluated by randomly selecting 10% of the citations entering each stage of the process prior to screening all papers. This pilot study will enable discussion and solve disagreement before carrying out the full selection process by the two reviewers (adapted from 21).

First stage

- Does the title/abstract make reference to a primary research study published in a peer-reviewed journal?
- Does the title/abstract refer to a disease control strategy of interest?

The potential answers are 'yes', 'no' or 'unclear', the last meaning that the question above cannot be answered by only the information given in the abstract. Articles classified as 'no' by both reviewers will be excluded. Articles with 'unclear' or 'yes' answers by both reviewers (VMS and SP) will go the next phase. Articles classified differently by the two reviewers will be reviewed by a third reviewer (CW) to resolve the conflict; this will be discussed among all three as necessary (VMS, SP, and CW) (adapted from 22, 23).

Second stage

During the second stage of full-text screening, interest will be focused on the methods section. Two independent reviewers (VMS and SP) will carry out this task using

Covidence. Those studies that meet inclusion criteria will go the next phase. Conflict will be resolved with the third reviewer.

- Is the study design a RCT or an observational study?
- Does the study report a comparison or control group where the intervention strategy was not applied?
- Does the study report morbidity and/or mortality caused by naturally occurring BRD or NCD in beef calves from 24 h of birth until weaning?

Studies will only be included in case they get a combination of at least 'yes' or 'unclear' answers. All of those which receive a 'no' will be excluded. Conflict will be resolved among the two reviewers and a third if necessary (adapted from 22, 23).

Data Extraction

The data extraction process will be carried out by using Endnote X9 (The EndNote Team, Philadelphia, PA). Two reviewers will independently extract data from all eligible studies (VMS and SP), and a third reviewer will supervise (CW).

Data to be extracted include:

- **General information**: bibliographic information (journal name, language, country, year, authors, funding information)
- **Study design**: type of study, sample size
- **Unit of observation**: individual or herd
- **Population characteristics:** breed, sex, age, production system
- **Pathogens:** species
- **Intervention/exposure assessed and comparator:** characteristics of the intervention/exposure (e.g. commercial name for vaccines, concentration, dose, route of administration)
- **Outcomes:** case definition, estimate (adjusted and unadjusted) confidence intervals, standard errors, P-values, odds ratios, risk ratios/relative risk.

Outcome Prioritization

Morbidity and mortality will be the main outcomes of interest.

Risk of Bias Assessment

This process will be carried out by two independent reviewers (VMS and SP) and a pilot study will be done in order to resolve conflict among the reviewers based on the Cochran Review Handbook (20).

The risk of bias will be evaluated using a 'Risk of Bias' tool developed by the Cochrane Collaboration. Studies will be evaluated individually in terms of internal validity by two reviewers qualitatively (low, high, and unclear). This tool can be adapted to veterinary science and focuses on information bias, selection bias, and confounding (20). Each domain is addressed firstly with specific questions outlined below. Responses to the questions will be registered to justify the responses given. After answering the questions, a risk-of-bias judgement will be made for each domain (21). Finally, a global risk of bias will be determined by allocating the lowest risk of bias in any of the three evaluated domains (19).

Selection bias is caused by factors affecting the selection of study subjects (22). The selection bias associated with external validity will not be taken into account. This domain will be approached using the following signalling questions:

- Besides treatment, were calves assigned to control and treatment groups in systematically different ways?
- Did sampling methods differ systematically between control and treatment groups?

Low risk of sample selection bias examples:

- *Calves were randomly allocated to the different groups.*
- *The calves belonged to the same herd and breed* (adapted from 21).

Information bias is caused by factors relating to attaining precise information on the exposure, outcome, and covariates (22). This domain will be approached using the following questions:

- Have the definitions of cases of BRD and/or NCD been clearly defined?
- Have the methods used to determine NCD and/or BRD been carried out in such a way that assure truthfulness in the diagnosis? (adapted from 21).

Low risk of information bias example:

- *The diagnosis has been carried out by the combination of clinical disease and laboratory methods.*

Confounding bias is caused by the effects of factors other than the exposure of interest on the observed association (22). The question that will address this type of bias is the following:

- Were measures taken into account to reduce potential confounding?

Examples of low risk of confounding:

- *Treatment was randomly assigned to calves or herds.*
- *Characteristics such as husbandry practices were matched between control and treatment groups.*
- *The statistical approaches used adjusted for potential confounding* (adapted from 21).

Data Synthesis

The evidence will be synthesized into a narrative review. If there is sufficient data from homogeneous studies that report quantitative outcomes, a meta-analysis will be carried out. Furthermore, publication bias will be evaluated using funnel plots, where possible (23).

CONCLUSIONS

The overall objective of this systematic review is to examine carefully the available literature on disease control strategies used to prevent infectious morbidity and mortality in pre-weaned calves. This will help the decision-making process when applying interventions in beef herds by producers and herd veterinarians and suggestions made by policymakers. Moreover, the systematic review will suggest gaps in knowledge that require more research in the future.

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