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# Effect of probiotics on performance and health of dairy calves: protocol for a systematic review and meta-analysis

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Author Contributions: RBL: Assist to develop search strategy and literature search. Data screening, extraction, statistical analysis, and protocol and manuscript preparation.

EDF: Develop search strategy and literature search, edit protocol.

CBW: Review methodology and statistical analysis, edit protocol and manuscript.

MEAC: Review methodology and statistical analysis, edit protocol and manuscript.

NSDR: Assist, edit and review protocol and manuscript.

Amendments: Any amendments to this protocol will be documented and justified in the final systematic review.

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## INTRODUCTION

**Rationale:** For over 60 years, antimicrobials have been used to both prevent and treat diseases in food animals (Xiong et al., 2018). However, the global concern with antimicrobial resistance has been increased the interest in alternative products, such as probiotics, that might reduce the use of antimicrobials. The International Scientific Association for Probiotics and Prebiotics defined probiotics as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”(Hill et al., 2014). The mechanisms used by probiotics to promote health benefits to their host are not fully elucidated. However, it seems that, in general, probiotics modulate the host’s gut microbiota and immune system (Ma et al., 2018).

Some studies have shown the supplementation of probiotics to dairy calves to reduce incidence of diarrhea and promote growth (Foditsch et al., 2015; Fomenky et al., 2017). On the other hand, results from other studies have indicated that prebiotic supplementation has no effect (He et al., 2017) or even negative (Corbett et al., 2015) effect on health or performance of calves.

Previous systematic reviews (SR) evaluated the effect of probiotics on performance (Frizzo et al., 2011) and health (Signorini et al., 2012) of dairy calves. However, both SRs addressed only lactic acid bacteria, excluding other important probiotics, such as yeasts. The latest SR was published 8 years ago, and since then several new studies have been published. Moreover, according to O'Connor et al. (2014) the median survival time of systematic review is 5.5 years for human research.

**Objectives:** The first objective of this review is to identify, summarize, appraise, and discuss the current literature on probiotic supplementation for dairy calves. The second objective is to evaluate the effect of probiotic supplementation on performance and health of dairy calves. The research question addressed in this protocol and in the future systematic review is: does the probiotic supplementation effect performance or health of dairy calves?

- a) Population: dairy calves (up to 7 months of age) of both sexes
- b) Intervention: probiotic supplementation (only as prophylactic, not therapeutic use)
- c) Comparator: placebo or no probiotic supplementation
- d) Outcomes: any performance measurement [e.g. body weight, average daily gain, body traits (heart girth, wither height, hip width, or body length), feed efficiency, dry matter intake, gastrointestinal tract measurements (volatile fatty acid concentration, rumen pH, papilla length and papilla width)] or any health measurement [e.g. serum metabolites (glucose and beta-hydroxybutyrate), immunoglobulins, cytokines, fecal score, diarrhea incidence, pneumonia incidence, mortality, days on treatment, microbiota and microbiome].

## **METHODS**

**Eligibility criteria:** Besides the PICO elements described above, the systematic review will include only primary research studies, and of these, randomized and non-randomized controlled trials which are available in English, Spanish and Portuguese. No restriction for date will be imposed other than that of the databases searched. The studies can be published and non-published since the primary data is reported.

**Information sources:** Electronic searches were conducted using the following electronic databases: Biosis (Web of Science, 1926 to present), CAB Abstracts (CAB Direct, 1973 to present), Medline (PubMed, 1966 to present), and Scopus (Scopus, 1996 to present). Grey literature was searched to find unpublished data using Dissertations and Theses Database (ProQuest, 1861 to present). The bibliography of relevant studies was hand searched. The search was conducted between February 27<sup>th</sup> and March 3<sup>rd</sup> of 2020.

**Search strategy:** Based on the PICO elements, the search is described (search strategy specifically for PubMed) in table 1.

## Study records

**Data management:** The studies identified in the searches were uploaded to the reference manager Sciwheel formerly known as F1000 (Faculty of 1000 Limited, London, UK) and duplicates were removed. The de-duplicated results were exported to the Covidence systematic review management software (Veritas Health Innovation, Melbourne, AU).

**Selection process:** Two screenings were conducted by two independent reviewers (RBL and another reviewer), first assessing manuscript title and secondly abstracts. The title screening used the following questions:

- 1) Does the title describe a study involving dairy calves?
- 2) Does the title describe a study with probiotic supplementation?

The abstract screening used the following questions:

- 1) Does the abstract describe a primary intervention study?
- 2) Does the abstract describe a study involving dairy calves supplemented with probiotic?
- 3) Does the abstract describe one or more of the measurements in performance (e.g., average daily gain, feed efficiency) or health (e.g., fecal score, diarrhea incidence,)?

Studies were excluded if both reviewers answer “no” for one of the questions. Only studies with “maybe” or “yes” answers were selected for following step. Conflicts between inclusion and exclusion by the two reviewers were discussed until a consensus was reached. A pilot test was conducted in 30 abstracts and the reviewers were trained on systematic review methodology.

A full manuscript screening was performed by RBL on the remnant studies. This screening included the 3 previous abstract questions plus:

- 4) Is the study a controlled trial?
- 5) Is the study written in English, Spanish or Portuguese?
- 6) Is the probiotic a supplementation strategy (prophylactic not treatment for sick animals)?
- 7) Is the study population (dairy calves) equal or less than 7 months old?

Studies were excluded if RBL answer “no” for one or more of the questions. The exclusion reason was recorded at this screening level.

**Data collection process:** Data from eligible studies is being extracted by RBL into an electronic spreadsheet and it will be reviewed by another reviewer. Data extraction forms, adapted from previous studies, were tested on 5 studies randomly selected by RBL.

General information data consist of: 1) journal name, 2) language, 3) country, 4) author affiliation, 5) year of publication, 6) year study was performed, 7) month study was performed, 8) funding information.

Population characteristics consist of: 1) breed, 2) sex, 3) age, 4) housing system, 5) type production system (conventional vs organic), 6) assessment of passive transfer, 7) commercial or research herd.

Intervention and comparator data consist of: 1) description of comparator, 2) commercial name of probiotic, 3) single or multistrain, 4) genera, 5) scientific name, 6) concentration, 7) dose, 8) via of administration (e.g. whole milk, milk replacer), 9) duration of supplementation.

Outcomes: For continuous outcomes (e.g. average daily gain) the following information will be extracted: 1) number of experimental units for each treatment level, 2) least square or contrast means for each treatment level, 3) mean differences from control, 4) unit of results, 5) lower/upper 95% CI, 6) standard error, 7) P-value, and 8) time point of each measurement.

For dichotomous outcomes (e.g. occurrence of diarrhea) information: 1) number of positive experimental units per treatment group, 2) proportion of positive experimental units per treatment group, 3) total number of experimental units per treatment group, 4) unit of results, 5) odd ratio, 6) relative risk, 7) lower/ upper 95% CI, 8) P- value, and 9) time point of each measurement.

## **Data items**

**Outcomes and prioritization:** The definitions of outcomes for performance and health are described in table 2. The main performance outcomes are average daily gain and feed efficiency, and the secondary performance outcomes are body weight, body traits (heart girth, wither height, hip width, or body length), dry matter intake and rumen development indicators (volatile fatty acid concentration, ruminal pH, papilla length and papilla width). The main health outcomes are fecal score and diarrhea incidence and the secondary health outcomes are serum metabolites (glucose, beta-hydroxybutyrate), immunoglobulins, cytokines, pneumonia incidence, mortality, days on treatment, and rumen and gut microbiota and microbiome.

The prioritization of the performance outcomes was based on their impact on animal growth, weaning age, and economic results. The health outcomes were prioritized based on their easiness to evaluate gut health and also, they are frequently used. Moreover, fecal score is a feasible indicator for farm use.

**Risk of bias assessment:** Risk of bias of randomized studies will be assessed for each outcome by RBL, using the Cochrane risk of bias 2.0 tool with the necessary adaptations to fit the specific review question.

**Data synthesis:** If more than 3 studies investigated similar treatments with the same outcome a meta-analysis will be conducted. A random effects meta-analysis will be conducted. Studies will be weighted using the inverse variance method. Heterogeneity between studies will be assessed using Cochran's  $Q$  statistic and  $I^2$  statistic. Heterogeneity will be explored via sub-group analysis and/or meta-regression, if enough studies are found for a single outcome. A sub-group analysis will be performed categorizing the studies in pre- and postweaning and according with probiotics usage. If there are more than 10 studies, publication bias will be investigated using funnel plots, Begg's adjusted rank correlation, and Egger's test.

**Table 1.** Terms and results of the search strategy used to identify studies.

Search ID	Terms	Pubmed	CAB Direct	Scopus	Biosis	ProQuest
#1 population	“calf”OR “calves”[tiab] OR “veal”[tiab] OR “preweaned dairy heifers”[tiab]	64,421	102,176	95,378	34,452	5,602
#2 Intervention	“direct fed microbial”[tiab] OR DFM[tiab] OR “probiotic”[tiab] OR “probiotics”[tiab] OR "Probiotics"[Mesh] OR “faecalibacterium”[tiab] OR “lactobacilli”[tiab] OR “LAB”[tiab] OR “MSPB”[tiab] OR “CSPB”[tiab] OR “lactobacillus”[tiab] OR “propionibacterium”[tiab] OR “bacillus”[tiab] OR “pediococcus”[tiab] OR “enterococcus”[tiab] OR “enterococcus”[tiab] OR “saccharomyces”[tiab] OR “lactococcus”[tiab] OR “megasphaera”[tiab] OR “bifidobacterium”[tiab] OR “faecalibacterium”[tiab] OR "Digestive System Diseases/prevention and control"[Mesh] OR "Dietary Supplements"[Mesh] OR "Dietary Supplements/administration and dosage"[Mesh] OR "Dietary Supplements/therapeutic use"[Mesh] OR "Dietary Supplements/therapy"[Mesh] OR "Lactobacillus/therapeutic use"[Mesh] OR "Propionibacterium"[Mesh] OR "Bacillus"[Mesh] OR "Pediococcus"[Mesh] OR "Enterococcus"[Mesh] OR "Saccharomyces"[Mesh] OR "Lactococcus"[Mesh] OR "Megasphaera"[Mesh] OR "Bifidobacterium"[Mesh] OR "Faecalibacterium"[Mesh]	553,003	305,648	968,182	171,887	44,356
#3 Outcomes	“fecal score”[tiab] OR “faecal score”[tiab] OR “weight gain”[tiab] OR “feed efficiency”[tiab] OR “diarrhea”[tiab] OR “diarrhoea”[tiab] OR “diarrheal”[tiab] OR “diarrhoeal”[tiab] OR “scours”[tiab] OR “scouring”[tiab] OR “intestinal development”[tiab] OR “intestinal bacterial community”[tiab] OR “microbiome”[tiab] OR “microbiomes”[tiab] OR “microbiota”[tiab] OR “microbial community”[tiab] OR “gut flora”[tiab] OR “intestinal flora”[tiab] OR “microbial flora”[tiab] OR “growth”[tiab] OR “health”[tiab] OR “mortality”[tiab] OR "Diarrhea/microbiology"[Mesh] OR "Diarrhea/mortality"[Mesh] OR "Diarrhea/veterinary"[Mesh] OR "Cattle/growth and development"[Mesh] OR "Microbiota"[Mesh] OR “gut health”[tiab] OR "Weight Gain"[Mesh]	3,987,048	2,297,396	10,221,498	984,443	519,527
#4	#1 AND #2 AND #3	661	2,126	1,021	85	44

Table 2. Definition of main and secondary outcomes.

<b>Outcome</b>	<b>Definition</b>
Average daily gain	rate of weight gain per day over a specified period
Feed efficiency	ratio of feed intake to live weight gain
Body traits	indirect method to estimate the body weight
Heart girth	circumference of the animal just behind the withers
Body length	distance from the point of the shoulders to the ischium.
Hip width	distance between the left and right of femurs
Wither height	distance from the floor beneath the calf to the top of the withers directly above the center of the shoulder
Dry matter intake	amount of feed consumed per day on a moisture-free basis
Papilla length	distance from the tip to the base of the papilla along its axis
Papilla width	measure of the halfway of perpendicular papilla length
Ruminal pH	hydrogen ion concentration in rumen content
Volatile fatty acid concentration	concentration of acetate, propionate, and butyrate in the rumen content
Beta-hydroxybutyrate	measurement of the concentration of this ketone body in blood
Glucose	measurement of the concentration of this hexose in blood
Immunoglobulin	measurement of the concentration of IgG, IgA, IgM or IgE in blood
Fecal score	visual evaluation of the fecal consistency and an indirect indicator of the severity and the presence of diarrhea
Diarrhea incidence	proportion of the calves identified as diarrheic within a specified period
Pneumonia incidence	proportion of the calves identified with pneumonia within a specified period
Mortality	number of calf deaths during the specific time
Cytokines	concentration of signaling proteins that can be pro- or anti-inflammatory in blood
Days on treatment	the duration of systemic therapy that calves received during the experimental time
Microbiota	the microorganisms present in the rumen or gut
Microbiome	the total genome of microorganisms that reside in the rumen or gut



### Stage of Review at Time of This Submission

<b>Stage</b>	<b>Started</b>	<b>Completed</b>
Searches	Yes	Yes
Search Results Screened Against Eligibility Criteria	Yes	Yes
Data Extraction	Yes	No
Data Analysis	No	No

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