Title: The efficacy of antibiotic treatments in dairy cows at dry-off to prevent new intra-mammary infections during the dry-period or clinical mastitis during early lactation: A protocol for a systematic review.

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Author contributions:
All authors contributed to the development of the review question and the methodology described in this proposal. HW and JG developed the search strategy. JMS drafted the protocol, with input and final approval of all co-authors.

Registration:
This protocol is archived in the University of Guelph's institutional repository (The Atrium; https://atrium.lib.uoguelph.ca/xmlui/handle/10214/10046) 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 (Liberati et al., 2009). This protocol is reporting using the items (headings) recommended in the PRISMA-P guidelines (Moher et al., 2015).

Support. Funding support for this systematic review / meta-analysis / network meta-analysis, including the development of the protocol, was provided by The Pew Charitable Trusts.

Introduction.

Rationale: The majority of antibiotic use in the dairy industry is for the treatment and prevention of intramammary infections (IMI); in the Netherlands, approximately 60 % of all antimicrobial use in dairy is for this purpose, with two-thirds being dry cow therapy (Lam et al., 2012). In the United States, over 90 % of dairy cows receive dry cow therapy after every lactation (USDA-APHIS, 2016), with the goal of treating or preventing IMI during the dry period. These infections are strongly associated with risk of development of clinical mastitis in the first two weeks post-calving, which represents the highest risk period for this disease (Green et al., 2002). To combat this, blanket dry cow therapy (intramammary antimicrobial treatment of all quarters of all cows after the last milking of the lactation) was recommended for decades as part of a comprehensive strategy to reduce IMI in the dry period (Neave et al., 1969), and has been widely adopted in North America and the United Kingdom (Ruegg, 2017). Although cow-

level selective dry cow therapy has been in use in some regions for several decades (Schultze, 1983), interest has more recently increased worldwide, in part driven by concern for antimicrobial use and its relationship with the development of antimicrobial resistance between species (WHO, 2015), including nation-specific regulations (Santman-Berends et al., 2016). Selective dry cow therapy has been employed because it is a means to rapidly reduce the amount of antimicrobials used in dairy cattle (Vanhoudt et al., 2018), rather than because it is known to contribute importantly to antimicrobial resistance (Oliver et al., 2011).

With a greater concern for prudent antibiotic use in the dairy industry, it is important that decision making with regards to dry cow therapy at both the cow and herd levels be evidence-based. Choosing ineffective antibiotics, or using antibiotic when not warranted, unnecessarily contributes to use while having little impact on controlling disease, which has substantial bearing to both profitability and animal welfare (Leslie & Petersson-Wolfe, 2012). Systematic reviews of randomized controlled trials yield the highest level of evidence for efficacy of treatment under field conditions (Sargeant and O'Connor, 2014), and comparative efficacy can be examined using network meta-analysis for multiple comparisons. Establishing the efficacy of both cow-level antibiotic therapy and herd-level dry cow antibiotic protocols for the prevention of IMI will serve to improve decision makers' ability to engage in effective stewardship of antibiotics.

Objectives: The objective of this protocol is to describe the methods for a systematic review and network meta-analyses to address the efficacy of antibiotic dry cow treatments to prevent mastitis. The specific review questions to be addressed in this protocol (and the subsequent review) are as follows:

1. At the individual cow level: What is the efficacy of antibiotic treatments at dry-off to prevent new IMI during the dry-period or clinical mastitis during the subsequent lactation? The specific PICO elements, which will define the eligibility criteria, are as follows:
   i. *Population:* Dairy cows after their first (or greater) lactation without existing IMI at cessation of milking.
   ii. *Intervention:* Dry-cow interventions containing antibiotics given systemically or intra-mammary with or without other concurrent dry cow treatment.
   iii. *Comparator:* Non-antibiotic preventive intervention, different antibiotic, placebo, or no treatment.
   iv. *Outcomes:* Critical outcomes will include i) incidence of incidence of IMI during the dry-cow period immediately following the intervention, ii) incidence of IMI during the first 30 days of the subsequent lactation and iii) incidence of clinical mastitis during the first 30 days of the subsequent lactation. Secondary outcomes will include total antibiotic use during the first 30 days of the subsequent lactation, milk production during the subsequent lactation, somatic cell count during the first test of the subsequent lactation or the average of the first 3 tests of the subsequent lactation, and the risk of culling due to mastitis during the subsequent lactation.

2. At the group level: What is the efficacy of antibiotic treatment of all quarters of all cows in a group at dry-off compared to selective dry-cow treatment?

i. *Population:* Groups of dairy cows at cessation of milking after their first (or greater) lactation.
ii. *Intervention:* Blanket dry-cow treatment with an antibiotic-containing product.
iii. *Comparator:* Selective dry-cow treatment regime.
iv. *Outcomes:* Critical outcomes will include incidence of clinical mastitis during the first 30 days of the subsequent lactation, and reduction in new or existing IMI during the dry-cow period or during the first 30 days of lactation. Secondary outcomes will include total antibiotic use, milk production, somatic cell count, and the risk of culling due to mastitis during the subsequent lactation, as defined at the individual-level, but amalgamated at the group level.

Methods

Eligibility criteria: In addition to eligibility criteria as described in the PICO elements described above, eligibility criteria will include publication in English. Both published and non-published (grey literature) studies are eligible, provided they report the results of a primary research study with a concurrent comparison group using an eligible study design.

Study designs eligible: Controlled trials with natural disease exposure will be eligible. During full-text eligibility screening, we will identify studies that appear to address the review questions but using an observational design or an experimental design with deliberate disease induction; however, these studies will not be included in further steps of the review.

Information sources:

We will conduct the literature search in a range of relevant bibliographic databases and other information sources containing both published and unpublished literature. Table 1 presents the resources to be searched.

Table 1: Databases and information sources to be searched

Database / information source	**Interface / URL**
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	Ovid SP
CAB Abstracts	CAB Interface
Science Citation Index	Web of Science
Conference Proceedings Citation Index – Science	Web of Science
Agricola	Proquest

We will also hand-search the table of contents of the following relevant conferences from 1997 to 2018:

- Proceedings of the American Association of Bovine Practitioners;

- World Association for Buiatrics;
- National Mastitis Council Proceedings

The FDA website containing the Freedom of Information New Animal Drug Approvals (NADA) summaries also will be searched.

Search strategy:

A Science Citation Index (Web of Science) search strategy designed to identify studies of antibiotic treatments during the dry-off period in dairy cattle is presented in Table 2. The search strategy employs a multi-stranded approach to maximize sensitivity. The conceptual structure is as follows:

- Dairy cows AND dry off AND antibiotics;

OR

- Dry cow AND antibiotics;

OR

- A precise search for dry cow therapy, management, interventions, strategies or treatments in order to retrieve any records missed by the two combinations above.

Table 2: Search strategy to identify studies of antibiotic treatments during the dry-off period in dairy cattle in Science Citation Index (Web of Science)

# 14	#13 OR #12	893
# 13	TS=(("dry cow" OR "dry cows") NEAR/3 (therap* OR manag* OR intervention* OR treat* OR strateg*))	411
# 12	#11 AND #7	712
# 11	#10 OR #9 OR #8	593,401
# 10	TS=("albamycin" OR "amoxicillin" OR "amoxycillin" OR "ampicillin" OR "benzathine" OR "cathomycin" OR "cefalexin" OR "cefapirin" OR "cefalonium" OR "cefquinome" OR "ceftiofur" OR "cephalexin" OR "cephapirin" OR "cephalonium" OR "cephapirin" OR "chlortetracycline" OR "cloxacillin" OR "CTC" OR "danofloxacin" OR "dicloxacillin" OR "dihydrostreptomycin" OR "enrofloxacin" OR "erythromycin" OR "florfenicol" OR "framycetin" OR "gamithromycin" OR "gentamicin" OR "gentamycin" OR "lincomycin" OR lincosamide* OR "neomycin" OR "novobiocin" OR "oxytetracycline" OR "penethamate" OR "penicillin" OR "pirlimycin" OR "piroline" OR "spectinomycin" OR "sulfadimethoxine" OR "sulfafurazole" OR "sulfamethoxazole" OR "sulfisoxazole" OR "sulphadimethoxine" OR "tetracycline" OR "tildipirosin" OR "tilmicosin" OR "trimethoprim" OR "tulathromycin" OR "tylosin")	147,813
# 9	TS=(antimicrobial* OR "anti-microbial*" OR antibiotic* OR "anti-biotic*" OR antibacterial* OR "anti-bacterial*" OR antiinfect* OR anti-infect* OR bacteriocid* OR bactericid* OR microbicid* OR "anti-mycobacteri*" OR antimycobacteri*)	507,630
# 8	TS=("SDCT" OR "BDCT")	140
# 7	#6 OR #5	9,647

6 TS=("dry cow" OR "dry cows") 1,186
5 #4 AND #3 8,965
4 TS=("drying off" OR "dry off" OR "dried off" OR "dry up" OR "drying up" OR "dried up" OR "drying period*" OR "dry period*" OR "dry udder*" OR "dry teat*" OR "pre-partum" OR "prepartum" OR (("end" OR finish* OR stop* OR ceas*) NEAR/3 lactat*) OR nonlactat* OR "non-lactat*" OR postlactat* OR "post-lactat*" OR postmilk* OR "post-milk*" OR "involution" OR "steady state") 236,415
3 #2 OR #1 486,431
2 TS=(ayrshire* OR "brown swiss*" OR "busa" OR "busas" OR canadienne* OR dexter* OR "dutch belted*" OR "estonian red*" OR fleckvieh* OR friesian* OR girolando* OR guernsey* OR holstein* OR illawarra* OR "irish moiled*" OR jersey* OR "meuse rhine issel*" OR montbeliarde* OR normande* OR "norwegian red*" OR "red poll" OR "red polls" OR shorthorn* OR "short horn*") 53,889
1 TS=("cow" OR "cows" OR "cattle" OR heifer* OR "dairy" OR "milking" OR "bovine" OR "bovinae" OR buiatric*) 460,464

The search strategies will not be limited by date, language, or publication type.

We will conduct searches using each database listed in the protocol, translating the strategy appropriately to reflect the differences in database interfaces and functionality.

Study records:

Data management: We will download the results of searches in a tagged format and load them into bibliographic software (EndNote). The results will be de-duplicated using several algorithms. We will save results from resources that do not allow export in a format compatible with EndNote in Word or Excel documents as appropriate and manually de-duplicate. The de-duplicated search results 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, abstracts and titles will be screened for eligibility. Two reviewers will independently evaluate each citation for relevance using the following questions:

1) Does the study involve antibiotic-containing dry cow treatments in dairy cattle at the individual level or an evaluation of group-level strategies for administering antibiotic-containing dry cow treatments (such as selective treatment versus blanket treatment)?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
2) Is there a concurrent comparison group? (i.e. controlled trial with natural or deliberate disease exposure or analytical observational study)?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
3) Is the full text available in English?

YES (include for full text screening), NO (EXCLUDE), UNCLEAR (include for full text screening)

Citations will be excluded if both reviewers responded "no" to any of the questions. Any disagreements will be resolved by consensus. If consensus cannot be reached, the article will be marked as "unclear" and will advance to full text screening. A pre-test will be conducted by all reviewers on the first 250 abstracts to ensure clarify of questions and consistency of understanding of the questions.

Following title/abstract screening, eligibility will be assessed through full-text screening. The same questions will be used as for the title / abstract screening. Two reviewers will independently evaluate the full text articles, with any disagreements resolved by consensus. If consensus cannot be reached, a third reviewer will be used.

Data collection process: Data will be extracted by two reviewers working independently. Any disagreements will be resolved by consensus or, if consensus cannot be reached, a third reviewer will be used. Authors will not be contacted to request missing data or to clarify published results. A form for data extraction will be created for this review in DistillerSR® and pre-tested on 4 full text articles to ensure question clarity.

Data items:

Study level data to be extracted include:

- Study design: experimental with natural disease exposure, experimental with deliberate disease exposure ("challenge trial"), or analytical observational
- Country
- Commercial versus research trials
- Year the study was collected
- Months of data collection
- Breed of cattle
- Lactation number (mean for entire group or mean by group if provided)
- Definition of intervention:
    - Antibiotic(s) used, route of administration, frequency of administration, dose, any concurrent treatments,
    - In addition, for the group level review question, details on the definition of selective dry cow therapy.
- Unit of allocation (Cluster (pen) or individual)
- Description of comparison group

The above data will be collect for all of the primary hypothesis-testing studies that are identified as relevant at full text screening (i.e., experimental studies with natural disease exposure, experimental studies with deliberate disease induction, and analytical observational

studies). The arm level data, described below, will be extracted only for experimental studies with natural disease exposure.

Arm level data collected:

- Number of animals enrolled
- Number of animals lost to follow up
- Number of animals analyzed
- Any additional concurrent treatments – studies with additional treatments will be considered as separate treatments arms to studies with only an antibiotic-containing dry cow product.

Outcomes and prioritization:

Critical outcomes (in order of prioritization):

- Incidence of clinical mastitis during the first 30 days of the subsequent lactation
- Reduction in new IMI during the dry-cow period (individual level) or new and existing IMI during the dry-cow period (group level).
- Reduction of new IMI during the first 30 days of lactation (individual level) or new and existing IMI during the dry-cow period (group level).

Secondary outcomes (in order of prioritization):

- Total antibiotic use to treat clinical mastitis during the first 30 days of the subsequent lactation.
- Milk production during the subsequent lactation
- Somatic cell count the first test of the subsequent lactation, or the average of the first 3 tests of the subsequent lactation.
- Risk of culling due to mastitis during the subsequent lactation.

These outcomes were prioritized based on their impact on animal health and welfare and their economic importance. Formal evaluation of these criteria for prioritization was not undertaken.

Data will be collected to describe the outcomes that were evaluated for all eligible studies, regardless of study design. The specific outcome data, as described below, will be extracted only for experimental studies with natural disease exposure.

Outcome data to be collected:

1) Incidence of clinical mastitis during the subsequent lactation
    a. Case definition of clinical mastitis
    b. Level at which outcome data were measured (quarter, composite individual, group)

2) Outcomes related to IMI
    a. Method of determining the study subjects were free of IMI at dry-off (individual level review question):

i. Negative culture at dry off (extract data on quarter or composite)
ii. Somatic cell count below a threshold (extract data on threshold and time period for assessment)
iii. No clinical case of mastitis during specified duration (extract data on duration)
iv. Other (specify)
v. Not assessed – excluded from meta-analysis, as cannot distinguish incident from prevalent cases.

b. Level at which the outcomes were measured (quarter, composite individual, group)
c. Method of diagnosis of IMI status:
    i. Number of milk samples used to classify IMI status and timing of sampling for cultures
    ii. Whether National Mastitis Council (NMC) Laboratory Methods were stated as used
    iii. If other methods were used in parallel or exclusively e.g. PCR; Petrifilm or selective media
d. Type of bacteria:
    i. Individual bacteria results will be extracted for: Coliforms, Strep. uberis, Strep. agalactica, Staph. aureus
    ii. Grouped bacteria results will be extracted for: Major contagious mastitis pathogens (Staph. aureus and Strep. agalactia), and Major environmental mastitis pathogens (Strep. uberis and coliforms)

For each of the primary and secondary outcomes, we will extract the possible metrics in the following order:

- 1st priority: Adjusted summary effect size ($_{adjusted}$ risk ratio or $_{adjusted}$ odds ratio, mean differences for continuous outcomes) and variables included in adjustment and corresponding precision estimate.
- 2nd priority: Unadjusted summary effect size
- 3rd priority: Arm level risk of the outcome, or arm level mean of the outcome (continuous outcomes)
- For cluster-randomized designs, the approach to the analysis of non-independent observations i.e., not reported, ‘multilevel model,' a ‘variance components analysis' or may use ‘generalized estimating equations (GEEs),' among other techniques.
- Variance components

If variance estimates are not reported, but the authors provide the data necessary to calculate them using standard formulas, we will calculate these data. If results are provided only in graphical form, we will estimate the numerical results using WebPlotDigitizer

(https://automeris.io/WebPlotDigitizer/), if the full text is in a suitable format for using this resource.

Risk of bias in individual studies: Risk of bias will only be assessed for controlled trials with natural disease exposure. Risk of bias assessment will be performed at the outcome level for each of the critical outcomes using the Cochrane risk of bias instrument (Higgins et all, 2016), with the signaling questions modified as necessary for the specific review question. The ROB-2.0 for clustered –RCT and individual RCTs will be used depending upon the study design. These tools are available at https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool.

Data synthesis:

Network meta-analysis. Network meta-analysis (aka mixed treatment comparison meta-analysis) will be conducted for each of the primary outcomes and separately for the individual level and group level questions, as the group level question by necessity combines incident and prevalent IMI. Network meta-analysis will use the approach described by NICE Decision Support Unit technical document (Dias et al., 2014; O'Connor et al., 2013, O'Connor et al., 2016). The approach to reporting will use the PRISMA- NMA (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx). Planned a priori sub-group analyses will be conducted for randomized versus non-randomized trials and, for the group level review question, by method of selecting the cows for treatment.

Meta-bias(es): Small study effects ("publication bias") will be assessed for all antibiotic-comparator combinations where there are at least 10 studies in the meta-analysis. If feasible, we will use approaches to assessing publication bias in the network of evidence using previously proposed approaches (Mavridis et al., 2013; Mavridis et al., 2014).

Confidence in cumulative evidence: The quality of evidence for each critical outcome will be assessed using the approach proposed by GRADE (GRADE, 2015, Puhan et al., 2014), while also considering the nature of the network meta-analysis (Jansen et al., 2011).

Discussion:

This systematic review will provide a synthesis of the current evidence regarding the efficacy of antibiotic-containing dry cow treatments at the individual level for preventing mastitis and treatment strategies at the group level for preventing and treating mastitis during the dry cow period and early lactation. Results will be helpful for veterinarians and dairy producers when making evidence-informed decisions regarding the use of antibiotic-containing dry cow treatment. The results also will be helpful for identifying specific gaps in knowledge related to the efficacy of these products for targeting additional research.

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