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Antimicrobial-based dry cow therapy approaches for cure and prevention of intramammary infections: a protocol for a systematic review and meta-analysis

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Abstract

In dairy herds, application of antimicrobials at drying-off is a common mastitis control measure. This article describes a protocol for systematic review and meta-analysis to address three crucial points regarding antimicrobial usage at drying-off: (1) comparative efficacy of antimicrobials used for preventing new and eliminating existing intramammary infections (IMI); (2) comparison of selective and blanket dry cow therapy approaches in preventing new and eliminating existing IMI; and (3) assessment of the extra prevention against new IMI that can be gained from using antimicrobial-teat sealant combinations versus antimicrobials alone. Five PICO (Population, Intervention, Comparator, Outcome) questions were formulated to cover the three objectives of the review. Medline, CAB Abstracts, Web of Science, and conference proceedings will be searched along with iterative screening of references. Articles will be eligible if: (1) published after 1966; (2) written in English or French; and (3) reporting field clinical trials and observational studies, conducted on dairy cows at drying-off, with at least one antimicrobial-treated group and one IMI-related outcome. Authors will independently assess the relevance of titles and abstracts, extract data, and assess bias and the overall quality of evidence. Results will be synthesized and analyzed using pairwise and network meta-analysis. The proposed study will significantly update previously conducted reviews.

Introduction

Intramammary infections (IMI) are a perpetual threat to the productivity and, consequently, the profitability of the dairy industry worldwide (Halasa *et al.*, 2007). Dry cow therapy (DCT; i.e. treatment of all or some cows with antimicrobials at drying-off) is a cornerstone of mastitis control. DCT is recommended for both treatment of existing IMI and for prevention of new IMI acquisition during the dry period, and various drugs have been specifically designed for such use. Despite the controversy surrounding prophylactic use of antimicrobials in production animals, the National Mastitis Council's Recommended Mastitis Control Program still suggests treatment of all cows (i.e. blanket DCT) at drying-off (NMC, 2006). Recently, however, identification of infected cows at drying-off (using diagnostic tests) and treatment of infected cows only, also known as selective DCT, has been the object of research (Berry and Hillerton, 2002; Cameron *et al.*, 2013). It has also been shown that a teat sealant (TS) can be used in conjunction with blanket or selective DCT to prevent IMI acquisition during the dry period (Sanford *et al.*, 2006; Cameron *et al.*, 2014, 2015). Therefore, on modern dairy farms, managers have to make decisions regarding: (1) the type of antimicrobials to be used at drying-off; (2) whether all (blanket DCT) or some (selective DCT) cows will be treated at drying-off; and (3) whether a TS will be used in conjunction with the antimicrobial treatment. The objective of this protocol is to describe the methodology for a systematic review and meta-analysis of the various antimicrobial-based DCT strategies that can be used at drying-off to cure or prevent IMI. This review will complement an ongoing review on non-antimicrobial drying-off strategies (Francoz *et al.*, 2016).

Systematic Review

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Objectives

The general objective of this review is to identify and compare the different antimicrobial-based strategies that can be used at drying-off to treat and prevent IMI in dairy cows. The specific objectives are described in the following five PICO (Population, Intervention, Comparator, Outcome) questions.

Choice of antimicrobial at drying-off

(1) In dairy cows (i.e. the population), which antimicrobial treatment (i.e. the comparators) when administered at dry-off (i.e. the intervention) is the most efficient for preventing new IMI (i.e. the outcome)?
(2) In infected dairy cows (i.e. the population), which antimicrobial treatment (i.e. the comparators) when administered at dry-off (i.e. the intervention) is the most efficient for eliminating existing IMI (i.e. the outcome)?

Blanket versus selective dry-cow treatment

(3) In dairy cows (i.e. the population), is selective DCT (i.e. the intervention) as efficient as blanket DCT (i.e. the comparator) in preventing new IMI (i.e. the outcome)?
(4) In infected dairy cows (i.e. the population), is selective DCT (i.e. the intervention) as efficient as blanket DCT (i.e. the comparator) in eliminating existing IMI (i.e. the outcome)?

Complementing an antimicrobial treatment with a TS

(5) In dairy cows (i.e. the population), how does the efficacy of an antimicrobial–TS combination administered at dry-off (i.e. the intervention) compared with an antimicrobial alone (i.e. the comparator) for preventing new IMI (i.e. the outcome)?

Materials and methods

This protocol is written in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement (Moher *et al.*, 2015). The systematic review and network meta-analysis (NMA) will be reported following the PRISMA-NMA extension statement to structure the contents of the final report (Hutton *et al.*, 2015).

Eligibility criteria

Study design

Controlled trials, randomized or not (i.e. cows/quarters allocated to interventions by non-randomization methods), will be included in our systematic review. In addition, studies in which cows were naturally or experimentally infected with any type of mastitis-causing pathogen will be retained. Both split udder and split herd designs will be included. Based on the experience of Francoz *et al.* (2017), the number of observational studies (case–control and cohort) answering our PICO questions is expected to be nil or very low. These study designs, however, will not be excluded *a priori*. Sometimes, the distinction between non-randomization trials and cohort studies is not quite clear, so they will be included, along with case–control studies, as 'non-randomized studies of interventions' (NRSI) (O'Connor and Sargeant, 2014; Di Girolamo *et al.*, 2017). Other study designs, including cross-sectional studies and descriptive studies such as case-series, case-reports, or expert opinions will be excluded. Review articles and meta-analyses will not be included *per se*; however, every single study involved in those reviews will be evaluated for inclusion.

Population

The population of interest will be lactating dairy cows at drying-off; tropical and exotic breeds will be excluded. For evaluating IMI elimination, infected quarters (or cows) at drying-off will be our target population. Because infected quarters at drying-off can still acquire new IMI by a different pathogen over the dry period, both non-infected and infected quarters (or cows) at drying-off will be included when assessing the prevention of new IMI.

Interventions and comparators

For the first two PICO questions, the interventions are all antimicrobials that can be administered by all routes with any dose; the corresponding comparators are placebo or no treatment, or active controls if other antimicrobials (with the same treatment regimen regarding blanket vs. selective and use of TSs) were used. For the third and fourth PICO questions, the interventions are selective DCT regimens involving any antimicrobials as described above; the comparators are blanket DCT regimens for the same antimicrobials. For the fifth PICO question, the interventions are antimicrobial–TS combinations involving any antimicrobials as described above; the comparators are the same antimicrobials used without the TS. Studies investigating the efficacy of TS alone will be excluded, since this topic is already under investigation in an ongoing review (Francoz *et al.*, 2016).

Outcomes

The primary outcomes under investigation will be IMI incidence risk for the first, third, and fifth PICO questions and IMI cure risk for the remaining PICO questions. Since some studies may only report on IMI prevalence post-calving, this outcome will also be considered as a primary outcome (a proxy for IMI incidence and cure risk). For determination of the quarter (or cow) IMI pre-dry and post-calving statuses, only studies using the following diagnostic tests will be retained: milk somatic cell count (SCC), milk bacteriological culture (external laboratory or on farm), and polymerase chain reaction (PCR). In studies using milk bacteriological culture or PCR as a diagnostic test, milk samples will have to have been collected aseptically. Moreover, the post-calving IMI status will have to have been measured within 14 days of calving, to ensure that the infection or cure most likely occurred during the dry period. A quarter will be deemed to have experienced a new IMI when a specific pathogen species is isolated in the calving or post-calving samples from a quarter that was free of the pathogen species in the drying-off sample. Furthermore, a cure of IMI will have occurred if a specific pathogen species was present at drying-off and not found in the post-calving sample.

Report characteristics

To be included, articles will have to be published after 1966, because the oldest article retained in a previous review on this topic was published in 1967 (Halasa *et al.*, 2009*a*, 2009*b*). In addition, articles will have to be written in English or French. Finally, if two or more articles present results from the same trial (e.g. preliminary vs. final results), only the most complete article will be included.

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Information sources

Three electronic sources of information will be used: Medline, CAB Abstracts, and Web of Science. These sources have shown to cover most of the veterinary literature (Grindlay *et al.*, 2012). Conference proceedings from the National Mastitis Council and the American Association of Bovine Practitioners will also be searched. In addition, the list of references from each included paper will be searched to identify additional publications not initially obtained by the database search.

Search strategy

A search strategy was developed with search terms adapted from the Halasa *et al.* (2009*a*, 2009*b*) and Francoz *et al.* (2016, 2017) papers. The search terms were divided into four components describing: (1) the population of interest (i.e. dairy cows); (2) the outcome studied (i.e. mastitis); (3) the specific period of interest (i.e. the dry period); and (4) the interventions and comparators (i.e. antimicrobials and/or TS). The Boolean operator 'AND' was used to combine the four components, while the 'OR' operator was used to join the terms within each component. Search terms and keywords have been adapted to the specifications required for each database. Development of the search terms and elaboration of the search strategy were done in collaboration with a librarian (Rafael Rangel Braga), Faculté de Médecine Vétérinaire, Université de Montréal, as per (Shamseer *et al.*, 2015). The algorithm for searching each database is presented in Supplementary Appendix 1.

Study records

Data management

All search result citations will be imported and managed in EndNote bibliographic software (version X8.2 for Windows, Thomson Reuters, New York, NY, USA), then duplicate records will be detected automatically, based on title, author(s) and publication year, and further screened out manually. After full retrieval of articles, a custom-built Access database (version 2016, Microsoft Corp., Redmond, WA, USA) will be used for data extraction.

Selection process

In order to identify potentially relevant studies, each title and abstract will be evaluated by two independent reviewers. Each abstract will be reviewed by one of the first two authors (M. A. and F. K.), and one of the other co-authors will be selected to act as the second reviewer. A screening checklist designed according to the predefined inclusion and exclusion criteria will be used to assess the relevance of the abstracts. Only abstracts with a positive or unclear response to all questions will be eligible to proceed to the next stage, and only when the reviewers agree. Any disagreement will be resolved by consensus among the research team. Reviewers will be blinded to author names, journal, and year of publication when reviewing the abstracts. The screening tool is included in the study protocol as a part of the supplementary materials in Appendix 2.

A second evaluation will be conducted to retain only citations where a full text is available in French or English, and where all answers to the checklist of Appendix are 'yes'. This evaluation will be done by two independent reviewers, in the same fashion as described above. A PRISMA flow diagram will be used to document the flow of records (Moher *et al.*, 2009).

Data collection process

A data extraction form will be developed for the current project based on the forms used in the previous systematic review projects (Dufour *et al.*, 2011; Francoz *et al.*, 2016, 2017). Data extraction will be performed by three independent reviewers (M. A. and F. K. as well as one of the other co-authors). Any discrepancies in the extracted data will be resolved by consensus among the research team.

Authors of studies, for which some of the needed information is unclear or missing, will be contacted for clarification via email, and a follow-up email will be sent 2 weeks later if no feedback is received. Then, authors will be provided 2 more weeks to respond. If there is no response from authors and the missing information is crucial, the study will not proceed to the meta-analysis.

Data items

The following information will be extracted: (1) study characteristics: year of publication, type of publication (journal article vs. conference proceeding), country; (2) study methods: study design (RCT, NRSI or case–control), type of exposure (natural IMI vs. experimental challenge), the study's main objective (e.g. non-inferiority trial, analysis of risk factors); (3) population-related information: number of herds, number of cows, number of quarters, inclusion criteria (age, breed, minimal or maximal planned dry period length, and other inclusion and exclusion criteria), and study unit (quarter, cow, or herd); (4) intervention and comparator-related information: antibiotic (trade name, active ingredient, dose, route and frequency of administration, and treatment duration if multiple administrations were needed), TS (trade name, active ingredient, dose, route (systemic vs. intramammary infusion) and frequency of application, and treatment duration, if applied more than once), description of negative control (in particular, whether a placebo or no treatment was used), and for selective DCT the approach by which infected cows/quarters were selected for treatment at drying-off; (5) outcome-related information: unit of assessment (cow vs. quarter), diagnostic tests for the detection of IMI (SCC, bacteriological culture, or PCR), thresholds used for the definition of IMI incidence and cure risk, follow-up time, results for targeted outcomes; and (6) quality-related information: whether intention-to-treat analysis was used, and whether an *a priori* sample size calculation was reported.

Outcome and prioritization

Primary outcomes are: IMI cure risk and IMI incidence risk over the dry period, and post-calving IMI prevalence. Secondary outcomes that will be extracted are: early lactation (i.e. 0–4 months), clinical mastitis incidence, subsequent lactation milk production, and SCC, and for studies investigating selective DCT, proportion of untreated cows.

Risk of bias in individual studies

Clarity, completeness, and accuracy of reporting are going to be assessed using a full or reduced (modified) checklist of items based on the REFLECT statement (O'Connor *et al.*, 2010) for controlled trials and STROBE-VET statement (Sargeant *et al.*, 2016) for observational studies.

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Sources of bias will be assessed as part of the data extraction using the revised Cochrane risk of bias tool (RoB 2.0) for randomized trials (Higgins *et al.*, 2016). Five domains will be used to assess the bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The risk of bias will be reported as 'low risk', 'high risk', or 'unclear'. An overall risk of bias judgment for the outcome is based on the collective domain-level judgments. Additional considerations will be made for different trial designs (simple parallel-group trials, cluster-randomized trials, and cross-over trials). For NRSI, the Cochrane ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions; Sterne *et al.*, 2016) tool will be used.

Data synthesis and meta-bias

Descriptive results of all selected studies will be computed. Incidence (risk) ratios (RR) will be computed for each comparison in each study. For both IMI incidence and cure, the ratio will be computed by dividing incidence (cure) of IMI in treated quarters/cows by incidence (cure) of IMI in control quarters/cows. The number needed to treat for either preventing or curing one case of IMI will be computed whenever data are available (Schunemann *et al.*, 2017). Secondary outcome analyses will be determined by the number of articles reporting them.

Pairwise meta-analysis will be conducted to synthesize the results of studies addressing the last three PICO questions. For the first two questions, pairwise comparisons will be used for the studies with similar comparisons, either active to non-active control or active to active treatment arms. The RR from each study will be pooled using a random-effects model because of the anticipated variability between trials.

Meta-regression will be used to identify the underlying sources of heterogeneity. Potential explanatory variables include: publication year and type, study design, exposure type, diagnostic test, type of antimicrobial, type of TS, dose, route, bias-domain variables, and baseline risk. If the underlying risk contributes both substantially and significantly to the between-study heterogeneity, a random slopes model will be implemented in either a Bayesian or a frequentist framework, as described by Dohoo *et al.* (2007). If the number of studies for a given comparison is sufficient, a multivariable model may be developed based on epidemiological and statistical considerations.

Sensitivity analyses will be performed by eliminating each study, one at the time, to investigate the impact of each individual study on the overall summary effect. Publication bias will be assessed graphically using funnel plots and if asymmetry is noted, a contour-enhanced funnel plot will be sketched to investigate the cause of asymmetry (Peters *et al.*, 2008).

For the first two review questions, and as the data allow, a NMA will be used to combine and compare treatment effects of all antimicrobials, by integrating direct and indirect evidence (Lu and Ades, 2004; Caldwell *et al.*, 2005; Jansen *et al.*, 2008; White *et al.*, 2012; Dias *et al.*, 2018*a*, 2018*b*). Interventions that cannot be included in the NMA will be summarized and narratively described in the final review.

Confidence in cumulative evidence

The quality of evidence for all outcomes will be rated, by two review authors (M. A. and F. K.), independently, as 'high', 'moderate', 'low', or 'very low' following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology (Schünemann *et al.*, 2013). Any discrepancies will be resolved by consensus within the research team. Judgments will be justified, documented, and incorporated into the reporting of results for each outcome. For NMA, the quality of each direct and indirect effect estimate will be rated according to Brignardello-Petersen *et al.* (2018). A summary of findings table will be prepared using GRADE pro software (GRADEpro GDT: GRADEpro Guideline Development Tool [Software], 2015).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1466252318000051.

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Role of funder. As per the research agreement, aside from providing financial support, the funders have no role in the design and conduct of the studies, data collection and analysis, or interpretation of the data. Researchers maintain independence in conducting their studies, own their data, and report the outcomes regardless of the results. The decision to publish the findings rests solely with the researchers.

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