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## Invited review: Effectiveness of precalving treatment on postcalving udder health in nulliparous dairy heifers: A systematic review and meta-analysis

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### ABSTRACT

Clinical mastitis affects 3% of primiparous dairy cattle (heifers) in the first month after calving. Additionally, the prevalence of intramammary infection (IMI) in the months before first calving is high, resulting in a high prevalence of heifers calving with IMI. Precalving therapy is an accepted recommendation for reducing mastitis in multiparous cows, but prophylactic treatment for heifers is uncommon in North America. Objectives of this study were to (1) quantify changes in postcalving udder health in heifers following application of a precalving treatment; (2) compare effectiveness among various types of treatments; and (3) compare effectiveness of various types of treatments against specific pathogens. A systematic review was conducted comparing interventions aimed at improving udder health in heifers. Of 62 included studies, 48 clinical trials were used in a meta-analysis. Data were synthesized using a random effects model for meta-analysis, followed by sub-group analyses comparing treatment types, and specific pathogens with statistical testing using meta-regression. Occurrence of mastitis (defined as elevated somatic cell count, clinical mastitis, and IMI) was reduced in treated heifers compared with untreated controls with a pooled risk ratio of treated to untreated heifers of 0.56 (95% confidence interval: 0.47 to 0.67). Upon stratification by treatment types, teat sealants and combination therapies (vaccines and antimicrobials; antimicrobials and teat sealants; and all 3) were most effective at improving udder health with pooled risk ratios of 0.40 (95% confidence interval: 0.30 to 0.52) and 0.34 (95% confidence interval: 0.25 to 0.45), respectively. Antimicrobials and vaccines also reduced occurrence of IMI and subclinical and clinical mastitis when compared with untreated heifers. Al-

though variation was observed in the pathogen-specific effectiveness of treatments at reducing rates of disease, antimicrobials, teat sealants, and combinations of vaccines or teat sealants with antimicrobials were consistently effective, whereas vaccines were only effective for contagious pathogens. Recommendations for use of antibiotics should consider their relative benefit while also considering potential for increasing antimicrobial resistance.

**Key words:** heifer, mastitis, prepartum, treatment, meta-analysis

### INTRODUCTION

Mastitis is one of the most economically important diseases in the dairy industry (Seegers et al., 2003) as it has implications not only for animal health and welfare, but also for milk quality and production. The occurrence of mastitis is not only high in lactating cows, but also in heifers in the first weeks after calving (De Vlieghe et al., 2012; Naqvi et al., 2018). Heifers with (sub)clinical mastitis, IMI, or both are often not identified because they are not milked, and therefore their teats and milk typically are not examined (De Vlieghe et al., 2012). However, the prevalence of IMI in the months before the first calving is high, resulting in a high prevalence of heifers calving with IMI (De Vlieghe et al., 2012).

Although nonlactating heifers are not included in standard mastitis prevention plans like the 5-point schedule (Neave et al., 1969) or the relatively recent NMC 10-point plan (NMC, 2004), a variety of treatments to prevent or cure IMI in these heifers has been studied. Following a review on heifer mastitis (De Vlieghe et al., 2012), the NMC published a 10-point plan specifically for controlling heifer mastitis. In this new set of recommendations, only 2 were specific to heifers, whereas the others were similar to recommendations in the first 10-point plan. Some commonly used precalving treatments are vaccines, non-antimicrobial teat sealants, short- and long-term antimicrobials, and combinations of these treatments. Many studies have

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been conducted on effects of a single type of treatment in heifers (Edinger et al., 2000; Santos et al., 2004; Roy et al., 2007; Pellegrino et al., 2008). However, very few studies have compared types of therapies, and their results have been inconsistent (McDougall et al., 2009).

Previous studies have demonstrated and quantified a net positive benefit of various precalving treatments (Ataee et al., 2009; Duplessis et al., 2014; Passchyn et al., 2014), as well as characterizing pathogens causing ensuing infections. Systematic reviews have been conducted on the effectiveness of antimicrobial treatments in heifers (Nickerson, 2009), non-antibiotic strategies for prevention and control of mastitis in heifers (McDougall et al., 2009), and vaccines for lactating cows (Middleton et al., 2009), whereas reviews of postpartum mastitis and mastitis control have also described preventive treatments in heifers and lactating cows (Pyörälä, 2008; De Vliegher et al., 2012). However, no review has focused on quantifying treatment effectiveness in heifers, or compared efficacy of precalving treatment types using a meta-analysis to estimate overall effect size. Objectives of this study were therefore to (1) synthesize results from previous studies to determine and compare effectiveness of various types of precalving therapies aimed at improving udder health; and (2) determine and compare effectiveness of various types of precalving therapies against types of pathogens, grouped by etiology.

## MATERIALS AND METHODS

This systematic review and meta-analysis was conducted following a pre-specified protocol created using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (Shamseer et al., 2015).

### *Data Sources and Literature Search*

Online databases searched were CAB Abstracts, Web of Science (complete collection), AGRICOLA, MedLine, and SCOPUS, from inception to September 2017. In addition, 2 individuals (SAN and DBN) hand-searched references of existing reviews on the subject. Gray literature consisted of a search through all available conference proceedings in relevant conferences, as well as websites of pharmaceutical companies and the Proceedings of the World Buiatrics Congress (2000–2014) on The International Veterinary Information Service website. In addition, proceedings of the American Dairy Science Association (1957–2017) and National Mastitis Council (NMC; 1989–2017) annual meetings were searched. Experts in the field were also

contacted for information about potential ongoing or unpublished studies, and were identified through the review process or through direct communications at conferences (Mastitis Research Worker's meeting in November 2016, and NMC annual meeting in January 2017). No publication date or language filter was applied to the search, and the search was conducted as recommended (Egger et al., 2008).

The search strategy was split into 3 main components corresponding to the population of interest, intervention type, and study outcome. The population of interest included primigravid to primiparous dairy cattle, with the intervention having to be applied during pregnancy and udder health measured after calving. The interventions of interest were any kind of treatment applied precalving aimed specifically at improving udder health. This was intended to exclude interventions such as feed additives intended to improve overall health and growth, as it did not address the primary question of targeted and individual treatment of heifers. Full details of the search terms used are provided (Appendix).

### *Study Eligibility and Selection*

An initial screen of all titles was performed by 2 individuals (SAN and DBN) to determine if manuscripts were eligible for full text review for inclusion in the systematic review. If the title was not detailed enough to decide about moving forward with full-text screening, the abstract was scrutinized by 1 of the reviewers (SAN) to determine whether it was eligible. A manuscript needed to meet 2 conditions to be considered for a full text review: (1) The manuscript had to report on primary data; and (2) the manuscript had to report on an intervention aimed at improving udder health (no vaccines for other conditions such as leucosis, or treatment with anthelmintic products), although it may not necessarily be the primary aim of the study (comparing mastitis in 2 regions where a particular product may not be allowed).

This initial screen was designed to be fairly broad to encompass as many potentially relevant manuscripts for full text review. A full text review was then conducted on all of these screened manuscripts to ensure that some aspect of intervention was addressed in the manuscript. The reason for this full text screening step in the systematic review was that the second condition described above could have resulted in manuscripts whose primary goal was not assessing intervention effectiveness, but was included as a covariate in their analysis. As it was not the primary goal of the study, it may not have been reported in the abstract and a full text screening would capture these manuscripts.

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