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Invited review: Selective treatment of clinical mastitis in dairy cattle

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ABSTRACT

Treatment of clinical mastitis (CM) and use of antimicrobials for dry cow therapy are responsible for the majority of animal-defined daily doses of antimicrobial use (AMU) on dairy farms. However, advancements made in the last decade have enabled excluding nonsevere CM cases from antimicrobial treatment that have a high probability of cure without antimicrobials (no bacterial causes or gram-negative, excluding *Klebsiella* spp.) and cases with a low bacteriological cure rate (chronic cases). These advancements include availability of rapid diagnostic tests and improved udder health management practices, which reduced the incidence and infection pressure of contagious CM pathogens. This review informed an evidence-based protocol for selective CM treatment decisions based on a combination of rapid diagnostic test results, review of somatic cell count and CM records, and elucidated consequences in terms of udder health, AMU, and farm economics. Relatively fast identification of the causative agent is the most important factor in selective CM treatment protocols. Many reported studies did not indicate detrimental udder health consequences (e.g., reduced clinical or bacteriological cures, increased somatic cell count, increased culling rate, or increased recurrence of CM later in lactation) after initiating selective CM treatment protocols using on-farm testing. The magnitude of AMU reduction following a selective CM treatment protocol implementation depended on the causal pathogen distribution and protocol characteristics. Uptake of selective treatment of nonsevere CM cases differs across regions and is dependent on management systems and adoption of udder health programs. No economic losses or animal welfare issues are expected when adopting a selective versus blanket CM treatment protocol. Therefore, selective CM treatment of nonsevere cases can be a practical tool to aid AMU reduction on dairy farms.
Key words: antimicrobial use, dairy cattle, clinical mastitis, selective treatment, rapid diagnostic tests

INTRODUCTION

In the dairy industry, antimicrobials are most frequently used for dry cow therapy or for treatment of clinical mastitis (**CM**) when measured using animal-defined daily doses (Kuipers et al., 2016; Stevens et al., 2016; Lardé et al., 2021). It is widely recognized that antimicrobial use (**AMU**) drives emergence and main-

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tenance of antimicrobial resistance (**AMR**) (Davies and Davies, 2010; Holmes et al., 2016). Although clear evidence of the contribution of livestock-associated AMU toward AMR in human health care settings is lacking, this does not affect increased public pressure to reduce AMU on dairy farms as outlined in the Global Action Plan on Antimicrobial Resistance by the World Health Organization, the World Organization for Animal Health, and the Food and Agriculture Organization (WHO, 2015; WOAH, 2016; FAO, 2021). Fortunately, interventions aimed at reducing AMU in livestock can decrease AMR prevalence, in both livestock and humans (Tang et al., 2017; Nobrega et al., 2020). Not surprisingly, effects of reducing AMU in livestock on AMR in human pathogens potentially acquired from livestock were more prominent in people having direct contact with livestock compared with the general public (Tang et al., 2017).

Considering that nonselective, or blanket, antimicrobial treatment of CM is a common practice in countries with large dairy industries (e.g., the United States and Brazil; USDA, 2016; Tomazi and dos Santos, 2020), interventions such as selective antimicrobial treatment of CM and selective dry cow therapy represent an opportunity for targeted AMU reduction (McCubbin et al., 2022). The main principle of selective antimicrobial treatment of nonsevere cases of CM is to treat only cases with a high probability to be responsive to antimicrobials (e.g., gram-positive CM). Avoiding routinely treating all CM cases with antimicrobials is possible due to reduced incidence and prevalence of CM caused by contagious pathogens, improvements in udder health management practices, and advancements in diagnostic technologies during recent decades. Promotion of the 5-point mastitis control plan (Neave et al., 1969) reduced the incidence of CM caused by contagious pathogens by focusing on improved milking hygiene and blanket dry cow therapy. Now, in many regions across the world with confined housing systems, a large proportion of CM cases are caused by gram-negative, environmental bacteria. Thus, several plans were developed with further guidance to curb infection pressures of environmental pathogens—for example, the 10-point plan developed by the National Mastitis Council (NMC, n.d.), the mastitis control plan (Bradley et al., 2009), and the 7-point plan (Hemling, 2017). In addition, some farmers and veterinarians have gained access to several rapid diagnostic test options, allowing for identification of causal pathogen or pathogen group (gram-positive and gram-negative) and CM cases where no bacteria are detected in the milk at time of diagnosis. Both developments have contributed to selective CM treatments.

In addition to reduced AMU, selective CM treatment protocols also offer the opportunity to facilitate from the use of critically important antimicrobials (e.g., aminoglycosides, cephalosporins) to the use of highly important antimicrobials (e.g., cloxacillin); this is already enforced by legislation in certain regions, such as Quebec, Canada (Roy et al., 2020).

In recent years, many studies have assessed selective CM treatment protocol outcomes, including a meta-analysis comparing efficacy of selective to blanket CM treatment protocols (De Jong et al., 2023). In this narrative review, we will first summarize core principles and elements of a selective CM treatment protocol and subsequently use those principles and available literature to provide an evidence-based, generalized protocol that can inform farmers and their herd veterinarians in designing a tailored selective CM treatment strategy. In addition, positive and negative consequences associated with adopting a selective CM treatment protocol will be summarized, as well as adoption rates of selective CM principles around the globe. Finally, we will suggest areas for future research to address current knowledge gaps regarding selective CM treatment protocols.

PRINCIPLES OF SELECTIVE CLINICAL MASTITIS TREATMENT STRATEGIES

The decision-making process to administer antimicrobials for a CM case most likely caused by bacteria is guided by aims of achieving clinical cure, achieving bacteriological cure, and minimizing negative health and economic consequences. The objective of selective CM treatment is to reduce and refine AMU by treating only CM cases with substantially higher odds of bacteriological cure when treated with antimicrobials and not treating CM cases that will (likely) not benefit from antimicrobial treatment. This can be achieved by considering clinical signs associated with the current CM case, potential causal agent, pathogen-related factors (e.g., virulence profile), and cow-related factors (e.g., SCC and CM history) that may affect cure (Ruegg, 2018).

We will provide a comprehensive overview of each of these elements and suggest a practical implementation in a treatment protocol (Figure 1). Although other cow factors such as parity and lactation stage also affect clinical cure, they lack important roles when considering antimicrobial administration for CM cases (Pinzón-Sánchez and Ruegg, 2011). Regarding antimicrobial susceptibility testing of causal bacterial pathogen, although important, results are typically not available in time and will therefore not influence the decision to administer antimicrobials. Nevertheless, susceptibility profiles can be useful in guiding treatment of refrac-

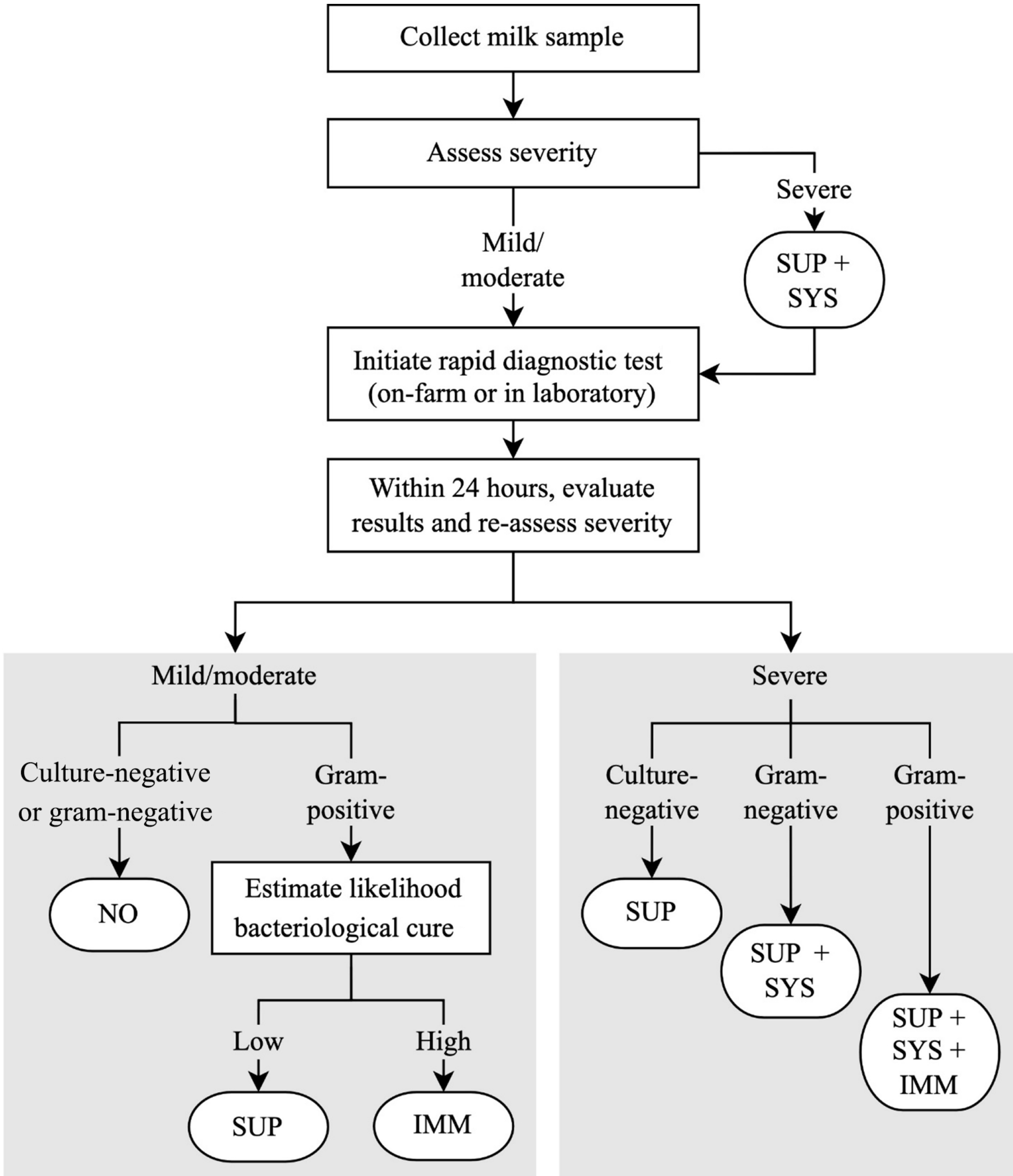

Figure 1. Proposed protocol for selective treatment of clinical mastitis based on a review of the available literature. Farms where gram-negative cases are caused by pathogens other than *Escherichia coli* (such as *Klebsiella* spp.) are recommended to use a species-specific diagnostic test to ensure evaluating antimicrobial treatment for *Klebsiella* spp. To estimate the likelihood of bacteriological cure for gram-positive cases, it is recommended that farms review clinical mastitis history and recent SCC records. SUP = supportive treatment with nonsteroidal anti-inflammatory drugs; SYS = consider systemic antimicrobials; NO = no antimicrobials; IMM = intramammary antimicrobials.

tory cases or future cases of CM caused by the same pathogen.

Severity

Severity of CM is typically classified as mild (visible changes limited to the milk), moderate (also inflammatory signs of the infected quarter), or severe (also signs of systemic illness; Sears and McCarthy, 2003). According to the severity of CM, various treatment strategies may be initiated. For mild and moderate CM, rapid diagnostic tests can be used to inform treatment decisions. Several studies reported that awaiting test results for a maximum of 24 h before making antimicrobial treatment decisions does not affect bacteriological and clinical cure rates, regardless of smaller sample size (among others, Lago et al., 2011a,b; Vasquez et al., 2017; Griffioen et al., 2021).

Typically, severe cases receive a combination of antimicrobial treatment and supportive treatment (e.g., anti-inflammatories), with antimicrobials often being administered systemically (Oliveira and Ruegg, 2014; Krömker and Leimbach, 2017). There is no information available for severe cases on whether delayed antimicrobial treatment (local or systemic) affects treatment outcomes, as current studies only included nonsevere CM. Preference for immediate administration of systemic antimicrobials is common and rooted in perceived risk of sepsis. However, accounts of sepsis are sparse, and available studies report on bacteremia; they identified bacteremia in 11% to 32% of severe CM (Wenz et al., 2001; Brennecke et al., 2021). Although these proportions are relatively low, predicting risk of bacteremia and subsequently septicemia for individual CM cases is nearly impossible, which has contributed to the standard practice in many countries to treat severe CM cases with systemic antimicrobials. Hence, a recommendation regarding delayed antimicrobial treatment in severe CM cases cannot be made. However, for all severe CM cases, a rapid diagnostic test should be initiated, which may lead to revision of the initial treatment decision when the test result is available.

Identifying Causal Agent

Occurrence of CM is the result of an inflammatory response to an IMI. Depending on etiology, a substantial proportion of CM cases are detected after successful bacteriological clearance has already occurred (Ruegg, 2021). For example, in a recent meta-analysis, 40% of CM milk samples collected in Canada, the United States, and Brazil did not yield bacterial growth (Kurban et al., 2022). Such instances, where viable bacteria are not detected in the milk from the affected udder and bacteriological culture of a milk sample is negative, regardless of methodology used, should not be considered for antimicrobial treatment unless clinical signs are severe. In addition, IMI caused by *Mycoplasma* spp. and nonbacterial pathogens such as yeasts and algae should not be treated with antimicrobials, as they are not susceptible to commonly used intramammary antimicrobials that target bacteria. These pathogens will often produce negative routine bacteriological cultures.

When a mild or moderate case is caused by a gram-negative IMI (e.g., *Escherichia coli*), antimicrobial treatment is not indicated, as such cases of CM have a high spontaneous cure rate (Wilson et al., 1999; Leininger et al., 2003; Schmenger and Krömker, 2020), even though a small percentage of cases lead to persistent infections (Döpfer et al., 1999). Hence, use of antimicrobials for mild and moderate *E. coli* cases does not improve bacteriological cure rates (Suojala et al., 2013). When the gram-negative agent is identified as *Klebsiella* spp., antimicrobial treatment is indicated, as it does lead to higher bacteriological cure rates (Fuenzalida and Ruegg, 2019), although it is likely that effects of antimicrobial treatment will vary according to pathogen-level characteristics, as a network meta-analysis revealed significant heterogeneity and inconsistency when evaluating effects of antimicrobial treatment for CM caused by *Klebsiella* spp. (Nobrega et al., 2020).

If >1 quarter has clinical signs, it is recommended that milk from all affected quarters be tested independently (i.e., quarter milk culture), as intramammary infections with different pathogens in different quarters cannot be ruled out (Paixão et al., 2017).

Not only is it crucial when using selective CM treatment to have an accurate identification of the group of pathogens involved, identification should also be available within 24 h after detecting the CM case. Although bacterial identification of CM samples is typically done in laboratories (e.g., regional laboratories or veterinary clinics), identification is often not available in 24 h. Similarly, transportation of the sample to the laboratory often precludes a 24-h turnaround (Griffioen et al., 2016; Wemette et al., 2020). However, several commercial on-farm rapid diagnostic tests are now available. These tests can identify the causal agent up to at least the level of the cell wall structure (i.e., Gram staining), in line with recommendations from the European Union (2015/C 299/04). On-farm use of rapid tests can reduce wait times, facilitate testing, and provide results when diagnostic laboratories may be closed (e.g., weekends or holidays).

Numerous rapid tests intended for on-farm use are commercially available (Malcata et al., 2020). These systems are predominantly based on culture and identification of mastitis-causing pathogens via selective media on plates or in tubes. Sensitivity to identify gram-positive bacteria ranges from 59% to 98%, and specificity ranges from 48% to 97% (Malcata et al., 2020). Quick turnaround is crucial in the decision-making process, considering the desire of farmers for a fast time to result (Griffioen et al., 2016) and the aforementioned absence of evidence that delayed initiation of antimicrobial treatment within 24 h for mild or moderate CM cases affects bacteriological cure.

In conclusion, selective CM treatment protocols should intend to distinguish CM caused by gram-positive bacteria from CM caused by gram-negative bacteria and only consider gram-positive cases for antimicrobial treatment. All severe cases should be treated immediately with antimicrobials (preferably systemic), but the need for antimicrobials will be reassessed based on causative agent. On farms with a high prevalence of

Klebsiella spp., a diagnostic test that can differentiate between *E. coli* and *Klebsiella* spp. (both are gram-negative bacteria) is recommended to ensure cases of *Klebsiella* CM receive antimicrobial treatment.

Expected Probability of Cure

In combination with bacterial identification, cow-level SCC and CM history can be used to identify CM cases with high probability of cure (Ruegg, 2018) and should be weighted together with results of rapid diagnostic tests to make a balanced decision on whether antimicrobial treatment is indicated. Persistent high SCC (i.e., chronic subclinical mastitis) is typically defined as composite SCC >200,000 cells/mL on at least 2 of 3 consecutive SCC records (Gonçalves et al., 2020). Somatic cell count data are readily available to farmers and veterinarians if the farm participates in regular DHIA or similar schemes, although availability of such services varies across regions and farmers. When CM caused by *Staphylococcus aureus* or *Streptococcus uberis* has been preceded by persistent high SCC levels, the likelihood of intramammary antimicrobial treatment resulting in a bacteriological cure is low (compared with CM cases that were not preceded by long-lasting high SCC levels; Barkema et al., 2006; Samson et al., 2016). For example, *Staph. aureus* can reside within the udder and udder tissue and cause chronic IMI with periodic clinical signs (Sol et al., 2000).

Similarly, when CM was preceded by at least 1 CM case in the same lactation, a lower bacteriological cure rate was predicted compared with CM cases that were not preceded by a CM case (Pinzón-Sánchez and Ruegg, 2011), irrespective of causative agent. However, with *Strep. uberis* CM, the occurrence of CM earlier in lactation did not seem to influence bacteriological cure (Samson et al., 2016). Regardless, utilizing CM history requires good record keeping of every CM case (not only those that receive antimicrobials).

For both situations (mild or moderate CM preceded by consistently high SCC or a previous CM case), 1 study reported that use of nonsteroidal anti-inflammatory drugs (**NSAID**) compared with antimicrobial treatment did not affect cure rates (Krömker et al., 2021). Therefore, when possible with available SCC data and CM record keeping, an evaluation should be made on a per-case basis of SCC history, CM history, and the results of rapid diagnostic tests (gram-positive or gram-negative) to predict the likelihood of clinical cure for the current CM case.

Unfortunately, there is a lack of consensus on the number of CM cases and SCC thresholds to consider, the time frame, and whether information should be based on quarter- or cow-level data. If likelihood of clinical cure is deemed low, antimicrobial treatment should be withheld (Ruegg, 2018) and NSAID and other supportive therapies administered, as a similar bacteriological cure and clinical cure can be achieved (Krömker et al., 2021).

OTHER CONSIDERATIONS

Cow and Farm Priorities

In addition to results of rapid diagnostic tests, SCC, and CM history, the farmer's priority or assigned value of specific cows also influences treatment decisions for mild or moderate CM cases. Assigned value is influenced by cow characteristics such as parity, lactation stage, milk yield, reproductive status, temperament, and genetic potential of offspring (Vaarst et al., 2002; Schmenger et al., 2020). Although there is no evidence that any of these factors influence clinical cure rate in cases of mild or moderate CM, less valuable cows might receive fewer antimicrobial treatments, will be evaluated less often, or are even withheld from treatment and placed on a do-not-breed or cull list (Vaarst et al., 2002).

In addition to cow-specific priorities, farm priorities such as need to fill milk quota, maintaining a low bulk tank SCC, culling protocols, availability of replacement heifers in case of culling, and need to maximize cash flow or other economic considerations can also affect general treatment protocols (Vaarst et al., 2003). These decisions are often made on a per-cow basis and relate to the general udder health and reproductive status of the herd, among other factors (Vaarst et al., 2003). None of the farm priorities will affect odds of clinical cure for an individual CM case but can influence the value of a cow presented with CM at a given time and influence whether treatments are withheld.

As priority or assigned value is very farm- and context-specific, it is not possible to reflect those considerations in a selective treatment protocol, but they can be an explanation for deviations in compliance with selective CM treatment protocols. Herds might also choose not to use antimicrobials for certification purposes (e.g., organic milk) and therefore be ineligible for application of selective CM treatment.

Susceptibility Profiles

Identifying whether causal bacteria of a CM case are gram-positive or gram-negative is key in a selective treatment strategy. However, even when antimicrobial treatment is indicated, it can be helpful to know antimicrobial susceptibility of the CM pathogen to optimize treatment. The Veterinary Antimicrobial

Susceptibility Testing committee of the Clinical and Laboratory Standards Institute has established clinical breakpoints of penicillin-novobiocin combination, ceftiofur, pirlimycin, and cefoperazone for all bovine mastitis pathogens, by measuring antimicrobial concentrations in milk throughout each treatment regimen (Toutain et al., 2017). However, not all intramammary antimicrobials are included, and the Clinical and Laboratory Standards Institute method does not account for variations in antimicrobial concentrations throughout the udder due to udder anatomy and host-immune responses (Toutain et al., 2017). Therefore, susceptibility knowledge cannot be used to predict clinical or bacteriological cures on a per-case basis and should only be used to guide future choice of antimicrobials (and not decision to treat).

Examples of commercially available rapid on-farm systems that offer crude sensitivity testing are Mastatest (Mastaplex), which identifies within 24 h the in vitro susceptibility of cultured mastitis pathogen against 3 major antimicrobial groups (Jones et al., 2019); MastDecide +Plus (Veterinary Enterprises Europe B.V.), which provides a 1-point MIC test for penicillin within 12 to 14 h (Leimbach and Krömker, 2018); and Speed Mam Color (Virbac), which performs bacterial identification and sensitivity testing within 48 h. A commercial PCR assay (PathoProof Complete-16 PCR Assay, Thermo Scientific) widely used in Finland provides information on the presence of blaZ-gene coding for β-lactamase production within 4 h and guides antimicrobial treatment choice. If an on-farm sensitivity test is not available, samples can be submitted to a laboratory, although the interval to result will often be prolonged. If results cannot be produced within 24 h, antimicrobial choice should be based on outcomes of susceptibility tests of previous CM cases with the same causal pathogen in the same herd, or information from regional or national monitoring systems.

Administration Route

Mild and Moderate Cases. Systemic application of antimicrobials for mild and moderate CM, either in addition to intramammary AMU or as a sole treatment, is common in certain regions. However, potential associations between AMR in NAS and *Staph. aureus* in the udder and systemic antimicrobial treatments (calculated as antimicrobial drug use rate using daily dosages) have been implied (Nobrega et al., 2018; Stevens et al., 2018). Regardless, the choice of intramammary versus systemic AMU is most often informed by availability of antimicrobial treatment options and withholding times. Hence, in countries such as the United States, no antimicrobials are currently approved for systemic treatment of CM. In Nordic countries, awaiting test results is common, and based on etiology, systemic treatment is provided in addition to intramammary treatment (Päivi J. Rajala-Schultz, University of Helsinki, Finland, personal communication).

There is limited evidence that systemically applied antimicrobials outperform intramammary application. For example, invasive pathogens such as *Staph. aureus* or *Strep. uberis* can reside in deeper tissue layers (Erskine et al., 2003; Pyörälä, 2009); however, not all systemic antimicrobials are capable of reaching therapeutic concentrations (Ehinger et al., 2006; Pyörälä, 2009). Consequently, pharmacological characteristics should be evaluated. For example, compared with intramammary treatments, systemic use of penicillin, aminoglycosides, and cephalosporins did not improve treatment outcomes (McDougall, 1998; Hillerton and Kliem, 2002; Sérieys et al., 2005; Wenz et al., 2005; Kalmus et al., 2014; Svennesen et al., 2022). Further, although macrolides, trimethoprim, tetracyclines, and fluoroquinolones are among antimicrobials that disperse throughout the udder (Erskine et al., 2003), only a few studies have compared their efficacy with other compounds, with contrasting conclusions (Pyörälä and Pyörälä, 1998; McDougall et al., 2007). Furthermore, not all pathogen × antimicrobial combinations have been extensively tested for either administration route or combination.

Nonetheless, when >1 quarter is affected, systemic AMU may be preferred compared with intramammary treatment. On farms with automated milking systems, systemic AMU might be more practical, as cows are not used to having their udders touched and farms have no parlor, which complicates intramammary treatment.

Severe Cases. Antimicrobials for severe CM are often administered systemically (Oliveira and Ruegg, 2014; Krömker and Leimbach, 2017) to mitigate the risk of bacteremia and subsequently risk of sepsis, as mentioned earlier. When evaluating existing literature, regarding *E. coli*, no difference in treatment response was reported for systemic administration of ceftiofur in addition to intramammary pirlimycin (Erskine et al., 2002). There was also no difference in mortality (within 7, 21, or 180 d) or culling rate (within 6 mo) between those treated with systemic fluoroquinolones versus supportive treatments only (Suojala et al., 2010; Persson et al., 2015). Similarly, there was no difference in bacteriological cure rates in *E. coli*–challenged quarters treated systemically or intramammarily with cefquinome (Shpigel et al., 1997). However, there is evidence that systemic antimicrobial administration for severe *E. coli* CM caused less severe milk production decreases in cows treated with systemic cefquinome (Shpigel et al., 1997; Suojala et al., 2013) and faster recovery from reduced milk production in cows receiving systemic fluoroquinolone only (compared with no treatment) after *E. coli* challenge (Poutrel et al., 2008).

Nonetheless, differences in legislation among countries affect availability of antimicrobial drugs approved for CM treatment. In the United States, no antimicrobials are currently FDA approved for systemic CM treatment. Under extralabel guidelines, systemic antimicrobials approved for use in lactating cows can be prescribed by veterinarians if approved products (i.e., intramammary products) are not expected to be efficacious. Regardless, systemic antimicrobials are commonly administered for severe CM treatment in the United States (Oliveira and Ruegg, 2014).

Supportive Treatments

Although the nature of cows inhibits them from displaying signs of pain, there is a general agreement that CM is painful and compromises welfare (Petersson-Wolfe et al., 2018). As such, regardless of antimicrobial treatment, administration of NSAID to alleviate pain and discomfort is recommended for all severe CM cases and is common practice in some countries (Hewson et al., 2007; Breen, 2017).

In addition to treating pain, for mild and moderate cases, NSAID can have other benefits. For *E. coli* mastitis, numerous challenge trials have associated administration of flunixin, carprofen, or ketoprofen with lower rectal temperatures, lower heart rate, and improvements in rumen motility and clinical signs (Anderson et al., 1986; Anderson and Hunt, 1989; Lohuis et al., 1991; Wagner and Apley, 2004; Vangroenweghe et al., 2005; Banting et al., 2008; Zimov et al., 2011; Yeiser et al., 2012; Chapinal et al., 2014). In naturally occurring gram-positive and gram-negative CM, coadministration of meloxicam with cefalexin or penethamate improved bacteriological cure (McDougall et al., 2015) and lowered SCC and culling (McDougall et al., 2009). No differences in bacteriological cure or recurrence rate were reported in gram-negative cases treated with ketoprofen compared with no antimicrobial treatment (Latosinski et al., 2020).

Milk withdrawal times and availability of NSAID products also influence their use. It is also important to note that long-term treatment with NSAID nonselective for the COX-2 receptor (such as flunixin and ketoprofen) has been associated with side effects such as decreased renal perfusion and gastric ulceration (Orr et al., 2014). Thus, consideration of NSAID for mild and moderate CM cases should be discussed between herd veterinarian and producer, considering farm production goals, cow welfare, and costs. Other types of supportive treatments (including rehydration fluids, frequent milk-out, oxytocin, calcium, hypertonic saline, and corticosteroids) are sometimes considered as part of CM treatment protocols (Roberson, 2012; Oliveira and Ruegg, 2014; Persson Waller et al., 2016). However, there are insufficient studies to evaluate effectiveness of most supportive therapies (Leslie and Petersson-Wolfe, 2012; Francoz et al., 2017), although available evidence indicated no added benefit of oxytocin and frequent milking on resolving clinical signs and achieving cure (Francoz et al., 2017).

Drying off or "blinding" a quarter for temporary or permanent milk cessation is sometimes considered for quarters affected by recurrent CM, chronic IMI (Vaarst et al., 2006; Pinzón-Sánchez and Ruegg, 2011), or therapy-resistant IMI (Tho Seeth et al., 2016). This can be achieved by discontinuing milking of the affected mammary quarters or via the use of chemicals (Middleton and Fox, 2001), although the latter is not allowed because of animal welfare concerns (Harwood et al., 2009). Drying off an active quarter is painful, especially when milk yield is high (Skarbye et al., 2018), and cessation of milk production should be done gradually in conjunction with potent long-acting NSAID.

COW AND FARM OUTCOMES

Udder Health

When considering implementing a selective CM treatment protocol, it is important to identify potential negative consequences. As reviewed by Malcata et al. (2020), sensitivity and specificity of rapid diagnostic tests vary, which can result in cases left untreated that should have received antimicrobial treatment and vice versa. In a recent systematic review and meta-analysis, we identified and reviewed 13 studies comparing selective CM treatment protocol impacts on udder health parameters to a blanket CM treatment protocol (De Jong et al., 2023). The systematic review concluded that for bacteriological cure, a selective CM protocol was not inferior to a blanket CM protocol. Furthermore, the review found no evidence to assume a difference between cases treated according to a blanket or selective CM protocol in terms of new IMI risk, recurrence of CM later in lactation, return of SCC to baseline, average lactational milk yield, and risk of culling. The only non–clinically relevant difference detected was a slight increase in days from treatment to clinical cure in the selective treatment group (0.4 d), but certainty of evidence was low, as 3 of the 4 studies reporting this outcome measure came from the same research group, and 2 of the 4 studies used the same research farm.

Table 1. Reduction of antimicrobial use in relation to the proportion of clinical mastitis samples that were culture-negative, gram-negative, and gram-positive[1]

				Proportion treated			Mean doses per case		
Study	CN	GN	GP	Blanket	Selective	Reduction	Blanket	Selective	Reduction
Lago et al. (2011a,b)	0.33	0.25	0.34	1.00	0.44	0.56			
MacDonald (2011)	0.28	0.10	0.46	1.00	0.60	0.40			
Mansion-de Vries et al. (2016)	0.31	0.23	0.21				8.47	3.08	0.64
Lago et al. (2016a)	0.54	0.08	0.34	1.00	0.46	0.54	3.33	1.52	0.54
Lago et al. (2016b)	0.37	0.11	0.47	1.00	0.28	0.72	3.29	1.13	0.66
Vasquez et al. (2017)	0.30	0.34	0.35	1.00	0.32	0.68			
Kock et al. (2018)	0.26	0.09	0.44				4.76	3.07	0.36[2]
McDougall et al. (2018)	0.09	0.09	0.77	0.98	0.80	0.18	2.38[3]	1.72[3]	0.28
Bates et al. (2020)	0.09	0.03	0.76				1.7[3]	1.3[3]	0.24
Schmenger et al. (2020)	0.35	0.16	0.38				5.74	1.54	0.73
Bazzanella et al. (2020)[4]	0.40	0.17	0.42	0.84	0.48	0.42[2]			
Griffioen et al. (2021)[5]	0.19	0.22	0.64	0.86	0.68	0.21[2]			
Borchardt and Heuwieser (2022)	0.17[6]	0.13[6]	0.70[6]	1.00	0.70	0.30			

[1]CN = culture-negative; GN = gram-negative; GP = gram-positive.

[2]Uneven pathogen distribution between selective and blanket treatment group.

[3]Daily doses.

[4]Selective treatment protocol where only CN and mild GN clinical mastitis cases were not treated with antimicrobials.

[5]Selective treatment protocol where only CN clinical mastitis cases were not treated with antimicrobials.

[6]Results from rapid diagnostic test, for selective treatment group only.

The included studies originated from North America, Europe, and New Zealand and covered a range of farm sizes, farming systems, and mastitis pathogen profiles.

Antimicrobial Use

For all 13 studies identified in the aforementioned systematic review and meta-analysis (De Jong et al., 2023), pathogen distribution and reported AMU reductions are presented in Table 1. The relationship between pathogen distribution and reported AMU reduction was further explored via a linear model using software package lme4 (Bates et al., 2015) in RStudio version 1.2.5033 (R Core Team 2019, R Foundation for Statistical Computing). For each included study (n = 13), proportion of AMU reduction was calculated as follows: (blanket AMU − selective AMU)/(blanket AMU), with AMU defined as either mean antimicrobial doses provided or proportion of cases receiving antimicrobial treatment, depending on the metrics reported. When both metrics are reported, preference is given to proportion of cases treated. The only explanatory variable was proportion of cases identified as gram-negative or culture-negative. Unit of analysis was study, as information aggregated per farm was not available in most studies. Results of the linear model are displayed in Figure 2, along with a 95% confidence interval (ggplot2 package, Wickham, 2016). Residuals were plotted against fitted values and reviewed alongside quantile-quantile plots to assess model assumptions. The fitted model could be denoted as $y = 0.06 + 0.91x$, meaning that for a 10-percentage-point increase in proportion of cases identified as gram-negative or culture-negative, proportion AMU reduced increased by 9.1 percentage points (95% CI: 0.4% to 14.1%). Percentage point is used to indicate the difference between 2 percentages. For example, the difference between 20% and 30% is 10 percentage points. The adjusted coefficient of determination of the model was

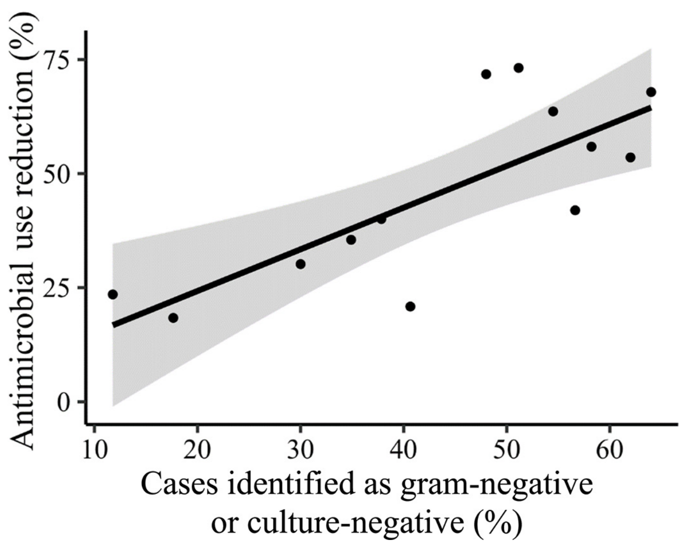

Figure 2. Effect of pathogen distribution on reduction of antimicrobials used. Adjusted $R^2 = 0.56$; P-value = 0.002; each dot represents the outcomes of 1 study; 95% confidence interval indicated in gray.

0.56, indicating a strong association between pathogen distribution of CM cases and achievable AMU reduction.

On farms that have not yet implemented a selective CM treatment protocol, bulk tank SCC can be used to approximate pathogen distribution of subclinical cases and hence potential AMU reduction (Rainard et al., 2018). In farms where the majority of CM is identified as gram-negative or culture-negative, bulk tank SCC is most often low and a relatively large reduction in AMU can be expected when applying a selective CM treatment protocol. In high-SCC herds (bulk tank SCC >250,000 cells/mL), not only most subclinical mastitis cases but typically many CM cases are caused by gram-positive bacteria (Barkema et al., 1998; Olde Riekerink et al., 2008). The high prevalence of gram-positive, often contagious, bacteria is likely due to suboptimal milking hygiene practices, suboptimal milking machine function, and purchase of replacement heifers instead of rearing their own, resulting in a higher incidence of IMI with contagious mastitis pathogens such as *Staph. aureus*, *Strep. uberis*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*, although *Strep. uberis*, *Strep. agalactiae*, and *Strep. dysgalactiae* IMI can also have environmental causes (Fenlon et al., 1995; Olde Riekerink et al., 2006). In contrast, farms with good udder health management and a low bulk tank SCC will on average have a higher incidence of environmental pathogen IMI and CM (Barkema et al., 1998; Rysanek et al., 2009).

For example, Kock et al. (2018) reported that in a German dairy herd (bulk tank SCC <400,000 cells/mL), 9% of the CM cases were gram-negative and 26% of cases were culture-negative, resulting in 36% less AMU in the selective CM treatment group compared with the blanket group. Vasquez et al. (2017) reported that in a single New York dairy herd, 34% of CM cases were gram-negative and 30% of samples were culture-negative, which corresponded with an AMU reduction of 68% as compared with blanket treatment. In New Zealand, similar to the United Kingdom and Ireland, a large proportion of IMI and CM cases are caused by *Strep. uberis* (Bradley et al., 2007; Petrovski et al., 2009; Keane et al., 2013). Not surprisingly, in New Zealand McDougall et al. (2018) achieved a relatively limited 18% reduction in AMU among selectively treated CM cases, as only 9% of CM samples were culture-negative and 9% were gram-negative. Housing factors such as choice of bedding and the decision to pasture cows also influence the type of mastitis pathogens responsible for a proportion of CM cases. For example, farms that pasture cows for some or the entire lactation typically have a higher proportion of cases caused by streptococci, particularly *Strep. uberis*.

Not only do CM cases receive fewer antimicrobial treatments when a selective CM treatment protocol is used, there is also a lower risk of a follow-up treatment (Lago et al., 2011a; Kock et al., 2018). This implies that when there is knowledge of bacterial presence and type of causative agent if bacteria are present, farmers may be less prone to initiate another antimicrobial treatment when there is no resolution of clinical signs. Lastly, overall CM incidence in a herd influences the potential absolute AMU reduction that can be achieved with a selective treatment protocol. Therefore, udder health management needs to be optimized to simultaneously reduce both infection pressure by infectious gram-positive pathogens and incidence rate of CM (Barkema et al., 2013).

Economic Consequences

Only a few studies modeled the costs and benefits of a selective CM treatment protocol compared with a blanket treatment protocol (Pinzón-Sánchez et al., 2011; Kessels et al., 2016; Down et al., 2017). In these 3 studies, a key element of the selective CM treatment protocols was on-farm culture of CM cases to inform antimicrobial treatment. Direct costs associated with the selective treatment protocols included costs for analyzing milk samples (labor and costs of the plates). Potential benefits to selectively treating CM cases were described as reduced treatment costs and reduced days out of the tank as milk can be delivered once the CM has clinically cured and no withdrawal period is required for the untreated cases. Indirect costs included production losses as a result of CM and potential culling and replacement costs, although these costs are not affected by application of a selective CM treatment protocol. In addition, Pinzón-Sánchez et al. (2011) also included potential production losses due to persistent IMI and risk of transmission of *Staph. aureus* to other cows. Kessels et al. (2016) also included potential reproduction losses.

Overall, costs of CM have been consistently reported as reduced compared with a selective CM treatment protocol based on rapid diagnostic tests to a blanket treatment protocol. Using a fixed pathogen distribution of 30% gram-positive, 30% gram-negative, and 35% culture-negative CM cases (5% other), highest net returns were in the selective treatment group (Kessels et al., 2016). Even if a small reduction (maximum 5%) in bacteriological cure was assumed in the selective treatment group, a selective treatment protocol based on on-farm culture results was still beneficial if <50% of CM cases were gram-positive (Down et al., 2017). When considering effects of CM in early lactations only, expected monetary values of CM cases treated using a

Table 2. Reports of adoption of selective treatment for clinical mastitis[1]

Manuscript	Study design	Region	Treatment adoption
González Pereyra et al. (2015)	Survey	Argentina[2]	94% of CM cases treated
Tomazi and dos Santos (2020)	Longitudinal study	Southeastern Brazil, 2014–2016	Of recorded CM cases, 97% treated with antimicrobials
USDA (2016)	Survey and in-person interviews	United States, 2014	Majority (87%) of cows with CM were treated with antimicrobials
Aghamohammadi et al. (2018)	Survey	Canada, 2015	A median of 90% of CM cases were treated with antimicrobials in all herds, including both organic and commercial
Raymond et al. (2006)	Survey	Washington State, 2005	88% of respondents treated most affected animals with antibiotics
Kayitsinga et al. (2017)	Survey	Florida, Michigan, Pennsylvania[2]	About 35% and 20% of the farms reported that they frequently or always treated cases of CM with intramammary antimicrobials, respectively
McDougall et al. (2017)	Focus groups and survey	New Zealand, 2014	76% of veterinarians stated that for the 10 most recent CM cases for which therapy had been prescribed, the prescription was based on culture results in <4 of these 10 cases
Deng et al. (2020)	Interviews	The Netherlands, 2017	Majority (67%) of farmers did not treat all CM cases with antimicrobials but select cows for treatment
Thomson et al. (2008)	Survey	Finland[2]	Only 37% of veterinarians used the recommended methods to make treatment decisions

[1]CM = clinical mastitis.

[2]Date of collection period not specified.

selective treatment protocol were either comparable to a blanket treatment protocol or lower (depending on 2- or 5-to-8-d antimicrobial treatments; Pinzón-Sánchez et al., 2011). More specifically, for a 5-to-8-d blanket treatment protocol, costs were lowest for scenarios with 15% and 35% gram-positive cases compared with the scenario with 70% gram-positive CM cases (Pinzón-Sánchez et al., 2011).

The most important factors influencing costs were differences in days out of the bulk tank, costs of antimicrobial treatment (Down et al., 2017), and assumed milk price (Pinzón-Sánchez et al., 2011). None of the studies included costs associated with a decreased risk of antimicrobial contamination of the bulk tank when applying a selective CM treatment protocol. Costs of the use of the rapid diagnostic system were negligible in each model, even though different cost estimates were used. However, each of these economic analyses used different parameters, parameter estimates, and models, making a direct comparison of results challenging. Only Down et al. (2017) incorporated direct results from an on-farm study (Lago et al., 2011a) to inform bacteriological cure risk differences between the 2 groups.

In addition to the 3 studies discussed, an additional study calculated costs of selective versus blanket CM treatment protocols implemented on a single farm in Germany (Mansion-de Vries et al., 2016). Assuming €5.50 per cultured CM sample (including labor and equipment), cost per CM case was lower in the selective CM treatment group compared with the blanket group. However, costs associated with milk losses were not included in this analysis.

Regardless, the limited available studies indicate that a selective CM treatment protocol either has similar or lower costs compared with blanket CM treatment protocols. Therefore, when selective CM treatment protocols are adopted, farms will not experience increased economic losses and, depending on the udder pathogen distribution in the herd, adoption of a selective CM treatment will often be economically beneficial.

ADOPTION OF SELECTIVE CLINICAL MASTITIS TREATMENT PROTOCOLS

The proportion of dairy farms implementing selective antimicrobial treatment of CM varies among countries (Table 2). In southeastern Brazil and Argentina, >90% of CM cases on farms are treated with antimicrobials (González Pereyra et al., 2015; Tomazi and dos Santos, 2020). Blanket antimicrobial treatment also is the norm in the United States and Canada, as 87% to 90% of CM cases are treated with antimicrobials (USDA, 2016; Aghamohammadi et al., 2018). However, regarding the number of farms adopting a selective CM treatment approach, Raymond et al. (2006) reported that 88% of farmers in Washington State treated all cases with antimicrobials, whereas Kayitsinga et al. (2017) reported that just 55% of farmers in the eastern United States treated the majority of CM cases with antimicrobials, although few cultured milk samples.

In New Zealand, bacteriological testing of CM cases is being increasingly adopted by veterinarians, with 24% of surveyed veterinarians indicating they have culture results for at least 4 of the last 10 CM cases for which they prescribed antimicrobials (McDougall et al., 2017), although this does not meet the formal definition of a selective CM treatment protocol. In Australia, a selective treatment approach utilizing on-farm culture is common on large dairies (>2,000 cows). In smaller, pasture-based herds (260 cows on average), on-farm tests are mainly used to identify *Staph. aureus* IMI to guide treatment and culling decisions (John House, University of Sydney, Camden, NSW, Australia, personal communication). On larger dairy farms in China, all CM cases are treated with antimicrobials (Jian Gao, China Agricultural University, Beijing, China, personal communication).

In many European countries, including Sweden, Denmark, Finland, Germany, the Netherlands, and Austria, CM treatment should be veterinarian supervised, and the new European Union (**EU**) Regulation 2019/6 (REF) strengthens this approach for all EU member states. In addition, use of bacterial etiology and sensitivity to inform treatment is widely encouraged (Firth et al., 2017; Armstrong et al., 2018). For example, in the Nordic countries, microbiological testing of milk samples is very common before antimicrobial treatments are used for any IMI (Rajala-Schultz et al., 2021).

Many countries in the EU and elsewhere have also developed national targets to monitor and generally aim to reduce AMU. As a result, in the Netherlands, for example, AMU for curative intramammary use has reduced along with a reduced preventive use, although udder health parameters improved (Santman-Berends et al., 2016). In a Dutch study, among farmers of 1 veterinary practice, 67% indicated in 2017 that they selected CM cows for treatment (Deng et al., 2020). In Norway, there was a 50% reduction in antimicrobial CM treatments between 1994 and 2007 (Østerås and Sølverød, 2009), partly attributed to the implemented mastitis prevention programs. Similarly, in the United Kingdom, intramammary antimicrobial CM treatments were reduced 25% between 2015 and 2020 (RUMA, 2020), a change attributed largely to mastitis control programs. For Finland, although numbers regarding antimicrobial CM treatments are not available, surveyed veterinarians indicated that in approximately 70% of CM cases for which antimicrobials were prescribed, diagnostic test results were considered (Thomson et al., 2008).

Differences among regions are predominantly influenced by pathogen distribution, udder health management, and legislation. For example, farms with a proportion of their milking herd on pasture typically experience more *Strep. uberis* CM cases (Klaas and Zadoks, 2018) that would benefit from antimicrobial treatment. In addition, dairy operations in countries such as Pakistan, Iran, and China experience a high proportion of CM cases caused by gram-positive pathogens (Hameed et al., 2008; Hashemi et al., 2011; Gao et al., 2017). As mentioned earlier, when only a small proportion of CM cases are caused by gram-negative pathogens, a selective treatment protocol will not result in major reduction of antimicrobial treatments. This is unfortunate, as often regions with a low proportion of gram-negative IMI also have the highest AMR levels among mastitis pathogens (e.g., *Staph. aureus*; Molineri et al., 2021). In these regions, first the prevalence of gram-positive IMI needs to be reduced following the same path that many other countries have taken through adoption of the 5-point contagious mastitis control plan.

Legislation also influences antimicrobial availability and the frequency with which they are used to treat CM, which may explain differences among countries in similar geographical regions. In the EU, Regulation 2019/6 (REF), which came into effect January 2022 (European Commission, 2022), instructs that antimicrobials can only be administered after diagnosis by a veterinarian. In Sweden, AMU is further discouraged because only pharmacies are allowed to dispense antimicrobials (Armstrong et al., 2018). In Denmark, Belgium, and the Netherlands, limitations regarding the amount of antimicrobials stored on-farm may drive farmers to adopt practices that improve udder health and reduce CM incidence and subsequently reduce AMU (Armstrong et al., 2018). More specifically to the Netherlands, a comprehensive set of regulations consisting of, among others, AMU benchmarking at farm level, mandatory veterinary supervision of AMU, restrictions on the use of critically important antimicrobials, and introduction of mandatory selective dry cow treatment protocols has greatly reduced AMU in dairy farming and mastitis-related AMU (Speksnijder et al., 2015; Santman-Berends et al., 2021).

Increasing uptake of selective CM treatment protocols without legislation requires recognizing that implementation of on-farm rapid diagnostic tests requires substantial motivation and dedication from producers and their staff. Properly using and interpreting on-farm testing systems is essential and requires training and frequent practice. Hence, input from veterinarians or technical staff is important to monitor and preserve quality (Sipka et al., 2021). In addition, a sufficiently high number of CM cases per month may be necessary to maintain knowledge. Thus, smaller dairy herds and those with a low incidence of CM (<2 cases per month) may struggle to adopt a selective CM treatment protocol. In addition, it is suggested to have multiple people on a farm that are familiar with aseptic milk sampling and use of their on-farm diagnostic test, to ensure availability despite weekends, holidays, high-workload times, and employee changeover.

KNOWLEDGE AND TECHNOLOGY GAPS

Although multiple studies have indicated benefits of selective antimicrobial treatment of CM, some knowledge and technology gaps have been identified; their closure may further optimize selective treatment protocols and improve uptake.

Investigating the potential for NSAID to replace antimicrobial treatment for mild and moderate cases could refine the proposed selective CM treatment protocol and augment AMU reduction while having a positive impact on animal well-being. For chronic cases, there appears to be no difference in bacteriological cure, clinical cure, and recurrence when treating with NSAID instead of intramammary β-lactam antimicrobials (Krömker et al., 2021). However, the impact of treatment with NSAID to treat nonchronic mild and moderate cases of various etiologies on bacteriological and clinical cure has not been reported.

Antimicrobial use could be further refined if antimicrobial treatment of severe CM cases could be delayed, thereby allowing for rapid diagnostics, similar to mild and moderate cases. For example, studies on a limited number of antimicrobial classes concluded that administration of systemic antimicrobials for severe *E. coli* cases does not affect cure. However, severe CM cases are often excluded from studies comparing selective CM protocols with blanket protocols. This prohibits evaluation of effects of delayed treatment decisions in on-farm decision-making.

Diagnostic accuracy of several on-farm rapid diagnostic tests is not optimal. Comparing outcomes of on-farm tests with conventional laboratory analyses, Lago et al. (2011a; Minnesota Easy Culture System biplate) indicated 14% of CM cases in the no-treatment group were actually caused by gram-positive bacteria. Furthermore, McDougall et al. (2018; CHROMagar Check-up) reported 22% of CM in the no-treatment group should have received antimicrobials. These reports underscore the low sensitivity of bacterial culture, even for pathogens that would require treatment such as *Strep. dysgalactiae* (Dohoo et al., 2011). Misclassifications of gram-positive cases as no treatment could have contributed to the trend of higher SCC outcomes in selectively treated cows. However, despite these suboptimal values, an effect on clinical or bacteriological cures between groups treated with a selective CM treatment protocol based on on-farm culturing compared with groups treated according to a blanket CM treatment protocol was not detected in reviewed studies (De Jong et al., 2023). Regardless, the predictive value of rapid diagnostic tests can be improved, including tests that differentiate *Klebsiella* spp. from other gram-negative pathogens that do not require treatment. A more practical solution is sending a second sample to a veterinary laboratory. However, added labor and cost of testing will increase the costs associated with a selective treatment protocol and might not be in the interest of the dairy farmers.

Polymerase chain reaction technology can be used as an alternative rapid diagnostic test to culture-based methods. Polymerase chain reaction tests can provide results more quickly and detect smaller bacterial quantities and thus may provide a more accurate interpretation compared with culture methods. In addition to higher accuracy, PCR is better able to identify mastitis pathogens in culture-negative samples (Taponen et al., 2009), although identification of bacterial DNA does not imply the presence of viable bacteria (Koskinen et al., 2010). In Finland, PCR is widely used, almost exclusively for mastitis diagnostics (Rajala-Schultz et al., 2021). Although some PCR tests are commercially available (e.g., PathoProof PCR assays from Thermo Fisher Scientific), they are not intended for on-farm use and infrastructure is not always sufficient to ensure a quick turnaround when conducting PCR at veterinary laboratories. This further reduces the feasibility of PCR as a rapid test in many regions. Investments in availability of rapid, preferably on-farm, PCR tests will increase options to adopt selective CM treatment protocols.

Although there is consensus on the predictive ability of SCC and CM history to identify CM cases with a low probability of clinical cure, more evidence regarding specific thresholds is lacking and criteria described in various selective CM treatment protocols are insufficiently substantiated. By collecting data from farms that use rapid diagnostic tests on CM samples and have excellent record keeping, patterns may be identified regarding SCC, mastitis history, and cure rates. These patterns may support the definition of identification criteria for CM cases with a low expected chance of bacteriological cure, which, in turn, can be validated as part of selective CM treatment protocols.

Adoption of automated milking systems is increasing worldwide, and their use challenges conventional CM detection and treatment considerations (Naqvi et al., 2022). However, as no studies evaluating selective versus blanket CM treatment protocols have been conducted on farms with automated milking systems, we were unable to include those parameters in this review. Regardless, automated milking systems provide a wide range of information, including milk conductivity and frequent SCC reports. Hence it is worth investigating how the abundance of data generated through automated milking systems can be used to inform CM treatment protocols.

To promote selective CM antimicrobial treatments and subsequently reduce AMU on farms, it is important that protocols are easy to understand and tailored to the farm-specific context. McDougall et al. (2018) reported that 23% of producers in their study did not comply with their selective CM treatment protocol and did not follow treatment recommendations. Schmenger et al. (2020) reported that 56% of cases allocated to the selective CM treatment protocol were not treated according to protocol, most often due to not providing NSAID. Although we hypothesized earlier that protocol compliance may be influenced by perceived value of the cow at time of the treatment decision, this has not been confirmed. Regardless, there are many other factors that influence farmers' AMU, which should also be taken into consideration, including their prediction of treatment outcomes, ability to accurately judge the animal's health, and relationship with the herd veterinarian (Farrell et al., 2021; Rees et al., 2021). To minimize noncompliance, selective CM treatment protocols will need to be specific to each region's current CM treatment practices, context, capabilities of the farmer and farm workers, and most importantly, an understanding of the target group's motivations, opportunities, and social influences (Lam et al., 2017).

In summary, there are several areas that need to be addressed, including the use of NSAID for mild and moderate cases, potential delays in systemic antimicrobial treatment for severe CM cases, negative predictive values of rapid diagnostic tests, availability of PCR as a cow-side diagnostic tool, criteria for the use of SCC and CM history in selective CM treatment protocols, application of selective protocols on farms with automated milking systems, understanding of target group to enhance uptake, and protocol compliance. Addressing these gaps may mitigate negative consequences and optimize use of selective CM treatment protocols.

CONCLUSIONS

Substantial scientific evidence supports that not all CM cases benefit from antimicrobial treatment. Therefore, correctly identifying CM cases that benefit from antimicrobial treatment is key to supporting judicious AMU in the dairy industry. Characteristics and history of the herd and the individual cow should be considered in the treatment decision of CM. This should be accompanied by a relatively fast basic identification of the CM causative organism. Several rapid diagnostic tests are currently available to assist farmers in presumptive identification of the causative organism and inform treatment decisions. The majority of literature did not report any negative udder health consequences (e.g., clinical cure, bacteriological cure, SCC, culling rate, milk production, or recurrence) after initiating selective CM protocols using on-farm testing methods, although coadministration of NSAID improved outcomes. No negative economic consequences were noted with selective versus blanket treatment protocols. Uptake of selective CM treatment protocols depends on legislation, management systems, and adoption of udder health control programs. The level of AMU reduction after implementation of a selective protocol depends on the pathogens responsible for CM. Therefore, the presented selective CM treatment protocol is a valuable tool to reduce AMU on dairy farms.

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REFERENCES

Aghamohammadi, M., D. Haine, D. F. Kelton, H. W. Barkema, H. Hogeveen, G. P. Keefe, and S. Dufour. 2018. Herd-level mastitis-associated costs on Canadian dairy farms. Front. Vet. Sci. 5:100. https://doi.org/10.3389/fvets.2018.00100.

Anderson, K. L., and E. Hunt. 1989. Anti-inflammatory therapy in acute endotoxin-induced bovine mastitis. Vet. Res. Commun. 13:17–26. https://doi.org/10.1007/BF00366848.

Anderson, K. L., A. R. Smith, R. D. Shanks, L. E. Davis, and B. K. Gustafsson. 1986. Efficacy of flunixin meglumine for the treatment of endotoxin-induced bovine mastitis. Am. J. Vet. Res. 47:1366–1372.

Armstrong, D., W. Koops, and J. Ekström. 2018. Euro Dairy: Practical strategies to reduce antimicrobial use in dairy farming. Accessed Dec. 6, 2022. https://ec.europa.eu/research/participants/

documents/downloadPublic?documentIds=080166e5c0d054f7&appId=PPGMS.

Banting, A., S. Banting, K. Heinonen, and K. Mustonen. 2008. Efficacy of oral and parenteral ketoprofen in lactating cows with endotoxin-induced acute mastitis. Vet. Rec. 163:506–509. https://doi.org/10.1136/vr.163.17.506.

Barkema, H. W., S. De Vliegher, S. Piepers, and R. N. Zadoks. 2013. Herd level approach to high bulk milk somatic cell count problems in dairy cattle. Vet. Q. 33:82–93. https://doi.org/10.1080/01652176.2013.799791.

Barkema, H. W., Y. H. Schukken, T. J. G. M. Lam, M. L. Beiboer, H. Wilmink, G. Benedictus, and A. Brand. 1998. Incidence of clinical mastitis in dairy herds grouped in three categories by bulk milk somatic cell counts. J. Dairy Sci. 81:411–419. https://doi.org/10.3168/jds.S0022-0302(98)75591-2.

Barkema, H. W., Y. H. Schukken, and R. N. Zadoks. 2006. Invited review: The role of cow, pathogen, and treatment regimen in the therapeutic success of bovine *Staphylococcus aureus* mastitis. J. Dairy Sci. 89:1877–1895. https://doi.org/10.3168/jds.S0022-0302(06)72256-1.

Bates, A., R. Laven, O. Bork, M. Hay, J. McDowell, and B. Saldias. 2020. Selective and deferred treatment of clinical mastitis in seven New Zealand dairy herds. Prev. Vet. Med. 176:104915. https://doi.org/10.1016/j.prevetmed.2020.104915.

Bates, D., M. Machler, B. Bolker, and S. Walker. 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw. 67:1–48. https://doi.org/10.18637/jss.v067.i01.

Bazzanella, B., K. Lichtmannsperger, V. Urbantke, A. Tichy, T. Wittek, and M. Baumgartner. 2020. Effect of on-farm milk culturing on treatment outcomes and usage of antimicrobials in mastitis therapy—A field study. Wien. Tierarztl. Monatsschr. 107:135–146.

Borchardt, S., and W. Heuwieser. 2022. Comparison of immediate blanket treatment versus a delayed pathogen-based treatment protocol for clinical mastitis using an on-farm culture test at a commercial German dairy farm. Antibiotics (Basel) 11:368. https://doi.org/10.3390/antibiotics11030368.

Bradley, A., J. Breen, M. Green, and C. Bullock. 2009. Mastitis control plan. Vet. Rec. 164:345. https://doi.org/10.1136/vr.164.11.345.

Bradley, A. J., K. A. Leach, J. E. Breen, L. E. Green, and M. J. Green. 2007. Survey of the incidence and aetiology of mastitis on dairy farms in England and Wales. Vet. Rec. 160:253–258. https://doi.org/10.1136/vr.160.8.253.

Breen, J. 2017. The importance of non-steroidal anti-inflammatory drugs (NSAIDs) in mastitis therapeutics. Livestock (Lond.) 22:182–185. https://doi.org/10.12968/live.2017.22.4.182.

Brennecke, J., U. Falkenberg, N. Wente, and V. Krömker. 2021. Are severe mastitis cases in dairy cows associated with bacteremia? Animals (Basel) 11:410. https://doi.org/10.3390/ani11020410.

Chapinal, N., C. E. Fitzpatrick, K. E. Leslie, and S. A. Wagner. 2014. Short communication: Automated assessment of the effect of flunixin meglumine on rumination in dairy cows with endotoxin-induced mastitis. Can. J. Anim. Sci. 94:21–25. https://doi.org/10.4141/cjas2013-071.

Davies, J., and D. Davies. 2010. Origins and evolution of antibiotic resistance. Microbiol. Mol. Biol. Rev. 74:417–433. https://doi.org/10.1128/MMBR.00016-10.

de Jong, E., L. Creytens, S. De Vliegher, K. D. McCubbin, M. Baptiste, A. A. Leung, D. Speksnijder, S. Dufour, J. R. Middleton, P. L. Ruegg, T. J. G. M. Lam, D. F. Kelton, S. McDougall, S. M. Godden, A. Lago, P. J. Rajala-Schultz, K. Orsel, V. Krömker, J. P. Kastelic, and H. W. Barkema. 2023. Selective treatment of nonsevere clinical mastitis does not adversely affect cure, somatic cell count, milk yield, recurrence, or culling: A systematic review and meta-analysis. J. Dairy Sci. 106:1267–1286. https://doi.org/10.3168/jds.2022-22271.

Deng, Z., T. J. G. M. Lam, H. Hogeveen, M. Spaninks, N. Heij, M. Postema, T. van Werven, and G. Koop. 2020. Antimicrobial use and farmers' attitude toward mastitis treatment on dairy farms with automatic or conventional milking systems. J. Dairy Sci. 103:7302–7314. https://doi.org/10.3168/jds.2019-17960.

Dohoo, I. R., J. Smith, S. Andersen, D. F. Kelton, and S. Godden. 2011. Diagnosing intramammary infections: Evaluation of definitions based on a single milk sample. J. Dairy Sci. 94:250–261. https://doi.org/10.3168/jds.2010-3559.

Döpfer, D., H. W. Barkema, T. J. G. M. Lam, Y. H. Schukken, and W. Gaastra. 1999. Recurrent clinical mastitis caused by *Escherichia coli* in dairy cows. J. Dairy Sci. 82:80–85. https://doi.org/10.3168/jds.S0022-0302(99)75211-2.

Down, P. M., A. J. Bradley, J. E. Breen, and M. J. Green. 2017. Factors affecting the cost-effectiveness of on-farm culture prior to the treatment of clinical mastitis in dairy cows. Prev. Vet. Med. 145:91–99. https://doi.org/10.1016/j.prevetmed.2017.07.006.

Ehinger, A. M., H. Schmidt, and M. Kietzmann. 2006. Tissue distribution of cefquinome after intramammary and "systemic" administration in the isolated perfused bovine udder. Vet. J. 172:147–153. https://doi.org/10.1016/j.tvjl.2005.02.029.

Erskine, R. J., P. C. Bartlett, J. L. VanLente, and C. R. Phipps. 2002. Efficacy of systemic ceftiofur as a therapy for severe clinical mastitis in dairy cattle. J. Dairy Sci. 85:2571–2575. https://doi.org/10.3168/jds.S0022-0302(02)74340-3.

Erskine, R. J., S. Wagner, and F. J. DeGraves. 2003. Mastitis therapy and pharmacology. Vet. Clin. North Am. Food Anim. Pract. 19:109–138. https://doi.org/10.1016/S0749-0720(02)00067-1.

European Commission. 2022. Press release IP/22/663: Veterinary medicines: New rules to promote animal health and fight antimicrobial resistance now apply. Accessed Dec. 6, 2022. https://ec.europa.eu/commission/presscorner/detail/en/ip_22_663.

FAO (Food and Agriculture Organization). 2021. Evaluation of FAO's role and work on antimicrobial resistance (AMR). Thematic evaluation series. Accessed Dec. 6, 2022. https://www.fao.org/3/cb3680en/cb3680en.pdf.

Farrell, S., C. McKernan, T. Benson, C. Elliott, and M. Dean. 2021. Understanding farmers' and veterinarians' behavior in relation to antimicrobial use and resistance in dairy cattle: A systematic review. J. Dairy Sci. 104:4584–4603. https://doi.org/10.3168/jds.2020-19614.

Fenlon, D. R., D. N. Logue, J. Gunn, and J. Wilson. 1995. A study of mastitis bacteria and herd management practices to identify their relationship to high somatic cell counts in bulk tank milk. Br. Vet. J. 151:17–25. https://doi.org/10.1016/S0007-1935(05)80059-4.

Firth, C. L., A. Käsbohrer, C. Schleicher, K. Fuchs, C. Egger-Danner, M. Mayerhofer, H. Schobesberger, J. Köfer, and W. Obritzhauser. 2017. Antimicrobial consumption on Austrian dairy farms: An observational study of udder disease treatments based on veterinary medication records. PeerJ 5:e4072. https://doi.org/10.7717/peerj.4072.

Francoz, D., V. Wellemans, J. P. Dupré, J. P. Roy, F. Labelle, P. Lacasse, and S. Dufour. 2017. Invited review: A systematic review and qualitative analysis of treatments other than conventional antimicrobials for clinical mastitis in dairy cows. J. Dairy Sci. 100:7751–7770. https://doi.org/10.3168/jds.2016-12512.

Fuenzalida, M. J., and P. L. Ruegg. 2019. Negatively controlled, randomized clinical trial to evaluate intramammary treatment of nonsevere, gram-negative clinical mastitis. J. Dairy Sci. 102:5438–5457. https://doi.org/10.3168/jds.2018-16156.

Gao, J., H. W. Barkema, L. Zhang, G. Liu, Z. Deng, L. Cai, R. Shan, S. Zhang, J. Zou, J. P. Kastelic, and B. Han. 2017. Incidence of clinical mastitis and distribution of pathogens on large Chinese dairy farms. J. Dairy Sci. 100:4797–4806. https://doi.org/10.3168/jds.2016-12334.

Gonçalves, J. L., C. Kamphuis, H. Vernooij, J. P. Araújo Jr., R. C. Grenfell, L. Juliano, K. L. Anderson, H. Hogeveen, and M. V. dos Santos. 2020. Pathogen effects on milk yield and composition in chronic subclinical mastitis in dairy cows. Vet. J. 262:105473. https://doi.org/10.1016/j.tvjl.2020.105473.

González Pereyra, V., M. Pol, F. Pastorino, and A. Herrero. 2015. Quantification of antimicrobial usage in dairy cows and preweaned calves in Argentina. Prev. Vet. Med. 122:273–279. https://doi.org/10.1016/j.prevetmed.2015.10.019.

Griffioen, K., G. E. Hop, M. M. C. Holstege, A. G. J. Velthuis, and T. J. G. M. Lam. 2016. Dutch dairy farmers' need for microbiological mastitis diagnostics. J. Dairy Sci. 99:5551–5561. https://doi.org/10.3168/jds.2015-10816.

Griffioen, K., A. G. J. Velthuis, G. Koop, and T. J. G. M. Lam. 2021. Effects of a mastitis treatment strategy with or without on-farm testing. J. Dairy Sci. 104:4665–4681. https://doi.org/10.3168/jds.2019-17871.

Hameed, S., M. Arshad, M. Ashraf, M. Avais, and M. A. Shahid. 2008. Prevalence of common mastitogens and their antibiotic susceptibility in Tehsil Burewala, Pakistan. Pak. J. Agric. Sci. 45:182–183.

Harwood, D., A. Murphy, E. Kelly, S. Rizvi, and J. Fitzgerald. 2009. Managing chronically mastitic cows. Vet. Rec. 164:407. https://doi.org/10.1136/vr.164.13.407-a.

Hashemi, M., M. Kafi, and M. Safdarian. 2011. The prevalence of clinical and subclinical mastitis in dairy cows in the central region of Fars province, south of Iran. Iran. J. Vet. Res. 12:236–241. https://doi.org/10.22099/ijvr.2011.71.

Hemling, T. C. 2017. 7 point plan for mastitis control. M2 Magazine, 18. Accessed Dec. 6, 2022. https://m2-magazine.org/7-point-plan-mastitis-control/.

Hewson, C. J., I. R. Dohoo, K. A. Lemke, and H. W. Barkema. 2007. Canadian veterinarians' use of analgesics in cattle, pigs, and horses in 2004 and 2005. Can. Vet. J. 48:155–164.

Hillerton, J. E., and K. E. Kliem. 2002. Effective treatment of *Streptococcus uberis* clinical mastitis to minimize the use of antibiotics. J. Dairy Sci. 85:1009–1014. https://doi.org/10.3168/jds.S0022-0302(02)74161-1.

Holmes, A. H., L. S. P. Moore, A. Sundsfjord, M. Steinbakk, S. Regmi, A. Karkey, P. J. Guerin, and L. J. V. Piddock. 2016. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet 387:176–187. https://doi.org/10.1016/S0140-6736(15)00473-0.

Jones, G., O. Bork, S. A. Ferguson, and A. Bates. 2019. Comparison of an on-farm point-of-care diagnostic with conventional culture in analysing bovine mastitis samples. J. Dairy Res. 86:222–225. https://doi.org/10.1017/S0022029919000177.

Kalmus, P., H. Simojoki, T. Orro, S. Taponen, K. Mustonen, J. Holopainen, and S. Pyörälä. 2014. Efficacy of 5-day parenteral versus intramammary benzylpenicillin for treatment of clinical mastitis caused by gram-positive bacteria susceptible to penicillin in vitro. J. Dairy Sci. 97:2155–2164. https://doi.org/10.3168/jds.2013-7338.

Kayitsinga, J., R. L. Schewe, G. A. Contreras, and R. J. Erskine. 2017. Antimicrobial treatment of clinical mastitis in the eastern United States: The influence of dairy farmers' mastitis management and treatment behavior and attitudes. J. Dairy Sci. 100:1388–1407. https://doi.org/10.3168/jds.2016-11708.

Keane, O. M., K. E. Budd, J. Flynn, and F. McCoy. 2013. Pathogen profile of clinical mastitis in Irish milk-recording herds reveals a complex aetiology. Vet. Rec. 173:17. https://doi.org/10.1136/vr.101308.

Kessels, J. A., E. Cha, S. K. Johnson, F. L. Welcome, A. R. Kristensen, and Y. T. Gröhn. 2016. Economic comparison of common treatment protocols and J5 vaccination for clinical mastitis in dairy herds using optimized culling decisions. J. Dairy Sci. 99:3838–3847. https://doi.org/10.3168/jds.2015-10385.

Klaas, I. C., and R. N. Zadoks. 2018. An update on environmental mastitis: Challenging perceptions. Transbound. Emerg. Dis. 65:166–185. https://doi.org/10.1111/tbed.12704.

Kock, J., N. Wente, Y. Zhang, J. H. Paduch, S. Leimbach, D. Klocke, C. C. Gelfert, and V. Krömker. 2018. Udder health effects of an evidence-based mastitis therapy concept in northwestern Germany. Milk Science International 71:14–20. https://doi.org/10.25968/MSI.2018.4.

Koskinen, M. T., G. J. Wellenberg, O. C. Sampimon, J. Holopainen, A. Rothkamp, L. Salmikivi, W. A. van Haeringen, T. J. G. M. Lam, and S. Pyörälä. 2010. Field comparison of real-time polymerase chain reaction and bacterial culture for identification of bovine mastitis bacteria. J. Dairy Sci. 93:5707–5715. https://doi.org/10.3168/jds.2010-3167.

Krömker, V., and S. Leimbach. 2017. Mastitis treatment—Reduction in antibiotic usage in dairy cows. Reprod. Domest. Anim. 52:21–29. https://doi.org/10.1111/rda.13032.

Krömker, V., A. Schmenger, D. Klocke, E. M. Mansion-de Vries, N. Wente, Y. Zhang, and S. Leimbach. 2021. Non-inferiority trial investigating the efficacy of non-steroidal anti-inflammatory drugs and antimicrobial treatment of mild to moderate clinical mastitis in dairy cows with long-lasting udder diseases. Front. Vet. Sci. 8:660804. https://doi.org/10.3389/fvets.2021.660804.

Kuipers, A., W. J. Koops, and H. Wemmenhove. 2016. Antibiotic use in dairy herds in the Netherlands from 2005 to 2012. J. Dairy Sci. 99:1632–1648. https://doi.org/10.3168/jds.2014-8428.

Kurban, D., J.-P. Roy, F. Kabera, A. Fréchette, M. M. Um, A. Albaaj, S. Rowe, S. Godden, P. R. F. Adkins, J. R. Middleton, M.-L. Gauthier, G. P. Keefe, T. J. DeVries, D. F. Kelton, P. Moroni, M. Veiga dos Santos, H. W. Barkema, and S. Dufour. 2022. Diagnosing intramammary infection: Meta-analysis and mapping review on frequency and udder health relevance of microorganism species isolated from bovine milk samples. Animals (Basel) 12:3288. https://doi.org/10.3390/ani12233288.

Lago, A., S. M. Godden, R. Bey, P. L. Ruegg, and K. Leslie. 2011a. The selective treatment of clinical mastitis based on on-farm culture results: I. Effects on antibiotic use, milk withholding time, and short-term clinical and bacteriological outcomes. J. Dairy Sci. 94:4441–4456. https://doi.org/10.3168/jds.2010-4046.

Lago, A., S. M. Godden, R. Bey, P. L. Ruegg, and K. Leslie. 2011b. The selective treatment of clinical mastitis based on on-farm culture results: II. Effects on lactation performance, including clinical mastitis recurrence, somatic cell count, milk production, and cow survival. J. Dairy Sci. 94:4457–4467. https://doi.org/10.3168/jds.2010-4047.

Lago, A., D. Luiz, D. Pearce, C. Tovar, and J. Zaragoza. 2016a. Effect of the selective treatment of gram-positive clinical mastitis cases versus blanket therapy. J. Anim. Sci. 94(suppl_5):75–76. https://doi.org/10.2527/jam2016-0156.

Lago, A., C. Tovar, J. Zaragoza, D. Luiz, and D. Pearce. 2016b. The treatment of only environmental streptococci clinical mastitis cases reduced antibiotic use, days out of the tank, recurrence of clinical mastitis and a tendency to reduce culling. J. Anim. Sci. 94(suppl_5):75. https://doi.org/10.2527/jam2016-0155.

Lam, T. J. G. M., J. Jansen, and R. J. Wessels. 2017. The RESET Mindset Model applied on decreasing antibiotic usage in dairy cattle in the Netherlands. Ir. Vet. J. 70:5. https://doi.org/10.1186/s13620-017-0085-x.

Lardé, H., S. Dufour, M. Archambault, J. Massé, J.-P. Roy, and D. Francoz. 2021. An observational cohort study on antimicrobial usage on dairy farms in Quebec, Canada. J. Dairy Sci. 104:1864–1880. https://doi.org/10.3168/jds.2020-18848.

Latosinski, G. S., M. J. Amzalak, and J. C. F. Pantoja. 2020. Efficacy of ketoprofen for treatment of spontaneous, culture-negative, mild cases of clinical mastitis: A randomized, controlled superiority trial. J. Dairy Sci. 103:2624–2635. https://doi.org/10.3168/jds.2019-17504.

Leimbach, S., and V. Krömker. 2018. Laboratory evaluation of a novel rapid tube test system for differentiation of mastitis-causing pathogen groups. J. Dairy Sci. 101:6357–6365. https://doi.org/10.3168/jds.2017-14198.

Leininger, D. J., J. R. Roberson, F. Elvinger, D. Ward, and R. M. Akers. 2003. Evaluation of frequent milkout for treatment of cows with experimentally induced *Escherichia coli* mastitis. J. Am. Vet. Med. Assoc. 222:63–66. https://doi.org/10.2460/javma.2003.222.63.

Leslie, K. E., and C. S. Petersson-Wolfe. 2012. Assessment and management of pain in dairy cows with clinical mastitis. Vet. Clin. North Am. Food Anim. Pract. 28:289–305. https://doi.org/10.1016/j.cvfa.2012.04.002.

Lohuis, J. A. C. M., T. Werven, A. Brand, A. S. J. P. A. M. Miert, E. Rohde, B. Ludwig, P. Heizmann, and W. F. Rehm. 1991. Pharmacodynamics and pharmacokinetics of carprofen, a non-steroidal anti-inflammatory drug, in healthy cows and cows with *Escherichia coli* endotoxin-induced mastitis. J. Vet. Pharmacol. Ther. 14:219–229. https://doi.org/10.1111/j.1365-2885.1991.tb00830.x.

MacDonald, K. A. R. 2011. Evaluation of a 3M Petrifilm on-farm mastitis culture system and treatment decision algorithm for clinical mastitis in Canada. PhD thesis. University of Prince Edward Island, Charlottetown, PE, Canada.

Malcata, F. B., P. T. Pepler, E. L. O'Reilly, N. Brady, P. D. Eckersall, R. N. Zadoks, and L. Viora. 2020. Point-of-care tests for bovine clinical mastitis: What do we have and what do we need? J. Dairy Res. 87(S1):60–66. https://doi.org/10.1017/S002202992000062X.

Mansion-de Vries, E. M., J. Lücking, N. Wente, C. Zinke, M. Hoedemaker, and V. Krömker. 2016. Comparison of an evidence-based and a conventional mastitis therapy concept with regard to cure rates and antibiotic usage. Milk Science International 69:27–32. https://doi.org/10.25968/MSI.2016.6.

McCubbin, K. D., E. de Jong, T. J. G. M. Lam, D. F. Kelton, J. R. Middleton, S. McDougall, S. De Vliegher, S. Godden, P. J. Rajala-Schultz, S. Rowe, D. C. Speksnijder, J. P. Kastelic, and H. W. Barkema. 2022. Invited review: Selective use of antimicrobials in dairy cattle at drying-off. J. Dairy Sci. 105:7161–7189. https://doi.org/10.3168/jds.2021-21455.

McDougall, S. 1998. Efficacy of two antibiotic treatments in curing clinical and subclinical mastitis in lactating dairy cows. N. Z. Vet. J. 46:226–232. https://doi.org/10.1080/00480169.1998.36094.

McDougall, S., E. Abbeloos, S. Piepers, A. Rao, S. Astiz, T. van Werven, J. Statham, and N. Perez-Villalobos. 2015. Addition of Metacam® (Meloxicam) to the treatment of clinical mastitis improves subsequent reproductive performance. Pages 61–63 in Proc. 2015 British Mastitis Conference. The Dairy Group, Worcester, UK.

McDougall, S., K. E. Agnew, R. Cursons, X. X. Hou, and C. R. W. Compton. 2007. Parenteral treatment of clinical mastitis with tylosin base or penethamate hydriodide in dairy cattle. J. Dairy Sci. 90:779–789. https://doi.org/10.3168/jds.S0022-0302(07)71562-X.

McDougall, S., M. A. Bryan, and R. M. Tiddy. 2009. Effect of treatment with the nonsteroidal antiinflammatory meloxicam on milk production, somatic cell count, probability of re-treatment, and culling of dairy cows with mild clinical mastitis. J. Dairy Sci. 92:4421–4431. https://doi.org/10.3168/jds.2009-2284.

McDougall, S., C. W. R. Compton, and N. Botha. 2017. Factors influencing antimicrobial prescribing by veterinarians and usage by dairy farmers in New Zealand. N. Z. Vet. J. 65:84–92. https://doi.org/10.1080/00480169.2016.1246214.

McDougall, S., J. Niethammer, and E. M. Graham. 2018. Antimicrobial usage and risk of retreatment for mild to moderate clinical mastitis cases on dairy farms following on-farm bacterial culture and selective therapy. N. Z. Vet. J. 66:98–107. https://doi.org/10.1080/00480169.2017.1416692.

Middleton, J. R., and L. K. Fox. 2001. Technical note: Therapeutic cessation of lactation of *Staphylococcus aureus*-infected mammary quarters. J. Dairy Sci. 84:1976–1978. https://doi.org/10.3168/jds.S0022-0302(01)74640-1.

Molineri, A. I., C. Camussone, M. V. Zbrun, G. Suárez Archilla, M. Cristiani, V. Neder, L. Calvinho, and M. Signorini. 2021. Antimicrobial resistance of *Staphylococcus aureus* isolated from bovine mastitis: Systematic review and meta-analysis. Prev. Vet. Med. 188:105261. https://doi.org/10.1016/j.prevetmed.2021.105261.

Naqvi, S. A., M. T. M. King, R. D. Matson, T. J. DeVries, R. Deardon, and H. W. Barkema. 2022. Mastitis detection with recurrent neural networks in farms using automated milking systems. Comput. Electron. Agric. 192:106618. https://doi.org/10.1016/j.compag.2021.106618.

Neave, F. K., F. H. Dodd, R. G. Kingwill, and D. R. Westgarth. 1969. Control of mastitis in the dairy herd by hygiene and management. J. Dairy Sci. 52:696–707. https://doi.org/10.3168/jds.S0022-0302(69)86632-4.

NMC (National Mastitis Council). n.d. Recommended mastitis control program. Accessed Dec. 6, 2022. https://www.nmconline.org/wp-content/uploads/2020/04/RECOMMENDED-MASTITIS-CONTROL-PROGRAM-International.pdf.

Nobrega, D. B., J. De Buck, and H. W. Barkema. 2018. Antimicrobial resistance in non-*aureus* staphylococci isolated from milk is associated with systemic but not intramammary administration of antimicrobials in dairy cattle. J. Dairy Sci. 101:7425–7436. https://doi.org/10.3168/jds.2018-14540.

Nobrega, D. B., S. A. Naqvi, S. Dufour, R. Deardon, J. P. Kastelic, J. De Buck, and H. W. Barkema. 2020. Critically important antimicrobials are generally not needed to treat nonsevere clinical mastitis in lactating dairy cows: Results from a network meta-analysis. J. Dairy Sci. 103:10585–10603. https://doi.org/10.3168/jds.2020-18365.

Olde Riekerink, R. G. M., H. W. Barkema, D. F. Kelton, and D. T. Scholl. 2008. Incidence rate of clinical mastitis on Canadian dairy farms. J. Dairy Sci. 91:1366–1377. https://doi.org/10.3168/jds.2007-0757.

Olde Riekerink, R. G. M., H. W. Barkema, S. Veenstra, D. E. Poole, R. T. Dingwell, and G. P. Keefe. 2006. Prevalence of contagious mastitis pathogens in bulk tank milk in Prince Edward Island. Can. Vet. J. 47:567–572.

Oliveira, L., and P. L. Ruegg. 2014. Treatments of clinical mastitis occurring in cows on 51 large dairy herds in Wisconsin. J. Dairy Sci. 97:5426–5436. https://doi.org/10.3168/jds.2013-7756.

Orr, J., T. Geraghty, and K. Ellis. 2014. Anti-inflammatories in cattle medicine. Livestock (Lond.) 19:322–328. https://doi.org/10.12968/live.2014.19.6.322.

Østerås, O., and L. Sølverød. 2009. Norwegian mastitis control programme. Ir. Vet. J. 62(Suppl 4):S26–S33. https://doi.org/10.1186/2046-0481-62-S4-S26.

Paixão, M. G., L. R. Abreu, R. Richert, and P. L. Ruegg. 2017. Milk composition and health status from mammary gland quarters adjacent to glands affected with naturally occurring clinical mastitis. J. Dairy Sci. 100:7522–7533. https://doi.org/10.3168/jds.2017-12547.

Persson, Y., J. Katholm, H. Landin, and M. J. Mörk. 2015. Efficacy of enrofloxacin for the treatment of acute clinical mastitis caused by *Escherichia coli* in dairy cows. Vet. Rec. 176:673. https://doi.org/10.1136/vr.102667.

Persson Waller, K., V. Hardemark, A. K. Nyman, and A. Duse. 2016. Veterinary treatment strategies for clinical mastitis in dairy cows in Sweden. Vet. Rec. 178:240. https://doi.org/10.1136/vr.103506.

Petersson-Wolfe, C. S., K. E. Leslie, and T. H. Swartz. 2018. An update on the effect of clinical mastitis on the welfare of dairy cows and potential therapies. Vet. Clin. North Am. Food Anim. Pract. 34:525–535. https://doi.org/10.1016/j.cvfa.2018.07.006.

Petrovski, K. R., C. Heuer, T. J. Parkinson, and N. B. Williamson. 2009. The incidence and aetiology of clinical bovine mastitis on 14 farms in Northland, New Zealand. N. Z. Vet. J. 57:109–115. https://doi.org/10.1080/00480169.2009.36887.

Pinzón-Sánchez, C., V. E. Cabrera, and P. L. Ruegg. 2011. Decision tree analysis of treatment strategies for mild and moderate cases of clinical mastitis occurring in early lactation. J. Dairy Sci. 94:1873–1892. https://doi.org/10.3168/jds.2010-3930.

Pinzón-Sánchez, C., and P. L. Ruegg. 2011. Risk factors associated with short-term post-treatment outcomes of clinical mastitis. J. Dairy Sci. 94:3397–3410. https://doi.org/10.3168/jds.2010-3925.

Poutrel, B., M. R. Stegemann, O. Roy, F. Pothier, N. Tilt, and M. Payne-Johnson. 2008. Evaluation of the efficacy of systemic danofloxacin in the treatment of induced acute *Escherichia coli* bovine mastitis. J. Dairy Res. 75:310–318. https://doi.org/10.1017/S0022029908003348.

Pyörälä, S. 2009. Treatment of mastitis during lactation. Ir. Vet. J. 62(S4):S40. https://doi.org/10.1186/2046-0481-62-S4-S40.

Pyörälä, S. H., and E. O. Pyörälä. 1998. Efficacy of parenteral administration of three antimicrobial agents in treatment of clinical mastitis in lactating cows: 487 cases (1989–1995). J. Am. Vet. Med. Assoc. 212:407–412.

Rainard, P., G. Foucras, D. Boichard, and R. Rupp. 2018. Invited review: Low milk somatic cell count and susceptibility to mastitis. J. Dairy Sci. 101:6703–6714. https://doi.org/10.3168/jds.2018-14593.

Rajala-Schultz, P., A. Nødtvedt, T. Halasa, and K. Persson Waller. 2021. Prudent use of antibiotics in dairy cows: The Nordic approach to udder health. Front. Vet. Sci. 8:623998. https://doi.org/10.3389/fvets.2021.623998.

Raymond, M. J., R. D. Wohrle, and D. R. Call. 2006. Assessment and promotion of judicious antibiotic use on dairy farms in Washing-

ton State. J. Dairy Sci. 89:3228–3240. https://doi.org/10.3168/jds.S0022-0302(06)72598-X.
Rees, G. M., K. K. Reyher, D. C. Barrett, and H. Buller. 2021. "It's cheaper than a dead cow": Understanding veterinary medicine use on dairy farms. J. Rural Stud. 86:587–598. https://doi.org/10.1016/j.jrurstud.2021.07.020.
Roberson, J. R. 2012. Treatment of clinical mastitis. Vet. Clin. North Am. Food Anim. Pract. 28:271–288. https://doi.org/10.1016/j.cvfa.2012.03.011.
Roy, J.-P., M. Archambault, A. Desrochers, J. Dubuc, S. Dufour, D. Francoz, M.-È. Paradis, and M. Rousseau. 2020. New Quebec regulation on the use of antimicrobials of very high importance in food animals: Implementation and impacts in dairy cattle practice. Can. Vet. J. 61:193–196.
Ruegg, P. L. 2018. Making antibiotic treatment decisions for clinical mastitis. Vet. Clin. North Am. Food Anim. Pract. 34:413–425. https://doi.org/10.1016/j.cvfa.2018.06.002.
Ruegg, P. L. 2021. What is success? A narrative review of research evaluating outcomes of antibiotics used for treatment of clinical mastitis. Front. Vet. Sci. 8:639641. https://doi.org/10.3389/fvets.2021.639641.
RUMA (Responsible Use of Medicines in Agriculture Alliance). 2020. Targets task force report 2020—Responsible use of antibiotics in UK farming, progress against 2020 targets, new targets 2021–2024. Accessed Dec. 6, 2022. https://ruma.org.uk/wp-content/uploads/2022/07/RUMA-REPORT-021220.pdf.
Rysanek, D., M. Zouharova, and V. Babak. 2009. Monitoring major mastitis pathogens at the population level based on examination of bulk tank milk samples. J. Dairy Res. 76:117–123. https://doi.org/10.1017/S0022029908003816.
Samson, O., N. Gaudout, E. Schmitt, Y. H. Schukken, and R. Zadoks. 2016. Use of on-farm data to guide treatment and control mastitis caused by *Streptococcus uberis*. J. Dairy Sci. 99:7690–7699. https://doi.org/10.3168/jds.2016-10964.
Santman-Berends, I. M. G. A., J. M. Swinkels, T. J. G. M. Lam, J. Keurentjes, and G. van Schaik. 2016. Evaluation of udder health parameters and risk factors for clinical mastitis in Dutch dairy herds in the context of a restricted antimicrobial usage policy. J. Dairy Sci. 99:2930–2939. https://doi.org/10.3168/jds.2015-10398.
Santman-Berends, I. M. G. A., K. W. H. van den Heuvel, T. J. G. M. Lam, C. G. M. Scherpenzeel, and G. van Schaik. 2021. Monitoring udder health on routinely collected census data: Evaluating the short- to mid-term consequences of implementing selective dry cow treatment. J. Dairy Sci. 104:2280–2289. https://doi.org/10.3168/jds.2020-18973.
Schmenger, A., and V. Krömker. 2020. Characterization, cure rates and associated risks of clinical mastitis in Northern Germany. Vet. Sci. 7:170. https://doi.org/10.3390/vetsci7040170.
Schmenger, A., S. Leimbach, N. Wente, Y. Zhang, A. M. Biggs, and V. Kroemker. 2020. Implementation of a targeted mastitis therapy concept using an on-farm rapid test: Antimicrobial consumption, cure rates and compliance. Vet. Rec. 187:401. https://doi.org/10.1136/vr.105674.
Sears, P. M., and K. K. McCarthy. 2003. Diagnosis of mastitis for therapy decisions. Vet. Clin. North Am. Food Anim. Pract. 19:93–108. https://doi.org/10.1016/S0749-0720(02)00074-9.
Sérieys, F., Y. Raguet, L. Goby, H. Schmidt, and G. Friton. 2005. Comparative efficacy of local and systemic antibiotic treatment in lactating cows with clinical mastitis. J. Dairy Sci. 88:93–99. https://doi.org/10.3168/jds.S0022-0302(05)72666-7.
Shpigel, N. Y., D. Levin, M. Winkler, A. Saran, G. Ziv, and A. Böttner. 1997. Efficacy of cefquinome for treatment of cows with mastitis experimentally induced using *Escherichia coli*. J. Dairy Sci. 80:318–323. https://doi.org/10.3168/jds.S0022-0302(97)75941-1.
Sipka, A., M. Wieland, F. Biscarini, R. M. Rossi, N. Roman, C. Santisteban, P. Moroni, and D. V. Nydam. 2021. Short communication: Comparative performance of 3 on-farm culture systems for detection of mastitis pathogens interpreted by trained and untrained observers. J. Dairy Sci. 104:4936–4941. https://doi.org/10.3168/jds.2020-19166.
Skarbye, A. P., M. A. Krogh, and J. T. Sorensen. 2018. The effect of individual quarter dry-off in management of subclinical mastitis on udder condition and milk production in organic dairy herds: A randomized field trial. J. Dairy Sci. 101:11186–11198. https://doi.org/10.3168/jds.2018-14794.
Sol, J., O. C. Sampimon, H. W. Barkema, and Y. H. Schukken. 2000. Factors associated with cure after therapy of clinical mastitis caused by *Staphylococcus aureus*. J. Dairy Sci. 83:278–284. https://doi.org/10.3168/jds.S0022-0302(00)74875-2.
Speksnijder, D. C., D. J. Mevius, C. J. M. Bruschke, and J. A. Wagenaar. 2015. Reduction of veterinary antimicrobial use in the Netherlands: The Dutch success model. Zoonoses Public Health 62:79–87. https://doi.org/10.1111/zph.12167.
Stevens, M., S. Piepers, K. Supré, and S. De Vliegher. 2018. Antimicrobial consumption on dairy herds and its association with antimicrobial inhibition zone diameters of non-*aureus* staphylococci and *Staphylococcus aureus* isolated from subclinical mastitis. J. Dairy Sci. 101:3311–3322. https://doi.org/10.3168/jds.2017-13365.
Stevens, M., S. Piepers, K. Supré, J. Dewulf, and S. De Vliegher. 2016. Quantification of antimicrobial consumption in adult cattle on dairy herds in Flanders, Belgium, and associations with udder health, milk quality, and production performance. J. Dairy Sci. 99:2118–2130. https://doi.org/10.3168/jds.2015-10199.
Suojala, L., L. Kaartinen, and S. Pyörälä. 2013. Treatment for bovine *Escherichia coli* mastitis—An evidence-based approach. J. Vet. Pharmacol. Ther. 36:521–531. https://doi.org/10.1111/jvp.12057.
Suojala, L., H. Simojoki, K. Mustonen, L. Kaartinen, and S. Pyörälä. 2010. Efficacy of enrofloxacin in the treatment of naturally occurring acute clinical *Escherichia coli* mastitis. J. Dairy Sci. 93:1960–1969. https://doi.org/10.3168/jds.2009-2462.
Svennesen, L., A. Skarbye, M. Farre, and C. Kirkeby. 2022. Treatment of clinical mastitis: Intramammary or in combination with parenteral administration of penicillin? Pages 426–427 in 31st World Buiatrics Congress, Madrid, Spain.
Tang, K. L., N. P. Caffrey, D. B. Nóbrega, S. C. Cork, P. E. Ronksley, H. W. Barkema, A. J. Polachek, H. Ganshorn, N. Sharma, J. D. Kellner, and W. A. Ghali. 2017. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: A systematic review and meta-analysis. Lancet Planet. Health 1:e316–e327. https://doi.org/10.1016/S2542-5196(17)30141-9.
Taponen, S., L. Salmikivi, H. Simojoki, M. T. Koskinen, and S. Pyörälä. 2009. Real-time polymerase chain reaction-based identification of bacteria in milk samples from bovine clinical mastitis with no growth in conventional culturing. J. Dairy Sci. 92:2610–2617. https://doi.org/10.3168/jds.2008-1729.
Tho Seeth, M., N. Wente, J.-H. Paduch, D. Klocke, M. Hoedemaker, and V. Krömker. 2016. Drying-off single udder quarters of dairy cattle during lactation using a casein hydrolysate. Milk Sci. Int. 69:23–26. https://doi.org/10.25968/MSI.2016.5.
Thomson, K., M. Rantala, M. Hautala, S. Pyörälä, and L. Kaartinen. 2008. Cross-sectional prospective survey to study indication-based usage of antimicrobials in animals: Results of use in cattle. BMC Vet. Res. 4:15. https://doi.org/10.1186/1746-6148-4-15.
Tomazi, T., and M. V. dos Santos. 2020. Antimicrobial use for treatment of clinical mastitis in dairy herds from Brazil and its association with herd-level descriptors. Prev. Vet. Med. 176:104937. https://doi.org/10.1016/j.prevetmed.2020.104937.
Toutain, P. L., A. Bousquet-Mélou, P. Damborg, A. A. Ferran, D. Mevius, L. Pelligand, K. T. Veldman, and P. Lees. 2017. En route towards European clinical breakpoints for veterinary antimicrobial susceptibility testing: A position paper explaining the VetCAST approach. Front. Microbiol. 8:2344. https://doi.org/10.3389/fmicb.2017.02344.
USDA. 2016. Dairy 2014, milk quality, milking procedures, and mastitis on U.S. dairies, 2014. Accessed Dec. 6, 2022. https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy14/Dairy14_dr_Mastitis.pdf.
Vaarst, M., T. W. Bennedsgaard, I. Klaas, T. B. Nissen, S. M. Thamsborg, and S. Østergaard. 2006. Development and daily management of an explicit strategy of nonuse of antimicrobial drugs in

twelve Danish organic dairy herds. J. Dairy Sci. 89:1842–1853. https://doi.org/10.3168/jds.S0022-0302(06)72253-6.

Vaarst, M., B. Paarup-Laursen, H. Houe, C. Fossing, and H. J. Andersen. 2002. Farmers' choice of medical treatment of mastitis in Danish dairy herds based on qualitative research interviews. J. Dairy Sci. 85:992–1001. https://doi.org/10.3168/jds.S0022-0302(02)74159-3.

Vaarst, M., S. M. Thamsborg, T. W. Bennedsgaard, H. Houe, C. Enevoldsen, F. M. Aarestrup, and A. de Snoo. 2003. Organic dairy farmers' decision making in the first 2 years after conversion in relation to mastitis treatments. Livest. Prod. Sci. 80:109–120. https://doi.org/10.1016/S0301-6226(02)00310-X.

Vangroenweghe, F., L. Duchateau, P. Boutet, P. Lekeux, P. Rainard, M. J. Paape, and C. Burvenich. 2005. Effect of carprofen treatment following experimentally induced *Escherichia coli* mastitis in primiparous cows. J. Dairy Sci. 88:2361–2376. https://doi.org/10.3168/jds.S0022-0302(05)72914-3.

Vasquez, A. K., D. V. Nydam, M. B. Capel, S. Eicker, and P. D. Virkler. 2017. Clinical outcome comparison of immediate blanket treatment versus a delayed pathogen-based treatment protocol for clinical mastitis in a New York dairy herd. J. Dairy Sci. 100:2992–3003. https://doi.org/10.3168/jds.2016-11614.

Wagner, S. A., and M. D. Apley. 2004. Effects of two anti-inflammatory drugs on physiologic variables and milk production in cows with endotoxin-induced mastitis. Am. J. Vet. Res. 65:64–68. https://doi.org/10.2460/ajvr.2004.65.64.

Wemette, M., A. G. Safi, W. Beauvais, K. Ceres, M. Shapiro, P. Moroni, F. L. Welcome, and R. Ivanek. 2020. New York State dairy farmers' perceptions of antibiotic use and resistance: A qualitative interview study. PLoS One 15:e0232937. https://doi.org/10.1371/journal.pone.0232937.

Wenz, J. R., G. M. Barrington, F. B. Garry, K. D. McSweeney, R. P. Dinsmore, G. Goodell, and R. J. Callan. 2001. Bacteremia associated with naturally occurring acute coliform mastitis in dairy cows. J. Am. Vet. Med. Assoc. 219:976–981. https://doi.org/10.2460/javma.2001.219.976.

Wenz, J. R., F. B. Garry, J. E. Lombard, R. Elia, D. Prentice, and R. P. Dinsmore. 2005. Short communication: Efficacy of parenteral ceftiofur for treatment of systemically mild clinical mastitis in dairy cattle. J. Dairy Sci. 88:3496–3499. https://doi.org/10.3168/jds.S0022-0302(05)73034-4.

WHO (World Health Organization). 2015. Global action plan on antimicrobial resistance. Accessed Dec. 6, 2022. https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf.

Wickham, H. 2016. Ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag, New York.

Wilson, D. J., R. N. Gonzalez, K. L. Case, L. L. Garrison, and Y. T. Gröhn. 1999. Comparison of seven antibiotic treatments with no treatment for bacteriological efficacy against bovine mastitis pathogens. J. Dairy Sci. 82:1664–1670. https://doi.org/10.3168/jds.S0022-0302(99)75395-6.

WOAH (World Organisation for Animal Health). 2016. The OIE strategy on antimicrobial resistance and the prudent use of antimicrobials. Accessed Dec. 6, 2022. https://www.woah.org/fileadmin/Home/eng/Media_Center/docs/pdf/PortailAMR/EN_OIE-AMRstrategy.pdf.

Yeiser, E. E., K. E. Leslie, M. L. McGilliard, and C. S. Petersson-Wolfe. 2012. The effects of experimentally induced *Escherichia coli* mastitis and flunixin meglumine administration on activity measures, feed intake, and milk parameters. J. Dairy Sci. 95:4939–4949. https://doi.org/10.3168/jds.2011-5064.

Zimov, J. L., N. A. Botheras, W. P. Weiss, and J. S. Hogan. 2011. Associations among behavioral and acute physiologic responses to lipopolysaccharide-induced clinical mastitis in lactating dairy cows. Am. J. Vet. Res. 72:620–627. https://doi.org/10.2460/ajvr.72.5.620.

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