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EPIDEMIOLOGIC APPROACH TO ANTIBIOTIC DRY COW THERAPY IN DAIRY HERDS

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DOCTORAL DISSERTATION

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Essentially, all models are wrong, but some are useful.

George E. P. Box

ABSTRACT

The nonlactating period is a critically important time for dairy cow health and optimal subsequent milk yield. Regarding udder health, at the beginning and end of this period, cows are most susceptible to new intramammary infections. In addition, dry-off is also the optimal time to cure any existing mammary-gland infections. Hence, intramammary-infused antibiotic dry cow therapy (DCT) after final milking is an important and widely used mastitis control measure. DCT can be administered either to all quarters of all cows or only to infected cows or quarters. The global antibiotic resistance problem causes an increasing need to reduce antibiotic use in livestock, but a shift in management should not harm animal welfare or impair farm profitability. Although selective treatment of only infected cows is a more sustainable approach, accurate and cost-effective identification of cows or quarters in need of medication is a challenge. The objective of this epidemiologic study was to determine ideal drying-off practices to maintain good udder health and productivity while implementing prudent use of antibiotics. The specific focus of interest was on DCT, and an additional aim was to examine risk factors for post-calving udder health problems and reduced milk yield.

The three cohort studies comprised retrospective herd- and cow-level dairy-herd-recording data registered from conventional, commercial Finnish dairy farms. The first study evaluated herd-level associations between milk somatic cell count (SCC), milk yield, and various farm characteristics, with an emphasis on antibiotic usage at dry-off. The second study investigated whether the herd-level DCT practice was associated with cow-level udder health in early lactation. The third study determined cow-level milk yield and SCC differences within the first half of lactation between selectively DCT-treated and -untreated cows.

Results show that herd-level selective-DCT strategy, even with a very moderate proportion of medicated cows, is no hindrance to maintenance of low herd-average SCC and good milk yield. Regardless of the farm's DCT practice, average milk yield increased over time, while average SCC remained rather constant. However, the large variation between farms in average yield and SCC over DCT practices suggests the need for farm-specific protocols. The practice of treating all cows in a herd was associated with lower test-day SCC within early lactation compared with the selective-DCT practice. Moreover, a DCT-treated cow on a selective-DCT farm had lower SCC after calving than did an untreated cow. This indicates that DCT continues to be an effective mastitis control practice. Most selective-DCT farms administered DCT to only one-third of their cows, or less. The DCT effect on milk yield differed depending on late-lactation SCC, so that a higher SCC near dry-off led to an increased difference in yield between treated and untreated cows within the first half of lactation. A missed DCT for a high-SCC cow thus had an adverse effect on subsequent lactation milk yield and on SCC, highlighting the need for accurate selection of cows to be treated. Risk factors associated with higher post-calving SCC included high late-lactation

SCC, lactational mastitis treatment, high parity, high preceding-lactation average SCC, and high milk yield near dry-off.

Rising awareness of the selective-DCT approach currently is emerging in those countries where it is common to treat all cows at the end of lactation. The successful implementation of selective DCT on Finnish farms will hopefully encourage these countries to gradually reduce antibiotic use in dairy livestock. Such a development would perhaps have a positive effect on consumer confidence in the dairy industry. On Finnish dairy farms, rapid structural change in agriculture continues, and therefore maintaining the current low consumption of antibiotics requires optimal farm management, professional advice, and active monitoring.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications which are referred to in the text by their Roman numerals:

I **Niemi, R.E.**, Vilar, M.J., Dohoo, I.R., Hovinen, M., Simojoki, H., Rajala-Schultz, P.J. 2020. Antibiotic dry cow therapy, somatic cell count, and milk production: Retrospective analysis of the associations in dairy herd recording data using multilevel growth models. *Preventive Veterinary Medicine* 180: 105028. doi: 10.1016/j.prevetmed.2020.105028.

II **Niemi, R.E.**, Hovinen, M., Vilar, M.J., Simojoki, H., Rajala-Schultz, P.J. 2021. Dry cow therapy and early lactation udder health problems — Associations and risk factors. *Preventive Veterinary Medicine* 188:105268. doi: 10.1016/j.prevetmed.2021.105268.

III **Niemi, R.E.**, Hovinen, M., Rajala-Schultz, P.J. 2022. Selective dry cow therapy effect on milk yield and somatic cell count: A retrospective cohort study. *Journal of Dairy Science* 105: 1387–1401. doi: 10.3168/jds.2021-20918.

ABBREVIATIONS

AMS	automatic milking system
AR(1)	first-order autoregressive covariance structure
CI	confidence interval
CM	clinical mastitis
CMT	California mastitis test
DCT	dry cow therapy
DHI	dairy herd improvement
DIM	days in milk
ECM	energy-corrected milk
ETS	external teat sealant
ICC	intraclass correlation coefficient
IMI	intramammary infection
IQR	interquartile range
ITS	intramammary teat sealant
lnSCC	naturally log-transformed somatic cell count
MLD	milk leukocyte differential test
NAS	non-aureus staphylococci
NPV	negative predictive value
OCC	online cell counter
OR	odds ratio
PCR	polymerase chain reaction
PPV	positive predictive value
SCC	somatic cell count
Se	sensitivity
Sp	specificity

1 INTRODUCTION

Mastitis is the most prevalent and costly disease in dairy cows (Rajala-Schultz et al., 1999; Halasa et al., 2007). In addition, it is the most frequent cause for administration of antibiotic medications on dairy farms (Pol and Ruegg, 2007; Saini et al. 2012a; Stevens et al., 2016). Mastitis does not emerge in any population randomly but is instead a multifactorial disease resulting from a mixture of genetic, environmental, and management causes. During the nonlactation period, cows experience major physiological and management changes (Smith and Todhunter, 1982; Bradley and Green, 2004). As a consequence, they are highly susceptible to new intramammary infections (IMI) especially immediately after the milk cessation as well as during the periparturient period (Neave et al., 1950; Ward and Schultz, 1974; Smith et al., 1985a; Bradley and Green, 2004). Although IMI typically does not produce clinical symptoms during nonlactation (Smith and Todhunter, 1982; Smith et al., 1985a), persistent IMI over the dry period is a usual cause of clinical mastitis after calving (Neave et al., 1950; Bradley and Green, 2000; Green et al., 2002). A reduction in the number of infections during nonlactation may thus lead to a substantial reduction in the incidence of clinical mastitis during early lactation. Overall, the nonlactation period is significantly related to milk yield, to milk quality, to disease prevalence, and to dairy-farm economics.

The extensive use of antibiotics to treat and prevent infections began after the 1930s. The prevalence of mastitis in dairy herds was high in the 1960s, and the nonlactation phase had already been identified as a high-risk period for new IMI (Neave et al., 1950, 1969; Dodd et al., 1964). As a result, intramammary antibiotic dry cow therapy (DCT) at the end of lactation became one of the key measures in the management and control of bovine mastitis (Dodd et al., 1969; Neave et al., 1969; Philpot, 1969; Natzke, 1971). Early studies and reviews recommended treatment of all cows at dry-off, and this approach rapidly became the ongoing standard practice worldwide (Dodd et al., 1969; Neave et al., 1969; Natzke, 1971). At the same time, however, continuing controversy began over whether only infected cows should be treated instead of all cows. Unlike most other countries, the Nordic countries chose to recommend selective antibiotic medications at dry-off as their national treatment recommendation, and the selective-DCT approach has therefore always been the prevailing practice in the Nordic region (Nordic Guidelines for Mastitis Therapy, 2009; Vilar et al., 2018; Persson Waller et al., 2021; Rajala-Schultz et al., 2021).

The increasing emergence and spread of antimicrobial-resistant pathogens is a global crisis that threatens human and animal health as well as ecology and the environment (Laxminarayan et al., 2013; Pruden et al., 2013; WHO, 2015; OIE, 2016; EMA and EFSA, 2017). Awareness of the need to control this crisis has led to regulations and guidelines on antibiotic usage, and the prophylactic use of antibiotics in livestock is no longer considered justified. Moreover, responsible antibiotic use likely enhances consumer confidence in the dairy industry (Boogaard et al., 2011). DCT accounts for a large proportion of the total antibiotics used on dairy farms, and a switch from medicating all cows to medicating only selected cows has proven to significantly reduce antibiotic consumption (Scherpenzeel et al., 2014; Vanhoudt et al., 2018; Vasquez et al., 2018; Rowe et al., 2020a; Kabera et al., 2021a). The challenge of selective DCT, especially in large herds, is to identify those cows in need of treatment reliably, quickly and, above all, economically. The common means to identify cows and quarters with infections at the end of lactation include monitoring somatic cell counts, examining mastitis history, and obtaining microbiological results of milk samples (Torres et al., 2008; Rowe et al., 2020a; b; Kabera et al., 2021b).

The main objective of this thesis was to improve our understanding of optimal drying-off practices to maintain good udder health and milk yield while implementing prudent use of antibiotics. Of particular interest was antibiotic DCT, but a supplemental aim was to investigate various risk factors for post-calving udder health problems and reduced milk yield. The three retrospective, observational cohort studies examined the effect of antibiotic DCT strategies, together with various risk factors, on udder-health problems and reduced milk yield. International experimental research on selective-DCT strategy over the years has been in part contradictory (Berry and Hillerton, 2002a; McDougall, 2010; Rajala-Schultz et al., 2011; Cameron et al., 2014; Scherpenzeel et al., 2014; Rowe et al., 2020a; b). Furthermore, the herd-level selective-DCT strategy nowadays demands research interest because of the antibiotic resistance problem, the availability of nonantibiotic teat sealants, and the low prevalence of predominantly contagious mastitis pathogens in modern dairy herds. As selective DCT is widely implemented on Finnish dairy farms, the Finnish Dairy Herd Improvement data offered us the opportunity to test our research goal in natural, nonexperimental surroundings. An accurate understanding of the pros and cons of selective-DCT practice requires, in addition to experimental research data, observational research data from herds that routinely use selective DCT.

2 REVIEW OF THE LITERATURE

2.1 Nonlactating period

Prior to the next calving, milk production ceases, and this last phase of the lactation cycle is commonly referred to as the dry period. Nonlactation is essential for the regeneration of mammary tissue and for the optimal subsequent milk production (Swanson, 1965; Coppock et al., 1974; Oliver and Sordillo, 1989; Capuco and Akers, 1999; Pezeshki et al., 2010). In addition, it enhances the health of a cow and her newborn calf (Godden, 2008; van Knegsel et al., 2013; van Hoeij et al., 2016). The generally accepted dry-period length is between 40 to 60 days, but its recommended length has been an ongoing debate since at least the early 1800s (Arnold and Becker, 1936; Bachman and Schairer, 2003; van Knegsel et al., 2013). Too short a dry period is associated with a decreased milk yield and an increased infection risk (Andersen et al., 2005; Kuhn et al., 2006; Pezeshki et al., 2010; van Knegsel et al., 2013; van Hoeij et al., 2016). Too long a period, on the other hand, is related to over-conditioning, metabolic diseases, and reduced lifetime-milk yields (Kuhn et al., 2006; van Knegsel et al., 2014).

The three functional phases of a nonlactating period are active involution, steady state involution, and colostrogenesis (Smith and Todhunter, 1982; Bradley and Green, 2004). Active involution begins as soon as regular milking ceases and lasts approximately 21 to 30 days (Smith and Todhunter, 1982; Hurley, 1989). Milk accumulation in the udder is thought to trigger bovine mammary involution (Smith and Todhunter, 1982; Hurley, 1989; Wilde et al., 1999). Systemic hormone levels and local intra-mammary mechanisms are likely to control involution, but the specific triggering mechanisms are not yet fully understood (Wilde et al., 1997, 1999).

During the active involution, milk secretion and synthesis of milk-specific components decline (Schanbacher and Smith, 1975; Hurley, 1989). At the same time, concentration of lactoferrin, immunoglobulins, and serum-derived components increase (Welty et al., 1976; Hurley, 1989). As the involution progresses, the altered composition of glandular secretion improves resistance to udder infections (Smith and Todhunter, 1982; Hurley, 1989). Lactoferrin in particular has important immunological properties, and it is both bacteriostatic and bactericidal (Oliver and Sordillo, 1989; Rainard and Riollet, 2006). During the active involution, lactoferrin becomes a major protein in mammary secretion (Smith et al., 1971; Welty et al., 1976; Smith and Todhunter, 1982). In comparison to some other mammalian species, both controlled cell death and tissue regeneration after cessation of milking are slower in bovine mammary gland tissue (Holst et al., 1987; Oliver and Sordillo, 1989; Wilde et al., 1997; Capuco and Akers, 1999). Throughout the entire nonlactation, however, cell turnover increases and may promote optimal milk production in the next lactation (Capuco and Akers, 1999; Wilde et al., 1999).

During the steady state involution, the udder is in a fully involuted, nonlacting phase (Smith and Todhunter, 1982). The fluid amount in the udder is only 27 to 408 grams, and the concentration of antibacterial components remains high compared to their concentration in the lactation phase (Smith et al., 1971; Smith and Todhunter, 1982). The length of the steady state depends on the length of the dry period. Active involution must be completed before mammary gland redevelopment and colostrogenesis can begin (Hurley, 1989). In order to maximize lifetime-milk yield, the optimal dry period should probably proceed immediately after active involution to the redevelopment and onset of milk secretion without any steady state phase (Hurley, 1989). When the dry period lasts 60 days or more, it includes the steady state (Smith and Todhunter, 1982).

Hormonally mediated colostrogenesis is considered to begin 15 to 20 days before calving (Smith and Todhunter, 1982). When the dry period is less than 40 days, active involution is likely to overlap with this so-called transition phase, which can lead to deficient mammary development for the following lactation (Hurley, 1989). As colostrogenesis begins, secretory epithelial cells start to regenerate and differentiate (Smith and Todhunter, 1982). The amount of fluid begins to increase, and one to three days prior to calving, this increase becomes very rapid (Hartmann, 1973). Milk-specific components again increase, while lactoferrin concentration declines (Hartmann, 1973; Schanbacher and Smith, 1975; Sordillo et al., 1997). The vital antibodies for the newborn calf accumulate in the milk (Larson et al., 1980; Godden, 2008). As a consequence, immunoglobulin concentration reaches its peak during colostrogenesis (Smith and Todhunter, 1982; Sordillo et al., 1997).

Mammary secretion somatic cell count (SCC) increases during the first week of involution and remains at between one to three million cells per mL during the steady state (Smith and Todhunter, 1982; Nickerson, 1989). Perhaps due to the dilution effect, SCC gradually decreases as re-accumulation of milk begins during colostrogenesis (Nickerson, 1989). Normal bovine colostrum, however, typically contains a high amount of immunologically active leukocytes that are likely to be important for the newborn calf (Godden, 2008). If the quarters are uninfected, the milk SCC rapidly decreases during the first week after calving (Nickerson, 1989; Barkema et al., 1999a).

In uninfected quarters, the major cell type in differential SCC is macrophages. These eliminate degenerated secretory epithelial cells, milk components, and bacteria during involution (Smith and Todhunter, 1982; Nickerson, 1989). During the steady state, differential SCC remains similar to that in the involution phase (Nickerson, 1989). Two weeks prior to calving, the lymphocyte amount declines substantially, thus causing a relative increase in the number of macrophages and neutrophils (Smith and Todhunter, 1982; Nickerson, 1989). In the infected udder, both SCC and differential SCC differ from those in the healthy udder. If the nonlactating mammary gland is infected, SCC remains at over 30 million cells per mL, and at all phases of the dry period, the predominant cell type in differential SCC is neutrophils instead of macrophages (Nickerson, 1989).

Important anatomical defense barriers against mastitis are the teat orifice and the teat canal (Oliver and Sordillo, 1988; Pantoja et al., 2020). During the early involution, teat canals transiently shorten and dilate due to the accumulated milk, and hence the udder becomes more susceptible to infections (Oliver and Sordillo, 1988; Nickerson, 1989; Bradley and Green, 2004). As the involution progresses, the canal is sealed by a plug, which is derived from the teat-canal keratin (Cousins et al., 1980; Nickerson, 1989; Bradley and Green, 2004). This natural keratin plug forms an effective physical barrier preventing bacteria from entering the udder (Cousins et al., 1980; Oliver and Sordillo, 1988; Nickerson, 1989; Capuco et al., 1992; Dingwell et al., 2004). In addition, keratin contains bactericidal and bacteriostatic constituents that may prevent bacterial multiplication (Capuco et al., 1992). Re-accumulation of milk prior to calving again shortens and dilates teat canals, and keratin plugs may disappear (Oliver and Sordillo, 1988; Nickerson, 1989; Bradley and Green, 2004).

2.2 Intramammary infections during nonlactating period

2.2.1 Etiology and prevalence

Dairy cows are highly susceptible to new IMI during the dry period (Neave et al., 1950; Cousins et al., 1980; Oliver and Mitchell, 1983; Berry and Hillerton, 2002b; Bradley and Green, 2004; Bradley et al., 2015). The new infection rate of environmental pathogens can be up to 10 times as high as during lactation (Smith et al., 1985a). Particularly the involution and transition phases are high risk periods for new IMI (Neave et al., 1950; Ward and Schultz, 1974; Smith et al., 1985a; Bradley and Green, 2004). In their much-cited classical study, Neave et al. (1950) revealed that the majority of new dry-period infections developed during the first three weeks of nonlactation, and about half of these infections persisted over the whole dry period. In agreement, Ward and Schultz (1974) reported that new IMI occurred mostly during the first week after dry-off and during the periparturient period. Later, Smith et al. (1985a) found that, when the average dry period length of the cows was 63 days, IMI rate increased during the first and last quarter of the dry period.

Increased susceptibility to IMI during early involution results from several changes (Bradley and Green, 2004). As milking ceases, colonized bacteria are no longer flushed out of the teat duct along with the milk. Post-milking, teat disinfection ends. Dilatation of the teat canal and absence of a protective keratin plug at the beginning of the involution both facilitate bacterial penetration into the teat duct (Nickerson, 1989; Dingwell et al., 2004). As a consequence of active involution, resistance to infections in the mammary gland increases, but the involution process is gradual and requires the usual 21 to 30 days. (Smith and Todhunter, 1982; Hurley, 1989). The fully involuted udder with keratin plugs in its teat canals is highly resistant to new IMI (Cousins et al., 1980; Smith and Todhunter, 1982; Smith et al., 1985a; Oliver and Sordillo, 1988; Nickerson, 1989; Dingwell et al., 2004). Towards the end of the dry period, mastitis risk increases again due to the decrease in lymphocyte number and lactoferrin concentration, as well as due to the probably more opened up teat canals lacking keratin plugs

(Smith and Todhunter, 1982; Oliver and Sordillo, 1988; Nickerson, 1989). Furthermore, any antibiotic DCT given at dry-off will no longer provide protection at the end of the dry period (Schultze, 1983; Smith et al., 1985a).

The reported dry-period rates of new infections of quarters, when the quarters received no antibiotic treatment at dry-off, range from 3.8% to 35.1% (Neave et al., 1950; Oliver and Mitchell, 1983; Eberhart, 1986; Williamson et al., 1995; Berry and Hillerton, 2002a; b). Some of the infections could persist in the mammary gland throughout the dry period, and some may recover spontaneously (Neave et al., 1950; Oliver and Mitchell, 1983; Bradley and Green, 2000). Quantitatively, more than half of the new infections may persist over the dry period (Neave et al., 1950; Oliver and Mitchell, 1983), yet spontaneous recovery rates for some pathogen types can reach 70% or more (Smith et al., 1985a; Bradley et al., 2010; Vasquez et al., 2018). This large variation in infection rates is probably in part explained by differences in diagnostic criteria, in IMI definitions, and in sampling protocols. Moreover, the variation is understandable, as the prevalence of different causative mastitis pathogens varies between herds and regions as well as between seasons and years (Bradley and Green, 2004; Dingwell et al., 2004). The risk of new IMI consists of multifactorial relations between the cow, the management, the environment, and the mastitis pathogens. Further research would provide the benefit of a more accurate perception of new infection rates in healthy, untreated quarters during the dry period in modern dairy herds.

Extensive research demonstrates that new IMI acquired during nonlactation results mainly from environmental coliform and streptococcal bacteria (Oliver and Mitchell, 1983; Smith et al., 1985a; Bradley and Green, 2000; Berry and Hillerton, 2002b; a; Dingwell et al., 2002, 2004; Scherpenzeel et al., 2014; Bradley et al., 2015). In modern dairy herds, non-aureus staphylococci (NAS) appear to be another typical major cause of new IMI in the dry period (Odensten et al., 2007; Pantoja et al., 2009b; Newman et al., 2010; Rajala-Schultz et al., 2011; Bradley et al., 2015; Gott et al., 2016; Rowe et al., 2020a). NAS are classified as minor pathogens that, unlike major pathogens, usually cause only moderate elevations in SCC (Barkema et al., 1999a; Piepers et al., 2010). The majority of dry-period-derived NAS infections seem to undergo a spontaneous cure, and the prevalence usually returns to that observed prior to dry-off soon after calving (Oliver and Mitchell, 1983; Bradley and Green, 2004; Cameron et al., 2014; Vasquez et al., 2018). Piepers et al. (2010) reported that, in heifers, NAS infection within the first eight DIM lowered clinical mastitis incidence during their first lactation compared with incidence in those uninfected. This suggests that early lactation IMI caused by NAS may not prove a matter of serious concern.

Staphylococcus aureus and other predominantly contagious pathogens spread principally during milking. They are a probable cause of new infections in the dry period mostly in those herds where their prevalence is high, leading to increased infection pressure from the environment outside the milking event (Neave et al., 1950; Pankey et al., 1982; Berry and Hillerton, 2002b). Klaas and Zadoks (2018) stated that, because contagious transmission routes are subjected to standard mastitis control measures on modern dairy farms, environmentally derived mastitis is nowadays their most common and costly type of mastitis. Epidemiologically, new infections caused by environmental pathogens are the main prevention challenge during the dry period, because the exposure is likely to continue throughout the entire period, and it is perhaps even higher (Eberhart, 1986).

2.2.2 Impact on clinical mastitis

The mammary gland's internal environment efficiently prevents rapid bacterial growth during the dry period, and thus, IMI usually does not cause clinical symptoms during nonlactation (Smith and Todhunter, 1982; Smith et al., 1985a). Infections are typically subclinical until calving, and some remain so postpartum. However, persistent IMI over the dry period may be a frequent cause of clinical mastitis during the subsequent early lactation (Neave et al., 1950; Bradley and Green, 2000; Green et al., 2002). In most clinical cases occurring during early lactation, IMI had already existed in that quarter within the dry period (Green et al., 2002; Bradley and Green, 2004). Therefore, reducing the number of new infections during the dry period may significantly reduce the incidence of clinical mastitis during early lactation.

According to Neave et al. (1950), about half of all persistent IMI over the dry period begins already to show clinical symptoms during the first two weeks after calving. If a quarter is infected with an enterobacterial pathogen during the dry period, it is more likely to experience clinical mastitis due to that same pathogen within the subsequent early lactation (Bradley and Green, 2000). DNA-fingerprinting identification confirmed that in 52.6% of the environmental mastitis cases within the first 100 DIM, the causal pathogen had already colonized the udder during the dry period, when all the cows received DCT, and the farm's bulk-tank SCC was less than 250,000 cells/mL (Bradley and Green, 2000). Although more than 20 years have passed since that UK study, thus far no one has repeated that experiment, and hence, confirmation of generalizability to different farming facilities and locations is lacking.

2.2.3 Risk factors

Mastitis is a multifactorial disease resulting from a complex combination of genetic, environmental, and management factors. It is the most common disease in dairy livestock worldwide but does not occur randomly in a population. Epidemiologists search for the determinants that influence mastitis incidence as well as ones that influence other health-related events. Table 1 summarizes some principal determinants related to drying off and assumed to affect the risk of intramammary infection during nonlactation.

Table 1. Drying-off-related determinants affecting risk of intramammary infection (IMI) at calving. All cows and quarters examined received antibiotic DCT at dry-off, except for the Schukken et al. (1993) experiment, in which only half a cow's four quarters received DCT. IMI identification was based on microbiological culture results.

Determinant	Sample	Measure of association	Reference
Teat-canal closes within 6 wk vs. no closure	1178 quarters 300 cows	OR[a] 0.6 (0.33, 0.96) OR 0.3 (0.1, 0.7)	Dingwell et al. (2004)[e]
Milk leaking vs. no leakage	68 cows	RR 6.1 (*p* ≤0.03)[b]	Schukken et al. (1993)[f]
	544 quarters	OR 28.9 (2.5, 336.7)	Gott et al. (2016)[f]
Milk yield at dry-off			
≥16.4 kg/d vs. <10.7 kg/d	315 quarters	OR 7.05 (1.66, 30.0)	Newman et al. (2010)[f]
>5-kg increase over 12.5 kg/d	96 cows, 116 lactations	OR 1.77 (1.2, 2.7)	Rajala-Schultz et al. (2005)[e]
1 L increase	467 cows	OR 1.06 (1.00, 1.12)[c]	Huxley et al. (2002)[f]
Gradual milk cessation vs. abrupt milk cessation	544 quarters, primiparous 542 quarters, multiparous	OR 0.29 (0.12, 0.68) OR 2.78 (1.34, 5.75)	Gott et al. (2016)[f]
	315 quarters	OR 4.16 (1.41, 12.3)	Newman et al. (2010)[f]
Teat-end hyperkeratosis vs. no hyperkeratosis	1178 quarters 300 cows	OR 1.7 (1.0, 2.7) OR 2.5 (1.1, 5.4)	Dingwell et al. (2004)[e]
IMI at dry-off vs. uninfected	417 quarters		Newman et al. (2010)[f]
Infected with major pathogen		OR 7.61 (2.82, 20.5)	
Infected with minor pathogen		OR 3.28 (1.14, 9.47)	
Previous-lactation SCC average ≥225,000 cells/mL vs. <225,000 cells/mL	179 cows	OR 6.60 (1.58, 22.0)[d]	Pinedo et al. (2012)[f]

[a] Odds ratio and 95% confidence interval
[b] Risk ratio for an IMI by major pathogen
[c] New IMI caused by *Enterobacteriaceae*
[d] IMI diagnosis based on composite milk sample instead of quarter milk sample
[e] Observational study
[f] Experimental controlled trial

Teat-canal closure

After dry-off, the keratin plug may not form in all teat canals, and lack of this natural sealant appears to cause an increased risk of new IMI for such quarters compared to the risk in closed quarters (Capuco et al., 1992; Williamson et al., 1995; Dingwell et al., 2004; Table 1). According to the prospective cohort study by Dingwell et al. (2004), 53% of the quarters were sealed with a keratin plug within the first week after dry-off, and 68% of the quarters were sealed within the first three weeks. Six weeks after dry-off, however, 23% of the quarters still had open teat canals. In an earlier experimental study by Williamson et al. (1995), 50% of quarters had open teat canals 10 days after dry-off, and 3 to 5% of quarters were open over the entire dry period. The majority of the clinical mastitis cases occurred in the early dry period, and virtually all of them occurred in the quarters that were open at the time of mastitis identification (Williamson et al., 1995). For the total of 1333 quarters, the overall rate of new clinical IMI identified was only 3.9%. About half these quarters had received DCT at dry-off.

The proportion of open teat canals apparently varies considerably between herds. In the North-American study, the proportion of unclosed quarters six weeks after dry-off ranged from 7% to 63% (Dingwell et al., 2004). A similar between-farm variation was apparent in the European prospective cohort study that reported the farm-level percentages of closed quarters two and six weeks after dry-off (Bradley et al., 2015). That multicenter study was unable to confirm that slow teat closure or failure of teat closure was associated with a risk of IMI during the dry period. According to the authors, this may be due to the strong influence of farm-level factors and should not lead to understatement of the importance of cow- and quarter-level factors.

High milk yield seems to be related to delayed keratin plug formation. Dingwell et al. (2004) were the first to reveal that milk yield prior to dry-off influences teat-closure time. If the daily milk yield on the day prior to dry-off was more than 21 kg, the hazard for delayed teat closure was 1.8 times as high than if the daily yield was less than that. In agreement, Odensten et al. (2007) reported that cows producing from 5 to 11.4 kg/day within the week before dry-off had significantly fewer open teat canals two weeks after dry-off than did higher-yielding cows.

According to a hypothesis proposed in the literature, bacteria are linked to keratin plug formation, and antibiotic DCT therefore hasten teat closure (Berry and Hillerton, 2002b; Bradley and Green, 2004). This hypothesis is based on the study observation that teat-canal closure was faster among cows that received DCT at dry-off (Williamson et al., 1995). The candidate bacteria are the minor pathogens in phylum *Corynebacterium* sp. that have keratinolytic traits (Berry and Hillerton, 2002b; Bradley and Green, 2004). This complex theory has not yet proven convincing. The possible association of *Corynebacterium* sp. with the occurrence of new IMI is contradictory. Studies report that *Corynebacterium* sp. infection may lead to increased susceptibility to mastitis in general and may elevate the risk for new IMI during the dry period (Pankey et al., 1985; Hogan et al., 1988; Berry and Hillerton, 2002a), even in quarters that receive an artificial teat sealant (Berry and Hillerton, 2002b).

Other studies, however, propose that *Corynebacterium* sp IMI could provide protection against new infections during both lactation- and dry periods (Rainard and Poutrel, 1988; Green et al., 2002, 2005). Hopefully, future studies will seek more knowledge on factors associated with the speed of teat-canal closure.

Milk yield

Evidence supports the general assumption that high milk yield at the point of dry-off leads to increased post-calving IMI risk (Oliver et al., 1956a; Huxley et al., 2002; Dingwell et al., 2004; Rajala-Schultz et al., 2005; Odensten et al., 2007; Newman et al., 2010; Madouasse et al., 2012; Table 1). Only a few studies over the years have been unable to support this finding (Natzke et al., 1975; Bradley et al., 2015; Gott et al., 2016). Considering the association between late lactation yield and the udder-health indicator SCC, a cow with a high yield on her last test day seem more likely to have an SCC over 200,000 cells/mL at the first test day after calving (Green et al., 2007, 2008; Madouasse et al., 2012; Henderson et al., 2016). This association could even last longer, up until the start of mid-lactation (Gott et al., 2017).

Although studies illustrate the impact of milk yield on IMI risk, it is hard to deduce the optimal milk amount at dry-off. Further investigations may perhaps help to determine it more precisely. At a yield-level of 12.5 kg/day at dry-off, the risk of IMI caused by an environmental bacterium increased by 77% for every five kilograms of extra milk (Rajala-Schultz et al., 2005; Table 1). Among cows with uninfected quarters at dry-off, the likelihood of post-calving infection in a quarter increased as that cow's weekly-yield prior to dry-off increased (Newman et al., 2010). For those cows producing over 16.4 kg/day during the previous week prior to dry-off, the risk of having an infected quarter at calving was 7 times as high as that of cows producing less than 10.7 kg/day during the previous week (Table 1). However, among cows having already an infected quarter at dry-off, lower milk yield was no longer a protective factor against post-calving IMI. Odensten et al. (2007) reported that in cows producing from 5 to 11.4 kg/day during the week prior to dry-off, the number of quarters with IMI was significantly lower in the week after calving compared with the number for those cows producing more. This difference was no longer noticeable 4 weeks after calving, indicating that the association may not necessarily be long-lasting. The conclusion proposed is that a daily yield of 15 kg or less at dry-off should be the target milk yield, which would improve udder health compared to a choice of higher daily yields (Vilar and Rajala-Schultz, 2020).

Milk leakage

Milk leaking from teats during drying off raises the risk for IMI and for clinical mastitis during the dry period (Schukken et al., 1990, 1991, 1993; Elbers et al., 1998; Table 1). A lower milk quantity in the udder reduces intramammary pressure (Rovai et al., 2007) and the risk for milk leakage (Tucker et al., 2009; Bertulat et al., 2013; Hop et al., 2019; De Prado-Taranilla et al., 2020). Although milk may leak at any stage of the lactation cycle and at all levels of milk yield (Persson Waller et al., 2003; Klaas et al., 2005), sudden milk accumulation in the udder during dry-off raises the risk of milk leakage specifically at this point of the lactation cycle (Tucker et al., 2009). Less than 5% of relatively low-yielding grazing cows leaked milk during the week before dry-off, but the proportion increased rapidly after the final milking (Tucker et al., 2009). Up to 56% of high-yielding and 15% of low-yielding cows may leak milk after dry-off (Bertulat et al., 2013). According to Gott et al. (2016), each 4.5 kg increase in daily milk yield above 18 kg/day at dry-off doubled the risk of milk leakage after dry-off. Similarly, based on the Hop et al. (2019) clinical trial, milk yield more than 18 kg/day on a day prior to dry-off raised the odds for milk leakage by 3.2-fold. A recent study involving 41 European commercial herds found that cows producing more than 13 kg/day prior to dry-off were significantly more likely to leak milk after dry-off than were cows producing less than 13 kg/day (De Prado-Taranilla et al., 2020).

Drying-off methods

Since the 1930s, studies have examined various drying-off methods and their effect on the last-day milk yield and mastitis risk (Wayne and Macy, 1933; Oliver et al., 1956b; a; Natzke et al., 1975) Compared to the cows included in these early studies, modern cows produce considerably more milk at the time of drying off, and thus research on particular drying-off methods continues (Zobel et al., 2015; Gott et al., 2016, 2017; Hop et al., 2019; Larsen et al., 2021). In the future, pharmaceutical products may enter the market for milk-yield manipulation at dry-off (Vilar and Rajala-Schultz, 2020; Larsen et al., 2021). The useful non-pharmaceutical methods to reduce milk yield and milk leakage are feed restriction and gradual milk cessation (Tucker et al., 2009; Newman et al., 2010; Zobel et al., 2013; Gott et al., 2016, 2017; Rajala-Schultz et al., 2018; Vilar and Rajala-Schultz, 2020; Larsen et al., 2021). Despite their feasibility, in many countries the prevailing milk-cessation method is abrupt without any prior management changes (Dingwell et al., 2001; Bertulat et al., 2015; Fujiwara et al., 2018). A modern dairy cow can produce up to 25 to 35 kg milk per day at the time of drying off, and the average amount of milk ranges from about 7 to 26 kg/day (Bradley et al., 2015; Larsen et al., 2021)

Gradual milk cessation appears to efficiently reduce milk yield and thus to benefit udder health through lower yields (Newman et al., 2010; Gott et al., 2016; Vilar and Rajala-Schultz, 2020; Larsen et al., 2021). The milk cessation method seems to be a confounder between the association of last milk yield and IMI status at calving (Newman et al., 2010). This may be one likely reason for the observation that gradual milk cessation seems to have a somewhat contradictory influence on the odds of having IMI at calving (Newman et al., 2010; Gott et al., 2017; Table 1). Once-per-day milking during the final week prior to dry-off reduced milk yield by about a third compared to the yield in cows whose milking was abruptly stopped (Gott et al., 2016). This finding agrees with that of Larsen et al. (2021). Consistently, the average final-week yield of 74 kg in the gradual milk-cessation experimental group was about 40% less than was the final-week yield of 129 kg in the abrupt milk-cessation group (Newman et al., 2010).

On AMS-milking farms, feed allocation may be controlled by both diluting the energy concentration of the lactational partial mixed ratio served ad libitum and reducing the intake of concentrate from AMS (Larsen et al., 2021), or only by the latter procedure alone (France et al, 2022). In the Danish clinical trial, abruptly dried-off cows produced about 25 kg/day prior to dry-off, whereas cows dried off by reducing either feeding or milking frequency produced approximately 30% less than the 25 kg/day, and cows dried off by reducing both feeding and milking frequency produced approximately 45% less (Larsen et al., 2021). This magnitude of yield reduction in modern Holstein cows aligns with figures previously observed for considerably lower-yielding-grazing cows in a similar factorial 2 x 2 design arrangement (Tucker et al., 2009). Compared with gradual milk cessation alone, excessive feed restriction, however, can lead to a negative energy balance (Larsen et al., 2021). The latter can result in undesirable metabolic stress and hunger. Even reducing the intake of concentrate from AMS without changes in the concentration of partial mixed ratio, feed restriction reduces milk yield, but reducing milking frequency seems to reduce the amount of milk more effectively (France et al, 2022). Moderate feed restriction, together with gradual milk cessation, will reduce milk production but is unlikely to lead to the disadvantages from excessive feed restriction.

It is worth noting that gradual milk cessation may favorably affect mastitis susceptibility by accelerating the active involution phase and by raising the concentration of protective components in the milk (Natzke et al., 1975; Bushe and Oliver, 1987; Vilar and Rajala-Schultz, 2020). In addition, reduced milk amount at dry-off promotes cow comfort and welfare during a stressful lactation-stage change, which fact should not be ignored (Zobel et al., 2013, 2015; Rajala-Schultz et al., 2018; Vilar and Rajala-Schultz, 2020). Overall, the gradual milk cessation method seems to have more advantages than disadvantages.

IMI status and mastitis history

Both infection status at dry-off and preceding mastitis history apparently influence mastitis resistance during the dry period. Based on bacteriological examinations, Natzke et al. (1975) reported that the rate of new infections during the dry period in a herd was higher when the prevalence of infections at dry-off was higher. Quarters already infected at dry-off appear more susceptible to new infections during the dry period (Neave et al., 1950; Rindsig et al., 1978; Berry and Hillerton, 2002b; Newman et al., 2010). Despite antibiotic medication for all quarters and an overall cure rate of 84%, quarters infected at dry-off were more likely to be infected again at calving than were uninfected quarters (Newman et al., 2010; Table 1). When the incidence of infections is assessed on the basis of the udder health indicator SCC, results support those results that are based on bacteriology. During the past decades, studies have consistently reported that an SCC over the threshold of 200,000 cells/mL prior to dry-off is associated with an SCC exceeding this threshold on the first test-day after calving, when compared to cows with a lower SCC prior to dry-off (Green et al., 2008; Madouasse et al., 2012; Henderson et al., 2016; Vanhoudt et al., 2018). In addition, an SCC over 200,000 cells/mL prior to dry-off is linked to increased clinical mastitis incidence during the subsequent early lactation (Green et al., 2007; Whist and Østerås, 2007; Pantoja et al., 2009a; Pinedo et al., 2012). Cows with an average SCC greater than 225,000 cells/mL in the previous lactation were more likely to be diagnosed with mastitis pathogens in a composite milk sample at calving and were more likely to experience a clinical or subclinical case of mastitis during the following early lactation (Pinedo et al., 2012; Table 1). This indicates that not only the late-lactation mastitis history but also the long-term mastitis history may affect mastitis susceptibility during the dry period.

Teat-end hyperkeratosis

Hyperplasia of the teat orifice's keratin layer is a prevalent pathology associated with several cow- and herd factors (Pantoja et al., 2020). Severe hyperkeratosis predisposes the quarter to clinical and subclinical infections. (Dingwell et al., 2004; Breen et al., 2009; Dufour et al., 2012; Pantoja et al., 2016, 2020). Dingwell et al. (2004) discovered that about one-quarter of the cows had at least one damaged teat end, and these quarters were significantly more likely to acquire a new IMI during the dry period than were the undamaged quarters (Table 1). Teat-end hyperkeratosis was likewise a cow risk factor. Cows with at least one cracked teat end at dry-off were more likely to develop a new postpartum IMI (Table 1).

Age

Because parity elevates the risk for adverse teat conditions, older cows thus show a higher prevalence of teat-end hyperkeratosis (Neijenhuis et al., 2000; Pantoja et al., 2016). Parity is also an independent risk factor for IMI, and an older cow is more susceptible to clinical mastitis (Dohoo et al., 1981; Dohoo and Meek, 1982; Pantoja et al., 2009a). Increasing SCC with age is mainly the result of an increased prevalence of infections in older cows, although the SCC may increase slightly with age even if the cow is not an IMI-carrier (Natzke et al., 1972; Dohoo et al., 1981; Dohoo and Meek, 1982). As the cow ages, the anatomical and immunological defense mechanisms of the udder and teat deteriorate (Cousins et al., 1980), which impairs mastitis resistance. Regarding only the dry period, Neave et al. (1950) showed that infections occurred more often in older cows, and their infections were more persistent and more likely to show clinical symptoms. Similarly in later experiments, the occurrence of new IMI caused by environmental mastitis pathogens is greater among higher parity cows during the dry period (Ward and Schultz, 1974; Oliver and Mitchell, 1983; Smith et al., 1985a). In addition to more frequently acquiring new IMI and suffering more persistent IMI, older cows appear to have a worse cure rate throughout their nonlactation period, based both on milk sampling (Browning et al., 1994; Gott et al., 2016) and on SCC measurements (Green et al., 2008; Madouasse et al., 2012; Henderson et al., 2016).

Farm characteristics

In addition to cow factors, farm factors play a major role in the occurrence of mastitis in a herd during the nonlactation (Barkema et al., 1999b; Barnouin et al., 2004; Green et al., 2007; Breen et al., 2009; Dufour et al., 2011). Most farm-specific factors associated with overall udder health are related to hygienic practices (Barkema et al., 1998; Barnouin et al., 2004;

Green et al., 2007; Breen et al., 2009; Dufour et al., 2011). Issues related particularly to dry-period-derived infections are drying-off hygiene and farm management of dry cows. Farm-management factors associated with an increased cow composite SCC during the first month after calving comprised procedures at drying off, bedding management, stocking density, and method of grazing (Green et al., 2008). Furthermore, farm-management factors associated with the risk of having clinical mastitis in a subsequent early lactation included management of the early and late dry-period accommodation, calving areas, routine body condition scoring at drying off, and having a pasture rotation policy of grazing dry cows (Green et al., 2007). Combined housing of dry cows and heifers likely leads to an increased incidence rate of clinical mastitis in heifers (Barkema et al., 1999b), and keeping dry cows among lactating cows leads to an increased rate of clinical mastitis within the first 30 DIM post calving (Green et al., 2007). In their international cohort study, Bradley et al. (2015) found a lack of association between IMI risk over the dry period and several cow- and quarter factors and proposed that this finding does not diminish the importance of cow factors, but instead highlights the variation evident between different farms.

2.3 Dry cow therapy

2.3.1 Effect on udder health

Dry cow antibiotic therapy (DCT) at the end of lactation is an effective and widely used mastitis control tool for nonlactating cows. After Neave et al. (1950) discovered that cows were particularly susceptible to mastitis during the dry period, the need arose to find control measures against infections acquired specifically during this phase. In the 1960s, the prevalence of IMI in herds could be as high as 50% (Dodd et al., 1964; Neave et al., 1969; Philpot, 1969), and antibiotic treatments were generally recommended to reduce the duration of IMI as part of the widespread mastitis control program called the Five-point Plan (Dodd et al., 1969; Neave et al., 1969). At the same time, reviews described the benefits of administering antibiotic intramammary products at dry-off (Philpot, 1969; Natzke, 1971). DCT thus quickly became a routine practice to eliminate existing intramammary infections and to prevent new infections in the dry period.

Until the late 1970s, the emphasis on mastitis prevention was mainly against the organisms *Streptococcus agalactiae* and *Staphylococcus aureus* (Murphy, 1956; Ruegg, 2017). Later, attention was drawn more to the coliforms and other environmental pathogens which are now common causes of mastitis worldwide (Smith et al., 1985b; Ruegg, 2017; Klaas and Zadoks, 2018). Intramammary infections present in the periparturient period have significant economic consequences because of lowered milk yield, reduced milk quality, and increased clinical mastitis prevalence (Rajala-Schultz et al., 1999; Bradley and Green, 2000; Halasa et al., 2007). Therefore, farmers understandably attempt to lessen these concerns by using dry-cow products. Although dry cow antibiotics cure infections present at dry-off and may lead to a reduction in new IMI rate, complete elimination of all IMIs is virtually impossible to achieve. For DCT-treated cows, results indicate that infections acquired during the transition phase are more likely to affect the post-calving incidence of clinical mastitis than are those already present at dry-off (Green et al., 2002).

Considering the existing infections at the point of dry-off, the proportion of infected quarters based on microbiological analysis ranges from 12% to 50%, with the most recent figure reported being 25.4% (Oliver and Mitchell, 1983; Green et al., 2002; Newman et al., 2010; Rajala-Schultz et al., 2011; Cameron et al., 2014; Scherpenzeel et al., 2014; Rowe et al., 2020a). The majority of IMI diagnosed was caused by the minor pathogens NAS and *Corynebacterium* spp., with NAS prevalence ranging from 6.7% to 14.8% and *Corynebacterium* spp. from 1.1 to 35.7% (Oliver and Mitchell, 1983; Green et al., 2002; Newman et al., 2010; Rajala-Schultz et al., 2011; Cameron et al., 2014; Scherpenzeel et al., 2014; Rowe et al., 2020a). This large variation is probably in part due to the differing diagnostic criteria, IMI classifications, and sampling procedures between studies. However, the udder health of the herds and cows selected obviously affects the prevalence of IMI at dry-off as well. Vasquez et al. (2018) defined a low-risk cow as one having SCC ≤200,000 cells/mL on the last test day, an average SCC ≤200,000 cells/mL over the last 3 test days, no signs of clinical mastitis at dry-off, no antibiotic treatments in the last 30 days, and no more than one clinical mastitis event in their preceding lactation. All other cows were classified as being high-risk cows. In low-risk cows that were not so likely to benefit from DCT, the proportion of quarters with IMI at dry-off was around 10% (Vasquez et al., 2018). In high-risk cows that were likely to benefit from DCT, around 30% of quarters were culture positive. In both groups, the majority of IMI quarters were infected by the minor pathogens (Vasquez et al., 2018).

Rowe et al. (2020a) enrolled all cows having four functional quarters, an expected dry period length of 30 to 90 days, no recent antibiotic or anti-inflammatory treatments, no clinical mastitis, and no lameness or poor body condition. All seven study herds had an average bulk milk SCC less than 250,000 cells/mL. Of the 1,144 cows enrolled, 670 (59%) had at least one infected quarter. To compare, Torres et al. (2008) sampled 647 cows from four herds at dry-off, and the prevalence of infected cows was 32%. When cows were classified according to udder health data, Rajala-Schultz et al. (2011) reported that in cows with SCC <200,000 cells/mL in the preceding 3 months, the cow-level prevalence of IMI at dry-off was approximately 20%, and in cows with SCC ≥200,000 cells/mL in the preceding 3 months or clinical mastitis during lactation, 44%. On the basis of fairly similar classification criteria, Vasquez et al. (2018) observed that the cow-level IMI prevalence was 70.7% in high-risk cows and 29.4% in low-risk cows.

Natzke (1981) suggested that DCT products cure around 70 to 98% of infections and reduce the rate of new IMI from approximately 14% to 7% of quarters. According to one meta-analysis, the average cure rate after DCT was 78% (95% CI 71, 81), and the cure rate was

1.78 (95% CI 1.51, 2.10) times as high during the dry period and early lactation for DCT-treated quarters compared with untreated quarters (Halasa et al., 2009a). More recently published overall cure risks for DCT-treated quarters are 84% (Newman et al., 2010), 78% to 85.5% (Bradley et al., 2010), 93% to 95% (Vasquez et al., 2018), and 86.8% (Rowe et al., 2020a). The recovery from *Staph. aureus* infection is dependent on several cow-, pathogen-, and treatment factors, and as a consequence, cure rates vary considerably (Barkema et al., 2006; Exel et al., 2021). Regarding the cure in the dry period, reported cure risks for *Staph. aureus* over the dry period range after DCT from 25% to 79% (Williamson et al., 1995; Berry and Hillerton, 2002a; Newman et al., 2010). Generally, antimicrobial resistance prevalence appears to be uncommon in the bovine *Staph. aureus*, *Escherichia coli*, and *Klebsiella* spp. mastitis pathogens and do not demonstrate any obvious increase over the years (Saini et al., 2012b; De Jong et al., 2018).

A spontaneous cure also appears to be quite frequent. A spontaneous cure in untreated quarters over the dry period has been documented for all pathogens to be 46% (95% CI 37, 56; Halasa et al., 2009a), for coliforms and environmental streptococci to be 67 to 69% (Smith et al., 1985a), and for minor pathogens, 69.7% (Bradley et al., 2010). Regarding NAS-infected quarters, spontaneous cure was 44% for *Staphylycoccus* spp. (Halasa et al., 2009a) and 77% for NAS (Vasquez et al., 2018). In comparison, the reported cure in DCT-treated *Staphylycoccus* spp -infected quarters was 77% (Halasa et al., 2009a), and in DCT-treated NAS quarters 91% (Vasquez et al., 2018). These results suggest that the spontaneous cure of NAS-infections occurred quite frequently, and DCT improved the cure rate even more.

Despite the use of DCT, new infections still appear during the dry period. In DCT-treated quarters, the new IMI rate over the dry period ranges from 6.4% to 25% at the quarter level (Godden et al., 2003; Dingwell et al., 2004; Pantoja et al., 2009b; Arruda et al., 2013). The causative pathogens may either not be sensitive to the drug used, or they may cause the infection at the end of the dry period, when the concentration of the drug is no longer sufficient to inhibit bacterial growth (Schultze, 1983; Smith et al., 1985a). Smith et al. (1985a) noticed that DCT reduced the overall rate of new streptococcal infections, and this effect was primarily due to 6- to 7-fold lower rates in the first quarter of the dry period in comparison to figures for DCT-untreated cows. The rate of new coliform infections was not affected by DCT, and thus results lead to the conclusion that DCT appeared to be advantageous, especially for reducing environmental Streptococcal IMI during the early dry period (Smith et al., 1985a). This conclusion was later supported by the meta-analysis, which determined that DCT significantly reduced new IMI caused by *Streptococcus* spp. but did not prevent new IMI caused by coliforms (Halasa et al., 2009b). The availability of different DCT antibiotics varies between countries. Products containing framycetin show extended activity against Gram-negative organisms and can reduce the incidence of clinical coliform mastitis during the first 100 DIM after calving (Bradley and Green, 2001).

2.3.2 Herd-level strategies

The Five-point Mastitis Control Plan formulated in the 1960s provided a feasible system for reducing subclinical and clinical mastitis in herds. One of the five key control measures in the plan was DCT-treatment for all cows as a regular routine at drying off (Dodd et al., 1969; Neave et al., 1969). It was already then that the ongoing controversy began over whether to treat all cows or only infected cows. Natzke (1971) stated that recommendations for DCT vary widely between authorities and reviewed the various possible methods of selecting cows for DCT. Based on the information available, Natzke's review finally concluded that the preferred method was the antibiotic treatment of all quarters of all cows at dry-off. This practice is nowadays commonly known as blanket DCT. The following year, evidence showed that blanket DCT and post-milking teat disinfection reduce the amount of new IMI by approximately half in those herds implementing these practices compared with the IMI in herds not undergoing post-milking teat dipping and DCT (Eberhart and Buckalew, 1972). Researchers noticed, however, that these practices were more efficient in reducing herd-level *Staph. aureus* and *Strep. agalactiae* prevalence than in reducing coliform and environmental streptococci.

Ward and Schultz (1974) compared blanket DCT strategy to selective DCT strategy, with the selection criterion being to carry out DCT only for cows with a prior diagnosis of clinical mastitis. The result was that selective DCT indicated reduced IMI cure, increased new IMI rate, and increased number of clinical mastitis cases compared to results with blanket DCT. As several results and reviews seemed to support the practice of treating all cows, blanket DCT rapidly became the ongoing standard practice in North America, the United Kingdom, and several other countries (Bertulat et al., 2015; USDA, 2016; More et al., 2017; Fujiwara et al., 2018). Nevertheless, interest in selective DCT continued, and its use was considered recommendable in herds with a low incidence of mastitis (Rindsig et al., 1978, 1979; Poutrel and Rainard, 1981; Schultze, 1983). Nordic countries hence ended up establishing the selective-DCT practice, which has always been their recommended national treatment strategy (Vilar et al., 2018; Persson Waller et al., 2021; Rajala-Schultz et al., 2021).

Antibiotic resistance in bacteria is an ancient natural phenomenon whose dissemination and evolution has been influenced by the widespread use of antibiotics in humans, animals, and agriculture after the 1930s (Levy and Marshall, 2004; Davies and Davies, 2010; D'Costa et al., 2011; Perry and Wright, 2013; Surette and Wright, 2017). Antibiotic administration causes selective pressure on bacterial strains and favors antibiotic-resistant bacteria over susceptible bacteria (Levy and Marshall, 2004). Strong warnings date back even to the 1960s, when the *New England Journal of Medicine* stated that ignoring antibiotic resistance could lead to a serious health threat (Anonymous, 1966). According to a review by Davies and Davies (2010), the first recommendations calling for a ban on the use of nontherapeutic antibiotics in animals and agriculture appeared as early as 1969. Wider global awareness of antibiotic resistance began to increase in the late 1980s, and collaborative education, regulation, and surveillance to combat the problem began. Subsequently, Eberhart (1986) urged dairy professionals to bear in mind the reasons for avoiding the generally accepted widespread use of blanket DCT. These included its cost and the possible emergence of antibiotic resistance. Nowadays, antibiotic resistance is officially a severe global health threat, for which the situation is still worsening (WHO, 2015; OIE, 2016; EMA and EFSA, 2017). In addition, overuse of antibiotics causes a significant hazard to global ecology and to the environment (Larsson et al., 2007; Laxminarayan et al., 2013; Pruden et al., 2013). The key strategies to manage this crisis are improving hygiene and reducing the excessive use of antibiotics (McEwen and Collignon, 2018).

The goal of reducing IMI in the dry period by nonantibiotic methods led to development of commercially available teat sealants. An internal teat sealant (ITS) functions as a physical barrier in the teat canal and closes it in the same way as does the natural keratin plug (Berry and Hillerton, 2002b; Huxley et al., 2002; Godden et al., 2003). ITS can be administered alone for uninfected quarters and with DCT for infected quarters. Meta-analyses consistently show that ITS is an evidence-based method to effectively prevent mastitis during the dry period (Halasa et al., 2009b; Rabiee and Lean, 2013; Winder et al., 2019a; b; Kabera et al., 2021b). The efficacy of an external teat sealant (ETS) is dependent on the duration of sealant adherence. Conclusions as to the effect of ETS on the incidence of new IMI are not as clear as for ITS (Lim et al., 2007).

Livestock production is under dual pressure to reduce antibiotic consumption due to pressure both from consumers and from regulations against antibiotic use. In 2015, the European Commission advised the avoidance of prophylactic antibiotic treatments in all livestock (European Commission, 2015), and a few European countries restricted the use of antibiotics by legislation (Gussmann et al., 2018; Vanhoudt et al., 2018). Current European Union legislation became applicable in all European Union member states in January 2022 and bans prophylactic antibiotics other than in exceptional cases (European Union, 2018). This legislation does not allow routine antibiotic use to compensate for poor hygiene or inadequate farm management. DCT products account for a major proportion of antibiotic use in non-organic dairy livestock (Pol and Ruegg, 2007; Saini et al. 2012a; Stevens et al., 2016). Evidence shows that the shift from blanket DCT to selective DCT causes a substantial decrease in antibiotic consumption (Scherpenzeel et al., 2014; Vanhoudt et al., 2018; Vasquez et al., 2018; McParland et al., 2019; Kabera et al., 2020; Rowe et al., 2020a). Based on a meta-analytic estimate, selective medication at dry-off reduced the use of antibiotics by 66% (95% CI 49, 80) compared to the systematic medication of all cows (Kabera et al., 2021b). Given the low prevalence of antibiotic resistance among major mastitis pathogens (Saini et al., 2012b; De Jong et al., 2018), it could be argued that the blanket-DCT practice is justified. Animal microbiomes, however, consists mostly of commensal bacteria, and the transfer of resistance features within them is still poorly known (Pärnanen et al., 2018). Moreover, because inappropriate antibiotic medication use is a major contributor to antimicrobial resistance, all such use should be strongly science-based (Laxminarayan et al., 2013; McEwen and Collignon, 2018). The global antibiotic resistance problem, the availability of ITS as a nonantibiotic alternative, and the low prevalence of *Strep. agalactiae* and *Staph. aureus* in modern dairy herds have all led to herd-level DCT strategy being currently a research topic of intense interest.

In experimental studies, a comparison of blanket-DCT strategy with selective DCT strategy has yielded conflicting results. The reported negative health effects of selective DCT were increased incidence of new infections, increased hazard of clinical mastitis, and increased post-calving SCC (Schukken et al., 1993; Berry and Hillerton, 2002a; McDougall, 2010; Scherpenzeel et al., 2014). Possible reasons for this failure of selective DCT may be that the selection criteria for IMI detection were too imprecise or that ITS was not used to protect against the new IMI. The meta-analysis by Halasa et al. (2009b) showed that blanket DCT gave better protection against new IMI than did selective DCT, but that this effect was dependent upon whether the selection criteria for DCT was at the cow or quarter level. The results of this meta-analysis align with the previous meta-analytic risk ratio showing that selective DCT led to a higher risk for new IMI than did blanket DCT (Robert et al., 2006).

When all the cows studied did not receive ITS, selectively DCT-treated cows with low composite SCC prior to dry-off had approximately 35,000 cells/mL lower SCC during the subsequent lactation than did untreated low-SCC cows (Rajala-Schultz et al., 2011). This effect, however, varied between herds. Moreover, the herd-average SCC of those farms ranged from 162,000 to 340,000 cells/mL. These findings seem to indicate that leaving the likely uninfected cows without DCT did not harm udder health on some farms, but this was not obvious for every farm examined. Similarly, Bradley et al. (2010) explored the fact that low-SCC cows treated with DCT and ITS were not more likely to be culture-negative at calving than were low-SCC cows treated with ITS only. The most recent selective-DCT trials have systematically administered ITS to all quarters of all cows, and only DCT treatment varied between groups studied. According to these results, blanket DCT and selective DCT appeared not to differ regarding quarter-level cure or regarding new IMI risk (Cameron et al., 2014; Vasquez et al., 2018; Rowe et al., 2020a), in SCC during subsequent lactation (Cameron et al., 2015; McParland et al., 2019; Rowe et al., 2020b), in clinical mastitis risk (Cameron et al., 2014; Vasquez et al., 2018; Rowe et al., 2020b), in milk yield (Cameron et al., 2015; Vasquez et al., 2018; Rowe et al., 2020b), or in culling events (Vasquez et al., 2018; Rowe et al., 2020b).

Kabera et al. (2020) conducted a trial comprising two selective-DCT groups and two blanket-DCT groups, all quarter-based. The classification of quarters as uninfected and infected was based on an on-farm culture system. In one selective-DCT group and one blanket-DCT group, quarters that received antibiotics at dry-off did not receive concurrent ITS. The uninfected quarters that were dried-off without antibiotics always received ITS. No significant difference appeared between these four groups in quarter-level cure and new IMI risk over the dry period. In addition, between these groups, incidence of clinical mastitis, somatic-cell score, and milk yield during the subsequent lactation did not differ. To sum up, the study found no differences between the DCT strategies, but in addition, it found no differences between antibiotic use alone and antibiotic-ITS combination use.

Two recent meta-analyses determined the efficacy of selective DCT compared to that of blanket DCT (Winder et al., 2019b; Kabera et al., 2021b). These studies yielded similar conclusions. For experiments not using ITS, risk of new IMI during the dry period and risk of having IMI at calving were both higher for selectively-treated cows than for blanket-treated cows. Regarding the concurrent use of ITS with DCT, the interpretation from both analyses seems to be that for studies including ITS for all cows in all groups, the risk of new IMI, risk of IMI at calving, risk of clinical mastitis in early lactation, SCC after calving, and milk yield during the first month did not differ between selectively-treated and blanket-treated cows. The two main limitations of these meta-analyses were that the number of studies involved was small, and the studies were spread over a wide time-period of 46 years. ITS usage may explain part of the large heterogeneity in the original analysis, but other factors explaining the heterogeneity remained unresolved.

Antibiotic dry-treatment strategies are only one control measure among other important factors, and DCT is unable to compensate for major deficiencies in farming facilities, in herd management, or in hygiene (Green et al., 2007, 2008). The prevalence of IMI at calving varies considerably between different herds and different countries, which demonstrates that mastitis status at calving is a multifactorial consequence of multiple determinants (Bradley et al., 2015). Appropriately, in the 1980s, two reviews raised concerns that the successes with antibiotics likely discouraged efforts to develop alternative or additional solutions for dry-period IMI prevention (Eberhart, 1986; Oliver and Sordillo, 1988). To emphasize this perception, Oliver and Sordillo (1988) stated, “It is unfortunate, perhaps, that so much research attention has focused on studies of antibiotic therapy during the dry period.” This comment might be in part true even decades later.

2.3.3 Selection of cows for treatment

The challenge for selective DCT is to correctly identify cows in need of treatment at the end of lactation. Natzke (1971) suggested feasible ways to select infected cows, and these were to examine bacteriological milk samples, perform screening tests, or evaluate preceding lactation clinical mastitis history. All of these are possible methods even today. Since then, experimental trials have assessed the approximate diagnostic sensitivity of several approaches to detect infection, either alone or in combination, some of which are summarized in Table 2. Based on these summarized results, the parameters chosen tended to maximize negative predictive values (NPV) rather than positive predictive values (PPV), indicating that studies sought to maximize the success of recognizing all infected cows and quarters. Optimally, the IMI diagnosis will be accurate, up-to-date, cost-effective, and practical, thus being truly correct in supporting the decision to treat or not to treat at drying off.

Table 2. Diagnostic accuracy of screening cows and quarters with intramammary infection during drying off. The referent test is a bacteriological culture of a single milk sample.

Parameter	Se 95% CI	Sp 95% CI	PPV 95% CI	NPV 95% CI	Prevalence 95% CI	Reference
On-farm quarter-milk culture	62.0 58.6, 65.6	82.2 74.0, 89.5	29.4 20.7,39.4	94.8 90.8, 97.4	16.2 11.0, 22.7	Kabera et al. (2021a)
Laboratory quarter-milk culture	67.4 55.8, 81.2	79.6 76.4, 83.0	39.0 27.8, 51.3	92.8 87.8, 96.4	16.2 11.0, 22.7	Kabera et al. (2021a)
CMT for late lactation quarter, cut point ≥ distinct thickening but no tendency to form a gel	41.1 29.8, 52.4	78.1 72.5, 83.7	39.5 28.5, 50.5	79.2 73.7, 84.8	25.8	Godden et al. (2017)
Last 3 test-days SCC <200,000, no CM during lactation or CM <90 DIM with SCC <100,000 during the rest of lactation	69.4 62.9, 75.4	63.3 58.5, 67.9	49.7 43.9, 55.4	79.8 75.1, 83.9	34.3 30.7, 38.1	Torres et al. (2008)
Last 3 test-day SCC <100,000, no CM during lactation	84.2 78.8, 88.8	35.1 30.5, 39.8	40.4 35.9, 45.0	80.9 74.6, 86.4	34.3 30.7, 38.1	Torres et al. (2008)
Last test day: SCC <100,000, primiparous	77.7 64.7, 88.0	91.3 87.0, 95.1	63.3 46.5, 79.0	95.5 91.7, 98.0	16.2 11.0, 22.7	Kabera et al. (2021a)
Last test day: SCC <200,000, multiparous	75.3 55.8, 87.3	84.0 78.8, 89.3	47.2 32.0, 63.7	94.7 89.0, 97.6	16.2 11.0, 22.7	Kabera et al. (2021a)

Se = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval, CMT = California mastitis test, CM = clinical mastitis

Culture-based diagnostics and isolate identification constitute the gold standard for diagnosing mastitis (Sanford et al., 2006). The disadvantages commonly mentioned are the large number of culture-negative samples and the material- and labor costs of sampling. One major advantage is that, in addition to being a tool for individual cow-selection, the milk microbiological analysis provides essential information on the causal mastitis pathogens of a herd, and this information is useful in targeted mastitis prevention. The culture-guided selection of cows by use of various on-farm culture systems has proven to be a well-functioning method to implement selective DCT and has shown no adverse effects on IMI dynamics during the dry period compared with effects of blanket DCT (Cameron et al., 2014, 2015; Patel et al., 2017; Kabera et al., 2020; Rowe et al., 2020a; b). In a recent trial, DCT was selectively administered after the on-farm culturing only to those quarters from which aseptically collected milk samples tested positive (Rowe et al., 2020a; b). Based on the partial budget analysis, this method was estimated to have an average positive economic impact for farmers compared with that of blanket DCT, hence refuting the idea that bacterial culture is too expensive to implement in practice (Rowe et al., 2021). Kabera et al. (2021a) investigated the test-accuracy estimates for laboratory and on-farm quarter-milk culture with Bayesian models. The negative predictive values of culture tests were comparable to the negative predictive values of cow-level SCC, but the positive predictive values were lower (Table 2).

In the Nordic region, farmers take multiple microbiological milk samples before the treatment decision, both during the lactation and at drying off (Vilar et al., 2018; Persson Waller et al., 2021; Rajala-Schultz et al., 2021). In addition, farmers take follow-up samples after treatments for mastitis, if necessary. Cow- and pathogen-specific treatment recommendations and routine information on staphylococcal beta-lactamase production motivate producers to take milk samples. Instead of on-farm culturing, milk samples in Nordic countries are most often sent to a laboratory (Persson Waller et al., 2021; Rajala-Schultz et al., 2021). Polymerase chain reaction (PCR) is the principal method of analysis in Finland. Other Nordic countries use mainly bacteriologic culturing (Rajala-Schultz et al., 2021).

The California mastitis test (CMT) and milk leukocyte differential (MLD) test are cow-side diagnostic tools that can be used to differentiate infected cows at drying off (Poutrel and Rainard, 1981; Godden et al., 2017). Sensitivities and specificities for diagnosing IMI from late-lactation quarter-milk samples were fair to good for both CMT (Table 2) and MLD (Godden et al., 2017). The milk SCC is currently the most widely used mastitis indicator for individual cows and within herds, and the Dairy Herd Improvement (DHI) association provides easily available, regular test-day composite SCC measurements for individual cows. The SCC of an uninfected udder is considered to be less than 100,000 cells/mL (Sordillo et al., 1997). The threshold often used both in research and in practice is an SCC of 200,000 cells/mL, because cows with an SCC above this are likely to have an IMI in one or more of their quarters (Dohoo and Leslie, 1991; Schepers et al., 1997; Djabri et al., 2002; Pantoja et al., 2009b). Specificity of the SCC ≥200,000 cell/mL threshold ranges from 0.64 to 0.89 and sensitivity from 0.66 to 0.90 (McDermott et al., 1982; Dohoo and Leslie, 1991; Schepers et al., 1997; Pantoja et al., 2009b; Kabera et al., 2021a). The accuracy of SCC screening depends on the mastitis pathogens involved, the number of infected quarters, the time of milk sampling, and the limitations in milk microbiological examination. The advantage is that the DHI data is available on the farm at no extra cost or delay. An online cell counter (OCC) is available for an automatic milking system (AMS), and the cell count changes are suitable for continuous on-farm monitoring of bovine udder health. Because the agreement between OCC measurements and DHI-derived SCC measurement has proven to be reasonably good (Nørstebø et al., 2019), OCC probably is thus an option for selecting cows for dry treatment on AMS farms.

The SCC criteria used to select cows for DCT is a contributor to the economics of selective DCT compared with blanket DCT (Scherpenzeel et al., 2016). Whether one or more composite SCC measurements should be used to distinguish infected cows from those uninfected seems somewhat unclear. Moreover, combination screening using SCC and clinical mastitis history with or without bacteriologic culture or cow-side testing might be beneficial for the achievement of a good selection outcome. Scherpenzeel et al. (2014) selected cows for DCT based on only the last SCC recording prior to dry-off, and defined low SCC as <150,000 cells/mL for primiparous cows and <250,000 cells/mL for multiparous cows. This selection method, together with lack of ITS usage, affected udder health negatively compared with blanket DCT. Torres et al. (2008) selected uninfected cows at dry-off based on the different selection criteria that combined various SCC measurement thresholds with clinical mastitis history of the preceding lactation (Table 2). The conclusion was that infected cows were distinguished from uninfected cows at the highest correct classification rate by a threshold of SCC <200,000 cells/mL on each of the last three monthly tests before dry-off for cows without clinical mastitis during the preceding lactation, and by a threshold of <100,000 cells/mL during the rest of lactation for cows with clinical mastitis during the first 90 DIM. Rajala-Schultz et al. (2011) observed that cows selected by using these same criteria had 95.6% of their quarters uninfected at dry-off based on cultured milk samples. Furthermore, less-worrisome NAS was the most common cause of infection in the low-SCC infected quarters, which supports the idea that the chosen selection criteria may have been quite optimal for the herds studied.

Recent US trials used slightly different combinations of SCC and mastitis history for differentiating the uninfected cows from those infected. Vasquez et al. (2018) defined a low-risk cow as one having an average SCC over the last three tests before dry-off of ≤200,000 cells/mL, an SCC of ≤200,000 cells/mL on the last test, and no more than one case of clinical mastitis in the preceding lactation. Their trial showed that low-risk cows had 90% of their quarters uninfected at dry-off, and 60% of IMI in low-risk quarters at dry-off were due to NAS, which results align with those of Rajala-Schultz et al. (2011). In the multi-site experiment, a low-SCC cow was specified to be a cow with SCC ≤200,000 cells/mL during the lactation and with a maximum of one clinical mastitis identification in the preceding lactation. When ITS was given for all quarters of all cows studied, neither of these versions of selection proved to be harmful to udder health compared to blanket DCT.

Using Bayesian latent class models, Kabera et al. (2021a) examined the diagnostic accuracy of DHI-derived composite SCC data to detect infected quarters at dry-off. The data originated from nine Canadian dairy herds with a bulk-tank SCC <250,000 cells/mL and comprised 282 cows. The SCC measurements were estimated for three different methods: the last SCC within 50 days prior to dry-off, the last three SCC prior to dry-off, and all available test-day SCC records during the preceding lactation. When using only the last test-day SCC prior to dry-off, a threshold of 100,000 cells/mL for primiparous cows and 200,000 cells/mL for multiparous cows appeared to be fairly accurate (Table 2). Adding quarter-level milk culture information to the SCC information improved the test accuracy, which is logical. The conclusion was that the last test-day SCC alone could be a suitable selection criteria for farmers to implement due to its accuracy, ease, and simplicity.

Cows with a low SCC at dry-off but a clinical mastitis diagnosis during their lactation are not DCT treated consistently in the studies. For instance, cows were defined to be DCT treated by the following different criteria: one or more mastitis episodes during the preceding lactation (Schultze, 1983; Torres et al., 2008; Rajala-Schultz et al., 2011), mastitis twice or more during the preceding lactation (Vasquez et al., 2018; Rowe et al., 2020a; b), mastitis during the last three months of lactation (Bradley et al., 2010; Cameron et al., 2014, 2015), or mastitis during the first 90 DIM and after that an SCC ≥100,000 (Torres et al., 2008). In contrast, some studies did not take into account for any case the clinical mastitis history of lactation in their selection of cows (Scherpenzeel et al., 2014; McParland et al., 2019; Kabera et al., 2021a). Pantoja et al. (2009a) discovered that quarters with at least one case of clinical mastitis during the previous lactation were over four times as likely to have clinical mastitis during the subsequent early lactation than were quarters without, although all quarters received both DCT and ITS. Of clinical mastitis cases diagnosed after calving, 96% appeared to be new cases that originated during the lactation. This indicates that cows that had clinical mastitis during the lactation are good candidates at least for ITS due to their high mastitis susceptibility, but possibly also are candidates for DCT, depending perhaps on the severity and cause of their previous clinical mastitis.

Most often, cows have only one or two quarters infected, and selective DCT is possible to implement by treating only the infected quarters instead of routinely treating all four quarters of an infected cow (Patel et al., 2017; Kabera et al., 2020; Rowe et al., 2020a). The main benefit of treating at the quarter level is greater reduction in antibiotic use. Treating all quarters of an infected cow may, however, have some advantages. Quarters within the same cow are not completely independent of each other, which interdependence is evidenced by intra-class correlation coefficients for IMI and for high SCC (Barkema et al., 1997; Berry and Meaney, 2006; Rowe et al., 2020a). The sensitivity of a single milk sample to detect IMI could be low for certain pathogens, such as some *Staph. aureus* strains, which could be intermittently shed in milk after a quarter has become infected (Sears et al., 1990; Walker et al., 2013). Hence, interpreting culture results at cow-level could lead to increased sensitivity. This view is supported by meta-analysis showing that when the selection unit was the cow, selective DCT and blanket DCT did not differ in their protection against new IMI during a dry period, but when the selection-unit was the quarter, blanket DCT gave better protection than did selective DCT (Halasa et al., 2009b). The low prevalence of *Strep. agalactiae* and *Staph. aureus* in modern dairy herds may in part explain why quarter-level, on-farm-culture-based selective DCT performed as well as did blanket DCT in recent studies (Patel et al., 2017; Kabera et al., 2020; Rowe et al., 2020a; b). Time will tell whether further studies on quarter-based selective DCT will produce parallel results and whether this selection strategy will become the standard practice on dairy farms.

2.3.4 Economic aspects

From the producers' point of view, the selective-DCT approach should maintain udder health and milk yield equal to that of the blanket-DCT approach without substantial additional costs. Most economic models over the years show that a selective-DCT strategy is profitable, but the ideal extent of antibiotic treatment at dry-off is highly farm specific (Huijps and Hogeveen, 2007; Halasa et al., 2010; Down et al., 2016; Scherpenzeel et al., 2018; Hommels et al., 2021; Rowe et al., 2021). Huijps and Hogeveen (2007), who performed stochastic modeling to simulate IMI dynamics around the dry period, predicted the economic consequences of DCT for *Strept. agalactiae, Strep. dysgalactiae, Strep. uberis, Staph. aureus,* and *E. coli*. The result was that the average costs of the different DCT strategies varied very little. The difference between the blanket DCT, selective DCT, and no DCT was therefore mainly due to the variation in costs due to mastitis around the dry period. Selective DCT seemed to be the most profitable option. However, since small changes were able to shift the economically optimal decision toward blanket DCT, the authors suggested that it is necessary to do a farm-specific calculation of the costs. Similar stochastic modeling by Halasa et al. (2010) indicated that blanket DCT seemed to have the lowest total annual net cost of the IMI caused by *Staph. aureus, Strep. uberis, Strep. dysgalactiae,* and *E. coli* during the dry period, but the differences observable between the various strategies were again very minor.

A more recent stochastic partial budget analysis has suggested that both culture-based and SCC-based selective DCT could be implemented in US herds without negatively affecting udder health or farm profitability (Rowe et al., 2021). In agreement, Hommels et al. (2021) reported that blanket DCT was more expensive than selective DCT in large US dairy herds and suggested that the approximate treatment proportion for primiparous cows could be 30% and for multiparous cows 88%. Their study did not include any selection criteria for cows at dry-off, but instead performed a sensitivity analysis on milk price, antibiotic price, and risk ratio of mastitis in the subsequent lactation. Similarly, regarding the benefit of selective DCT, the cost-effectiveness of interventions for mastitis control during the dry period in UK herds showed that selecting cows individually for DCT was very likely to be a more cost-effective intervention than a herd-level DCT strategy. That study did not comment on possible selection criteria, however (Down et al., 2016).

Scherpenzeel et al. (2018) built a model to fit a scenario with the lowest costs for mastitis associated with the dry period while restricting the percentage of DCT-treated cows. The herds were defined to have either low, average, or high bulk-tank SCC. The incidence of clinical and subclinical mastitis varied at cow level. For all herds, selective DCT appeared to be a more profitable option than blanket DCT. The differences between blanket DCT and selective DCT were small, but when the bulk-tank SCC and clinical mastitis incidence were lower, selective DCT raised the financial profits more. The optimal percentage of DCT-treated cows varied widely based on their health status. To illustrate, at an average level of clinical mastitis, for the herd with bulk-tank SCC ≥250,000 cells/ mL but <400,000 cells/mL, the maximum percentage of DCT-treated cows was 40%. In comparison, for the herd with bulk-tank SCC ≥150,000 cells/ mL but <250,000 cells/mL, the maximum percentage of DCT-treated cows dropped to 20%. Similarly, in all types of herds, the extent of DCT could be reduced from 100% without negative economic consequences. These results align with the Bayesian estimated prevalence of cows in need of DCT treatment at dry-off, which in herds with an average bulk-tank SCC less than 250,000 cells/mL, was 16.2% (95% CI 11.0, 22.7) (Kabera et al., 2021a).

To conclude, economics does not appear to be a strong argument against reducing the use of DCT, especially on farms with average or below-average bulk-tank SCC and clinical mastitis incidence. Because selective DCT could be advantageous for public health, and controlling antibiotic resistance on a farm could prove to be a positive return for a farmer, these potential benefits may perhaps justify a selective-DCT approach, even if it proves to be slightly more expensive than a blanket-DCT approach. Nevertheless, these factors cannot be included in the economic models comparing DCT approaches. Fear of worsening udder health due to selective DCT is understandably high, and therefore it is unlikely that the change from long-term blanket-DCT practice to selective-DCT practice will occur solely for financial reasons. Instead, it is likely that in future, governmental regulations will promote reduced antibiotic usage and will eventually result in less comprehensive antibiotic use also at dry-off. In the Netherlands, legislative changes have guided the national shift from blanket DCT to selective DCT with very encouraging consequences (Lam et al., 2017; Vanhoudt et al., 2018), and it would be desirable for other countries to follow their example. In terms of the overall profitability of the dairy industry, growing consumer concern about antibiotic usage in food-animal production should be taken seriously (Boogaard et al., 2011).

3 AIMS

The main aim was to examine sound drying-off practices in order to assist dairy farmers in maintaining good bovine udder health and productivity. Particular interest was in antibiotic DCT, but a supplemental aim was to investigate various risk factors for post-calving udder health problems and reduced milk yield.

The specific aims were to determine:

1. herd-level associations between differing DCT approaches, average SCC, and annual milk production, taking into account differences in farm characteristics (Study I).

2. whether herd-level variability occurred in average SCC and milk production over time, and whether this variability differed between various DCT approaches (Study I).

3. associations between herd-level DCT approach and cow's early lactation udder health problems while taking into account the effect of cow characteristics (Study II).

4. number of DCT treatments on Finnish selective-DCT approach farms based on DHI records (Study III).

5. milk yield and composite SCC differences during the first half of lactation between selectively DCT-treated and -untreated cows, taking into account risk factors for reduced milk yield and high SCC (Study III).

4 MATERIALS AND METHODS

4.1 Study population

The target population comprised Finnish dairy farms belonging to the national dairy-herd-recording system, equivalent to DHI. Figure 1 outlines the farm-level formation of the study populations (I−III). Preliminary retrospective data included herd- and cow-level Finnish dairy-herd-recording data registered on 271 dairy farms whose farmers responded to a questionnaire in January to May 2017. This questionnaire was available to dairy farmers who were part of the Finnish DHI-recording system in 2016. During that year, the recording system included approximately 70% of Finnish herds and 80% of Finnish cows. Of approximately 5,400 farms, responding farms numbered 715. Of these respondents, farms that granted approval to use their DHI data for research totaled 271. After our data accuracy assessment, the final study population comprised 241 conventional farms (I, II). Of these 241 farms, Study III utilized a subset of 172 farms whose standard practice was selective DCT. The study populations appeared to be representative of the target population, although their mean herd size was slightly larger, their milk production higher, and their SCC lower than usual on Finnish dairy farms.

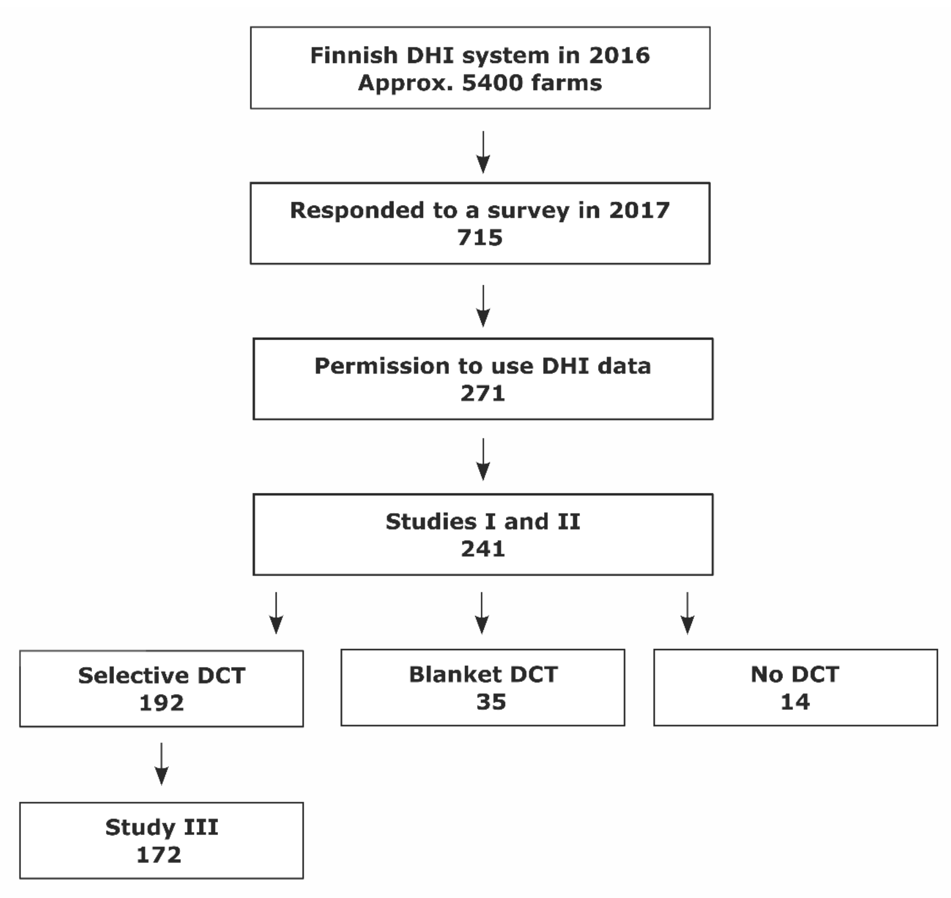

Figure 1. Study population formation at farm level (Studies I−III).

4.2 DHI data

The DHI data source was the Finnish Milk Recording database (MTech Digital Solutions, Vantaa, Finland). The herd-level data were registered during 2012–2016 and the cow-level data during 2015–2017. Table 3 summarizes herd- and cow-level DHI-derived information included in the original Studies I to III. Herd-level DHI data comprised annual average SCC and annual average milk yield per cow. The dairy-herd-recording association calculates the herd's annual average SCC and milk production from repeated test-day measurements of the individual cows on each farm. The common test-day interval for cow-level milk yield measurements was one month, and for composite SCC measurements either one or two months.

Table 3. Summary of DHI-derived information in Studies I–III.

Information	Specification	Descriptive results	Covariate in final models
Herd level			
Annual average milk yield	Kg/cow	I, II, III	I
Annual average SCC	× 1,000 cells/mL	I, II, III	I
Parity	Average parity of farm on last day of a year	I, II, III	
Herd size	Average number of adult cows during a year	I, II, III	I
Calving interval	Average interval in days	II, III	
Cow level			
305-day milk yield	Kg	II, III	III
305-day ECM	Kg	II, III	
Test-day milk yield	Kg/d	II, III	II, III
Preceding lactation peak milk yield	Max test-day yield during 0–120 DIM, kg/d	II	II
Approx. milk yield prior to dry-off	Approx. test-day yield 79 d prior to calving, kg/d	II	II
Test-day SCC	× 1,000 cells/mL	II, III	III
Preceding lactation average SCC	Min 5 and max 27 SCC counts, × 1,000 cells/mL	II	II
DCT at dry-off	Yes, no	III	III
Lactational mastitis treatment	Yes, no	II, III	II, III
DIM prior to dry-off	Days	II, III	II, III
Dry period length	Days	II, III	III
Parity at calving	Number of calvings	II, III	II
Season at calving	Dec-Feb, March-May, June-Aug, Sep-Nov	III	III
Breed	Finnish Ayrshire, Holstein	II,III	III
Culling information	Due to mastitis, due to other causes, no culling	III	

4.3 DCT

The 2017 survey provided information about both herd-level DCT practice and duration of that practice. The three DCT-treatment practices were selective DCT, blanket DCT, and no DCT (Figure 1, Table 4). The duration of the practice on the farms was one of the following: less than 1 year, from 1 to 5 years, or more than 5 years. The populations studied included only those farms whose duration of the DCT practice reported to be in use was one year or more (I−III, Table 4). For farms whose standard practice was selective DCT, the survey information covered the farmers' estimate of the proportion of DCT-treated cows on their farm (Table 4).

During the study period, the three antibiotic dry-cow products on the Finnish market contained benzylpenicillin 400,000 IU and framycetin 100 mg (Umpimycin vet, Boehringer Ingelheim Vetmedica GmbH, Germany), cloxacillin 500 mg (Orbenin retard vet, Zoetis Finland Oy, Finland), and ampicillin 250 mg and cloxacillin 500 mg (Kloxerate retard, Norbrook Laboratories Limited, Ireland).

Table 4. Summary of survey-derived herd characteristics in Studies I−III.

Information	Specification	Descriptive results	Covariate in final models
DCT approach	Selective DCT, blanket DCT, no DCT	I, II, III	I,II
Milking system	Pipeline, parlor, AMS	I, II, III	I
Change in milking system in 2012−2016	Yes, no	I	I
Duration of DCT approach in 2017	1–5 years, >5 years	I, II, III	
ITS administration at dry-off	Yes, no	I	
Desired milk yield at dry-off	<10 kg, 10–15 kg, >15 kg	I	
Average dry period length	≤8 weeks, >8 weeks	I	
Region	Provinces based on postal codes	I	
Approximate proportion of selectively DCT-treated cows	<25%, 25%, 50%, >50%	I, II, II	
Microbiological analysis of milk samples at dry-off	Yes, no	I, II	

4.4 Survey-derived herd characteristics

The study farms were geographically located in 17 different provinces, and the total number of Finnish provinces at that time was 19 (Figure 2). The data showed regional clustering into provinces with the highest dairy livestock density. Farms performed their milking either with a parlor milking system, with an AMS, or with a pipeline system. Of the 241 farms, 30 farms reported a change in their milking system either to a parlor or to an AMS during 2012−2016. Table 4 contains the summary of survey-derived herd information included in the original Studies I−III.

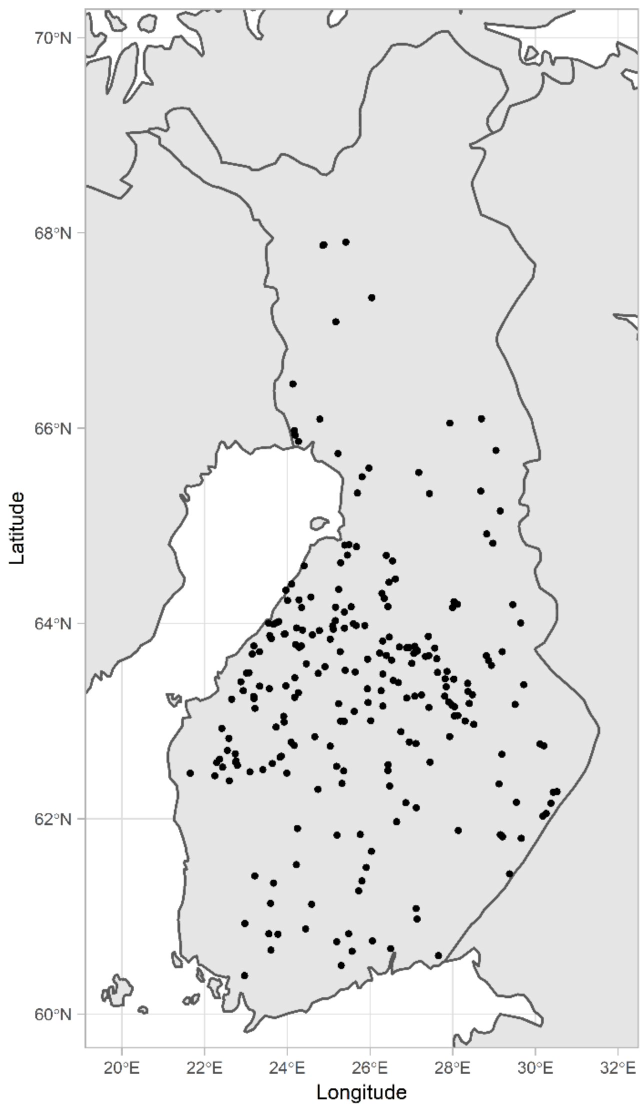

Figure 2. Geographical distribution of the 241 study farms**.**

4.5 Data accuracy assessment

Special effort went into ensuring that the observational data were as accurate, precise, and error-free as possible. The main details are summarized here, with a more detailed description available in each Materials and Methods of the original Studies I to III.

The farms included were conventional farms with an average herd size of more than 10 adult cows (I−III). The cows included had a dry-period length within 30 to 90 days and the dry-off dates between autumn 2015 and the end of 2017 (II, III). For all these cows, the first test-day SCC was within 5 to 45 DIM (II, III), to ensure that the first SCC measurement was neither too near to, nor too far after calving (Barkema et al., 1999a).

The date of dry-off was missing for approximately 4% of the cows. Due to the possibility of an unusually short dry period, the exclusion criterion was to reject any cows with test-day measurements made within 40 days before calving and with a missing dry-off date (II). Conversely, due to the possibility of an unusually long dry period, the excluded cows were cows without test-day measures within 120 days before calving and a missing dry-off date (II). Because such information was considered necessary for these analyses, all cows lacking a dry-off date were excluded from Study III.

Finnish farms can receive antibiotics only by prescription from a veterinarian. Thus, farmers start antibiotic treatments under the guidance or supervision of a veterinarian. Cow-level lactational mastitis treatments in the health-recording database are coded to represent clinical or subclinical mastitis. Because these codes lack information on symptoms or symptom severity, all lactational mastitis treatments were uniformly defined as mastitis treatment (II, III).

A separate cow-level record code differentiates DCT from other mastitis treatment codes. On some farms, the required DCT-treatment records are maintained only on the farm and are not transferred to the dairy herd recording system. Consequently, for a few study farms, DHI data lacked reliable data on individual dry-cow treatments. Thus, Study II included in its analyses herd-level DCT information. The exclusion criterion of Study III was to reject farms with ≥40% fewer DCT-treatment records than expected based on the survey, because those farms may have had deficits in their DCT-record transfers. This difference was a farm-specific absolute difference between survey-based treatment proportion and DHI-based treatment proportion. Additionally, DCT-treated cows with more than a 14-day difference between dry-off date and DCT-treatment date were excluded from Study III.

4.6 Statistical analysis

Study I analyses were performed with R version 3.5.1 (R Core Team, 2018) using R Studio Version 1.1.463 (RStudio Team, 2016), Study II analyses with R version 4.0.0 (R Core Team, 2018) using R Studio Version 1.3.959 (RStudio Team, 2020), and Study III analyses with R version 4.0.3 (R Core Team, 2020) using R Studio Version 1.4.1106 (RStudio Team, 2021).

Study I comprised two continuous herd-level response variables, which were annual average of individual cow SCC (×1,000 cells/mL) and annual average milk production per cow (×1,000 kg). The cross-sectional analysis for 2016 was carried out using a multiple linear regression. The method for 2012–2016 longitudinal analysis was a multilevel growth-modeling framework using random coefficient models.

Study II examined three cow-level response variables. These were the odds of having milk SCC ≥200,000 cells/mL on the first test-day 5–45 DIM (binary), the odds of mastitis treatment within 45 DIM (binary), and the mean milk lnSCC (× 1,000 cells/mL) during 5–120 DIM (continuous). Only one lactation was selected for each cow. The model for the binary outcomes was a generalized linear mixed-effects model with logit link function and a random herd effect. The model for the continuous outcome was a Gaussian linear mixed-effects model with a random herd effect.

In Study III, the continuous response variables of two models were cow-level milk yield (kg/d) and lnSCC × 1,000 cells/mL, which were repeatedly measured on test days during the first 154 DIM. Due to the lack of independence between repeated measurements within cows and between cows within the same herd, the statistical tool was a Gaussian linear mixed-effects model with two-level random intercepts, cows nested within herds, and a first-order autoregressive correlation structure AR(1). In both these time-series analyses, the lactation curve was modeled as proposed by Wilmink (1987).

The primary covariates of interest were herd-level DCT approach (I, II) and cow-level DCT at dry-off (III). Other covariates that were included in the final models of statistical analyses (I−III) are in Tables 3 and 4.

5 RESULTS

5.1 Herd-level DCT strategies (I-III)

5.1.1 Treatment extent in Finland (I-III)

Selective DCT was the prevailing management practice. Of the 241 farms, 192 (80%) were selective-DCT farms, 35 (14%) were blanket-DCT farms, and 14 (6%) no-DCT farms (Figure 1, I, II). On these farms, the duration of the farm's DCT practice was 1 to 5 years in 51 (21%) farms and more than 5 years in 190 (79%) (I, II). Of the 172 selective-DCT farms included in Study III (Figure 1), the duration of the selective DCT practice was from 1 to 5 years in 33 (19%) of the farms and more than 5 years in 139 (81%). Blanket DCT was a more widespread practice on large AMS farms compared with other milking-system farms (I, II). The minor group of farms that implemented drying off without DCT were almost entirely pipeline-equipped tie-stall farms (I, II). More than 50% of blanket-DCT farms and more than 80% of selective-DCT farms took milk samples for bacteriological examination at dry-off (I, II). Approximately 35% of farms utilized ITS for at least some of their cows at dry-off (I, II). ITS usage was more common on the AMS farms, with 30 (53%) of the 57 AMS farms using ITS.

Based on the 2017 survey, 73% of the 192 selective-DCT farms DCT-treated up to a quarter of their cows, and 9% of these farms treated more than half their cows at dry-off (I, II). According to the DHI records, the herd-level number of selectively DCT-administered cows was only slightly larger than expected based on the survey figures (III). The mean herd-level proportion of DCT-treated multiparous cows was 21%, and the median (IQR) herd-level DCT-treatment proportion was 12.5% (from 3.3% to 33.3%). The total proportion of DCT-treated cows in Study III was 25% (1,176/4,720). Overall, the majority of the selective-DCT farms treated with antibiotics only a moderate proportion of their cows at dry-off (III). These treatment proportions were consistent with the SCC-based prevalence of subclinical mastitis prior to dry-off (II, III).

5.1.2 Udder health and milk yield at herd level (I)

Compared with selective DCT, blanket DCT was not associated with annual herd-average SCC (× 1,000 cells/mL) either in cross-sectional analysis (95% CI −28.07, 13.73, p=0.50) or in longitudinal analysis (95% CI −34.08, 1.27, p=0.07) (Figures 3 and 4). Similarly, blanket DCT compared with selective DCT was not associated with annual herd-average milk yield (× 1,000 kg/cow) either in cross-sectional analysis (95% CI −0.16, 0.59, p=0.26) or in longitudinal analysis (95% CI −0.15, 0.51, p=0.28) (Figures 5 and 6).

The 2012−2016 between-year variability in herd-average SCC and milk yield across the three DCT groups was minor, and the greatest variability was between farms. Because ICC serves as a measure of similarity between observations within each cluster, our ICC values showed that SCC and milk production observations within a herd across the years remained similar. When modeling SCC, annual ICC values ranged from 0.61 to 0.70 and when modeling milk yield, from 0.83 to 0.85.

Considering the five years, herd-average SCC (× 1,000 cells/mL) did not change over time (95% CI −1.79, 2.53, p=0.74) (Figure 4). Herd-average milk yield increased approximately 130 kg/cow for each additional year from 2012 onwards (0.13 × 1,000 kg/cow, 95% CI 0.10, 0.15, p <0.0001) (Figure 6). The negative correlation of −0.35 between intercepts and slopes of the random coefficient models showed that farms with low milk yield in 2012 gained more milk than did those with high milk yield.

5.1.3 Udder health at early lactation (II)

Herd-level blanket DCT strategy compared with selective DCT strategy lowered the odds of a cow having SCC ≥200,000 cells/mL on the first test-day post calving. The OR for blanket DCT compared with selective DCT was 0.69 (95% CI 0.54, 0.88, p-value=0.003). When assessing the odds of a cow receiving mastitis treatment within 45 DIM post calving, the OR for blanket DCT compared with selective DCT was 0.67 (95% CI 0.45, 1.02, p=0.06). The estimated cow-level mean lnSCC during the first four months post calving was lower for cows housed on a blanket-DCT farm than for those housed on a selective-DCT farm. The beta coefficient of lnSCC was −0.23 × 1,000 cells/mL (95% CI −0.39, −0.07, p=0.002). At a composite mean SCC of 100,000 cells/mL, this corresponds to a reduction in mean SCC of 20,000 cells/mL.

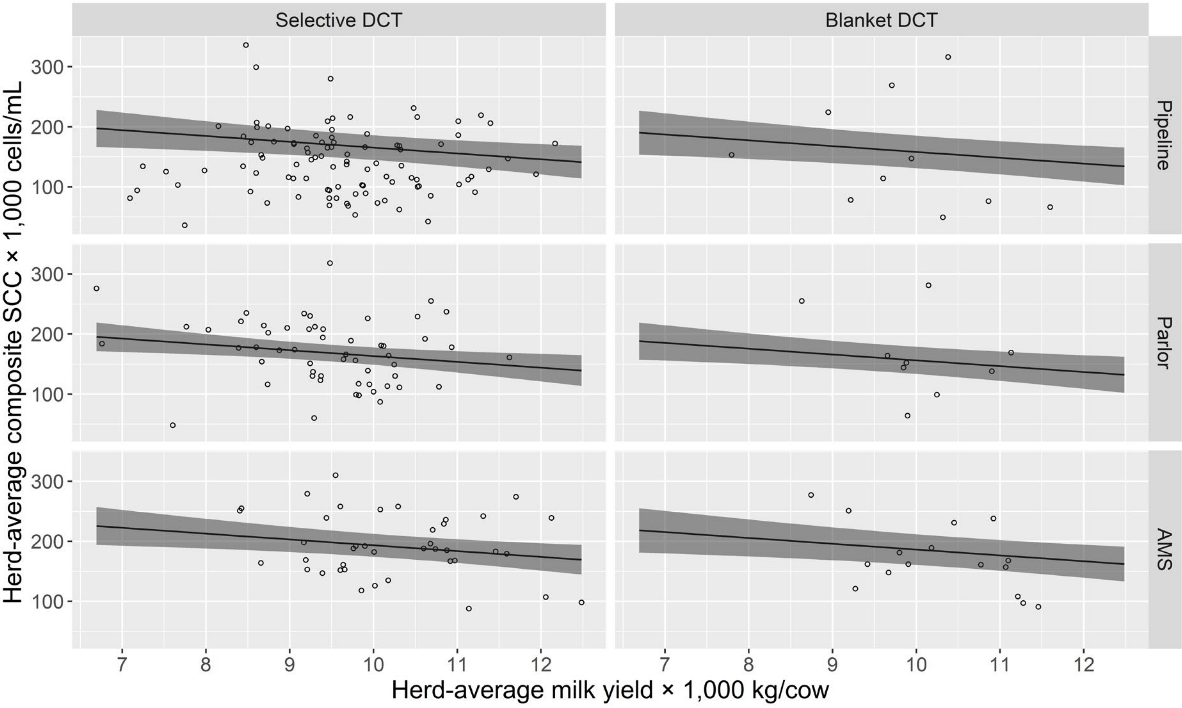

Figure 3. Fitted linear regression for herd-average SCC from 241 dairy herds in 2016 (Study I). Predicted herd-average SCC versus herd-average milk yield ± 95% CI for a selective-DCT practice farm and a blanket-DCT practice farm divided by their milking-system types. Average herd size is set to be equal to the mean herd size of approximately 50 cows. The model is taking into account the interaction between herd size and milking system.

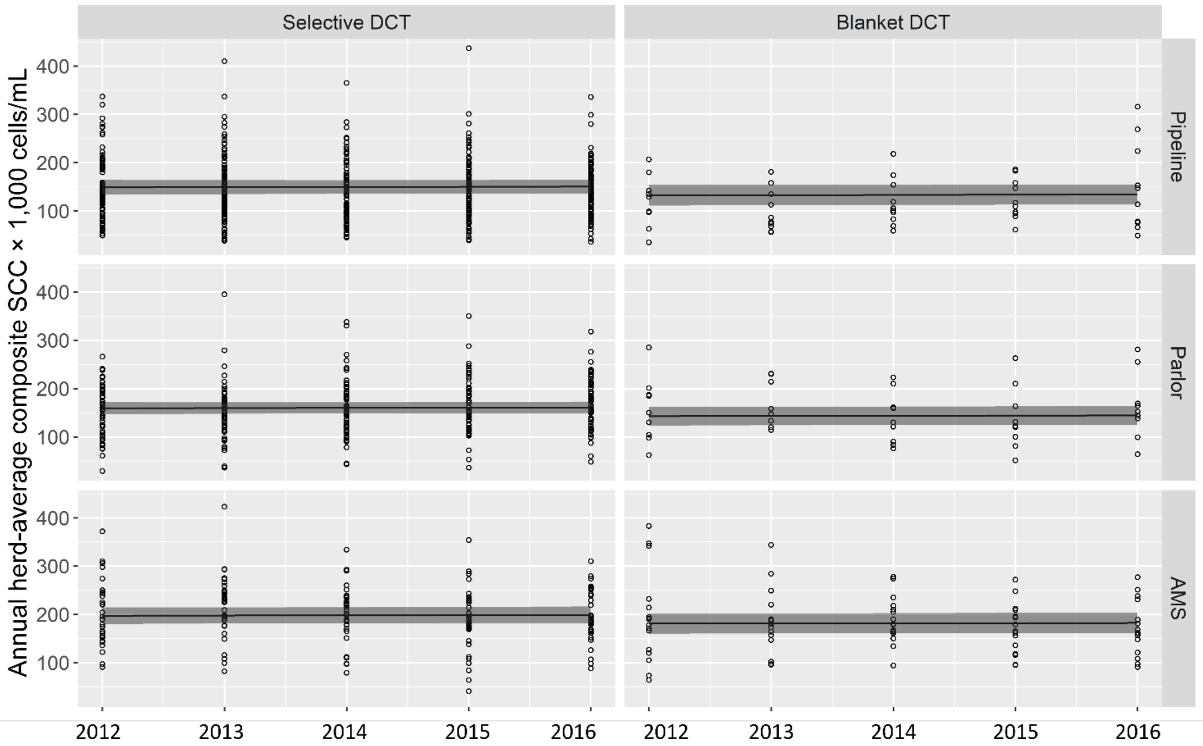

Figure 4. Fitted multilevel growth model for annual herd-average composite SCC, based on 1195 recordings from 241 dairy herds in 2012−2016 (Study I). Predicted herd-average SCC ± 95% CI for a selective-DCT practice farm and a blanket-DCT practice farm divided by their milking-system types. Average herd size and annual herd-average milk yield are set to be equal to the mean herd size of approximately 50 cows and mean milk yield of approximately 9,500 kg/cow. The model is taking into account the interaction between herd size and milking system.

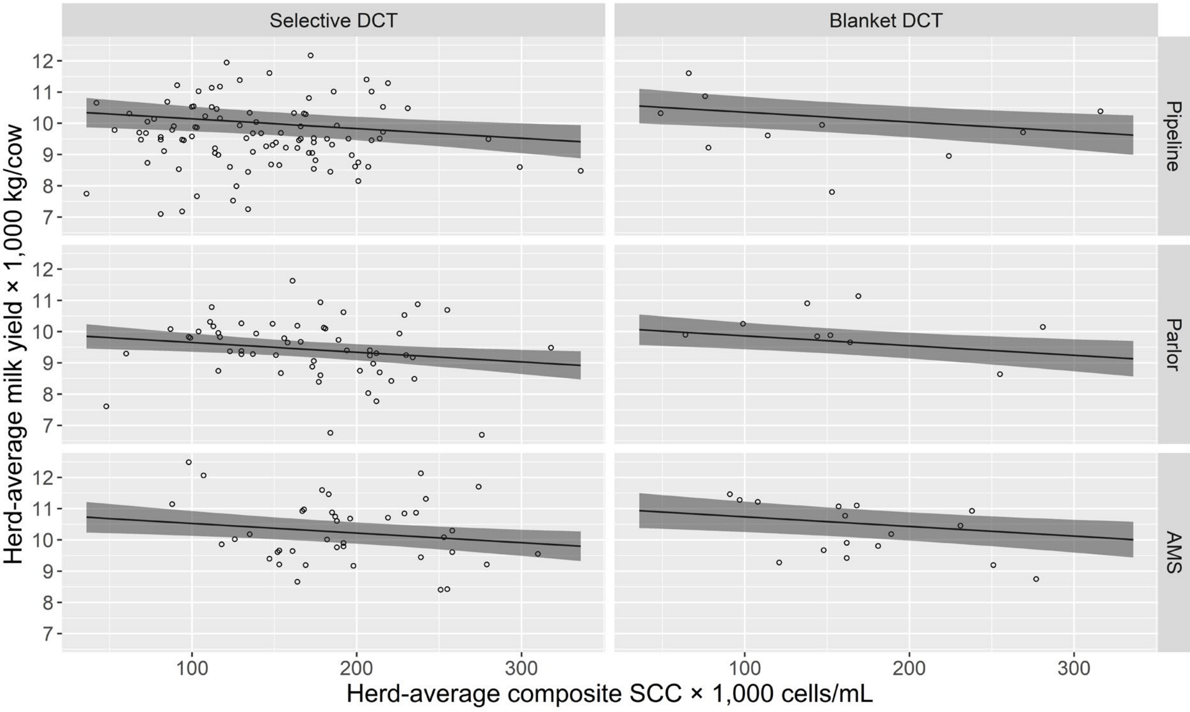

Figure 5. Fitted linear regression for herd-average milk yield from 241 dairy herds in 2016 (Study I). Predicted herd-average milk yield versus herd-average SCC ± 95% CI for a selective-DCT practice farm and a blanket-DCT practice farm divided by their milking-system types. Average herd size is set to be equal to the mean herd size of approximately 50 cows. The model is taking into account the interaction between herd size and milking system.

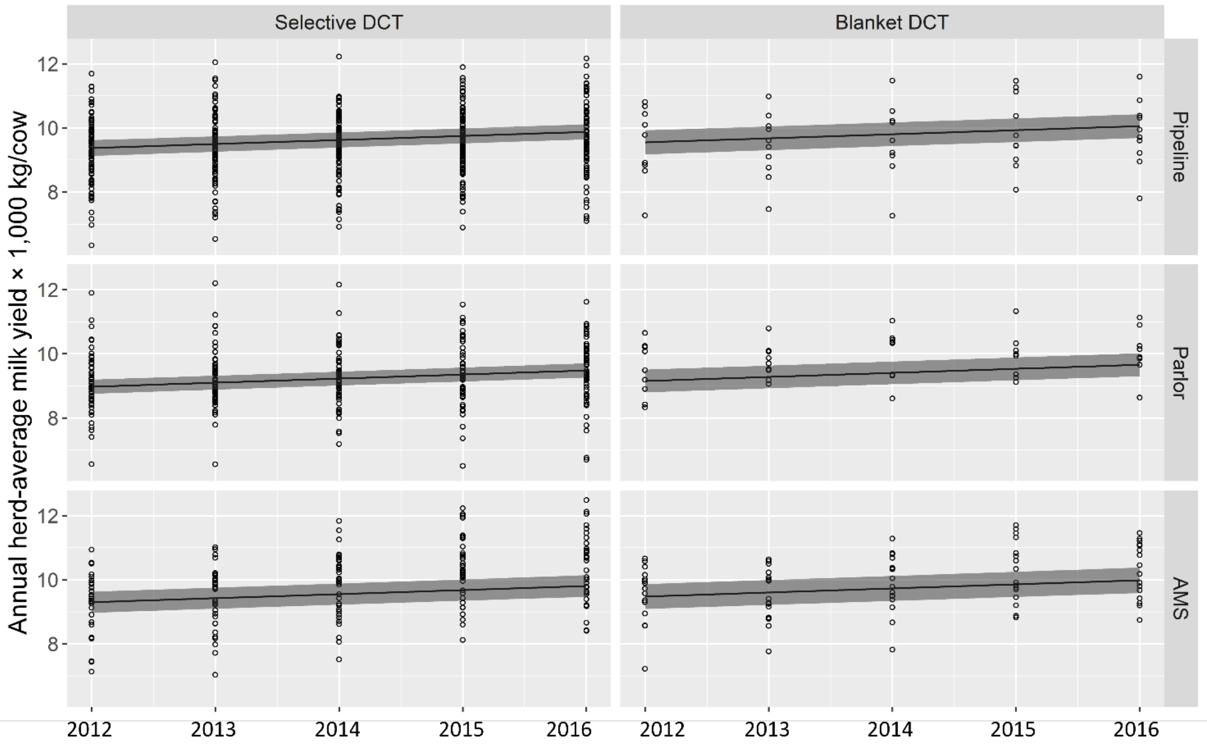

Figure 6. Fitted multilevel growth model for annual herd-average milk yield per cow, based on 1195 recordings from 241 dairy herds in 2012−2016 (Study I). Predicted herd-average milk yield ± 95% CI for a selective-DCT practice farm and a blanket-DCT practice farm divided by their milking-system types. These farms did not renew their milking system during the period. Average herd size and annual herd-average composite SCC are set to be equal to the mean herd size of approximately 50 cows and mean SCC of 160,000 cells/mL. The fitted model is taking into account the interaction between herd size and milking system.

5.2 Selective DCT effect on the first half of lactation (III)

Of the 1,176 selectively DCT-treated cows, 387 (33%) had a test-day SCC ≥200,000 before dry-off and 234 (20%) had one or more mastitis recordings during their preceding lactation. Of the 3,544 untreated cows, 683 (19%) had an SCC ≥200,000 prior to their dry-off and 332 (9%) had mastitis treatment during the preceding lactation. Overall, of all 4,720 cows, 1,070 (23%) had an SCC ≥200,000 in the most recent measurement prior to dry-off and 566 (12%) had mastitis treatment during preceding lactation.

The cow-level time series analysis indicated that antibiotic DCT had a dissimilar effect on the subsequent lactation milk yield depending on test-day SCC prior to dry-off. A higher last test-day SCC correlated with a greater yield difference between DCT-treated and untreated cows. At a SCC of 200,000 cells/mL prior to dry-off, the result corresponds to a milk yield increase of 0.97 kg/d during 154 DIM for DCT-treated cows compared to those untreated. Regarding a lower count, at a SCC of 100,000 cells/mL on a last test-day, the result corresponds to a yield increase of 0.75 kg/d (Figure 7). The beta coefficient of DCT treatment versus no treatment was 0.75 (95% CI 0.33, 1.16, p=0.0004), the beta coefficient of last test-day lnSCC was −0.20 (95% CI −0.30, −0.03, p=0.02), and the beta coefficient of two-way interaction DCT treatment x last test-day lnSCC versus no treatment x last test-day lnSCC was 0.32 (95% CI 0.03, 0.62, p=0.03).

The received DCT at dry-off reduced test-day lnSCC during 154 DIM post-calving when compared to SCC of untreated cows. At a SCC of 200,000 cells/mL on the last test-day prior to dry-off, the result corresponds to a SCC decrease of approximately 20,000 cells/mL at 45 DIM for DCT-treated cows compared to untreated cows. In comparison, at a SCC of 100,000 cells/mL prior to dry-off, the result corresponds to a SCC decrease of approximately 16,000 cells/mL at 45 DIM (Figure 8). The beta coefficient of lnSCC was −0.28 × 1,000 cells/mL (95% CI −0.37, −0.20, p <0.0001).

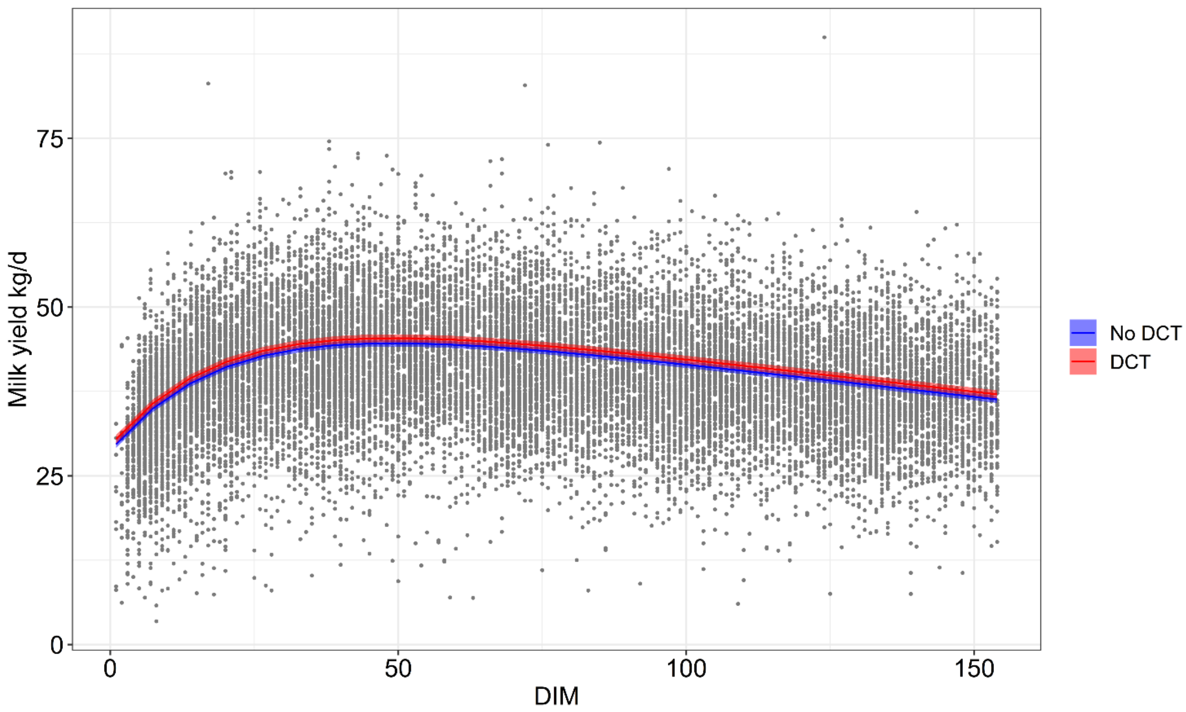

Figure 7. Fitted linear mixed model for milk yield within 154 DIM, based on 4,720 cows from 172 dairy herds (Study III). Predicted lactation curve ± 95% CI for a Holstein cow treated and untreated with antibiotic DCT. LnSCC 0-90 days before drying is set to be equal to an SCC of 100,000 cells/mL. The cow had no postpartum mastitis treatments and the dry-period equaled 60 days. Calving season is winter. Other covariates in the model are set to be equal to the mean (305-day milk yield, DIM on the last test day prior to dry-off, mean SCC postpartum, and milk yield 0–90 days before dry-off). The fitted model is taking into account the interaction between DCT and lnSCC 0–90 days prior to dry-off.

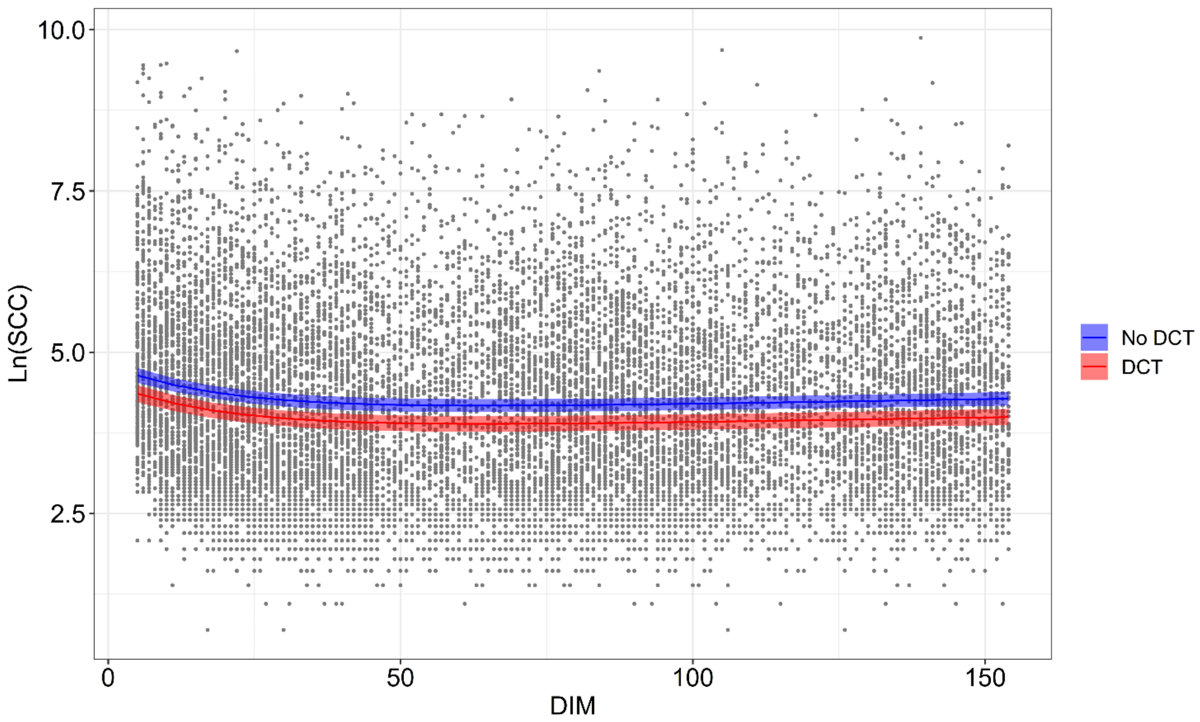

Figure 8. Fitted linear mixed model for naturally log-transformed composite SCC (x 1,000 cells/mL) within 154 DIM, based on 4,720 cows from 172 dairy herds (Study III). Predicted lnSCC ± 95% CI for a Holstein cow treated and untreated with antibiotic DCT. LnSCC 0-90 days before dry-off is set to be equal to an SCC of 100,000 cells/mL. The cow had no pre- or postpartum mastitis treatment. Calving season is winter. Other covariates in the model are set to be equal to the mean (305-day milk yield, test-day milk yield post calving, and milk yield 0–90 days before dry-off).

5.3 Risk factors for impaired udder health and reduced milk yield (I−III)

5.3.1 Herd level (I)

Taking into account the interaction between a farm's milking-system type and its average herd size, AMS-equipped farms had higher average SCC than did other milking-system types (Figures 3 and 4). In 2016, AMS was also associated with higher average milk yield per cow compared with other milking systems (Figure 5). Increase in average herd size by 10 cows above the median herd size of 40 cows had virtually no effect on SCC or milk production on AMS and on parlor farms.

5.3.2 Cow level (II, III)

Having earlier udder health problems appeared to relate to udder health problems again in the following lactation. Higher mean SCC in the preceding lactation raised the odds of a cow's having SCC ≥200,000 cells/mL again on the first test-day after calving and the odds of a cow's receiving post-calving mastitis treatment (II). The mean SCC during the preceding lactation explained most of the variance in mean lnSCC during 120 DIM when compared with other covariates studied (II). Considering the first half of the lactation, a higher SCC prior to dry-off was associated with higher lnSCC again post calving (Figure 9, III). In alignment, cows treated for mastitis during either preceding or subsequent lactation had a higher post-calving lnSCC during 154 DIM than did cows untreated for mastitis (III).

Results indicated that higher milk yield was associated with impaired udder health (II, III). Cows that produced more on a test-day near dry-off were more likely to have SCC ≥200,000 cells/mL on a first test-day post-calving (II). The preceding lactation 305-day yield and late lactation test-day milk yield were associated with lnSCC so that higher milk yield led to higher lnSCC (II, III). The odds of a cow receiving mastitis treatment post-calving were higher for cows with a higher yield near dry-off and for cows with a higher preceding lactation peak yield (II).

A dry period over 30 days was associated with higher milk yields (III) but not with SCC, when the longest possible dry period was 90 days (II, III). High parity raised the odds of a cow's having SCC ≥200,000 cells/mL at the first test-day post-calving and was associated with higher mean lnSCC in early lactation (II). Based on a large DIM on the last test-day prior to dry-off, a longer preceding lactation raised the odds for a high SCC on the first test day post-calving (II), but was not associated with longer-term SCC (II, III). A longer lactation was associated with higher milk yields (III).

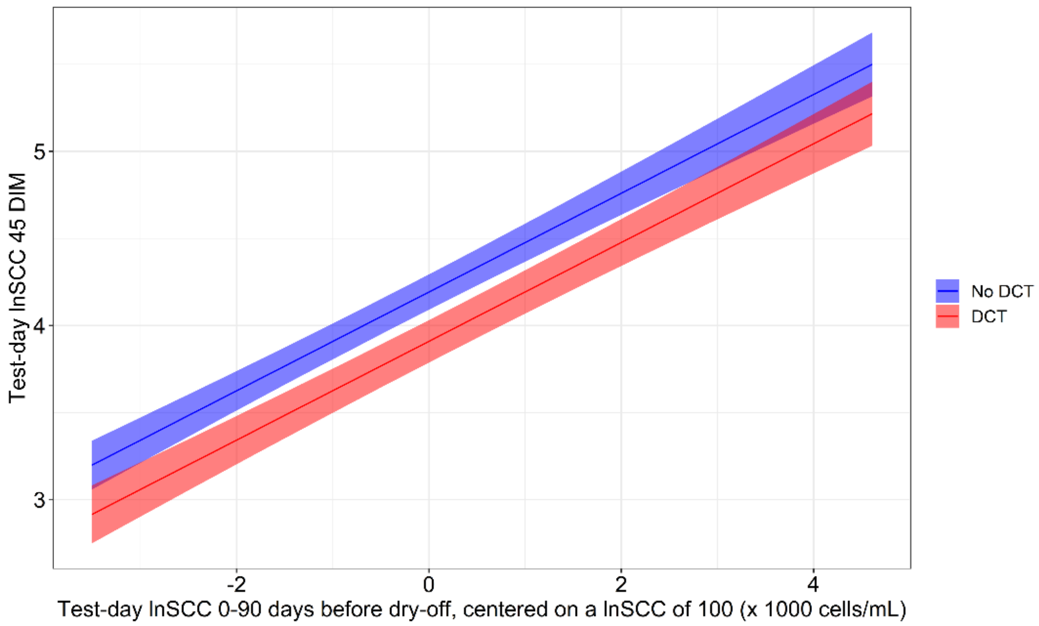

Figure 9. Fitted linear mixed model for naturally log-transformed composite SCC (x 1,000 cells/mL), based on 4,720 cows from 172 dairy herds (Study III). Predicted lnSCC on a test-day 45 DIM ± 95% CI versus last test-day lnSCC prior to dry-off for a Holstein cow treated and untreated with antibiotic DCT. The cow had no pre- or postpartum mastitis treatments. Calving season is winter. Other covariates in the model are set to be equal to the mean (305-day milk yield, test-day milk yield post-calving, and milk yield 0–90 days before dry-off).

6 DISCUSSION

6.1 Nordic characteristics of mastitis therapy

Prudent use of antibiotics for livestock is a long-standing practice in all Nordic countries (Ekman and Østerås, 2003; Rajala-Schultz et al., 2019, 2021; Persson Waller et al., 2021). According to European Medicines Agency reports, sales of the various veterinary antimicrobial classes, expressed as mg sold per population correction unit (PCU), are, among all European countries, lowest in the Nordic countries (EMA, 2021). These reports also clearly reveal that the antibiotic-sale differences within Europe are large.

The Nordic countries have joint Nordic guidelines for mastitis treatment, which recommend narrow-spectrum antibiotic usage, microbiological knowledge of causal mastitis pathogens, assessment of treatment prognosis, and selective-DCT practice (Nordic Guidelines for Mastitis Therapy, 2009). Furthermore, due to Nordic legislation, antibiotics are available for animals only by prescription, and veterinarians are not allowed to profit from any prescription medicine sale.

As in the other Nordic countries, selective DCT is a routine management on the majority of Finnish farms (Vilar et al., 2018). Our study was the first to present national DCT-treatment proportions for selective-DCT farms based on the DHI records. Their overall DCT use was low, and most farms medicated at dry-off a maximum of a one-third of their cows. This information parallels earlier-described DCT-treatment information (Ekman and Østerås, 2003; Vilar et al., 2018). Additionally, our research demonstrated that the amount of mastitis treatment during lactation was likewise low. This low extent of mastitis therapy was consistent with the prevalence of subclinical mastitis among the cows studied as well as with the formerly reported Finnish prevalence of subclinical mastitis and the incidence rate of clinical mastitis (Hiitiö et al., 2017; Rajala-Schultz et al., 2021).

6.2 DCT, udder health, and milk yield at herd level

As selective DCT is not a widely established standard practice worldwide, studies exploring the influence of DCT strategies on the within-herd dynamics of udder health or yield development are few. In the Netherlands, dairy farmers switched from a blanket-DCT strategy to a selective-DCT strategy due to their national legislative changes in 2012. This restricted antibiotic policy does not appear to have had any detrimental effect on national bulk milk SCC, clinical mastitis incidence rate, or herd-level proportion of new and cured IMI after the dry period (Santman-Berends et al., 2016; Lam et al., 2017; Vanhoudt et al., 2018). At the same time, the consumption of antibiotics in Dutch dairy herds has decreased considerably (Kuipers et al., 2016; Lam et al., 2017; Vanhoudt et al., 2018).

In agreement with the Dutch observational studies, our study succeeded in demonstrating that selective-DCT practice appears not to be a hindrance to long-term good udder health or milk production. Finnish selective-DCT farms were able to maintain a low average SCC, a good milk yield, and an upward trend in their yield development compared to blanket-DCT farms, even with a very moderate treatment percentage. The Dutch milk SCC values are rather similar, but their antibiotic usage appears to be more frequent both during lactation and at dry-off (Santman-Berends et al., 2016; Vanhoudt et al., 2018; Krattley-Roodenburg et al., 2021).

The large variation between herds in yield and SCC across various DCT approaches suggests the need for farm-specific counseling. Selective DCT has been recently viewed as a cost-effective practice, especially in herds with good udder health (Scherpenzeel et al., 2018; Hommels et al., 2021; Rowe et al., 2021). This indicates that redundant DCT usage for a herd with good udder health and missed DCT treatments on a herd with udder-health challenges are likely suboptimal practices. The veterinarians and dairy advisers should regularly assess farm's DCT-administration protocols and other drying-off practices alongside with their other dairy health advising. In agreement with this, several previous studies highlight the need for herd-specific mastitis-control measures for drying off (Rajala-Schultz et al., 2011; Bradley et al., 2015; Scherpenzeel et al., 2016, 2018; Gussmann et al., 2018).

The dairy industry has undergone profound changes in all developed countries over the past decades, leading to an increase in herd size and a decrease in herd number (Barkema et al., 2015). This fast structural change has happened in Finnish agriculture as well, and farms are more dependent on hired, nonfamily labor (Väre, 2010; Natural Resources Institute Finland, Helsinki, Finland). Despite the restructuring, however, national milk production volume has remained nearly the same. Nowadays, farming facilities vary considerably, which was apparent also in our research data. This constant ongoing development further emphasizes the need for farm-specific protocols in order to minimize human error and ensure consistency of practice (Barkema et al., 2015).

During the study period, only approximately one-third of study farms administered ITS at dry-off. This herd-level ITS usage was not associated in Study I with herd-level SCC or yield. According to a 2017 survey, ITS utilization was more common on larger parlor- or AMS-equipped farms in Finland (Vilar et al., 2018). Among Swedish producers, ITS usage seems even lower than that of Finnish producers. Only 18% of Swedish producers responding to the recent survey answered that they use ITS (Persson Waller et al., 2021). Farms with AMS or parlor milking, as in Finland, and farms producing >11,000 kg ECM implemented more ITS at dry-off. Of Swedish farmers using ITS, 85% thought that teat sealants improve udder health during the next lactation. Meta-analyses consistently state that ITS provides good protection against IMI over the dry period (Halasa et al., 2009b; Rabiee and Lean, 2013; Winder et al., 2019a; b; Kabera et al., 2021b). The most recent meta-analysis concludes that in herds with bulk milk SCC under 250,000 cells/mL, if ITS is administered to DCT-untreated, healthy quarters, the selective-DCT approach and blanket-DCT approach do not differ in IMI cure, in IMI prevention, and in early-lactation clinical mastitis prevention (Kabera et al., 2021b).

Milking cows with AMS was related to higher herd-average SCC and milk yield. This finding aligns with others' research (Hovinen et al., 2009; Hiitiö et al., 2017; van den Borne et al., 2021) and with the national statistics (Finnish Association for Milk Hygiene, Helsinki, Finland). The blanket-DCT strategy was more common on AMS farms and on farms with higher average yield, and this situation appears to be similar in Swedish dairy farming (Persson Waller et al., 2021). The higher herd-average SCC and management differences related to larger herd size are possible reasons to use a blanket-DCT strategy on these farms. The increase in milk yield after launching AMS milking is likely related to a more frequent milking interval and possibly to a shift towards an improved barn environment (Jacobs and Siegford, 2012).

6.3 DCT, udder health, and milk yield at cow level

Many experimental studies over the decades report DCT effects on postpartum udder health. Study designs, IMI definitions, and study populations vary, and their results seem somewhat contradictory. Meta-analyses state that selective DCT compared to blanket DCT results in increased post-calving IMI risk, but if all of the DCT-untreated, healthy cows in the trials have been receiving ITS at dry-off, the evidence for this difference seems lacking (Robert et al., 2006; Halasa et al., 2009b; Winder et al., 2019a; b; Kabera et al., 2021b). Several experimental trials conclude that selective DCT had little to no negative impact on postpartum udder health (Bradley et al., 2010; Rajala-Schultz et al., 2011; Cameron et al., 2014, 2015; Vasquez et al., 2018; McParland et al., 2019; Rowe et al., 2020b; a), but the opposite results exist as well (Ward and Schultz, 1974; Schukken et al., 1993; Berry and Hillerton, 2002a; McDougall, 2010; Scherpenzeel et al., 2014).

One Dutch cohort study has reported that DCT treatment with or without ITS raised the odds for low test-day SCC after calving (Vanhoudt et al., 2018). Consistently, Study II showed that the first test-day SCC ≥200,000 cells/mL after calving was less likely, if a cow was on a blanket-DCT farm, when compared with a cow on a selective-DCT farm. Confounding bias may play a part, because potentially certain types of producers are more likely than others to use blanket DCT and to implement other management practices that may also affect first test-day SCC. However, udder health during the preceding lactation was evidently associated with udder health after calving. Based on Study III, DCT reduced post-calving SCC during the first half of lactation when compared to SCC in untreated cows, but at the same time, higher SCC near dry-off correlated with higher post-calving SCC. In agreement, a US study found that DCT-treated high-SCC cows had a higher post-calving SCC than did untreated low-SCC cows, whereas DCT-treated low-SCC cows had lower post-calving SCC than did untreated low-SCC cows (Rajala-Schultz et al., 2011).

According to experimental trials, postpartum milk yield does not differ between selectively DCT-treated and untreated low-SCC cows (Rajala-Schultz et al., 2011; Cameron et al., 2015; Vasquez et al., 2018; Rowe et al., 2020b). McParland et al. (2019) reported that low-SCC cows treated with both antibiotics and ITS at dry-off produced 0.67 kg/day less milk across the whole subsequent lactation compared with the milk yield of low-SCC cows treated with ITS solely, the result thus being in favor of selective DCT. This difference in yield between the two groups was not observable during the first 35 DIM or the first 120 DIM after calving, although it would be expected to detect the potential effect of DCT specifically in early lactation. Thus, the yield difference might have been due to DCT-independent causes.

To our knowledge, Study III may be the first observational study to compare yield differences between DCT-treated and untreated cows on farms that routinely used selective DCT. Results indicated that the difference in daily milk yield between DCT-treated and untreated cows decreased as test-day SCC near dry-off decreased, and vice versa. As test-day SCC near dry-off increased, daily yield difference between DCT-treated and untreated cows increased. A missed DCT treatment led to an unwanted effect on milk yield and SCC during the first half of lactation. These results emphasize the significance of accurate selection of cows to be treated.

6.4 Preceding lactation and nonlactating period

Apparently some high-SCC cows suffer from chronic or recurrent mastitis, and receiving antibiotics may perhaps only temporarily improve their condition. On the contrary, a cow with a healthy udder seems less likely to develop mastitis later on. Several research findings support these perceptions. Pantoja et al. (2009a) discovered that the odds of clinical mastitis within the first 120 DIM were 4.2 times as high (95% CI 1.8, 10.0) in quarters with at least one case of clinical mastitis during the previous lactation than in quarters without, although all cows studied received routine coliform vaccine, and all quarters received both DCT and ITS. A slightly older Australian study observed that cows infected in their preceding lactation contributed 76% of all IMI at the calving and almost 70% at the subsequent-mid lactation (Browning et al., 1994). Newman et al. (2010) revealed that DCT-treated infected quarters had significantly higher odds of having IMI after a dry period than did DCT-treated uninfected quarters, whereas the overall cure rate over the dry period was as high as 84%. Persistent infection in a quarter over a dry period appears to raise the odds of suffering clinical mastitis in early lactation compared to the odds of uninfected quarters (Green et al., 2002; Pantoja et al., 2009a).

Lipkens et al. (2019) reported that, based solely on their SCC measurements across the dry period, cows with a test-day SCC <200,000 cells/mL prior to and after the dry period have the lowest SCC throughout the following lactation, when compared to the SCC of cows with cured, new, or chronic infection. Furthermore, studies indicate that a higher test-day SCC prior to dry-off is associated with increased post-calving SCC and with increased odds of developing clinical mastitis (Green et al., 2007, 2008; Whist and Østerås, 2007; Pinedo et al., 2012; Henderson et al., 2016; Gott et al., 2017; Vanhoudt et al., 2018). In agreement, Studies II and III determined that higher long-term test-day SCC and last test-day SCC during the preceding lactation correlated with higher SCC during the subsequent lactation. The cows with long-term high SCC during the preceding lactation were also more likely to be treated for mastitis at the beginning of the following lactation. Cows suffering either from chronic or recurrent mastitis elevate the infectious pressure within a herd. Due to the poor treatment response, antibiotic treatment during lactation is an unsustainable and non-profitable option for the management of such cows (Gussmann et al., 2019a; b).

Based on a recent survey, Dutch dairy farmers considered that reduced milk yield at dry-off, in addition to optimal hygiene, is an important management factor for the success of selective-DCT practice (Krattley-Roodenburg et al., 2021). Gradual milk cessation is a routine management practice on virtually all Finnish farms, and a typical yield at the last milking is less than 15 kg (Vilar et al., 2018). Despite the yield decrease before dry-off, Studies II and III found that a higher daily yield near dry-off was related to higher SCC after calving, which aligns with earlier findings (Green et al., 2008; Madouasse et al., 2012; Henderson et al., 2016; Gott et al., 2017). In contrast to our research, previous studies have been performed in herds using the blanket-DCT approach. Similarly, if milk yield at the point of dry-off increases, IMI shortly after calving seems to be more common (Oliver et al., 1956a; Dingwell et al., 2004; Rajala-Schultz et al., 2005; Odensten et al., 2007; Newman et al., 2010), with only a few studies reporting otherwise (Natzke et al., 1975; Gott et al., 2016). Probable explanations for the influence of end-lactation milk yield on postpartum udder health are that high-yielding dairy cows have an increased tendency to leak milk (Schukken et al., 1993; Tucker et al., 2009) and that they more often have deficient teat-canal closure after dry-off (Dingwell et al., 2004).

Green et al. (2007) observed that 305-day yield and the last test-day milk yield prior to dry-off, although associated with post-calving SCC, were not associated with rate of clinical mastitis during the first month after calving. On the contrary, Study II indicated that a high milk yield in late lactation raised the likelihood for mastitis treatment during the first month after calving. In addition to the late lactation milk yield, our results indicated that higher milk yield also in other phases of lactation was associated with higher post-calving SCC and higher odds of mastitis treatment. This may have been a consequence of the increased susceptibility of high-yielding cows to production diseases such as mastitis (Ingvartsen et al., 2003; Dobson et al., 2007; Martin et al., 2018). The downside to this issue is that mastitis and other production diseases reduce milk yield (Rajala-Schultz et al., 1999; Bareille et al., 2003; Gröhn et al., 2004). The present results correspondingly showed that post-calving mastitis treatment and higher post-calving SCC were associated with lower post-calving milk yield.

The usual cause of a lactation lasting longer than optimal is delayed conception, which is a common problem in high-yielding cows (Dobson et al., 2007; Bedere et al., 2018). Similarly, the current results show that a longer preceding lactation was associated with higher milk yield in the following lactation. Milk yield of dairy cows has rapidly increased during recent decades due to efficient breeding and improved farm management. As a disadvantage, the fertility of high-yielding dairy cows has declined along with their steadily increasing milk yield (Royal et al., 2000; Dobson et al., 2007). Additionally, high-yielding cows show a decrease in body-condition score in early lactation and are more susceptible to production diseases, which in turn further impairs their reproductive performance (Butler, 2003; Dobson et al., 2007; Bedere et al., 2018). Study II suggested that a longer preceding lactation seems to raise the odds for a high SCC on the first test day after calving, and this finding aligns with previous research findings (Henderson et al., 2016). Study III indicated that, during the following lactation, length of preceding lactation was associated only with yield and not with long-term SCC.

Whereas the typical dry period length is around 40 to 60 days, dry-period length in Studies II and III was limited to 30 to 90 days. Dry-period length was not associated with the udder health indicators. This finding agrees with the conclusions of the van Knegsel et al. (2013) meta-analysis. However, a dry period of more than 30 days was associated with increased daily yield during the first half of lactation, when we limited the maximum dry-period length to 90 days. Earlier research reported that after a 30-day dry period, yield is lower than after a 60-day dry period (Church et al., 2008). That result and our findings parallel the conclusion that shortening the dry period to under 40 days likely reduces milk production, and thus highlight the essential requirement of mammary-gland regeneration during the dry period (Swanson, 1965; Coppock et al., 1974; Hurley, 1989; Capuco and Akers, 1999).

6.5 Selection of cows for treatment

The most complex part of implementing selective DCT is to select cows that need the antibiotic treatment so that the labor is sufficiently cost-effective and accurately performed even in large herds. Compared to DHI-derived composite SCC, a quarter-level SCC would be more accurate, but is not usually readily available. On Finnish farms, the decision-making includes assessing udder health history and covers both subclinical and clinical mastitis (Vilar et al., 2018). The recommended two main indications for DCT are high SCC, especially near dry-off and typically in more than one measure, and clinical mastitis during the preceding lactation. SCC history is based on DHI measurements, on AMS information, on California mastitis testing, or is based on a combination of these. Sending quarter milk samples for microbiological analysis is a common, long-standing practice in Finland (Espetvedt et al., 2013; Rajala-Schultz et al., 2021). Thus, microbiological analyses of presumably infected quarters often supplements other udder-health information and supports treatment decisions as well as DCT-product choices (Vilar et al., 2018).

Clinical mastitis history combined with a composite SCC threshold above or below 200,000 cells/mL at least once during the last three months prior to dry-off is a suitable strategy for categorizing cows as either DCT-treated or untreated (Torres et al., 2008; Vasquez et al., 2018). Recently, Kabera et al. (2021a) estimated diagnostic test accuracies and determined that the lower SCC threshold could be 100,000 cells/mL in primiparous cows and 200,000 cells/mL in multiparous cows. Results indicate that with these separate thresholds, using only the most recent test-day SCC was sufficiently accurate. However, quarter-level bacteriological milk culture improved the accuracy and reduced antibiotic use. It appears that the farms we observed followed, at least partially, selection criteria similar to those described in experimental studies. The proportion of preceding-lactation mastitis treatments and high-SCC cows in Study III was larger among DCT-treated cows than among DCT-untreated cows. Based solely on mastitis-treatment records, Finnish farmers' selection criteria seem to be optimal, because the post-calving proportions of mastitis treatments between DCT-treated and -untreated cows during the first half of lactation were similar. The proportion of DCT-treated cows in Study III was equivalent to the proportion of cows with SCC ≥200,000 cells/mL near dry-off in Studies II and III. However, our observational data comprised also DCT-untreated cows having a high SCC on the last test-day prior to dry-off, and based on the results, these cows would have benefited from the medication.

Presumably, lower SCC thresholds could facilitate farmers' switching from blanket DCT to selective DCT. The SCC thresholds of the Dutch guidelines are 50,000 cells/mL for multiparous cows and 150,000 cells/mL for primiparous cows ≤6 week before dry-off (Vanhoudt et al., 2018). Many farmers, however, are apparently unaware of these national guidelines, although their standard practice is selective DCT (Krattley-Roodenburg et al., 2021). Like Finnish farmers, Dutch farmers have considered DCT to be appropriate for low-SCC cows with clinical mastitis or with high SCC in their preceding lactation (Krattley-Roodenburg et al., 2021). Less commonly described reasons for DCT were old age, milk leakage, and high milk yield (Krattley-Roodenburg et al., 2021). Most of the Swedish selective-DCT farms selected cows for treatment using SCC at the last milking, clinical mastitis history, and Swedish udder health class, which is calculated from the composite SCC at two to three consecutive milk recordings (Persson Waller et al., 2021). Like Finnish farmers, Swedish farmers seem to take milk samples at dry-off prior to their treatment decision, although in Sweden the sampling did not seem to be quite as common as in Finland (Persson Waller et al., 2021).

Rowe et al. (2020b) reported that when selection in their experimental trial was based on microbiological culture, the proportion of selectively DCT-treated quarters ranged in herds from 32% to 62%, and when selection was based on SCC and mastitis history, the proportion ranged from 19% to 68%. Based on Bayesian estimation, the estimated median herd-prevalence of IMI that should be DCT-treated at dry-off was 16.2% (95% CI 11.0, 22.7) in herds with an average bulk-tank SCC of less than 250,000 cells/mL (Kabera et al., 2021a). Based on economic estimation, Hommels et al. (2021) suggested that the approximate treatment percentage for primiparous cows could be 30% and for multiparous cows 88%. Study III determined that the median herd-proportion of DCT-treated cows on Finnish selective-DCT farms was 12.5% (95% CI 3.3, 33.3). This treatment prevalence is similar to these recent estimates and indicates that the number of animals treated may have been quite ideal. Because the prevalence of subclinical mastitis varies, the percentage of treated cows between farms should be expected to vary, as well.

6.6 Strengths and limitations

Observational studies do not allow the drawing of any causal inferences, but instead only suggest their existence. Experimental studies are therefore necessary to definitively determine the causal relationships. The main advantage is, however, that observational studies describe the phenomena the way that they occur in their natural settings. Correct understanding of the advantages and disadvantages of selective DCT requires observational research data from commercial farms that routinely use selective DCT.

Selection bias occurs when the survey sample does not accurately represent the population. If selection bias was strong on the survey-derived farms included in Studies I−III, results may be less generalizable for all Finnish dairy herds. The comparison of our data with general data showed only small discrepancies between farms studied and Finnish farms in general, and the farm characteristics indicated that the responding farms were representative of the Finnish dairy industry at the time of the study.

Although the DHI data is a useful and valued information source for farmers and dairy experts, it is secondary data not originally recorded for scientific purposes. Extra work went into minimizing any inaccuracies and errors. Despite the disadvantages of utilizing secondary data, our observational research allowed numerous observations from various herds over a wide geographical area.

Imbalance between the various DCT groups may have limited the power to identify statistically significant differences between them in Studies I and II. Because the selective DCT was the prevailing management practice in Finland, the small group size in other DCT-practice groups reflected Finnish antibiotic policy and management practices. Studies do not report any post-hoc power calculations, as the literature shows that post-hoc power calculations are generally not useful and provide no additional insights after CI calculations (Hoenig and Heisey, 2001; Dohoo et al., 2014).

Study I described associations, and although its modeling work did not try to take into account confounding, most of the potential confounders between the DCT approach and SCC relationship or the DCT approach and milk-yield relationship were included in the models. Moreover, no intermediate variables appeared to be included. Thus, the presented estimates are, perhaps, not that far from the actual causal relationship.

A possible cause for misclassification bias in the longitudinal analyses of Study I is that a portion of the farms reported a shift in their DCT practice during the five-year investigation period. Duration of a farm's DCT approach was, however, tested as a covariate in all longitudinal analyses, and showed no significant effect on the fit of the models. Although the shift in management did not affect cross-sectional analyses, the results of cross-sectional analyses compared with longitudinal analyses were similar for the DCT approach.

The main limitation of Study II is that, instead of cow-level DCT treatment records, herd-level information about the DCT practice was the main explanatory covariate in the models. Although the proportion of treated cows on selective-DCT farms varied, the majority of these farms treated only up to one-fourth of their cows at dry-off. This approximation deviated only slightly from the DHI-based treatment records in Study III.

Study III did not include any cow-level information on whether ITS were administered at dry-off to a cow either alone or concurrently with antibiotics. However, we were able to report that approximately one-third of farms utilized ITS for their cows at dry-off during the investigation period. Moreover, in Study III, the need for DCT was based on SCC prior to dry-off and preceding lactation mastitis treatment. The actual IMI status of the cows based on bacteriological results may have been known to the producers but not to the researchers. However, often the treatment decision on farms is made based on SCC and mastitis history without knowledge of the milk-sample result.

Boxplots in Study III show visually the collinearity between last test-day SCC and DCT. One would have thought in advance that there would have been a stronger relationship between these two variables. Nevertheless, the data included also a considerable number of DCT-untreated cows with a composite SCC ≥200,000 during late lactation. Collinearity leads to increases in standard errors and therefore to loss of significance. However, in our study the collinearity between last test-day SCC and DCT was at a tolerable level and did not cause loss of significance for these two predictor variables.

Study I is an ecological study considering the association between herd-level exposures and herd-level outcome. Study II is an individual-level study examining the effect of a contextual herd-level variable. Finally, Study III is an individual study describing associations between individual exposures and individual outcomes. Based on Study I alone, one cannot draw conclusions about individual cow-level associations, whereas based on Study III alone, one cannot draw conclusions about the effect on subsequent herd parameters of applying a DCT approach to a herd. There is a richness in combination of study designs in this thesis, and this is its important strength.

6.7 Future implications

Hopefully, the successful implementation of restricted antibiotic strategy and selective DCT in dairy livestock in the Nordic region will encourage other countries to gradually reduce antibiotic use in livestock, and thus meet the constantly increasing demands for ethical and sustainable food production (Boogaard et al., 2011; Laxminarayan et al., 2013; McEwen and Collignon, 2018). The Nordic countries serve as a good example of how the combination of strict legislation and comprehensive recommendations can lead to prudent use of antibiotics in livestock without compromising animal health. The current good situation is highly appreciated in Finnish society as well as among producers, and this serves as an additional incentive. Compliance with the recommendations is due to willingness, trust, and cooperation among all the stakeholders. On the other hand, as Nordic dairy farming continues to restructure and increase in herd sizes, maintaining the current low sales of antibiotics will require optimal farm management, effective advising, and careful monitoring. Education, information exchange, and maintaining trust are essential, and they require continuous, versatile cooperation.

It would be desirable for microbiological analysis of milk samples to become common practice also outside the Nordic region. Regular and comprehensive microbiological quarter-milk analyses provide crucial information on the main causal pathogens, on antimicrobial susceptibility, and on mastitis-treatment effectiveness in herds (Ruegg, 2018; Gussmann et al., 2019a; b). Identification of specific infection pathways on a farm require information about the known pathogens and the onset of infections in relation to lactation cycle, cow characteristics, and season. Bacteriologic diagnosis leads to targeted and more effective mastitis prevention and should therefore be worth the cost. Moreover, microbiological analysis of milk samples is achievable as a tool to control the spread of pathogens that behave contagiously and have a significant effect on cow health, ones such as *Strep. agalactiae* and *Staph. aureus*. PCR allows even the rapid and reliable diagnosis of *Mycoplasma bovis* infection from milk samples.

Despite extensive research on selective DCT, a cost-effective and accurate method for selecting cows in need of treatment is still a central research topic. It remains uncertain whether the commonly used composite SCC threshold of 200,000 cells/mL is optimal for selection of cows to be treated, and whether primiparous cows and multiparous cows should have separate thresholds (Dufour and Dohoo, 2012; Kabera et al., 2021a). After the current work, our ongoing experimental field-trial aims to evaluate variation in cure rates and new infection rates between selectively DCT-treated and untreated cows over the dry period. This trial is taking into account differing cow characteristics and aims to utilize automatically collected data from AMS. Special emphasis is on cows with a last test-day SCC of between 100,000 and 250,000 cells/mL.

During the past five decades, milk yields worldwide have steadily increased due to efficient breeding and improved farm management. Although research shows that milk yield at dry-off influences udder health on subsequent lactation, the actual evidence-based optimal milk yield at dry-off, along with applicable guidelines for farmers, remains unresolved. As milk yield increases, milking speed potentially has more effect on farm labor costs. The relationship between milking speed and mastitis susceptibility is multifactorial and complex, thus making this an intriguing topic for future research. Favoring a fast flow-rate in breeding is likely to affect teat anatomy and may result in increased mastitis susceptibility (Marete et al., 2018). Slow milking speed probably affects mastitis incidence as well, and therefore the optimal milking speed is assumed to be intermediate. Evidence is almost non-existent as to the ideal milking speed and the relation of milking speed to mastitis susceptibility during the nonlactating period.

7 CONCLUSIONS

Due to ongoing restructuring of the Finnish dairy industry, farming facilities, average SCC, and milk production vary extensively across Finnish dairy farms. Therefore, assessing and advising on optimal drying-off management should be a farm-specific routine performed by experts in the dairy field.

The following conclusions are based on the results of Studies I−III:

1. Herd-level DCT strategy was not distinctly associated with herd-average SCC and annual milk production on Finnish farms. Guidelines for the prudent use of antibiotics and prevailing selective DCT practice did not hinder dairy farms from maintaining low average SCC and good milk production.

2. Despite the farm's DCT management practice, annual milk production increased over time, while herd-average SCC seemed to remain quite constant. The variability in herd-average SCC and milk production across the various herd-level DCT approaches seemed low over time, and most of the variability was between farms.

3. Blanket DCT was associated with lower post-calving SCC, which indicates that DCT is an effective mastitis control measure. Risk factors associated with high post-calving SCC were high parity, high preceding-lactation average SCC, and high milk yield near dry-off. Risk factors associated with early lactation mastitis treatment were high preceding-lactation milk yield and high preceding-lactation average SCC. Cows with high milk yield, especially near dry-off, and cows with persistently high SCC thus require attention when farmers assess the next lactation of a cow and make treatment decisions at dry-off.

4. The majority of the conventional Finnish selective-DCT farms medicated with antibiotics a maximum of a one-third of their cows at dry-off.

5. DCT-untreated cows with a high end-lactation SCC were likely to experience udder health problems during subsequent lactation. Composite SCC prior to dry-off affected milk yield differently in DCT-treated cows than in untreated cows, and a higher SCC prior to dry-off led to an increased difference in yield between treated and untreated cows. Contrariwise, as SCC before dry-off decreased, yield difference between DCT-treated and untreated cows decreased. DCT reduced SCC during the following lactation. Risk factors associated with higher post-calving SCC included a high late-lactation SCC and lactational mastitis treatment. A missed DCT treatment for a high-SCC cow had an adverse effect on subsequent lactation milk yield and SCC, which emphasizes the importance of accurate selection of cows to be treated.

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ORIGINAL ARTICLES