Dry-off treatment of dairy-cows : methods to guide targeted antimicrobial use

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Abstract

One of the most common indications for the use of antimicrobials in dairy cattle is the administration of long-acting antibiotic products for drying off. Antibiotic dry cow therapy (ADCT) has proven itself over decades to be an efficient tool to cure existing udder infections and to reduce the number of new infections in the following lactation. However, from a One Health perspective, the routine use of antibiotics is controversial. As the use of antibiotics increases the risk of selecting antimicrobial resistant bacteria, the administration of antibiotic dry cow tubes should be restricted to cows with a proven infection with known mastitis pathogens or those at an increased risk of a new infection during the dry period.

As part of the D4Dairy research project, a cohort study was carried out to investigate whether the selective use of ADCT could lead to a reduction in the total antimicrobial use, without negatively influencing the udder health of the dairy herd. To determine the frequency of udder infections prior to dry-off, as well as the frequency of new infections, bacteriological milk cultures were carried out before dry-off and at the beginning of the subsequent lactation.

The results of the bacteriological milk cultures at the time of dry-off collated during the D4Dairy field study were used as ‘gold standard’ to develop a practical and cost-effective model for an animal-specific decision-making tool for selective ADCT. Therefore, the diagnostic results were combined with the data collected via the national milk monitoring scheme and the Austrian health monitoring program. Two statistical model approaches (Generalized Estimating Equations (GEE), Random Forest) were applied to predict the diagnostic result on animal level. The agreement between the predictions and the observed result of the bacteriological milk culture was evaluated for those two models, as well as for the selective ADCT recommendations carried out on farm in the D4Dairy field study. The best predictive performance was obtained using a random forest model. However, the test set was rather small. To validate the results, a larger amount of data from routine recordings from the Austrian milk performance recording system was used to train and test the random forest.

Selective dry cow therapy (SDCT) based on herd- and cow-specific somatic cell counts have the potential to reduce antibiotic dry-cow treatments without increasing the risk of deterioration of the udder health status of a herd. With a statistical prediction model like random forest, the use of antibiotics could be reduced even further.

Keywords: targeted dry-off treatment, antibiotic use, decision support, random forest, statistical modelling.
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Introduction

The use of antibiotics at the time of drying off dairy cows has been an integral part of udder health programs for decades. Antibiotic dry cow therapy (ADCT) is still a standard procedure of good agricultural practice on dairy farms today.

Concerns exist that uncritical use of antibiotics in livestock will reduce the effectiveness of antibiotics in humans due to the emergence of multi-resistant bacteria, which are increasingly being detected in humans and in the environment. The use of antibiotics as a management measure when drying off dairy cows is therefore subject to growing criticism.

The pattern of pathogens causing mastitis in dairy cattle has changed in recent years. *Staphylococcus aureus* has replaced *Streptococcus agalactiae* as the most common problem species. Antibiotic dry cow treatment can be effective in *Staphylococcus aureus* infected cows, but the cure rates vary considerably (Barkema *et al*., 2006). Udder infections with Enterobacteriales and *Streptococcus uberis* occur predominantly during lactation and require treatments in the acute phase of the disease (Pinzon-Sanchez and Ruegg, 2011). Antibiotic dry cow treatment should be limited to infected cows and to cows at high infection risk. A systematic use of antibiotics for all cows for dry cow treatment (blanket dry cow treatment, BDCT) is rarely justified. The selective use of antibiotics for drying off (selective dry cow treatment, SDCT) is necessary to avoid losses in milk production due to udder diseases (Cameron *et al*. 2015, Niemi *et al*. 2022).

SDCT is based on the selection of infected cows and cows whose udder health is at risk, with the aim of ensuring the highest possible udder health while at the same time keeping the use of antibiotics as low as possible. Various herd-related and cow-related parameters are used for this selection. In addition to high sensitivity and specificity of the selection criteria used for SDCT, the selection methods must also be practical and financially affordable (McCubbin *et al*. 2022). The basic requirements for successfully implementing an SDCT concept are, in addition to a low bulk milk somatic cell count, a low prevalence of infections with udder-associated mastitis pathogens (Cameron *et al*. 2014), a low incidence of clinical mastitis, good hygiene management at the time of drying off, as well as the ongoing monitoring of the udder health status of the herd (Kabera *et al*. 2020, Santman-Berends, I. M. G. A. *et al*. 2020, Rowe *et al*. 2020a).

The aim of the study at hand was to validate an existing expert-knowledge-based method for SDCT (Biggs *et al*. 2016, Bradley *et al*. 2015, Lipkens *et al*. 2019) and to develop a data-based method to routinely identify animals with a high risk of developing an udder disease at the time of drying-off, for which ADCT is then recommended. A good validated dry-off strategy could thus minimize the antibiotic use while maintaining udder health.

Material and methods

Cohort study

As part of the D4Dairy research project “Measures to reduce antibiotic resistance”, a cohort study was carried out to investigate whether the targeted use of antibiotics for dry-off treatment could reduce overall antibiotic consumption without negatively affecting the udder health of dairy herds. The field study was set up in 31 dairy herds which were not randomly selected (Table 1). 16 herds (case herds) got monthly recommendations for each individual cow to use or not to use an antimicrobial dry cow treatment based on the calculated weighted somatic cell count of the total herd, the

Table 1. Herds characteristics of cohort study participants.

		Case	Control
Number of herds		16	15
Number of cows		1206	1056
Type of farming activity	Full-time	15	13
	Part-Time	1	2
Husbandry system	Freestall	16	14
	Tie-stall	0	1
Predominant breed		Simmental	Simmental, Holstein
Milking technique	AMS	3	3
	Heringbone	6	7
	Side-by-side	5	3
Antibiotic dry cow treatment	Blanket	0	7
	Selective	15	7
	Case-by-case basis	1	1

individual cow somatic cell count of the last two milk recordings before drying off, the lactation number (primiparous, multiparous) (Biggs *et al*. 2016). In 15 herds (control herds) the management of dry-off treatments was carried out as usual (blanket DCT, various SDCT methods). Bacteriological culture of milk samples was conducted before dry-off, after calving and for every mastitis case. Data on antimicrobial use with respect to dry-off treatment were collated. Using this data the dry-off strategies were assessed using cure rate, new infection rate and antimicrobial use as outcome parameters.

Antimicrobial use

For the evaluation of the amount of antibiotics, which was used for antimicrobial dry cow treatment, the dosed based indicator TD (treatment days; Sanders *et al*. 2020) for the use of dry cow tubes was applied. The number of unit doses of antibiotics licensed for dry-cow therapy which were sold to the farmers during the study period was summed up and this figure was divided by the sum of days the cows were kept in the study herds during the study period and multiplied by 365. This number of treatment days for ADCT per cow per year was corrected by the calving interval and the replacement rate of heifers of the corresponding herd (Formula 1).

$$\#\boldsymbol{TD_{365}DCT} = \sum_{i=1}^{n} \frac{\#\,UD/udder\ _{(route\ intramam\,-\,DC)}\ in\ period\ P}{\#\,cow \cdot days\ in\ period\ P\ (days)} \times 365 \times \frac{calving\ interval\ in\ period\ P\ (herd,\ days)}{365} \times \left(1 + \frac{\#\,cow\ LN = 1 \cdot days\ in\ period\ P\ (days)}{\#\,cow \cdot days\ in\ period\ P\ (days)}\right)$$

Formula 1: **#TD$_{365}$DCT** (number of treatment days per cow per year for ADCT) = number of unit doses (UD) per udder given to any cow of a population within 1 year (1 UD = 4 injectors of an antibiotic licensed for intramammary use in dry-cow therapy).

Statistical modelling (data-based selection method)

A data-based, cow-specific dry-off recommendation should aim to provide antibiotics at dry-off only for cows that are infected with a mastitis pathogen or that are at increased risk of a new infection. The data collected in the cohort study was used to statistically model the result of bacteriological milk testing at the time of drying off, however only major mastitis pathogens were considered.

The binary diagnostic result (major / negative) was used as target variable for two statistical approaches. On the one hand a GEE (Generalized Estimating Equations) model with a logistic link function and an exchangeable covariance structure, accounting for similarities among cows and farms, was applied to a training data set (85 % of the observations), on the other hand a random forest model (Breiman, 2001) was trained, and both methods were validated on the same test set. Recordings from the national milk monitoring scheme and the Austrian health monitoring program (e.g. somatic cell count of the last three milk records before the date of the diagnostic test, mastitis diagnosis in the current lactation, somatic cell count at herd level) were used as explanatory (feature) variables in the two models.

For the random forest feature selection is implicitly included in building the different trees. A stepwise forward model selection (Hastie *et al*., 2001) procedure was used to select an optimal GEE model. Each feature was added to the model and the variable with the lowest Quasi-Likelihood Information Criterion (Pan, 2001) was selected in each step.

Predictions from those two models were compared with the observed diagnostic results for a test set that contained 15 % of the observations. Predictive performance was assessed by different performance measures: accuracy, sensitivity, specificity, and f1-score.

To compare the two data-based approaches with the method based on expert-knowledge (Biggs *et al*., 2016), the D4Dairy field study recommendations were evaluated for the same test set and the same performance measures were calculated. The data was split to ensure that any given animal was only observed in one of the two data subsets.

All statistical analysis were performed using the statistical software R, version 4.3.2 (R Core Team, 2023) and the packages geepack (Hojsgaard *et al*., 2006), ranger (Wright and Ziegler, 2017) and caret (Kuhn, 2008).

Extended data set

To validate the data-based decision approach, an extended data set, using bacteriological test data, milk performance data and herd health data from the Austrian cattle data network including 18,810 observations was provided.

Again, the data was split into a training set (85 %) and a test set (15 %), ensuring that an individual animal could only occur in one subset, and a random forest was tuned on the training set. Predictions from the random forest and the SDCT method (Biggs *et al*., 2016) were evaluated on the same test set using the same performance measures (accuracy, sensitivity, specificity and f1-score) as for the D4Dairy field study.

Results

Cohort study: Cure, new infections

Of 4,241 quarter milk samples taken before drying off 3,741 (88.2%) tested negative in the microbiological culture. In 240 (5.7%) of quarter milk samples a major pathogen (*Staphylococcus aureus*, Streptocooci, Enterococci, Enterobacteria, Trueperella) was detected. Interestingly Streptococci were the most common pathogen found in these samples, followed by Enterobacteria. The within-herd percentage of tested cows infected with a major pathogen before drying off varied between 0% and 57%.

The SCC at the last milk recording prior to calving in cows, which were infected with a major pathogen was - as expected – significantly higher than the SCC in cows, which were negative (not infected) in the bacteriological culture, but there was a not negligible overlap in individual cow somatic cell count data of major and not infected (negative) cows (Figure 1).

For 694 lactations the infection status before drying off (and within 100 days before the day of calving) and within 100 days after calving was evaluated. There were no significant differences between the groups of cows which were treated with an antibiotic at drying off and cows, which were not treated with an antimicrobial drying-off product regarding new infections after calving and persistent infections. Due to bacteriological testing of all cows without consideration of the udder health status, there were significantly more cows with no infection in the group, which were not treated with an antibiotic as well as significantly more cured cows in the ADCT-group (Table 2).

No significant differences between herds which received an individual cow recommendation for DCT (case herds) and herds which treated cows at drying off as usual (control herds) for any infection status could be proved. Significantly more cows were cured in the groups treated with an antibiotic (ADCT group) regardless of whether case- or control-herds, which is a clear indication for the effectiveness of antimicrobial dry cow therapy (Table 3).

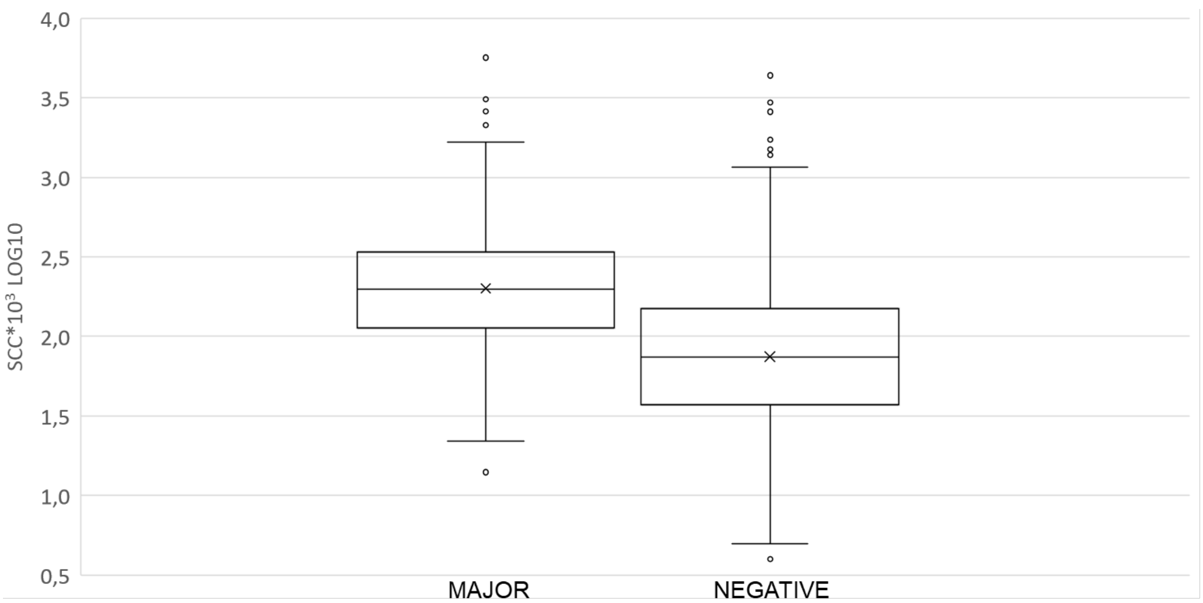

Figure 1. Individual cow somatic cell count (ICSCC) at the last milk recording prior to calving and status of intramammary infection (infected with a major pathogen = MAJOR or not infected = NEGATIVE).

Table 2. Evaluation of the drying-off strategy: cure rates, new infection rates.

Status of infection	Total		Dry cow therapy ADCT		Dry cow therapy no ADCT	
No infection	404	58%	215	50%	189*	73%
New infection	89	13%	47	11%	42	16%
Cure	171	25%	146*	34%	25	10%
Persistently infected	30	4%	26	6%	4	2%

* significant Pearson´s Chi-squared test

Table 3. Evaluation of the drying-off strategy in case-herds (individual cow recommendation for DCT) and control herds (DCT as usual): cure rates, new infection rates.

Status of infection	Total		Case herds ADCT		Case herds No ADCT		Control herds ADCT		Control herds No ADCT	
No infection	404	58%	80	47%	107	75%	135	51%	82	70%
New infection	89	13%	22	13%	24	17%	25	9%	18	15%
Cure	171	25%	58*	34%	10	7%	88*	33%	15	13%
Persistently infected	30	4%	10	6%	2	1%	16	6%	2	2%

* significant Pearson´s Chi-squared test.

Cohort study: Antimicrobial use for dry-cow treatment (ADCT)

The antimicrobial use for ADCT was higher in control herds compared to case herds (mean $\#TD_{365}DCT$ = 0,783 and 0,585 respectively). The difference of the means was significant (t-Test (mean) p = 0.043), but the medians were not (Mood´s Median-Test (median) p = 0.134). The most likely reasons for this „weak“ association are the relatively small number of study herds and the fact, that some kind of „selective“ dry cow treatment was implemented in most control herds as well.

Data-based selection method

Performance measures were evaluated for the GEE, the random forest and the applied recommendation (Biggs *et al*., 2016) on a test set containing 121 observations, of which 23 had a major pathogen test result in the bacteriological milk culture (Table 4). The GEE had the highest sensitivity, the random forest achieved the highest accuracy, specificity and f1-score. As data was imbalanced regarding the two outcome categories (major /negative) the f1-score provides a more reliable performance measure, especially compared with the accuracy.

Table 4. Comparison of predictions for a positive result of bacteriological milk tests before drying-off for the D4Dairy data set.

	Recommended ADCT (Biggs et al. 2016)	Generalized Estimating Equations*	Random Forest
Accuracy	0.752	0.719	0.876
Sensitivity	0.652	0.739	0.565
Specificity	0.776	0.714	0.949
F1-score	0.500	0.500	0.634

* A cut-off value of 0.19 was used to classify the odds predicted by the GEE model into positive bacteriological milk cultures or negative tests. This was determined using an ROC analysis.

Extended data set

The extended data set contained 59 % negative and 41 % major findings of the bacteriological milk cultures. The test set consisted of 2,838 observations (1,167 with major finding). Performance measures were evaluated for the SDCT method (Biggs *et al*, 2016) and the random forest model (Table 5). Due to the superior predictive performance of random forest, the GEE model predictions for the extended data set were not included.

Table 5. Comparison of predictions for a positive result of bacteriological milk tests before drying-off for the extended data set.

	Recommended ADCT (Biggs et al. 2016)	Random Forest
Accuracy	0.645	0.700
Sensitivity	0.593	0.519
Specificity	0.681	0.827
F1-score	0.579	0.588

Discussion

Udder infections can heal during the dry period. Cure was more common in cows that were treated with an antibiotic at drying-off than in untreated cows, which is in accordance with other authors (Halasa *et al*. 2009a, Halasa *et al*. 2009b).

The selection of cows for ADCT did not lead to more new infections compared to herds that got no recommendation for SDCT. No significant difference in new infections could be proved between the group of cows that received ADCT and the group that did not as well as between case- and control-herds.

The detection of udder infections before drying-off using bacteriological milk testing offers a higher level of reliability for selecting cows for ADCT than indirect selection methods (Rowe *et al*. 2021). However, selection based on bacteriological milk tests involves significantly more effort, time, materials and costs (Rowe *et al*. 2021, Rowe *et al*. 2020b) than selecting cows based on individual milk cell counts.

The diagnosis of udder infections prior to dry-off by bacteriological milk culture provides greater diagnostic certainty than indirect methods to select cows for ADCT based on individual somatic cell counts (SCC), but is associated with significantly higher levels of labour, time, materials, and overall costs.

When setting a somatic cell count threshold for ADCT, it must be noted that with lower limits more cows that are not infected are treated with an antibiotic (Scherpenzeel, C.G.M. *et al*. 2016). In our study different thresholds were used for first-lactating cows (lower threshold value) and for cows in further lactations (higher threshold value) (McCubbin *et al*. 2022, McDougall *et al*. 2021). Additionally different thresholds depending on the calculated weighted somatic cell count of the total herd were used (Biggs *et al*., 2016) to take the increasing risk of new infections due to a high prevalence of chronic udder infections into account. However, the comparison of the prediction models demonstrates, that the selection for ADCT based on herd-, cow- and lactation-specific cell count thresholds alone recommends the use of antibiotics more often than is actually necessary.

The relationship between udder infections, the results of milk performance testing, the lactation age of the cows, and udder health indicators of a herd is complex and could not be well explained with a GEE model because no interactions between individual factors as well as non-linear combinations of the features were taken into account in a first step. With a statistical prediction model such as random forest, an even more precise selection of cows for ADCT could be made, but the data set used was rather small. Model comparisons are more reliable when a broader test data set can be used. Therefore, the random forest model was trained with an extended data set, using bacteriological test data, milk performance data and herd health data from the Austrian cattle data network.

The extended data set resulted mostly from routine recordings without a project setting on the farm. Consequently, in most cases bacteriological milk tests were run only in suspicious cases. Therefore, the results of the bacteriological milk tests were more balanced than in the D4Dairy observations, where each cow had to be examined by bacteriological milk tests. Differences in accuracy and f1-score were smaller for this data set, however they still were better for the random forest. Sensitivity was slightly better for the applied SDCT method, whereas the specificity was clearly higher for the random forest approach. This underlines the conclusion that ADCT was recommended more frequently for the applied SDCT method (Biggs *et al*., 2016), than a bacteriological milk test would have implied. Random forest results would have recommended less antibiotic use. However, due to the marginally lower sensitivity, a few more infections would have been missed compared to the SDCT method (Rowe *et al*. 2021).

All presented methods are based on herd- and cow-specific parameters like somatic cell count and lactation period, whereas the random forest considers much more variables up to three time points before time of drying-off. Consequently, it is possible to get more differentiated recommendations by using the random forest model.

Conclusions

In farms that do not use microbiological milk testing on a regular basis before drying off, the individual somatic cell counts of the last milk recordings before dry-off and the lactation number (first-lactating cows, cows in subsequent lactations) are the key decision-making parameters for the selection of cows for ADCT. The use of antibiotics for drying off can be reduced using a SDCT method based on the weighted somatic cell count of the herd, the cell counts of the individual cows before drying off and the lactation age. The SDCT procedure used in this study did not worsen udder health. With a statistical prediction model like random forest, the use of antibiotics could be reduced even further. The results of this study can be used for the development of a dry cow treatment decision tool that could be integrated into a dairy herd management software. This tool is intended to support farmers and veterinarians in the widespread implementation of SDCT procedures.

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