Prophylactic Effects of Two Selective Dry Cow Strategies Accounting for Interdependence of Quarter

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ABSTRACT

Infusion of a long-acting antibiotic preparation at drying off in dairy cows as a prophylactic therapy is usually recommended for all quarters where it is in use. Studying the effectiveness of such treatment using quarter as the unit of analysis assumes that each quarter within a cow has a risk of being infected independent of the other quarters of the cow. Failure to account for interdependence of quarters within a cow may lead to inaccurate variance estimates and errors in assessing treatment effects. Data from two trials assessing different dry-cow strategies were examined for interdependence of infection between quarters. Logistic regression with a variance inflation factor or a multilevel analysis was used to assess the effect of antibiotic and internal teat-sealant dry cow strategies. Parity and infection status at drying off were covariates in the analysis. Interdependence of the risk of quarter infections within control-group cows was demonstrated in both dry-cow antibiotic and teat-seal trials. However, cows that received either of these treatments did not demonstrate interdependence. Treated quarters in both trials were 3.0 times less likely to acquire a new infection at calving compared with the untreated controls. Quarters in cows of parity 3 or greater were also at an increased risk in the antibiotic treatment trial. In both trials, quarters with either *Corynebacterium* spp. or coagulase-negative staphylococci infections at drying off had an increased risk of a new intramammary infection at calving. This study has demonstrated the beneficial and comparable effects of antibiotic and teat seal dry cow strategies; both decreased the risk of intramammary infection at calving. The application of dry-cow strategies at the cow level and not the quarter level is also supported. (**Key words:** antibiotic, internal teat sealant, intramammary infection, Orbeseal)

Abbreviation key: VIF = variance inflation factors.

INTRODUCTION

Although dry-cow therapy as a prophylactic control measure is not usually carried out on an individual quarter basis within a cow, it has been recommended as a therapeutic measure for individual quarters within a cow (Østerås and Sandvik, 1996). Categorical data on response to treatment when the cow is the unit of treatment can be analyzed by several methods, but it has to be clear whether the cow or the quarter is the experimental unit of analysis. Using quarter as the experimental unit assumes that each quarter within a cow has a risk of being infected independent of the other quarters. It may be suggested that the quarters within a cow are more alike in susceptibility to clinical mastitis in lactation than would be expected based on independence of quarters (Swenson, 1979; Batra et al., 1977; Adkinson et al., 1993; Barkema et al., 1997). However, such calculations have not been made for cows during the dry period.

Any deviation from the expected frequencies for quarter infections within cow, if they are not independent, could be attributed to common risk factors, such as mammary gland conformation, immune competency, or exposure of the quarter due to close proximity to other infected quarters. In most studies in which only infected quarters were treated at drying off and uninfected quarters were left untreated, it has been demonstrated that significantly more new infections have occurred in the previously uninfected quarters (Browning et al., 1990; Browning et al., 1994; Ward and Shultz, 1974; Williamson et al., 1995). This has led to the recommended treatment of all quarters of those cows with one or more quarters infected (Ward and Shultz, 1974; Browning et al., 1990; Browning et al., 1994; Williamson et al., 1995). Knowledge of whether quarter independence of intramammary infection occurs over the dry period could influence how dry cow therapy is best applied (either as a prophylactic or therapeutic measure).

In this paper, data from two different dry cow strategy trials were analyzed (Berry and Hillerton, 2002a,b). Since the objectives of the studies were to test treatment efficacy at the quarter level and since treatment was

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applied at the cow level, some statistical control was required. Ignoring quarter interdependence could lead to an underestimation of the variance and an associated increase in Type 1 error (i.e., the probability of declaring that a significant difference existed when in reality it did not). Many statistical software packages contain procedures such as Glimmix in SAS (SAS Inst., Cary, NC) or MlwiN in Stata (Stata Corp., College Station, TX) that enable multilevel analyses, thus accounting for clustering in datasets. The size of the dataset and the number of observations within the strata may, however, limit these procedures and may lead to computational problems and nonconvergence (Zadoks et al., 2001).

The data were first analyzed for evidence of clustering of intramammary infection within the cow. Using this information, the protective effect of the two dry-cow strategies was then quantified. Variance inflation factors (VIF) may be used to correct for effect estimates (interdependence between observations) using adjustment for intracow correlation (the strength of the clustering) (Donald, 1993; 1994; Barkema et al., 1997). This method is compared with the Glimmix macro of SAS (Version 8.2) where the strata-specific variance is directly estimated and then used to calculate the correlations.

MATERIALS AND METHODS

Data Sets

Two independent studies were conducted to evaluate two different strategies for the prevention of new intramammary infection in dry cows: 1) selective dry-cow antibiotic therapy (Cepravin, Schering-Plough Animal Health, Uxbridge, U.K.), where cows were randomly allocated to either a dry-cow antibiotic treatment of all quarters or were left untreated (Berry and Hillerton, 2002a); and 2) selective teat sealer, where cows were chosen at random either to receive an internal teat sealant (Orbeseal, Pfizer Inc., Sandwich, U.K.) infused into all quarters or were left untreated (Berry and Hillerton, 2002b).

Treatments in both trials were allocated at the cow level, but infection status at drying off and calving was determined at the quarter level.

A single 15-ml foremilk sample from each teat was collected according to IDF (1981) recommendations. Samples were taken 1 wk prior to drying off, at drying off, within 24 h of calving where possible, and 7 to 14 d after calving. Extra samples were taken if any of the previous samples were not suitable, or for confirmation of infection. Most cows had at least one extra postcalving sample taken. Sampling at predrying-off, drying off, and postcalving was usually on the same day each

week and samples were stored at 4°C and assayed within 24 h of collection. Microbiological examination was carried out according to IDF (1981) recommendations. An infection was defined as isolation of the same pathogen in two consecutive samples or two out of three samples, or isolation of a pathogen from a quarter with signs of clinical mastitis (IDF, 1981).

The antibiotic and teat sealant trials included cattle on four and seven farms, respectively. For the current study, analyses were conducted only on the results from the cows in two of the herds that were used in both of the earlier trials. Both of these herds were located at the Institute for Animal Health (Compton, U.K.) and managed as commercial herds. They also represented the largest portion of the sample size in both of the trials and were under common management as dry cows. All cows in these herds were used and these cows were either uninfected or infected only with *Corynebacterium* spp. or CNS. This in contrast to the other herds where a proportion of cows were infected, primarily with *Staphylococcus aureus*, or only a selected proportion of the herd was used. Use of data from these other herds could have introduced other potentially confounding factors into the analysis. Any cows with fewer than four functioning quarters were excluded from the quarter interdependence analysis.

Statistical Analyses

Quarter distribution. It has been reported from previous analyses on clinical mastitis in lactation, that infections were more likely to occur in the rear quarters than in the front quarters (Batra et al., 1977; Adkinson et al., 1993; Barkema et al., 1997). However, this varies according to pathogen. For example, summer mastitis is more likely to occur in front quarters (Hillerton et al., 1995). To determine that infections at calving were not occurring more frequently in one quarter, infection status at calving with respect to treatment group by quarter was analyzed with the GLM procedure in the Minitab statistical computer package (release 12.21, Minitab Inc., State College, PA) using the following model:

$$IC = Q + TX + Q \times TX$$

where IC is infection status at calving, Q is quarter, and TX is treatment group, $Q \times TX$ is the interaction between quarter and treatment.

Quarter interdependence. The prevalence of intramammary infection at calving was categorized according to the number of infected quarters within a cow and compared with the expectations based on the assumption that intramammary infections of quarters

were independent. The expected number of infected quarters per cow was determined by a binomial probability distribution using the following formula (Barkema et al., 1997):

$$P(x) = \binom{4}{x} P_r^x (1 - P_r)^{4-x}$$

where $P(x)$ = probability that x of the four quarters would have an intramammary infection and P_r = overall proportion of quarters with an intramammary infection. The difference between the observed and expected distributions was tested using a goodness-of-fit test in the FREQ procedure of the SAS system (SAS Inst., Inc., Cary, NC).

Treatment effects. Logistic regression was used to model infection status by quarter at calving to control for potential confounding factors using the Genmod procedure of the SAS system. A fixed VIF was calculated for each trial and used to correct variance in the analyses. This took into account the intraclass correlation for quarter infections.

The intraclass correlation (ρ) is calculated using the following equation:

$$\rho = \frac{MSB - MSW}{MSB + (m - 1)MSW}$$

where (ρ) = intraclass correlation, m = mean number of quarters per cow, MSW = mean square variance within cow, and MSB = mean square variance between cows.

Variance inflation factor is calculated using the following formula:

$$\alpha = 1 + (m - 1)\rho$$

where α = variance inflation factor and m = mean number of quarters per cow.

The Glimmix macro within the SAS system was used for the multilevel analysis of infection status at calving. Quarters were nested within cows and variance estimates were obtained between quarters (i.e., within cows) and between cows.

The outcome variable (response) was infection status at calving measured at the quarter level. In addition to the effect of the dry-cow strategy (the treatment), parity and infection status at drying off were also examined. The study population had a small number of higher parity cows, resulting in a homogeneous distribution of parities. Therefore, the parity information was classified as either parity two or parity three and greater. The parity number is for the lactation following the trial dry period. Infection status at drying off was defined as uninfected or infected with either *Corynebacterium* spp. or CNS.

The final model was chosen by a forward stepwise procedure, where a variable was included in the model if it led to a significant ($P < 0.05$) change in deviance. The final model was confirmed by a corresponding backward selection procedure.

RESULTS

Data Sets

In the selective dry-cow antibiotic trial, there were 110 cows in the treated group and 122 cows in the untreated group available for the analysis. One cow had been removed from each group because it had only three functioning quarters. In the trial to assess the efficiency of an internal teat sealant, there were 84 cows in the treated group and 82 cows in the untreated group available for analysis. One cow in the untreated group had been removed because it had only three functioning quarters. The distributions of infection status category for each treatment group by parity, in each dry-cow strategy study, are presented in Table 1. In the teat seal study, the major difference observed was the increased prevalence of *Corynebacterium* spp. in parity-two cows for both treatment groups, compared with the selective dry-cow antibiotic trial. The incidence of *Corynebacterium* spp. for the parity-three and greater cows was comparable between the two trials.

Quarter distribution. There were no statistical differences in infection status at calving with respect to front or rear or left or right quarters for either trial ($P = 0.579$ for quarter and $P = 0.703$ for quarter treatment interaction in the selective dry cow trial and $P = 0.982$ for quarter and $P = 0.703$ for quarter treatment interaction in the teat seal trial).

Quarter interdependence. The expected number of cows with a given number of quarters infected was not always greater than one. In these cases, the goodness-of-fit tests were performed by aggregating the data to the point where the expected number of infected quarters was greater than one. There was significant quarter interdependence in both the antibiotic ($P < 0.001$) and teal seal ($P < 0.001$) trials (Figures 1a and 2a). There were more uninfected cows and cows infected in multiple quarters, as well as fewer cows with only one infected quarter, than were expected from the binomial distribution. The same pattern was observed in the untreated groups of both trials (Figures 1b and 2b). However, there was no evidence of quarter interdependence in cows that received either the antibiotic or teat seal treatments (Figures 1c and 2c).

Treatment effects. The final models generated by VIF and Glimmix were the same for each trial (Tables 2 and 3). In the selective dry-cow antibiotic trial, parity was included in the final model. However, for the selec-

Table 1. Distribution of quarters at calving with respect to parity and infection status at drying off for the selective antibiotic and teat-seal dry-cow strategy trials.

Quarter status: Total quarters:	Antibiotic trial		Teat seal trial	
	Treated (%)	Untreated (%)	Treated (%)	Untreated (%)
Parity two				
Uninfected	181 (85.4)	189 (85.9)	61 (66.3)	71 (65.7)
Infected with <i>Corynebacteria</i> spp.	9 (4.2)	14 (6.4)	21 (22.7)	12 (11.1)
Infected with CNS	22 (10.4)	17 (7.7)	10 (10.8)	25 (23.2)
Parity three or more				
Uninfected	152 (67.3)	179 (66.8)	168 (68.8)	142 (64.5)
Infected with <i>Corynebacteria</i> spp.	54 (23.9)	68 (25.4)	59 (24.2)	68 (30.9)
Infected with CNS	22 (9.8)	21 (7.8)	17 (7.0)	10 (4.6)

tive teat seal trial, parity did not significantly improve the final model and was not included. There were no interactions between parity and infection status at drying off for either trial. It was noted that the two statistical methods generated very similar odds ratios (with the exception of the odds ratio for quarters infected

Corynebacterium spp. in the selective dry-cow antibiotic trial), although it appears from the odds ratio confidence intervals that the more precise estimates were obtained using Glimmix. In both trials, the dry-cow antibiotic therapy and teat seal had a significant effect on infection status at calving when assessed using both

Figure 1. Observed and expected distribution of cows by number of infected quarters in the antibiotic dry-cow strategy trial (n = 232). A) all cows, B) untreated cows, C) treated cows. Goodness of fit test performed to the levels shown in figures.

Figure 2. Observed and expected distribution of cows by number of infected quarters in the teat seal dry cow strategy trial (n = 214). A) all cows, B) untreated cows, C) treated cows. Goodness of fit test performed to the levels shown in figures.

Table 2. Final model of infection status at calving for the antibiotic dry-cow strategy: variance inflation factor model ($\alpha = 1.9484$) upper lines; Glimmix model lower lines.

Variable	Coefficient	Estimate (odds ratio)	95% confidence limits
Intercept	-2.7376	—	—
	-4.3069	—	—
Treatment ¹	-1.1957	0.302	0.101–0.907
	-1.4516	0.234	0.149–0.369
Parity ²	0.7666	2.15	0.731–6.34
	1.0376	2.82	1.79–4.45
Infected at drying off ³			
<i>Corynebacteria</i> spp.	0.6955	2.00	0.642–6.26
	1.7348	5.67	4.10–7.84
CNS ⁴	0.8102	2.25	0.522–9.68
	0.6004	1.82	1.35–2.46

¹Treated cows relative to untreated cows.

²Parity >2 relative to parity <2.

³Cows infected at drying off relative to cows uninfected at drying off.

⁴CNS = coagulase-negative staphylococci.

Table 3. Final model of infection status at calving for the teat seal strategy: variance inflation factor model ($\alpha = 1.5855$) upper lines; Glimmix model lower lines.

Variable	Coefficient	Estimate (odds ratio)	95% confidence limits
Intercept	-2.4755	—	—
	-3.6926	—	—
Treatment ¹	-1.2058	0.299	0.106–0.844
	-1.4488	0.235	0.149–0.371
Infected at drying off ²			
<i>Corynebacteria</i> spp.	1.0681	2.91	1.06–7.99
	1.3912	4.02	2.81–5.75
CNS ³	1.1053	3.02	0.799–11.4
	1.2192	3.38	2.54–4.50

¹Treated cows relative to untreated cows.

²Cows infected at drying off relative to cows uninfected at drying off.

³CNS = coagulase-negative staphylococci.

Table 4. Variance estimates from Glimmix models.

Trial	Variation Source	Estimate
Antibiotic	Cows	5.7497
	Quarters	0.1673
	Residual	0.2317
Teat seal	Cows	4.0016
	Quarters	0
	Residual	0.2789

the VIF and Glimmix models. In the selective dry-cow antibiotic trial, an antibiotic-treated quarter was less likely to acquire a quarter infection at calving compared with the untreated controls ($OR_{VIF} = 3.3$; $OR_{Glimmix} = 4.2$; Table 2). Quarters infected at drying off with either *Corynebacterium* spp. ($OR_{VIF} = 2.0$; $OR_{Glimmix} = 5.67$; Table 2) or CNS ($OR_{VIF} = 2.25$; $OR_{Glimmix} = 1.82$; Table 2) were more likely to acquire an intramammary infection than those uninfected at drying off. Quarters from cows of parity three or greater were more likely to be infected than parity-two cows ($OR_{VIF} = 2.15$; $OR_{Glimmix} = 2.82$; Table 2).

In the selective dry-cow teat seal trial, a teat seal treated quarter was less likely to acquire a quarter infection at calving compared with the untreated controls ($OR_{VIF} = 3.3$; $OR_{Glimmix} = 4.3$; Table 3). Quarters infected at drying off with either *Corynebacterium* spp. ($OR_{VIF} = 2.91$; $OR_{Glimmix} = 4.02$; Table 3) or CNS ($OR_{VIF} = 3.02$; $OR_{Glimmix} = 3.38$; Table 2) were more likely to acquire an intramammary infection than those uninfected at drying off. The parity was not significant for either model.

The largest variance component was due to the cow in both the antibiotic and the teat seal trials (Table 4). The variance due to the quarter was estimated to be 0 in the teat seal trial.

DISCUSSION

There were no statistical differences in infection status at calving with respect to front or rear or left or right quarters for either of these dry period trials. This is in contrast to studies on quarter distribution of clinical and subclinical mastitis during lactation (Adkinson et al., 1993; Barkema et al., 1997). Previously for the lactation period, a lower incidence of intramammary infection and elevated cell count were found in fore quarters compared with hindquarters (Adkinson et al., 1993; Barkema et al., 1997). They observed little difference between the left and right halves of the udder although the right hindquarter was shown to have a higher cell count.

In both the antibiotic and teat seal treated groups quarter interdependence was not observed. This may

be a reflection of the low number of infected quarters observed in these trials. However, it is more likely to demonstrate the protective effect of treatment through the reduction of quarter interdependence. Previous work, using incidence scores for the number of quarters infected by cow, indicated that dry-cow therapy would be expected to alter the underlying frequency distribution and ignored any cows treated with dry-cow therapy in the analysis (Funk et al., 1982). This independence is in contrast to the untreated groups of the present trials, where quarter interdependence resulted in a decrease in the number of cows with one quarter infected and an increase the number of cows with either uninfected quarters or three or four quarters infected, compared with the expected distribution. This could be due to an individual cow susceptibility factor or to a pathogen exposure factor.

In this study, both VIF and Glimmix methods identified and controlled for clustering of infections within cows in the antibiotic trial based on 47 out of 232 cows with at least one quarter infected. However, the Glimmix model generated an estimate of 0.00 for variance due to quarters in the teat seal trial. In this case, there were 36 out of 166 cows with at least one quarter infected. Agreement between the VIF and Glimmix methods may have been achieved if more cows had been infected, thereby increasing the number of clusters available for analysis. This is a potential weakness of the Glimmix method when it is applied to relatively small datasets. Although using data from other herds could have expanded the data set, it may have been potentially biased since only a proportion of cows was used in some herds due to previous selection of cows.

In uninfected cows, it is not common practice to undertake prophylactic treatment on individual quarters. The work presented here augments the argument for treating all quarters in a cow at drying off rather than treating only the infected quarter. If there were individual cow susceptibility, there would still be an increased risk for the other three untreated quarters, as demonstrated by previous studies using selective quarter treatment (Browning et al., 1990; 1994; Østerås and Sandvik, 1996; Barkema et al., 1997).

Proximity to clinical infection in other quarters within a cow has been shown to be a risk factor in clinical mastitis studies in lactation (Adkinson et al., 1993; Barkema et al., 1997). The data that were modeled in this study had no quarters infected at drying off with *Staphylococcus aureus*. In the complete datasets for both dry-cow trials (Berry and Hillerton, 2002a,b), there were a few quarters infected at drying off with pathogens other than *Corynebacterium* spp. or CNS, and these were primarily due to *S. aureus*. There

were 27 cows with a quarter infected in the selective dry-cow trial and 35 in the teat-seal trial.

Proximity to infections, particularly with *S. aureus*, has been highlighted as a possible risk factor in the dry period (Ward and Shultze, 1974; Browning et al., 1990; 1994; Østerås et al., 1991; 1994; Williamson et al., 1995; Østerås and Sandvik, 1996). The challenge by *S. aureus* may be from sites other than the udder or from other cows. In these two dry-cow trials, only one cow with a quarter already infected with *S. aureus* acquired a new *S. aureus* infection in another quarter. This would suggest that there is a greater challenge within the cow from quarters infected with *S. aureus* during lactation than in the dry period.

Analysis of data on treatment efficacy must take into account all possible factors, such as herd, cow, and quarter (when looking at intramammary data), to control for a possible clustering effect. One method to avoid intraclass correlation within the cow is to treat at the quarter level. This may be accomplished by applying a split-udder design, to control for interdependence due to the contagiousness of a pathogen (Lam et al., 1997). Other methods that may be used to correct for interdependence or clustering involve statistical correction and covariates included in the analysis.

For the selective antibiotic trial, taking into account quarter interdependence, it can be concluded that dry-cow treatment, the absence of infection at drying off, and being in the second parity had a positive effect on reducing the number of new quarter infections at calving. Within the selective teat-seal trial, only teat seal and infection status at drying off, not parity, had positive effects on new quarter infections at calving when taking into account quarter interdependence.

There are two possible reasons for this: either both parity and infection status at drying off have an effect on new quarter infections at drying off and the effect of infection status at drying off is greater than that of parity, or parity has a confounding influence on infection status at drying off. From both sets of descriptive data, an increase in the prevalence of quarters with *Corynebacterium* spp. was noted from parity two to parity three and greater. This increase was greatest for the selective dry-cow antibiotic dataset. There was also a different prevalence of *Corynebacterium* spp. at drying off in parity-two cows. The selective dry-cow trial had half the number of quarters with *Corynebacterium* spp. infections at drying off in parity two than did the selective teat seal trial. Whereas there were no interactions between infection status at drying off and parity, this difference in distribution could account for the differences seen for parity between the two trials.

CONCLUSIONS

The results of this study indicate that quarters that are untreated during the dry period are not independent with respect to risk of an intramammary infection at calving. Treatment with either a dry-cow antibiotic or an internal teat seal may have resulted in independence of quarter infection risk, although the sample size may have been too small to demonstrate an effect. Both treatments were comparable in their effect on the incidence of new intramammary infections at calving. The results also add weight to the argument that prophylactic treatment should be used in the cow rather than at the quarter level since this not only reduces the number of new infections but also the number of cows with new infections in multiple quarters. It also confirms that infection status at drying off and parity are factors to be considered in dry-cow treatment strategies. Finally, this study demonstrates that, whenever possible, experiments should be designed and analyzed to account for quarter interdependence.

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