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Self-cure rates in American dairy cows infected with *Staphylococcus aureus* at drying off

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ABSTRACT

Reeve-Johnson L, Nickerson SC, Self-cure rates in dairy cows infected with Staphylococcus aureus ***at drying off, Online Journal of Veterinary Research, 11 (2) : 67-78, 2007.*** In a large multicentric study, several factors were demonstrated to be linked to the ability of dairy cows to spontaneously or self cure (without dry cow therapy) over the nonlactating period from natural intramammary infections (IMI) caused by *Staphylococcus aureus*. These factors included parity of cow, somatic cell count (SCC), site-specific factors, length of dry period, and the number of quarters initially infected. A predictive model was developed for the likelihood of self cure based upon the SCC of cows at dry-off to aid the prioritization of treatment or culling decisions.

Key words: dry period, mastitis, self-cure, Staphylococcus aureus.

INTRODUCTION

Bovine mastitis is one of the most costly diseases of food-producing animals in the US and Europe. Cow mortality, impaired production, increased treatment costs, decreased milk quality, and potential human health concerns are among the consequences of infection of the bovine mammary gland. *Staphylococcus aureus* is one of the most difficult organisms to treat, especially during lactation, and there are no intramammary infusion products currently available that effectively eliminate *S. aureus* IMI from herds.

The end of lactation is a common time to administer antimicrobial therapy to *S. aureus*-infected cows because antibiotics are able to remain in the udder at higher concentrations for prolonged periods to effect a cure (Sol, 1994, Osteras, 1999). This study examined the self-cure rate in nontreated *S. aureus*-infected cows to determine the baseline against which product efficacy should be assessed, and to identify factors that affect the ability of cows to spontaneously cure an infection without intramammary treatment.

MATERIALS AND METHODS

A multicentric study was initiated involving 10 herds in 5 disparate geographic locations in the US. All study sites conformed strictly to a uniform predetermined protocol. Bacteriology was conducted using the same methodology in a single laboratory for samples collected from the 10 herds. All sample collection phases of the study were conducted in accordance with Good Clinical Practice for Veterinary

Studies standards, and the laboratory phase was conducted according to Good Laboratory Practice standards. An independent Quality Assurance inspection was used to validate these 2 practices prior to and during the trial.

Herds with a history of *S. aureus* infection were screened based on past bacteriological analyses and elevated bulk SCC, and if the herd prevalence of S.aureus was $\geq$ 15%, then the herd was selected. Milk samples from all cows in these herds were cultured, and cows were enrolled based upon bacteriological evidence of *S. aureus* infection. Microbiological procedures were conducted in accordance with the methodology recommended in the Center for Veterinary Medicines of the Federal Drug Administration (CVM/FDA) Guideline (NMC, 1996). The Fossomatic cell counter (A/N Foss Electric, Hillerod, Denmark) was calibrated up to 20 x 108 cells/ml, and counts above this were recorded as >20 x 108 cells/ml rather than a value being ascribed from outside the calibrated range. Dairy cows in their first to fifth lactation, and ready for drying off were enrolled in the study. Recommended procedures (NMC) were followed for the aseptic collection and preparation of all milk samples taken at the study sites. Fore stripping of each teat was practiced prior to sampling to reduce the risk of sample contamination. Samples were frozen in their collection vials for dispatch to the laboratory for quarter SCC (QSCC) and bacteriology. Blood agar with 0.1% esculin was used for the culture of bacteria from the milk samples. All cows had at least 3 functional quarters, were confirmed pregnant by palpation per rectum, and were in good body condition. Cows were excluded from the study if they received antibiotic therapy (except topical or foot bath treatments) from the day of the first milk sample collection (d -14 to d -7 relative to dry-off) until the end of the trial.

Bacterial cultures of quarter milk samples collected d -14 to d -7 before drying off and on the day of drying off were compared with bacterial cultures from each quarter of each cow collected on 5 to 8 DIM, 11 to 17 DIM, and 19 to 25 DIM; QSCC were determined from samples collected d -14 to d -7 before dry-off and at 5-8 DIM. To qualify as an infected quarter, one or both of the predry-off samples needed to culture positive for *S. aureus*. Infected quarters were considered cured only if all of the postcalving samples cultured negative for the infecting bacterium.

A generalized linear mixed model was used to analyze the cow and quarter cure rate data. The analysis used a logit link function, a binomial error likelihood, and restricted pseudolikelihood approach (Wolfinger and O'Connell, 1993). Factors included in the model were investigator, herd within investigator, and parity. Somatic cell count and number of quarters infected were considered as cow-level covariates. Investigator and herd within investigator were random factors; parity, SCC coefficient, and number of quarters infected were fixed factors.

Over 40 herds were screened for *S. aureus* infection and 10 herds were included in this study, 2 from each of 5 disparate geographical locations. The final study population of *S. aureus*-infected cows that met the criteria from which a complete set of bacteriological samples from all functional quarters at each sample time was obtained, formed a study population of 341 cows. The herd identity, location, herd size, and breed of cattle are provided in Table 1.

Table 1. Herd identifier, location, size, breed type, and number of *S. aureus*-infected cows.

Herd	Location	Herd size	Type	Presence of separate *S. aureus* 'sub-herd'	No. of *S. aureus* infected cows
1	Louisiana	100	Jersey	No	50
2	Louisiana	300	Holstein	No	16
3	California	2000	Holstein	Yes	97
5	Colorado	1500	Holstein	Yes	10
6	Colorado	300	Holstein	No	0
7	California	1700	Holstein	Yes	81
9	Michigan	120	Holstein	No	21
11	New York	55	Holstein	No	30
12	New York	1500	Holstein	Yes	9
13	Michigan	130	Holstein	No	27

Herds 9 and 11 used tie-stall barns for milking and winter housing; all others had free stalls and milked in herringbone parlors.

RESULTS

Table 2 shows the number of cows with 1, 2, 3, or 4 quarters infected for each site. At all sites except 1 and 11, most cows had only one quarter infected (median = 69%). In herd 11, 80% had 2 or more quarters infected including 40% with 3 quarters infected. In herd 1, 64% of cows had 2 or more quarters infected including 40% with 2 quarters infected. Two other sites had over 10% of cows with more than 2 quarters infected (herds 7 and 9), and all sites had between 10 and 40% of cows with 2 quarters infected.

Table 2. Number (percentage) of cows with 1, 2, 3, or 4 quarters infected for each site

Herd	No. quarters infected				Number of
	1	2	3	4	cows in herd
1	18 (36)	20 (40)	7 (14)	5 (10)	50
2	11 (69)	4 (25)	0	1 (6)	16
3	54 (55)	36 (37)	3 (3)	4 (3)	97
5	9 (90)	1 (10)	0	0	10
7	59 (72)	11(14)	9 (11)	2 (2)	81
9	12 (57)	5 (24)	4 (19)	0	21
11	6 (20)	6 (20)	12 (40)	6 (20)	30
12	8 (89)	1 (11)	0	0	9
13	21 (77)	6 (22)	0	0	27
Total no. cows infected	198 (58)	90 (26)	35 (10)	18 (5)	341

Self Cure Rates by Parity: The bacteriological self-cure rate from *S. aureus* infection during the nonlactating period was established at each site. The self-cure rate in primiparous cows was 13.1%, which was over 2-fold greater than the self cure rate of multiparous cows (5.2%). There were site differences in self-cure rates, and the range was 0 to 20%. The overall summary of mean cure rates at each sample point was calculated either by averaging the mean cure rates of each site (unweighted mean) or by dividing the total number of cows cured in the entire study by the total number of infected cows enrolled (weighted mean). These 2 values are illustrated in **Table 3**.

Table 3. Unweighted and weighted means of cow cure rates (percentage).

	DIM 5-8	DIM 11-17	DIM 19-25
Unweighted mean	13.4	7.9	7.9
Weighted mean	7.8	6.0	6.0

The latter method gives more weighting to herds with larger numbers of infected cows and could lead to a bias in the overall mean cure rate due to a site effect in one large herd. In this study, the cure rates were lowest at the 2 largest sites, thus the weighted mean of the cure rate is lower than the unweighted mean. With a large number of sites of a similar size, the weighted approach might be favored, whereas with a small number of herds or where there is a large difference in herd size, the unweighted approach may be more suitable. Both methods are presented; although, overall the trends are similar.

At each sample time, the self-cure rates at the 2 largest sites (California) were significantly lower ($P \leq 0.05$) than the other sites, with the exception of primiparous cows for which the unweighted mean self-cure rate was 14.3% at 2 California sites and 8.3% at the others (not significant). Approximately half of the cows originated from these 2 sites, it was therefore decided to compare the data of the 2 California sites with the combined data from the other sites while also examining the difference in cure rates between primiparous and multiparous cows.

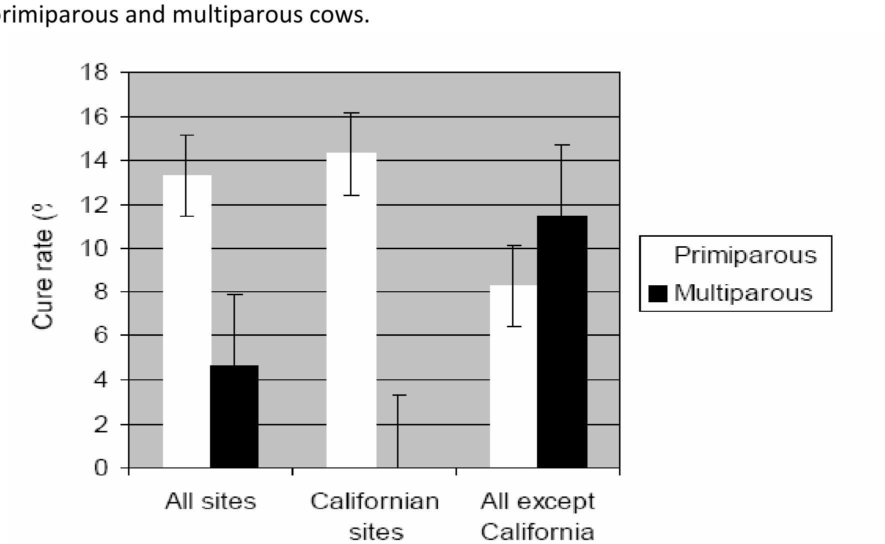

Figure 1. Weighed mean cure rate for 265 S Aureus-infected cows by treatment and parity for all sites with and without California sites. Data were collected from 140 cows at Californian sites and 125 at the other sites

None of the other sites had enough cows to be used as a stand-alone comparison. The difference in cure rate at each of the bacteriological sampling times is illustrated in Figure 2.

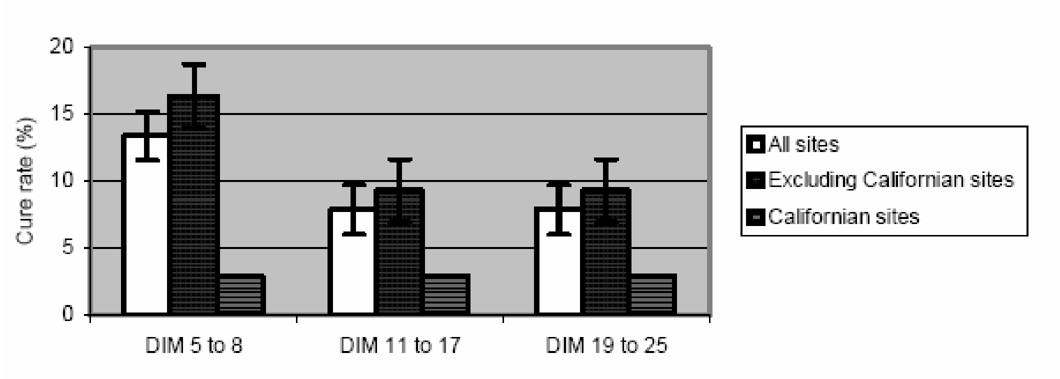

Figure 2. percentage cure for all cows infected with S aureus at drying off for each of 3 postcalving sampling times

When the site effects were considered, the cure rates at the 2 largest (California) sites were significantly ($P \leq 0.05$) lower than those at the other sites. Quarter Cure Rate by QSCC Before Dry-Off The quartiles of the infected QSCC were determined to be: 1st quartile 0 to 1140 x 10^3/mL; 2nd quartile 1141 x 10^3 to 3187 x 10^3/mL, 3rd quartile 3188 x10^3 to 8514 x 10^3/mL, and 4th quartile > 8514 x 10^3/mL. The cure rate by parity, treatment, and QSCC is illustrated in **Figure 3**.

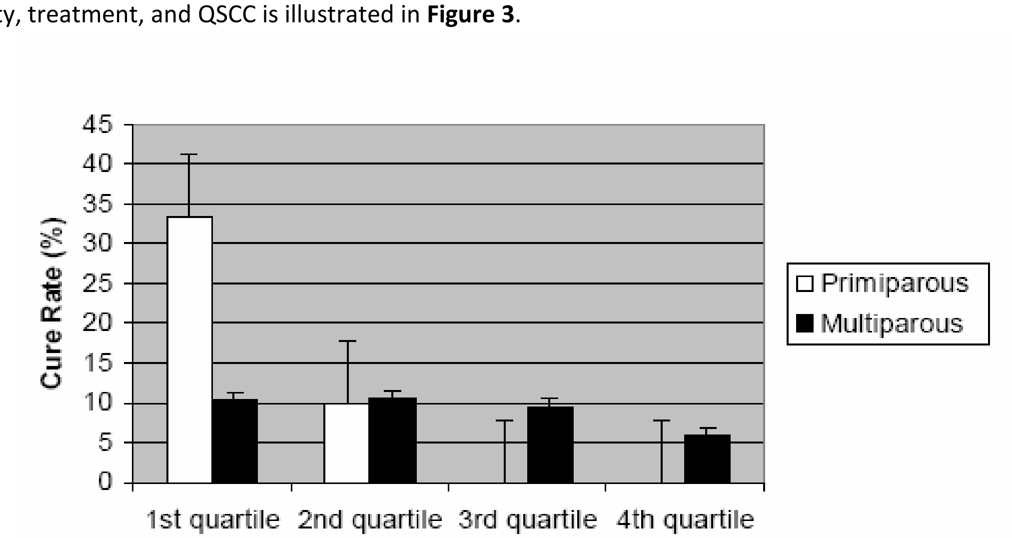

Figure 3. Quarter cure rate sorted by parity and quartile SCC for infected quarters. The quartiles of infected quarter SCC were determined to be 1st quartile 0 to 1140 x 10^3/mL: 2nd quartile 1141 x 10^3 to 3187 x 10^3/mL, 3rd quartile 3188 x 10^3 to 8514 x 10^3/Ml, and 4th quartile >8514 x 10^3/mL.

When quarter cure rate was determined according to the quartile of SCC, it was found that quarters in higher SCC cows (3rd and especially 4th quartile) whether multiparous or primiparous, were less likely to self cure. In all cases, the quarters

of cows from the quartile with the highest SCC, whether primiparous or multiparous, had a significantly lower ($P \leq 0.05$) cure rate than quarters from cows in the first or second quartile the difference was not significant to those in the 3rd quartile.

Cow Cure Rate by QSCC Before Dry-Off: If instead, cows were adopted as the experimental unit and were sorted according to the QSCC of the highest quarter, the quartiles were: 1st quartile: 0 to 1255 x 10^3/mL, 2nd quartile: 1256 x to 3039 x 10^3/mL, 3rd quartile: 3040 x 10^3 to 8543 x 10^3/mL, and 4th quartile: >8543 x 10^3/mL. The cow cure rate (the elimination of infection in all quarters) by parity and SCC is illustrated in Figure 4 below.

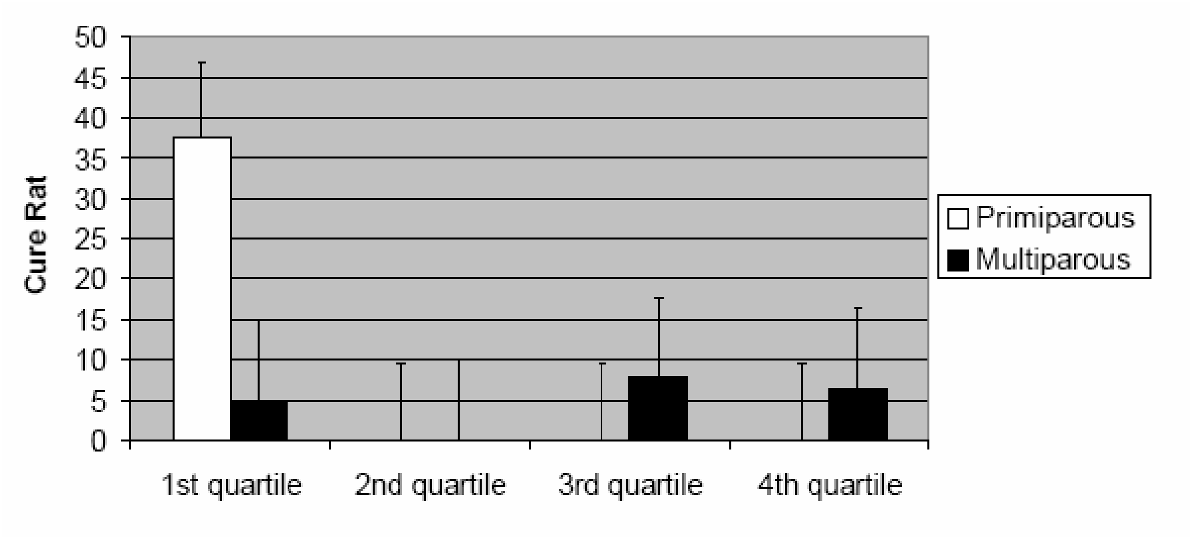

Figure 4. Overall cow cure rate, sorted by parity and quartile of the quarter SCC. Cows were sorted according to the highest SCC from any infected quarter. If instead cows were adopted as the experimental unit and were sorted according to the SCC of the highest quarter, then the quartiles were 1st quartile 1255 x 10^3 :2nd quartile 3039 x 10^3 ; 3rd quartile 8543 x 10^3 ; and 4th quartile > 8514 x 10^3.

Overall, it was seen that for multiparous cows (and primiparous cows above the first quartile), cure rate was very low (<8%). Primiparous cows with SCC <1.25 x 10^6 had self cure rate of 37.5%.

Cow Cure Rate by Presence or Absence of Segregation of S. aureus-Infected Cows**:** When those herds where cows were segregated into sub-herds containing all cows in which *S.aureus* IMI had been already detected (Herds 3,4,7,12) were compared with those where this management tool was not used, it was found that segregation of cows was associated with a decreased self-cure rate in multiparous cows from 10 to 2% ($P \leq 0.05$) and from 11 to 10% (nonsignificant) in primiparous cows. Self-cure rate decreased from 9 to 2% ($P \leq 0.05$) as herd size increased in multiparous cows, yet tended to increase in primiparous cows (nonsignificant); this effect is illustrated in Figure 5 on the next page.

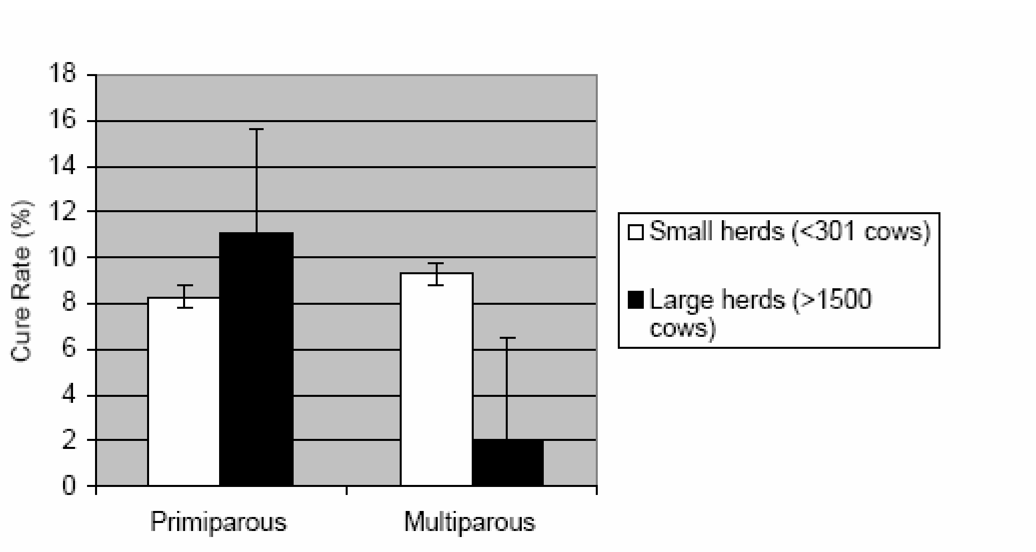

Figure 5. Cow cure rate fro *S aureus* infections of the mammary gland and parity according to herd size

Cow Cure Rate When Sorted by Herds with Greater than or Less than the Median Number of S. aureus-Infected Cows in the Herd: The lower the number of *S. aureus*-infected cows in the herd, the better the cure rate in both primiparous and multiparous cows. This is illustrated in **Figure 6 below**, in which the herd is categorized according to whether there were more than or less than the median number of *S. aureus*-infected cows across all sites present in that herd.

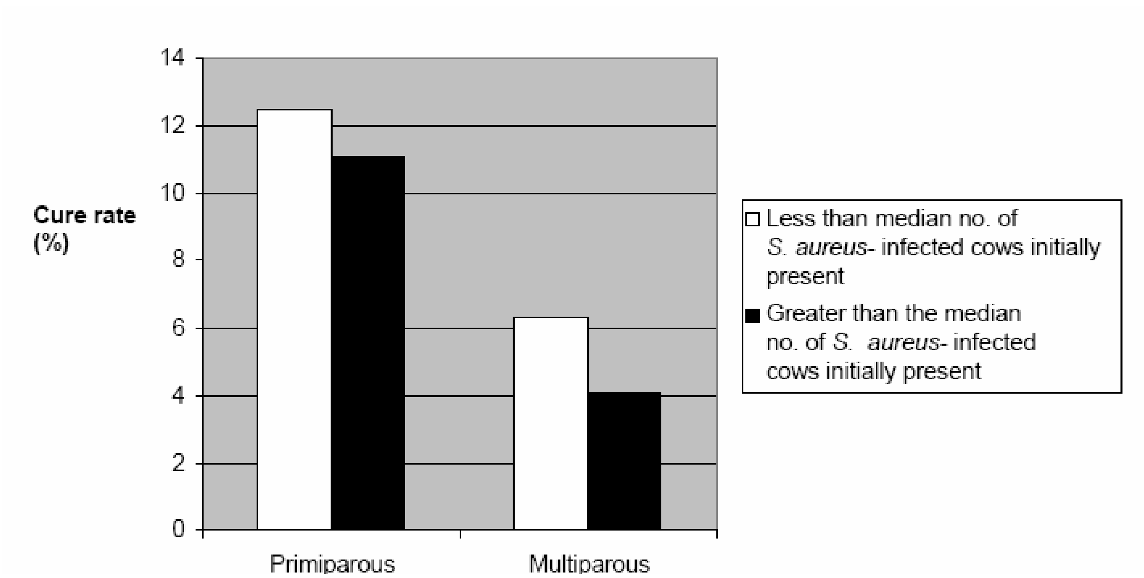

Figure 6. Cow cure rate by parity and treatment using the median number of *S. aureus* infected cows as a predictor of cure rate

Cow Cure Rate by Length of the Dry Period: There was no self cure in either primiparous or multiparous cows within the longest quartile of dry period (77 to 90 d). Dry periods of 35 to 48 d (the lowest quartile) were associated with better cure rates (23%). There were not enough primiparous cows in the upper or bottom quartiles of the dry period (3 in each) to compare results with multiparous cows.

Cow Cure Rate by Number of Quarters Initially Infected: If number of quarters infected per udder was greater than 2, the self-cure rate decreased to 0. Seven percent of cows with 1 quarter infected self cured, 8% of cows with 2 quarters self cured, and none with 3 or 4 quarters self cured.

Cow Cure Rate Sorted by Other Factors: There were no associations between month of calving and the cure rate, month of drying off and the cow self-cure rate, or quarter location within udder and cure rate.

Statistical Interpretation of Results: The experimental unit was the individual cow, and the bacteriological and SCC data were recorded for each quarter for each cow during the study; however, cure was judged on individual cow cure rate. The statistical prerequisite was that the cows should be across a minimum of 4 investigators with a total of 6 herds.

A generalized linear mixed model was used to analyze the cow and quarter cure data, which included a variance component estimate, which confirmed that there was no cure rate interaction with the investigator. **Table 4** shows coefficients of fitting fixed effects on a log scale, the estimated $\log_{10}$ (predry-off SCC) was used to generate the cure rate data for various SCC as given in **Table 5**.

Table 4. Coefficients of fitted fixed effects on logit scale

Effect	Level	Estimate	*Standard error*
Intercept	-	2.5961	1.4585
Parity	Multiparous	-1.3753	0.4707
	Primiparous	0	-
$\log_{10}$(pre-drying-off SCC)	-	-.7692	0.4080

Table 5. LS-Means of cure rates at various average predrying off QSCC

SCC = 100,000	Self cure	22 %
SCC = 200,000	Self cure	19 %
SCC = 300,000	Self cure	17 %
SCC = 400,000	Self cure	15 %
SCC = 500,000	Self cure	14 %
SCC = 750,000	Self cure	13 %
SCC = 1,000,000	Self cure	12 %
SCC = 1,500,000	Self cure	10 %
SCC = 2,000,000	Self cure	10 %

This could be very useful as a predictive indicator of likelihood of cure if the QSCC is known. The coefficient of $\log_{10}$ (pretreatment SCC) is –0.7692, thus as exp(–0.7692) is 0.46, a ten-fold increase in SCC approximately halves the odds in favor of a cure. For example, if odds where 1:1 (probability of cure, 50%), then they become 1 to 2 (probability of cure of 33%) with a ten-fold increase in predrying off SCC.

DISCUSSION

The definition of the quarter or the cow as the determinative statistical unit affects the trial design and the number of cows that should be included. In terms of bacteriology, the quarter is the relevant unit, and it is by bacteriological cure that efficacy is defined in both the Committee for Veterinary Medicinal Products (CVMP) (CVMP, 1999) and CVM/FDA guidelines (CVM, 1995). However, quarter cure rates within a cow have been shown not to be independent (Thorburn, 1990). Using the cow as the statistical unit takes account of confounding factors specific to the cow that influence the capability of a cow to cure infection either with or without treatment.

In this study, the self-cure rate of *S. aureus* IMI of primiparous cows was found to be 13.1%, and that of multiparous cows was 5.2%. There was a decline in the cure rate of 5.5% between the first and the third sample using the unweighted approach or a decline of 1.8% using the weighted approach (Table 3). The decline may be due to intermittent shedding of the organism or insufficiently sensitive bacteriological examination; alternatively, it might be due to reinfection of the same quarter in the cow with a new organism either of the same or a different strain (Reeve-Johnson, 2003).

Site differences were observed, and these were attributed to the presence or absence of segregation of *S. aureus*-infected cows from the rest of the herd, herd size, and parity. The data were analysed for risk factors associated with a decrease in cow and quarter rates. Significant risk factors were found to be high SCC, increasing numbers of quarters infected, segregation of infected cows, and increasing parity, all of which decreased cure rates.

A statistical model was constructed to predict self-cure rates, which illustrated that the chance of a successful self cure effectively halves with a 10-fold increase in SCC. Given adequate data, a similar model could be constructed using the other risk factors identified. The predictive value of models such as this can help in making treatment and culling decisions.

Data gathered by Whitaker et al. (2000) indicated that overall average total culling rate dairy cows in UK was 22%, of which 3.6% was for mastitis, and that clinical mastitis was recorded in 36.6% of cows each year. However, there was marked interherd variation in that the 10% of herds with the fewest cases of mastitis had an average of 8.3 cases per 100 cows, while the worst 25% had 70 cases per 100 cows. The mean bulk tank milk SCC (BTSCC) was 140,000 cells/mL, with the highest individual herd monthly SCC figure being 515,000 and the lowest 14,000/mL. A combination of management factors as well as cow factors such as yield, parity, and genetic predisposition contribute to herd differences. This study used a statistical model that was specifically factored for investigator, herd, and geography to avoid herd factors confounding the analysis of the contributions of other variables to the cure rate.

One herd factor examined in this study was the contribution of the presence or absence of segregation of *S. aureus*-infected cows into a discrete subherd of cows. This has been recommended as a means of decreasing the spread of *S. aureus* infection as an interim method of control (Zecconi and Piccinini, 1999). Although this practice limits the transmission of contagious mastitis pathogens to uninfected cows in the rest of the herd, the result is the creation of a subherd with a 100% prevalence of *S. aureus* infection. These data supported the conclusion that it is more difficult to cure infected cows within *S. aureus* subherds. Presumably, this is due to constant reinfection from contact with infected animals.

The mean self-cure rates in the 2 largest herds were significantly lower ($P \leq 0.05$) than those for the mean of the other sites combined. This may be partly due to their adoption of *S. aureus* subherds, although other herds adopting this practice had higher cure rates. The density of infected cows within the segregated groups may be another factor. These *S. aureus*-infected groups of cows were large (79 and 81 cows at the 2 Californian sites compared with 9 and 10 cows at the other 2 sites that used segregation) and were not housed in proportionately larger pens; thus, the mean area per infected cow was decreased, and the probability of making contact with infected cows was increased. In the 6 herds that did not segregate infected cows as a management tool, infected cows were dispersed throughout the entire herd. Additionally, in herds using segregation, many more infected cows are milked in succession, and there is a greater likelihood of infection occurring at this time even with rigorous hygiene protocols. Finally, in small herds, there is often a sole dairyman who detects mastitis and other health problems, and that individual follows up on the management of these cases. Thus, measures such as the initiation of treatment are often started more quickly and consistently than in large herds in which shifts of milkers operate a constant throughput system

The increased self-cure rates of primiparous cows above those of multiparous cows is consistent with the body of literature. This supports the approach in which primiparous and multiparous cow data are analyzed separately as 2 populations of cows with inherently different capacities for curing IMI. Nickerson et al. (1995) illustrated superior self cure and treatment response rates to *S. aureus* mastitis in

breeding age and pregnant dairy heifers. The self cure rate of these cows was 59%, and the quarter self cure rate was 46% overall.

The QSCC was strongly indicative of the likelihood of self cure, both for the quarter concerned and using the highest QSCC as an indicator of cure likelihood for the cow. Previous research also found that the cure rate of *S. aureus*-infected quarters diminishes as the SCC prior to drying off increases, and that there is a significantly lower cure rate in quarters with a SCC of greater than 1 million cells/ml (Sol et al., 1994). Schukken et al. (1993) showed, in a university herd with a low BTSCC, that there was a low prevalence of major pathogens, and they speculated that the benefit for reducing IMI is low. Thus, our high SCC *S. aureus* problem herds made an interesting test population in a scenario in which the value of an effective product would be maximized. In their low SCC herd, these workers observed a 75% self-cure rate in nontreated cows. All cows in this study were infected with Staph. aureus and very few had low QSCC. For example, there were only 3 cows below 100,000 cells/ml. The predictive value of this model therefore increases at the higher QSCC. The geometric mean predrying off QSCC in Staph. aureus infected quarters from our data was 2,900,000 cells/ml. This is higher than the mean of 1,500,000 to 1,820,000 cells/ml quoted by another researcher for Staph. aureus infected quarters (Erskine, 1992).

The largest 2 herds in this study had significantly lower cure rates ($P \leq 0.05$). Whitaker et al. (2000) using data from a large survey of UK dairy herds did not find any relationship between herd size and mastitis rate, but a tendency for higher yielding herds to have more mastitis. In the case of the 2 larger herds they were high yielding herds but milk yields were not tracked for most of the other herds involved so this cannot be confirmed. 295 296 297 298 299 300 301 302 303 304
As the number of quarters infected per cow increased, there was a decrease in the cow cure rates. None of the cows infected in all 4 quarters were cured, and there was a significant decrease in the ability to cure the fourth quarter as compared to the ability to cure a quarter in a cow with either no other, one other or two other quarters infected ($P \leq 0.05$). This may be evidence of debilitating mastitis and an immunocompromised state, the increased risk of cross infection between quarters within the same cow, or increased genetic susceptibility of these animals.

There was a significantly greater chance of both a self cure and cure by treatment in a primiparous cow versus a multiparous cow ($P \leq 0.05$), dry period length was also a significant risk factor and there was no self cure in either primiparous nor multiparous cows within the longest dry period quartile. The self cure and treatment cure rates significantly decreased ($P \leq 0.05$) in both primiparous and multiparous cows as the number of quarters infected increased or the pre-drying off QSCC increased.

The factors identified above agree in some respects with other work, yet contrast in others. Few studies have been done on non treated *S. aureus* infected cows, the most conclusive results are from trials of antimicrobial therapies. Sol et al. (1994) analyzed data from 5 day cow antibiotic therapy trials, which included 406 *S. aureus* infected quarters from 283 cows on 73 farms. They identified a number of factors associated with failure of antibiotics to cure cows. The probability of an infected quarter decreased when SCC increased, when another quarter was infected in the same cow, when the infection was in a hind quarter or when the percentage of samples that was positive for S.aureus was higher before drying off. Osteras et al. (1999) identified a number of determinants of success or failure for the elimination of major pathogens (mainly S.aureus and Streptococcus dysgalactiae) in a study including 686 cows from 288 different herds in Norway. They found better elimination of these pathogens to be associated with a lower mean value of the last three composite SCC before dry cow therapy and that cows with a major pathogen in the right hind quarter at dry off or at least 1 case of acute clinical mastitis during the previous lactation were more likely to have a major pathogen in the next lactation (odds ratio = 4.1 and 3.6, respectively).

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