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The use of a cephalonium containing dry cow therapy and an internal teat sealant, both alone and in combination

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ABSTRACT

The dry period is a critical time in the lactation cycle, being the optimum time to cure existing intramammary infection (IMI) as well as encompassing the periods of highest susceptibility to new infection. Currently, IMI in the dry period is controlled with antibiotic dry cow therapy. The aim of this randomized control trial was to investigate different dry cow therapy regimens by stratifying cows by likely infection status at drying off in herds with low somatic cell count (SCC; bulk milk SCC <250,000 cells/mL) in southwest England. All quarters in 890 cows were recruited. The recruited cows were categorized as either infected or uninfected on the basis of SCC and clinical mastitis history. Ipsilateral quarters within each cow were randomly allocated to receive 1 of 4 different treatment regimens according to their infection category. Quarters in high-SCC infected cows were allocated to receive antibiotic dry cow therapy either alone or in combination with an internal teat sealant; quarters in low-SCC uninfected cows were allocated to receive teat sealant either alone or in combination with antibiotic dry cow therapy. All quarters were sampled for bacteriology at drying off and again within 10 d post-calving. Quarters were subsequently monitored for clinical mastitis for the first 100 d of lactation. The mass of residual sealant was assessed immediately post-calving to allow assessment of the association of sealant retention with treatment efficacy. Models were constructed to assess the efficacy of the different regimens in preventing IMI. Apparent cure rates of existing IMI with major pathogens were consistently >90% in quarters receiving antibiotic. Combination treatment of high-SCC infected cows resulted in an increased likelihood of being pathogen free post-calving (odds ratio = 1.40; 95% credibility interval = 1.03–1.90). The benefits of combination treatment of low-SCC uninfected cows were less clear. With respect to clinical mastitis, combination treatment of high-SCC infected cows resulted in a decreased likelihood of developing clinical mastitis in the first 100 d of the subsequent lactation (odds ratio = 0.68; 95% credibility interval = 0.48–0.98). The retention of the internal sealant was adversely affected by its use in combination with antibiotic dry cow therapy.
Key words: dry cow therapy, cephalonium, intramammary infection, teat sealant

INTRODUCTION

The rigorous implementation of mastitis control plans in recent years resulted in a dramatic change in both the incidence and etiology of bovine mastitis (Bradley, 2002). Historically, these control programs were focused on contagious mastitis pathogens and the control of bulk milk SCC (**BMSCC**; Dodd et al., 1969), an important part of which was the recommendation to implement whole-herd antibiotic dry cow therapy (Smith et al., 1967; Wilson et al., 1972).

The dry period is well acknowledged as being the optimal time to cure existing IMI (Wilson et al., 1972) as well as being a period of high risk for the acquisition of new IMI (Smith et al., 1985; Oliver, 1988). Research investigated the importance of infections acquired during the dry period and demonstrated how these infections influence the rate of clinical mastitis in the subsequent lactation (Bradley and Green, 2000). Importantly, research highlighted the potential importance of the dry period in the epidemiology of both environmental and contagious mastitis pathogens, and that dry period interventions can influence both the incidence and etiology of such infections (Bradley and Green, 2001; Huxley et al., 2002); one such example is the ability to reduce the incidence of clinical mastitis in early lactation caused by *Enterobacteriaceae* through selecting therapy with extended activity against these pathogens (Bradley and Green, 2001).

The renewed interest in the role of the dry period in mastitis control, coupled with the unfortunate public

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perception of prophylactic antibiotic use, led to an interest in nonantibiotic approaches to control IMI. This interest focused on the prevention of new IMI in cows with low SCC that were uninfected at drying off (**DO**) and culminated in studies investigating the utility of internal teat sealants in the prevention of new IMI in the dry period (Woolford et al., 1998; Berry and Hillerton, 2002a; Huxley et al., 2002). Once the efficacy had been demonstrated in low-SCC uninfected cows, an obvious extension was to combine the use of an internal teat sealant with antibiotic (combination treatment) in high-SCC infected cows, thereby combining the benefits of enhanced cure with antibiotics with the enhanced ability of sealants to prevent new IMI (Godden et al., 2003; Newton et al., 2008).

However, despite evidence to the contrary (Woolford et al., 1998), an assumption was made that the clear benefits of combination treatment in high-SCC infected cows could be extrapolated to low-SCC uninfected cows and that there would be a clear advantage to the use of combination treatment in all cows regardless of infection status at DO. However, this assumption is not currently sustained by scientific evidence.

Therefore, the primary aim of the research outlined was to investigate the efficacy of combination treatment in both cows that were infected and uninfected at DO in terms of reduction in IMI and incidence of clinical mastitis in the first 100 d of the subsequent lactation. A secondary aim was to assess the recovery of the internal teat sealant after calving and to determine whether this was affected by the use of the product in combination with an oil-based antibiotic dry cow therapy.

MATERIALS AND METHODS

Herd Selection

Six commercial dairy herds in southwest England (Somerset and Wiltshire) were enrolled. Herds were selected on the basis of existing records and participation in an individual cow milk recording scheme (to allow collation of historic SCC data). No strict criteria were imposed pertaining to BMSCC or clinical mastitis incidence, though herds typically had BMSCC <250,000 cells/mL.

Cow Selection

Cows eligible for enrollment were in good health, had 4 functional quarters free of significant teat lesions, and had monthly individual cow SCC recordings for at least the 3 mo previously. Cows enrolled did not have systemic or intramammary antibiotics or antiinflammatory agents in the 30 d before the last milking and had an expected dry period length of at least 54 d.

Study Protocol

Enrollment. Farms were visited weekly, and cows were enrolled to the study on the day of DO. At enrollment, key cow details such as breed, parity, estimated milk yield, individual cow SCC history, treatment history, and estimated calving date were collected from farm records. Additional data such as the presence or absence of teat lesions were recorded at the time of recruitment. Prior to the final milking of the lactation and before treatment administration, each animal was identified and physically examined for suitability on the basis of the exclusion criteria. Duplicate milk samples were collected for bacteriological examination and a single sample for SCC evaluation was collected from each quarter of each eligible animal using a method described previously (Bradley and Green, 2000).

Treatment Allocation and Administration. At DO, cows were categorized as high-SCC infected or low-SCC uninfected using clinical mastitis and SCC history; cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group.

In the high-SCC infected group, within each cow, ipsilateral quarters were randomly allocated to receive either antibiotic alone (**AB**; 250 mg of cephalonium, Cepravin Dry Cow, Intervet Schering-Plough Animal Health, Milton Keynes, UK) or combination treatment (**ABTS**; 250 mg of cephalonium, Cepravin Dry Cow, Intervet Schering-Plough Animal Health; 65% bismuth subnitrate in a mineral oil base, OrbeSeal Pfizer Animal Health, Sandwich, UK). In the low-SCC uninfected group, within each cow, ipsilateral quarters were randomly allocated to either teat sealant alone (**TS**) or combination treatment (**TSAB**). The quarter was the experimental unit, although subsequent multivariable analysis took into account the effect of clustering of quarters within cows.

At each trial site, within the high-SCC infected and low-SCC uninfected groups the combination treatment was allocated to the left or the right side of the udder in the first cow recruited; thereafter, treatments were allocated on an alternate basis according to the order that cows were recruited. Importantly, this approach ensured a balanced allocation of treatments to each side of the udder within each trial site and that allocation was temporarily matched even when small numbers of cows were recruited at a site. This approach was necessary to address any potential proclivity caused by housing

design, cows lying on one side, and any temporal variation in challenge given that environmental pathogens were the most likely cause of infection in the dry period in the modern dairy herd.

Dry cow therapy was administered by a member of the study team following strict aseptic precautions. Where appropriate, antibiotic dry cow therapy was infused into the teat cistern of a quarter and massaged into the udder. The teat sealant was carefully instilled into the teat sinus either as a stand-alone treatment or following treatment with antibiotic dry cow therapy as appropriate. Following treatment administration, quarters were dipped with a post-milking disinfectant and cows were confined to a loafing yard for at least 30 min before moving to new accommodations.

Dry Period Management. Following treatment and until calving, animals were subjected to the usual dry cow husbandry practices for the farm and were regularly observed by the owner, herdsperson, or other suitably qualified person. Any disease or concurrent treatments were recorded. All cases of clinical mastitis were recorded and sampled for bacteriological analysis.

Teat Sealant Recovery at Calving. At calving, or as soon as practicable thereafter, farmers and herdspersons assessed and recorded the presence or absence of residual TS in each of the quarters according to a standard operating procedure and following training; in the event that a quarter had been suckled, this was noted. The first 50 mL of secretion (including strict foremilk) was collected from all quarters, regardless of whether they originally received sealant, into a prelabeled tube (1 tube per quarter). Each tube was frozen on farm until collected and returned to the laboratory.

Post-Calving. Duplicate quarter milk samples were collected for bacteriological examination at the first weekly visit after each cow had calved. At the same time, a milk sample was taken from each quarter for enumeration of the quarter SCC. Samples collected more than 10 d after calving were excluded from the analysis of efficacy as measured by the cure and acquisition of IMI during the dry period.

Clinical Mastitis Monitoring. Farm personnel, trained in detection and aseptic sampling of clinical mastitis, monitored cows for the presence of clinical mastitis throughout the study period and collected a pretreatment aseptic quarter milk sample when cases occurred. These samples were frozen on farm and stored until the next routine visit.

Laboratory Procedures

All milk samples collected were maintained at or below 8°C during transport to the laboratory for analysis. Microbiological investigation and SCC were carried out using the standard milk sample examination techniques, which exceeded the standard recommended by the International Dairy Federation (1981), International Standard 13366–1:1997 (E) and 13366–2:1997 (G). A more complete description of these techniques is outlined below.

Ten microliters of secretion was inoculated onto sheep blood agar and Edward's agar; 100 μL of secretion was inoculated onto MacConkey agar to enhance the detection of *Enterobacteriaceae*. Plates were incubated at 37°C and read at 24, 48, and 72 h. Organisms were identified and quantified using standard laboratory techniques (Quinn et al., 1994; NMC, 1999). *Escherichia coli* were identified by colony morphology, oxidase, and indole tests; other *Enterobacteriaceae* were identified using a microtube identification system (RapiD 20 E, bioMérieux, Basingstoke, UK).

Somatic cell count was determined using the Fossomatic method (Delta CombiScope – Model FTIR 400, Drachten, the Netherlands) according to the FIL International Dairy Federation 148 A: 95 norm (International Dairy Federation, 1995).

Samples collected and frozen on farm were thawed prior to centrifugation at 3,000 × *g* for 5 min. Secretion was decanted, leaving the remnants of teat sealant and other solids in the base of the tube. Tubes were inverted and allowed to drain fully before weighing to establish the mass of retrieved solids (teat sealant).

Assessment of Efficacy

Isolation of an organism was considered indicative of an IMI. A sample was considered contaminated if >3 pathogens were cultured from a sample. If this occurred, the duplicate sample was submitted for bacteriological analysis (Bradley and Green, 2000). Several outcomes were assessed as outlined below.

The overall and species-specific cure rate were estimated and compared between groups. A cure was defined as the absence of a pathogen in the post-calving sample that had been present at DO.

The overall and species-specific new infection rates were estimated and compared between groups. A new infection was defined as the presence of a pathogen in the post-calving sample that had not been present at DO. Therefore, a quarter infected with 1 pathogen at DO was eligible to acquire a new infection with a different pathogen.

Successful dry period outcomes were estimated and compared between groups using methods described previously (Newton et al., 2008). A successful outcome was defined in 2 ways: 1) the absence of a major pathogen from the post-calving sample, and 2) the absence

Table 1. Key characteristics of the 6 study farms[1]

Item	Farm ID					
	D	F	G	H	S	T
Approximate herd size, cows in milk (n)	300	200	250	220	150	610
Predominant breed	G	HF	HF	HF	HF	HF
Animals recruited (n)	224	123	137	91	89	226
Geometric mean bulk milk SCC in the 5 mo before the study ($\times 10^3$ cells/mL)	118	172	172	240	163	193
Dry cow winter housing	C, Y	C, Y	C, Y	Y	C	C, Y
Predominant dry cow summer housing	P	C, Y	P	P	P	Y
Predominant dry cow bedding	Straw	Sand	Straw	Straw	Straw	Straw

[1]G = Guernsey; HF = Holstein-Friesian; C = free stalls; Y = covered straw yards; P = pasture.

of any mastitis pathogen (major or minor) from the post-calving sample.

The overall and species-specific incidence rate of clinical mastitis was assessed in the first 100 d of lactation and compared between products.

Data Collation and Statistical Analyses

Data were collated and initially analyzed using Excel and Access 2003 (Microsoft Corp., Redmond, WA) and Minitab 15.1 (Minitab Inc., State College, PA). Descriptive and graphical analyses were carried out to explore the data. Where appropriate, groups were compared using the Kruskal-Wallis test because data were not normally distributed. Univariable analysis of treatment efficacy was performed using the chi-square test to investigate differences in proportions between groups. A layered Bonferroni correction was used to allow for multiple comparisons where appropriate (Darlington, 1990). Analysis of infected and uninfected cows was done separately.

Multilevel logistic regression models were specified with the response variables 1) absence of IMI post-calving (successful outcome) or 2) clinical mastitis on 1 or more occasions within the first 100 d post-calving. Random effects were included for cow (level 2) to account for correlations within the data (i.e., quarters within cows). Potential confounding factors such as farm, DIM, milk yield at DO, dry period length, and parity were tested and included in final models only if they influenced the treatment effect, which in any event they did not. The models took the general form

$$\text{Response}_{ij} \sim \text{Bernoulli}(\text{probability} = \mu_{ij})$$

$$\text{logit}(\mu_{ij}) = \alpha + \beta_1 TX_{ij} + \beta_2 X_{ij} + \beta_3 X_j + v_j$$

$$v_j \sim \text{normal distribution } (\text{mean} = 0, \sigma^2{}_v),$$

where the subscripts i and j = ith quarter and the jth cow, respectively; μ_{ij} = the fitted probability of the response in quarter i of cow j; α = regression intercept; TX_{ij} = covariate treatment; β_1 = coefficient for TX_{ij}; X_{ij} = vector of quarter-level covariates; β_2 = coefficients for X_{ij}; X_j = vector of cow-level covariates; β_3 = coefficients for X_j; v_j = random effect reflecting residual variation between cows; and $\sigma^2{}_v$ = between-cow variance. Parameter estimation and assessment of model fit were conducted within a recently described Markov chain Monte Carlo framework (Browne, 1998; Green et al., 2004).

RESULTS

A total of 890 (457 high-SCC infected and 433 low-SCC uninfected) cows were enrolled between July 2007 and April 2008 from the 6 farms in the study; details of the number of cows recruited from each farm and farm management are outlined in Table 1. Data from a total of 810 and 839 cows were incorporated into the analyses pertaining to dry period IMI and clinical mastitis, respectively. Eighty animals were not available for inclusion in the analyses for the following reasons: animals either were not pregnant or calved beyond the end of the study (n = 45), animals were not sampled within 10 d post-calving (n = 21), animals were not allocated to the correct treatment group (n = 6), and both of the screening samples of animals were contaminated such that an assessment of new IMI or cure could not be accurately undertaken (n = 8).

The key indices and traits relating to animals included in the final analysis of efficacy are shown in Table 2. Unsurprisingly, cows categorized as infected at DO, compared with cows categorized as uninfected, were of higher parity [3 (2–4) vs. 2 (1–3), median and interquartile range; $P < 0.05$], were lower yielding [6 (5.0–10.4) vs. 9 (6.0–20.1) L; $P < 0.05$], and had longer dry periods [62 (56–72) vs. 59 (54–65) d; $P < 0.05$].

Table 2. Summary of data from cows (419 infected, 391 uninfected) and quarters (838 infected, 782 uninfected) included in the analysis of product efficacy as measured by cure and acquisition of IMI during the dry period[1]

	Infected				Uninfected			
Item	Mean	Median	Minimum	Maximum	Mean	Median	Minimum	Maximum
Parity	3.32	3[a]	1	10	2.34	2[b]	1	13
Dry period length (d)	70	62[a]	3	306	61	59[b]	2	167
Milk yield at drying off (L)	9.6	6[a]	1	41.4	13.7	9[b]	1	50
Individual cow SCC ($\times 10^3$ cells/mL)								
1 mo before drying off	492	307[a]	12	6,041	84	75[b]	6	198
2 mo before drying off	329	229[a]	16	7,112	73	64[b]	5	199
3 mo before drying off	276	193[a]	12	4,367	67	54[b]	1	196

[a,b]Means within a row with different superscripts differ ($P < 0.05$).

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group.

Univariable Analysis

Prevalence of Infection. The prevalence of the key mastitis pathogens at DO and post-calving in the high-SCC infected and low-SCC uninfected categories are described in Tables 3 and 4, respectively. When comparing within infection category (i.e., infected or uninfected), no significant differences in the prevalence of infection at DO were identified. There were significant differences in the prevalence of pathogens present post-calving. Quarters in high-SCC infected cows treated with ABTS were less likely infected with a major pathogen (112/838 vs. 83/838; $P < 0.05$) or a minor pathogen (270/838 vs. 230/838; $P < 0.05$) than those treated with AB. When the likelihood of being free of any pathogen post-calving was considered, the ABTS-treated quarters in high-SCC infected cows were more likely (506/838 vs. 560/838; $P < 0.05$) pathogen-free than those treated with AB. When considering quarters treated in low-SCC uninfected cows, quarters receiving TSAB treatment were not significantly less likely infected compared with quarters treated with TS alone, with the exception of the prevalence of IMI at calving with coagulase-positive staphylococci and *Streptococci* spp. combined (23/782 vs. 11/782; $P < 0.05$). There was a trend for TSAB-treated quarters in the low-SCC uninfected group to be more likely to be pathogen free post-calving than TS-treated quarters (492/782 vs. 526/782; $P = 0.07$).

Apparent Dry Period Cure Rate. The pathogen-specific apparent cure rates for the mastitis pathogens are shown in Table 5. No significant differences in the cure rates were identified for any of the major or minor pathogens when each were considered and compared between treatment groups within infection categories. Cure rates were exceptionally high in all treatment groups, with pathogen-specific cure rates consistently in excess of 90% for all susceptible species.

Apparent Dry Period New IMI Rate. The pathogen-specific apparent new infection rates for the key mastitis pathogens are shown in Table 6. No significant differences in the new infection rates were identified for any of the major or minor pathogens when each were considered and compared between treatment groups within infection categories.

Dry Period Outcomes. Dry period outcomes for each of the treatment groups are shown in Table 7. When comparing within treatment categories, there was no significant difference in the number of quarters curing or acquiring an IMI during the dry period. There was a significant difference in the number of quarters experiencing a successful dry period outcome, defined as being pathogen free post-treatment. Combination-treated quarters in the high-SCC infected cows category were more likely to be pathogen free post-calving than were quarters treated with AB (500/830 vs. 554/831; $P < 0.05$). There was a trend for TSAB-treated quarters in the low-SCC uninfected cows category to be pathogen free post-calving compared with quarters treated with TS alone (489/777 vs. 523/779; $P = 0.08$).

Clinical Mastitis. A total of 262 cases of clinical mastitis occurred in 227 quarters during the dry period and in the first 100 d of the subsequent lactation. For the purposes of assessing efficacy, only the first case occurring in each quarter was considered. The number of cases and etiology of the first case in each quarter are shown in Table 8. In the high-SCC infected cow category, quarters of ABTS-treated cows were less likely to develop clinical mastitis than were quarters of AB-treated cows (59/862 vs. 84/862; $P = 0.03$). Combination-treated quarters were less likely to suffer a case of clinical mastitis caused by a major mastitis pathogen (30/862 vs. 59/862; $P = 0.002$) or an enterobacterial pathogen (11/862 vs. 24/862; $P = 0.03$). In the low-SCC uninfected cow category, there was no significant difference in the proportion of quarters suffering a case

Table 3. Prevalence of mastitis pathogens at each of the sampling time points, restricted to quarters and cows eligible for assessment of product efficacy (high-SCC infected cows)[1]

	Drying off				Post-calving			
	AB (no. of quarters = 838)		ABTS (no. of quarters = 838)		AB (no. of quarters = 838)		ABTS (no. of quarters = 838)	
Item	n	%	n	%	n	%	n	%
Streptococcus uberis	29	3.46	33	3.94	21	2.51	14	1.67
Escherichia coli	16	1.91	7	0.84	28	3.34	20	2.39
Aerococcus spp.	14	1.67	20	2.39	14	1.67	10	1.19
Coagulase-positive staphylococci	12	1.43	12	1.43	8	0.95	3	0.36
Enterococcus spp.	8	0.95	7	0.84	11	1.31	4	0.48
Bacillus spp.	4	0.48	6	0.72	1	0.12	3	0.36
Yeast spp.	4	0.48	2	0.24	11	1.31	8	0.95
Unspeciated gram-negative	3	0.36	5	0.60	8	0.95	9	1.07
Streptococcus spp.	3	0.36	5	0.60	0	0.00	1	0.12
Mucor spp.	2	0.24	1	0.12	3	0.36	3	0.36
Streptococcus dysgalactiae	2	0.24	4	0.48	0	0.00	3	0.36
Aspergillus spp.	1	0.12	3	0.36	2	0.24	2	0.24
Pseudomonas spp.	1	0.12	0	0.00	2	0.24	1	0.12
Arcanobacterium pyogenes	0	0.00	0	0.00	1	0.12	0	0.00
All *Enterobacteriaceae*	22	2.63	14	1.67	38	4.54	24	2.86
Staph./Strep. spp.[2]	54	6.44	59	7.04	39	4.65	25	2.98
Other major pathogens	2	0.24	2	0.24	2	0.24	3	0.36
All major pathogens[3]	100	11.93	107	12.77	112	13.37[a]	83	9.90[b]
Coagulase-negative staphylococci	268	31.98	257	30.67	213	25.42	178	21.24
Corynebacterium spp.	352	42.00	345	41.17	95	11.34	86	10.26
All minor pathogens[3]	510	60.86	494	58.95	270	32.22[a]	230	27.45[b]
No growth	286	34.13	306	36.52	506	60.38[a]	560	66.83[b]
Contaminated	2	0.24	3	0.36	6	0.72	4	0.48
Total[3]	550	65.63	529	63.13	325	38.78	274	32.70

[a,b]Means within a row within sampling time points with different superscripts differ ($P < 0.05$).

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows.

[2]Coagulase-positive staphylococci and all *Streptococcus* species.

[3]Totals may not equal sum of the individual pathogens as a result of mixed infections.

of clinical mastitis; however, quarters receiving TSAB were more likely to develop clinical mastitis caused by *E. coli* (9/816 vs. 1/816; $P = 0.01$) or an enterobacterial pathogen (12/816 vs. 1/816; $P = 0.002$).

Retention of Teat Sealant. A total of 3,176 quarters were sampled post-calving for the purposes of determining the quantity of residual solids; 429 quarters were excluded from the analysis because they had been suckled before sampling (Table 9). There was variation in the residual mass of solids recovered within treatment groups, with all groups having quarters from which no solids were recovered. The mass of solids recovered from individual combination-treated quarters (ABTS and TSAB combined) was less than that from individual quarters receiving TS (0.16 vs. 0.38 g; $P < 0.0001$).

Multivariable Analysis

Dry Period Outcomes. Several different outcomes were investigated, including the likelihood of a quarter being free of a major mastitis pathogen post-calving and of being free of any pathogen post-calving (i.e., no growth post calving). The potential confounding influence of the presence of infection at DO was tested in all models. The findings of these models are shown in Table 10. In the high-SCC infected category, compared with AB-treated quarters, ABTS-treated quarters had increased odds of being free of a major mastitis pathogen post-calving (odds ratio = 1.40; 95% credibility interval = 1.03–1.90) or of no growth post-calving (odds ratio = 1.32; 95% credibility interval = 1.08–1.61). No significant differences were identified between the treatment groups in the low-SCC uninfected cow category.

Clinical Mastitis. The findings of the models investigating factors that influence clinical mastitis are shown in Table 11. The proportion of quarters developing clinical mastitis during the dry period and in the first 100 d of lactation was compared between treatment groups within each of the treatment categories.

Table 4. Prevalence of mastitis pathogens at each of the sampling time points, restricted to quarters and cows eligible for assessment of product efficacy (low-SCC uninfected cows)[1]

	Drying off				Post-calving			
	TS (no. of quarters = 782)		TSAB (no. of quarters = 782)		TS (no. of quarters = 782)		TSAB (no. of quarters = 782)	
Item	n	%	n	%	n	%	n	%
Streptococcus uberis	2	0.26	7	0.90	9	1.15	7	0.90
Escherichia coli	7	0.90	8	1.02	13	1.66	19	2.43
Aerococcus spp.	10	1.28	14	1.79	6	0.77[a]	15	1.92[b]
Coagulase-positive staphylococci	1	0.13	3	0.38	5	0.64	2	0.26
Enterococcus spp.	5	0.64	1	0.13	5	0.64	2	0.26
Bacillus spp.	4	0.51	2	0.26	3	0.38	1	0.13
Yeast spp.	0	0.00	1	0.13	6	0.77	8	1.02
Unspeciated gram-negative	4	0.51	3	0.38	11	1.41	6	0.77
Streptococcus spp.	4	0.51	2	0.26	1	0.13	0	0.00
Mucor spp.	0	0.00	0	0.00	1	0.13	1	0.13
Streptococcus dysgalactiae	1	0.13	0	0.00	4	0.51	0	0.00
Aspergillus spp.	0	0.00	0	0.00	2	0.26	5	0.64
Pseudomonas spp.	0	0.00	1	0.13	1	0.13	2	0.26
Arcanobacterium pyogenes	0	0.00	0	0.00	2	0.26	1	0.13
All *Enterobacteriaceae*	8	1.02	13	1.66	18	2.30	22	2.81
Staph./Strep. spp.[2]	13	1.66	13	1.66	23	2.94[a]	11	1.41[b]
Other major pathogens	5	0.64	8	1.02	8	1.03	2	0.26
All major pathogens[3]	41	5.24	54	6.91	77	9.85	65	8.31
Coagulase-negative staphylococci	233	29.80	248	31.71	191	24.42	170	21.74
Corynebacterium spp.	218	27.88	210	26.85	100	12.79	91	11.64
All minor pathogens[3]	367	46.93	370	47.31	255	32.61	224	28.64
No growth	403	51.53	397	50.77	492	62.92	526	67.26
Contaminated	5	0.64	1	0.13	0	0.00	2	0.26
Total[3]	374	47.83	384	49.10	290	37.08	254	32.48

[a,b]Means within a row within sampling time points with different superscripts differ ($P < 0.05$).

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows.

[2]Coagulase-positive staphylococci and all *Streptococcus* species.

[3]Totals may not equal sum of the individual pathogens as a result of mixed infections.

Combination-treated quarters in the high-SCC infected cow category were less likely to develop clinical mastitis (odds ratio = 0.68; 95% credibility interval = 0.48–0.98), whereas TSAB in the low-SCC uninfected category was not significantly different from TS.

DISCUSSION

The data and results outlined demonstrate the efficacy of the broad-spectrum, first generation cephalosporin, cephalonium, in the treatment and prevention of IMI in nonlactating dairy cows. In particular, cephalonium was highly effective in the treatment of existing IMI, with cure rates consistently in excess of 90% for all pathogens. These results support studies conducted in similar farms in the United Kingdom (Berry and Hillerton, 2002b; Newton et al., 2008).

Consistent with other research, with respect to control of IMI post-calving, ABTS treatment was more effective than AB treatment alone (Godden et al., 2003; Berry and Hillerton, 2007; Newton et al., 2008). Interestingly, in this study in which the effect of combination treatment was studied in cows of differing infection status at DO, the benefits of combining antibiotics and an internal teat sealant in low-SCC uninfected cows was less clear. This study failed to demonstrate increased odds of being pathogen free post-calving when using TSAB compared with using TS alone in low-SCC uninfected cows. This does not mean that there is no effect, but it may be that any such effect was too small to detect given the power.

Dry cow therapy efficacy is more often assessed by measuring cure and new IMI rates. Such traditional approaches limit the power of such efficacy studies and their ability to identify biologically relevant differences in treatment outcome. The use of pathogen free status at calving or freedom from a major mastitis pathogen is a more biologically relevant measure because it

Table 5. Apparent dry period cure rates of the mastitis pathogens[1]

	Infected cows				Uninfected cows			
	AB (no. of quarters = 830)		ABTS (no. of quarters = 831)		TS (no. of quarters = 777)		TSAB (no. of quarters = 779)	
Item	n	%	n	%	n	%	n	%
Streptococcus uberis	26	92.9	30	93.8	2	100	7	100
Escherichia coli	15	93.8	7	100	7	100	8	100
Aerococcus spp.	12	92.3	19	95	10	100	14	100
Coagulase-positive staphylococci	11	91.7	12	100	0	—	3	100
Enterococcus spp.	8	100	7	100	5	100	1	100
Bacillus spp.	4	100	6	100	4	100	2	100
Yeast spp.	1	25.0	0	—	0	—	0	—
Unspeciated gram-negative	3	100	5	100	4	100	3	100
Streptococcus spp.	3	100	5	100	4	100	2	100
Mucor spp.	2	100	1	100	0	—	0	—
Streptococcus dysgalactiae	2	100	4	100	0	—	0	—
Aspergillus spp.	1	100	3	100	0	—	0	—
Pseudomonas spp.	1	100	0	—	0	—	1	100
Arcanobacterium pyogenes	0	—	0	—	0	—	0	—
All *Enterobacteriaceae*	21	95.5	13	92.3	8	100	13	100
Staph./Strep. spp.[2]	50	92.6	56	94.9	11	84.6	13	100
Other major pathogens	2	100	2	100	5	100	8	100
All major pathogens	91	91.9	101	97.1	41	100	49	100
Coagulase-negative staphylococci	181	68.6	189	74.1	139	59.7	166	66.9
Corynebacterium spp.	307	88.2	310	90.4	175	80.3	180	86.1
All minor pathogens	488	79.8	499	83.5	314	69.7	346	75.7
Total	579	81.4	600	85.5	355	72.2	395	78.0

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows; TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows; n = number of infections at drying off that experienced a dry period cure

[2]Coagulase-positive staphylococci and all *Streptococcus* species.

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combines both aspects of dry cow therapy efficacy and allows assessment of the overall variable most likely to affect cow health and profitability.

With respect to clinical mastitis, in a similar manner to earlier research (Newton et al., 2008), ABTS treatment in high-SCC infected cows was beneficial, with a reduction in clinical mastitis in the first 100 d of the subsequent lactation. Interestingly, the reduction in clinical mastitis was less marked than in a similar study conducted when shorter acting, narrow-spectrum antibiotic dry cow therapy was used (Newton et al., 2008), suggesting that there may be benefit in the use of broad-spectrum, longer acting dry cow therapies when such products are used in the absence of an internal sealant. Again, the pattern in low-SCC uninfected cows was less clear; overall, there was no difference in the proportion of quarters affected in the 2 groups. The incidence of clinical mastitis caused by *E. coli* and *Enterobacteriaceae* was significantly increased when both AB and TS were used in combination. This finding supports reports of antibiotic dry cow therapy being a risk factor for coliform mastitis at calving (Schukken et al., 1989) and suggests that the result of using AB in combination with TS in low-SCC uninfected cows was to change the etiology of clinical mastitis in the next lactation without affecting the overall incidence. Given the efficacy of an internal TS in reducing gram-negative IMI in the dry period and subsequent clinical mastitis (Huxley et al., 2002), it is interesting to note that the use of an internal TS in addition to AB in low SCC cows did not reduce the apparent increased risk of these cows developing coliform mastitis; this is undoubtedly an area in need of further research.

There was a significant change in the etiology of IMI post-calving, with quarters of low-SCC uninfected cows receiving TSAB being significantly less likely to be infected with a major staphylococcal or streptococcal pathogen. It may be that this change in etiology and reduction in minor pathogens influenced the likelihood of clinical enterobacterial mastitis in the subsequent lactation (Green et al., 2002, 2005; Bradley and Green, 2004).

A secondary measure was the finding with respect to recovery of the internal TS. Residual solids were reported rather than sealant because visual inspection

Table 6. Apparent dry period new IMI rates for the mastitis pathogens[1]

	Infected cows				Uninfected cows			
	AB (no. of quarters = 830)		ABTS (no. of quarters = 831)		TS (no. of quarters = 777)		TSAB (no. of quarters = 779)	
Item	n	%	n	%	n	%	n	%
Streptococcus uberis	19	2.35	12	1.49	9	1.15	7	0.90
Escherichia coli	27	3.28	20	2.41	13	1.68	19	2.45
Aerococcus spp.	13	1.58	9	1.10	6	0.78	15	1.95
Coagulase-positive staphylococci	7	0.85	3	0.36	4	0.51	2	0.26
Enterococcus spp.	11	1.33	4	0.48	5	0.64	2	0.26
Bacillus spp.	1	0.12	3	0.36	3	0.39	1	0.13
Yeast spp.	8	0.96	6	0.72	6	0.77	7	0.90
Unspeciated gram-negative	8	0.96	9	1.08	11	1.41	6	0.77
Streptococcus spp.	0	0.00	1	0.12	1	0.13	0	0.00
Mucor spp.	3	0.36	3	0.36	1	0.13	1	0.13
Streptococcus dysgalactiae	0	0.00	3	0.36	3	0.38	0	0.00
Aspergillus spp.	2	0.24	2	0.24	2	0.26	5	0.64
Pseudomonas spp.	2	0.24	1	0.12	1	0.13	2	0.26
Arcanobacterium pyogenes	1	0.12	0	0.00	2	0.26	1	0.13
All *Enterobacteriaceae*	37	4.53	24	2.91	18	2.33	22	2.86
Staph./Strep. spp.[2]	34	4.34	23	2.95	21	2.73	11	1.43
Other major pathogens	2	0.24	3	0.36	8	1.10	2	0.26
All major pathogens[3]	104		79		75		70	
Coagulase-negative staphylococci	128	22.54	112	19.28	95	17.37	88	16.48
Corynebacterium spp.	54	11.11	52	10.57	56	9.95	62	10.84
All minor pathogens[3]	182		164		151		150	
Total[3]	286		243		226		220	

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows; TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows; n = number of new infections acquired.

[2]Coagulase-positive staphylococci and all *Streptococcus* species.

[3]Total number of IMI including mixed infections.

identified not only foreign matter but also what may have been the carrier gel of the dry cow antibiotic in some samples. All treatment groups demonstrated a maximum mass of recovered solids, which exceeded that administered in the form of sealant; this could have been for a variety of reasons. Some quarters in the group treated only with AB may have received TS in error at DO, or the additional mass could have been attributed to foreign bodies or residual gel from the antibiotic dry cow formulation. Less TS was recovered

Table 7. Summary of the quarter-level dry period outcomes for each of the treatment groups[1,2]

	Infected cows		Uninfected cows	
Item	AB	ABTS	TS	TSAB
Quarters treated (n)	830	831	777	779
Quarters infected at drying off (n)	546	529	379	384
Quarters uninfected at drying off (n)	284	302	398	395
Quarters uninfected post-calving (n)	500[a]	554[b]	489	523
Quarters experiencing a dry period cure (n)	189	206	293	290
Quarters becoming infected during the dry period (n)	95	96	105	105

[a,b]Means within a row within treatment categories with different superscripts differ ($P < 0.05$).

[1]Values may differ from those in Tables 3, 4, 5, and 6 as a result of exclusion of data from quarters in which a sample was contaminated either at drying off or post-calving.

[2]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows; TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows.

Table 8. Summary of first-quarter cases of clinical mastitis occurring in quarters eligible for inclusion in the analysis of efficacy as measured by the occurrence of clinical mastitis[1]

	Infected cows		Uninfected cows	
Item (n)	AB (no. of quarters = 862)	ABTS (no. of quarters = 862)	TS (no. of quarters = 816)	TSAB (no. of quarters = 816)
Escherichia coli	17	9	1[a]	9[b]
Streptococcus uberis	11	6	4	3
Coagulase-positive staphylococci	5	2	1	
Klebsiella spp.	3	1		2
Yeast spp.	3	2		3
Arcanobacterium pyogenes	2			
Lactococcus spp.	2			
Streptococcus dysgalactiae	2	1		2
Serratia spp.	2	1		1
Unspeciated gram-negative	2		1	
Enterobacter spp.	1			
Enterococcus spp.	1	2		2
Proteus spp.	1			
Pseudomonas spp.	1			
Aspergillus spp.		1		
Bacillus spp.		1		
Streptococcus spp.			1	
All *Enterobacteriaceae*	24[a]	11[b]	1[a]	12[b]
Mixed infection	6	4	3	5
All major pathogens	59[a]	30[b]	11	27
Coagulase-negative staphylococci	3	5	3	5
Corynebacterium spp.	1	2	1	
Coagulase-negative staphylococci and *Corynebacterium* spp.		2		
All minor pathogens	4	9	4	5
No growth	10	10	11	4
No sample	10	10	14	8
Contaminated	1		1	
Total	84[a]	59[b]	41	44

[a,b]Means within a row within treatment categories with different superscripts differ ($P < 0.05$).

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows; TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows.

post-calving from quarters treated with the TS in combination with an oil-based antibiotic formulation than from quarters treated with TS alone. Although this did not affect efficacy as measured, it does raise questions about the suitability of the current formulation when used in combination with oil-based antibiotics. It is likely that the 2 products were miscible and may, if applied in combination, result in a change in the viscosity of the TS, which may affect its ability to function as a plug. The reduction in the amount of TS recovered

Table 9. Summary of the quantity of residual solids recovered from quarters in each of the treatment groups when sampled immediately post-calving

Treatment group[1]	n	Mean (g)	Median (g)	Minimum (g)	Maximum (g)
AB	716	0.17	0.05[a]	0.00	5.36
ABTS	720	0.65	0.14[b]	0.00	6.33
TS	659	1.27	0.38[c]	0.00	6.34
TSAB	652	0.78	0.20[b]	0.00	5.24

[a–c]Means within a column with different superscripts differ ($P < 0.05$).

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows; TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows.

Table 10. Summary of the findings for the multilevel models relating to post-calving outcomes for the infected and uninfected cow categories[1]

Outcome	Intercept	Treatment group	Treatment coefficient	SE	Treatment odds ratio	95% credibility interval	
						Lower	Upper
High-SCC infected cows (reference category = AB)							
No growth post-calving	0.507	ABTS	0.277	0.10	1.32	1.08	1.61
Free of a major pathogen post-calving	−2.02	ABTS	0.334	0.15	1.40	1.03	1.90
Low-SCC uninfected cows (reference category = TS)							
No growth post-calving	0.529	TSAB	0.167	0.10	1.18	0.96	1.45
Free of a major pathogen post-calving	−2.14	TSAB	−0.149	0.17	0.86	0.61	1.22

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows; TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows.

could have been a result of loss of the product from the gland or a result of increased dispersal post-infusion; either or a combination of the 2 are biologically plausible. The apparent effect on retention of the TS when used in combination with an oil-based dry cow therapy questions the compatibility of such products; it may be that the use of a water-based antibiotic formulation in combination with the internal TS would be more appropriate.

This study presents several conundrums to the practitioner. It reinforces the need for careful selection and targeting of dry cow therapies and demonstrates the need for both AB and nonantibiotic approaches. It appears to support the need to stratify herds according to mastitis etiology and pathogen prevalence as well as cows on the basis of likely infection status. The data suggest that in herds with a high prevalence of gram-positive pathogens (and high BMSCC) liberal use of AB in both low- and high-SCC cows may be justified because the imperative is to decrease the overall prevalence of infection. Conversely, in herds with a low prevalence of gram-positive infection (and low BMSCC) the priority may be to optimize control of gram-negative infection and minimize the use of AB in low-SCC cows. Although this approach may be optimal, it is important to consider the technical ability of farm personnel because the use of internal TS alone demands the highest level of aseptic technique.

CONCLUSIONS

The decision of whether to treat cows with both antibiotic dry cow therapy and an internal TS appears complex. Whereas significant benefits are associated with ABTS in high-SCC infected cows at DO, the benefits of TSAB in low-SCC uninfected cows appear less clear. This research suggests that the decision to combination-treat low-SCC uninfected cows is not straightforward and needs to be tempered by the prevalence of different pathogens within the herd as well as the need to manage the current level of BMSCC.

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Table 11. Summary of the findings for the multilevel models relating to clinical mastitis outcomes for each of the cow categories[1]

Outcome	Intercept	Treatment group	Treatment coefficient	SE	Treatment odds ratio	95% credibility interval	
						Lower	Upper
High-SCC infected cows (reference category = AB)							
Clinical mastitis	−2.37	ABTS	−0.381	0.18	0.68	0.48	0.98
Low-SCC uninfected cows (reference category = TS)							
Clinical mastitis	−0.356	TSAB	−0.116	0.18	0.89	0.62	1.28

[1]Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group; all other animals (with complete records) were allocated to the infected group. AB = antibiotic only treatment in infected cows; ABTS = combination treatment in infected cows; TS = internal teat sealant treatment in uninfected cows; TSAB = combination treatment in uninfected cows.

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