

## Dry Cow Therapy – An Update

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### Introduction

The use of antibiotic dry cow therapy (DCT) and the treatment of intramammary infection (IMI) at drying off has been a cornerstone of mastitis management and control over the past six decades (Bradley, 2002). This use along with the other control strategies outlined in the NIRD Five Point Plan has led to a dramatic change in the incidence and aetiology of clinical and sub-clinical mastitis. This change can be summarised as a decrease in the prevalence of contagious mastitis pathogens and an increase in the importance of the environmental pathogens such as *S. uberis* and *E. coli* on the vast majority of well-managed dairy units (Erskine et al., 1988; Barkema et al., 1998; Bradley, 2002). These changes have necessitated a rethink in our approach and our rationale for the use of antibiotics in mastitis control. This paper briefly reviews the role of the dry period in mastitis epidemiology and, in the light of recent research, the use of both antibiotic and non-antibiotic dry cow therapy in the management of intramammary infection during the dry period.

### The Importance of the Dry Period in Mastitis Epidemiology

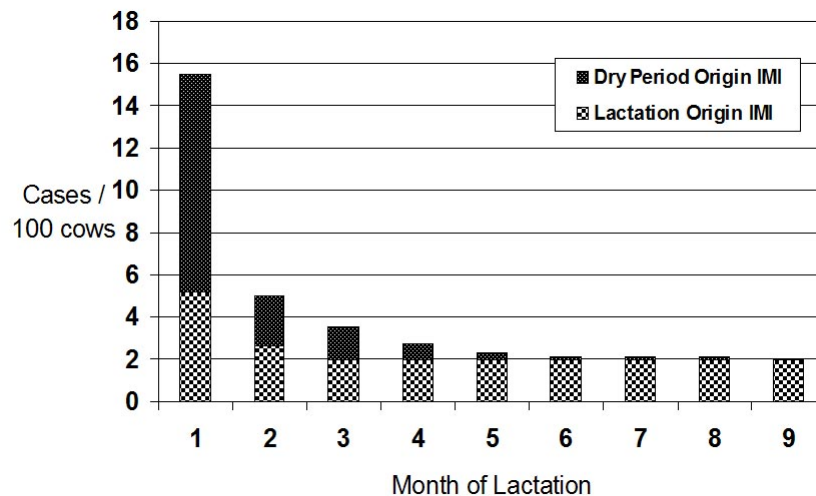
The importance of the dry period in mastitis control has been recognised for many years (Smith et al., 1966; Smith et al., 1967), which was reflected in the importance given to antibiotic DCT in the Five Point Plan (Neave et al., 1966; Neave et al., 1969; Kingwill et al., 1970). More recently, driven by the changes in mastitis aetiology, interest has centred on the role of the dry period in environmental mastitis epidemiology, though here again from as long ago as the 1940's the susceptibility of the non-lactating mammary gland to new IMI with environmental organisms has been documented (Murphy & Hanson, 1943). This susceptibility to new IMI has been confirmed in a number of studies around the world under a host of different management systems (Eberhart & Buckalew, 1977; Oliver & Mitchell, 1983; Smith et al., 1985; Todhunter et al., 1991; Williamson et al., 1995; Bradley & Green, 2001; Berry & Hillerton, 2002; Bradley & Green, 2002). All recent studies, in conventionally managed herds, with moderate somatic cell counts have confirmed that the environmental pathogens are the most significant cause of new IMI during the dry period. In the 'modern' dairy herd, using antibiotic DCT, the vast majority of infections present at calving are new IMIs, the majority of which are acquired in the transition period; in these well managed herds persistence of infection from drying off is rare and the 'cure' rates achieved with antibiotic DCT are high.

Differences in IMI have been reported between farms and between seasons of the year, suggesting that the force of infection during the dry period depends in part on external conditions (Green et al., 2005). This research also found that the probability of isolating some bacterial species during the dry period was influenced by the presence of other species. It is likely, therefore, that the risk of new IMI during the dry period and the likelihood of cure is the result of a complex interaction between the host, the environment and the pathogens and more research in this area would be beneficial.

## The Impact of Dry Period Intramammary Infections on Clinical Mastitis in the Subsequent Lactation

Experimental evidence has demonstrated the ability of infections acquired during the dry period to remain quiescent within the udder, subsequently causing clinical mastitis early in the next lactation (McDonald & Anderson, 1981). More recently, research in the UK using the latest molecular techniques has confirmed this phenomenon in the field and demonstrated that over 50% of all environmental mastitis occurring in early lactation (1<sup>st</sup> 100 days) resulted from infections acquired during the dry period. This research also demonstrated that quarters that became infected during the dry period were significantly more likely to succumb to clinical mastitis with the same pathogen in the subsequent lactation than uninfected quarters (Bradley & Green, 2001; 2002). Furthermore additional studies demonstrated that selection of a DCT with extended activity against gram -ve organisms could result in a 53% reduction in clinical coliform mastitis in early lactation as compared to a DCT with no gram -ve activity (Bradley & Green, 2001), confirming the importance of the dry period in environmental mastitis epidemiology.

As outlined above the acquisition of new IMIs in the dry period can have a dramatic impact on the incidence and distribution of clinical mastitis in the subsequent lactation, and in fact much of the peak in clinical mastitis seen in early lactation can be attributed to dry period infection (Green et al., 2002), as illustrated in Figure 1. This is a particularly useful tool when assessing herd management and targeting control strategies. It is important to remember that infections acquired in the late dry and transition periods are most likely to have a major influence on clinical mastitis in the subsequent lactation (Green et al., 2002) than those acquired shortly after drying off.



**Figure 1:** Data showing the origin of infection (dry period or lactation) in cases of clinical mastitis (Data from Green *et al*, 2002).

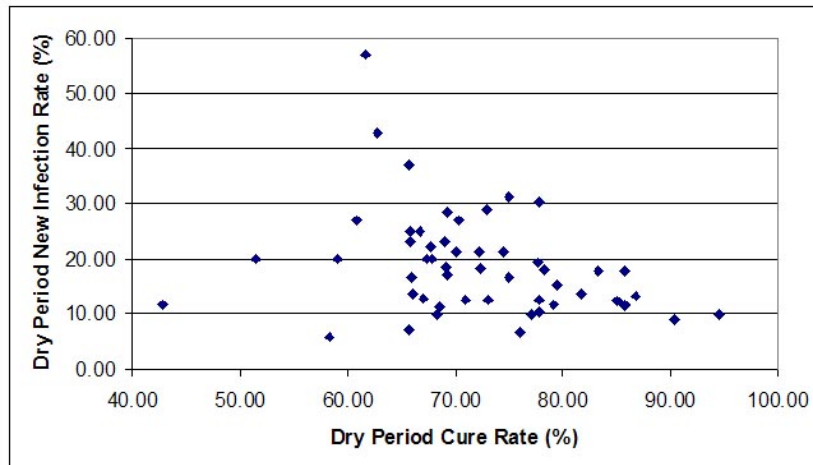
### Prevalence, Incidence and Aetiology of Intramammary Infection

In a recent study in the UK, 52 herds were assessed using individual cow somatic cell counts, for the prevalence of chronic IMIs, IMIs at drying off, the acquisition of new IMIs during the dry period and apparent dry period cure rates over a twelve-month period. In addition, clinical mastitis patterns and incidence rates were assessed as a means of assessing the importance of the dry period on mastitis epidemiology on individual units. The findings of these analyses are summarised in Table I. In summary, there was a wide variation in all of the indices calculated with herds falling both above and below the target level. It is interesting to note the relationship between apparent dry period cure and new infection rates as illustrated in Figure 2.

Interestingly a recent survey of the aetiology of sub-clinical mastitis in the UK has identified *Streptococcus uberis* as the major pathogen most commonly causing elevation of individual cow somatic cell counts accounting for 22.5% of all isolates. In contrast the coagulase +ve *staphylococci* and *enterobacteriaceae* accounted for 16.1% and 6.7% respectively. This has implications for DCT selection as the spectrum of sensitivity of these pathogens is likely to differ and persistent *Escherichia coli* infections often appear to self-cure irrespective of the therapy selected.

**Table 1:** Key Udder Health Parameters from 52 UK Dairy Herds

	Min	Max	Mean	Median	Target
Chronic IMI Rate (%)	4.37	36.17	16.26	15.69	<10
IMI Rate at Drying Off (%)	13.56	52.10	32.40	33.56	<25
New IMI Rate during the Dry Period (%)	5.88	57.14	18.82	17.86	<10
Dry Period Cure Rate (%)	42.86	94.44	72.08	70.64	>85
1st 30 day Clinical Mastitis Incidence Rate (cases/cow year)	0.48	5.73	2.49	2.38	<1



**Figure 2:** An illustration of the relationship between apparent dry period cure and new infection rates in 52 UK dairy herds

The profile of mastitis pathogens causing new IMIs during the dry period will vary between farms and in different parts of the world. However, the pathogens involved will also vary in different seasons and years on an individual unit, and it is important to take this into consideration when developing control strategies to be implemented on farm. Undoubtedly we still have much to learn about the risk factors associated with development and cure of IMIs during the dry period, these risk factors need to be identified by further research. However, even without a full understanding of all the risk factors involved we can make rational decisions and implement effective control strategies on farm.

**The Role of Dry Cow Therapy**

The role of DCT can essentially be split into two distinct functions:

1. the cure of existing IMIs present at drying off
2. the prevention of new IMIs during the dry period.

When the Five Point Plan was first conceived DCT primarily filled its first function as large numbers of cows were infected with a major pathogen at drying off. However, more recently the emphasis has changed and in the majority of modern dairy herds the primary function of dry cow therapy is the prevention of new IMIs rather than the treatment of existing infections; this change has led to

the advent of internal teat sealants and non-antibiotic approaches to dry period mastitis control. That said there are still significant numbers of cows, which are infected at drying off that require treatment, albeit that the pathogens we are trying to combat may have changed (see later).

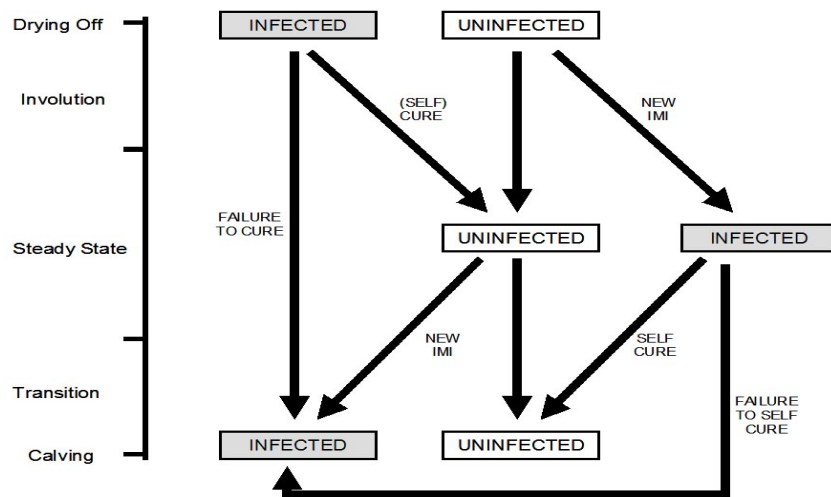
### **The Rationale for Antibiotic Dry Cow Therapy**

There is good evidence to support the use of antibiotic DCT as it is well known that failure to treat cows leads to unacceptably high levels of new IMIs at calving (Berry & Hillerton, 2002) and DCT has been demonstrated to be more effective than lactating cow therapy in combating existing IMIs (Bradley et al., 2003). The physiological and immunological changes that occur in the mammary gland at drying off have been well-studied (Sordillo et al., 1997) and it is worth considering what impact these changes may have on the likelihood of cure of existing IMIs.

There are a number of factors, which are thought to underlie the higher cure rates that are seen when treating IMIs during the dry period. The first of these are those relating to the opportunity the dry period offers to use longer acting antibiotic formulations at a higher dose than can be realistically achieved during lactation, without risk of contamination of the bulk tank. However, some of the physiological and immunological changes occurring during involution are also likely to influence the outcome of treatment. Firstly, following the cessation of milking, leucocyte concentrations (Jensen & Eberhart, 1981; McDonald & Anderson, 1981) and the mammary environment becomes more conducive to leucocyte function (Sordillo & Nickerson, 1988) as fat and casein concentrations in the mammary secretion drop. Immunoglobulin concentrations are also higher in the non-lactating gland (Eberhart, 1986), and this coupled with an increasing concentration of the lysosomal enzymes and the lactoperoxidase system in the dry udder are likely to facilitate cure. Another possible factor that may contribute to cure rates is the increased rate of cell renewal and apoptosis of senescent cells during a dry period (Capuco & Akers, 1999), this increased rate of apoptosis may lead to the release of intracellular organisms and the destruction of micro abscesses in the alveolar ducts thereby increasing the exposure of pathogens to antibiotics. Finally, lactoferrin concentrations rapidly rise following the initiation of involution. This rise is in concentration coupled with decreased in citrate concentration is well known to inhibit the growth of enterobacterial organisms, mediated via the binding of iron (Sordillo et al., 1987; Sordillo et al., 1997). However, lactoferrin also has a number of other roles in the mammary gland, which are less commonly considered which can impact on both gram +ve and gram -ve organisms. As well as being immunomodulatory to leucocytes (Smith & Oliver, 1981) and acting synergistically with IgG<sub>1</sub> against *E. coli* and *Klebsiella spp* (Oliver & Bushe, 1987), lactoferrin can also directly impact the likelihood of cure. More specifically, a synergistic action of lactoferrin and antibiotic as has been reported for *E. coli* (Sanchez & Watts, 1999) and *S. aureus* (Diarra et al., 2002; Diarra et al., 2003), with recent studies demonstrating that lactoferrin can restore the susceptibility of beta-lactamase producing *S. aureus* to penicillin by inhibiting beta-lactamase activity (Diarra et al., 2002).

### **The Role of Teat Sealants**

Whilst considering those factors in the dry gland, which increase the chance of cure, it is important not to overlook the fact that the dry gland also passes through phases of increased susceptibility to new infection, exacerbated by factors such as delayed formation of the keratin plug (Williamson et al., 1995; Dingwell et al., 2001). The impact of this is not that it affects the likelihood of cure of an existing infection *per se*, but more that a high rate of new IMI can result in a perception of a poor cure rate, as illustrated in Figure 3. For this reason, it may be that, in the field, the best option for improving the 'apparent' cure rate during the dry period may be through the improvement of prophylaxis. This prophylaxis is probably best achieved by the use of internal and external teat sealants, the development of which has allowed a paradigm shift in our approach to dry cow therapy. Internal teat sealants have been demonstrated to significantly reduce the prevalence of intramammary infection at calving both when used alone in quarters uninfected at drying off and when used in combination with antibiotics in quarters infected at drying off (Huxley et al., 2002; Newton et al., 2007).



**Figure 3:** An illustration of the possible outcomes for individual quarters during the dry period.

### Route of Administration of Dry Cow Therapy

The intramammary route is the route of choice for delivery of DCT and has the advantages of being well researched, as well as allowing the delivery of high local concentrations of antibiotic and also allows the use of antibiotics that would not normally partition to the udder when administered systemically. Its disadvantages are the risks of both physiological and anatomical damage to the streak canal and inoculation of organisms at the time of infusion. The use of systemic antibiotic therapy has been advocated as a way of enhancing the cure rate of infected quarters. This approach may have merit in a small number of 'valuable' cows, or in situations where producers are keen to retain as many cows as possible within the herd. Its main drawback, which probably precludes its widespread use is cost effectiveness (Bradley et al., 2003); the increase in cure rate achieved above intramammary therapy alone is probably insufficient to justify the cost of treatment.

### Dry Cow Therapy - Design Considerations

A detailed knowledge of the pharmacokinetics of DCT is beyond the scope of this paper; however, it is useful to consider some of the properties that are important in the distribution and efficacy of intramammary antibiotics. The ideal DCT should achieve high initial concentrations throughout the udder parenchyma in order to affect a kill of existing pathogens; this should then be followed by a prolonged period of release of antibiotic to prevent new infections. Ideally the antibiotic should be retained within the udder (with only limited absorption into the systemic circulation) and will be rapidly milked out following calving.

The rate of absorption and distribution of antibiotics from an intramammary formulation is governed by a number of factors. Aluminium monosterate complexes penicillins and is used along with hydrophobic globules to facilitate prolonged release of antibiotic which would otherwise be rapidly distributed and absorbed into the systemic circulation. Particle size has also been demonstrated to affect the rate and efficiency of distribution of intramammary products (Ehinger & Kietzmann, 2000) and may prove beneficial in ensuring the MIC is exceeded throughout the udder. The distribution of drugs following intramammary administration is summarised in Table 2. Absorption from the mammary gland into the systemic circulation is by passive diffusion; the rate of this diffusion is affected by the aqueous and lipid solubilities the degree of protein binding and the pKa (which results in the 'ion trapping' of basic drugs in the udder and the rapid absorption of acidic drugs). These properties result in the rapid absorption of drugs such as the aminopenicillins and the relatively poor absorption of drugs such as dihydrostreptomycin and framycetin.

**Table 2:** Typical distribution of classes of antibiotics through the mammary gland following intramammary infusion (adapted from Ziv (1980).

Good Distribution	Moderate Distribution	Poor Distribution
Penethamate	Cephalonium	Dihydrostreptomycin
Aminopenicillins	Cloxacillin	Framycetin
	Nafcillin	Neomycin

### Antibiotic Spectrum and Pathogen Sensitivity

A summary spectrum of activity, of the antibiotics available in dry cow, against the major mastitis pathogens is outlined in Table III. As discussed earlier, the primary pathogens causing significant persistent IMIs at drying off are *Streptococcus uberis*, *Staphylococcus aureus*, and other streptococci. It is interesting to note that despite over 30 years of extensive use there are still no recorded resistant to cloxacillin in *S. aureus* strains isolated from bovine milk (Booth, 1997).

**Table 3:** Typical spectrum of activity of antibiotics commonly found in DCT formulations in the UK

	Gram +ves	B-Lactamase S. aureus	Gram -ves
Penicillins/Penethemate	+++	-	-
Ampicillin	++	-	+
Cloxacillin / Nafcillin	+++	+++	-
Cephalonium	++	++	++
Cefquinome	++	++	++
Dihydrostreptomycin	+	++	+++
Framycetin / Neomycin	++	++	+++

As a principle of prudent use of antibiotics it is best practice to select as narrow a spectrum product as possible to cure and prevent IMIs. However, a conundrum exists because dry cow therapy has the dual purpose of treatment and prevention, and often the pathogens we are trying to treat are different to the ones we are trying to prevent. On that basis DCT is probably one of the few examples of a product where 'poly-pharmacy' is justified in order to optimise the spectrum and pharmacokinetics for the combination of pathogens commonly involved.

One possible solution to this dilemma is likely to be the development of approaches using both antibiotic DCT and teat sealants. External sealants have been available for a number of years and provide an obvious supplement to antibiotic DCT. However, more recently studies have demonstrated the efficacy of using an internal teat sealant in combination with antibiotic DCT. These studies have demonstrated a significant benefit of this combination approach over the use of narrow spectrum antibiotics alone (Godden et al., 2003) when used on all cows irrespective of infection status at dry off; combination quarters acquiring significantly fewer infections during the dry period and also having significantly lower ICSCCs in the subsequent lactation.

### The Levels of Application of Dry Cow Therapy

The prescription of DCT can essentially be approached at the herd, cow or quarter level. In the past DCT has often been prescribed in a blanket manner with all cows in the herd receiving the same product. However, this is unlikely to be the most appropriate approach because it is unusual for the same pathogen on a farm to be responsible for chronic IMI at drying off as well as new IMI during the dry period: An antibiotic for treating persistent *Staphylococcus aureus* infections is unlikely to be the product of choice for preventing new coliform IMIs in the late dry period. Selecting treatments at the quarter level proves difficult. This approach raises practical as well as regulatory issues but research has also demonstrated that it is unlikely to be the most cost effective approach to managing IMIs in the dry period when taking a selective approach to DCT use (Browning et al., 1990).

Application of DCT at the cow level provides the most appropriate approach to prescription. This approach relies on the ability to be able to reliably differentiate between infected and uninfected cows and becomes increasingly important if one is considering non-antibiotic approaches to preventing new IMIs in cows uninfected at drying off.

### **Product Selection**

Another key to successful dry cow udder health management is to establish a picture of the aetiology and epidemiology of mastitis on a unit, thereby informing the practitioner's decision with respect to product selection; some of the tools available for this approach are outlined below. There is a large amount of data available to the practitioner to aid in making evidence based decisions about product selection and use. BMSCCs as well as individual cow somatic cell counts on recording farms can be used to establish a picture of herd prevalence of subclinical intramammary infection (Green et al., 2002). Clinical mastitis data and figures on lactating tube usage are also valuable indicators (Green et al., 2002). However, it is vital to supplement this data with strategic use of bacteriology. It is definitely worthwhile culturing a proportion of high SCC cows within the herd towards the end of lactation, not necessarily to make treatment decisions on the individual cows sampled but more to establish a picture of the pathogens causing subclinical infection in the herd, thereby informing therapy selection for treatment. Culturing a proportion of clinical mastitis cases is often the most valuable indicator when making decisions about DCT (Green et al., 2002). Culture of selected cases can help to build up a picture of mastitis aetiology on a unit as samples from clinical cases early in lactation will give an indication of the main cause of new IMI during the dry period and samples from recurrent cases in later lactation are likely to indicate which pathogens are causing sub-clinical infection at drying off.

### **Identifying the Infected Cow**

The generally accepted method currently applied to identify infected cows in a dairy herd is the use of cow level SCCs. The threshold applied for identification of infected cows varies around the world and should be influenced by local factors such as milk quality payments and frequency of cell count recording. However, there is a sound body of international evidence to suggest that 200,000 cells/ml is a sensible threshold to implement (Dohoo & Leslie, 1991; Schepers et al., 1997; Bradley et al., 2002). When using individual cow SCCs it is important not to base decisions on just one or two counts and recordings should be interpreted in the light of other production data. Cows in late lactation will tend to experience a slight rise in SCC (irrespective of infection status) (Schepers et al., 1997) and may not be infected even if they breach the 200,000 threshold – in contrast cows which remain below the 200,000 threshold but experience a dramatic rise in SCC may have suffered an infection event.

It is also important to emphasise that when using individual cow somatic cell counts (or any other criteria) as an indicator of infection status the exact threshold used on a unit needs to be arrived at after taking into account a number of factors, including among others the current BMSCC, the prevalence and species of contagious pathogen on the unit, the producers target BMSCC as well as the philosophy and ability of the unit's staff. A balance needs to be struck between the need to remove current infections and the optimal treatment for preventing new IMIs. However, if there is any doubt, it is probably best to err on the side of caution and if there is any doubt about a cow's infection status she should be treated as infected as DCT provides the best opportunity to effect a cure in a sub-clinically affected cow.

### **To Treat or not to Treat?**

One of the 'keys' to successful DCT use is the selection of which cows are appropriate to treat and which cows are appropriate to cull. A variety of criteria to aid in this decision have been put forward over the years and are outlined in Table 4 below. The aim has to be to select cows in which there is a good chance of obtaining a cure. The chance of a cure is affected by a number of bacterial, cow and herd factors and also the choice of therapeutic agent. A number of these factors are

beyond our control. However, in principle older cows with higher somatic cell counts (SCC), with multiple quarters infected, on poorly managed units will be more difficult to cure (Sol et al., 1994; Schukken et al., 2001). In a similar manner, one needs to consider factors likely to influence the likelihood of acquisition of a new intramammary infection, as outlined in Table 5.

**Table 4:** Factors influencing the likelihood of cure of pre-existing intramammary infections

<b>Increasing likelihood of cure</b>	<b>Decreasing likelihood of cure</b>
<b><u>Cow Factors</u></b>	
↓ SCC ↓ Parity ↓ Number of infected quarters	↑ SCC ↑ Parity ↑ Number of infected quarters
<b><u>Bacterial factors</u></b>	
Susceptible	Resistant
	Specific avoidance factors (eg intracellular) Presence of virulence factors
<b><u>Antibiotic Factors</u></b>	
Good distribution and exceeding MIC throughout udder tissue	Poor distribution and failure to achieve MIC throughout the udder
<b><u>Herd Factors</u></b>	
↑ Hygiene ↓ BMSCC ↓ New IMI rate ↓ Prevalence of new <i>S. aureus</i> IMI	↓ Hygiene ↑ BMSCC ↑ New IMI rate ↑ Prevalence of new <i>S. aureus</i> IMI

**Table 5:** Factors influencing the likelihood of acquiring a new IMI during the dry period

<b>Increasing likelihood of a new IMI</b>	<b>Decreasing likelihood of a new IMI</b>
<b><u>Cow Factors</u></b>	
Severe hyperkeratosis of the teat end Absence of a functional keratin plug at the teat-end  Higher yield at drying-off	None, mild or moderate teat-end damage Keratin plug formed or augmented with an internal teat sealant  Yield < 10 litres or at least < 15 litres at drying off
<b><u>Bacterial factors</u></b>	
Presence of <i>C. bovis</i> at drying-off (keratinolytic properties?)	Presence of <i>C. bovis</i> in the late dry period
<b><u>Antibiotic Factors</u></b>	
Unhygienic DCT administration technique	Hygienic DCT administration technique Selection of a product with prolonged Gram negative activity Selection of an internal teat sealant
<b><u>Herd Factors</u></b>	
↑ Farm Hygiene ↓ BMSCC ↓ New IMI rate ↓ Prevalence of new <i>S. aureus</i> IMI	↓ Farm Hygiene ↑ BMSCC ↑ New IMI rate ↑ Prevalence of new <i>S. aureus</i> IMI

## Monitoring the Use and Measuring the Success of Dry Cow Therapy

A strategy and protocol needs to be in place to address cows that either abort or calve early following administration of DCT and also for identification of dry cows so as to prevent accidental contamination of the bulk tank. Preferably there should be a standard operating procedure for cows calving early and milk should either be tested on farm using a kit such as the DelvoSP (Gist-brocades BV, The Netherlands) or sent to a lab for analysis, before it is returned to the bulk tank.

It is also important to have a strategy in place for the monitoring of the efficacy of dry cow therapy both in curing existing and preventing new IMIs. It would not be cost effective to do this using bacteriology; however, the use of the CMT or SCC records provide a viable alternative. Screening cows known to have been infected at drying off, using the CMT in the first few weeks of lactation will facilitate the identification and removal of persistently infected quarters / cows that pose a risk to other quarters / cows in the herd. Probably the most useful way to monitor the ongoing success/failure of DCT is to monitor SCCs recorded in the last three and first three months of lactation as illustrated in Table 6 (as an alternative an assessment can be made by looking at the first SCC in lactation alone – this will allow a more rapid though arguably less precise assessment, though it will minimise any effect of infections acquired early in lactation).

An additional guide can also be got from looking at the distribution of clinical mastitis cases throughout lactation, an approach the authors find extremely useful; a high incidence of clinical mastitis in early lactation is probably an indication of a high level of intramammary infection during the dry period (Green et al., 2002), culture of a proportion of these cases is likely to give you an indication of the most important cause of new IMIs during the dry period. Using these approaches it is possible to monitor the ongoing success of DCT in a subjective manner and make logical, evidence based decisions about any changes.

**Table 6:** Using Individual Cow Somatic Cell Counts to Monitor the Success of Dry Cow Therapy

SCC pre drying off (cells/ml)	SCC post calving (cells/ml)	Reason	Treatment Outcome
< 200,000	< 200,000	New IMI prevented	Success
< 200,000	> 200,000	New IMI acquired	Failure
> 200,000	< 200,000	Existing IMI cured and new IMI prevented	Success
> 200,000	> 200,000	Existing IMI not cured or existing IMI cured and new IMI acquired	Failure

### Conclusion

In conclusion, the dry period offers the best opportunity during the lactation cycle to remove existing, persistent intramammary infections, though unfortunately this opportunity is tempered by an increased risk of new intramammary infection. In order to achieve the best cure rates it is important to select an appropriate antibiotic in the light of the prevailing mastitis epidemiology and aetiology on an individual unit. Whilst selection of the correct therapy is essential it is vital to ensure other aspects of dry cow management are optimised to ensure that good cure rates are translated into uninfected quarters at calving. Finally, it is essential to have a monitoring system in place to ensure that the therapy and management selections made are delivering the expected performance.

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