Optimising Decision Making in Mastitis Control

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Abstract

Mastitis remains one of the most common diseases of dairy cows and represents a large economic loss to the industry as well as a considerable welfare issue to the cows affected. Decisions are routinely made about the treatment and control of mastitis despite evidence being sparse regarding the likely consequences in terms of clinical efficacy and return on investment. The aim of this thesis was to enhance decision making around the treatment and prevention of mastitis using probabilistic methods.

In Chapter 2 and Chapter 3, decision making around the treatment of clinical mastitis was explored using probabilistic sensitivity analysis. The results from Chapter 2 identified transmission to be the most influential parameter affecting the cost of clinical mastitis at cow level and, therefore, highlighted how important the prevention of transmission was in order to minimise losses associated with clinical mastitis. The cost-effectiveness of an on-farm culture (OFC) approach to the treatment of clinical mastitis was explored in Chapter 3, and compared with the cost-effectiveness of a 'standard' approach commonly used in the UK. The results of this study identified that the OFC approach could be cost-effective in some circumstances but this was highly dependent on the proportion of Gram-negative infections and the reduction in bacteriological cure rate that may occur as a result of the delay before treatment. Therefore, in the UK, this approach is unlikely to be cost beneficial in the majority of dairy herds.

In Chapters 4, 5 and 6, decision making around the control of mastitis was explored utilising data from UK dairy herds that had participated in a nationwide mastitis control plan. In Chapter 4, mastitis control interventions were identified that were not currently practised by a large proportion of herds, and the frequency at which they were made a priority by the plan deliverers was also reported. In Chapter 5 and Chapter 6, the cost-effectiveness of specific mastitis control interventions was explored within an integrated Bayesian cost-effectiveness framework from herds with a predominance of environmental intramammary infections. Results from the Bayesian microsimulations identified that a variety of interventions would be cost effective in different farm circumstances. The cost-effectiveness of different interventions has been incorporated in a decision support tool to assist optimal decision making by veterinary practitioners in the field.

Publications

Chapter 2

Down, P. M., Green, M. J., Hudson, C. D. 2013. Rate of transmission: A major determinant of the cost of clinical mastitis. J. Dairy Sci. 96, 6301-6314

Chapter 3

Down, P. M., Bradley, A. J., Breen, J. E., Green, M. J. Factors affecting the cost-effectiveness of an on-farm culture approach for the treatment of clinical mastitis in dairy cows. Submitted to J. Dairy Sci. 2016

Chapter 4

Down, P. M., Bradley, A. J., Breen, J. E., Hudson, C. D., Green, M. J. 2016. Current management practices and interventions prioritised as part of a nationwide mastitis control plan. Vet. Record. 178:449

Chapter 5

Down, P. M., Bradley, Breen, J. E., A. J., Browne, W. J., Kypraios, T., Green, M. J. A Bayesian micro-simulation to evaluate the cost-effectiveness of interventions for mastitis control during the dry period in UK dairy herds. Submitted to Prev. Vet. Med. 2016

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Abbreviations

CM	Clinical mastitis
SCC	Somatic cell count
BMSCC	Bulk milk somatic cell count
IRCM	Incidence rate of clinical mastitis
CMDP	Clinical mastitis of dry-period origin
CMLP	Clinical mastitis of lactation origin
DPNIR	Dry-period acquired new intramammary infection
LNIR	Lactation acquired new intramammary infection
DPCR	Dry-period cure rate
DMCP	AHDB Dairy Mastitis Control Plan
EDP	Environmental dry-period
EL	Environmental lactation
CDP	Contagious dry-period
CL	Contagious lactation
RCT	Randomised controlled trial
PSA	Probabilistic sensitivity analysis
MCMC	Markov chain Monte Carlo
IMI	Intramammary infection
ml	Millilitres
DCT	Dry cow therapy
hr	Hour

Chapter 1
Introduction

1.1 Background

1.1.1 The importance of mastitis in dairy cows

Bovine mastitis can be defined as 'inflammation of the mammary gland' and can have either an infectious or non-infectious aetiology (Bradley, 2002). Bovine mastitis can be classified as being either clinical (CM), whereby gross changes are seen in the milk, or subclinical if no such changes are visible but changes in the secretion are present, such as an increase in somatic cell count (SCC). Mastitis is the most costly infectious disease affecting dairy cattle, accounting for 38% of the total direct costs of the common production diseases (Huijps et al., 2008; Kossaibati and Esslemont, 1997). A conservative estimate for the total cost of CM to the UK dairy industry alone is in excess of £168 million annually (Bradley, 2002). The cost of subclinical mastitis to the industry is harder to quantify as it is more variable and includes more hidden costs such as reduced yield, increased risk of culling and increased risk of clinical mastitis. However, a Dutch study found that the majority (55%) of the total cost of mastitis is caused by subclinical infections (Huijps et al., 2008).

Whilst the economic consequences of mastitis are reasonably well defined, the same is not true with respect to the impact that mastitis has on the welfare of the affected cows. There is, however, an increasing awareness within the industry of this aspect of the disease (Fitzpatrick et

al., 1998; Huxley and Whay, 2007; Leslie and Petersson-Wolfe, 2012) and a general acceptance of welfare guidelines such as the five freedoms (*Farm Animal Welfare Council Press Statement*, 1979) and advice given by the Farm Animal Welfare Council (Farm Animal Welfare Council, 2009) and European Food Safety Authority (Algers et al., 2009). One of the 'five freedoms' is "Freedom from Pain, Injury and Disease" and therefore, it is incumbent on all those working with dairy cows to be aware of the potential impact that mastitis has on the health and well-being of the dairy cow population.

Other factors which have been shown to motivate farmers to improve mastitis management include job satisfaction, external recognition from peers and improved milk quality (Valeeva et al., 2007). In addition to these incentives for reducing mastitis in dairy cows, there is also increasing pressure on the industry to reduce the use of antimicrobial drugs in food-producing animals because of possible implications for human health through the emergence of antibiotic-resistant strains of bacteria (White and McDermott, 2001). This pressure has led to the banning of some antimicrobial drugs from use in food producing animals in certain countries already (Page, 1991) and has prompted a widespread call for governments to implement stricter controls on the use of 'high risk' antimicrobial drugs such as 3rd and 4th generation cephalosporins and fluoroquinolones (EFSA, 2011). Given that the treatment of mastitis accounts for the majority of the total antimicrobial drug usage on most dairy farms (Pol and Ruegg, 2007), this represents a further compelling

reason for striving to reduce mastitis in dairy cows and to consider carefully how we apply the use of antimicrobial drugs in the treatment and control of mastitis.

1.1.2 Mastitis pathogens

Most cases of mastitis occur in response to a bacterial infection of the mammary gland, but other agents that are known to cause mastitis in dairy cows include mycoplasmas, yeasts and algae. More than 130 different pathogens have been associated with bovine mastitis (Watts, 1988). The vast majority of mastitis in the UK is of bacterial origin with just four species (*Escherichia coli, Streptococcus uberis, Staphylococcus aureus and Streptococcus dysgalactiae*) accounting for over 70% of all diagnoses made (Anon, 2009).

Mastitis pathogens have historically been classified as either 'contagious' or 'environmental' (Blowey and Edmondson, 2010). Contagious bacteria commonly exist within the mammary gland and are transmitted from cow to cow during the milking process (Radostits et al., 1994). They are associated with persistent infections which are reflected by a raised SCC. The bacteria most likely to behave in a contagious manner include *Staphylococcus aureus*, *Streptococcus dysgalactiae* and *Streptococcus agalactiae*. Environmental bacteria are not adapted to survive in the host but are opportunistic invaders from the cow's environment. These are generally acquired between milkings, multiply, instigate an immune response and are rapidly dealt with by the immune system resulting in a transient increase in SCC. The bacteria most likely to infect cows via the

environment include the *Enterobacteriacae* and *Streptococcus uberis.* The distinction between contagious and environmental pathogens is not clear cut and there appears to be some overlap of transmission behaviour within pathogen species. This has been highlighted by studies that have demonstrated persistent infections with both *Strep. uberis* (Todhunter et al., 1995; Zadoks et al., 2003) and *E. coli* (Bradley and Green, 2001a; Döpfer et al., 1999; Hill and Shears, 1979; Lam et al., 1996b) in addition to studies that have shown that *E. coli* is quite capable of causing recurrent infections (Bradley and Green, 2001a; Lam et al., 1996b). It is not possible, therefore, to definitively categorise a mastitis pathogen as being contagious or environmental based on bacteriology alone and any bacteriology results should be interpreted in light of the mastitis epidemiology for a given farm (Green, 2012).

Mastitis pathogens have also historically been classified as either 'major' or 'minor' pathogens based on the inflammatory response that they engender and their propensity to cause clinical signs. The 'major' pathogens comprise *Staph. aureus*, *Strep. dysgalactiae*, *Strep. agalactiae*, *Strep. uberis* and the *Enterobacteriacae*. The 'minor' pathogens comprise the *Corynebacterium* spp. and the coagulase-negative *Staphylococcus* spp (CNS). The 'minor' pathogens are generally associated with mild immune responses and rarely with clinical signs, however, as discussed previously, this classification is often considered to be too simplistic as some strains of *Staph. aureus* are coagulase negative and could, therefore, be classed as 'minor' pathogens which they are not (Green, 2012).

1.1.3 Historical perspective in the UK

In the 1940's, the average herd size in the UK was approximately 15 cows (Bradley, 2002) and the average bulk milk somatic cell count (BMSCC) was approximately 750,000 cells/ml (Booth, 1997). This situation changed considerably in the 1960's with the introduction of the 5-point plan which was devised from research at the National Institute for Research in Dairying in Reading (Kingwill et al., 1970; Neave et al., 1969, 1966; Smith et al., 1967). The plan consisted of the rapid identification and treatment of clinical mastitis, the routine application of antibiotic dry cow therapy at drying off, post-milking teat disinfection, the culling of chronically infected cows and the routine maintenance of the milking machine. This was further compounded by the implementation of EC Milk Hygiene Directive (92/46) that stipulated an upper BMSCC of 400,000 cells/ml for milk destined for human consumption and the addition of financial bonuses offered to producers via the milk buyers for the production of milk with lower SCC. The result of the 5-point plan and the EC milk hygiene directive was a rapid reduction in BMSCC from over 600,000 cells/ml in 1967 to just over 400,000 cells/ml in 1982 (Booth, 1997) and a reduction in the incidence of CM from over 150 cases/100 cows/year to around 40 cases/100 cows/year over the same period of time (Wilesmith et al., 1986; Wilson and Kingwill, 1975). The main driver behind the success of the 5-point plan appeared to be in reducing Gram-positive infections caused by contagious pathogens, the prevalence of which has reduced dramatically since the 1960's. A study by Wilson and Kingwill. (1975) showed that contagious pathogens accounted for almost

60% of clinical mastitis cases in 1967 whereas Bradley et al. (2007b) showed that they accounted for just 10% by 2005.

1.1.4 Current UK Situation

With respect to the current situation in the UK, the average herd size is currently 133 cows (AHDB Dairy, 2014) and the most recent study suggested that the incidence rate of clinical mastitis was likely to be between 47 and 65 cases per 100 cows per year (Bradley et al., 2007b). This is higher than many previous estimates (Berry, 1998; Milne et al., 2002; Peeler et al., 2000, 2002), but in line with several others (Bradley and Green, 2001b; Kossaibati et al., 1998; Wilesmith et al., 1986). All of these studies have the potential of introducing selection bias as a result of farmers having to volunteer to participate in the surveys.

The average BMSCC is currently around 167,000 cells/ml, and this has reduced each year since 2009 (DairyCo, 2015), which corresponds with the time that the national mastitis control plan was launched in the UK (Figure 1-1).

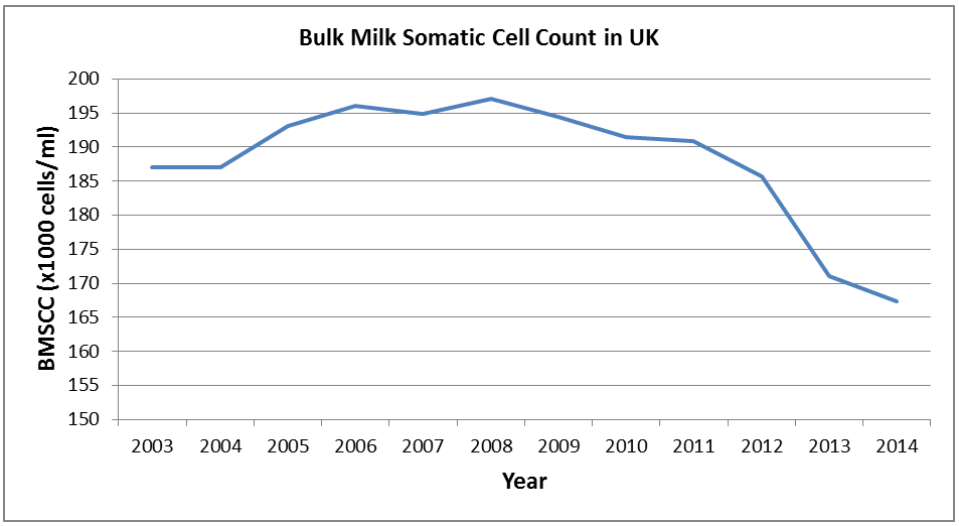


Figure 1-1 UK average bulk milk somatic cell count over time. *(DairyCo, 2015)*

The aetiology of clinical mastitis in the UK, taken from the study by Bradley et al. (2007b), suggests that pathogens traditionally classified as 'environmental' now predominate, accounting for around 60% of positive samples, with *Strep. uberis* being the most common pathogen. In contrast, pathogens traditionally classified as 'contagious' accounted for around 13% of diagnoses made. This finding is in broad agreement with previous studies (Bradley and Green, 2001b; Milne et al., 2002; Wilesmith et al., 1986) that all show that 'environmental' pathogens are the main cause of clinical mastitis in most UK dairy herds.

1.1.5 Measuring mastitis

The primary measures of mastitis in dairy cows are the incidence rate of clinical mastitis (IRCM), which is typically reported in cases/100 cows/year, and somatic cell count, which is typically reported in cells/ml.

Clinical mastitis

The conventional approach to CM analysis has been focused on the reporting of basic quarter and cow rates and incidences as well as certain ratios, such as the case-to-cow-case ratio (total number of quarter-cases/number of cow-cases) (Bradley et al., 2008a). Whilst the absolute rates and ratios give some indication as to the extent and likely aetiology of mastitis on a particular dairy farm, they are less informative when it comes to the targeting of mastitis control interventions and, for this, a different approach is required. One such approach is to categorise CM by its putative origin based on the temporal occurrence during the lactation cycle in which it presents, with cases that occur in early lactation

attributed to the dry period (Bradley et al., 2008b). This approach stems from studies that demonstrated that intramammary infections may be acquired from the environment during the dry period (Berry and Hillerton, 2002; Bradley and Green, 2001c; Eberhart and Buckalew, 1977; Oliver and Mitchell, 1983; Smith et al., 1985; Todhunter et al., 1991; Williamson et al., 1995), and that these infections are able to persist in the udder and cause CM in the subsequent lactation (Green et al., 2002; McDonald and Anderson, 1981). In the study by Green et al. (2002), it was demonstrated that over 50% of all environmental mastitis occurring in the first 100 days of lactation resulted from infections acquired during the dry period. A subsequent study demonstrated that much of the peak in clinical mastitis seen in early lactation can be attributed to dry period infections, particularly cases occurring in the first month of lactation (Green et al., 2002). Therefore, the incidence rate of clinical mastitis in the first 30 days of lactation can be a useful proxy for the rate of dry-period origin infections (Bradley et al., 2008b), and this novel approach has been demonstrated as being helpful in the targeting of mastitis interventions at herd level (Green et al., 2007b).

The target commonly used in the UK for clinical mastitis of dry-period origin is <1 in 12 (1 case for every 12 cows in the herd per year) and the target for clinical cases of lactation origin (clinical cases after the first 30 days of lactation) is typically <2 in 12, giving an overall rate of fewer than 3 in 12 cows affected in a lactation cycle (Bradley et al., 2008b) (Figure 1-2 and Figure 1-3).

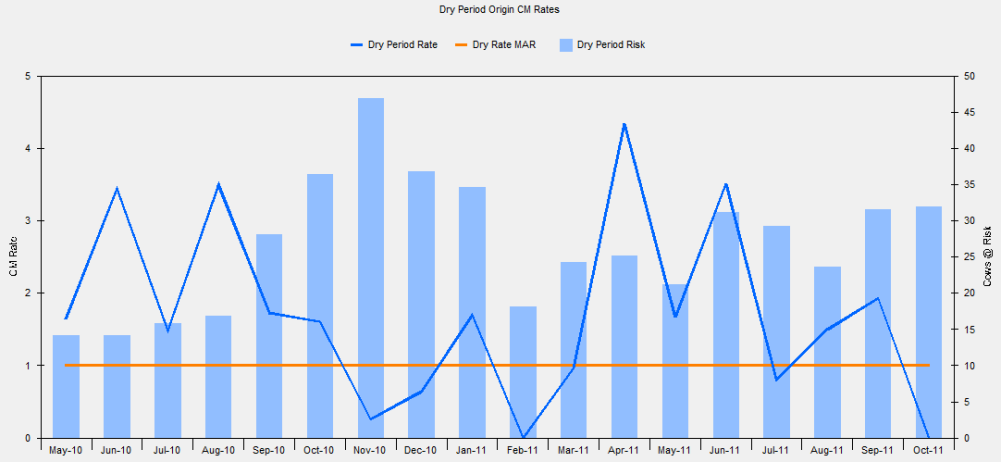


Figure 1-2 Cases of clinical mastitis of dry-period origin plotted over time. The light blue bars illustrate the number of cows at risk and the dark blue line illustrates the rolling 3-recording rate of dry period new infections. MAR = maximum advisable rate (target). (TotalVet©)

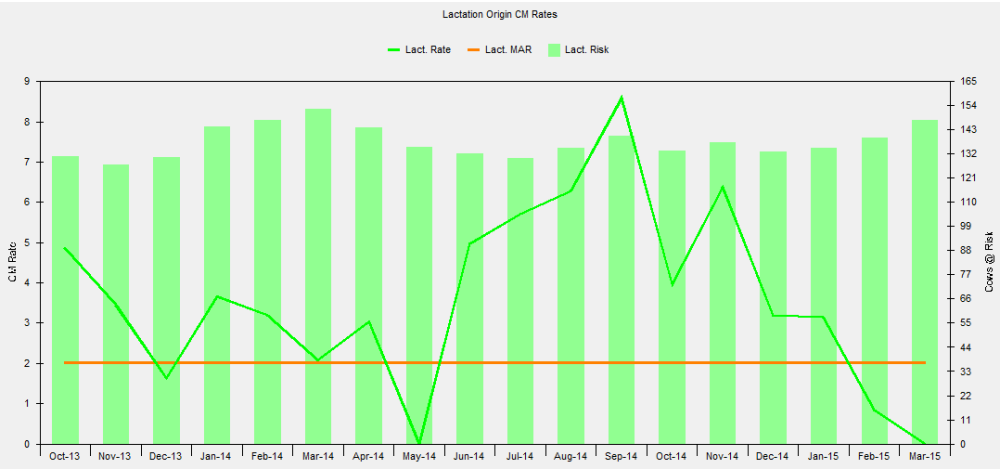


***Figure 1-3 Cases of clinical mastitis of lactation origin plotted over time*.** The light green bars illustrate the number of cows at risk and the dark green line illustrates the rolling 3-recording rate of lactation origin infections. (TotalVet©)

Somatic cell count

The majority of somatic cells found in milk are leukocytes including macrophages, lymphocytes and neutrophils (Lee et al., 1980; Sordillo et al., 1997). The number of somatic cells in milk is known to be affected primarily by intramammary infections (Schepers et al., 1997) due to the massive influx into the udder of peripheral neutrophils (Paape et al., 2002; Sordillo et al., 1997), making it a useful marker of subclinical mastitis.

Cow level SCC data is relatively easy to collect and readily available in most milk recorded herds, compared with CM data, and the concentrations of somatic cells are used to categorise individual cows as 'infected' or 'uninfected' according to defined thresholds. An SCC of < 100,000 cells/ml is generally accepted to indicate the absence of infection (Sordillo et al., 1997), whereas a SCC > 200,000 cells/ml is indicative of a bacterial infection (Brolund, 1985; Schepers et al., 1997). The widely accepted threshold above which cows are considered to be 'infected' is 200,000 cells/ml although test sensitivity is reduced at this threshold in herds with a high prevalence of 'minor' pathogens (Dohoo and Leslie, 1991). Therefore, most standard approaches to measuring subclinical mastitis in dairy herds focus on the movements of cows above and below this threshold. Historically, SCC analysis typically comprised the proportion of cows above 200,000 cells/ml, the proportion of the herd chronically infected (> 200,000 cells/ml for 2 or more consecutive recordings) and the bulk milk somatic cell count (SCC of composite milk sample from all milking cows). With advances in computer software, it is possible to perform an in-depth and robust SCC analysis whereby specific SCC indices are used to characterise the mastitis epidemiology for a particular dairy farm. Commonly reported SCC parameters now include the lactation new infection rate (LNIR) which is a measure of the proportion of cows moving from a SCC < 200,000 cells/ml, to a SCC > 200,000 cells/ml each month, dry period new infection rate (DPNIR) which is a monthly measure of the proportion of cows that have a SCC > 200,000 cells/ml at the first milk recording after calving that had a SCC <

200,000 cells/ml at the last milk recording before being dried-off and dry period cure rate which is a monthly measure of the proportion of cows that had a SCC < 200,000 cells/ml at the first milk recording after calving that had a SCC > 200,000 cells/ml at the last milk recording before being dried-off (Bradley et al., 2007a).

As with CM data, the relative importance of the dry-period may also be reflected in somatic cell count trends such as the dry-period new infection rate and the dry-period cure rate. Common targets for these are <10%/month and >85%/month respectively, however, the dry period cure rate tends to decrease as the rate of dry period new infection rate increases, as a result of reinfection of previously high SCC quarters that had cured earlier during the dry-period, and this needs to be factored into the interpretation of dry-period data (Figure 1-4 and Figure 1-5).

The lactation new infection rate (LNIR) provides a measure of the proportion of cows acquiring a new intramammary infection between consecutive milk recordings and this can also be a useful measure of the relative importance of the dry-period versus lactation (Figure 1-6). A common target is 5-7%/month moving from SCC < 200,000 cells/ml to > 200,000 cells/ml, although the UK mean is likely to be nearer 10%/month (Green, 2012).

Figure 1-4 Dry period new infection rate over time. The dark blue bars represent the percentage of cows, within 30 days of calving with a somatic cell count > 200,000 cells/ml; the light yellow and light green bars illustrate the number of cows at the first recording (and < 30 days in milk) and the number defined as 'infected', respectively; the red line illustrates the rolling 3-monthly rate of dry period new infections and the orange line represents the target. (TotalVet©).

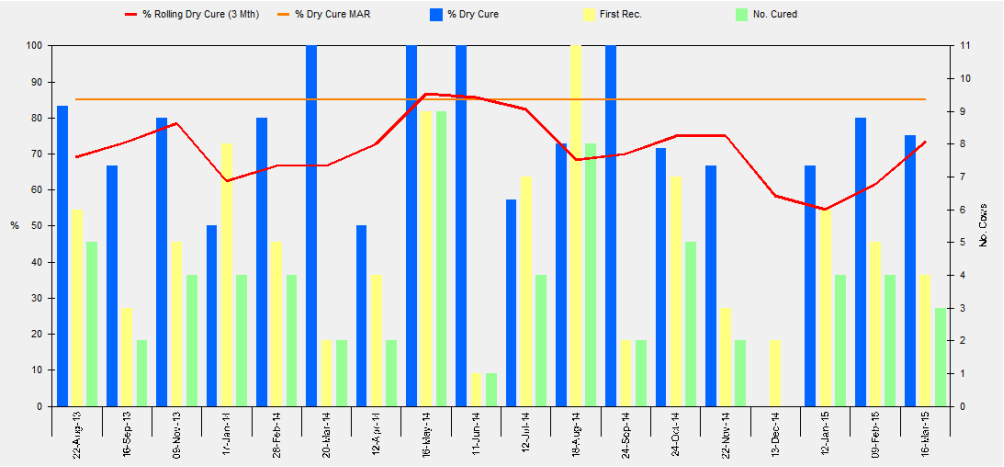


***Figure 1-5 Dry period cure rate over time*.** The dark blue bars represent the percentage of cows, within 30 days of calving with a somatic cell count < 200,000 cells/ml that had a SCC > 200,000 cells/ml at their last milk-recording prior to drying-off; the light yellow and light green bars illustrate the number of eligible cows (SCC > 200,000 cells/ml at their last milk recording prior to drying-off) at the first recording (and < 30 days in milk) and the number defined as 'cured', respectively; the red line illustrates the rolling 3-monthly rate of dry period cure rate and the orange line represents the target. (TotalVet©)

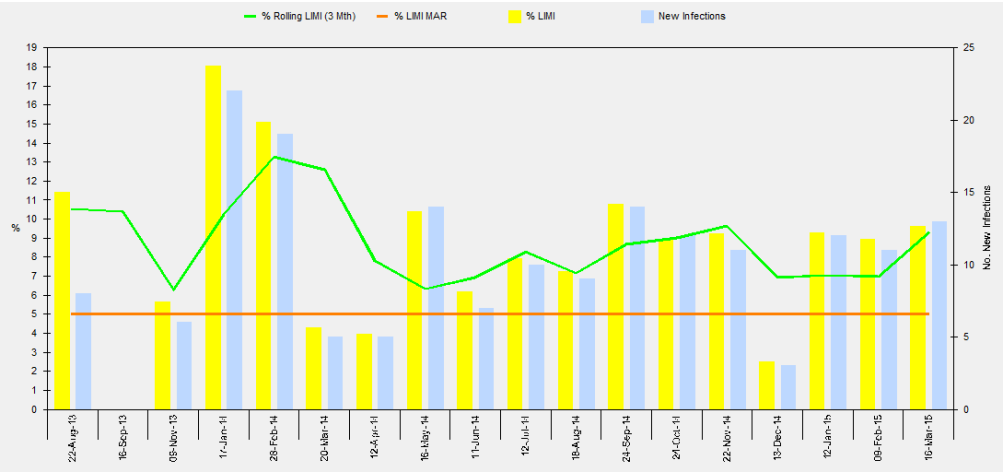


Figure 1-6 Lactation new infection rate over time. The yellow bars represent the percentage of animals at each recording (of those eligible) that experience a lactation new infection (i.e. move from SCC < 200,000 cells/ml to SCC > 200,000 cells/ml). The light green bars indicate the number of animals experiencing a lactation new infection. The green line provides a 3-monthly rolling average rate and the orange line represents the target. (TotalVet©)

Both clinical mastitis and somatic cell count data can be used to provide an insight into whether the pathogens present on a specific dairy farm are behaving in a predominantly environmental manner or in a predominantly contagious manner. This is based on the observation that contagious pathogens tend to cause persistent infections and have a lower cure rate following treatment than environmental pathogens (Sears and McCarthy, 2003). A herd with a predominance of pathogens behaving in a contagious manner will, therefore, tend to have a high prevalence of 'infected' (SCC > 200,000 cells/ml) and chronically 'infected' cows (SCC > 200,000 cells/ml for 2 of the previous 3 consecutive recordings) at a particular time point (Bradley et al., 2007a) (Figure 1-7). They would also tend to have a reduced cure rate of the 1st clinical mastitis cases in lactation (Figure 1-8), as defined as no recurrence of clinical disease and either 2 consecutive cow somatic cell counts < 100,000 cells/ml or 3 < 200,000 cells/ml.

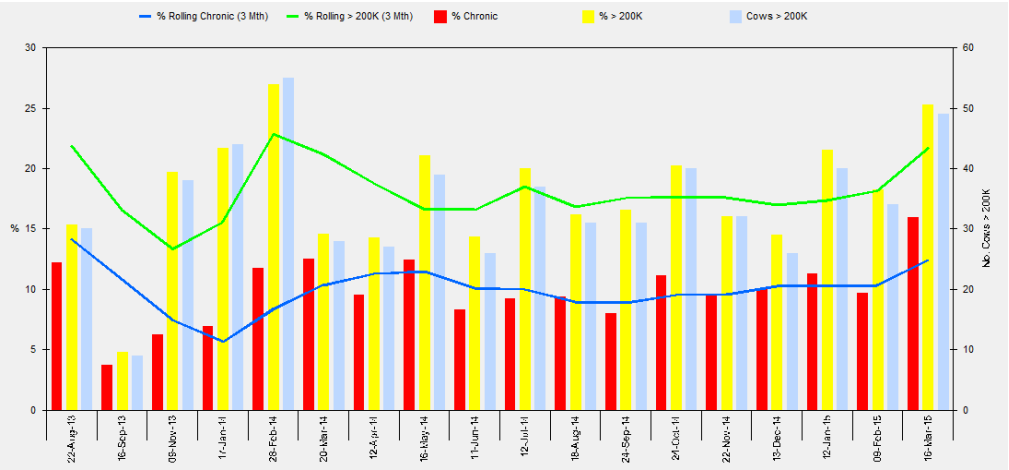


Figure 1-7 Percentage of cows infected and chronically infected over time. The yellow bars represent the percentage of the milking herd with a SCC > 200,000 cells/ml; the light blue bars indicate the number of animals with a SCC > 200,000 cells/ml; the red bars show the percentage of the milking herd defined as chronically infected (SCC > 200,000 cells/ml for 2 of the last 3 consecutive recordings). The green line provides a 3-monthly rolling average proportion of the herd with a SCC > 200,000 cells/ml and the blue line is the 3-monthly rolling average proportion of the herd chronically 'infected'. (TotalVet©)

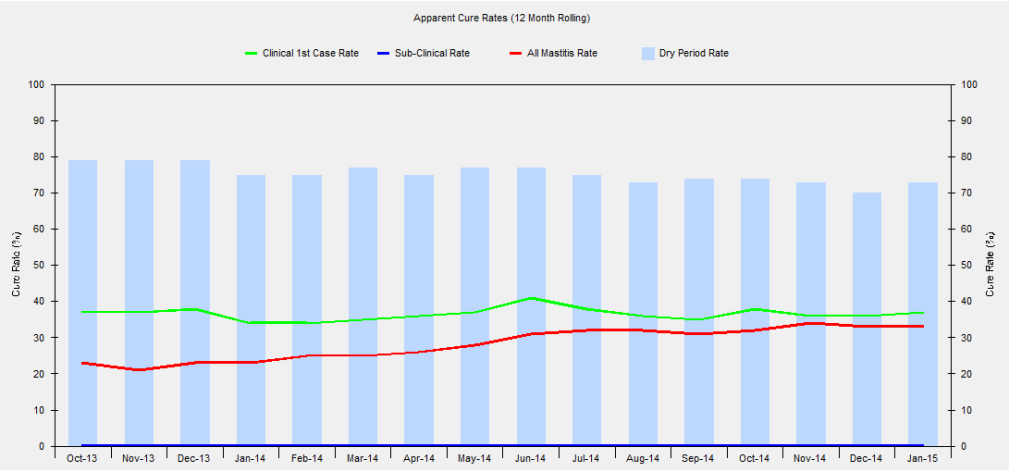


Figure 1-8 Apparent cure rates over time. The light blue bars indicate the monthly dry-period cure rate as measured by somatic cell count (percentage of cows < 30 days in milk with a SCC < 200,000 cells/ml that had a SCC > 200,000 cells/ml at the last milk recording before drying-off); the green line indicates the 12-month rolling average clinical 1st case cure rate (no recurrence of clinical disease after a 1st clinical case and either 2 consecutive SCC < 100,000 cells/ml or 3 consecutive SCC < 200,000 cells/ml); the red line indicates the 12-month rolling average all case cure rate (no recurrence of clinical disease after a clinical case and either two consecutive SCC < 100,000 cells/ml or three consecutive SCC < 200,000 cells/ml); the blue line indicates the 12-month rolling average subclinical case cure rate (either two consecutive SCC < 100,000 cells/ml or three consecutive SCC < 200,000 cells/ml after the treatment of a subclinical case) *no subclinical cases were treated in this herd. (TotalVet©).

Using the CM and SCC parameters in this way to characterise the epidemiology of mastitis for a given farm, both in terms of the putative source of the majority of new infections as well as the likely behaviour of pathogens present on the farm, is one of the key features of the UK national mastitis control scheme (Green et al., 2007b).

1.2 Mastitis Control

Whilst bulk milk somatic cell counts and the prevalence of subclinical mastitis have decreased nationally, the incidence of CM remains a problem for many dairy herds. It has been demonstrated that BMSCC and IRCM are not correlated (Barkema et al., 1998b), and that as BMSCC reduces, the variation in the IRCM observed increases (Barkema et al., 1998b). It has also been reported that herds with a low BMSCC tend to have higher levels of environmental mastitis than herds with a higher BMSCC (Barkema et al., 1998b; Elbers et al., 1998; Erskine et al., 1988; Hutton et al., 1990), which is in agreement with the reported shift in the aetiology of mastitis cases in the UK, as referred to previously. The challenge with respect to environmental mastitis is that the interventions that have successfully controlled contagious mastitis do not appear to have the same efficacy against the causes of environmental mastitis and, therefore, a different approach is required.

1.2.1 Risk factors associated with clinical mastitis

During the last 40 years, there have been a vast number of published studies reporting associations between quarter-level, cow-level and herd-level risk factors and the incidence of clinical mastitis. Most of these

studies were performed outside of the UK and the findings are, therefore, not always applicable to the UK context. They range from small-scale studies investigating one specific risk factor (e.g. post-milking teat disinfection) to large-scale studies looking at many risk factors in a specific 'type' of herd (e.g. low BMSCC). Despite these limitations, a number of specific risk factors were common to two or more of these studies.

Certain aspects of management that increased the exposure of cows to environmental pathogens were consistently associated with an increased IRCM, such as housing on straw yards (Barnouin et al., 2005; Peeler et al., 2000) and cleaning out the straw yards housing the milking cows less often than every 6 weeks (O'Reilly et al., 2006). Low frequency of cubicle cleaning (Elbers et al., 1998; Schukken et al., 1991, 1990) and a low quantity of bedding in cubicles (Elbers et al., 1998; Schukken et al., 1991) were both associated with an increased IRCM. Hygiene of calving pens, specifically the frequency of disinfection/cleaning and quantity of bedding were also negatively correlated with IRCM in several studies (Barkema et al., 1999a; Elbers et al., 1998; Peeler et al., 2000). The size of the air inlet in milking cow sheds was positively correlated with the IRCM caused by *Strep. uberis* in one study (Barkema et al., 1999a), but the presence of an air inlet along the roof was associated with a reduced risk of clinical mastitis caused by *Staph. aureus* in another study (Schukken et al., 1991). The source of the cows' drinking water was associated with an increased risk of clinical mastitis when originating from a stream or a well

as opposed to public sources (Barkema et al., 1999a; Schukken et al., 1991, 1990).

Aspects of management related to the milking process were also identified by several studies, including the application of post-milking teat disinfection (Barkema et al., 1999a; Elbers et al., 1998; Peeler et al., 2000; Schukken et al., 1991, 1990), the practice of foremilking (Barkema et al., 1999a; Elbers et al., 1998; O'Reilly et al., 2006; Peeler et al., 2000; Schukken et al., 1990), which were both associated with an increased IRCM. The wearing of gloves during milking (O'Reilly et al., 2006; Peeler et al., 2000) was associated with an increased IRCM, as was the wet preparation of teats before milking (Barkema et al., 1999a; Schukken et al., 1991). The drying of wet teats with a cloth after premilking preparation was associated with an increased IRCM in one study (Barkema et al., 1999a) and a decreased IRCM in another (O'Reilly et al., 2006). The proportion of cows leaking milk either just before or after milking seemed to be important, with several studies reporting a positive correlation with the IRCM (Elbers et al., 1998; O'Reilly et al., 2006; Peeler et al., 2000; Schukken et al., 1991, 1990).

Other cow-level factors that were associated with IRCM include breed and milk yield, with Meuse-Rhine-Yssel breeds being associated with an increased risk (Elbers et al., 1998; Schukken et al., 1991, 1990) as well as Holstein-Friesians (Barkema et al., 1999a) and Swedish-Holsteins (Nyman et al., 2007) and higher milk yields being positively correlated

with IRCM (Barnouin et al., 2005; Chassagne et al., 1998; O'Reilly et al., 2006; Schukken et al., 1990).

1.2.2 Risk factors associated with somatic cell count

Due to the relative availability of SCC data, there are a considerable number of risk factor studies relating herd management with BMSCC and these have been reviewed recently (Dufour et al., 2011). A key strength of this review was its ability to identify practices that have shown consistent associations with SCC under differing circumstances and which are therefore most likely to be relevant to the largest number of dairy farms.

Management variables related to the milking process were some of the most consistent including wearing gloves during milking, which was associated with a low SCC (Bach et al., 2008; Hutton et al., 1991; Rodrigues et al., 2005), the use of automatic cluster removal systems, which was associated with a low SCC (Barkema et al., 1998a; Hutton et al., 1990; Jayarao et al., 2004; Smith and Ely, 1997; Wenz et al., 2007) and post-milking teat disinfection, which was associated with a low SCC (Barkema et al., 1998a; Erskine and Eberhart, 1991; Erskine et al., 1987; Hutton et al., 1991; Khaitsa et al., 2000). The order of milking (e.g. milking high SCC and clinical mastitis cases last) has been associated with a low SCC in several studies (Barnouin et al., 2004; Hutton et al., 1991; Wilson et al., 1995) as has inspecting the milking machine at least annually (Barkema et al., 1998a; Erskine et al., 1987; Hutton et al., 1990; Rodrigues et al., 2005) and keeping cows standing after milking (Barkema et al., 1998a; Barnouin et al., 2004). It is interesting to note that wearing gloves

during milking and post-milking teat disinfection were both associated with an increased incidence of CM despite being associated with a reduced SCC. This highlights how poorly correlated CM and SCC are (Barkema et al., 1998b), and why it is important, therefore, to consider the risk factors for CM and SCC separately.

With respect to housing, the use of cubicle housing (Bartlett et al., 1992; Khaitsa et al., 2000; Smith and Ely, 1997; Wenz et al., 2007) with sand beds (Bewley et al., 2001; Jayarao et al., 2004; Wenz et al., 2007) was associated with the lowest SCC, as was increased cleanliness of the calving pens (Barkema et al., 1998a; Barnouin et al., 2004).

Other variables consistently associated with a reduced SCC included the application of blanket antibiotic dry cow therapy (Barkema et al., 1998a; Erskine and Eberhart, 1991; Erskine et al., 1987; Hutton et al., 1991; Rodrigues et al., 2005; Wenz et al., 2007), the daily inspection of dry cow udders (Barkema et al., 1998a) and the application of the California Mastitis Test (Erskine et al., 1987; Rodrigues et al., 2005).

1.2.3 Implications of study design

The vast majority of our current knowledge with respect to mastitis control stems from observational studies using cross-sectional study designs. There are several potential reasons for this, including that they are relatively cheap and quick to perform and usually cover a broader range of subjects (Feinstein, 1989). However, there are significant limitations related to study design that need to be considered when appraising evidence arising from such studies such as confounding,

interactions and non-randomisation (Martin, 2013). Due to the systematic biases introduced by these factors and the associated propensity for the inflation of positive effects (Sacks et al., 1982), observational studies are typically used as hypothesis-generating and are considered to be a weak source of evidence for causality (Concato et al., 2000). Despite improvements in observational study design and methodology (Benson and Hartz, 2000; Concato et al., 2000), intervention or 'experimental' studies remain the 'gold-standard' for assessing the clinical effectiveness of therapeutic agents/medical interventions (Abel and Koch, 1999; Byar et al., 1976; Feinstein, 1984). However, there are relatively few intervention studies reported in the veterinary literature regarding mastitis control (Green et al., 2007b) and those that have been performed have been conducted at the cow level rather than the herd level. Some recent examples of these include blanket dry cow therapy versus selective dry cow therapy (Bradley et al., 2010), use of a mastitis vaccine (Bradley et al., 2015) and the treatment of subclinical mastitis (van den Borne et al., 2010b).

There have been several criteria proposed to assess the likelihood that the relationship between an observed risk factor and a disease is causal and these include temporality, consistency, biologic gradient and experimental evidence (Schukken et al., 1990); another simple consideration is plausibility. Plausibility simply refers to the biologic plausibility of a causal relationship given the current state of knowledge. For example, it was reported in one study that the increased cleanliness of

the calves was associated with a decreased risk of clinical mastitis caused by *E. coli* in the milking herd (Barkema et al., 1999a). It would be very difficult to arrive at a biologically plausible reason for this association to be causal but far more likely is that the cleanliness of the calves reflects some other characteristic, such as the attitude or skill of the farmer, which was not directly measured in the study, which could have a closer relationship with the incidence of clinical mastitis.

1.2.4 The Agriculture and Horticulture Development Board Dairy Mastitis Control Plan

All of the data reported and analysed in Chapters 4, 5 and 6 of this thesis originated from UK dairy herds that had participated in the AHDB Dairy Mastitis Control Plan (DMCP). Background information and a detailed description of the DMCP process are provided below.

In 2003, the UK dairy levy board (Milk Development Council) invited tenders for a research partner to develop and test a mastitis control plan developed and based on the risk factors in the veterinary literature. This culminated in a randomised controlled clinical trial (RCT) carried out on 52 commercial dairy herds in England and Wales in 2004/2005 with the aim of determining whether a clearly defined, structured plan for mastitis control, implemented in herds with an increased incidence of clinical mastitis, would reduce the incidence of clinical and subclinical disease. Results from the RCT showed a mean reduction in the proportion of cows affected with clinical mastitis of 22% (having accounted for confounders) in intervention herds compared with the control herds, in addition to

reductions of around 20% in the incidence of clinical and subclinical infections (Green et al., 2007b). After some further developments, the AHDB Dairy Mastitis Control Plan (DMCP) was launched at a national level in April 2009. The DMCP was delivered by trained 'plan users', consisting of veterinary practitioners and dairy consultants that had participated in 2 days of training, and a level of supervision and support was provided by the group of specialist bovine veterinarians that originally devised the DMCP.

The DMCP consists of 3 main stages: i) analysis of herd data to assess patterns of mastitis and categorisation of each herd according to those patterns, ii) assessment of the current farm management and, based on deficiencies identified, prioritisation of the most important management changes required, and iii) frequent monitoring of the farm data to assess the subsequent impact on CM and SCC.

The first stage is arguably the most important (and novel) element of the DMCP, whereby SCC and CM data for each herd are interpreted using specialised analytical software and one of 4 'diagnoses' assigned according to the putative origin and cause of the majority of new infections as described previously. The 4 potential diagnoses are as follows:

- **environmental** pathogens of mainly **dry period** origin ('EDP')
- **environmental** pathogens of mainly **lactation** origin ('EL')
- **contagious** pathogens of mainly **dry period** origin ('CDP')
- **contagious** pathogens of mainly **lactation** origin ('CL')

The next element involves a visit to the farm during which a comprehensive questionnaire/survey is completed covering all aspects of management relevant to mastitis control (377 questions/observations). The answers to the questionnaire are inputted into a bespoke software package called the 'ePlan' together with the 'diagnosis' and management deficiencies that are relevant to the 'diagnosis' are highlighted. At this stage, the plan user would typically prioritise approximately 5-10 interventions to discuss further with the herd manager and agreement sought on which ones to implement in the first instance. Once the interventions have been agreed and implemented, the plan user monitors the herd data (typically at 3-monthly intervals) to ensure that the plan is kept up to date and relevant to the herd.

The key features of the DMCP approach are that it is farm-specific (unlike the 5-point plan) and utilises the farm data to help target mastitis control advice. It is also evidence-based, and has been proven to be effective in an RCT. Since the DMCP was launched at a national level in 2009, over 350 plan users have been trained to deliver it, and over 2000 UK dairy herds are estimated to have participated in the scheme.

1.3 Statistical methods used in this thesis

Economic evaluation is increasingly used to inform decisions about which healthcare interventions to fund from available resources (Briggs and Gray, 1999). There is a need for analytic methods used for economic evaluation to compare new technologies with the full range of alternative options and reflect uncertainty in evidence in the conclusions of the

analysis (Smith et al., 2004), all of which can be achieved with decision analytic modelling.

Decision analysis, defined as a systematic approach to decision making under uncertainty (Raiffa, 1968), has been widely established in the human healthcare sector (Hunink et al., 2014; Sox et al., 1988). A decision analytic model uses mathematical relationships to define a series of possible consequences, and the likelihood of each consequence is expressed as a probability with an associated cost and outcome (Briggs and Gray, 1999). An important feature of decision modelling is to acknowledge and incorporate the inevitable uncertainty surrounding decisions. For example, apparently very similar herds will respond differently to a specific mastitis intervention and, therefore, the likelihood of a particular response can be expressed as a probability distribution in the model. The process of populating a decision model usually involves some form of evidence synthesis, whereby evidence is compiled from multiple different sources, and there are many different approaches to this (Spiegelhalter et al., 2004). Statisticians are increasingly using Bayesian methods for evidence synthesis in decision models for economic evaluation (Ades et al., 2006b) a key feature of which is the requirement for parameters to be specified as probability distributions (Felli and Hazen, 1999).

1.3.1 Bayesian approach

A Bayesian approach has been defined as 'the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation and

reporting of a health-care evaluation' (Spiegelhalter et al., 2004). At its most fundamental level, it deals with how our pre-existing opinion about the likely effect of a specific mastitis intervention, for example (known as the prior distribution), is altered, having observed some new data (likelihood) to arrive at a final opinion about the effect of the mastitis intervention (known as the posterior distribution). The mathematical method proposed for this is known as Bayes' theorem, after the Reverend Thomas Bayes, an 18th Century minister who first described the theorem which essentially weights the likelihood from the new data with the relative plausibilities defined by the prior distribution (Spiegelhalter et al., 2004).

From a decision maker's perspective, a Bayesian approach allows the combining of information from diverse sources, can encompass expert judgement, addresses quantitatively all relevant sources of uncertainty, and incorporates new information as it accrues sequentially, therefore maximising the efficiency with which new knowledge is translated into clinical practice (Parmigiani, 2002). Many clinical research questions can most naturally be answered by assessing the probability that a particular hypothesis is true or false, having observed a relevant set of data (Gurrin et al., 2000) (e.g. the probability that a specific mastitis intervention would result in a net saving of £1000 after 12 months). Unfortunately, questions such as these cannot be readily answered within the conventionally applied 'frequentist' framework. Statistical inference within the frequentist framework is based upon *p* values that reflect the

probability of obtaining a particular pattern of results in a repeated series of identical hypothetical experiments, on the basis of a hypothesis that is assumed to be true (Burton et al., 1998; Gurrin et al., 2000). To establish the probability that a hypothesis is true given a set of data, one first needs to consider how plausible the hypothesis was in the first place (Nuzzo, 2014; O'Hagan, 2003) and, therefore, the weight of evidence required to support it. The updating of our 'prior' or existing knowledge is a key component of Bayesian inference, and one of the key advantages of the Bayesian approach is that the resulting posterior distribution can be used to provide clinically relevant and direct answers to all kinds of questions, including the probability that a particular hypothesis is correct (O'Hagan, 2003). It also removes the reliance upon significance testing and the use of arbitrary thresholds of 'significance' (Greenland and Poole, 2013; Gurrin et al., 2000), meaning the clinician is able to make their own judgement as to what is clinically 'significant' according to the degree of uncertainty they are comfortable with.

There are numerous Bayesian approaches to economic decision modelling (Spiegelhalter et al., 2004), and the two simulation-based approaches used in this thesis are: (i) probabilistic sensitivity analysis, using Monte Carlo methods and (ii) a related integrated approach using Markov chain Monte Carlo methods (MCMC) and micro-simulation.

1.3.2 Probabilistic sensitivity analysis

A technique now widely adopted by the human healthcare sector for analysis of the cost-effectiveness of new and existing treatments is

probabilistic sensitivity analysis (PSA) (Briggs et al., 2002; Brown et al., 2006). Indeed, the National Institute for Clinical Excellence (NICE) now requires all cost-effectiveness analyses submitted to the institute to utilise PSA (Claxton et al., 2005). Whilst this form of analysis has widespread acceptance within the human healthcare sector, there are relatively few examples of its use in the veterinary literature (Detilleux, 2004; Hudson et al., 2015, 2014).

The main feature of PSA is that all input parameters are specified as full probability distributions (probabilistic), rather than point estimates (deterministic), to represent the uncertainty surrounding their values. This parameter uncertainty can then be propagated through the cost-effectiveness model so that imprecision in model outputs is transparent (Briggs et al., 2002). For example, rather than using a point estimate for the probability of clinical cure after the treatment of CM of, say, 60%, we might choose a probability distribution covering the range 40-80% instead, accepting that we don't know the precise figure but being fairly confident that it lies somewhere within this range. Then, at each iteration of the model, a different value is taken from the specified range and used as the basis for the cost-effectiveness calculations. By repeating this process thousands of times, many different scenarios can be explored. The relative importance of different model parameter values on the outcome of interest can then be evaluated irrespective of model complexity.

The process of randomly drawing values from within a specified probability distribution is commonly known as Monte Carlo simulation (Metropolis, 1987) and was first utilised as a research tool for the development of nuclear weapons during the second world war. Monte Carlo methods have been used across many areas of science and business with the primary purpose of evaluating integrals or sums by simulation rather than exact or approximate algebraic analysis (Spiegelhalter, 2004).

PSA has become a popular modern method for determining the uncertainty in the outcomes of cost-effectiveness studies because of the uncertainty in input parameters (Boshuizen and van Baal, 2009). There have been concerns that the use of deterministic or univariate sensitivity analysis may underestimate overall uncertainty (Briggs, 2000) and become difficult to interpret with large numbers of parameters, especially if any are correlated (Claxton et al., 2005). Such concerns have led to the development of PSA based on Monte Carlo simulation methods (O'Brien et al., 1994), as PSA permits the analyst to examine the effect of joint uncertainty in the variables of an analysis without resorting to the wide range of results generated by extreme scenario analysis (Briggs and Gray, 1999). Parameter correlation is propagated automatically, providing meaningful sensitivity analysis regardless of parameter correlation (Ades et al., 2006a).

Given that the literature is often quite sparse concerning many of the model inputs required, assumptions are usually necessary for this kind of model and this can result in unreliable conclusions being drawn if this

uncertainty is not properly investigated. By using PSA, we can reflect the level of uncertainty by defining the parameters as distributions that are transparent. The distributions used do require a degree of judgement and this has to be carried out in an open and transparent way and based on current literature wherever possible.

1.3.3 Integrated approach and micro-simulation

The traditional approach to cost-effectiveness analysis involves a two-stage process whereby parameter estimates and intervals are first obtained based on subjective judgements, data analysis or a combination of the two and, secondly, distributions for the parameter estimates are then assumed and inputted into a separate model to evaluate the cost-effectiveness. An alternative approach is the integrated or unified approach which is a fully Bayesian analysis that simultaneously carries out the evidence synthesis and cost-effectiveness analysis. The integrated approach requires all of the available evidence to be specified as prior distributions which are then revised by Bayes theorem using MCMC simulation to derive posterior distributions. The effects of the resulting posterior distributions are simultaneously propagated through the cost-effectiveness model which is then used to make predictions.

There are many examples of this integrated approach in the human medical literature (Bravo Vergel et al., 2007; Cooper et al., 2004, 2003; Gillies et al., 2008; O'Hagan and Stevens, 2001; Welton et al., 2008) but examples in the veterinary literature are relatively sparse (Archer et al., 2014a, 2014b, 2013a, 2013b; Green et al., 2010).

The key features of the integrated approach are: (i) it provides a systematic framework for relating uncertainty about model input parameters to uncertainty in the computational results of the cost-effectiveness model; (ii) it makes full allowance for any inter-relationships between model input parameters; and (iii) it removes the need to make parametric distributional assumptions and facilitates sensitivity analyses (Cooper et al., 2004).

A common problem when trying to base clinical decisions on the results of cost-effectiveness models is that it is often difficult to interpret all of the model outcomes and apply them to the decisions that need to be made (e.g. if a herd level interpretation is required from a cow-level model). For this reason, it is often helpful to perform a 'follow-on' simulation involving the trajectories of individual cows/herds which can then be used as an estimate of the expected outcome in a population of cows/herds. This is known as micro-simulation, and, by using this tool, it is possible to replicate carefully controlled clinical trials varying only the exposure of interest, which would often otherwise be very expensive to perform and could give rise to ethical concerns.

1.3.4 Markov Chain Monte Carlo for parameter estimation

MCMC was invented shortly after Monte Carlo methods following a study simulating a liquid in equilibrium with its gas phase (Metropolis et al., 1953). The resulting 'Metropolis algorithm' was generalised by Hastings to become the 'Metropolis-Hastings algorithm' (Hastings, 1970), a special

case of which became known as the Gibbs sampler (Geman and Geman, 1984) which is widely used today and was used in this thesis.

MCMC is an effective means of sampling from the posterior distribution despite the precise form of the posterior distribution being unknown. A Markov chain is created by continually updating parameter estimates until a stable state is reached, known as convergence. Each parameter estimate in the chain depends only on the previous estimate, so the chain gradually becomes independent of past values, including initial conditions. Any inferences required are derived from the sampled values which together form an approximation of the posterior distribution of interest.

A Markov Chain should converge to a stationary or non-variant state and the sampling process up to convergence is usually termed 'burn in'. Determining if a chain has converged can be difficult (Gilks et al., 1995) but methods used in this thesis included the visual assessment of chain stability and the Brooks-Gelman-Rubin convergence diagnostic (Brooks and Gelman, 1998; Gelman and Rubin, 1992). Following convergence, Markov Chains are typically continued for thousands of iterations to estimate parameters, after which, the initial 'burn-in' iterations are discarded and parameter estimates at each iteration used for onward prediction and simulation.

1.4 Aims of the thesis

1.4.1 Summary

The overall aim of the thesis was to explore the cost of clinical mastitis and cost-effectiveness of different approaches to mastitis treatment and specific mastitis control interventions using probabilistic methods that incorporated uncertainty. The results of the decision analytic models should facilitate decision making by enabling direct statements of probability to be inferred about specific clinical hypotheses. Bayesian approaches were used throughout the thesis to capture and propagate sources of uncertainty that were identifiable.

1.4.2 Overview of Chapters

Transmission and the cost of clinical mastitis (Chapter 2)

The aim of Chapter 2 was to use probabilistic sensitivity analysis to evaluate the relative importance of different components of a model designed to estimate the cost of clinical mastitis. A particular focus was placed on the importance of pathogen transmission relative to other factors, such as milk price or treatment costs.

The cost-effectiveness of an on-farm culture approach compared with a standard approach for the treatment of clinical mastitis in dairy cows (Chapter 3)

In Chapter 3, an adaptation of the PSA model developed in Chapter 2 was used to explore factors affecting the cost-effectiveness of an on-farm culture approach versus a standard approach for the treatment of clinical mastitis. The main aim of this study was to help veterinary decision

makers identify the types of dairy herds for which the on-farm culture approach was likely to be cost-effective by exploring different simulated scenarios.

Current management practices and interventions prioritised as part of a nationwide mastitis control plan (Chapter 4)

Chapter 4 presents descriptive performance and management data taken from a sample of UK dairy farms that have participated in the AHDB Dairy Mastitis Control Plan and identifies important mastitis prevention practices that were not widely implemented. The aim was to develop an appreciation of current management practices such that this might aid the understanding of why mastitis remains a significant problem on many UK dairy farms and provide useful insights into which interventions are perceived to be most important for different types of farms.

A Bayesian micro-simulation to evaluate the cost-effectiveness of specific interventions for mastitis control during the dry period (Chapter 5)

The aim of Chapter 5 was to estimate the cost-effectiveness of specific mastitis interventions that had been implemented in UK dairy herds that had participated in the DMCP and that had an EDP diagnosis. The cost-effectiveness under different circumstances was assessed using an integrated Bayesian micro-simulation approach.

A Bayesian micro-simulation to evaluate the cost-effectiveness of specific interventions for mastitis control during lactation (Chapter 6)

The aim of Chapter 6 was to estimate the cost-effectiveness of specific mastitis interventions that had been implemented in UK dairy herds that had participated in the DMCP and that had an EL diagnosis. As with

Chapter 5, the cost-effectiveness under different circumstances was assessed using an integrated Bayesian micro-simulation approach. An important end goal of this and the previous study was to integrate the results of the micro-simulation into a decision support tool that would facilitate the prioritisation of mastitis control interventions by veterinary practitioners and advisors. The decision support tool is not in itself a part of this thesis, but it is currently ongoing work building on the data presented within.

Chapter 2
Transmission and the cost of clinical mastitis

2.1 Introduction

Mastitis remains one of the most common diseases of dairy cows and represents a large economic loss to the industry as well as a considerable welfare issue to the cows affected (Bradley, 2002; Halasa et al., 2007). Despite being an infectious disease, concentration is often focussed on the individual animal with respect to treatment, cost and management. The risk posed to the rest of the herd from infected individuals and the potential impact of disease transmission on the cost of a case of clinical mastitis (CM) is often overlooked.

The cost of CM is made up of direct costs (e.g. discarded milk, cost of medicines, labour) and indirect costs (e.g. loss of future production, increased culling), and varies considerably between farms (Huijps et al., 2008). Whilst the direct costs are more apparent to the producer, they are reported to comprise only a small proportion of the overall cost of CM compared to the less obvious indirect costs (Huijps et al., 2008; Kossaibati and Esslemont, 2000). Several studies have taken all of the direct and indirect costs into account and have produced average figures of £111 (Bar et al., 2008), £167.41 (Huijps et al., 2008), £175.60 (Kossaibati and Esslemont, 2000) and £341.17 (Hagnestam-Nielsen and Ostergaard, 2009) for the cost of a case of CM. Whilst this information is useful, such

'average' figures are difficult to interpret for an individual producer unless they happen to be the 'average' farm. Whilst some recent studies have investigated the impact of transmission on the overall cost of CM at herd level (Halasa, 2012; Halasa et al., 2009; van den Borne et al., 2010a), most studies have not evaluated the impact that within-herd transmission may have on the cost of CM at cow-level, nor how important this may be relative to the other factors that make up the overall cost of a case of CM.

A technique now widely adopted by the human healthcare sector for analysis of the cost-effectiveness of new and existing treatments is probabilistic sensitivity analysis (PSA, see 1.3.2) (Briggs et al., 2002; Brown et al., 2006). The main feature of this technique is that all input parameters in a cost effectiveness model are specified as full probability distributions, rather than point estimates, to represent the uncertainty surrounding their values. This parameter uncertainty can then be propagated through the cost effectiveness model so that imprecision in model outputs is transparent (Briggs et al., 2002). The relative importance of different model parameter values on the outcome of interest can then be evaluated irrespective of model complexity.

The purpose of Chapter 2 was to use PSA to evaluate the relative importance of different components of a model designed to estimate the cost of CM. The model included the potential for pathogen transmission between cows and was an extension of a previously described model structure (Steeneveld et al., 2011). A particular aim was to assess the

importance of the rate of transmission relative to other factors, such as milk price or the cost of therapeutic agents.

2.2 Materials and Methods

2.2.1 Model Structure

A stochastic Monte Carlo model was developed using WinBUGS 1.4.3 software (Lunn et al., 2000) (WinBUGS code provided in Appendix 1). This was used to simulate a case of CM (CM1) at the cow level and to calculate the associated costs simultaneously for 5 treatment protocols as defined by Steeneveld et al. (2011). The 5 protocols used were 3 days of antibiotic intramammary treatment (treatment 1), 5 days of antibiotic intramammary treatment (treatment 2), 3 days of intramammary and systemic antibiotic treatment (treatment 3), 3 days intramammary and systemic antibiotic treatment plus 1 day nonsteroidal anti-inflammatory treatment (treatment 4) and 5 days intramammary and systemic antibiotic treatment (treatment 5). The initial probability that the cow was cured bacteriologically was defined by a probability distribution based on the maximal cure rates given by Steeneveld et al. (2011) but rather than being pathogen-specific (e.g. *Staph aureus*, *Strep dysgalactiae/uberis* or *E coli*), a single distribution was used providing coverage of cure rates encompassing those for all of the pathogens modelled by Steeneveld et al. (2011). For example, for treatment 1 (3 days of intramammary treatment), the bacteriological cure rates given ranged from 0.80 for *E. coli* infections down to 0.40 for *Staph. aureus* infections, so the uniform distribution 0.40-0.80 was used for all

treatment 1 cases. After an initial treatment, there were 3 possible outcomes; complete cure (bacteriological plus clinical cure), clinical cure (with no bacteriological cure) or no cure (non-clinical and non-bacteriological cure) with probabilities based upon Steeneveld et al. (2011) (Table 2-1). The probability that a case was cured bacteriologically was assumed to be further influenced by whether the cow was systemically ill, the somatic cell count (SCC) at the time of treatment, the days in milk at the time of treatment, parity and whether it was a repeat case or not (Steeneveld et al., 2011) (Table 2-1). The cows that failed to cure bacteriologically were deemed to have an 80% chance of curing clinically (Steeneveld et al., 2011).

Table 2-1 Probability distributions specific to the 5 defined clinical mastitis antimicrobial treatment protocols used in a model designed to simulate the cost of a case of clinical mastitis

	Antimicrobial treatment regimen				
	Treatment 1	**Treatment 2**	**Treatment 3**	**Treatment 4**	**Treatment 5**
Application and duration (d)	Intramammary (3)	Intramammary (5)	Intramammary (3) + systemic (3)	Intramammary (3) + systemic (3) + nonsteroidal antiinflammatory drug (1)	Intramammary (5) + systemic (3)
Probability of bacteriological cure[1,2]	(0.40,0.80)	(0.60,0.80)	(0.60.0.80)	(0.63,0.83)	(0.70,0.90)
Probability of bacteriological cure after extended tx[1,2]	(0.30,0.90)	(0.50,0.90)	(0.50,0.90)	(0.53,0.93)	(0.60,0.99)
Cost of medicines (£)[1,3]	(5.58,6.97)	(9.30,11.62)	(32.00,36.00)	(43.00,47.00)	(36.00,40.00)
Treatment Time (hr)[1,2]	(0.53,0.87)	(0.87,1.20)	(0.58,0.92)	(0.63,0.97)	(0.92,1.25)
Milk withdrawal (d)[1,4]	(5.00,9.00)	(7.00,11.00)	(5.00,9.00)	(5.00,10.00)	(7.00,11.00)

[1]Uniform distribution with upper and lower limits specified
[2]Based upon Steeneveld et al. (2011)
[3]Based upon estimate of current retail price of commonly used preparations in the UK.
[4]Based upon commonly used preparations in the UK.

The model structure was adapted from the model described by Steeneveld et al. (2011) (Figure 2-1), which models the sequelae following a case of CM within a single lactation with the addition of a risk of transmission from cows that cured clinically but not bacteriologically. Cases that completely cured could either go on to finish the lactation or be culled within the remainder of the lactation. The probability of being culled was increased if the cow was systemically ill at the time of treatment. The cows that cured clinically but not bacteriologically could go on to finish the current lactation, be culled or have a clinical recurrence of the original case (CM2). If a cow did not cure, it would receive a repeat course of the initial treatment protocol resulting in the same 3 possible outcomes as previously outlined. Cows that failed to cure after a repeated course could either die or have the quarter dried-off. If a quarter was dried-off they could then go on to finish the lactation at a reduced level of milk production, or be culled (Table 2-2). The same sequence of events was modelled for CM2, but after CM3, the options became narrower. The cows that cured completely after CM3 could either end the lactation or be culled. The clinical (but not bacteriological) cures and the 'no-cures' were culled, as was the case in the model described by Steeneveld et al. (2011). The probabilities of a cow being culled varied according to whether the case was a first, second or third case. The distributions used in the model are shown in Table 2-1 and Table 2-2. Following each treatment for CM, the probability of a cow curing bacteriologically was selected from the

specified distribution, and, of those cows that failed to cure, 80% were assumed to cure clinically but not bacteriologically, as described by Steeneveld et al. (2011), The remaining cows were assumed to fail to cure.

A risk of transmission was included from cows that cured clinically but not bacteriologically (those that did not cure clinically received another treatment and were deemed to be not at risk of transmission at this point). The probability that a cow transmitted infection to a herdmate (Table 2-2) was taken from van den Borne et al. (2010) who reported estimated transmission rates over a 14 day period for infections caused by *Staph. aureus, Strep. uberis/dysgalactiae* and *E. coli*. A uniform distribution was specified (range 0.002 to 0.25, encompassing the estimates of van den Borne et al. (2010)) from which a value was selected at random at each iteration and used for each period of risk thereafter. The total period of transmission risk modelled was limited to 12 weeks split into 14 day intervals for CM1 and CM2. Therefore, the risk of transmission had a wide distribution to reflect and encompass all types of pathogen and strain. Thus, using one distribution, we could evaluate differences between a very low transmission pathogen and a very high transmission pathogen.

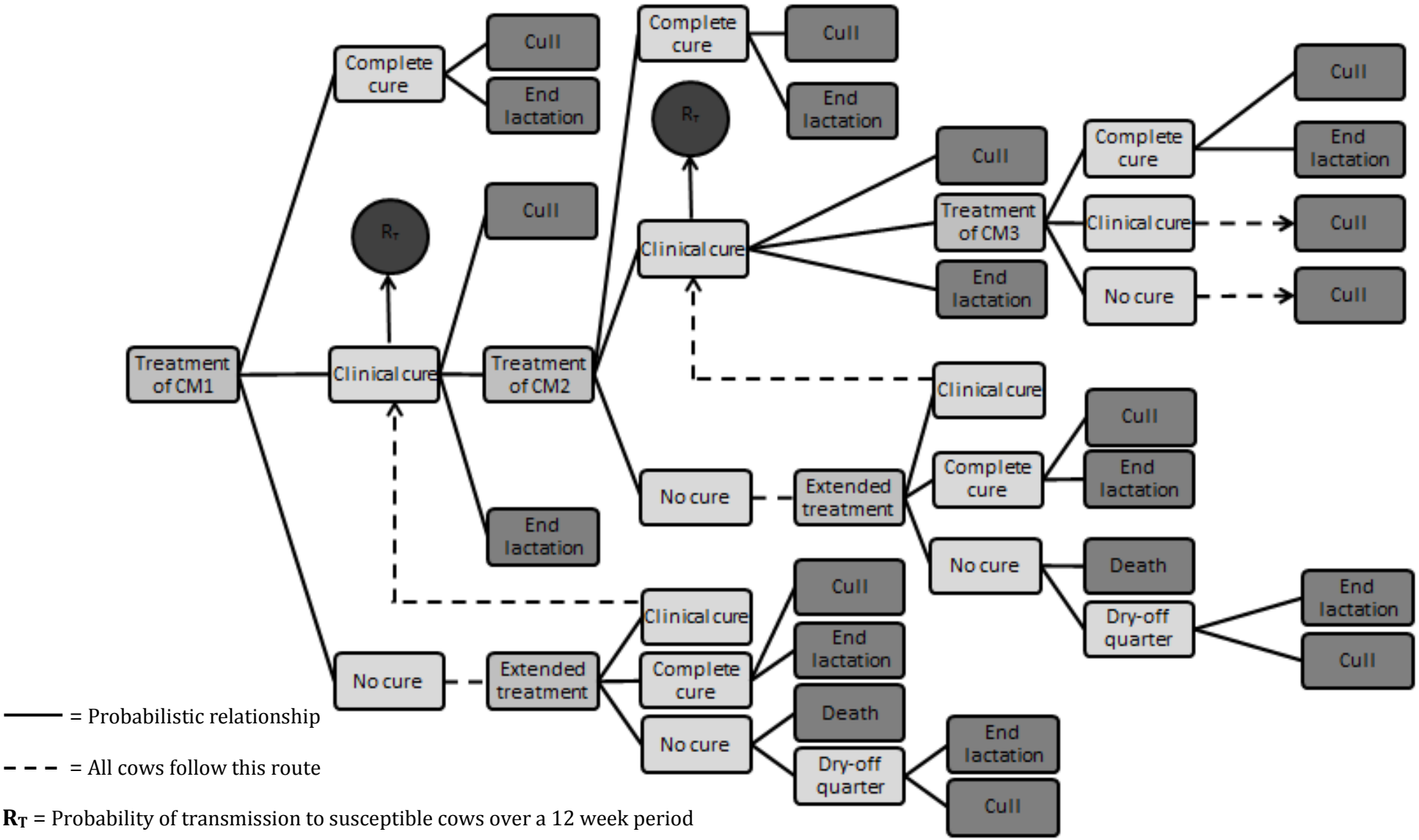


Figure 2-1 Schematic representation of the model designed to simulate the cost of a case of clinical mastitis. Complete cure=bacteriological and clinical cure. Clinical cure=non-bacteriological cure but clinical cure. No cure=no bacteriological or clinical cure. Cull=culled sometime within the remainder of the current lactation. Extended treatment=a repeat of the same treatment that the case received initially. R_T=risk of transmission. CM1=initial case of clinical mastitis. CM2=first clinical recurrence. CM3=second clinical recurrence.

Table 2-2 Probability distributions applicable to all 5 antimicrobial clinical mastitis (CM) treatment protocols used in the model designed to simulate the cost of a case of clinical mastitis

Input parameters	Upper and lower limits of uniform distribution	Source
Decrease in probability of bacteriological cure[1]		a
Parity ≥2	(-0.15,-0.05)	
Days in milk ≥60 days	(-0.15,-0.05)	
Cow is systemically ill	(-0.25,-0.15)	
SCC 200,000-500,000 cells/mL at most recent recording	(-0.15,-0.05)	
SCC >500,000 cells/mL at most recent recording	(-0.25,-0.15)	
Repeated case (>1st case in current lactation)	(-0.25,-0.15)	
Probability of being culled for bacteriologically noncured cases		a
Initial case	(0,0.32)	
Following first clinical recurrence (CM2)	(0.04,0.36)	
Probability of being culled for completely cured cases		a
Initial case	(0.04,0.06)	
Following first clinical recurrence (CM2)	(0.10,0.20)	
Following second clinical recurrence (CM3)	(0.20,0.30)	
Probability of death for nonclinical cured cases	(0.04,0.06)	a
Probability of drying-off quarter for nonclinical cured cases	(0.94,0.96)	a
Probability of being culled for cows with dried off quarters	(0.27,0.39)	a
Increase in all culling probabilities when cow is systemically ill	(0.05,0.15)	a
Probability of clinical flare-up for bacteriologically noncured cases	(0.05,0.12)	a
Probability of transmission after CM1 and CM2	(0.002,0.25)	b
Proportional yield loss		a
Case in 1st or 2nd month of lactation	(0.07,0.09)	
Case between months 3 and 6	(0.03,0.08)	
Case after month 6	(0,0.04)	
Parity ≥2	(0,0.02)	
305d Yield (Kg)	(7000,10000)	Author
Daily milk discard (Kg)	(5.00,50.00)	Author
Value of discarded milk (£/Kg)	(0.23,0.27)	(DairyCo, 2012a)
Cost of milk production (£/Kg)	(0.03,0.10)	c
Cost of labour (£/hr)	(1.00,15.87)	c
Cost of cull (£)	(120,720)	c, d
Cost of death (£)	(1200,2000)	DairyCo 2012b

[1] The value selected from this distribution was subtracted from the value selected from the bacteriological cure distribution.

a = based on Steeneveld et al. (2011)

b = based on Van den Borne et al. (2010)

c = based on Huijps et al. (2008)

d = based on Kossaibati & Esslemont. (2000)

The susceptible population was taken as the whole herd (99 cows) at the start of the transmission period and was reduced according to the number of cows that became infected after each 14 day period during the subsequent 12 weeks. Cow parities and stage of lactation of the susceptible population were not modelled separately; thus for simplicity, all susceptible cows we assumed to have an equal probability of acquiring an infection. All cows that were infected at the end of the previous 14 day period were eligible to transmit infection during the next 14 day period according to the defined probability distribution (Table 2-2). For example, if the cow treated at CM1 remained subclinically infected after treatment, it could transmit the infection to another cow in the herd during the following 14 day period. At the start of the subsequent 14 day period, there could now be 2 infectious cows able to transmit infection to another 2 cows during the next 14 day period. If 3 cows had become infected in addition to the original case, then the susceptible population would be reduced to 96 cows. The total number of infections accrued from CM1 and CM2 were combined and the costs of subsequent cases of CM were estimated by multiplying the cost from the original case (CM1) by the number of extra cases of CM caused by transmission of the original infection (thus assuming the same milk price, culling values and so on as for the initial case). A total cost of CM was derived by adding the costs from the original and secondary cases, following transmission. For example, if the cost of a case of CM was calculated to be £200 (excluding transmission) but the cow infected 2 herd mates, then the total cost (including transmission) would be calculated as £600 (£200 x 3).

2.2.2 Model input parameters

The model was parameterised (i.e. the model inputs selected) with distributions taken from the existing literature, from current commercial data and where no other information was available, on transparent assumptions made by the Dairy Herd Health Group, University of Nottingham (Table 2-1 and Table 2-2). The purpose was to enable exploration of the relationship between each model parameter and the overall cost-benefit of each treatment protocol over a wide range of possible scenarios. Whilst not a requirement of PSA, uniform distributions were used throughout the model to enable evaluation of the cost of CM over a spectrum of different scenarios without specifying which scenarios were more or less likely thereby minimising assumptions. This was not intended to represent the 'true' distribution of the input parameters (which are generally unknown), but simply to allow investigation over the whole of a realistic range of equally likely parameter values and, thus, treatment scenarios. After a large number of model iterations (4000 per treatment protocol), all combinations of treatment scenarios and other input parameters were effectively investigated, so that dependencies could be evaluated.

Where possible, distribution ranges were based on values from current literature. Where a point estimate was identified in the literature, a uniform distribution centred on that point was used, to allow sensitivity analysis of realistic values around this point estimate. For example, the increase in probability of a cow being culled within the remainder of

lactation when systemically ill was estimated to be 0.10 (Steeneveld et al., 2011). In our model a uniform distribution of 0.05-0.15 was used to evaluate this parameter over an enlarged but specified range. The distributions used for input parameters are shown in Table 2-1 and Table 2-2, along with the source or basis for the choice of each distribution.

Economic parameter distributions included the cost of medicines (Table 2-1), labour, milk withdrawal and loss of milk production, culling and death (Table 2-2). The cost of labour is subject to large variation quoted in the literature. For this reason a wide distribution was assigned to the hourly cost of labour with the upper limit taken from Huijps et al. (2008). The total time taken to treat each case of CM was assigned a distribution centred on the figures given by Steeneveld et al. (2011), surrounded by an additional variation of +/- 10 minutes. The total cost of labour was the product of the hourly rate and the total treatment time.

The length of milk withdrawal after CM was defined by a distribution based on the commonly used medicines in the UK and the amount of milk being discarded each day was taken from a plausible milk yield distribution (Table 2-1). The distribution defined for milk price was taken from DairyCo (2012a), and was based on the average UK milk price over the last 12 months (range: lowest price and highest price). The cost of milk production was based on Huijps et al. (2008), and assigned a uniform distribution to reflect the variability in the figure (Table 2-2).

The calculation of total yield loss following a case of CM was based on the herd 305 day yield, the parity of the animal and the stage of lactation in

which the infection occurred (Table 2-2). The distributions governing the percentage of total loss in 305 day milk yield were based on Hagnestam et al. (2007). The proportion of cases occurring at each stage postpartum and the proportion of cases affecting multiparous cows versus primiparous cows was governed by distributions based on Steeneveld et al. (2011) (Table 2-2). The cost associated with the total loss in milk yield was calculated according to the total loss in earnings (i.e. the quantity of milk multiplied by the milk price) minus the savings made in feed costs (i.e. the quantity of milk loss multiplied by the cost of production). All distributions are provided in Table 2-2.

The cost of culling a cow within the remainder of the current lactation was taken from a uniform distribution based on Huijps et al. (2008) and Kossaibati and Esslemont (2000), which included the slaughter value and replacement costs, with an appropriate range added to reflect the variability of this parameter (Table 2-2). The cost of the death of an individual was based on current UK average sales prices for freshly calved cows and heifers (DairyCo 2012b) which would be required to replace the dead cow in addition to the cost of carcass disposal (Table 2-2).

2.2.3 Model Simulation

The model was used to simulate 4000 cases of CM1 for each treatment protocol. At each iteration, all model input parameter values for that iteration were stored along with the calculated cost of a CM1 case: this data was then used for analysis.

At each model iteration a value for each input parameter was drawn from the probability distribution for that input parameter independent of other parameter values selected, and the model used to calculate a cost of CM based on those input values. At the next iteration, a new set of parameter values were selected at random and used to calculate a cost of CM. This process was repeated 4000 times for each of the 5 treatment protocols and the impact of each parameter on the cost of CM was evaluated.

2.2.4 Data analysis

Spearman rank correlation coefficients were calculated to explore the univariable associations between model input parameters and the cost of CM (Table 2-3). The strength of the relationship was evaluated using the Spearman rank rho (ρ) value.

Conventional first order multiple linear regression models were used to explore the relationships between model inputs (Table 2-1and Table 2-2) and the cost of CM for each of the treatment protocols (one model was constructed for each treatment protocol). A natural log transformation was required for the outcome variable (cost of CM) to give normality and homoscedasticity of the residuals. Model fit was assessed using a visual assessment of residuals and a Q-Q plot to evaluate normality. The influence of any outlying residuals was assessed using the Cook's D value. Predictor variables were selected by backward stepwise selection and variable coefficients that were significantly different from zero ($p<0.05$) were retained in the final model. All analysis was performed in R version 2.15.0 (R Development Core Team, 2012).

The relative 'importance' of the independent variables (model input parameters) on the cost of CM was assessed for each of the 5 treatment protocols by removing the variable from the model and observing the difference in the resulting R^2 value. This difference was then expressed as a proportion of the R^2 value of the complete model.

The final regression models were used to make predictions based on different cow and farm scenarios and to explore the predicted effect these would have on the overall cost of CM. This was undertaken by altering the value of each of the independent variables in the model in turn from their median value to the 97.5th percentile whilst keeping all other variables constant at their median value and recording the resulting change in the model output (cost of CM) as a percentage. This was performed using Microsoft Excel (2010).

2.3 Results

2.3.1 Data analysis

The Spearman rank correlation coefficients are presented in Table 2-3. The cost of CM was most closely associated with the risk of transmission of infection for all 5 treatment protocols. This was followed by the bacteriological cure rate, the cost of a cull, total loss in yield and the presence or absence of systemic illness.

The regression model fit was good for each of the 5 treatment protocols and outliers had no significant influence on the model output. The results of the regression analysis are illustrated in Figure 2-2. Transmission of

infection had the greatest influence on the overall cost of CM for all 5 treatment protocols and the number of cows infected as a result of CM1 ranged from 0 to 3 over the total 12 week period of risk (Table 2-4). This was followed by occurrence of systemic illness, cost of a cull and total yield loss during the remainder of the lactation. In total, 13 independent variables were retained in the final models (Figure 2-4). The relative importance of variables differed only slightly between the 5 treatment protocols; the general trends were similar throughout.

The most influential financial input was the cost of a cull which accounted for around 10% of the variance in the total cost of CM, followed by the cost of milk production, milk price and cost of labour. The cost of medicines was not found to be a significant predictor, and was excluded from the final models. The relationship between the most important independent variables and the cost of CM are displayed in Figure 2-3.

2.3.2 Scenarios

The regression models were used to explore the effect that changes to specific independent variables had on the overall cost of CM and the results from treatment 1 are displayed in Figure 2-4. An increase in the rate of transmission from 0.13 new cases/14 days to 0.25 new cases/14 days would increase the predicted cost of CM by up to 60%, whereas doubling the cost of labour from around £8.50/hr to £15.50/hr would only be expected to increase the cost of mastitis by around 5%. Systemic illness had a large effect on the total cost of CM (40%) if present due to the depressing effect this had upon the probability of bacteriological cure.

The cost of a cull had a moderate effect on the cost of CM with an increase from £420 to £702 resulting in a 15-20% increase in the overall cost.

Table 2-3 Spearman rank correlation coefficients measuring the statistical dependence between the specified variable and the total cost of clinical mastitis estimated in the complete model designed to simulate the cost of a case of clinical mastitis.

	Treatment 1	**Treatment 2**	**Treatment 3**	**Treatment 4**	**Treatment 5**
Transmission	0.70	0.68	0.71	0.70	0.64
Bacteriological cure rate[1]	-0.24	-0.10	-0.07	-0.13	-0.09
Cost of cull	0.23	0.24	0.24	0.24	0.25
Total yield loss	0.23	0.23	0.22	0.22	0.23
Not systemically ill	-0.23	-0.25	-0.25	-0.25	-0.27
Heifer	-0.15	-0.16	-0.16	-0.17	-0.17
Not a repeat case	-0.12	-0.14	-0.13	-0.14	-0.15
Milk price	0.10	0.11	0.11	0.11	0.11
SCC > 500,000 cells/ml[2]	0.10	0.09	0.09	0.08	0.09
Cost of milk production	-0.10	-0.10	-0.10	-0.11	-0.11
Less than 60 days in milk[3]	-0.09	-0.10	-0.10	-0.11	-0.11
Milk withdrawal[4]	0.09	0.07	0.07	0.12	0.07
Cost of labour	0.02	0.04	0.02	0.02	0.04
Cost of drugs	0.02	0.00	0.02	0.00	0.01

[1] Baseline bacteriological cure rate before further influence of systemic illness, parity, days in milk, somatic cell count and case number.
[2] Somatic cell count at the time of clinical mastitis.
[3] Less than 60 days in milk at the time of clinical mastitis case.
[4] Milk withdrawal during antibiotic treatment.

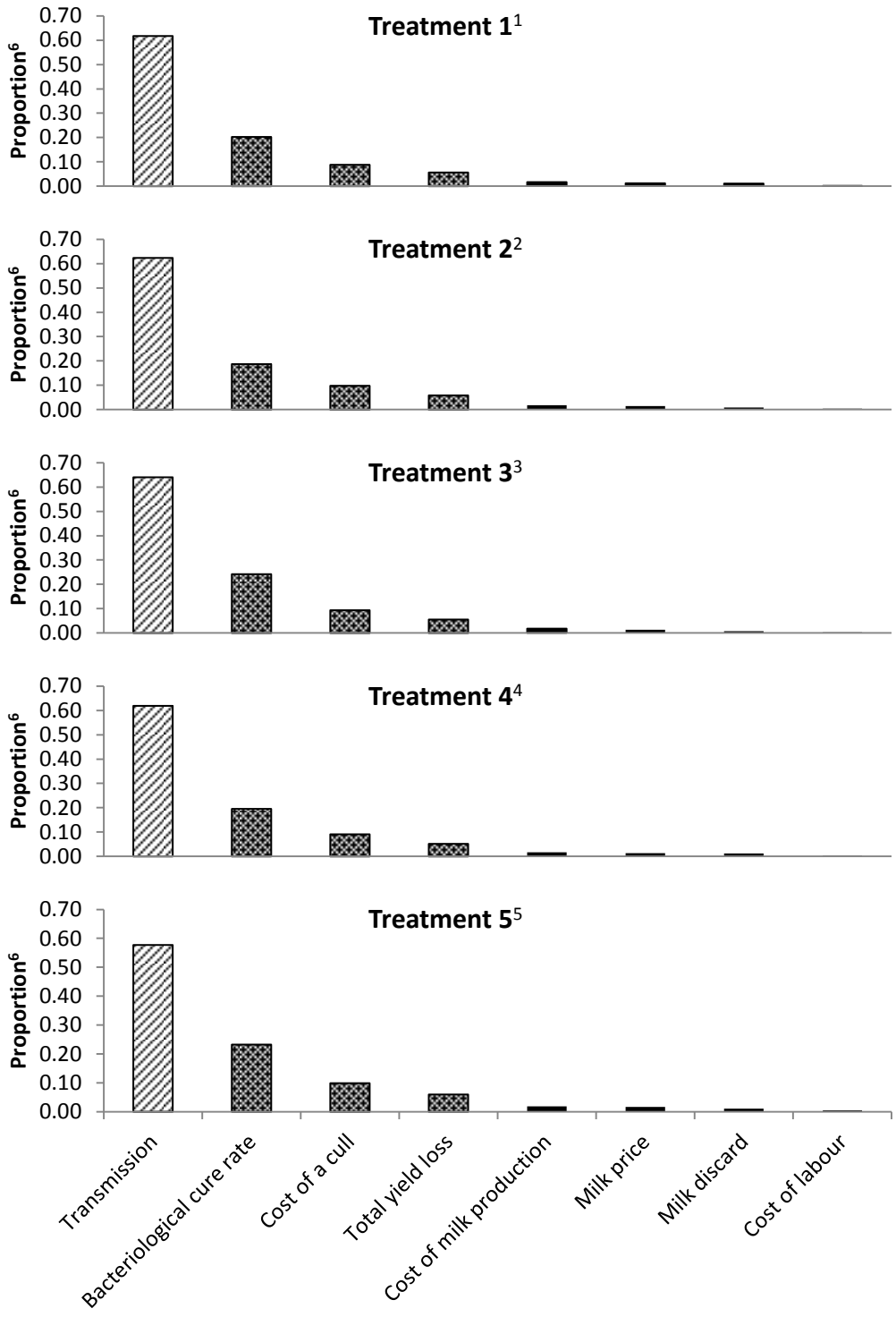


Figure 2-2 Bar charts depicting the proportion of variance in the total cost of clinical mastitis accounted for by each variable for each of the treatment protocols in a model designed to simulate the cost of a case of clinical mastitis [1]3 days of antibiotic intramammary treatment; [2]5 days of antibiotic intramammary treatment; [3]3 days of intramammary and systemic antibiotic; [4]3 days intramammary and systemic antibiotic plus 1 day NSAID; [5]5 days intramammary and systemic antibiotic; [6]Proportion of variance in the total cost of CM; [7]Including the effect of systemic illness, parity, days in milk, repeat case and somatic cell count at time of case; [8]Milk withdrawal during treatment.

Table 2-4 Breakdown of average (median) costs (£) associated with a case of clinical mastitis (CM) for each treatment protocol as predicted by a model designed to simulate the cost of a case of clinical mastitis (2.5th and 97.5th percentiles given in parenthesis).

	Antimicrobial treatment regimen				
	Treatment 1	**Treatment 2**	**Treatment 3**	**Treatment 4**	**Treatment 5**
Average proportion of total cost (%)					
Yield loss	44	41	41	39	38
Culling	22	20	20	19	19
Milk discard	23	27	20	20	23
Medicines	3	5	15	18	15
Labour	3	4	3	3	4
Cost (£) of original CM case (including flare-ups)	229	250	256	271	278
	(132; 353)	(144; 378)	(158; 382)	(169; 398)	(170; 412)
Median number of herd mates infected due to transmission	0.61	0.48	0.49	0.46	0.38
	(0.03;2.02)	(0.02;1.65)	(0.02;1.64)	(0.02;1.61)	(0.02;1.38)
Cost (£) of transmission	132	120	125	123	105
	(47; 471)	(47; 421)	(48; 425)	(51; 424)	(46; 363)
Total cost (£)	361	370	380	394	383
	(179; 824)	(192;799)	(206; 806)	(216; 775)	(216;775)

Treatment 1 = 3 days of antibiotic intramammary treatment; treatment 2 = 5 days of antibiotic intramammary treatment; treatment 3 = 3 days of intramammary and systemic antibiotic treatment; treatment 4 = 3 days intramammary and systemic antibiotic treatment plus 1 day NSAID; treatment 5 = 5 days intramammary and systemic antibiotic treatment

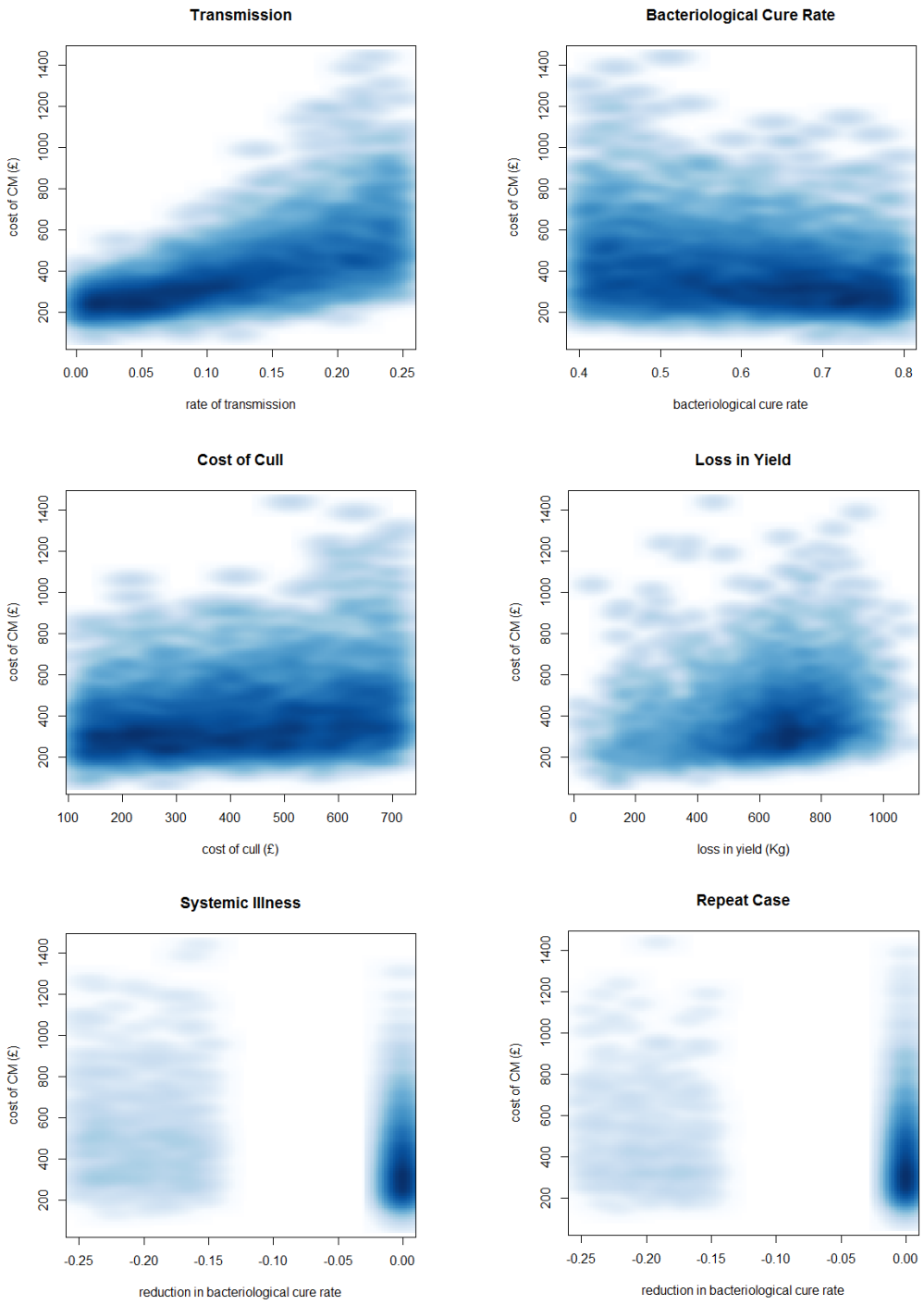


Figure 2-1 Series of scatterplots demonstrating the relationship between the predictor variable and the total cost of clinical mastitis (CM) for treatment 1 (3 days intramammary antibiotic) in a model designed to simulate the cost of a case of clinical mastitis.

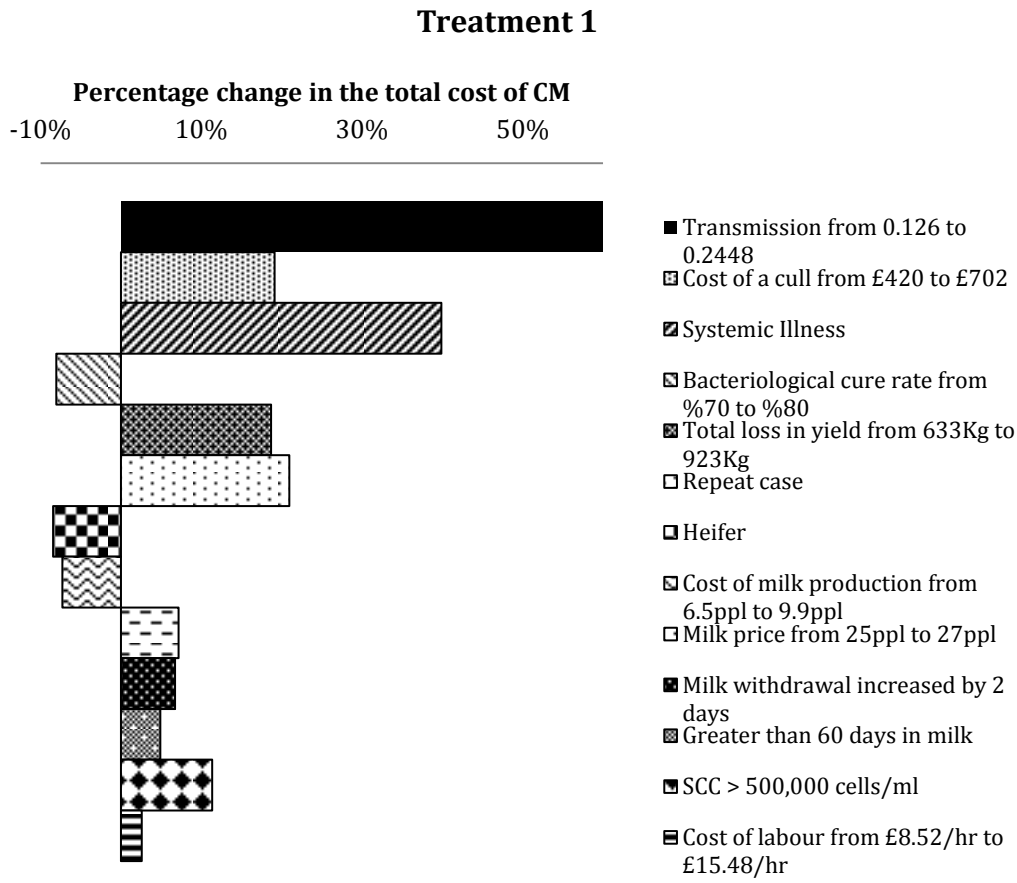


Figure 2-4 Tornado plot to demonstrate the predicted effect of a given change in one of the predictor variables on the total cost of clinical mastitis when all of the others remain constant. Treatment 1 = three days of intramammary antibiotic treatment. Transmission refers to the risk of transmission over a 14 day period

2.4 Discussion

The results suggest that the risk of transmission of infection has the greatest influence on the cost of a case of CM and this appeared to be the case by a wide margin. Indeed, a relatively small increase in the rate of transmission was associated with a large increase in cost (Figure 2-4) and this is consistent with a study by Halasa (2012) who reported that the total annual net cost of intramammary infection (IMI) was highly sensitive to the transmission rate of *Staph. aureus*.

The potential for transmission of IMI between cows is well established (Barkema et al., 2009) and yet despite this, relatively few studies exist that seek to quantify this phenomenon (Lam et al., 1996a; Zadoks et al., 2002, 2001). The transmission data from these studies has been used to inform some economic (Swinkels et al., 2005a,b; van den Borne et al., 2010) and epidemiological studies (Barlow et al., 2009) but these were all set in the context of treatment of subclinical mastitis. One study that did include transmission in a discrete-event model investigating the cost of pathogen-specific IMI in a herd of 100 dairy cows found that the total net cost was most sensitive to the transmission rate parameter (Halasa et al., 2009). A limitation of previous research on 'pathogen-specific' transmission rates is that the rate is likely to vary considerably between different strains of the 'same' pathogen. The advantage of using PSA, is that a single distribution could be used to encompass many different plausible rates (based on literature) and the importance of this parameter could be investigated without the need to make assumptions as to how a particular pathogen may or may not behave. Therefore, the variation in the transmission rate parameter in this study effectively takes into account known variation in pathogen and strain of bacteria. Whilst the use of uniform distributions means that no assessment is made as to which scenario is more or less likely and therefore which transmission value is most common, their use does mean that the relative importance of the different transmission values affecting the cost of CM can be robustly assessed across a wide range of plausible situations.

In the model described in this study, cows that cured bacteriologically following treatment could go on to either finish the lactation or be culled, and at no point could they transmit infection to other cows. Cows that remained subclinically infected could either end the lactation, be culled, or experience a repeat case of CM; during this time, they were considered 'eligible' to transmit infection whichever route they followed. Whilst this may represent a simplification of the biological reality, it is probably these subclinically infected cows that represent the major reservoir of contagious pathogens and the way in which those cows are managed could have a significant impact on the degree of between cow transmission and hence the cost of mastitis.

Transmission of contagious mastitis pathogens mainly occurs during milking (Fox and Gay, 1993) and measures aimed at reducing transmission therefore tend to focus on the milking process, the management of the cows at milking and the milking machine itself. A recent systematic review of the effect of udder health management practices on herd SCC highlighted the importance of wearing gloves whilst milking, the use of (well-adjusted) automatic cluster removal, application of post-milking teat disinfection, milking cows with CM or a high SCC last and the annual inspection of the milking machine (Dufour et al., 2011). Whilst such studies measuring association are not strong evidence of causality, they do highlight practices that are likely to help minimise the transmission of IMI and appear to be relatively well adopted by dairy farmers (Rodrigues et al., 2005; Olde Riekerink et al., 2010). The

segregation of infected cows represents a challenge for many producers both logistically and diagnostically, because creating an additional group may add to space and time pressures and a certain amount of expenditure and effort will be required to diagnose infected cows. Despite this, it would seem logical that keeping infectious cows separate to susceptible individuals should reduce spread and there is evidence to support this in the literature (Wilson et al., 1995; Middleton et al., 2001; Zecconi et al., 2003). A possible alternative to segregation is back-flushing the milking unit to prevent uninfected cows from being exposed to contaminated milking units from infectious cows (Keefe, 2012) and there is some evidence of its efficacy (Hogan et al., 1984; T. W. Smith et al., 1985). Whilst this may represent a significant investment to install, it may offer a pragmatic solution on farms for which in-parlour transmission appears to be a problem but for whom segregation is not a viable option.

The role of the milking machine in transmission of mastitis should not be ignored despite advancements aimed at reducing its involvement. It is considered to account for up to 20% of new IMI's in some herds although it is probably closer to around 10% in most 'average' herds provided the machine is appropriately configured (Mein, 2012). To minimise the risk of pathogen spread via the milking machine, it should be inspected at least annually (Dufour et al., 2011) which is especially pertinent given that 61% of UK parlours in one study (Berry et al., 2005) failed their annual test.

The measuring and hence monitoring of transmission remains challenging at present and has typically been estimated using SCC trends, CM incidence data and bacteriology (Barkema et al., 2009). Molecular epidemiological techniques (Zadoks and Schukken, 2006) are required to measure how much transmission is occurring, and these are not currently widely available in the commercial setting. This is however likely to change with advances in technology, and thus the ability to accurately quantify and monitor the degree of transmission in dairy herds should improve.

After transmission, the most important factors influencing the cost of CM were bacteriological cure rate, cost of a cull and loss in yield. This is consistent with other studies (Halasa, 2012; Heikkilä et al., 2012; Huijps et al., 2008). Van den Borne et al. (2010) also reported that cost of mastitis was sensitive to the bacteriological cure rate, with higher cure rates resulting in reduced costs due to mastitis when modelling the effect of lactational treatment of subclinical IMI's. Barlow et al. (2009) found that increasing the cure rate of subclinical IMI's was beneficial at some levels of transmission, but when transmission was high, it could be counterproductive, as it resulted in more uninfected cows (quarters) being available to be re-infected.

In the model used in this study, bacteriological cure rate was structured to be affected by cow factors such as parity, somatic cell count at the time of infection, systemic illness, case number and days in milk as described by Steeneveld et al. (2011). However, we used probability distributions

rather than point estimates for the cow factors and this resulted in a highly variable set of possible values for bacteriological cure rate, which we believe reflects real potential situations. As expected, factors that affect the probability of bacteriological cure had an important influence on the cost of CM, although more research would be useful to determine the real degree of variation in these values in the field and the reasons for such variation. The other parameters in the model such as milk price, length of milk withdrawal and the cost of labour proved to be of lesser significance to the cost of CM. Interestingly, the cost of medicines was found to have little bearing on the overall cost of a case of CM (Table 2-3).

In this study, the probability distributions used for the bacteriological cure rate reflected a greater degree of uncertainty associated with the least aggressive protocol (treatment 1) and an increased chance of cure for the more aggressive treatment protocols overall (Table 2-1). There was a large degree of overlap in the bacteriological cure rates for the different treatment protocols, and the same was true of the model outputs (Table 2-4) which showed that the overall cost of CM was very similar despite the treatment protocol selected. The relationship between the bacteriological cure rate and the cost of CM was variable which was likely to be a result of the increased width of the distribution used for treatment protocol 1 relative to the other treatment protocols. The median total costs (Table 2-4) were higher than most figures quoted in the literature as they included the costs incurred by any transmission that happened as a result of the case of CM which most other figures do not. So, rather than

representing the cost of a case of CM, it may be more appropriate to think of the values for total cost in Table 2-4 in terms of the 'room for investment' in preventing a case of CM. The median costs without taking into account transmission were higher than the equivalent figures quoted by Steeneveld et al. (2011), but these do not necessarily represent an 'average' cost for mastitis because with the use of uniform distributions in this study, the aim was to fully explore causes of variation in cost rather than averages. Treatment 1 (3 days intramammary antibiotic) resulted in the lowest median cost, as was found by Steeneveld et al. (2011), but also had the broadest range, which is intuitive given the increased risk of transmission, subclinical infection and culling associated with a reduced bacteriological cure rate. Therefore, and importantly, the treatment protocol selected appears to be much less important than other factors such as transmission. Steeneveld et al. (2011) hypothesised that the inclusion of transmission would favour the intensive antibiotic treatment regimens, and there was some evidence to support this hypothesis in the results from our model, with the most aggressive treatment protocol (treatment 5) being less highly correlated to the rate of transmission than the other protocols (Table 2-3) and resulting in fewer cows becoming infected due to transmission (Table 2-4). The increased bacteriological cure rate associated with treatment 5 was based on expert opinion rather than specific studies, but if intensive antibiotic treatment protocols were indeed found to reduce transmission, then our model would indicate that the potential economic benefits could be far greater than simply those

associated with the individual cow. More data on expected cure rates would be needed to improve our understanding of this aspect.

The use of modelling in economic evaluations is now widespread in the health-care sector as it enables the investigation of the likely range of outcomes (cost-effectiveness) under different assumptions even when the exact magnitude of key variables is unknown (Buxton et al., 1997). PSA has become the state-of-the-art method for determining the uncertainty in the outcomes of cost-effectiveness studies because of the uncertainty in input parameters (Boshuizen and van Baal, 2009). There are concerns that the use of deterministic or univariate sensitivity analysis may underestimate overall uncertainty (Briggs, 2000) and become difficult to interpret with large numbers of parameters especially if any are correlated (Claxton et al., 2005). Such limitations with other forms of sensitivity analysis have led to the development of PSA based on Monte Carlo simulation methods (O'Brien et al., 1994). PSA permits the analyst to examine the effect of joint uncertainty in the variables of an analysis without resorting to the wide range of results generated by extreme scenario analysis (Briggs and Gray, 1999). Parameter correlation is propagated automatically providing meaningful sensitivity analysis regardless of parameter correlation (Ades et al., 2006a). Given that the literature is often quite sparse concerning many of the model inputs required, assumptions are usually necessary for this kind of model and this can result in unreliable conclusions being drawn if this uncertainty is not properly investigated. By using PSA we can reflect the level of

uncertainty by defining the parameters as distributions that are specified and transparent. The distributions used do require a degree of judgement and this has to be carried out in an open and transparent way and based on current literature where possible.

Our model calculated transmission over a limited period of 12 weeks, a constraint primarily due to increasing model complexity. The amount of time that a cow remains infective following an IMI is dependent on many different factors, and, hence extremely variable. The duration of non-*agalactiae* streptococcal infections may range from 1 day up to 1 lactation (Todhunter et al., 1995; Zadoks et al., 2003), with a median of 42 days (Zadoks et al., 2003). For *Staph. aureus*, the average length of infectivity was found to be 115 days for herds practicing post-milking teat disinfection (Lam et al., 1997). Given these findings, the 12 week period that we used could have resulted in an under-estimation of the effect of transmission.

2.5 Conclusions

The rate of transmission was found to be by far the most influential parameter in a PSA investigating the factors affecting the cost of CM at the individual cow level. This was followed by bacteriological cure rate, cost of culling and loss of yield. The results from this study suggest that more emphasis should be placed on the reduction in the risk of transmission in dairy herds when seeking to minimise the economic impact of CM.

Chapter 3

The cost-effectiveness of an on-farm culture approach compared with a standard approach for the treatment of clinical mastitis in dairy cows

3.1 Introduction

Not only is mastitis important in terms of the economics, as reported in Chapter 2, but the treatment and prevention of mastitis is widely reported as the most common reason for antimicrobial drug use on dairy farms (González et al., 2010; Pol and Ruegg, 2007; Thomson et al., 2008). There is increasing pressure on the agricultural sector to reduce antimicrobial drug usage due to fears over antimicrobial resistance (AMR) (O'Neill, 2015), and the way in which antimicrobial drugs are applied with respect to the treatment of mastitis is, therefore, a sensible target. Conventionally, all cases of clinical mastitis would receive a course of antimicrobial agents but an alternative approach is the selective treatment of cases according to the results of an on-farm culture (OFC) system. With the OFC system, only cases that yield a Gram-positive or mixed culture are treated with antimicrobial drugs, resulting in many cases of clinical mastitis not being treated at all (Lago et al., 2011a). This was demonstrated recently in a study performed in 8 herds based in Minnesota, Wisconsin and Ontario,

which reported that 51% of cows enrolled in the OFC group received antimicrobial drugs as opposed to 100% of the cows enrolled in the conventional group. The same study reported no statistical differences between the two groups with respect to the bacteriological cure risk, the time taken to clinical cure, new intramammary infection risk, treatment failure risk or risk of removal from the herd within 21 days (Lago et al., 2011a).

Whilst OFC appears to be effective at reducing antimicrobial drug usage (Hess et al., 2003; Lago et al., 2011a; Neeser et al., 2006), little is known about factors influencing the overall cost-effectiveness of this approach and, therefore, the types of herds in which it is most likely to be cost-effective. The purpose of this chapter was to use probabilistic sensitivity analysis (PSA, see 1.3.2) to investigate the main factors that influence the cost-effectiveness of an OFC approach to treating clinical mastitis. The model used was an adaptation of the one reported in Chapter 2 with the addition of OFC-specific parameters based on previous research (Lago et al., 2011a). A specific aim was to identify the herd circumstances under which an OFC approach would be most likely to be cost-effective.

3.2 Materials and methods

3.2.1 Model structure

A stochastic Monte Carlo model was developed using OpenBUGS 3.2.2 software (Thomas et al., 2006). The model was used to simulate a case of clinical mastitis at the cow level and to calculate the associated costs

simultaneously when treated according to 2 different treatment protocols; i) a standard approach (3 tubes of intramammary antibiotic) and ii) an OFC programme as described by Lago et al. (2011a). The general model structure and assumptions were consistent irrespective of the treatment protocol applied, and was as described in Chapter 2 (Figure 2-1). An initial case of clinical mastitis (CM1) could either: i) cure bacteriologically, ii) cure clinically but remain subclinically infected, or iii) fail to cure (either clinically or bacteriologically). If CM1 failed to cure, then a repeat treatment (same as initial treatment) would be administered, and the same 3 outcomes permitted. If CM1 cured bacteriologically, then the cow could either end the lactation or be culled before the end of lactation. If CM1 cured clinically but not bacteriologically, then it could either end the lactation, be culled before the end of lactation, or have a repeat episode of clinical mastitis (CM2). CM2 would be treated according to the same protocol as CM1 and would then follow the same possible outcomes as CM1. A third clinical recurrence was permitted for subclinically infected cows (CM3) which were again treated in the same way as CM1 and CM2. If the cow remained subclinically infected after CM3 or failed to cure clinically, then the cow would be culled before the end of lactation. If the cow cured bacteriologically after CM3, then it could either finish the lactation or be culled before the end of lactation (Figure 2-1).

A risk of transmission parameter was included from cows that remained subclinically infected after CM1 and CM2. This represented the risk that

the infection was transmitted from the infected cow to one of the other 99 'susceptible' cows in the herd during a 12-week period. The 12-week period was split into 14-day blocks meaning the infected cow could infect another cow in the herd every 14-days. If infection did spread to another cow, then it too would be considered to be infectious during the subsequent 14-day blocks. For example, if a cow remained subclinically infected after CM1 and it transmitted an infection to another cow during the first 14-day block, then there would be 2 infectious cows at the start of the second 14-day block and the susceptible population would then be 98 cows.

3.2.2 Model input parameters

The model was parameterized with distributions based on existing literature and current commercial data where possible (Table 3-1). All parameter inputs were specified as uniform distributions with the purpose of simulating a wide variety of different scenarios without making assumptions as to which was the most likely. The distribution ranges were based on the literature wherever possible but if only point estimates were available then plausible ranges were added around the point estimate. The input parameters were the same as used in Chapter 2 with the addition of some OFC-specific parameters based on the study by Lago et al. (2011a) (Table 3-2).

3.2.3 On-farm culture specific input parameters

The OFC-specific input parameters comprised distributions reflecting changes to the bacteriological cure rate, the proportion of culture-positive

cases, the time taken to set-up and read the culture plates and the cost of a plate. The distribution for the reduction in bacteriological cure rate associated with the OFC protocol was uniform (-0.22-0), meaning the maximum reduction possible was 22% and the minimum was 0. This possible reduction in bacteriological cure rate arises because of the delay in treatment when using the OFC system. The middle value of 11% was the non-significant effect size reported by Lago et al. (2011a) which was the overall reduction in bacteriological cure rate in cases of clinical mastitis treated with the OFC protocol compared to cases treated with the standard approach. The distribution specifying the 'herd-level' proportion of Gram-positive cases was uniform (0.1-0.9), meaning the lowest proportion was 10% of cases with a Gram-positive culture and the highest proportion was 90%. This distribution reflects the wide spread of values identified in the study by Lago et al. (2011a). There were no published figures for the cost of the biplate used in the study or the time taken to set-up and evaluate the culture results so plausible ranges were estimated as (£1.00-1.40) and (30-60 mins) respectively. The distributions used for all other input parameters are listed in Table 3-1.

Table 3-1 Probability distributions applicable to both treatment protocols used in a model designed to simulate the cost of a case of clinical mastitis treated according to different treatment protocols

Input parameters	Upper and lower limits of uniform distribution	Source
Probability of bacteriological cure	(0.40,0.80)	a
Probability of bacteriological cure after extended treatment	(0.30,0.90)	a
Decrease in probability of bacteriological cure[1]		a
Parity ≥2	(-0.15,-0.05)	
Days in milk ≥60 days	(-0.15,-0.05)	
Cow is systemically ill	(-0.25,-0.15)	
SCC 200,000-500,000 cells/mL at most recent recording	(-0.15,-0.05)	
SCC >500,000 cells/mL at most recent recording	(-0.25,-0.15)	
Repeated case (>1st case in current lactation)	(-0.25,-0.15)	
Probability of being culled for bacteriologically noncured cases		a
Initial case	(0,0.32)	
Following first recurrence (CM2)	(0.04,0.36)	
Probability of being culled for completely cured cases		a
Initial case	(0.04,0.06)	
Following first recurrence (CM2)	(0.10,0.20)	
Following second recurrence (CM3)	(0.20,0.30)	
Probability of death for nonclinical cured cases	(0.04,0.06)	a
Probability of drying-off quarter for nonclinical cured cases	(0.94,0.96)	a
Probability of being culled for cows with dried off quarters	(0.27,0.39)	a
Increase in all culling probabilities when cow is systemically ill	(0.05,0.15)	a
Probability of clinical recurrence for bacteriologically noncured cases	(0.05,0.12)	a
Probability of transmission after CM1 and CM2	(0.002,0.25)	(Van den Borne, 2010)
Proportional yield loss		a
Case in 1st or 2nd month of lactation	(0.07,0.09)	
Case between months 3 and 6	(0.03,0.08)	
Case after month 6	(0,0.04)	
Parity ≥2	(0,0.02)	
305d Yield (Kg)	(7000,10000)	Author
Milk withdrawal (d)	(5.00,9.00)	b
Daily milk discard (Kg)	(5.00,50,00)	Author
Value of discarded milk (£/Kg)	(0.23,0.27)	(DairyCo, 2012a)
Cost of milk production (£/Kg)	(0.03,0.10)	c
Treatment Time (hr)	(0.53,0.87)	a
Cost of labour (£/hr)	(1.00,15.87)	c
Cost of drugs (£)	(5.58,6.97)	d
Cost of cull (£)	(120,720)	c; e
Cost of death (£)	(1200,2000)	DairyCo 2012b

[1] The value selected from this distribution was subtracted from the value selected from the bacteriological cure distribution

a=based on Steeneveld et al. (2011)

b= based on commonly used preparations in the UK

c= based on Huijps et al. (2008)

d= based on estimate of current retail price of commonly used preparations in the UK

e= based on Kossaibati & Esslemont (2000)

3.2.4 Model simulation

The model was used to simulate 5000 cases of CM1 for each treatment protocol. At each model iteration, a value was selected at random from within the ranges specified for each input parameter, independent of each other, and the associated costs calculated. The parameter values and overall cost were stored for each model iteration and were used for subsequent analysis. The difference in overall cost between the two protocols was calculated at each model iteration by subtracting the cost of the OFC approach from the cost of the standard approach. Therefore, a positive value would indicate that the standard approach was more cost-effective and a negative value would indicate that the OFC protocol was more cost-effective. The distribution specifying the herd-level proportion of Gram-positive cases would govern whether the case treated according to the OFC protocol was Gram-positive (or mixed infection) and, therefore, treated with antibiotics, or Gram-negative (or no growth) and, therefore, not treated with antibiotics. In this way, the impact of the proportion of Gram-positive cases on the overall cost-effectiveness of the OFC protocol could be assessed.

3.2.5 Data analysis

Spearman rank correlation coefficients were calculated to explore the univariable associations between model input parameters and the difference in cost between the standard and OFC treatment protocols (Table 3-2). The strength and direction of the relationships were evaluated using the Spearman rank rho (ρ) value. The outcome variable of

specific interest was the difference in cost between the two treatment protocols, however, additional model parameters were included to provide further insight into where cost differences arose. These were the cost of antimicrobial drugs, the difference in time taken to treat each case, the difference in milk withdrawal period and the difference in the rate of transmission.

Table 3-2 On-farm culture specific model input parameters used in a model designed to simulate the cost of a case of clinical mastitis treated according to different treatment protocols

Input parameters	Upper and lower limits of uniform distribution	Source
Proportion of culture-positive cases	(0.10,0.90)	Based upon Lago et al. (2011a)
Reduction in bacteriological cure rate	(-0.22,0.00)	Based upon Lago et al. (2011a)
Cost of plate (£)	(1.00,1.40)	Based upon current retail price
Culture time (hr)	(0.30.1.00)	Author

Descriptive analysis was performed to identify scenarios in which the OFC approach was most cost-effective. To facilitate this, the 5000 simulated cases were sub-divided into 3 groups according to the magnitude of reduction in bacteriological cure rate associated with the OFC protocol as compared with the standard approach: i) large difference (LD) group (17-22% reduction), ii) moderate difference (MD) group (>5-<17% reduction) and iii) small difference (SD) group (0-5% reduction). The difference in cost-effectiveness between the standard and OFC protocols was then assessed for the different groups and at different proportions of Gram-positive cases.

3.3 Results

3.3.1 Data analysis

Across all 5000 simulated cases, the standard protocol was the most cost-effective 68% of the time. The median cost related to a case treated with the standard protocol was £365 and the median cost related to a case treated with the OFC protocol was £382. The maximum difference in cost between the two protocols was £226 with a median of £19.

The Spearman rank correlation coefficients for the OFC-specific parameters are shown in Table 3-3. The difference in cost between the two protocols was most closely related to the difference in bacteriological cure rate and the proportion of Gram-positive cases. As the difference in bacteriological cure rate and proportion of Gram-positive cases increased, the difference in overall cost became higher, making the OFC protocol less cost-effective than the standard protocol. Both the cost of the biplate and the time taken to set-up and evaluate the biplates had a negligible relationship with the cost-effectiveness of the OFC protocol as measured by the Spearman rank correlation coefficients (Table 3-3).

With respect to the model input parameters common to both protocols, those significantly associated with the difference in cost were the difference in the milk withdrawal period (rho=0.75), difference in the cost of drugs (rho=0.61), difference in the time taken to treat the cow (and culture) (rho=0.61) and the difference in the rate of transmission (rho=0.51).

Table 3-3 Spearman rank correlation coefficients for on-farm specific model input parameters in a model designed to simulate the cost of a case of clinical mastitis treated according to different treatment protocols

Parameter	rho
Proportion culture-positive	0.31
Difference in bacteriological cure rate	-0.28
Cost of plate	0.0062
Culture time	0.02

3.3.2 Scenario and sensitivity analysis

The median difference in cost between the two protocols was plotted against the proportion of Gram-positive cases and this indicated that the proportion of Gram-positive cases would need to be less than 12% for the OFC protocol to be more cost-effective than the standard protocol (Figure 3-1). When the proportion of Gram-positive cases increased to 50%, the OFC protocol was on average £29 more expensive per case than the standard protocol. However, the difference in cost between the treatment groups was sensitive to the underlying bacteriological cure rate of Gram-positive cases. When clinical mastitis was subdivided according to whether the difference in bacteriological cure rate was small (SD) medium (MD) or large (LD) the difference in the cost-effectiveness of the treatments was as follows. The OFC protocol was more cost-effective than the standard protocol when the proportion of Gram-positive cases was less than 47% in the SD group (Figure 3-2) and less than 21% in the MD group (Figure 3-3). The OFC protocol was never more cost-effective than the standard protocol for cases in the LD group (Figure 3-4). Therefore, the underlying bacteriological cure rate was a key parameter determining relative cost-effectiveness of the treatment approaches.

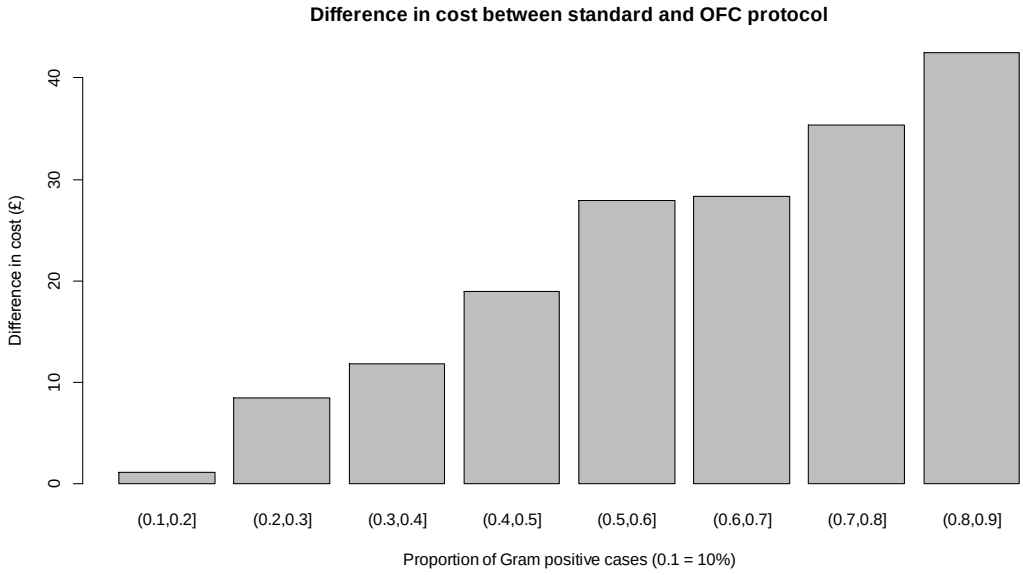


Figure 3-1 Difference in cost between standard and OFC protocol (all scenarios) taken from a model designed to simulate the cost of a case of clinical mastitis treated according to different treatment protocols A positive value for difference =standard protocol more cost-effective; a negative value = OFC protocol more cost-effective.

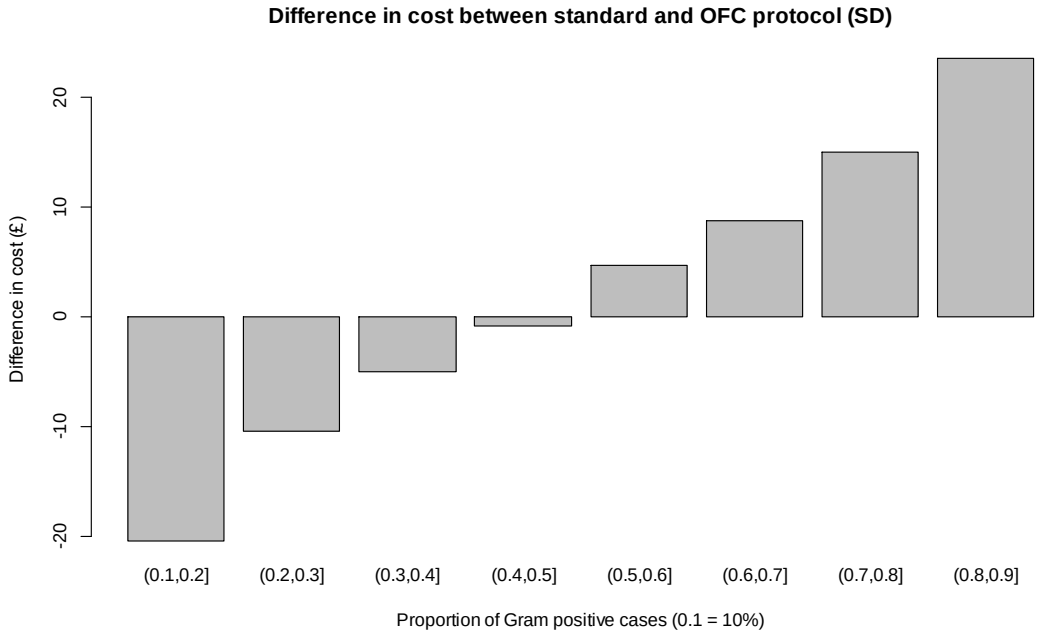


Figure 3-2 Difference in cost between standard and OFC protocol (SD) taken from a model designed to simulate the cost of a case of clinical mastitis treated according to different treatment protocols A positive value for difference =standard protocol more cost-effective; a negative value = OFC protocol more cost-effective. SD = 0-5% reduction in bacteriological cure rate compared with standard protocol.

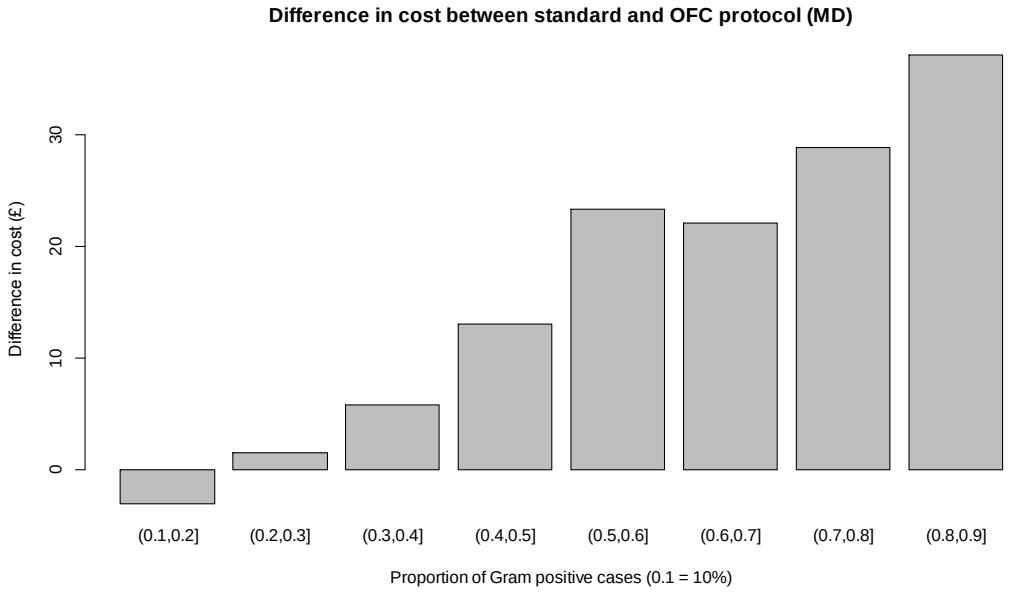


Figure 3-3 Difference in cost between standard and OFC protocol (MD) taken from a model designed to simulate the cost of a case of clinical mastitis treated according to different treatment protocols A positive value for difference =standard protocol more cost-effective; a negative value = OFC protocol more cost-effective. MD = 5-17% reduction in bacteriological cure rate compared with standard protocol.

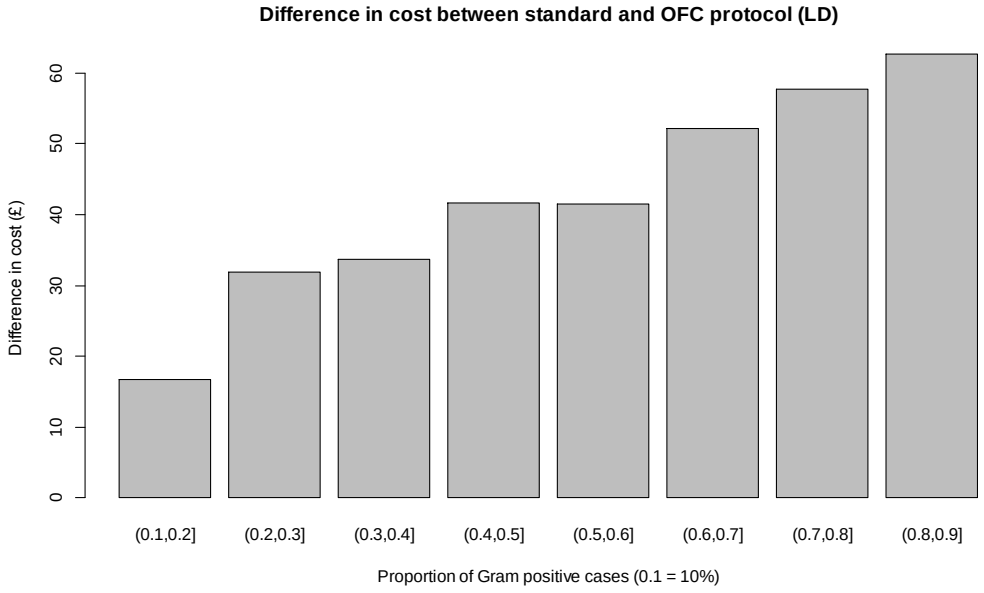


Figure 3-4 Difference in cost between standard and OFC protocol (LD) taken from a a model designed to simulate the cost of a case of clinical mastitis treated according to different treatment protocols A positive value for difference =standard protocol more cost-effective; a negative value = OFC protocol more cost-effective. LD = 17-22% reduction in bacteriological cure rate compared with standard protocol.

3.4 Discussion

The simulation analyses revealed that both the difference in the bacteriological cure rate due to a delay in treatment and the proportion of Gram-positive cases that occur on a dairy unit will have a fundamental impact on whether OFC will be cost-effective. There has undoubtedly been a shift in the aetiology of clinical mastitis towards environmental pathogens, with coliforms and no-growths frequently reported as accounting for approximately 50% of all clinical mastitis culture results (Bradley and Green, 2001b; Bradley et al., 2007b; Breen et al., 2009) as was the case in the study by Lago et al. (2011a). On this basis, it would be fair to assume that most dairy herds would expect to treat approximately 50% of clinical mastitis cases with antimicrobial drugs if utilizing an OFC approach. The reduction in bacteriological cure rate associated with OFC is more difficult to predict as there is very little published data on the extent to which cure is reduced by a delay in treatment of mastitis. However, a reduction of some degree is likely given the 24 hour delay in initiating antimicrobial treatment for the Gram-positive cases and the potential for Gram-positive cases to be incorrectly diagnosed as Gram-negative and therefore not treated, as was the case in 14% of the cases not treated with antibiotics in the study by Lago et al. (2011a). Given the results from this research, further work to quantify the likely reduction in bacteriological cure rate that will arise from this delay in treatment is critical if the cost-effectiveness and welfare implications of OFC are to be established.

One of the aims stated by the authors of the original OFC studies (Lago et al., 2011a, 2011b) was to use their results to evaluate the overall cost-benefit of using an OFC system, but to date, no data have been published. The results of this study serve to illustrate that an OFC approach for the treatment of clinical mastitis would probably not be cost-effective in many circumstances, in particular, not those in which Gram-positive pathogens represent more than 20% of all clinical cases. Since *Streptococcus uberis* and *Staphylococcus aureus* remain common mastitis pathogens on dairy units in many countries, the cost-effectiveness of OFC should be carefully scrutinised in these circumstances.

Whilst OFC will reduce total antimicrobial drug usage on farm, the effect on cow health and welfare and overall dairy farm profitability should be considered. The assertion that there is no 'significant' reduction in bacteriological cure from delayed treatment of Gram-positive pathogens is fragile and requires substantially more research with sufficient power to detect small differences in effect size. In the study by Lago et al. (2011a), statistical analysis revealed a non-significant difference of 11% in bacteriological cure risk between the standard and OFC groups. In that study, the sample size used meant that a difference ≥14% would have been needed between groups to detect the difference as being 'significant' (Lago et al., 2011a), and it therefore remains uncertain whether there is a true difference in bacteriological cure between groups. The sensitivity analysis in the current study suggests that a difference in cure rate of less

than 14% could certainly determine whether OFC is cost-effective, and therefore, larger studies to ascertain this true difference are needed.

Significant differences were reported in the pathogen-specific bacteriological cure rates in the study by Lago et al. (2011a), particularly with respect to *Klebsiella* spp. and *Staphylococcus aureus*. Whilst the reason for these differences is unknown, it is possible that the reduction in bacteriological cure rate associated with OFC is a result of delayed treatment, as was hypothesised by Lago et al. (2011a) and has been reported in a previous study (Hillerton and Semmens, 1999). Given the importance of this parameter, future research should include pathogen specific differences in bacteriological cure rates when treatment is delayed by using OFC.

In the current study, the overall proportion of Gram-positive cases was also shown to be related to the likelihood of cost-effectiveness of an OFC treatment programme. The proportion of Gram-positive cases was shown to be highly variable in the study by Lago et al. (2011a), in which the proportion of quarter cases receiving intramammary antibiotic treatment as a consequence of assignment to the OFC protocol ranged from 31%-89% in the 8 study herds. In the current study, the overall proportion of Gram-positive cases had to be less than 12% (depending on bacteriological cure rate) for OFC to be more cost-effective than the standard protocol. By this measure, OFC would not have been cost-effective in any of the herds in the study by Lago et al. (2011a). However, when cases were grouped according to the difference in bacteriological

cure rate, OFC would be cost-effective when the proportion of Gram-positive cases was less than 47% in the SD group and less than 21% in the MD group. The OFC approach would, therefore, be most suitable for herds in which Gram-negative pathogens are responsible for most clinical mastitis and where the treatment of cows using an OFC approach results in a minimal reduction in the bacteriological cure rate. In practice, it is possible to assess the proportion of Gram-positive cases on a unit and this will inform decision making on the likely cost benefit of OFC.

There may be a balance to be struck between reducing antimicrobial usage and possible deleterious effects in terms of cow welfare and farm finances; would the extra cost incurred by adopting an OFC approach be considered a price worth paying if it results in a reduction in antibiotic drug usage on dairy farms by 25%, as was estimated by Lago et al. (2011a)? If, for societal reasons, this was considered to be a price worth paying, there is also an issue of who should bear the cost. Whilst difficult, it is perhaps time such debates became transparent given the increasing pressure on antimicrobial drug usage and the potential risks posed by antimicrobial resistant bacteria. In the absence of legal jurisdiction, it is incumbent on those advising on animal health and welfare to ensure that the adoption of new technologies, such as OFC, are undertaken in light of comprehensive, transparent welfare and cost-effectiveness assessments.

Whilst the overall likelihood of cost-effectiveness was affected mostly by the proportion of Gram-positive cases and the difference in bacteriological cure rate, the parameters within the model that had the

largest impact on the difference in cost were the difference in milk-withdrawal period, the difference in the cost of drugs, the difference in culture and treatment time and the difference in rate of transmission. Clearly, OFC would be expected to reduce the amount of milk withdrawn from sale and the amount of money spent on drugs because a proportion of the cows would not receive any antimicrobial treatment and would therefore not incur any statutory milk withhold upon resolution of clinical signs. This is in agreement with Lago et al. (2011a) who reported a reduction in milk withdrawal period (5.2 days v 5.9 days) and quantity of antimicrobial drug usage (51% of OFC cases treated v 100% of standard cases treated) associated with OFC. The increase in labour required to acquire milk samples from clinical mastitis cases in an aseptic manner and plate out for culture is perhaps harder to assess and is likely to represent a cost not only in terms of the time taken, but also the opportunity cost incurred as a result of the herdsman being unable to perform other duties as a result. The distribution used in this study of 30-60 mins is, therefore, likely to be a realistic estimate for most circumstances. The large impact that transmission could have on the cost of a case of clinical mastitis has been reported in the previous chapter and it is not surprising therefore that it was closely related to the difference in cost between the standard and OFC approaches also. Whilst the risk would clearly be influenced by herd management and pathogen-specific factors, it could also be affected by any delay in treatment and differences in bacteriological cure rate associated with OFC, resulting in an increased

risk of transmission. This again would need to be assessed at the herd level.

There will inevitably be some unknown parameters in any cost-effectiveness model (Buxton et al., 1997) and these parameters will have a degree of uncertainty surrounding their true value. PSA permits the incorporation of this parameter uncertainty which is subsequently propagated through the model and is therefore reflected in the model outputs. PSA is widely considered to be an implementation of Bayesian statistics, because all parameters have a probability distribution, which is a distinguishing feature of the Bayesian approach (Boshuizen and van Baal, 2009; O'Hagan, 2003). One of the key advantages of the Bayesian approach in medicine is that it removes the reliance upon significance testing and the use of arbitrary thresholds of 'significance' (Greenland and Poole, 2013; Gurrin et al., 2000) meaning the clinician is free to make their own judgement as to what is clinically 'significant' according to the degree of uncertainty with which they are comfortable. In this study, the PSA allowed an evaluation of the parameters likely to be important in determining the cost-effectiveness of the OFC approach and has highlighted that more research is needed in this field before the technique can be recommended on a widespread basis.

3.5 Conclusions

The results of this study indicate that the proportion of Gram-positive cases and the difference in bacteriological cure rate between the two treatment approaches has the greatest impact on the probability that an

OFC approach would be more cost-effective than a standard approach for the treatment of clinical mastitis. The OFC approach appears to be suitable for herds in which Gram-negative pathogens are responsible for most clinical mastitis and where the treatment of cows according to the results of an OFC approach results in minimal reductions in the bacteriological cure rates. These results suggest that OFC will probably not be cost-effective for many herds, and that OFC should, therefore, only be adopted after careful consideration of the predominant pathogens present in each herd and an honest discussion about the uncertainty surrounding its overall cost-effectiveness.

Chapter 4

Current management practices and interventions prioritised as part of a nationwide mastitis control plan

4.1 Introduction

Having highlighted the significant cost of mastitis in Chapter 2 and the concerns about the quantity of antimicrobial drugs used to treat mastitis in Chapter 3, the focus of the remainder of the thesis is on the control of mastitis. All of the data reported and analysed in Chapters 4, 5 and 6 originated from UK dairy herds that have participated in the AHDB Dairy Mastitis Control Plan (DMCP, see 1.2.4)

A variety of studies have considered on-farm management practices relevant to mastitis control but there have been relatively few peer-reviewed studies from the UK (Fenlon et al. 1995, Green et al. 2007b, Green et al. 2008, Langford et al. 2009) and nothing as detailed as the DMCP questionnaire which has 377 questions and observations all relevant to mastitis control. A better appreciation of current management practices would aid the understanding of why mastitis remains such a problem on many UK dairy farms and provide useful insights into which interventions are perceived to be most important for different types of

farms. The purposes of this chapter were to report performance and management data taken from a sample of UK dairy farms that have participated in the DMCP and to identify important mastitis prevention practices that are not currently widely implemented. The frequency at which these deficiencies in management were prioritised by the plan deliverers was also reported to evaluate how important these management practices were perceived to be.

4.2 Materials and methods

4.2.1 AHDB Dairy Mastitis Control Plan (DMCP)

As described in Section 1.2.4, the DMCP consists of 3 main stages; i) analysis of the herd data to assess patterns of mastitis and categorisation of each herd according to those patterns; ii) assessment of the current farm management, and, based on deficiencies identified, prioritisation of the most important management changes required; and, iii) frequent monitoring of the farm data to assess the subsequent impact on CM and SCC. During stage ii), the answers to the questionnaire and the 'diagnosis' made are entered into the ePlan software package. Once all of the required information is entered, the programme identifies where the herd differs from 'best practice' in terms of mastitis control, and highlights specific interventions most relevant to the herd diagnosis. For example, a lack of pre-milking teat disinfection would only be highlighted if the herd had an Environmental Lactation (EL) diagnosis.

The plan deliverer would prioritise 5-10 of these interventions to be implemented on the farm. A three level ranking system was used for the interventions based on the strength of evidence from research, to assist the plan deliverer in prioritising which interventions to focus on; interventions supported by most evidence were made the priority for action (DairyCo, 2014).

4.2.2 Farm selection

Participating farms were included in this study if the herd performance data (e.g. SCC data and CM records) were available at the plan start date in addition to the ePlan data (the answers to the questionnaire, the herd diagnosis and the prioritised interventions).

4.2.3 Data collection

Herd performance data were submitted electronically by the plan deliverer when each farm was enrolled on the DMCP. Plan deliverers were contacted directly by the author and asked to send relevant ePlan data.

4.2.4 Data analysis

The herd performance and ePlan data were imported into Microsoft Access (Microsoft, 2010), checked and exported into Microsoft Excel (Microsoft, 2010) for analysis. The herds were grouped accordingly for analysis; EDP, EL, CDP/CL. The CDP/CL herds were grouped together due to similarities in the epidemiology and low numbers of herds assigned those contagious diagnoses.

Some of the parameters used to measure mastitis performance in the participating herds are defined in Table 4-1, and consisted of: bulk milk SCC (12 month mean calculated from individual cow somatic cell counts weighted for milk production), incidence rate of clinical mastitis (IRCM), new lactation origin infection incidence rate as measured by SCC (LNIR) and CM records (CMLP) and new dry period infection incidence rate as measured by SCC (DPNIR) and CM records (CMDP) (Bradley et al., 2008b, 2007a). Mann-Whitney-Wilcoxon tests were used to compare the mastitis parameters between the three groups of herds and a significance probability was set at $P \leq 0.05$ for a two-tailed test.

Table 4-1 Mastitis parameter definitions

Mastitis Parameter	Definition
Lactation new infection rate (LNIR)	The percentage of 'uninfected' cows (<200,000 cells/ml for the whole of the current lactation, or <200,000 cells/ml at the previous three milk recordings, or below 100,000 cells/ml at the previous two milk recordings if previously >200,000 cells/ml in this lactation) that crossed the 200,000 cells/ml threshold at the following milk recording. (Target <5% per month)
Dry period new infection rate (DPNIR)	The percentage of cows (and heifers) 'infected' (>200,000 cells/ml*) in the first 30d after calving that were 'uninfected' (<200,000 cells/ml) in the milk recording within 1 month of drying off. (Target <10% per month) (*>400,000 cells/ml if recorded within 5 days of calving)
Dry period cure rate (DPCURE)	The percentage of 'infected' cows (>200,000 cells/ml) prior to drying-off that were 'uninfected' (<200,000 cells/ml*) at the first milk recording after calving. (*<400,000 cells/ml if recorded within 5 days of calving)
Clinical mastitis of lactating period origin rate (CMLP)	The incidence rate of first (index) cases occurring in lactation, 31-305 days in milk. (Target <2 in 12 cows per lactation period)
Clinical mastitis of dry period origin rate (CMDP)	The incidence rate of first (index) cases occurring at <31 days in milk (likely dry period origin). (Target <1 in 12 cows per 30 day period)

The proportion of herds that were not performing each intervention was calculated, and the frequency with which each intervention was 'prioritised' by the plan deliverers was also calculated. The interventions were ranked according to the proportion of eligible herds that undertook them and the interventions that were least commonly practiced were reported.

4.3 Results

A total of 234 herds that had been enrolled on the DMCP between 2009-2012 were included in the study. The geographical location of the farms is shown in Figure 4-1. The median herd size was 184 cows (range 51-973) which is greater than the current UK average of 125 (DairyCo, 2013). The median 305 day milk yield of the 234 herds was 8463 litres (4297-12410) which is also greater than the current national average of 7445 litres (DairyCo, 2013).

Figure 4-1 Geographical location of herds in the study

4.3.1 Mastitis parameters

Differences between the mastitis parameters for the different groups of herds are shown in Table 4-2. The median bulk milk somatic cell count (BMSCC) for all herds was 208,000 cells/ml (range 74,000-809,000 cells/ml) and the median incidence rate of clinical mastitis (IRCM) was 57 cases/100 cows/year (range 6-164). The incidence of new lactation origin infections as measured by SCC (LNIR) and clinical mastitis records (CMLP) was higher for the herds with a Contagious Lactation/Contagious Dry Period and Environmental Lactation diagnosis than farms with an Enviromental Dry Period diagnosis. The apparent cure rate during the dry period as measured by SCC (DPCURE) was significantly higher in Environmental Lactation herds than the Environmental Dry Period and Contagious Lactation/Contagious Dry Period herds. The incidence of dry period origin infections as measured by CM data (CMDP) was significantly higher in the Environmnetal Dry Period herds than the herds with an Environmental Lactation or Contagious Lactation/Contagious Dry Period diagnosis (Table 4-2).

Table 4-2 General performance parameters and mastitis indices from the 234 UK dairy herds used in the study. Range of 12 month averages given (lowest-highest) with median value in parenthesis

	EDP	EL	CDP/CL	Overall (median)
Number	111	103	20	234
Herd Size	51-553(200)	52-973 (216)	74-390 (176)	51-973 (184)
305d Yield[1] (Litres)	4297-10663(8496)	4770-12410(8509)	6496-10198(7997)	4297-12410 (8463)
BMSCC[2] (x1000 cells/ml)	74-809 (220)	79-670 (221)	91-421(249)	74-809 (208)
IRCM[3] (cases/100 cows/year)	18-164 (65)	6-145 (58)	21-122 (58)	6-164 (63)
LNIR[4] (%)	4.1-19.2(8.5)[a]	4.6-20.7(9.3)	7.3-17.1(10.4)[b]	4.1-20.7(8.9)
DPNIR[5] (%)	5.3-38(19.2)[a]	5.8-50(15.6)[b]	9.3-32(18.8)[a]	0-63.6(17.25)
DPCURE[6]	46.2-96.1(72.7)[a]	53.8-92.6(76.8)[b]	44.7-89.1(68.7)[a]	44.7-96.1(74.15)
CMDP[7] (number of cases per 12 cows/%)	0.61-4.75 (1.82/15.17%)[b]	0.04-2.99 (1.01/8.42%)[a]	0.33-2.2 (1.04/8.67%)[a]	0.04-4.75 (1.36/11.33%)
CMLP[8] (number of cases per 12 cows/%)	0.70-4.94 (2.65/22.08%)[a]	0.34-6.97 (3.09/25.75%)[b]	1.96-4.61 (2.67/22.25%)	0.34-6.97 (2.78/23.17%)

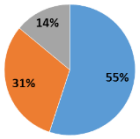
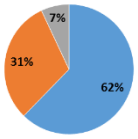
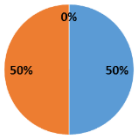
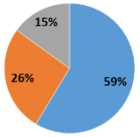
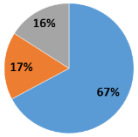
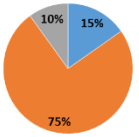
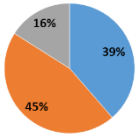
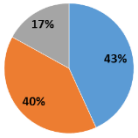
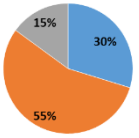
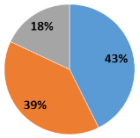
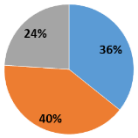
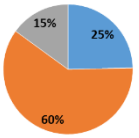
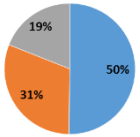
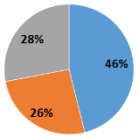
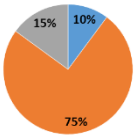
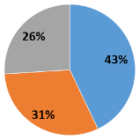
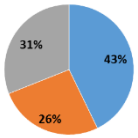
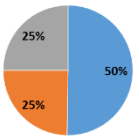
[1] Mean total milk yield/cow during the first 305 days of lactation for the herd
[2] Bulk milk somatic cell count - calculated from individual cow somatic cell counts weighted for milk production
[3] Incidence rate of clinical mastitis
[4] Lactation new infection rate (the percentage of cows previously <200,000 cells/ml cows crossing the 200,000 cells/ml threshold since the last monthly recording)
[5] Dry period new infection rate (the percentage of cows that have been recorded for the first time this lactation and are <31 days in milk that are >200,000 cells/ml and were <200,000 cells/ml at drying-off). Heifers are always assumed to be <200,000 cells/ml prior to first calving.
[6] Dry period cure rate (the percentage of cows that were recorded >200,000 cells/ml prior to drying-off that were <200,000 cells/ml at the first recording after calving.
[7] Incidence rate of first (index) clinical mastitis cases of dry period origin (<31 days in milk)
[8] Incidence rate of first (index) clinical mastitis cases of putative lactation origin (i.e. >30 days in milk)
[a,b] significantly different within row ($p \leq 0.05$)

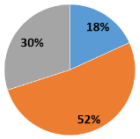
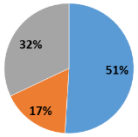
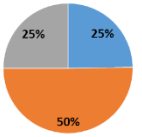
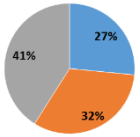
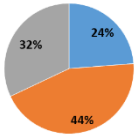
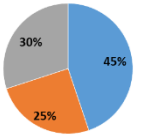
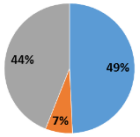
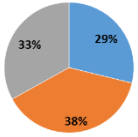
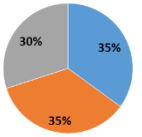
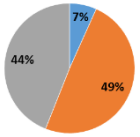
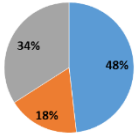
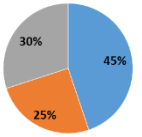
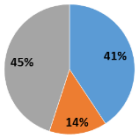
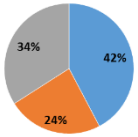
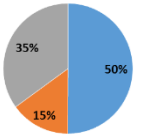
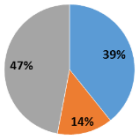
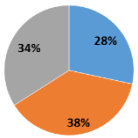
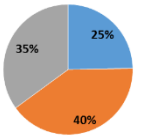
4.3.2 Herd Management Practices

The interventions that were most frequently found not to be undertaken in herds with different diagnoses are displayed in Table 4-3. Only those interventions relevant to each diagnosis were included in these results. The frequency at which interventions were prioritised by the plan deliverers is presented in Table 4-3. The number of interventions prioritised on each farm ranged from 1-92, with a median of 22.

The three least commonly practiced interventions in the EDP herds were the separation of heifers from dry cows prior to calving, allowing at least 4 weeks before returning dry cows to any one grazing, loafing or rest area after it has been use by cattle and not allowing dry cows to have access to any one lying area for more than 2 weeks. The three least commonly practiced interventions in the EL herds were grouping cows with a high SCC/CM separately and milking them last at each milking, using hot disinfectant to clean clusters that become dirty during milking and milking cows with a high SCC/CM last.

Table 4-3 Proportion of herds currently practising each intervention at the time of study, proportion of herds not practising each intervention that were prioritised by the plan deliverer and the proportion of herds not practising each intervention that were not prioritised by the plan deliverer (ranked in order of least commonly practiced).

EDP		EL		CDP/CL	
Pregnant heifers kept separate to dry cows prior to calving		Cows with a high SCC/CM are grouped separately and milked last at each milking.		Hot disinfectant is used to clean clusters that become dirty during milking.	
>4wks allowed before returning dry cows to any one grazing, loafing or rest area after it has been used by cattle		Hot disinfectant is used to clean clusters that become dirty during milking.		Cows with CM and high SCC milked last.	
Dry cows don't have access to any one lying area for >2 continuous weeks		Cows with CM and high SCC are milked last.		Clusters washed with hot disinfectant after milking a cow with CM or a high SCC.	
Cows calve in individual calving pens		Foremilking each quarter to detect mastitis.		Cows with a high SCC/CM grouped separately and milked last at each milking.	
Dry cows spend <2wks on the same pasture, paddock or field		Cows with CM and high SCC are milked with a separate cluster.		Liners are changed at least every 2500 milkings or 6 monthly.	
Alleyways, loafing and feed areas scraped at least twice daily (dry cows)		High SCC cows are clearly marked.		Cows are not dried-off during the milking process.	

Milk yield reduced to less than 15 litres before drying off		Cows with CM grouped separately to the main herd.		All high SCC cows are clearly marked.	
Use of different dry cow therapy products for different cows		Liners changed at least every 2500 milkings or 6 monthly.		Cows with CM and high SCC are milked with a separate cluster.	
Cleaning out dry cow straw yards completely at least once per month		Milking cows are not returned to any one grazing, loafing or rest area <4 weeks after it has been used by cattle.		Cows with CM grouped separately to the main herd.	
Dry cows provided with at least $3m^2$ loafing space/cow		Cows wait less than one hour to be milked.		Pregnant maiden heifers are kept separate to dry cows prior to calving.	
New clean, dry straw provided in dry cow yards at least once daily		Water trough space of >10cm per cow for all cows at all stages of the production cycle.		The parlour has in-line filters.	
Bedded lying area provided to dry cows of $1.25m^2$/1000L of milk/cow (herd annual milk yield)		Clusters washed with hot disinfectant after milking a cow with CM or a high SCC.		Post milking teat disinfection applied at cluster removal or within 30 seconds of cluster removal.	

Management not currently practiced at the time of the farm visit and prioritised by the plan deliverer

Management not currently practiced at the time of the farm visit and not prioritised by the plan deliverer

Management already practiced at the time of the farm visit

4.4 Discussion

The results of this study show that many mastitis-related management practices that are generally considered to be important were not widely performed in a large sample of UK dairy herds. This is one of the most comprehensive field studies of its kind and the first to group the herds according to the putative origin of new mastitis cases. This grouping is important as the most significant aspects of mastitis control for a CL herd are very different than those for an EDP herd, and, therefore, by grouping herds in this way, we are able to highlight the most relevant management 'deficiencies'.

4.4.1 EDP herds

Management of the dry cow/calving cow accommodation to maximise hygiene was an area of potential weakness highlighted in this study. Dry cows had continual access to the same pasture/lying area for more than 2 weeks in over 80% of EDP herds and were allowed to return to paddocks within 4 weeks of them being previously grazed in 85% of EDP herds. The 'graze 2, rest 4' strategy (i.e. graze the same paddock for no more than 2 continual weeks followed by at least a 4 week rest period) has been found to be very effective at reducing the risk of CM in the first 30 days after calving (Green et al., 2007b), and was commonly prioritised by the plan deliverers in this study.

The size of the bedded lying area for dry cows was insufficient in over half of the EDP herds in this study, despite research demonstrating the importance of this with respect to SCC in the first 30 days of lactation

(Green et al., 2008). Other practices not undertaken by the majority of EDP herds include adding fresh bedding to the dry cows daily and scraping alleyways, loafing and feed areas twice daily which have been associated with a reduced risk of CM in the first 30 days of lactation (Green et al., 2007b). Each of these examples was highly prioritised by the plan deliverers, reflecting the perceived importance associated with dry cow environmental management for these herds.

Less than 20% of the EDP herds used individual calving pens, despite evidence that they are associated with a reduced SCC and reduced incidence of CM (Barnouin et al., 2004; Bartlett et al., 1992; O'Reilly et al., 2006). This indicates that many cows are calving in the dry cow yards and almost 60% of EDP herds were failing to completely clean-out these straw yards on a monthly basis, which may result in increased CM (Peeler et al., 2000). The use of individual calving pens and the cleaning-out of dry cow yards were prioritised in 50% and 88% of cases respectively, once again reflecting the importance of dry period hygiene, but also possibly reflecting the practical difficulties that come with implementing individual calving pens on some dairy farms.

Almost 60% of the EDP herds were not selecting dry cow therapy (DCT) at cow-level in this study (DCT products selected according to the infection status at drying-off), and this was made a priority in 45% of the herds not doing so (Table 4-3). Whole-herd antibiotic DCT has been recommended as part of the 5-point plan for several decades (Neave et al., 1969), with the aim of curing existing IMI's and preventing new IMI's

during this time (Smith et al., 1966). There is, however, a growing body of evidence showing potential advantages to selecting DCT at the cow-level rather than the herd-level due to the impact on total antimicrobial usage on-farm (Scherpenzeel et al., 2014), as well as a reduction in CM caused by Gram-negative bacteria (Bradley et al., 2010) and a reduced overall risk of CM in the first 30 days of lactation (Green et al., 2007b).

Less than 30% of EDP herds were reducing yields to below 15 litres prior to drying-off, and this was only prioritised in 26% of cases suggesting that other interventions were deemed more important for most EDP herds. Increased yields at drying off have been associated with increased SCC (Green et al., 2008) and IMI at calving (Dingwell et al., 2004; Odensten et al., 2007; Rajala-Schultz et al., 2005), which is considered to be in-part as a result of delayed formation of the keratin plug in the teat due to milk leakage (Dingwell et al., 2004). Two strategies employed to reduce the milk yield prior to drying-off include feed restriction and reduced milking frequency (Bushe and Oliver, 1987), and, whilst both are effective, the restriction of feed followed by abrupt cessation of milking was associated with a reduced risk of IMI during the dry period (Tucker et al., 2009).

The vast majority (86%) of EDP herds mixed the heifers with the cows prior to calving. However, several studies have demonstrated that the mixing of maiden heifers and cows during the dry period is associated with increased rates of CM (Barkema et al., 1999a) and increased SCC (De Vliegher et al., 2004). Recent studies have also shown that heifers which have a raised SCC at the first milk recording post-partum, are less

productive over the whole of their lifetime and have decreased longevity (Archer et al., 2014a, 2013a; De Vliegher et al., 2005; Piepers et al., 2009), and this is probably why it was made a priority for 64% of these herds.

4.4.2 EL herds

For herds with an EL diagnosis, key focus areas include the management of the milking cows' environment as well as the milking routine and machine maintenance. The management of high SCC cows and those with CM featured prominently, and were rarely housed separately to the main herd in our study despite good evidence of the benefits of doing so (Middleton et al., 2001; Wilson et al., 1995; Zecconi et al., 2003). Where this is not possible, it is still preferable to milk these infected cows last, but again this was not practiced in 83% of the EL herds, despite the association with reductions in SCC (Barnouin et al., 2004; Hutton et al., 1991; Wilson et al., 1995). If neither of these approaches is practical, then a pragmatic solution may be to at least mark infected cows so they are easily identifiable and milk them with a separate cluster, but these were also poorly practiced despite evidence suggesting an association with reduced SCC (Barnouin et al., 2004).

Another aspect of management relating to the hygiene of the milking plant that was not widely practiced was the replacement of liners at the appropriate interval. This highlights the value in the DMCP approach in that it ensures that mastitis control measures that are often assumed to be universally implemented are investigated and rectified when found to be lacking.

The practice of foremilking was only carried out in approximately a quarter of the EL herds in this study despite being a legal requirement (European Commission, 2004). Foremilking is typically recommended to detect CM, and is also a means of premilking stimulation (Wagner and Ruegg, 2002). The application of foremilking is well established in mastitis control programmes (Rodrigues et al., 2005) as it facilitates the rapid detection of CM allowing for the prompt treatment and therefore increased likelihood of successful outcomes (Hillerton and Semmens, 1999).

Two thirds of the EL herds were not following the 'graze 2, rest 4' principle as described previously, and the same number of herds were allowing cows to wait for more than 1 hour to be milked. These aspects of environmental management could both result in an increased exposure of the cows teats to pathogens, in addition to the increased risk of lameness caused by increased waiting times prior to milking (Espejo and Endres, 2007).

4.4.3 CDP/CL herds

Many of the management practices least implemented by the CDP/CL herds were the same as for the EL herds, and focussed primarily on the risk of transmission during the milking process, as would be expected. Perhaps the most striking feature concerning these herds was how few of them grouped or milked cows according to their infection status, or replaced the liners at the correct interval, which for these herds is likely to be of paramount importance. This was reflected in the high proportion

of such interventions that were prioritised by the plan deliverers for the CDP/CL herds.

The majority of herds in this study (87%) were classified as having a predominantly environmental pattern of disease, divided almost equally between EDP and EL diagnoses. This was not unexpected, as it reflects the national trend for the increased importance of the cows' environment as a source of intramammary infections relative to the contagious spread of pathogens from cow to cow that were more common historically (Bradley 2002, Bradley et al., 2007a). Contagious pathogens are relatively well controlled by the 5 point plan which was introduced in the 1960's and adopted widely by dairy farmers in the UK (Bradley, 2002). Unfortunately, this strategy was not designed to control the environmental routes of transmission, and so a more farm-specific approach is required to identify risk factors and implement appropriate interventions accordingly.

The importance of the dry period with respect to mastitis control has been well documented (Bradley and Green, 2004), and it is known that a significant proportion of CM cases occurring within the first 30 days after calving will have been caused by infections acquired during the dry period (Bradley and Green, 2000; Green et al., 2002). For herds where these type of infections predominate, the impact that deficiencies in dry cow management may have on udder health and productivity can be profound, and should therefore be the focus of any mastitis control plan (Green et al., 2007b). Approximately half of the herds in this study were

assigned a dry period origin diagnosis and as this is the first large scale study to categorise herds in this way, it is not possible to say if this is typical of the national population.

Whilst representing a relatively large sample of UK dairy herds for this type of study, it is likely that the results are biased towards herds seeking veterinary input with respect to mastitis control rather than being representative of the national herd as a whole. However, this may provide a true reflection of dairy herds seeking veterinary input with respect to mastitis control, and therefore is of value to those involved in the delivery of these services. The majority of the herds included in this study were also based in the south-west of England (Figure 4-1) meaning that they may not necessarily be representative of herds in Wales, Scotland and the north of England.

The EDP herds had similar BMSCC and CM rates as the other herds in the study but were characterised by a significantly higher rate of CMDP than the other herds when the plan was first implemented as would be expected. They also had a significantly higher rate of DPNIR than the EL herds. Suggested targets for the rate of DPNIR and CMDP are 10% and 1 in 12 respectively, and the averages for the EDP herds in this study were considerably higher than these.

Herds with an EL diagnosis had a similar BMSCC and CM rate to the other herds in the study, but were characterised by significantly lower rates of DPNIR and significantly higher DPCURE rates then the other herds as well

as a significantly higher rate of CMLP than the EDP herds. Suggested targets for LNIR and CMLP are 5% and 2 in 12 respectively.

There were far fewer herds with a 'contagious' diagnosis in this study. The CDP/CL herds were characterised by a lower average milk yield than the other herds in the study and a higher BMSCC, which would be expected due to the increased chronicity associated with IMI's caused by 'contagious' pathogens (Bradley et al., 2007b). All other mastitis parameters were broadly similar to the other herds in the study with the exception of the dry period cure rate, which was the lowest of all the groups reflecting the increased challenge of curing infections caused by 'contagious pathogens'(Barkema et al., 2009).

The frequency with which the interventions reported in this study were prioritised by the plan deliverers varied widely. When interventions were not highly prioritised, this may reflect the presence of more pressing concerns in those particular herds or perhaps a lack of perceived efficacy. With a limited number of intervention studies from which to draw from, it is very difficult to have much certainty about the efficacy of most mastitis interventions at the individual herd level, and any uncertainty about the clinical and financial benefit of an intervention will affect the decision to implement it (Green et al., 2010; Huijps et al., 2010). Another reason why mastitis interventions may not have been implemented is that vets may sometimes make too many recommendations at once (Sorge et al., 2010), or fail to ascertain the farmers own priorities before addressing their own concerns (Derks et al., 2013). A useful continuation of this study would

be an investigation into what effect different management interventions or combinations of interventions may have on the mastitis performance, for different types of herd, thus facilitating an evidence-based approach to decision making.

4.5 Conclusions

The results of this study provide data on performance and management of UK dairy herds, grouped according to the main putative origin of new cases of mastitis. Many aspects of management that might be considered to be important in mastitis control were not being practiced by a large proportion of these herds. A better understanding of those practices not widely adopted by UK dairy farmers at present may aid practitioners in identifying and overcoming potential barriers to improved mastitis control in UK dairy herds.

Chapter 5

A Bayesian micro-simulation to evaluate the cost-effectiveness of specific interventions for mastitis control during the dry period

5.1 Introduction

Having highlighted current management practices and identified specific mastitis control interventions not widely practiced in Chapter 4, the objective of the next two chapters was to explore the cost-effectiveness of interventions that were implemented in herds during the study period. This analysis was performed separately for 'environmental dry period' (EDP) herds in Chapter 5 and 'environmental lactation' (EL) herds in Chapter 6.

The importance of the dry period with respect to mastitis control is now well established (Bradley and Green, 2000, 2004), however the precise interventions that reduce the risk of acquiring IMI during this time are not clearly understood.

There exists a vast body of literature reporting associations between various management practices and different measures of udder health e.g. Dufour et al. (2011). A potential limitation with risk factor studies is that they cannot always provide evidence of causation and so there remains a

large degree of uncertainty as to the likely impact that a specific intervention has and therefore its overall cost-effectiveness. Intervention studies can provide evidence of causation (Rubin, 2007; Martin, 2013), but there are very few intervention studies that have sought to measure the efficacy of specific mastitis control interventions within a cost-effectiveness framework (Green et al., 2010). Furthermore, uncertainty about the clinical and financial benefit of an intervention, will affect the decision to implement it (Green et al., 2010; Huijps et al., 2010). If potential interventions are to be prioritised in a rational and evidence-based way, cost benefit analyses are required that capture the uncertainty of the efficacy of interventions.

With limited resources available to a commercial dairy farm, it is important that potential mastitis interventions are prioritised not only according to their efficacy, but also on the likely return on investment. The efficient use of available resources requires an understanding of the opportunity costs whereby resources are allocated to fund one intervention at the expense of the potential 'benefits' afforded by an alternative intervention. This is the dilemma faced by veterinary decision makers, and with many possible mastitis interventions making claims on farm resources, it is necessary when deciding whether to employ resources in one area to be able to compare the probability of a net benefit in that area with all other potential areas where those resources could be employed (Briggs and Gray, 1999).

The aim of this chapter was to investigate the cost-effectiveness of mastitis control interventions to reduce IMI's caused by 'environmental' pathogens during the dry period. An integrated Bayesian cost-effectiveness framework (see 1.3.3) was used to construct a probabilistic decision model that could be used to inform clinical decision making.

5.2 Materials and methods

5.2.1 Data collection

All of the data were collected from UK dairy herds that had participated in the AHDB Dairy Mastitis Control Plan (DMCP, see 1.2.4) during 2009-2012 that were assigned an EDP diagnosis. There were 265 plan deliverers at the time of the study and each were asked to submit their ePlan data, which consisted of the answers to the questionnaire, the interventions prioritised and the herd 'diagnosis' for each of the farms they had visited. They were also asked to submit the herd health and performance data recorded on-farm, consisting of CM and SCC records, herd size and milk production data, covering the 12 months prior to the DMCP start date and the first 12 months from after the plan was implemented. Out of the 265 plan deliverers, 87 plan deliverers had the information and responded. From the 87 plan deliverers that responded, ePlan data were received for a total of 452 herds that had participated in the DMCP during 2009-2012. Complete herd health and performance data were available for 290 of the 452 herds submitted. The 87 plan deliverers that had responded were asked to specify the interventions that were actually implemented on-farm over the 12 months after the initial herd

visit. The plan deliverers submitted this information for 212 out of the 290 herds for which complete data were available. From the 212 herds with complete data, 77 herds were assigned an 'EDP' diagnosis and therefore used in this study. All of this information was collated in a Microsoft Access database (Microsoft Corp., Redmond, WA).

5.2.2 Data analysis

The clinical and subclinical mastitis data for each of the 77 herds were initially checked for completeness and any herds with incomplete records were excluded from the analysis; 73 herds out of the 77 had complete SCC data and were used for the SCC analysis and 64 herds out of the 77 had complete CM data and were therefore used for the CM analysis. In total, data from all 77 herds was used as some herds had complete SCC data and incomplete CM data and vice versa. The outcome of interest in this research was mastitis originating from infections acquired during the dry period as reflected by clinical mastitis and somatic cell count records. Therefore to measure this, the incidence rate of clinical mastitis during the first 30 days after calving (CMDP) was used (reported by DMCP participants as the number of cases/12 cows/month) which has been shown to be correlated to intramammary infections acquired during the dry period (Bradley and Green, 2000; Green et al., 2002), and the monthly percentage of cows that had a SCC < 200,000 cells/ml at the milk recording prior to drying off, that were > 200,000 cells/ml at the first milk recording after parturition (DPNIR), which has also been shown to be

indicative of new dry period intramammary infections (Bradley et al., 2002; Cook et al., 2002; Bradley and Green, 2005).

Interventions that had been implemented on at least two farms were identified and for each farm, categorised as 0 (not already implemented at the time of the initial farm visit and not implemented following the intervention visit), 1 (not already implemented at the time of the initial farm visit but implemented following the DMCP) or 2 (already implemented at the time of the initial farm visit or not applicable). Interventions were classified as not applicable when they concerned an area of management not relevant to a particular farm (e.g. management of dry cow cubicles on a farm that used straw yards to house the dry cows). Collinearity between covariates was assessed using Pearson product-moment correlation coefficients, and no significant collinearity was found.

A Bayesian one-step micro-simulation model was constructed in OpenBUGS version 3.2.2 (Lunn et al., 2009) separately for each of the two outcomes, incorporating a multiple regression model and an onwards cost-effectiveness micro-simulation, based on methods described previously (Spiegelhalter et al., 2004) (Example WinBUGS code provided in Appendix 2). Therefore the posterior distributions from the one-step micro-simulation model incorporated uncertainty in all model parameters (Figure 5-1).

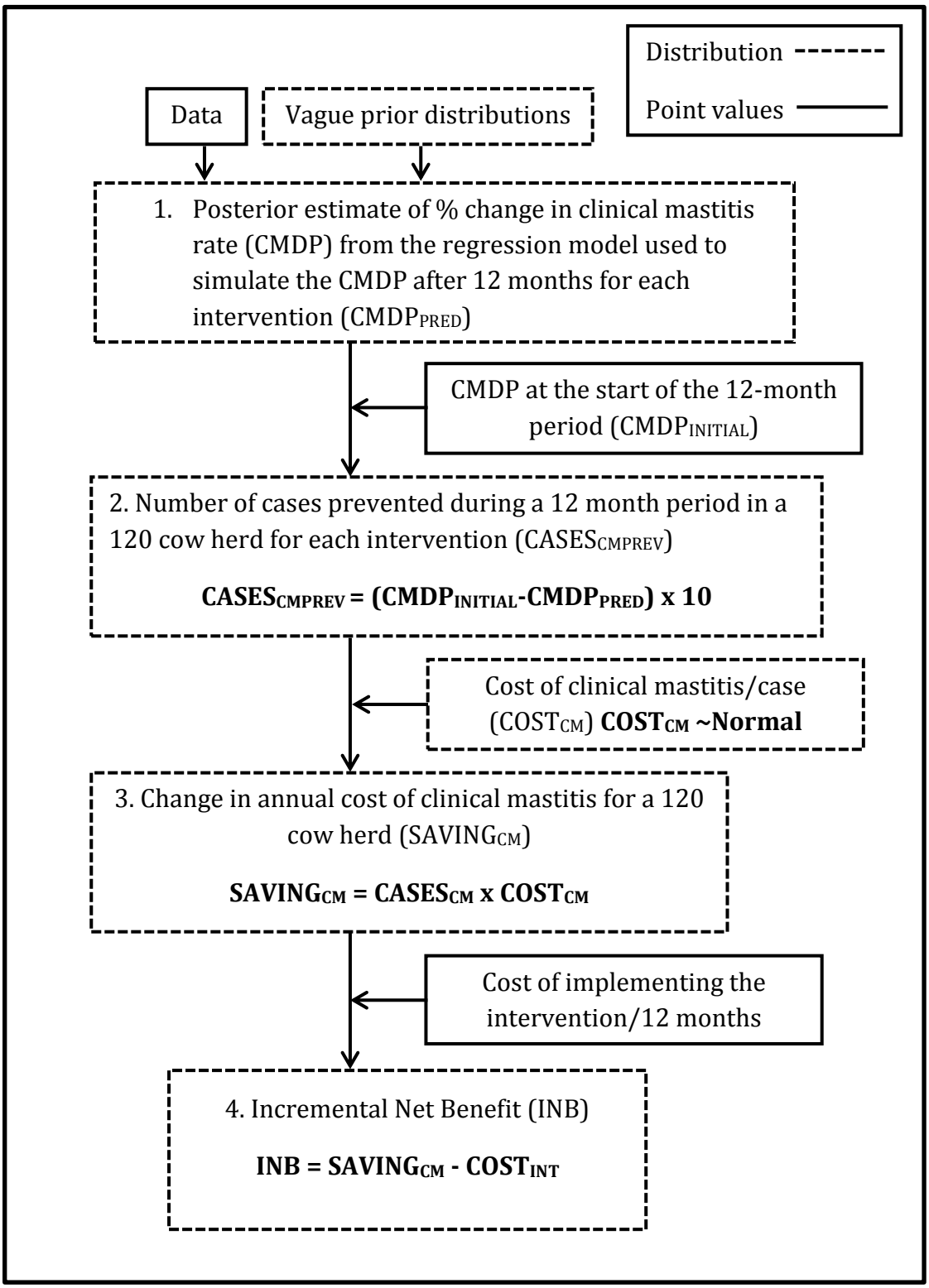


Figure 5-1 Overview of the 1-step micro-simulation procedure designed to simulate the cost-effectiveness of specific mastitis control interventions, using the clinical mastitis micro-simulation model as an example.

The regression models that were incorporated in the first stage of the micro-simulation models took the form;

$$\boldsymbol{Y_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{3i} + \cdots + \beta_p x_{pi} + \varepsilon_i \quad i = 1, \ldots, n} \qquad \textbf{(1)}$$

$$\boldsymbol{\varepsilon_i \sim N(0, \sigma_\varepsilon^2)}$$

where Y_i = the i^{th} observation of the outcome variable, β_0= intercept value, x_{pi} = the p^{th} predictor variable for the ith herd, β_p = the pth regression coefficient, ε_i = the residual error, p = number of predictor variables and n = the number of herds.

The outcome variable (Y_i) used for the clinical mastitis regression model was the percentage change in the CMDP rate during the 12 month period from implementation of the recommended interventions and the outcome variable (Y_i) used in the somatic cell count regression model was the percentage change in the DPNIR rate during this 12 month period. Both of these variables were approximately normally distributed (Figure 5-2 and Figure 5-3), and the influence of any outlying residuals was assessed using the Cook's D value.

Clinical mastitis regression model outcome

$$= \frac{\textbf{CMDP(12 months)} - \textbf{CMDP(initial)}}{\textbf{CMDP(initial)}} \textbf{ x 100}$$

Where CMDP(12 months) = the mean CMDP during the first 12 months after the mastitis control plan started and CMDP(initial) = the mean CMDP during the 12 months before the mastitis control plan started.

Somatic cell count regression model outcome

$$= \frac{\mathbf{DPNIR(12\ months) - DPNIR(initial)}}{\mathbf{DPNIR(initial)}} \mathbf{x\ 100}$$

Where DPNIR(12 months) = the mean DPNIR during the first 12 months after the mastitis control plan started and DPNIR(initial) = the mean DPNIR during the 12 months before the mastitis control plan started.

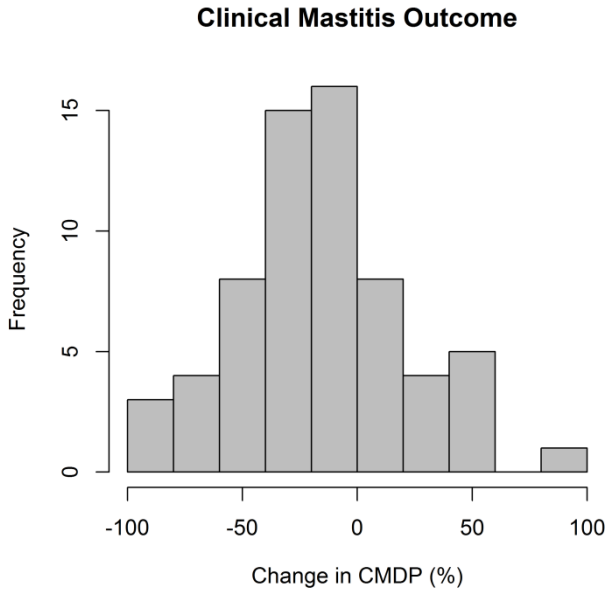


Figure 5-2 Distribution of the outcome variable for the clinical mastitis regression model used to predict the effectiveness of specific mastitis control interventions. CMDP = incidence rate of clinical mastitis in the first 30 days after calving.

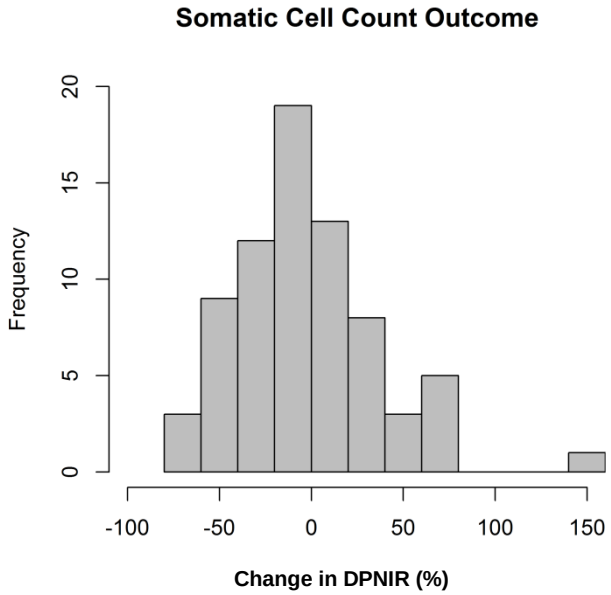


Figure 5-3 Distribution of the outcome variable for the somatic cell count regression model used to predict the effectiveness of specific mastitis control interventions. DPNIR = monthly percentage of cows that had a somatic cell count <200,000 cells/ml at the milk recording prior to drying off, that were >200,000 cells/ml at the first milk recording after parturition.

Vague prior distributions were used for model parameters as follows; σ_{ε}^{2}~Gamma(0.001,0.001), and β~Normal(0,10^{6}). The model predicted values for the outcome variables for each herd were compared with the observed data and displayed graphically to illustrate model performance. Full probability distributions of the intervention efficacy estimates from the regression models were carried forward in to the next stages of the micro-simulation model.

The purpose of the micro-simulation was to simulate the cost-effectiveness of each intervention in theoretical herds with a herd size of 120 cows, with different initial rates of CMDP and DPNIR and different costs associated with implementing each intervention (Figure 5-1). The

values for CMDP and DPNIR on the simulated farms prior to interventions being implemented were taken from actual data from 125 herds that had previously participated in the DMCP so that a range of plausible scenarios were used. The micro-simulation comprised the steps described below; each step was undertaken at each model iteration.

Step 1. The regression model (1) was used to obtain an estimate of the percentage change in the CMDP rate after a 12 month period for each intervention for a given herd. The initial CMDP rate increased or decreased according to the estimated percentage change and this resulted in a predicted new CMDP rate for each farm once it had implemented the intervention ($CMDP_{PRED}$).

Step 2. The number of cases that would be prevented during a 12 month period ($CASES_{CMPREV}$) in a 120 cow herd was then simulated for each intervention individually by multiplying the difference between the initial CMDP rate ($CMDP_{INITIAL}$) and the predicted CMDP rate ($CMDP_{PRED}$) by 10 to convert the denominator to be per 120 cows:

$$\mathbf{CASES_{CMPREV} = (CMDP_{INITIAL} - IRCM30_{PRED}) \; x \; 10}$$

Step 3. The change in annual cost of clinical mastitis for a 120 cow herd ($SAVING_{CM}$) was calculated at each iteration by multiplying the number of cases prevented ($CASES_{CMPREV}$) by the cost of a case of clinical mastitis ($COST_{CM}$):

$$\mathbf{SAVING_{CM} = CASES_{CM} x \; COST_{CM}}$$

A cost per case of clinical mastitis within 30 days of calving was specified as a full probability distribution, $COST_{CM}$~Normal (mean=313, sd=101), based on a stochastic simulation study in the UK (Green et al., 2009). A cost was selected at random from this distribution at each iteration and multiplied by the number of cases prevented to give an overall saving in pounds sterling associated with the implementation of each intervention.

Step 4. The incremental net benefit (INB) was calculated at each iteration to represent the overall net benefit after all 'savings' and 'costs' had been considered over the 12 month period:

$$\mathbf{INB_{CM} = SAVING_{CM} - COST_{INT}}$$

The cost of implementing each intervention ($COST_{INT}$) was specified as one of four different values taken from across a plausible spectrum ranging from a 'low cost' scenario (£250/12 months) to a 'high cost' scenario (£1000/12 months). Due to the huge inter-farm variation in the cost of implementing mastitis interventions, any specified range could be considered to be arbitrary. Therefore, rather than trying to predict the actual cost of implementing specific interventions, a range of values was specified to provide an indication as to how much 'room for investment' there was for each specific intervention. The actual cost of implementation can be entered in the decision support tool in order to make farm-specific predictions.

Parameters throughout the model were estimated from 10,000 Markov chain Monte Carlo (MCMC) iterations, following a burn-in of 1000

simulations. Three chains starting at 'overdispersed' initial values were simulated and convergence was assessed by comparing intra- and inter-chain variability using the Brooks-Gelman-Rubin diagnostic (Brooks and Gelman, 1998; Gelman and Rubin, 1992).

An indicator variable was set to 1 at each intervention when the micro-simulation model predicted an INB of £1000 or greater and otherwise to 0. The mean value of this indicator over the 10,000 iterations provided an estimate of the probability of exceeding a return of £1000. Predictions of INB were plotted for each of the four different values of $COST_{INT}$ to produce probabilistic cost-effectiveness curves that display the probability of saving, at least, £1000 over 12 months at different levels of mastitis for each intervention (Figure 5-4, Figure 5-5, Figure 5-6 and Figure 5-7). A cut point probability of ≥60% for a saving ≥£1000 in a 12 month period was used to label interventions as potentially cost-effective; these interventions are reported. A saving of £1000 in a 12 month period was considered by the authors to be a worthwhile saving for demonstration purposes but farmers will be able to stipulate their own desired level of saving in the decision support tool.

5.2.3 Somatic cell count micro-simulation model

The micro-simulation steps took the same form for the somatic cell count micro-simulation model except the cost of a case of DPNIR was defined by the normal distribution; $COST_{SCC} \sim$Normal (mean=290, sd=112) (Green et al., 2009).

5.3 Results

5.3.1 Herd parameters

The median size of the 77 herds selected for analysis was 187 cows (range 51-553) and the median 305d milk yield was 8611 kg (range 4297-10590). The median incidence rate of CM in the 12 months prior to mastitis interventions was 59.5 cases/100 cows/year (range 18-164) and the median 12 month average BMSCC was 206,000 cells/ml (range 74,000-398,000). The median CMDP rate at the time of the initial herd visit was 13 cases/100 cows/month (12 month average, range 0.25-36.25) and the median DPNIR was 18.35%/month (12 month average, range 1.9-43.8).

5.3.2 Interventions

A total of 112 interventions were evaluated in the analysis (see Appendix 3) and the number of farms implementing each of the interventions ranged from 2-15 (Table 5-1 and Table 5-2). Interventions that were found to be cost-effective in most scenarios were reported resulting in 13 interventions for the CM model and 9 interventions for the SCC model. The interventions could be broadly grouped into three categories; management of the dry cow environment, management of the calving cow environment and the selection and application of dry cow therapy.

5.3.3 Micro-simulation models

Regression model fit

Both regression models demonstrated a good ability to predict the incidence rate of CMDP and DPNIR for a given farm, with the model predictions explaining over 84% of the variability in the observed data in the clinical mastitis regression model (Figure 5-8) and 78% in the somatic cell count regression model (Figure 5-9).

Cost-effectiveness outcome

The probability of an incremental net benefit of at least £1000 for different interventions is provided in Table 5-1, Table 5-2, Figure 5-4, Figure 5-5, Figure 5-6 and Figure 5-7. Interventions in the clinical mastitis micro-simulation model that were cost-effective for most farms (>75% probability of saving £1000 with initial CMDP rate of 2 cases/12 cows and a $COST_{INT}$ of £500) were dry cow rations being formulated by a suitably qualified nutritionist as opposed to an unqualified person, selecting dry cow therapy (DCT) at cow level (selective) rather than at herd level (blanket), balancing calcium and magnesium in the dry cow rations, designing cubicles in such a way that 90% of dry cows lied in them correctly and not drying-off cows during foot trimming procedures. The interventions in the somatic cell count micro-simulation model that were cost-effective for most farms (>75% probability of saving £1000 with initial DPNIR of 20% and a $COST_{INT}$ of £500) were spreading bedding evenly in dry cow yards as opposed to poor bedding spreading, abrupt

drying off as opposed to once daily milking and calving in individual pens as opposed to communal yards.

Interventions in the clinical mastitis micro-simulation model that were sensitive to the cost of the intervention and the initial CMDP and therefore only likely to be cost-effective in certain scenarios included cleaning dry cow cubicles at least twice daily, calving in individual calving pens as opposed to communal yards, milking cows for the first time within 24 hours of calving and considering both antibiotic and non-antibiotic dry cow therapy approaches for low somatic cell count cows. Interventions in the somatic cell count micro-simulation model that were sensitive to the cost of the intervention and the initial DPNIR included milking cows for the first time within 24 hours of calving, removing calves from the cow within 24 hours of birth and differentiating infected from uninfected cows at drying off using SCC records from the current lactation.

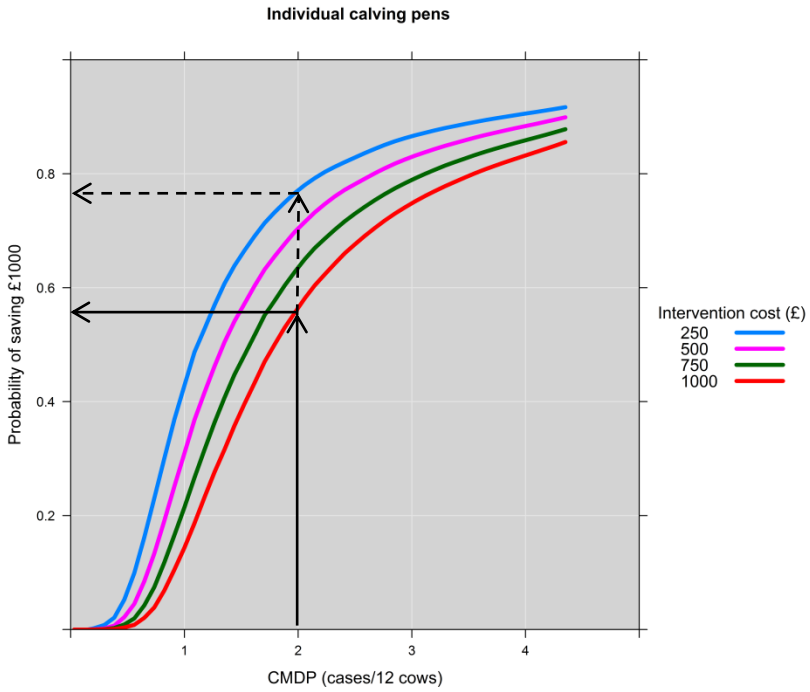


Figure 5-4 Probabilistic cost-effectiveness curve for use of individual calving pens. The arrows indicate how to read from the curve with the dashed line representing the probability of saving at least £1000 in 12 months at an intervention cost of £250 in a herd with a CMDP rate of 2 cases/12 cows. The solid arrow represents the probability of saving at least £1000 in 12 months at an intervention cost of £1000 in a herd with a CMDP rate of 2 cases/12 cows. *CMDP = incidence rate of clinical mastitis in the first 30 days after calving*

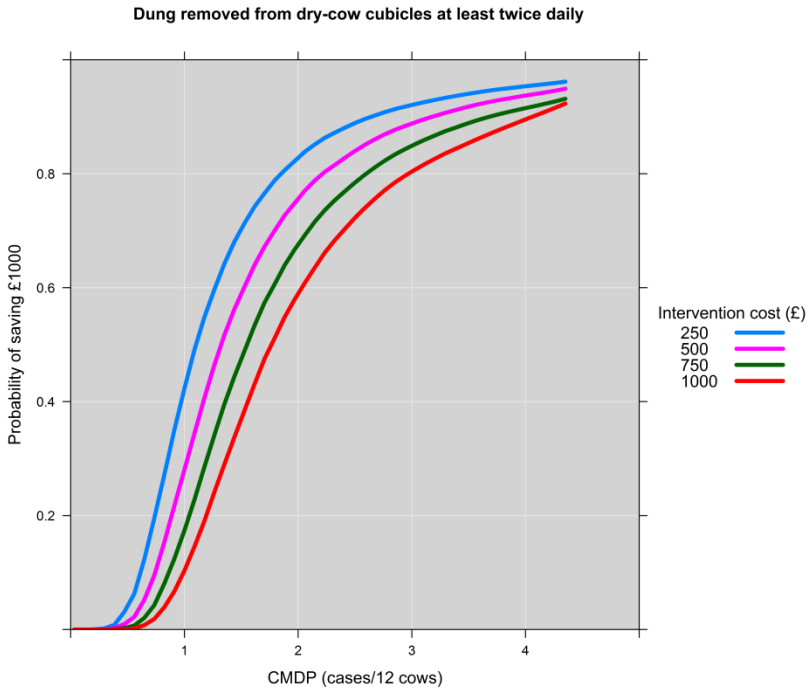


Figure 5-5 Probabilistic cost-effectiveness curve for removing dung from dry-cow cubicles at least twice daily. CMDP = incidence rate of clinical mastitis in the first 30 days after calving.

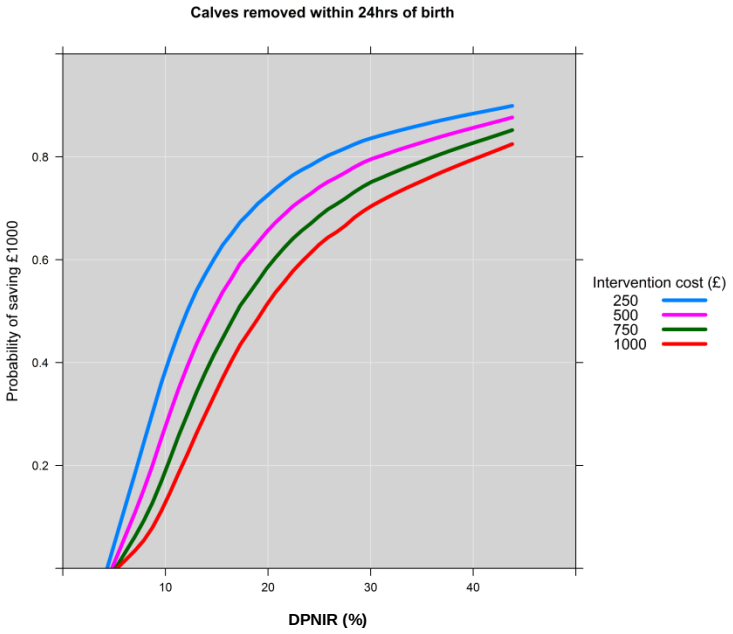


Figure 5-6 Probabilistic cost-effectiveness curve for removing calves within 24hrs of birth. DPNIR = monthly percentage of cows that had a somatic cell count <200,000 cells/ml at the milk recording prior to drying off, that were >200,000 cells/ml at the first milk recording after parturition.

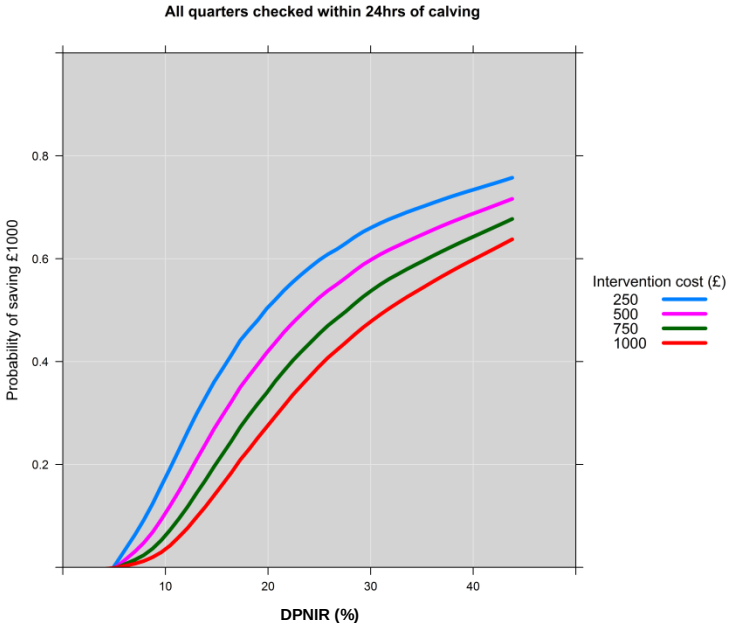


Figure 5-7 Probabilistic cost-effectiveness curve for checking all quarters within 24hrs of calving. DPNIR = monthly percentage of cows that had a somatic cell count <200,000 cells/ml at the milk recording prior to drying off, that were >200,000 cells/ml at the first milk recording after parturition.

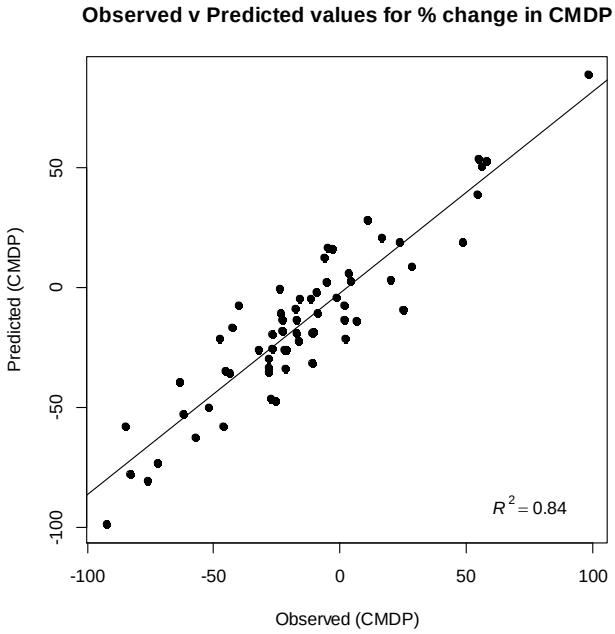


Figure 5-8 Scatterplot of observed and predicted values of the percentage change in CMDP. Predicted values were generated from the clinical mastitis regression model. CMDP = incidence rate of clinical mastitis in the first 30 days after calving

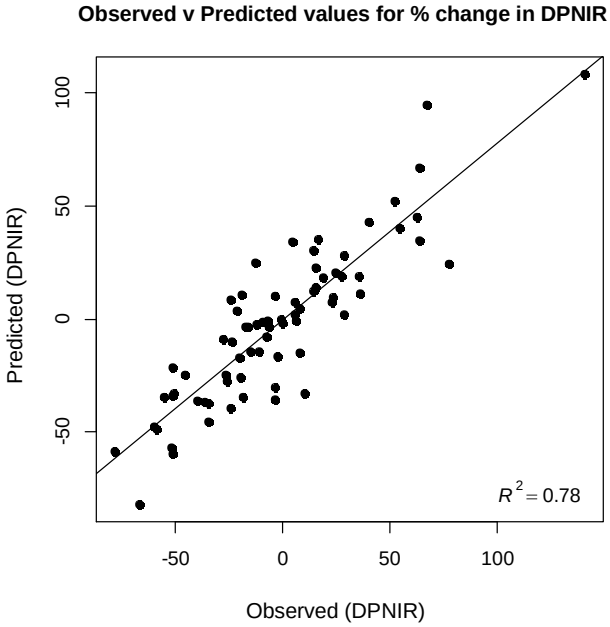


Figure 5-9 Scatterplot of observed and predicted values of the percentage change in DPNIR. Predicted values were generated from the somatic cell count regression model. *DPNIR = monthly percentage of cows that had a somatic cell count <200,000 cells/ml at the milk recording prior to drying off, that were >200,000 cells/ml at the first milk recording after parturition.*

Table 5-1 Probability of saving at least £1000 after 12 months as predicted by the micro-simulation model. The probabilities are given for different incidence rates of clinical mastitis in the first 30 days after calving (CMDP) and different costs of implementing the intervention. Interventions listed in order of cost-effectiveness

			Cost of Intervention (£)			
Intervention	**n**	**CMDP (cases/12 cows)**	**250**	**500**	**750**	**1000**
Dry cow rations should be formulated by a suitably qualified nutritional advisor	2	1.5	0.92	0.89	0.85	0.80
		2.0	0.95	0.94	0.92	0.89
		3.0	0.98	0.97	0.96	0.95
Dry cow therapy (DCT) should be selected at the cow level (a suitable product for each cow) rather than herd level	8	1.5	0.84	0.76	0.67	0.57
		2.0	0.92	0.88	0.83	0.77
		3.0	0.97	0.96	0.93	0.91
Calcium and magnesium should be balanced to prevent milk fever	4	1.5	0.77	0.71	0.65	0.58
		2.0	0.85	0.81	0.77	0.71
		3.0	0.90	0.88	0.86	0.84
Cows must not be dried off during foot-trimming	2	1.5	0.76	0.70	0.63	0.56
		2.0	0.83	0.79	0.75	0.70
		3.0	0.89	0.87	0.85	0.82
Cubicles should be designed such that at least 90% of dry cows will lie in them correctly at all times	2	1.5	0.74	0.67	0.60	0.54
		2.0	0.82	0.78	0.73	0.68
		3.0	0.88	0.86	0.84	0.81
Dung, soiling and wet bedding should be removed at least twice daily from dry cow cubicles	6	1.5	0.70	0.59	0.48	0.38
		2.0	0.83	0.76	0.68	0.60
		3.0	0.92	0.89	0.85	0.80
Cows should be milked for the first time within 24 hours of calving	7	1.5	0.70	0.60	0.50	0.40
		2.0	0.81	0.75	0.68	0.60
		3.0	0.90	0.87	0.83	0.79
Cows should calve in individual pens rather than yards rather than communal yards	3	1.5	0.65	0.56	0.47	0.39
		2.0	0.76	0.70	0.63	0.56
		3.0	0.86	0.82	0.78	0.74
Both antibiotic and non-antibiotic DCT approaches should be considered for low somatic cell count cows	7	1.5	0.50	0.39	0.29	0.21
		2.0	0.65	0.56	0.47	0.39
		3.0	0.80	0.74	0.68	0.62
Clean bedding material should be applied to dry cow cubicles at least once daily if using organic bedding	9	1.5	0.46	0.36	0.27	0.20
		2.0	0.61	0.52	0.44	0.36
		3.0	0.76	0.70	0.64	0.58
Straw yards for calving cows should be cleaned out completely at least once per month	15	1.5	0.40	0.28	0.20	0.13
		2.0	0.58	0.47	0.37	0.29
		3.0	0.74	0.67	0.60	0.53
Pasture must not be grazed for more than two consecutive weeks and must be rested for at least four weeks before cows are returned to graze	6	1.5	0.41	0.33	0.26	0.20
		2.0	0.52	0.45	0.39	0.33
		3.0	0.63	0.59	0.54	0.49
Calves must only be allowed to suckle their own dam to prevent the possible transfer of pathogens in milk between cows	14	1.5	0.28	0.19	0.12	0.07
		2.0	0.44	0.35	0.26	0.19
		3.0	0.64	0.56	0.48	0.41

Table 5-2 Probability of saving at least £1000 after 12 months as predicted by the micro-simulation model. The probabilities are given for different rates of DPNIR[1] and different costs of implementing the intervention. Interventions listed in order of cost-effectiveness

			Cost of Intervention (£)			
Intervention	**n**	**DPNIR[1] %**	**250**	**500**	**750**	**1000**
Cows should calve in individual pens rather than yards rather than communal yards	3	15	0.84	0.78	0.72	0.65
		20	0.90	0.86	0.83	0.78
		30	0.95	0.93	0.91	0.89
Drying off must be abrupt; that is, cows should not be milked once daily in the days prior to drying-off	5	15	0.84	0.78	0.72	0.65
		20	0.90	0.86	0.83	0.78
		30	0.95	0.93	0.91	0.89
Bedding should be spread evenly rather than unevenly in straw yards for dry cows	2	15	0.80	0.76	0.71	0.66
		20	0.86	0.83	0.79	0.76
		30	0.90	0.89	0.87	0.85
There must be good ventilation but without draughts in all calving cow housing	3	15	0.64	0.56	0.48	0.41
		20	0.73	0.67	0.61	0.55
		30	0.82	0.79	0.75	0.71
The calf should be removed from the cow within 24 hrs of birth after ensuring colostrum has been fed	5	15	0.62	0.53	0.44	0.36
		20	0.74	0.66	0.60	0.52
		30	0.84	0.80	0.76	0.72
Cows should be milked for the first time within 24 hours of calving	7	15	0.59	0.49	0.40	0.32
		20	0.72	0.64	0.56	0.48
		30	0.83	0.79	0.74	0.69
Dry cow therapy must be administered hygienically, as detailed in the standard operating procedure	12	15	0.52	0.43	0.34	0.26
		20	0.65	0.57	0.49	0.42
		30	0.78	0.73	0.68	0.63
You should differentiate infected from uninfected cows using somatic cell count records from the current lactation	3	15	0.42	0.34	0.27	0.21
		20	0.54	0.47	0.40	0.34
		30	0.66	0.61	0.56	0.51
Each quarter should be stripped within 4 hours of calving to check for mastitis	6	15	0.38	0.29	0.22	0.16
		20	0.52	0.44	0.36	0.29
		30	0.68	0.62	0.55	0.49

[1]DPNIR = monthly percentage of cows that had a SCC <200,000 cells/ml at the milk recording prior to drying off, that were >200,000 cells/ml at the first milk recording after parturition (12 month average).

5.4 Discussion

This study illustrates how the clinical efficacy of specific mastitis interventions can be quantified and incorporated into a Bayesian cost-effectiveness model using a one-stage micro-simulation. This is the first intervention study to explore cost-effectiveness of mastitis interventions within a Bayesian framework, the results of which are to be incorporated into a decision support tool that will be made available to veterinarians/advisors involved with implementing the AHDB Dairy Mastitis Control Plan in the United Kingdom.

Interventions relating to the design and comfort of dry cow cubicles such as designing cubicles in such a way that cows lie in them correctly and removing dung and wet bedding from cubicles at least twice daily were potentially cost-effective interventions in the clinical mastitis micro-simulation, and aspects of management related to these have been highlighted previously (Barkema et al., 1999b). This earlier study identified type of cubicle divider and thickness of cubicle bedding to be associated with the incidence rate of clinical mastitis. The hygiene of dry cow cubicles has been associated with changes in bulk milk somatic cell count (Barkema et al., 1998a) and clinical mastitis incidence rate (Schukken et al., 1991; Green et al., 2007b), and this highlights the need to provide comfortable, clean cubicles for dry cows as well as lactating cows.

Another aspect of the dry cow environment which is important but commonly overlooked is the grazing management and specifically the rotation of paddocks. In this study a ‘graze 2, rest 4’ policy was used

(paddocks are grazed for no more than 2 consecutive weeks and then rested for no less than 4 weeks), and whilst the effect of this intervention was relatively small in each of the micro-simulation models, the combined predicted reduction in clinical mastitis and somatic cell count would make this an intervention likely to be cost-effective, providing the cost to implement it was modest. This is in agreement with two previous studies that found this intervention to be associated with reduced somatic cell counts and clinical mastitis incidence in UK dairy herds (Green et al., 2007b, 2008), and emphasises the need to consider pasture contamination and ways to mitigate these risks.

The use of individual calving pens as opposed to communal yards had a high probability of cost-effectiveness, and this has been identified as an important risk factor by previous studies (Hutton et al., 1991; Bartlett et al., 1992; Barkema et al., 1998; Barnouin et al., 2004; O'Reilly et al., 2006). This effect may be due to a reduction in pathogen exposure but may also reflect indirectly, the negative impact of cross-suckling calves which has been associated with clinical mastitis incidence in the current study and previously (Green et al., 2007a). Cross-suckling would also be less likely to occur when calves are removed within 24 hours of calving and this intervention was associated with a moderate probability of a £1000 return in the somatic cell count micro-simulation model.

Selecting dry cow therapy at cow level was associated with a reduced CMDP rate, as has been reported previously (Green et al., 2007b). Since neither the products used nor the criteria applied to select between cows

was specified in this study, it remains unclear whether some approaches to selective dry cow therapy are superior to others.

Having a policy of using both antibiotic and non-antibiotic approaches when drying-off low somatic cell count cows was predicted to reduce the rate of CMDP and was very likely to be a cost-effective intervention. Importantly, such a policy will also reduce the quantity of antimicrobial usage on farm. With the increasing concerns about antibiotic resistance comes an increasing pressure on dairy farmers to reduce antibiotic usage (Call et al., 2008; Oliver et al., 2011). In herds such as these with a low prevalence of contagious mastitis and a relatively low bulk milk somatic cell count, the targeting of antibiotic dry cow therapy at cows infected at drying off and use of non-antibiotic teat-sealants in uninfected cows is a rational and effective approach to dry cow therapy (Huxley et al., 2002; Green et al., 2008; Bradley et al., 2010; Cameron et al., 2015). Irrespective of which dry cow therapy products are used at drying-off, interventions affecting the hygiene of the procedure itself, and the cleanliness of the environment in which it is performed, were shown to be potentially cost-effective in both models and confirms previous study findings (Peeler et al., 2000; Barnouin et al., 2004, 2005; Green et al., 2008).

Two interventions in the clinical mastitis micro-simulation model that were predicted to be highly cost-effective in most scenarios were the formulation of dry cow rations by a suitably qualified nutritional adviser and the balancing of calcium and magnesium to prevent milk fever. This is also in agreement with other studies investigating the role of nutrition in

mastitis control (Kremer et al., 1993; Oltenacu and Ekesbo, 1994; O'Rourke, 2009). These studies reported that mastitis was more likely to occur in cows diagnosed with clinical ketosis and cows deficient in vitamins and trace elements such as selenium, vitamin E, copper, zinc, vitamin A and β-carotene.

The uncertainty in clinical and financial outcome for an individual farm is important and illustrates the usefulness of using a probability distribution for anticipated financial returns. The integrated Bayesian model used in this analysis simultaneously derived the joint posterior distribution for all unknown parameters and propagated the effects through the predictive cost-effectiveness model. In this example, uncertainty in the cost of mastitis for each herd is included as well as the uncertainty of the effects of the interventions. There are several advantages of this approach, which have been outlined previously (Spiegelhalter and Best, 2003; Spiegelhalter et al., 2004). The main disadvantages of the unified Bayesian approach include the need for full MCMC software in order to obtain a solution although this is currently freely available (Lunn et al., 2000) and it can also be difficult to evaluate or check model accuracy (Green et al., 2010). Such unified Bayesian models are used widely in human medicine (Parmigiani, 2002; Spiegelhalter et al., 2004), but there are few examples in the veterinary literature (Green et al., 2010; Archer et al., 2014). They provide a useful method to improve the understanding of the uncertainties involved in clinical decision making and therefore have

much to offer the decision analyst and decision-maker (Cooper et al., 2004).

The results of this research were incorporated into a spreadsheet-based decision support tool to enable vets and farmers to explore different scenarios applicable to them. Farm-specific parameters can be entered and required savings specified, resulting in predictions that are relevant to each individual farm. For example, information regarding the herd size, current clinical and subclinical mastitis performance and costs can be inputted in addition to the cost of implementing each intervention. The level of saving required after 12 months is then specified according to the farmers needs and the decision support tool calculates the probability of making the specified level of return and displays this as a probability distribution so the uncertainty can be visualised. The decision support tool also allows different combinations of interventions to be evaluated simultaneously so that many different scenarios can be explored.

This research measured the cost-effectiveness of mastitis interventions in herds specifically with an 'EDP' diagnosis and as such it is difficult to know how these findings would translate to herds more generally. The results may have been influenced by participation bias due to characteristics common to the plan deliverers that submitted data compared with those that didn't. It is also likely that the results are biased towards herds seeking veterinary input with respect to mastitis control rather than being representative of the national herd as a whole. However, the data most likely provides a true reflection of dairy herds

seeking veterinary input with respect to mastitis control and is, therefore, of value to those involved in the delivery of these services.

5.5 Conclusions

In this study, data from 77 UK dairy herds were used to explore the cost-effectiveness of specific mastitis control interventions in herds with a particular problem with IMI's acquired during the dry period. The results from the Bayesian micro-simulation models were incorporated in a decision support tool that will assist optimal decision making by veterinary practitioners in the field.

Chapter 6

A Bayesian micro-simulation to evaluate the cost-effectiveness of specific interventions for mastitis control during lactation

6.1 Introduction

In the previous chapter, Bayesian micro-simulation models were used to explore the cost-effectiveness of specific mastitis control interventions in herds with a particular problem with IMI's acquired during the dry-period (EDP). In this chapter, the same methodology was applied to explore the cost-effectiveness of specific mastitis control interventions in herds with a particular problem with intramammary infections acquired during lactation (EL).

As discussed previously, the historical approach to mastitis control centred around generic advice, focussing on a few specific control measures such as the 5-point plan and the National Mastitis Council 10-point plan (National Mastitis Council, 2006). More recently, veterinarians have started to monitor somatic cell count records to manage individually infected cows (Biggs, 2005; Schukken et al., 2003), and to focus on milking routines and hygiene to manage the overall prevalence of infection within the herd. However, by focussing on the prevalence of

infection and controlling the risks of cow-to-cow transmission, there is a danger that the large number of risk factors associated with housing and pasture management, which are likely to be more important for most UK dairy herds, might be overlooked (Bradley et al., 2008b, 2007a). By measuring the cost-effectiveness of specific interventions implemented by EL herds in many different simulated scenarios, mastitis control interventions can be better prioritised according to each individual EL herds' circumstances.

The aim of this chapter was to investigate the cost-effectiveness of specific mastitis control interventions aimed at reducing IMI's caused by pathogens acquired from the environment, during lactation. As in the previous chapter, an integrated Bayesian cost-effectiveness framework was used to construct a probabilistic decision model that could be used to inform clinical decision making.

6.2 Materials and methods

6.2.1 Data collection

The data collection process was described in the previous two chapters (Sections 4.2.3 and 5.2.1)and the data used for this chapter came exclusively from herds in the dataset that were assigned an EL diagnosis. From the 212 herds with complete data, 75 herds were assigned an 'EL' diagnosis and therefore used in this study.

6.2.2 Data analysis

The clinical and subclinical mastitis data for each of the 75 herds were initially checked for completeness, and any herds with incomplete records were excluded from the analysis. 73 herds out of the 75 had complete SCC data and were used for the SCC analysis and 66 herds out of the 75 had complete CM data and were therefore used for the CM analysis. In total, data from all 75 herds was used as some herds had complete SCC data and incomplete CM data and vice versa.

The outcome of interest in this research was mastitis originating from infections acquired during lactation as reflected by clinical mastitis and somatic cell count records. To measure this, the incidence rate of clinical mastitis after the first 30 days of lactation (CMLP) was used (reported by DMCP participants as the number of cases/12 cows/month), as was the monthly percentage of cows that had a SCC > 200,000 cells/ml at the monthly milk recording, that were < 200,000 cells/ml at the previous monthly milk recording (LNIR).

The outcome variable used for the clinical mastitis regression model was the percentage change in CMLP during the 12 month period from implementation of the recommended interventions and the outcome variable used in the somatic cell count regression model was the percentage change in the LNIR during this 12 month period. Both of these variables were approximately normally distributed (Figure 6-1 and Figure 6-2), and the influence of any outlying residuals was assessed using the Cook's D value.

Clinical mastitis regression model outcome

$$= \frac{\mathbf{CMLP(12\ months) - CMLP(initial)}}{\mathbf{CMLP(initial)}}\ \mathbf{x\ 100}$$

Where CMLP(12months) = the mean CMLP during the first 12 months after the mastitis control plan started and CMLP(initial) = the mean CMLP during the 12 months before the mastitis control plan started.

Somatic cell count regression model outcome

$$= \frac{\mathbf{LNIR(12\ months) - LNIR(initial)}}{\mathbf{LNIR(initial)}}\ \mathbf{x\ 100}$$

Where LNIR(12months) = the mean monthly LNIR during the first 12 months after the mastitis control plan started and LNIR(initial) = the mean monthly LNIR during the 12 months before the mastitis control plan started.

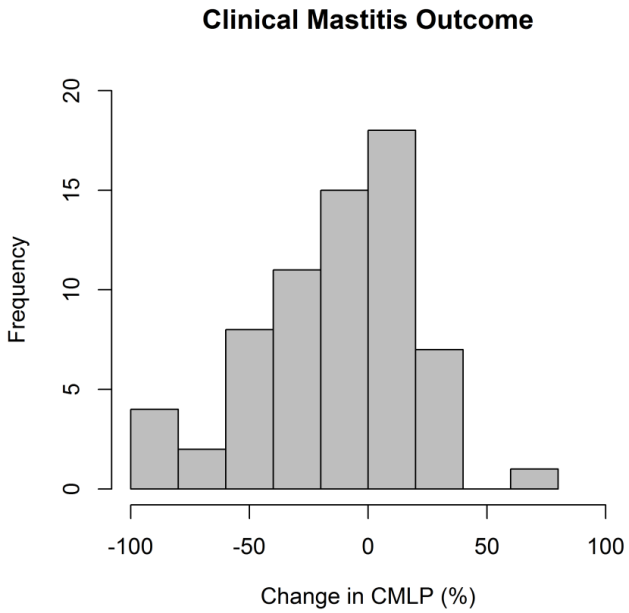


Figure 6-1 Distribution of the outcome variable for the clinical mastitis regression model used to predict the effectiveness of specific mastitis control interventions. CMLP = incidence rate of clinical mastitis after the first 30 days of lactation.

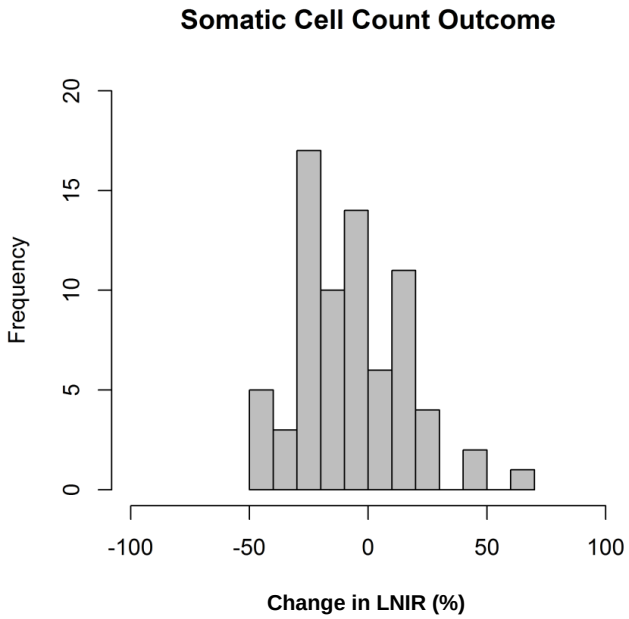


Figure 6-2 Distribution of the outcome variable for the somatic cell count regression model used to predict the effectiveness of specific mastitis control interventions. LNIR = the monthly percentage of cows that had a SCC >200,000 cells/ml at the monthly milk recording, that were <200,000 cells/ml at the previous monthly milk recording.

Interventions that had been implemented on at least two farms were identified and for each farm, categorised as 0 (not already implemented at the time of the initial farm visit and not implemented following the intervention visit), 1 (not already implemented at the time of the initial farm visit but implemented following the DMCP) or 2 (already implemented at the time of the initial farm visit or not applicable). Interventions were classified as not applicable when they concerned an area of management not relevant to a particular farm (e.g. management of loose yards on a farm that only used cubicles to house the milking cows). Collinearity between covariates was assessed using Pearson product-moment correlation coefficients, and no significant collinearity was found.

A Bayesian one-step micro-simulation model was constructed in OpenBUGS version 3.2.2 (Lunn et al., 2009) separately for each of the two outcomes, incorporating a multiple regression model and an onwards cost-effectiveness micro-simulation, following the same methods as described in the previous chapter (Figure 5-1).

The purpose of the micro-simulation was to simulate the cost-effectiveness of each intervention in theoretical herds with a herd size of 120 cows, with different initial rates of CMLP and LNIR and different costs associated with implementing each intervention. The values for CMLP and LNIR on the simulated farms prior to interventions being implemented were taken from actual data from 150 herds that had previously participated in the DMCP, so that a range of plausible scenarios were used.

Due to the way in which LNIR is calculated (i.e. the percentage of new intramammary infections/month), the number of cases prevented was multiplied by 12 to convert it from a monthly figure to an annual figure. This was the only difference between the SCC model in Chapter 5 and the SCC model in this chapter.

6.3 Results

6.3.1 Herd parameters

The median size of the 75 herds selected for analysis was 199 cows (range 76-973), and the median 305-day milk yield was 8424 kg (range 4770-12410). The median incidence rate of CM in the 12 months prior to mastitis interventions was 58.5 cases/100 cows/year (range 6-133), and the median 12-month average calculated BMSCC was 203,000 cells/ml (range 103,000-425,000). The median CMLP at the time of the initial herd visit was 26 cases/100 cows/month (12-month average, range 1.17-53.4) and the median LNIR rate was 9.7%/month (12-month average, range 4.4-21.4).

6.3.2 Interventions

A total of 131 interventions were evaluated in the analysis and the number of farms implementing each of the interventions ranged from 2-28 (Table 6-1 and Table 6-2). The interventions could be broadly grouped into three categories: hygiene of the milking cow environment, the milking routine and access to food and water.

6.3.3 Micro-simulation models

Regression model fit

Both regression models demonstrated a good ability to predict the incidence rate of CMLP and LNIR for a given farm, with the model predictions explaining 57% of the variability in the observed data in the clinical mastitis regression model (Figure 6-3) and 52% in the somatic cell count regression model (Figure 6-4).

Cost-effectiveness outcome

The probability of an incremental net benefit of at least £1000 for different interventions is provided in Table 6-1, Table 6-2, Figure 6-5, Figure 6-6, Figure 6-7 and Figure 6-8. Interventions in the clinical mastitis micro-simulation model that were cost-effective for most farms (>75% probability of saving £1000 with initial CMLP of 3.5 cases/12 cows and a $COST_{INT}$ of £500) were ensuring good fly control for all lactating cows and heifers through the summer period when flies are expected or apparent, use of drying agents to improve the dryness of cubicle beds for the milking cows and keeping the herd closed, with barriers to outside animals and people. All of the reported interventions in the somatic cell count micro-simulation model were cost-effective for most farms (>75% probability of saving £1000 with initial LNIR rate of 15% and a $COST_{INT}$ of £500) except giving cows access to water at all times (not be denied access for more than 1 hour in a 24 hour period).

Interventions in the clinical mastitis micro-simulation model that were less likely to be cost-effective included avoiding the milking cows from

having access to any one lying area for more than two continuous weeks, cleaning straw yards out completely at least once per month, providing a minimum of at least 2m²/cow of loafing space and the rotating of routes and gateways wherever possible should poaching occur.

Table 6-1 Probability of saving at least £1000 after 12 months as predicted by the micro-simulation model. The probabilities are given for different incidence rates of clinical mastitis after the first 30 days of lactation (CMLP) and different costs of implementing the intervention.

			Cost of Intervention (£)			
Intervention	**n**	**CMLP (cases/12 cows)**	**250**	**500**	**750**	**1000**
You should avoid letting milking cows have access to any one lying area for more than two continuous weeks	6	2.0	0.40	0.32	0.25	0.19
		3.5	0.61	0.56	0.50	0.45
		5.0	0.70	0.66	0.62	0.58
The herd should be closed, with barriers to outside animals and people	3	2.0	0.69	0.62	0.55	0.48
		3.5	0.83	0.80	0.76	0.72
		5.0	0.88	0.86	0.84	0.82
Drying agents could be used to improve the dryness of cubicle beds for the milking cows	3	2.0	0.98	0.96	0.94	0.91
		3.5	0.99	0.99	0.98	0.98
		5.0	1.00	1.00	0.99	0.99
You must ensure good fly control for all lactating cows and heifers through the summer period when flies are expected or apparent	3	2.0	0.87	0.84	0.80	0.76
		3.5	0.93	0.91	0.90	0.88
		5.0	0.95	0.94	0.93	0.92
Foremilking should be into a strip-cup or carried out with great care to avoid the spread of infection	2	2.0	0.55	0.49	0.43	0.38
		3.5	0.68	0.64	0.61	0.57
		5.0	0.73	0.71	0.69	0.66
You should rotate the use of routes and gateways wherever possible should poaching occur	5	2.0	0.49	0.41	0.34	0.27
		3.5	0.67	0.62	0.57	0.52
		5.0	0.74	0.71	0.68	0.65
There must be a minimum of at least 2m²/cow of loafing space	3	2.0	0.44	0.38	0.33	0.27
		3.5	0.59	0.55	0.51	0.47
		5.0	0.65	0.62	0.59	0.56
The success of mastitis treatments must be monitored by monitoring cow SCC in the months after treatment	6	2.0	0.58	0.50	0.42	0.35
		3.5	0.76	0.72	0.67	0.63
		5.0	0.82	0.80	0.77	0.74
Straw yards should be cleaned out completely at least once per month	5	2.0	0.39	0.32	0.26	0.21
		3.5	0.56	0.51	0.47	0.43
		5.0	0.63	0.60	0.57	0.53

Table 6-2 Probability of saving at least £1000 after 12 months as predicted by the micro-simulation model. The probabilities are given for different starting rates of LNIR[1] and different costs of implementing the intervention.

			Cost of Intervention (£)			
Intervention	**n**	**LNIR[1] (%/month)**	**250**	**500**	**750**	**1000**
The clusters must be squarely aligned and balanced centrally under all cows	7	10	0.74	0.72	0.69	0.67
		15	0.79	0.77	0.75	0.74
		20	0.80	0.79	0.78	0.77
There should be at least 0.6m feed space per cow in total for access to forage, concentrate or complete diet portions of the cows' feed.	3	10	0.82	0.81	0.80	0.78
		15	0.85	0.84	0.83	0.82
		20	0.86	0.85	0.84	0.84
You must maintain excellent housing conditions (as for winter) if cows have access to housed lying areas during the grazing months. (milking cows)	4	10	0.84	0.83	0.82	0.81
		15	0.86	0.86	0.85	0.84
		20	0.87	0.87	0.86	0.86
There should be a bedded lying area of 1.25m^2/1000L of milk/cow (herd annual milk yield)	7	10	0.74	0.72	0.69	0.67
		15	0.79	0.77	0.76	0.74
		20	0.81	0.79	0.78	0.77
A non-steroidal anti-inflammatory drug (NSAID) should be used when treating Grade 3 cases of clinical mastitis	3	10	0.85	0.84	0.82	0.81
		15	0.87	0.86	0.85	0.84
		20	0.88	0.87	0.87	0.86
There should be no significant pooling of liquid in housing, feeding and/or loafing areas	5	10	0.94	0.93	0.92	0.91
		15	0.96	0.95	0.95	0.94
		20	0.96	0.96	0.95	0.95
20 to 30 seconds must elapse after application of pre-milking teat disinfection, before teats are dried	9	10	0.79	0.77	0.74	0.72
		15	0.83	0.81	0.80	0.79
		20	0.85	0.84	0.83	0.82
There must be good ventilation, but without draughts in all milking cow housing	6	10	0.97	0.96	0.96	0.95
		15	0.98	0.98	0.97	0.97
		20	0.99	0.98	0.98	0.98
Cows should always have access to water (not be denied access for more than 1 hour in a 24 hour period)	5	10	0.72	0.70	0.68	0.66
		15	0.75	0.74	0.73	0.72
		20	0.77	0.76	0.75	0.74

[1] LNIR = the monthly percentage of cows that had a SCC >200,000 cells/ml at the monthly milk recording, that were < 200,000 cells/ml at the previous monthly milk recording.

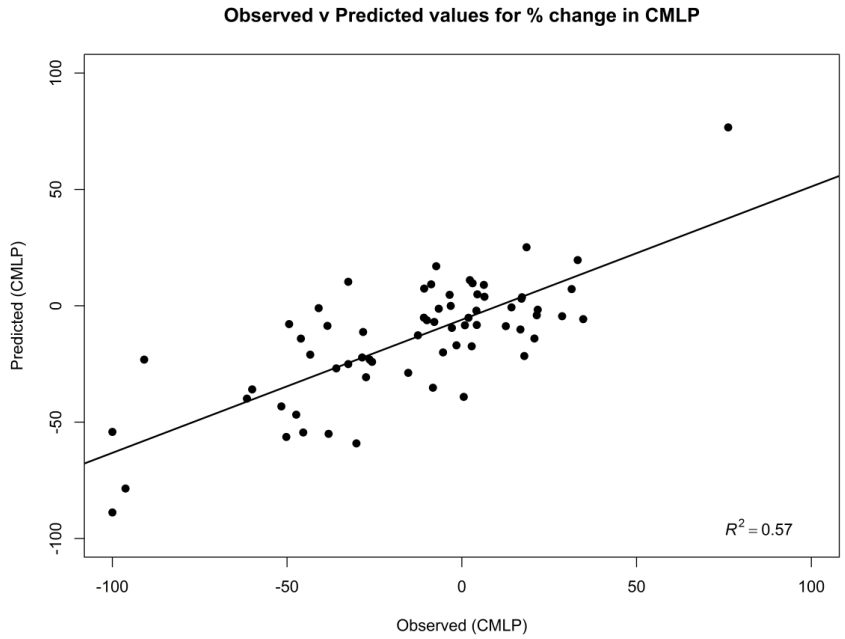


Figure 6-3 Scatterplot of observed and predicted values of the percentage change in the incidence rate of clinical mastitis after the first 30 days of lactation (CMLP). Predicted values were generated from the clinical mastitis regression model.

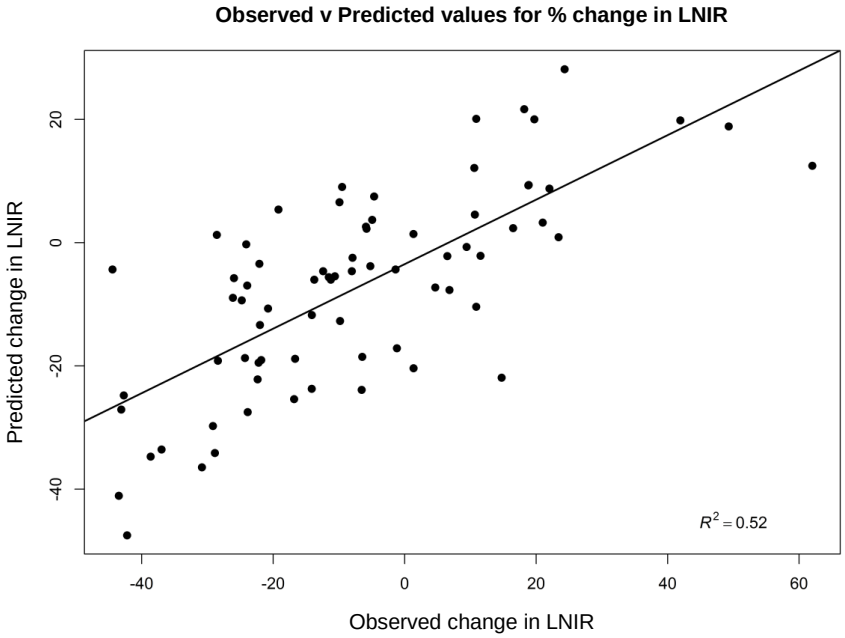


Figure 6-4 Scatterplot of the observed and predicted values of the monthly rate of LNIR. Predicted values were generated from the clinical mastitis regression model. LNIR = percentage of cows that had a SCC > 200,000 cells/ml at the monthly milk recording, that were < 200,000 cells/ml at the previous monthly milk recording.

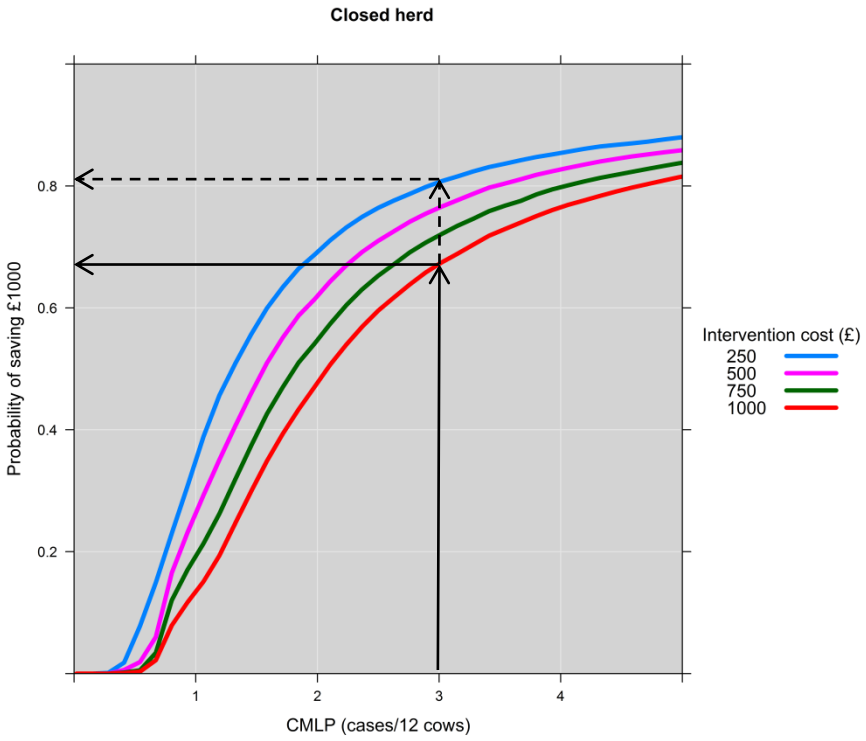


Figure 6-5 Probabilistic cost-effectiveness curve for keeping a closed herd. The arrows indicate how to read from the curve with the dashed line representing the probability of saving at least £1000 in 12 months at an intervention cost of £250 in a herd with a CMLP rate of 2 cases/12 cows. The solid arrow represents the probability of saving at least £1000 in 12 months at an intervention cost of £1000 in a herd with a CMLP rate of 3 cases/12 cows. CMLP = incidence rate of clinical mastitis after the first 30 days of lactation.

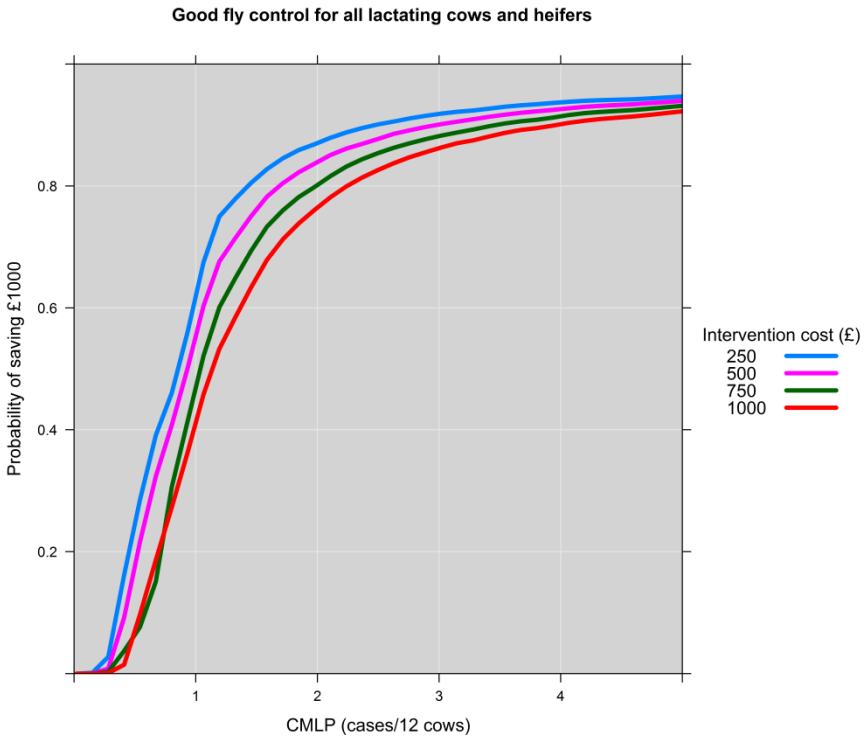


Figure 6-6 Probabilistic cost-effectiveness curve for having good fly control for all lactating cows and heifers. CMLP = incidence rate of clinical mastitis after the first 30 days of lactation.

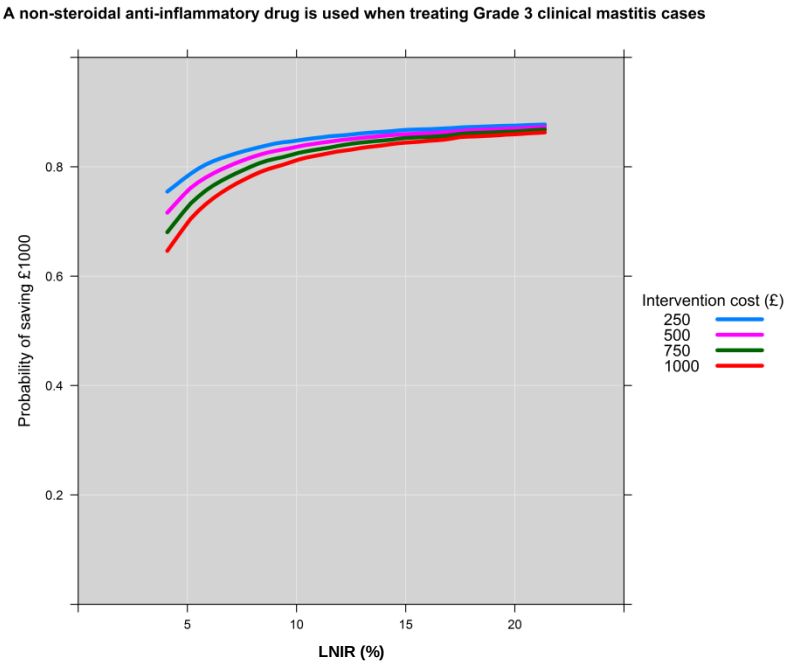


Figure 6-7 Probabilistic cost-effectiveness curve for using an NSAID when treating Grade 3 clinical mastitis cases. LNIR = percentage of cows that had a SCC > 200,000 cells/ml at the monthly milk recording, that were < 200,000 cells/ml at the previous monthly milk recording.

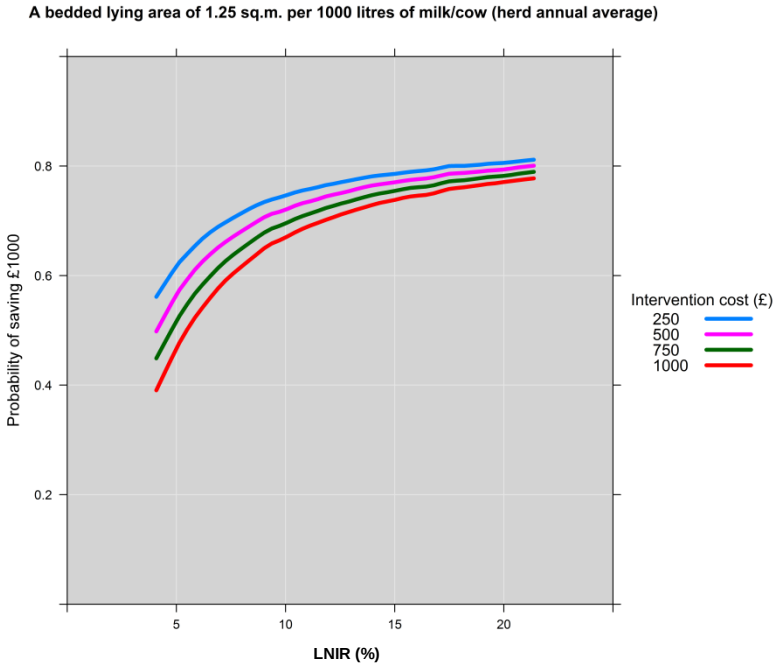


Figure 6-8 Probabilistic cost-effectiveness curve for having a bedded lying area of 1.25m^2/1000L of milk/cow. LNIR = percentage of cows that had a SCC > 200,000 cells/ml at the monthly milk recording, that were < 200,000 cells/ml at the previous monthly milk recording.

6.4 Discussion

This chapter illustrates how the clinical efficacy of specific mastitis interventions can be quantified and incorporated into a Bayesian cost-effectiveness model using a one-stage micro-simulation. The results of this and the previous chapter are to be incorporated into a decision support tool that will be made available to veterinarians/advisors involved with implementing the DMCP in the United Kingdom.

Interventions concerning the management of the milking cow environment featured prominently among those likely to be cost-effective for most dairy farmers, which is unsurprising given the epidemiology of the herds selected for this study. The loose-housing of milking cows in

straw yards has been frequently associated with an increased risk of clinical mastitis and increased somatic cell count (Bareille et al., 1998; Barnouin et al., 2005, 2004; O'Reilly et al., 2006). The results of this study would indicate that some of this risk could be mitigated cost-effectively by completely cleaning out straw yards at least once monthly and providing a bedded lying area of at least 1.25m^2/1000L of milk/cow (herd annual milk yield). This is in agreement with previous studies that have reported associations between the stocking density of straw yards (Bareille et al., 1998; Green et al., 2008) and the frequency at which straw yards are cleaned out (O'Reilly et al., 2006; Peeler et al., 2000) with somatic cell counts.

Other interventions more generally related to the milking cow environment that were likely to be cost-effective for most producers included avoiding any significant pooling of liquid in housing, feeding and/or loafing areas, ensuring good ventilation in all milking cow accommodation and maintaining excellent housing conditions when cows have access to housed lying areas during the grazing months. Access to and cleanliness of loafing areas has been associated with reduced herd somatic cell count previously (Barnouin et al., 2004; Bartlett et al., 1992), as has good ventilation (Schukken et al., 1991), but the maintenance of housing during the grazing period has not been directly linked with mastitis before. However, giving dry cows access to housing whilst grazed has been associated with increased somatic cell counts in early lactation (Green et al., 2008), and it could be that this reflects the sub-

optimal housing conditions that are likely to manifest when the accommodation is not in full-time use.

Other grazing-related interventions likely to be cost-effective in some circumstances included not letting milking cows have access to any one lying area for more than two continuous weeks and rotating the use of routes and gateways wherever possible should poaching occur. This finding is supported by previous work that has reported *Strep. uberis* surviving for extended periods on pasture (Lopez-Benavides et al., 2007) and farm tracks, especially in wet conditions (Lopez-Benavides et al., 2005). This is also in agreement with two previous studies that have demonstrated a reduced incidence of clinical mastitis and increased somatic cell count in the first 30 days of lactation by restricting the access of dry-cows to any one grazing area to less than 2 weeks followed by stock not grazing the pasture for a minimum of 4 weeks (Green et al., 2008, 2007a).

Several interventions related to the milking process were also found likely to be cost-effective for many producers, including allowing at least 20-30 seconds to elapse before wiping-off pre-milking teat disinfectant, ensuring that clusters are squarely aligned and balanced centrally under all cows and foremilking (into a strip-cup or at least carried out with great care to avoid the spread of infection). The application of pre-milking teat disinfection to reduce new intramammary infections, especially those caused by pathogens behaving in an environmental manner, is well established (Bennett, 1982; Oliver et al., 2001, 1993; Pankey et al., 1987;

Sérieys and Poutrel, 1996) although previous cost-effectiveness studies have failed to demonstrate an overall cost-benefit (Morton et al., 2014; Ruegg and Dohoo, 1997). Due to the time pressures associated with the milking process, milking staff may attempt to save time by reducing the interval between the application of pre-milking teat disinfection, and subsequent wiping of the teats, thereby potentially reducing the product efficacy. The results of this study suggest that allowing at least 20-30 seconds to elapse before wiping-off pre-milking teat disinfectant is likely to be cost effective for the majority of dairy farmers, and that cutting this contact time short may prove to be a false economy.

The practice of foremilking as a means of detecting cases of clinical mastitis has frequently been associated with an increased incidence rate of clinical mastitis (Elbers et al., 1998; O'Reilly et al., 2006; Peeler et al., 2000; Schukken et al., 1991) as has the use of a strip-cup when doing so (Bartlett et al., 1992). However, from these studies, it is not possible to establish if the practice of foremilking/using a strip-cup is causally related to the incidence of clinical mastitis or simply that herds that practice foremilking are more effective at diagnosing, and, as a consequence, report more cases of clinical mastitis. This intervention was only implemented by 2 herds, and therefore some caution should be exercised when considering the implications of this finding. However, it would seem prudent to practice foremilking in such a manner that any risk of transmitting infections to neighbouring cows is minimised, and this study provides some evidence that by doing so, any resulting increase

in labour could well be offset by reductions in the incidence of clinical mastitis.

Ensuring good fly control for all lactating cows and heifers through the summer period when flies are expected or apparent was very cost-effective in most scenarios due to the resulting reduction in clinical mastitis. Previous studies have demonstrated the ability of flies to transmit intramammary infections to heifers (Gillespie et al., 1999; Owens et al., 1998), and effective fly control has been associated with reduced risk of intramammary infections in heifers (Nickerson et al., 1995; Piepers et al., 2011). Whilst effective fly control is now a well-established aspect of heifer management, this study provides some much-needed evidence of the cost-effectiveness of effective fly control for the adult milking herd as well.

The cost-effectiveness of the use of drying agents to improve the dryness of cubicle beds for the milking cows was an interesting finding. The positive association between the moisture content of cubicle bedding and bacterial load is well accepted, as is the relationship between the number of bacteria present in cubicle bedding and the incidence of intramammary infections (Hogan et al., 1990, 1989). However, to date, evidence supporting the use of drying agents as an effective means of reducing the risk of mastitis has been lacking, and one previous study that reported an association between the use of drying agents and an increased somatic cell count (Bareille et al., 1998). Whilst no specific products can be

recommended, this study provides some evidence that they may play a useful and cost-effective role in some herds with a specific EL problem.

The use of a non-steroidal anti-inflammatory drug (NSAID) when treating grade 3 cases of clinical mastitis (defined as milk and udder changes and also signs of systemic illness) was likely to be cost-effective for the majority of dairy farmers due to an associated reduction in the rate of new IMI's as measured by SCC. Previous experimental *E. coli* and endotoxin models have demonstrated improved clinical parameters (e.g. reduced rectal temperature, reduced clinical signs and improved rumen function) associated with the administration of carprofen, flunixin meglumine and ketoprofen (Anderson et al., 1986; Banting et al., 2008; Shpigel et al., 1994; Vangroenweghe et al., 2005). One previous study reported a reduction in somatic cell count in cows with clinical mastitis (grades 1 or 2) treated with a parenteral antibiotic and meloxicam, compared with cows treated with a parenteral antibiotic only (McDougall et al., 2009), however, this finding was not accompanied by a cost-effectiveness analysis to help justify such an approach.

Interventions related to nutrition such as the provision of at least 60cm of feed-space per cow and not denying cows access to water for any more than 1hr/day resulted in reductions in the LNIR and were cost-effective in many circumstances. Whilst this is the first study to find a relationship between either of these interventions and somatic cell count, one previous study found an association between the increased number of feeding spaces/cow with a reduced incidence of *E.coli* mastitis (Barkema

et al., 1999a), and another study reported an increase in individual cow somatic cell count following a period of water deprivation (Reneau, 1986).

Two interventions that were cost-effective due to reductions in the incidence rate of clinical mastitis were having a closed herd, with barriers to people and other animals and the monitoring of the success of mastitis treatments by monitoring cow SCC in the months after treatment. The risks posed to a dairy herd by people, other animals and the purchasing of new animals are well known (Barkema et al., 2009), but, despite this, there is evidence that biosecurity measures, in general, are poorly implemented on cattle farms (Brennan and Christley, 2012) with poor or inappropriate knowledge-transfer often cited as a potential cause (Sayers et al., 2014). Given that the herd veterinarian remains a highly valued advisor to most dairy farmers (Hall and Wapenaar, 2012), there is a clear opportunity for the profession to engage more in the discussion concerning biosecurity measures and for effective biosecurity measures - including the monitoring of disease and having a closed herd; being established in more herds.

The fit of the regression models was not as good as the models reported in the previous chapter. This probably reflects the increased number of interventions implemented by EL herds compared with EDP herds meaning that interventions that were implemented by EL herds, were done so by fewer farmers, resulting in increased uncertainty in the predicted effect.

6.5 Conclusions

In this study, data from 75 UK dairy herds were used to explore the cost-effectiveness of specific mastitis control interventions in herds with a particular problem with IMI's originating from the cows' environment, acquired during lactation. The results from the Bayesian micro-simulation models demonstrate the probability of cost-effectiveness under different scenarios, which were incorporated in a decision support tool that will assist optimal decision making by veterinary practitioners in the field.

Chapter 7
Discussion and Conclusions

7.1 Discussion

This research used PSA and integrated Bayesian micro-simulation to explore factors affecting the cost of clinical mastitis, the cost-effectiveness of an on-farm culture approach for the treatment of mastitis and the cost-effectiveness of specific mastitis control interventions. For livestock health and disease-control decisions, information is needed on: (i) the disease and production system; (ii) the physical effects of disease and its subsequent effects on the production system; (iii) the incidence and/or prevalence of disease; (iv) technologies and options available to control disease and improve health and productivity; (v) the impact of disease and control options on other systems (e.g. on human health); (vi) evaluations of the effects of disease and of strategies for control (Bennett, 1992). The results described in this thesis have a particular role to play in providing information on the last of these aspects, informing decisions about the costs associated with mastitis treatment and describing the potential savings that are possible with specific mastitis interventions.

7.1.1 Treatment of clinical mastitis

Whilst the current incidence rate of clinical mastitis in the UK is unknown, it is likely to be approximately 47-65 cases/100 cows/year (Bradley et al., 2007b). There are currently around 1.9 million dairy cows in the UK

(AHDB Dairy, 2015), meaning that approximately 855,000-1,235,000 cases of clinical mastitis are treated every year in the UK. Given this large number of mastitis treatments each year and the associated financial, emotional and welfare implications, it is important that farmers and vets understand the relative importance of the factors affecting the cost of mastitis so that better decisions can be made about how to minimise any losses. In Chapter 2, the cost of a case of clinical mastitis was modelled for 5 different treatment protocols and a rate of transmission was included to simulate scenarios ranging from low-risk to high-risk of transmission. PSA was used so that all model input parameters were specified as probability distributions, thereby, capturing some of the uncertainty surrounding their true value. The rate of transmission was identified as the most important determinant of the total cost of a case of clinical mastitis, which was perhaps unsurprising, but what was arguably more surprising was the lack of available evidence on which to base the transmission rate input parameter on. The few studies that have included transmission rate parameters in mastitis models (Barlow et al., 2009; Halasa, 2012; Halasa et al., 2010; Swinkels et al., 2005; Swinkels et al., 2005; van den Borne et al., 2010a) have all based them on the results of a small number of studies (Lam et al., 1996a; Zadoks et al., 2002, 2001). Despite this limitation, some of this inherent uncertainty surrounding the likelihood of transmission is captured by the probability distribution, propagated through the model and reflected in model outputs.

Another interesting finding from Chapter 2 was that treatment protocol 1 (3 days of intramammary antibiotics) was the most cost-effective approach on average compared with the other more aggressive treatment regimes. This is in agreement with Steeneveld et al. (2011), as one might expect, given that many of the model inputs were common to both studies. Some caution needs to be exercised concerning this finding because the evidence for the bacteriological cure rates associated with treatment protocols 2-5 was minimal. As a result, the distributions used for protocols 3-5 were based entirely on the opinions of expert colleagues, which may be considered a weakness. However, it is known that the treatment of clinical mastitis during lactation typically results in modest bacteriological cure rates (Roberson, 2012), although this is clearly dependent on cow and pathogen factors (Barkema et al., 2006; Bradley and Green, 2009; McDougall et al., 2007), and it is therefore unlikely that more evidence would have altered the overall conclusions of this study. There will, of course, remain situations when a more aggressive treatment protocol is justified, based on specific cow or pathogen factors, and the more risk-averse dairy farmers may opt to treat for longer in return for a marginally increased certainty of bacteriological cure. Irrespective of the treatment protocol used, the study in Chapter 2 serves to highlight how important transmission is, relative to the other factors affecting the cost of clinical mastitis, which should be a key consideration when deciding how to manage cows with clinical mastitis.

The PSA model developed in Chapter 2 was adapted in Chapter 3 to compare the cost-effectiveness of the treatment of clinical mastitis based on the results of an on-farm culture approach (OFC) compared with a 'standard' treatment protocol of 3 days of intramammary antibiotic administered to all cases. To the authors knowledge, this is the first cost-effectiveness analysis to have been reported concerning the OFC system despite the first OFC studies being published in 2011 (Lago et al., 2011a, 2011b). On average, approximately 6 million intramammary tubes are used each year in the UK, which equates to approximately 1500 kg of active ingredient (Eckford et al., 2013). The use of OFC has the potential to reduce this figure quite considerably, but questions remain with respect to economic and ethical considerations given the reduction in bacteriological cure rates that may be associated with its use. In a recent report highlighting some of the challenges facing the future provision of farm animal veterinary services in the UK, one thing that farmers wanted/expected from their vets was the introduction of new technology and R&D support (Lowe, 2009). Given the high level of trust that most dairy farmers still have in the veterinary profession (Hall and Wapenaar, 2012), it is important that new technologies like OFC are introduced in light of comprehensive cost-effectiveness analyses that incorporate uncertainty in transparent and intuitive ways. The study in Chapter 3 concluded that despite reducing antibiotic usage, the OFC approach was unlikely to be more cost-effective than the standard approach for most dairy farms and should, therefore, only be adopted after careful consideration of the predominant pathogens present in each herd and an

honest discussion about the uncertainty surrounding its overall cost-effectiveness. A limitation of this study was the sparse evidence available on which to base the bacteriological cure model input parameter for the OFC-branch of the model. Given how sensitive the model outputs were to this parameter, it would have been preferable to have had more than one relatively small-scale study (Lago et al., 2011a) on which to base this distribution. The study by Lago et al. (2011a) reported an overall bacteriological cure risk of 71% for cows treated conventionally and 60% for those treated according to the results of OFC. At the pathogen level, the OFC-associated reduction in bacteriological cure risk for all Gram-negative infections was 16 percentage points (86% v 70%) and 25 percentage points (43% v 18%) for *Staph. aureus* infections. Similar differences were reported in an unpublished study performed in Canada which found an OFC-associated reduction in bacteriological cure risk of 13 percentage points for *Staph. aureus* infections (53% v 40%) and 18 percentage points for infections caused by Gram-positive pathogens other than *Staph. aureus* (71% v 53%) (MacDonald, 2011). A wide distribution was used in Chapter 3 to capture this uncertainty but clearly more research is needed to better understand the impact of OFC on bacteriological cure rates, the reasons for such reductions and ways in which they can be mitigated. At this time, as the OFC approach begins to be adopted by an increasing number of UK dairy farms and interest in the approach grows, the cost-effectiveness analysis from Chapter 3 will provide much-needed and timely support to practitioners when deciding how best to apply this new technology.

7.1.2 Mastitis control

Having highlighted the significant cost of mastitis in Chapter 2 and the concerns about the quantity of antimicrobial drugs used to treat mastitis in Chapter 3, the focus of the remainder of the thesis was on the control and prevention of mastitis which is, of course, the most effective way of reducing the cost of mastitis and the quantity of antimicrobial drugs used. All of the data used in these chapters came from UK dairy farms that had participated in the AHDB Dairy Mastitis Control Plan (DMCP, see 1.2.4) since it began in 2009. The DMCP is a rare example of an evidence-based, farm-specific approach to mastitis control that has been proven to reduce the risk of clinical and subclinical mastitis in the field (Green et al., 2007b). Other countries have tried similar initiatives, but have either failed to demonstrate any significant improvements in udder health as a result (Tschopp et al., 2015) or reported some improvements but were unable to provide a control group with which to compare the results (Lam et al., 2013). Since the DMCP was launched in 2009, over 300 plan deliverers have been trained, and over 2000 farms have had some involvement with the plan, representing approximately 20% of the national herd.

What was most disappointing given the success of the DMCP was the difficulty in acquiring data from participating vets and dairy herds and the variation in the quality of data that were provided. Much of the first 18 months of this project was spent contacting plan deliverers in a variety of different ways and persistently encouraging them to submit ePlan, farm

performance and intervention data for the herds that they had been involved with. By the end of the data collection period, complete data were submitted for 212 herds, which equated to approximately 20% of the herds that were eligible at the time, and far fewer than had been hoped for at the start of the project. The reasons for this are complex and multifactorial but relate generally to the broad, collaborative approach of the DMCP delivery model which is both a strength and a weakness. Firstly, the DMCP was not developed in such a way as to facilitate the comprehensive and robust collation of outcomes. During 2009-2012, there was no obligation for plan deliverers to upload ePlan and farm performance data to a central database (this has subsequently changed), and so it was not possible to know how much data really existed before the data collection phase began. Secondly, there was a significant problem with poor data quality and evidence of a lack of appreciation of the importance of data in understanding mastitis patterns on-farm. A lot of data was 'lost' due to the absence of clinical mastitis records and due to multiple diagnoses having been selected in the ePlan data (e.g. EDP and EL). As clinical mastitis cases are detected and recorded by the dairy farmers, there is a great deal of variation in the quantity and quality of these records, and when cases are not recorded in an electronic format they can be difficult to access by vets and researchers. Incomplete or absent clinical mastitis records hinder the ability of the plan deliverer to make an accurate assessment of the mastitis epidemiology for a particular dairy farm, which may explain why some of the farms were assigned multiple diagnoses. Equally, the somatic cell count and clinical mastitis

data may present a mixed picture, and deciding between an EDP and EL diagnosis, for example, might be challenging. The importance of assigning only one diagnosis is emphasised, however, during the plan deliverer training days, and so it was disappointing to find so many examples where this recommendation had not been followed. Thirdly, the plan deliverers themselves vary considerably in terms of occupation, IT and herd health skills and general enthusiasm for the scheme itself. A significant number of plan deliverers would have viewed the training as a form of continuing professional development and would not necessarily be in a position to implement any/many plans directly. Also, some plan deliverers may have found they struggled with the IT aspects of the DMCP approach or were unable to 'sell' it to their clients. As a result, the majority of plans implemented are delivered by a relatively small number of enthusiastic plan deliverers, which may explain to some extent why only 87 of the 265 plan deliverers contributed any data at all.

One of the consequences of obtaining fewer data than hoped is that of reduced study power and potentially fewer interventions to analyse in the study. The advantage of using a Bayesian framework in this context is that it doesn't rely on frequentist measures of statistical significance, and any uncertainty resulting from low study power should be reflected in the width of the posterior distributions. By adopting Bayesian methods, less potentially clinically useful information is discarded, leaving the clinical decision makers with more evidence on which to base their decisions. The limited amount of data also meant that it wasn't possible to investigate

the cost-effectiveness of combined interventions to see if there was any extra benefit derived by implementing two or more specific interventions in certain scenarios. One example of this was in Chapter 5, when 3 interventions related to the 'graze 2, rest 4' (paddocks are not grazed for more than 2 continuous weeks and at least 4 weeks must elapse before cows are returned to graze) intervention were combined as one parameter. This showed a greater effect when all three were implemented as opposed to each of them singly, and other such relationships may have been apparent with more data.

The limited amount of data from CDP/CL herds precluded them from the cost-effectiveness analysis, but given the significant amount already known about the effective control of contagious pathogens (Barkema et al., 2006) and the fact that CDP/CL herds only account for approximately 5% of herds participating in the DMCP (Bradley et al., 2012), there is arguably less of a need for this analysis at present.

Despite the challenges posed by the data collection process, the resulting dataset was the largest and most comprehensive of its kind and the first to have such detailed information on the mastitis epidemiology for each farm as well as current farm management practices. This has made it possible to investigate the cost-effectiveness of a large number of mastitis control interventions under different scenarios, which has not been done previously. Whilst we knew that the DMCP was effective overall, we hadn't previously had any means of knowing which interventions were most likely to be cost-effective for specific herds and, therefore, the

decision about which interventions to implement has, up until now, been based largely on practical considerations and intuition. Using the results from Chapter 5 and Chapter 6, it will now be possible to rank a selection of mastitis control interventions based on the probability of a specific return by way of a decision support tool, which will offer much needed evidence-based support to those delivering mastitis control services in the UK. This serves to highlight one of the key strengths of the Bayesian approach in that the resulting posterior distributions can be used to provide clinically relevant and direct answers to important questions including the probability that a particular hypothesis is correct.

The results of the descriptive analysis presented in Chapter 4 highlight that the average herd size and milk yield of the study farms were slightly higher than the current national averages. Given that the study farms were drawn from a convenience sample of farms that had participated in the national mastitis control scheme, there were inherent biases within the dataset and one might question how representative they are of the national population. However, they are likely to be representative of other herds participating in the DMCP at present or in the future and, therefore, the cost-effectiveness analysis should be of relevance to a large number of dairy herds in the UK and wider.

7.1.3 Potential future work

In general, approaches to providing advice on mastitis control may be divided into two types; 'reactive' and 'prospective'. The most prevalent approach historically has been the reactive approach, whereby a

veterinary practitioner or advisor is asked to assess a problem situation, whether long-standing or a sudden outbreak. Investigations typically include the analysis of farm records, and current management strategies including a farm assessment and some milk samples may be taken to assess pathogen involvement. A prospective approach to mastitis control incorporates many of the principles of herd health management; setting goals, on-going monitoring of disease and updating of management practices when goals are not achieved (Green, 2012; National Mastitis Council, 2006). The advantage of prospective mastitis management is that problems should be identified sooner than with reactive approaches and, as the average herd size gets larger and skilled farm labour units per cow are reduced, should ensure that resources and effort are directed to the areas that give the greatest returns.

The problem with both reactive and prospective approaches to mastitis control is that they rely on current farm information to define what is happening and therefore what to change. In this sense, they are both in fact 'reactive'. What the studies in Chapter 5 and Chapter 6 exemplify is a different approach that is likely to become more prevalent in the future, whereby current data are used to predict what is likely to happen in the future. In what might be termed 'predictive' mastitis control, accurate biological predictions would be made from current farm information.

With advances in on-farm technologies, scientific approaches and data handling capabilities, 'predictive' mastitis control is becoming a reality especially as the advancement of computer technology means that value

can now be derived from complex datasets to drive decision making in the so-called 'big data' revolution (Hudson, 2015).

The key to success with 'predictive' mastitis control approaches will be to make use of readily available information and to ensure results are relevant and accessible to the end user. The provision of appropriate (in terms of quantity, quality and form) and timely information to decision makers is vital if 'good' decisions (i.e. those which best achieve the objectives) are to be made (Bennett, 1992). The need for 'real-time' decision support tools has never been greater, as the sheer volume of data being generated on dairy farms can mean that 'good' decisions are not always intuitive. The results from Chapter 5 and Chapter 6 will be incorporated into a decision support tool that will facilitate the prioritisation of interventions based on the probability of cost-effectiveness in a way that is completely customisable to each individual farm's circumstances.

7.2 Conclusions

7.2.1 Chapter 2

The rate of transmission was found to be by far the most influential parameter in a PSA investigating the factors affecting the cost of CM at the individual cow level. This was followed by bacteriological cure rate, the cost of culling and loss of yield. The results from this study suggested that more emphasis should be placed on the reduction in the risk of

transmission in dairy herds when seeking to minimise the economic impact of CM.

7.2.2 Chapter 3

The results of this study indicated that the proportion of Gram-positive cases and the difference in bacteriological cure rate between the two treatment approaches had the greatest impact on the probability that an OFC approach would be more cost-effective than a standard approach for the treatment of clinical mastitis. The OFC approach appeared to be suitable for herds in which Gram-negative pathogens were responsible for most clinical mastitis and where the treatment of cows according to the results of an OFC approach resulted in minimal reductions in bacteriological cure rates.

7.2.3 Chapter 4

This study provided data on performance and management of UK dairy herds, grouped according to the main putative origin of new cases of mastitis. Many aspects of management that might be considered to be important in mastitis control were not being practiced by a large proportion of these herds. A better understanding of those practices not widely adopted by UK dairy farmers at present may aid practitioners in identifying and overcoming potential barriers to improved mastitis control in UK dairy herds.

7.2.4 Chapter 5

In this study, data from 77 UK dairy herds were used to explore the cost-effectiveness of specific mastitis control interventions in herds with a particular problem with mastitis acquired during the dry period. The results from the Bayesian micro-simulation identified many specific mastitis control interventions that were likely to be cost-effective in many different scenarios.

7.2.5 Chapter 6

In this study, data from 75 UK dairy herds were used to explore the cost-effectiveness of specific mastitis control interventions in herds with a particular problem with mastitis originating from the cows' environment, acquired during lactation. The results from the Bayesian micro-simulation models demonstrated the probability of cost-effectiveness under different scenarios, which were incorporated in a decision support tool that would assist optimal decision making by veterinary practitioners in the field.

7.2.6 Overall

The overall aim of the thesis was to explore the cost of clinical mastitis and cost-effectiveness of different approaches to mastitis treatment and specific mastitis control interventions using probabilistic methods that incorporated uncertainty. Bayesian approaches were used throughout the thesis to capture and propagate sources of uncertainty that were identifiable. The results from Chapters 2 and 3 highlight the need to consider the risk of transmission and the potential impact of delayed treatment when deciding how best to treat cases of clinical mastitis. The

results of the decision analytic models presented in Chapters 5 and 6 should facilitate decision making by allowing direct statements of probability to be inferred about specific mastitis control interventions. The research presented in this thesis as a whole, provides a greater understanding of the economics of the treatment and control of mastitis and aspects of this research will be made applicable to veterinary practitioners and dairy farmers through the development of a decision support tool.

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Appendices

Appendix 1

Example of the WinBUGS code for the cost of clinical mastitis model from Chapter 2.

```
{

#Optimal bacterial cure rates for the 5 treatment protocols
bacticure1 <- pathogencurerate1
pathogencurerate1~dunif(0.40, 0.80)

bacticure2 <- pathogencurerate2
pathogencurerate2~dunif (0.6, 0.8)

bacticure3 <- pathogencurerate3
pathogencurerate3~dunif(0.6,0.8)

bacticure4 <-pathogencurerate4
pathogencurerate4~dunif(0.63,0.83)

bacticure5 <- pathogencurerate5
pathogencurerate5~dunif(0.7,0.9)

#Cure rates if given extended tx i.e. range increased by +-0.1

bacticure1a <- pathogencurerate1a
pathogencurerate1a~dunif(0.30, 0.90)

bacticure2a <- pathogencurerate2a
pathogencurerate2a~dunif (0.5, 0.9)

bacticure3a <- pathogencurerate3a
pathogencurerate3a~dunif(0.5,0.9)

bacticure4a <-pathogencurerate4a
pathogencurerate4a~dunif(0.53,0.93)

bacticure5a <- pathogencurerate5a
pathogencurerate5a~dunif(0.6,0.99)


# CALCULATE PARITY NUMBER, DIM, ILL, REPEAT CASE, SCC
```

```
whichparity~dunif(0,1)
whichdim~dunif(0,305)
systillness~dunif(0,1)
whichcase~dunif(0,1)
rand~dunif(0,1)

parity2 <- step(whichparity-0.17) *parityeffect

dimover60<-step(whichdim-60)*dimeffect

systill<-step(systillness-0.85)*illeffect

repeatcase<-step(whichcase-0.92)*repeateffect

sccless200<-step(0.7-rand)

btwn200500<-(step(rand-0.7) - step(rand-0.9))*btwn200500effect

gt500<- step(rand-0.9)*gt500effect


#CALC COW EFFECTS ON BACTICURE RATE

parityeffect~dunif(-0.15, -0.05)
dimeffect~dunif(-0.15,-0.05)
illeffect~dunif(-0.25,-0.15)
repeateffect~dunif(-0.25,-0.15)
btwn200500effect~dunif(-0.15,-0.05)
gt500effect~dunif(-0.25,-0.15)

#Probability of bacterial cure
apcowbacticure1 <- bacticure1 +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure2 <-bacticure2 +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure3 <-bacticure3 +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure4 <-bacticure4 +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure5 <-bacticure5 +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

pcowbacticure1<-step(apcowbacticure1)*apcowbacticure1
pcowbacticure2<-step(apcowbacticure2)*apcowbacticure2
```

```
pcowbacticure3<-step(apcowbacticure3)*apcowbacticure3
pcowbacticure4<-step(apcowbacticure4)*apcowbacticure4
pcowbacticure5<-step(apcowbacticure5)*apcowbacticure5


#Probability of no cure
pnoncure1 <- 1-pcowbacticure1
pnoncure2 <- 1-pcowbacticure2
pnoncure3 <- 1-pcowbacticure3
pnoncure4 <- 1-pcowbacticure4
pnoncure5 <- 1-pcowbacticure5

#Probability of non bacterial but clinical cure
pcowclincure1 <- pnoncure1*0.8
pcowclincure2 <- pnoncure2*0.8
pcowclincure3 <- pnoncure3*0.8
pcowclincure4 <- pnoncure4*0.8
pcowclincure5 <- pnoncure5*0.8

#Probability of no bacterial or no clinical cure
pcownoncure1 <- 1-(pcowbacticure1 + pcowclincure1)
pcownoncure2 <- 1-(pcowbacticure2 + pcowclincure2)
pcownoncure3 <- 1-(pcowbacticure3 + pcowclincure3)
pcownoncure4 <- 1-(pcowbacticure4 + pcowclincure4)
pcownoncure5 <- 1-(pcowbacticure5 + pcowclincure5)

#CALCULATE TREATMENT COSTS ASSOCIATED WITH FIRST CASE

#cost in pounds
costofdrugs1~dunif(5.58,6.97)
costofdrugs2~dunif(9.30,11.62)
costofdrugs3~dunif(32,36)
costofdrugs4~dunif(43,47)
costofdrugs5~dunif(36,40)

#total treatment time in hours
treatmenttime1~dunif(0.53,0.87)
treatmenttime2~dunif(0.87,1.2)
treatmenttime3~dunif(0.58,0.92)
treatmenttime4~dunif(0.63,0.97)
treatmenttime5~dunif(0.92,1.25)

#hourly rate in pounds
labourcost~dunif(1,15.87)

#total cost of labour (£)
costoflabour1<-treatmenttime1*labourcost
costoflabour2<-treatmenttime2*labourcost
costoflabour3<-treatmenttime3*labourcost
```

```
costoflabour4<-treatmenttime4*labourcost
costoflabour5<-treatmenttime5*labourcost

#Length of milk discard in days
milkwithdrawal1~dunif(5,9)
milkwithdrawal2~dunif(7,11)
milkwithdrawal3~dunif(5,9)
milkwithdrawal4~dunif(5,10)
milkwithdrawal5~dunif(7,11)

#Amount of milk discarded each day (Kg)
dailymilkdiscard~dunif(5,50)

#Milk price (£/kg)
milkprice~dunif(0.23,0.27)

#Cost of milk production (£/Kg)
milkprodcost~dunif(0.03,0.1)

#Total cost of milk discard (£)
costofdiscard1<-milkwithdrawal1*dailymilkdiscard*milkprice
costofdiscard2<-milkwithdrawal2*dailymilkdiscard*milkprice
costofdiscard3<-milkwithdrawal3*dailymilkdiscard*milkprice
costofdiscard4<-milkwithdrawal4*dailymilkdiscard*milkprice
costofdiscard5<-milkwithdrawal5*dailymilkdiscard*milkprice

#Total cost of FIRST treatment (£)
txcost1<-costofdrugs1 + costoflabour1 + costofdiscard1
txcost2<-costofdrugs2 + costoflabour2 + costofdiscard2
txcost3<-costofdrugs3 + costoflabour3 + costofdiscard3
txcost4<-costofdrugs4 + costoflabour4 + costofdiscard4
txcost5<-costofdrugs5 + costoflabour5 + costofdiscard5

#CALCULATION OF COSTS ASSOCIATED WITH COWBACTICURE
#parameters taken from Hagnestam 2007/Steeneveld/Madouasse

herd305yield~dunif(7000,10000)

parity2Beffect~dunif(0,0.02)

parity2B <- step(whichparity-0.17) *parity2Beffect

btwn3and6yieldloss~dunif(-0.04,-0.01)
gt6yieldloss~dunif(-0.07,-0.05)
btwn3and6lact<-(herd305yield*-0.23)
gt6lact<-(herd305yield*-0.67)

casemonth1or2<-step(0.6-rand)
```

```
btwn3and6<-(step(rand-0.6) - step(rand-0.9))*btwn3and6yieldloss

gt6<- step(rand-0.9)*gt6yieldloss

btwn3and6effect<-(step(rand-0.6)-step(rand-0.9))*btwn3and6lact

gt6effect<-step(rand-0.9)*gt6lact

yieldloss~dunif(0.07,0.09)

totalyieldloss<-herd305yield*(yieldloss+parity2B+btwn3and6+gt6)

costoftotalyieldloss<-(milkprice*totalyieldloss)-
(milkprodcost*totalyieldloss)

#Can either end lactation or be culled. Cost of cull = 420 +- 300

pcull1~dunif(0.04,0.06)
costofcull~dunif(120,720)
pculltotal1<-pcull1+systill1
cull1a<-pculltotal1*pcowbacticure1
cull2a<-pculltotal1*pcowbacticure2
cull3a<-pculltotal1*pcowbacticure3
cull4a<-pculltotal1*pcowbacticure4
cull5a<-pculltotal1*pcowbacticure5

pendlactation1<-1-pculltotal1
endlactation1a<-pendlactation1*pcowbacticure1
endlactation2a<-pendlactation1*pcowbacticure2
endlactation3a<-pendlactation1*pcowbacticure3
endlactation4a<-pendlactation1*pcowbacticure4
endlactation5a<-pendlactation1*pcowbacticure5

cull1acosts<-cull1a*(costofcull+txcost1)
cull2acosts<-cull2a*(costofcull+txcost2)
cull3acosts<-cull3a*(costofcull+txcost3)
cull4acosts<-cull4a*(costofcull+txcost4)
cull5acosts<-cull5a*(costofcull+txcost5)

endlactcosts1a<-endlactation1a*(costoftotalyieldloss+txcost1)
endlactcosts2a<-endlactation2a*(costoftotalyieldloss+txcost2)
endlactcosts3a<-endlactation3a*(costoftotalyieldloss+txcost3)
endlactcosts4a<-endlactation4a*(costoftotalyieldloss+txcost4)
endlactcosts5a<-endlactation5a*(costoftotalyieldloss+txcost5)


#CALCULATE TREATMENT COSTS AFTER FAILURE TO CURE
(cownoncure)
```

```
# i.e Extended Treatment resulting in 3 outomes - cowbacticure1a,
cowclincure1a and cownoncure1a (range for cure rates increased due to
increased uncertainty)

#Probability of bacterial cure

apcowbacticure1a <- bacticure1a +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure2a <-bacticure2a +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure3a <-bacticure3a +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure4a <-bacticure4a +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

apcowbacticure5a <-bacticure5a +
(parity2+dimover60+systill+repeatcase+btwn200500+gt500)

pcowbacticure1a<-step(apcowbacticure1a)*apcowbacticure1a
pcowbacticure2a<-step(apcowbacticure2a)*apcowbacticure2a
pcowbacticure3a<-step(apcowbacticure3a)*apcowbacticure3a
pcowbacticure4a<-step(apcowbacticure4a)*apcowbacticure4a
pcowbacticure5a<-step(apcowbacticure5a)*apcowbacticure5a


cowbacticure1a<-pcowbacticure1a*pcownoncure1
cowbacticure2a<-pcowbacticure2a*pcownoncure2
cowbacticure3a<-pcowbacticure3a*pcownoncure3
cowbacticure4a<-pcowbacticure4a*pcownoncure4
cowbacticure5a<-pcowbacticure5a*pcownoncure5

#Probability of no cure
pnoncure1a<-1-pcowbacticure1a
pnoncure2a<-1-pcowbacticure2a
pnoncure3a<-1-pcowbacticure3a
pnoncure4a<-1-pcowbacticure4a
pnoncure5a<-1-pcowbacticure5a

#Probability of Clinical cure

pcowclincure1a<-pnoncure1a*0.8
pcowclincure2a<-pnoncure2a*0.8
pcowclincure3a<-pnoncure3a*0.8
pcowclincure4a<-pnoncure4a*0.8
pcowclincure5a<-pnoncure5a*0.8
```

```
cowclincure1a<-pcowclincure1a*pcownoncure1
cowclincure2a<-pcowclincure2a*pcownoncure2
cowclincure3a<-pcowclincure3a*pcownoncure3
cowclincure4a<-pcowclincure4a*pcownoncure4
cowclincure5a<-pcowclincure5a*pcownoncure5

#Probability of Non bacterial and Non clinical cure
pcownoncure1a <- 1-(pcowbacticure1a + pcowclincure1a)
pcownoncure2a <- 1-(pcowbacticure2a + pcowclincure2a)
pcownoncure3a <- 1-(pcowbacticure3a + pcowclincure3a)
pcownoncure4a <- 1-(pcowbacticure4a + pcowclincure4a)
pcownoncure5a <- 1-(pcowbacticure5a + pcowclincure5a)

cownoncure1a<-pcownoncure1a*pcownoncure1
cownoncure2a<-pcownoncure2a*pcownoncure2
cownoncure3a<-pcownoncure3a*pcownoncure3
cownoncure4a<-pcownoncure4a*pcownoncure4
cownoncure5a<-pcownoncure5a*pcownoncure5

#Calculation of costs associated with cowbacticurea (cull or endlactation)

cull1b<-pculltotal1*cowbacticure1a
cull2b<-pculltotal1*cowbacticure2a
cull3b<-pculltotal1*cowbacticure3a
cull4b<-pculltotal1*cowbacticure4a
cull5b<-pculltotal1*cowbacticure5a

endlactation1b<-pendlactation1*cowbacticure1a
endlactation2b<-pendlactation1*cowbacticure2a
endlactation3b<-pendlactation1*cowbacticure3a
endlactation4b<-pendlactation1*cowbacticure4a
endlactation5b<-pendlactation1*cowbacticure5a

cull1bcosts<-cull1b*(costofcull+(2*txcost1))
cull2bcosts<-cull2b*(costofcull+(2*txcost2))
cull3bcosts<-cull3b*(costofcull+(2*txcost3))
cull4bcosts<-cull4b*(costofcull+(2*txcost4))
cull5bcosts<-cull5b*(costofcull+(2*txcost5))

endlactcosts1b<-endlactation1b*(costoftotalyieldloss+(2*txcost1))
endlactcosts2b<-endlactation2b*(costoftotalyieldloss+(2*txcost1))
endlactcosts3b<-endlactation3b*(costoftotalyieldloss+(2*txcost1))
endlactcosts4b<-endlactation4b*(costoftotalyieldloss+(2*txcost1))
endlactcosts5b<-endlactation5b*(costoftotalyieldloss+(2*txcost1))

#Calculation of costs aasociated with cownoncurea (death or dry off)

costofdeath~dunif(1200,2000)
pdeath~dunif(0.04,0.06)
```

```
death1<-pdeath*cownoncure1a
death2<-pdeath*cownoncure2a
death3<-pdeath*cownoncure3a
death4<-pdeath*cownoncure4a
death5<-pdeath*cownoncure5a

costofdeath1<-death1*(costofdeath+(2*txcost1))
costofdeath2<-death2*(costofdeath+(2*txcost2))
costofdeath3<-death3*(costofdeath+(2*txcost3))
costofdeath4<-death4*(costofdeath+(2*txcost4))
costofdeath5<-death5*(costofdeath+(2*txcost5))

pdryoff<-1-pdeath
dryoff1<-pdryoff*cownoncure1a
dryoff2<-pdryoff*cownoncure2a
dryoff3<-pdryoff*cownoncure3a
dryoff4<-pdryoff*cownoncure4a
dryoff5<-pdryoff*cownoncure5a

pdryoffcull~dunif(0.27,0.39)
#range added to steeneveld value of 0.33

dryoffcull1<-pdryoffcull*dryoff1
dryoffcull2<-pdryoffcull*dryoff2
dryoffcull3<-pdryoffcull*dryoff3
dryoffcull4<-pdryoffcull*dryoff4
dryoffcull5<-pdryoffcull*dryoff5

costofdryoffcull1<-dryoffcull1*(costofcull+(2*txcost1))
costofdryoffcull2<-dryoffcull2*(costofcull+(2*txcost2))
costofdryoffcull3<-dryoffcull3*(costofcull+(2*txcost3))
costofdryoffcull4<-dryoffcull4*(costofcull+(2*txcost4))
costofdryoffcull5<-dryoffcull5*(costofcull+(2*txcost5))

pdryoffsurvive<-1-pdryoffcull
dryoffsurvive1<-pdryoffsurvive*dryoff1
dryoffsurvive2<-pdryoffsurvive*dryoff2
dryoffsurvive3<-pdryoffsurvive*dryoff3
dryoffsurvive4<-pdryoffsurvive*dryoff4
dryoffsurvive5<-pdryoffsurvive*dryoff5

dryoffyieldloss~dunif(0.13,0.17)
#range added to steeneveld value of 15% loss if 3 quarted

dryofftotalyieldloss<-herd305yield*dryoffyieldloss
costofdryofftotalyieldloss<-(milkprice*dryofftotalyieldloss)-
(milkprodcost*dryofftotalyieldloss)
```

```
costofdryoffsurvive1<-
dryoffsurvive1*(costofdryofftotalyieldloss+(2*txcost1))
costofdryoffsurvive2<-
dryoffsurvive2*(costofdryofftotalyieldloss+(2*txcost2))
costofdryoffsurvive3<-
dryoffsurvive3*(costofdryofftotalyieldloss+(2*txcost3))
costofdryoffsurvive4<-
dryoffsurvive4*(costofdryofftotalyieldloss+(2*txcost4))
costofdryoffsurvive5<-
dryoffsurvive5*(costofdryofftotalyieldloss+(2*txcost5))

#Calculation of costs associated with pcowclincure (cullc, endlactationc or
cm2)

pcull1c~dunif(0,0.32)
illeffect1~dunif(0.05,0.15)
systill1<-step(systillness-0.85)*illeffect1
pcull1ctotal<-(pcull1c+systill1)

cowclincure1total<-pcowclincure1+cowclincure1a
cowclincure2total<-pcowclincure2+cowclincure2a
cowclincure3total<-pcowclincure3+cowclincure3a
cowclincure4total<-pcowclincure4+cowclincure4a
cowclincure5total<-pcowclincure5+cowclincure5a

xcull1c<-pcull1ctotal*pcowclincure1
xcull2c<-pcull1ctotal*pcowclincure2
xcull3c<-pcull1ctotal*pcowclincure3
xcull4c<-pcull1ctotal*pcowclincure4
xcull5c<-pcull1ctotal*pcowclincure5

ycull1c<-pcull1ctotal*cowclincure1a
ycull2c<-pcull1ctotal*cowclincure2a
ycull3c<-pcull1ctotal*cowclincure3a
ycull4c<-pcull1ctotal*cowclincure4a
ycull5c<-pcull1ctotal*cowclincure5a

xcostcull1c<-xcull1c*(costofcull+txcost1)
xcostcull2c<-xcull1c*(costofcull+txcost1)
xcostcull3c<-xcull1c*(costofcull+txcost1)
xcostcull4c<-xcull1c*(costofcull+txcost1)
xcostcull5c<-xcull1c*(costofcull+txcost1)

ycostcull1c<-ycull1c*(costofcull+(2*txcost1))
ycostcull2c<-ycull1c*(costofcull+(2*txcost1))
ycostcull3c<-ycull1c*(costofcull+(2*txcost1))
ycostcull4c<-ycull1c*(costofcull+(2*txcost1))
ycostcull5c<-ycull1c*(costofcull+(2*txcost1))
```

```
pendlactation2<-1-(pcull1ctotal+pcm2)

xendlactation1c<-pendlactation2*pcowclincure1
xendlactation2c<-pendlactation2*pcowclincure2
xendlactation3c<-pendlactation2*pcowclincure3
xendlactation4c<-pendlactation2*pcowclincure4
xendlactation5c<-pendlactation2*pcowclincure5

yendlactation1c<-pendlactation2*cowclincure1a
yendlactation2c<-pendlactation2*cowclincure2a
yendlactation3c<-pendlactation2*cowclincure3a
yendlactation4c<-pendlactation2*cowclincure4a
yendlactation5c<-pendlactation2*cowclincure5a

xcostofendlactation1c<-xendlactation1c*(costoftotalyieldloss+txcost1)
xcostofendlactation2c<-xendlactation2c*(costoftotalyieldloss+txcost2)
xcostofendlactation3c<-xendlactation3c*(costoftotalyieldloss+txcost3)
xcostofendlactation4c<-xendlactation4c*(costoftotalyieldloss+txcost4)
xcostofendlactation5c<-xendlactation5c*(costoftotalyieldloss+txcost5)

ycostofendlactation1c<-
yendlactation1c*(costoftotalyieldloss+(2*txcost1))
ycostofendlactation2c<-
yendlactation2c*(costoftotalyieldloss+(2*txcost2))
ycostofendlactation3c<-
yendlactation3c*(costoftotalyieldloss+(2*txcost3))
ycostofendlactation4c<-
yendlactation4c*(costoftotalyieldloss+(2*txcost4))
ycostofendlactation5c<-
yendlactation5c*(costoftotalyieldloss+(2*txcost5))

pcm2~dunif(0.05,0.12)
#Taken from Steeneveld 2010

cm2tx1<-pcm2*(pcowclincure1+cowclincure1a)
cm2tx2<-pcm2*(pcowclincure2+cowclincure2a)
cm2tx3<-pcm2*(pcowclincure3+cowclincure3a)
cm2tx4<-pcm2*(pcowclincure4+cowclincure4a)
cm2tx5<-pcm2*(pcowclincure5+cowclincure5a)

costofcm2tx1<-cm2tx1*txcost1
costofcm2tx2<-cm2tx2*txcost2
costofcm2tx3<-cm2tx3*txcost3
costofcm2tx4<-cm2tx4*txcost4
costofcm2tx5<-cm2tx5*txcost5

#Costs associated with CM2

bpcowbacticure1b<-pcowbacticure1-0.2
```

```
bpcowbacticure2b<-pcowbacticure2-0.2
bpcowbacticure3b<-pcowbacticure3-0.2
bpcowbacticure4b<-pcowbacticure4-0.2
bpcowbacticure5b<-pcowbacticure5-0.2

pcowbacticure1b<-step(bpcowbacticure1b)*bpcowbacticure1b
pcowbacticure2b<-step(bpcowbacticure2b)*bpcowbacticure2b
pcowbacticure3b<-step(bpcowbacticure3b)*bpcowbacticure3b
pcowbacticure4b<-step(bpcowbacticure4b)*bpcowbacticure4b
pcowbacticure5b<-step(bpcowbacticure5b)*bpcowbacticure5b


#cure rates assoc with extended tx
bpcowbacticure1z<-pcowbacticure1a-0.2
bpcowbacticure2z<-pcowbacticure2a-0.2
bpcowbacticure3z<-pcowbacticure3a-0.2
bpcowbacticure4z<-pcowbacticure4a-0.2
bpcowbacticure5z<-pcowbacticure5a-0.2

pcowbacticure1z<-step(bpcowbacticure1z)*bpcowbacticure1z
pcowbacticure2z<-step(bpcowbacticure2z)*bpcowbacticure2z
pcowbacticure3z<-step(bpcowbacticure3z)*bpcowbacticure3z
pcowbacticure4z<-step(bpcowbacticure4z)*bpcowbacticure4z
pcowbacticure5z<-step(bpcowbacticure5z)*bpcowbacticure5z


# reduction of 0.2 taken from Steeneveld (as repeat case)

cowbacticure1b<-cm2tx1*pcowbacticure1b
cowbacticure2b<-cm2tx2*pcowbacticure2b
cowbacticure3b<-cm2tx3*pcowbacticure3b
cowbacticure4b<-cm2tx4*pcowbacticure4b
cowbacticure5b<-cm2tx5*pcowbacticure5b

#Probability of no cure
pnoncure1b<- 1-pcowbacticure1b
pnoncure2b<- 1-pcowbacticure2b
pnoncure3b<- 1-pcowbacticure3b
pnoncure4b<- 1-pcowbacticure4b
pnoncure5b<- 1-pcowbacticure5b

#Probability of non bacterial but clinical cure
pcowclincure1b<- pnoncure1b*0.8
pcowclincure2b<- pnoncure2b*0.8
pcowclincure3b<- pnoncure3b*0.8
pcowclincure4b<- pnoncure4b*0.8
pcowclincure5b<- pnoncure5b*0.8

cowclincure1b<-cm2tx1*pcowclincure1b
```

```
cowclincure2b<-cm2tx2*pcowclincure2b
cowclincure3b<-cm2tx3*pcowclincure3b
cowclincure4b<-cm2tx4*pcowclincure4b
cowclincure5b<-cm2tx5*pcowclincure5b

#Probability of no bacterial or no clinical cure
pcownoncure1b <- 1-(pcowbacticure1b + pcowclincure1b)
pcownoncure2b <- 1-(pcowbacticure2b + pcowclincure2b)
pcownoncure3b <- 1-(pcowbacticure3b + pcowclincure3b)
pcownoncure4b <- 1-(pcowbacticure4b + pcowclincure4b)
pcownoncure5b <- 1-(pcowbacticure5b + pcowclincure5b)

cownoncure1b<-cm2tx1*pcownoncure1b
cownoncure2b<-cm2tx2*pcownoncure2b
cownoncure3b<-cm2tx3*pcownoncure3b
cownoncure4b<-cm2tx4*pcownoncure4b
cownoncure5b<-cm2tx5*pcownoncure5b

#Costs assoc. with cowbacticure()b (either cull or endlactation)

pcull2~dunif(0.10,0.20)

systill2<-step(systillness-0.85)*illeffect1

cull1d<-(pcull2+systill2)*cowbacticure1b
cull2d<-(pcull2+systill2)*cowbacticure2b
cull3d<-(pcull2+systill2)*cowbacticure3b
cull4d<-(pcull2+systill2)*cowbacticure4b
cull5d<-(pcull2+systill2)*cowbacticure5b

costofcull1d<-cull1d*costofcull
costofcull2d<-cull2d*costofcull
costofcull3d<-cull3d*costofcull
costofcull4d<-cull4d*costofcull
costofcull5d<-cull5d*costofcull

pendlactation3<-1-(pcull2+systill2)

endlactation1d<-pendlactation3*cowbacticure1b
endlactation2d<-pendlactation3*cowbacticure2b
endlactation3d<-pendlactation3*cowbacticure3b
endlactation4d<-pendlactation3*cowbacticure4b
endlactation5d<-pendlactation3*cowbacticure5b

endlactcost1d<-endlactation1d*costoftotalyieldloss
endlactcost2d<-endlactation2d*costoftotalyieldloss
endlactcost3d<-endlactation3d*costoftotalyieldloss
endlactcost4d<-endlactation4d*costoftotalyieldloss
endlactcost5d<-endlactation5d*costoftotalyieldloss
```

```
#CALCULATE TREATMENT COSTS AFTER FAILURE TO CURE (extended
tx)

#Probability of bacterial cure
pcowbacticure1c<-pcowbacticure1z
pcowbacticure2c<-pcowbacticure2z
pcowbacticure3c<-pcowbacticure3z
pcowbacticure4c<-pcowbacticure4z
pcowbacticure5c<-pcowbacticure5z

cowbacticure1c<-pcowbacticure1c*cownoncure1b
cowbacticure2c<-pcowbacticure2c*cownoncure2b
cowbacticure3c<-pcowbacticure3c*cownoncure3b
cowbacticure4c<-pcowbacticure4c*cownoncure4b
cowbacticure5c<-pcowbacticure5c*cownoncure5b

#Probability of no cure
pnoncure1c<-1-pcowbacticure1c
pnoncure2c<-1-pcowbacticure2c
pnoncure3c<-1-pcowbacticure3c
pnoncure4c<-1-pcowbacticure4c
pnoncure5c<-1-pcowbacticure5c

#Probability of Clinical cure
pcowclincure1c<-pnoncure1c*0.8
pcowclincure2c<-pnoncure2c*0.8
pcowclincure3c<-pnoncure3c*0.8
pcowclincure4c<-pnoncure4c*0.8
pcowclincure5c<-pnoncure5c*0.8

cowclincure1c<-pcowclincure1c*cownoncure1b
cowclincure2c<-pcowclincure2c*cownoncure2b
cowclincure3c<-pcowclincure3c*cownoncure3b
cowclincure4c<-pcowclincure4c*cownoncure4b
cowclincure5c<-pcowclincure5c*cownoncure5b

#Probability of Non bacterial and Non clinical cure
pcownoncure1c <- 1-(pcowbacticure1c + pcowclincure1c)
pcownoncure2c <- 1-(pcowbacticure2c + pcowclincure2c)
pcownoncure3c <- 1-(pcowbacticure3c + pcowclincure3c)
pcownoncure4c <- 1-(pcowbacticure4c + pcowclincure4c)
pcownoncure5c <- 1-(pcowbacticure5c + pcowclincure5c)

cownoncure1c<-cownoncure1b*pcownoncure1c
cownoncure2c<-cownoncure2b*pcownoncure2c
cownoncure3c<-cownoncure3b*pcownoncure3c
cownoncure4c<-cownoncure4b*pcownoncure4c
cownoncure5c<-cownoncure5b*pcownoncure5c
```

```
#Calculation of costs associated with cowbacticure c (cull or endlactation)

cull1e<-(pcull2+systill2)*cowbacticure1c
cull2e<-(pcull2+systill2)*cowbacticure2c
cull3e<-(pcull2+systill2)*cowbacticure3c
cull4e<-(pcull2+systill2)*cowbacticure4c
cull5e<-(pcull2+systill2)*cowbacticure5c

endlactation1e<-pendlactation3*cowbacticure1c
endlactation2e<-pendlactation3*cowbacticure2c
endlactation3e<-pendlactation3*cowbacticure3c
endlactation4e<-pendlactation3*cowbacticure4c
endlactation5e<-pendlactation3*cowbacticure5c

cull1ecosts<-cull1e*(costofcull+(2*txcost1))
cull2ecosts<-cull2e*(costofcull+(2*txcost2))
cull3ecosts<-cull3e*(costofcull+(2*txcost3))
cull4ecosts<-cull4e*(costofcull+(2*txcost4))
cull5ecosts<-cull5e*(costofcull+(2*txcost5))

endlactcosts1e<-endlactation1e*(costoftotalyieldloss+(2*txcost1))
endlactcosts2e<-endlactation2e*(costoftotalyieldloss+(2*txcost1))
endlactcosts3e<-endlactation3e*(costoftotalyieldloss+(2*txcost1))
endlactcosts4e<-endlactation4e*(costoftotalyieldloss+(2*txcost1))
endlactcosts5e<-endlactation5e*(costoftotalyieldloss+(2*txcost1))

#Calculation of costs aasociated with cownoncurec (death or dry off)

death1c<-pdeath*cownoncure1c
death2c<-pdeath*cownoncure2c
death3c<-pdeath*cownoncure3c
death4c<-pdeath*cownoncure4c
death5c<-pdeath*cownoncure5c

costofdeath1c<-death1c*(costofdeath+(2*txcost1))
costofdeath2c<-death2c*(costofdeath+(2*txcost2))
costofdeath3c<-death3c*(costofdeath+(2*txcost3))
costofdeath4c<-death4c*(costofdeath+(2*txcost4))
costofdeath5c<-death5c*(costofdeath+(2*txcost5))

pdryoffc<-1-pdeath
dryoff1c<-pdryoffc*cownoncure1c
dryoff2c<-pdryoffc*cownoncure2c
dryoff3c<-pdryoffc*cownoncure3c
dryoff4c<-pdryoffc*cownoncure4c
dryoff5c<-pdryoffc*cownoncure5c

dryoffcull1c<-pdryoffcull*dryoff1c
```

```
dryoffcull2c<-pdryoffcull*dryoff2c
dryoffcull3c<-pdryoffcull*dryoff3c
dryoffcull4c<-pdryoffcull*dryoff4c
dryoffcull5c<-pdryoffcull*dryoff5c

costofdryoffcull1c<-dryoffcull1c*(costofcull+(2*txcost1))
costofdryoffcull2c<-dryoffcull2c*(costofcull+(2*txcost2))
costofdryoffcull3c<-dryoffcull3c*(costofcull+(2*txcost3))
costofdryoffcull4c<-dryoffcull4c*(costofcull+(2*txcost4))
costofdryoffcull5c<-dryoffcull5c*(costofcull+(2*txcost5))

pdryoffsurvivec<-1-pdryoffcull
dryoffsurvive1c<-pdryoffsurvivec*dryoff1c
dryoffsurvive2c<-pdryoffsurvivec*dryoff2c
dryoffsurvive3c<-pdryoffsurvivec*dryoff3c
dryoffsurvive4c<-pdryoffsurvivec*dryoff4c
dryoffsurvive5c<-pdryoffsurvivec*dryoff5c

costofdryoffsurvive1c<-
dryoffsurvive1c*(costofdryofftotalyieldloss+(2*txcost1))
costofdryoffsurvive2c<-
dryoffsurvive2c*(costofdryofftotalyieldloss+(2*txcost2))
costofdryoffsurvive3c<-
dryoffsurvive3c*(costofdryofftotalyieldloss+(2*txcost3))
costofdryoffsurvive4c<-
dryoffsurvive4c*(costofdryofftotalyieldloss+(2*txcost4))
costofdryoffsurvive5c<-
dryoffsurvive5c*(costofdryofftotalyieldloss+(2*txcost5))


#Calculation of costs associated with cowclincure b

pcull3~dunif(0.04,0.36)
#figure of 0.2 given by steeneveld

cowclincure1bctotal<-cowclincure1b+cowclincure1c
cowclincure2bctotal<-cowclincure2b+cowclincure2c
cowclincure3bctotal<-cowclincure3b+cowclincure3c
cowclincure4bctotal<-cowclincure4b+cowclincure4c
cowclincure5bctotal<-cowclincure5b+cowclincure5c

xcull1d<-(pcull3+systill2)*cowclincure1b
xcull2d<-(pcull3+systill2)*cowclincure2b
xcull3d<-(pcull3+systill2)*cowclincure3b
xcull4d<-(pcull3+systill2)*cowclincure4b
xcull5d<-(pcull3+systill2)*cowclincure5b

ycull1d<-(pcull3+systill2)*cowclincure1c
ycull2d<-(pcull3+systill2)*cowclincure2c
```

```
ycull3d<-(pcull3+systill2)*cowclincure3c
ycull4d<-(pcull3+systill2)*cowclincure4c
ycull5d<-(pcull3+systill2)*cowclincure5c

xcostcull1d<-xcull1d*(costofcull+txcost1)
xcostcull2d<-xcull2d*(costofcull+txcost2)
xcostcull3d<-xcull3d*(costofcull+txcost3)
xcostcull4d<-xcull4d*(costofcull+txcost4)
xcostcull5d<-xcull5d*(costofcull+txcost5)

ycostcull1d<-ycull1d*(costofcull+(2*txcost1))
ycostcull2d<-ycull2d*(costofcull+(2*txcost2))
ycostcull3d<-ycull3d*(costofcull+(2*txcost3))
ycostcull4d<-ycull4d*(costofcull+(2*txcost4))
ycostcull5d<-ycull5d*(costofcull+(2*txcost5))

pendlactation4<-1-(pcull3+systill2+pcm3)

xendlactation1d<-pendlactation4*cowclincure1b
xendlactation2d<-pendlactation4*cowclincure2b
xendlactation3d<-pendlactation4*cowclincure3b
xendlactation4d<-pendlactation4*cowclincure4b
xendlactation5d<-pendlactation4*cowclincure5b

yendlactation1d<-pendlactation4*cowclincure1c
yendlactation2d<-pendlactation4*cowclincure2c
yendlactation3d<-pendlactation4*cowclincure3c
yendlactation4d<-pendlactation4*cowclincure4c
yendlactation5d<-pendlactation4*cowclincure5c

xcostofendlactation1d<-xendlactation1d*(costoftotalyieldloss+txcost1)
xcostofendlactation2d<-xendlactation2d*(costoftotalyieldloss+txcost2)
xcostofendlactation3d<-xendlactation3d*(costoftotalyieldloss+txcost3)
xcostofendlactation4d<-xendlactation4d*(costoftotalyieldloss+txcost4)
xcostofendlactation5d<-xendlactation5d*(costoftotalyieldloss+txcost5)

ycostofendlactation1d<-
yendlactation1d*(costoftotalyieldloss+(2*txcost1))
ycostofendlactation2d<-
yendlactation2d*(costoftotalyieldloss+(2*txcost2))
ycostofendlactation3d<-
yendlactation3d*(costoftotalyieldloss+(2*txcost3))
ycostofendlactation4d<-
yendlactation4d*(costoftotalyieldloss+(2*txcost4))
ycostofendlactation5d<-
yendlactation5d*(costoftotalyieldloss+(2*txcost5))

pcm3~dunif(0.05,0.12)
#Taken from Steeneveld 2010
```

```
cm3tx1<-pcm3*(cowclincure1b+cowclincure1c)
cm3tx2<-pcm3*(cowclincure2b+cowclincure2c)
cm3tx3<-pcm3*(cowclincure3b+cowclincure3c)
cm3tx4<-pcm3*(cowclincure4b+cowclincure4c)
cm3tx5<-pcm3*(cowclincure5b+cowclincure5c)

costofcm3tx1<-cm3tx1*txcost1
costofcm3tx2<-cm3tx2*txcost2
costofcm3tx3<-cm3tx3*txcost3
costofcm3tx4<-cm3tx4*txcost4
costofcm3tx5<-cm3tx5*txcost5

#Costs associated with cm3 (Page 3 model)

cpcowbacticure1d<-pcowbacticure1b-0.2
cpcowbacticure2d<-pcowbacticure2b-0.2
cpcowbacticure3d<-pcowbacticure3b-0.2
cpcowbacticure4d<-pcowbacticure4b-0.2
cpcowbacticure5d<-pcowbacticure5b-0.2

pcowbacticure1d<-step(cpcowbacticure1d)*cpcowbacticure1d
pcowbacticure2d<-step(cpcowbacticure2d)*cpcowbacticure2d
pcowbacticure3d<-step(cpcowbacticure3d)*cpcowbacticure3d
pcowbacticure4d<-step(cpcowbacticure4d)*cpcowbacticure4d
pcowbacticure5d<-step(cpcowbacticure5d)*cpcowbacticure5d

# reduction of 0.2 taken from Steeneveld (as repeat case)

cowbacticure1d<-cm3tx1*pcowbacticure1d
cowbacticure2d<-cm3tx2*pcowbacticure2d
cowbacticure3d<-cm3tx3*pcowbacticure3d
cowbacticure4d<-cm3tx4*pcowbacticure4d
cowbacticure5d<-cm3tx5*pcowbacticure5d

#Probability of no cure
pnoncure1d<- 1-pcowbacticure1d
pnoncure2d<- 1-pcowbacticure2d
pnoncure3d<- 1-pcowbacticure3d
pnoncure4d<- 1-pcowbacticure4d
pnoncure5d<- 1-pcowbacticure5d

#Probability of non bacterial but clinical cure
pcowclincure1d<- pnoncure1d*0.8
pcowclincure2d<- pnoncure2d*0.8
pcowclincure3d<- pnoncure3d*0.8
pcowclincure4d<- pnoncure4d*0.8
pcowclincure5d<- pnoncure5d*0.8
```

```
cowclincure1d<-cm3tx1*pcowclincure1d
cowclincure2d<-cm3tx2*pcowclincure2d
cowclincure3d<-cm3tx3*pcowclincure3d
cowclincure4d<-cm3tx4*pcowclincure4d
cowclincure5d<-cm3tx5*pcowclincure5d

#Probability of no bacterial or no clinical cure
pcownoncure1d <- 1-(pcowbacticure1d + pcowclincure1d)
pcownoncure2d <- 1-(pcowbacticure2d + pcowclincure2d)
pcownoncure3d <- 1-(pcowbacticure3d + pcowclincure3d)
pcownoncure4d <- 1-(pcowbacticure4d + pcowclincure4d)
pcownoncure5d <- 1-(pcowbacticure5d + pcowclincure5d)

cownoncure1d<-cm3tx1*pcownoncure1d
cownoncure2d<-cm3tx2*pcownoncure2d
cownoncure3d<-cm3tx3*pcownoncure3d
cownoncure4d<-cm3tx4*pcownoncure4d
cownoncure5d<-cm3tx5*pcownoncure5d

#Costs assoc. with cowbacticure d (either cull or endlactation)

pcull4~dunif(0.20,0.30)
# pcull taken from steeneveld (p=0.25)

systill4<-step(systillness-0.85)*illeffect1

cull1f<-(pcull4+systill4)*cowbacticure1d
cull2f<-(pcull4+systill4)*cowbacticure2d
cull3f<-(pcull4+systill4)*cowbacticure3d
cull4f<-(pcull4+systill4)*cowbacticure4d
cull5f<-(pcull4+systill4)*cowbacticure5d

costofcull1f<-cull1f*costofcull
costofcull2f<-cull2f*costofcull
costofcull3f<-cull3f*costofcull
costofcull4f<-cull4f*costofcull
costofcull5f<-cull5f*costofcull

pendlactation5<-1-(pcull4+systill4)

endlactation1f<-pendlactation5*cowbacticure1d
endlactation2f<-pendlactation5*cowbacticure2d
endlactation3f<-pendlactation5*cowbacticure3d
endlactation4f<-pendlactation5*cowbacticure4d
endlactation5f<-pendlactation5*cowbacticure5d

endlactcost1f<-endlactation1f*costoftotalyieldloss
endlactcost2f<-endlactation2f*costoftotalyieldloss
endlactcost3f<-endlactation3f*costoftotalyieldloss
```

```
endlactcost4f<-endlactation4f*costoftotalyieldloss
endlactcost5f<-endlactation5f*costoftotalyieldloss

#CALCULATE TREATMENT COSTS AFTER FAILURE TO CURE (cull)

cull1g<-cownoncure1d
cull2g<-cownoncure2d
cull3g<-cownoncure3d
cull4g<-cownoncure4d
cull5g<-cownoncure5d

cull1gcosts<-cull1g*(costofcull+txcost1)
cull2gcosts<-cull2g*(costofcull+txcost2)
cull3gcosts<-cull3g*(costofcull+txcost3)
cull4gcosts<-cull4g*(costofcull+txcost4)
cull5gcosts<-cull5g*(costofcull+txcost5)

#Calculation of costs associated with cowclincure d

cull1h<-cowclincure1d
cull2h<-cowclincure2d
cull3h<-cowclincure3d
cull4h<-cowclincure4d
cull5h<-cowclincure5d

cull1hcosts<-cull1h*(costofcull+txcost1)
cull2hcosts<-cull2h*(costofcull+txcost2)
cull3hcosts<-cull3h*(costofcull+txcost3)
cull4hcosts<-cull4h*(costofcull+txcost4)
cull5hcosts<-cull5h*(costofcull+txcost5)

#Transmission 1a

trans0~dunif(0.002,0.25)
ptrans0<-trans0*(population0/100)
ptrans2<-ptrans0*(population2/100)
ptrans4<-ptrans0*(population4/100)
ptrans6<-ptrans0*(population6/100)
ptrans8<-ptrans0*(population8/100)
ptrans10<-ptrans0*(population10/100)

population0<-99
population2<-99-total2
population4<-99-total4
population6<-99-total6
population8<-99-total8
population10<-99-total10

trans1<-pcowclincure1+cowclincure1a
```

```
trans2<-ptrans0*trans1
trans3<-trans2*ptrans2
trans4<-ptrans2*trans1
trans5<-ptrans4*trans1
trans6<-trans4*ptrans4
trans7<-trans2*ptrans4
trans8<-trans3*ptrans4
trans9<-ptrans6*trans1
trans10<-trans5*ptrans6
trans11<-trans4*ptrans6
trans12<-trans6*ptrans6
trans13<-trans2*ptrans6
trans14<-trans7*ptrans6
trans15<-trans3*ptrans6
trans16<-trans8*ptrans6
trans17<-ptrans8*trans1
trans18<-trans9*ptrans8
trans19<-trans5*ptrans8
trans20<-trans10*ptrans8
trans21<-trans4*ptrans8
trans22<-trans11*ptrans8
trans23<-trans6*ptrans8
trans24<-trans12*ptrans8
trans25<-trans2*ptrans8
trans26<-trans13*ptrans8
trans27<-trans7*ptrans8
trans28<-trans14*ptrans8
trans29<-trans3*ptrans8
trans30<-trans15*ptrans8
trans31<-trans8*ptrans8
trans32<-trans16*ptrans8
trans33<-ptrans10*trans1
trans34<-trans17*ptrans10
trans35<-trans9*ptrans10
trans36<-trans18*ptrans10
trans37<-trans5*ptrans10
trans38<-trans19*ptrans10
trans39<-trans10*ptrans10
trans40<-trans20*ptrans10
trans41<-trans4*ptrans10
trans42<-trans21*ptrans10
trans43<-trans11*ptrans10
trans44<-trans22*ptrans10
trans45<-trans6*ptrans10
trans46<-trans23*ptrans10
trans47<-trans12*ptrans10
trans48<-trans24*ptrans10
trans49<-trans2*ptrans10
trans50<-trans25*ptrans10
```

```
trans51<-trans13*ptrans10
trans52<-trans26*ptrans10
trans53<-trans7*ptrans10
trans54<-trans27*ptrans10
trans55<-trans14*ptrans10
trans56<-trans28*ptrans10
trans57<-trans3*ptrans10
trans58<-trans29*ptrans10
trans59<-trans15*ptrans10
trans60<-trans30*ptrans10
trans61<-trans8*ptrans10
trans62<-trans31*ptrans10
trans63<-trans16*ptrans10
trans64<-trans32*ptrans10

total2<-trans2
total4<-total2+trans3+trans4
total6<-total4+trans5+trans6+trans7+trans8
total8<-
total6+trans9+trans10+trans11+trans12+trans13+trans14+trans15+tran
s16
total10<-
total8+trans17+trans18+trans19+trans20+trans21+trans22+trans23+tra
ns24+trans25+trans26+trans27+trans28+trans29+trans30+trans31+tra
ns32
total12<-
total10+trans33+trans34+trans35+trans36+trans37+trans38+trans39+tr
ans40+trans41+trans42+trans43+trans44+trans45+trans46+trans47+tra
ns48+trans49+trans50+trans51+trans52+trans53+trans54+trans55+tra
ns56+trans57+trans58+trans59+trans60+trans61+trans62+trans63+tra
ns64

#Transmission 2a

bptrans0<-trans0*(bpopulation0/100)
bptrans2<-bptrans0*(bpopulation2/100)
bptrans4<-bptrans0*(bpopulation4/100)
bptrans6<-bptrans0*(bpopulation6/100)
bptrans8<-bptrans0*(bpopulation8/100)
bptrans10<-bptrans0*(bpopulation10/100)

bpopulation0<-99
bpopulation2<-99-btotal2
bpopulation4<-99-btotal4
bpopulation6<-99-btotal6
bpopulation8<-99-btotal8
bpopulation10<-99-btotal10

btrans1<-pcowclincure2+cowclincure2a
```

btrans2<-bptrans0*btrans1
btrans3<-btrans2*bptrans2
btrans4<-bptrans2*btrans1
btrans5<-bptrans4*btrans1
btrans6<-btrans4*bptrans4
btrans7<-btrans2*bptrans4
btrans8<-btrans3*bptrans4
btrans9<-bptrans6*btrans1
btrans10<-btrans5*bptrans6
btrans11<-btrans4*bptrans6
btrans12<-btrans6*bptrans6
btrans13<-btrans2*bptrans6
btrans14<-btrans7*bptrans6
btrans15<-btrans3*bptrans6
btrans16<-btrans8*bptrans6
btrans17<-bptrans8*btrans1
btrans18<-btrans9*bptrans8
btrans19<-btrans5*bptrans8
btrans20<-btrans10*bptrans8
btrans21<-btrans4*bptrans8
btrans22<-btrans11*bptrans8
btrans23<-btrans6*bptrans8
btrans24<-btrans12*bptrans8
btrans25<-btrans2*bptrans8
btrans26<-btrans13*bptrans8
btrans27<-btrans7*bptrans8
btrans28<-btrans14*bptrans8
btrans29<-btrans3*bptrans8
btrans30<-btrans15*bptrans8
btrans31<-btrans8*bptrans8
btrans32<-btrans16*bptrans8
btrans33<-bptrans10*btrans1
btrans34<-btrans17*bptrans10
btrans35<-btrans9*bptrans10
btrans36<-btrans18*bptrans10
btrans37<-btrans5*bptrans10
btrans38<-btrans19*bptrans10
btrans39<-btrans10*bptrans10
btrans40<-btrans20*bptrans10
btrans41<-btrans4*bptrans10
btrans42<-btrans21*bptrans10
btrans43<-btrans11*bptrans10
btrans44<-btrans22*bptrans10
btrans45<-btrans6*bptrans10
btrans46<-btrans23*bptrans10
btrans47<-btrans12*bptrans10
btrans48<-btrans24*bptrans10
btrans49<-btrans2*bptrans10
btrans50<-btrans25*bptrans10

```
btrans51<-btrans13*bptrans10
btrans52<-btrans26*bptrans10
btrans53<-btrans7*bptrans10
btrans54<-btrans27*bptrans10
btrans55<-btrans14*bptrans10
btrans56<-btrans28*bptrans10
btrans57<-btrans3*bptrans10
btrans58<-btrans29*bptrans10
btrans59<-btrans15*bptrans10
btrans60<-btrans30*bptrans10
btrans61<-btrans8*bptrans10
btrans62<-btrans31*bptrans10
btrans63<-btrans16*bptrans10
btrans64<-btrans32*bptrans10

btotal2<-btrans2
btotal4<-btotal2+btrans3+btrans4
btotal6<-btotal4+btrans5+btrans6+btrans7+btrans8
btotal8<-
btotal6+btrans9+btrans10+btrans11+btrans12+btrans13+btrans14+btra
ns15+btrans16
btotal10<-
btotal8+btrans17+btrans18+btrans19+btrans20+btrans21+btrans22+btr
ans23+btrans24+btrans25+btrans26+btrans27+btrans28+btrans29+btra
ns30+btrans31+btrans32
btotal12<-
btotal10+btrans33+btrans34+btrans35+btrans36+btrans37+btrans38+b
trans39+btrans40+btrans41+btrans42+btrans43+btrans44+btrans45+bt
rans46+btrans47+btrans48+btrans49+btrans50+btrans51+btrans52+btr
ans53+btrans54+btrans55+btrans56+btrans57+btrans58+btrans59+btra
ns60+btrans61+btrans62+btrans63+btrans64

#Transmission 3a

cptrans0<-trans0*(cpopulation0/100)
cptrans2<-cptrans0*(cpopulation2/100)
cptrans4<-cptrans0*(cpopulation4/100)
cptrans6<-cptrans0*(cpopulation6/100)
cptrans8<-cptrans0*(cpopulation8/100)
cptrans10<-cptrans0*(cpopulation10/100)

cpopulation0<-99
cpopulation2<-99-ctotal2
cpopulation4<-99-ctotal4
cpopulation6<-99-ctotal6
cpopulation8<-99-ctotal8
cpopulation10<-99-ctotal10

ctrans1<-pcowclincure3+cowclincure3a
```

ctrans2<-cptrans0*ctrans1
ctrans3<-ctrans2*cptrans2
ctrans4<-cptrans2*ctrans1
ctrans5<-cptrans4*ctrans1
ctrans6<-ctrans4*cptrans4
ctrans7<-ctrans2*cptrans4
ctrans8<-ctrans3*cptrans4
ctrans9<-cptrans6*ctrans1
ctrans10<-ctrans5*cptrans6
ctrans11<-ctrans4*cptrans6
ctrans12<-ctrans6*cptrans6
ctrans13<-ctrans2*cptrans6
ctrans14<-ctrans7*cptrans6
ctrans15<-ctrans3*cptrans6
ctrans16<-ctrans8*cptrans6
ctrans17<-cptrans8*ctrans1
ctrans18<-ctrans9*cptrans8
ctrans19<-ctrans5*cptrans8
ctrans20<-ctrans10*cptrans8
ctrans21<-ctrans4*cptrans8
ctrans22<-ctrans11*cptrans8
ctrans23<-ctrans6*cptrans8
ctrans24<-ctrans12*cptrans8
ctrans25<-ctrans2*cptrans8
ctrans26<-ctrans13*cptrans8
ctrans27<-ctrans7*cptrans8
ctrans28<-ctrans14*cptrans8
ctrans29<-ctrans3*cptrans8
ctrans30<-ctrans15*cptrans8
ctrans31<-ctrans8*cptrans8
ctrans32<-ctrans16*cptrans8
ctrans33<-cptrans10*ctrans1
ctrans34<-ctrans17*cptrans10
ctrans35<-ctrans9*cptrans10
ctrans36<-ctrans18*cptrans10
ctrans37<-ctrans5*cptrans10
ctrans38<-ctrans19*cptrans10
ctrans39<-ctrans10*cptrans10
ctrans40<-ctrans20*cptrans10
ctrans41<-ctrans4*cptrans10
ctrans42<-ctrans21*cptrans10
ctrans43<-ctrans11*cptrans10
ctrans44<-ctrans22*cptrans10
ctrans45<-ctrans6*cptrans10
ctrans46<-ctrans23*cptrans10
ctrans47<-ctrans12*cptrans10
ctrans48<-ctrans24*cptrans10
ctrans49<-ctrans2*cptrans10
ctrans50<-ctrans25*cptrans10

```
ctrans51<-ctrans13*cptrans10
ctrans52<-ctrans26*cptrans10
ctrans53<-ctrans7*cptrans10
ctrans54<-ctrans27*cptrans10
ctrans55<-ctrans14*cptrans10
ctrans56<-ctrans28*cptrans10
ctrans57<-ctrans3*cptrans10
ctrans58<-ctrans29*cptrans10
ctrans59<-ctrans15*cptrans10
ctrans60<-ctrans30*cptrans10
ctrans61<-ctrans8*cptrans10
ctrans62<-ctrans31*cptrans10
ctrans63<-ctrans16*cptrans10
ctrans64<-ctrans32*cptrans10

ctotal2<-ctrans2
ctotal4<-ctotal2+ctrans3+ctrans4
ctotal6<-ctotal4+ctrans5+ctrans6+ctrans7+ctrans8
ctotal8<-
ctotal6+ctrans9+ctrans10+ctrans11+ctrans12+ctrans13+ctrans14+ctran
s15+ctrans16
ctotal10<-
ctotal8+ctrans17+ctrans18+ctrans19+ctrans20+ctrans21+ctrans22+ctra
ns23+ctrans24+ctrans25+ctrans26+ctrans27+ctrans28+ctrans29+ctrans
30+ctrans31+ctrans32
ctotal12<-
ctotal10+ctrans33+ctrans34+ctrans35+ctrans36+ctrans37+ctrans38+ctr
ans39+ctrans40+ctrans41+ctrans42+ctrans43+ctrans44+ctrans45+ctran
s46+ctrans47+ctrans48+ctrans49+ctrans50+ctrans51+ctrans52+ctrans5
3+ctrans54+ctrans55+ctrans56+ctrans57+ctrans58+ctrans59+ctrans60+
ctrans61+ctrans62+ctrans63+ctrans64

#Transmission 4a

dptrans0<-trans0*(dpopulation0/100)
dptrans2<-dptrans0*(dpopulation2/100)
dptrans4<-dptrans0*(dpopulation4/100)
dptrans6<-dptrans0*(dpopulation6/100)
dptrans8<-dptrans0*(dpopulation8/100)
dptrans10<-dptrans0*(dpopulation10/100)

dpopulation0<-99
dpopulation2<-99-dtotal2
dpopulation4<-99-dtotal4
dpopulation6<-99-dtotal6
dpopulation8<-99-dtotal8
dpopulation10<-99-dtotal10

dtrans1<-pcowclincure4+cowclincure4a
```

dtrans2<-dptrans0*dtrans1
dtrans3<-dtrans2*dptrans2
dtrans4<-dptrans2*dtrans1
dtrans5<-dptrans4*dtrans1
dtrans6<-dtrans4*dptrans4
dtrans7<-dtrans2*dptrans4
dtrans8<-dtrans3*dptrans4
dtrans9<-dptrans6*dtrans1
dtrans10<-dtrans5*dptrans6
dtrans11<-dtrans4*dptrans6
dtrans12<-dtrans6*dptrans6
dtrans13<-dtrans2*dptrans6
dtrans14<-dtrans7*dptrans6
dtrans15<-dtrans3*dptrans6
dtrans16<-dtrans8*dptrans6
dtrans17<-dptrans8*dtrans1
dtrans18<-dtrans9*dptrans8
dtrans19<-dtrans5*dptrans8
dtrans20<-dtrans10*dptrans8
dtrans21<-dtrans4*dptrans8
dtrans22<-dtrans11*dptrans8
dtrans23<-dtrans6*dptrans8
dtrans24<-dtrans12*dptrans8
dtrans25<-dtrans2*dptrans8
dtrans26<-dtrans13*dptrans8
dtrans27<-dtrans7*dptrans8
dtrans28<-dtrans14*dptrans8
dtrans29<-dtrans3*dptrans8
dtrans30<-dtrans15*dptrans8
dtrans31<-dtrans8*dptrans8
dtrans32<-dtrans16*dptrans8
dtrans33<-dptrans10*dtrans1
dtrans34<-dtrans17*dptrans10
dtrans35<-dtrans9*dptrans10
dtrans36<-dtrans18*dptrans10
dtrans37<-dtrans5*dptrans10
dtrans38<-dtrans19*dptrans10
dtrans39<-dtrans10*dptrans10
dtrans40<-dtrans20*dptrans10
dtrans41<-dtrans4*dptrans10
dtrans42<-dtrans21*dptrans10
dtrans43<-dtrans11*dptrans10
dtrans44<-dtrans22*dptrans10
dtrans45<-dtrans6*dptrans10
dtrans46<-dtrans23*dptrans10
dtrans47<-dtrans12*dptrans10
dtrans48<-dtrans24*dptrans10
dtrans49<-dtrans2*dptrans10
dtrans50<-dtrans25*dptrans10

```
dtrans51<-dtrans13*dptrans10
dtrans52<-dtrans26*dptrans10
dtrans53<-dtrans7*dptrans10
dtrans54<-dtrans27*dptrans10
dtrans55<-dtrans14*dptrans10
dtrans56<-dtrans28*dptrans10
dtrans57<-dtrans3*dptrans10
dtrans58<-dtrans29*dptrans10
dtrans59<-dtrans15*dptrans10
dtrans60<-dtrans30*dptrans10
dtrans61<-dtrans8*dptrans10
dtrans62<-dtrans31*dptrans10
dtrans63<-dtrans16*dptrans10
dtrans64<-dtrans32*dptrans10

dtotal2<-dtrans2
dtotal4<-dtotal2+dtrans3+dtrans4
dtotal6<-dtotal4+dtrans5+dtrans6+dtrans7+dtrans8
dtotal8<-
dtotal6+dtrans9+dtrans10+dtrans11+dtrans12+dtrans13+dtrans14+dtra
ns15+dtrans16
dtotal10<-
dtotal8+dtrans17+dtrans18+dtrans19+dtrans20+dtrans21+dtrans22+dtr
ans23+dtrans24+dtrans25+dtrans26+dtrans27+dtrans28+dtrans29+dtra
ns30+dtrans31+dtrans32
dtotal12<-
dtotal10+dtrans33+dtrans34+dtrans35+dtrans36+dtrans37+dtrans38+d
trans39+dtrans40+dtrans41+dtrans42+dtrans43+dtrans44+dtrans45+dt
rans46+dtrans47+dtrans48+dtrans49+dtrans50+dtrans51+dtrans52+dtr
ans53+dtrans54+dtrans55+dtrans56+dtrans57+dtrans58+dtrans59+dtra
ns60+dtrans61+dtrans62+dtrans63+dtrans64

#Transmission5a

eptrans0<-trans0*(epopulation0/100)
eptrans2<-eptrans0*(epopulation2/100)
eptrans4<-eptrans0*(epopulation4/100)
eptrans6<-eptrans0*(epopulation6/100)
eptrans8<-eptrans0*(epopulation8/100)
eptrans10<-eptrans0*(epopulation10/100)

epopulation0<-99
epopulation2<-99-etotal2
epopulation4<-99-etotal4
epopulation6<-99-etotal6
epopulation8<-99-etotal8
epopulation10<-99-etotal10

etrans1<-pcowclincure5+cowclincure5a
```

etrans2<-eptrans0*etrans1
etrans3<-etrans2*eptrans2
etrans4<-eptrans2*etrans1
etrans5<-eptrans4*etrans1
etrans6<-etrans4*eptrans4
etrans7<-etrans2*eptrans4
etrans8<-etrans3*eptrans4
etrans9<-eptrans6*etrans1
etrans10<-etrans5*eptrans6
etrans11<-etrans4*eptrans6
etrans12<-etrans6*eptrans6
etrans13<-etrans2*eptrans6
etrans14<-etrans7*eptrans6
etrans15<-etrans3*eptrans6
etrans16<-etrans8*eptrans6
etrans17<-eptrans8*etrans1
etrans18<-etrans9*eptrans8
etrans19<-etrans5*eptrans8
etrans20<-etrans10*eptrans8
etrans21<-etrans4*eptrans8
etrans22<-etrans11*eptrans8
etrans23<-etrans6*eptrans8
etrans24<-etrans12*eptrans8
etrans25<-etrans2*eptrans8
etrans26<-etrans13*eptrans8
etrans27<-etrans7*eptrans8
etrans28<-etrans14*eptrans8
etrans29<-etrans3*eptrans8
etrans30<-etrans15*eptrans8
etrans31<-etrans8*eptrans8
etrans32<-etrans16*eptrans8
etrans33<-eptrans10*etrans1
etrans34<-etrans17*eptrans10
etrans35<-etrans9*eptrans10
etrans36<-etrans18*eptrans10
etrans37<-etrans5*eptrans10
etrans38<-etrans19*eptrans10
etrans39<-etrans10*eptrans10
etrans40<-etrans20*eptrans10
etrans41<-etrans4*eptrans10
etrans42<-etrans21*eptrans10
etrans43<-etrans11*eptrans10
etrans44<-etrans22*eptrans10
etrans45<-etrans6*eptrans10
etrans46<-etrans23*eptrans10
etrans47<-etrans12*eptrans10
etrans48<-etrans24*eptrans10
etrans49<-etrans2*eptrans10
etrans50<-etrans25*eptrans10

```
etrans51<-etrans13*eptrans10
etrans52<-etrans26*eptrans10
etrans53<-etrans7*eptrans10
etrans54<-etrans27*eptrans10
etrans55<-etrans14*eptrans10
etrans56<-etrans28*eptrans10
etrans57<-etrans3*eptrans10
etrans58<-etrans29*eptrans10
etrans59<-etrans15*eptrans10
etrans60<-etrans30*eptrans10
etrans61<-etrans8*eptrans10
etrans62<-etrans31*eptrans10
etrans63<-etrans16*eptrans10
etrans64<-etrans32*eptrans10

etotal2<-etrans2
etotal4<-etotal2+etrans3+etrans4
etotal6<-etotal4+etrans5+etrans6+etrans7+etrans8
etotal8<-
etotal6+etrans9+etrans10+etrans11+etrans12+etrans13+etrans14+etran
s15+etrans16
etotal10<-
etotal8+etrans17+etrans18+etrans19+etrans20+etrans21+etrans22+etra
ns23+etrans24+etrans25+etrans26+etrans27+etrans28+etrans29+etran
s30+etrans31+etrans32
etotal12<-
etotal10+etrans33+etrans34+etrans35+etrans36+etrans37+etrans38+et
rans39+etrans40+etrans41+etrans42+etrans43+etrans44+etrans45+etra
ns46+etrans47+etrans48+etrans49+etrans50+etrans51+etrans52+etran
s53+etrans54+etrans55+etrans56+etrans57+etrans58+etrans59+etrans
60+etrans61+etrans62+etrans63+etrans64


#Transmission 1b

xptrans0<-trans0*(xpopulation0/100)
xptrans2<-xptrans0*(xpopulation2/100)
xptrans4<-xptrans0*(xpopulation4/100)
xptrans6<-xptrans0*(xpopulation6/100)
xptrans8<-xptrans0*(xpopulation8/100)
xptrans10<-xptrans0*(xpopulation10/100)

xpopulation0<-99
xpopulation2<-99-xtotal2
xpopulation4<-99-xtotal4
xpopulation6<-99-xtotal6
xpopulation8<-99-xtotal8
xpopulation10<-99-xtotal10
```

```
xtrans1<-cowclincure1b+cowclincure1c
xtrans2<-xptrans0*xtrans1
xtrans3<-xtrans2*xptrans2
xtrans4<-xptrans2*xtrans1
xtrans5<-xptrans4*xtrans1
xtrans6<-xtrans4*xptrans4
xtrans7<-xtrans2*xptrans4
xtrans8<-xtrans3*xptrans4
xtrans9<-xptrans6*xtrans1
xtrans10<-xtrans5*xptrans6
xtrans11<-xtrans4*xptrans6
xtrans12<-xtrans6*xptrans6
xtrans13<-xtrans2*xptrans6
xtrans14<-xtrans7*xptrans6
xtrans15<-xtrans3*xptrans6
xtrans16<-xtrans8*xptrans6
xtrans17<-xptrans8*xtrans1
xtrans18<-xtrans9*xptrans8
xtrans19<-xtrans5*xptrans8
xtrans20<-xtrans10*xptrans8
xtrans21<-xtrans4*xptrans8
xtrans22<-xtrans11*xptrans8
xtrans23<-xtrans6*xptrans8
xtrans24<-xtrans12*xptrans8
xtrans25<-xtrans2*xptrans8
xtrans26<-xtrans13*xptrans8
xtrans27<-xtrans7*xptrans8
xtrans28<-xtrans14*xptrans8
xtrans29<-xtrans3*xptrans8
xtrans30<-xtrans15*xptrans8
xtrans31<-xtrans8*xptrans8
xtrans32<-xtrans16*xptrans8
xtrans33<-xptrans10*xtrans1
xtrans34<-xtrans17*xptrans10
xtrans35<-xtrans9*xptrans10
xtrans36<-xtrans18*xptrans10
xtrans37<-xtrans5*xptrans10
xtrans38<-xtrans19*xptrans10
xtrans39<-xtrans10*xptrans10
xtrans40<-xtrans20*xptrans10
xtrans41<-xtrans4*xptrans10
xtrans42<-xtrans21*xptrans10
xtrans43<-xtrans11*xptrans10
xtrans44<-xtrans22*xptrans10
xtrans45<-xtrans6*xptrans10
xtrans46<-xtrans23*xptrans10
xtrans47<-xtrans12*xptrans10
xtrans48<-xtrans24*xptrans10
xtrans49<-xtrans2*xptrans10
```

```
xtrans50<-xtrans25*xptrans10
xtrans51<-xtrans13*xptrans10
xtrans52<-xtrans26*xptrans10
xtrans53<-xtrans7*xptrans10
xtrans54<-xtrans27*xptrans10
xtrans55<-xtrans14*xptrans10
xtrans56<-xtrans28*xptrans10
xtrans57<-xtrans3*xptrans10
xtrans58<-xtrans29*xptrans10
xtrans59<-xtrans15*xptrans10
xtrans60<-xtrans30*xptrans10
xtrans61<-xtrans8*xptrans10
xtrans62<-xtrans31*xptrans10
xtrans63<-xtrans16*xptrans10
xtrans64<-xtrans32*xptrans10

xtotal2<-xtrans2
xtotal4<-xtotal2+xtrans3+xtrans4
xtotal6<-xtotal4+xtrans5+xtrans6+xtrans7+xtrans8
xtotal8<-
xtotal6+xtrans9+xtrans10+xtrans11+xtrans12+xtrans13+xtrans14+xtran
s15+xtrans16
xtotal10<-
xtotal8+xtrans17+xtrans18+xtrans19+xtrans20+xtrans21+xtrans22+xtra
ns23+xtrans24+xtrans25+xtrans26+xtrans27+xtrans28+xtrans29+xtrans
30+xtrans31+xtrans32
xtotal12<-
xtotal10+xtrans33+xtrans34+xtrans35+xtrans36+xtrans37+xtrans38+xtr
ans39+xtrans40+xtrans41+xtrans42+xtrans43+xtrans44+xtrans45+xtra
ns46+xtrans47+xtrans48+xtrans49+xtrans50+xtrans51+xtrans52+xtrans
53+xtrans54+xtrans55+xtrans56+xtrans57+xtrans58+xtrans59+xtrans6
0+xtrans61+xtrans62+xtrans63+xtrans64

#Transmission 2b

yptrans0<-trans0*(ypopulation0/100)
yptrans2<-yptrans0*(ypopulation2/100)
yptrans4<-yptrans0*(ypopulation4/100)
yptrans6<-yptrans0*(ypopulation6/100)
yptrans8<-yptrans0*(ypopulation8/100)
yptrans10<-yptrans0*(ypopulation10/100)

ypopulation0<-99
ypopulation2<-99-ytotal2
ypopulation4<-99-ytotal4
ypopulation6<-99-ytotal6
ypopulation8<-99-ytotal8
ypopulation10<-99-ytotal10
```

ytrans1<-cowclincure2b+cowclincure2c
ytrans2<-yptrans0*ytrans1
ytrans3<-ytrans2*yptrans2
ytrans4<-yptrans2*ytrans1
ytrans5<-yptrans4*ytrans1
ytrans6<-ytrans4*yptrans4
ytrans7<-ytrans2*yptrans4
ytrans8<-ytrans3*yptrans4
ytrans9<-yptrans6*ytrans1
ytrans10<-ytrans5*yptrans6
ytrans11<-ytrans4*yptrans6
ytrans12<-ytrans6*yptrans6
ytrans13<-ytrans2*yptrans6
ytrans14<-ytrans7*yptrans6
ytrans15<-ytrans3*yptrans6
ytrans16<-ytrans8*yptrans6
ytrans17<-yptrans8*ytrans1
ytrans18<-ytrans9*yptrans8
ytrans19<-ytrans5*yptrans8
ytrans20<-ytrans10*yptrans8
ytrans21<-ytrans4*yptrans8
ytrans22<-ytrans11*yptrans8
ytrans23<-ytrans6*yptrans8
ytrans24<-ytrans12*yptrans8
ytrans25<-ytrans2*yptrans8
ytrans26<-ytrans13*yptrans8
ytrans27<-ytrans7*yptrans8
ytrans28<-ytrans14*yptrans8
ytrans29<-ytrans3*yptrans8
ytrans30<-ytrans15*yptrans8
ytrans31<-ytrans8*yptrans8
ytrans32<-ytrans16*yptrans8
ytrans33<-yptrans10*ytrans1
ytrans34<-ytrans17*yptrans10
ytrans35<-ytrans9*yptrans10
ytrans36<-ytrans18*yptrans10
ytrans37<-ytrans5*yptrans10
ytrans38<-ytrans19*yptrans10
ytrans39<-ytrans10*yptrans10
ytrans40<-ytrans20*yptrans10
ytrans41<-ytrans4*yptrans10
ytrans42<-ytrans21*yptrans10
ytrans43<-ytrans11*yptrans10
ytrans44<-ytrans22*yptrans10
ytrans45<-ytrans6*yptrans10
ytrans46<-ytrans23*yptrans10
ytrans47<-ytrans12*yptrans10
ytrans48<-ytrans24*yptrans10
ytrans49<-ytrans2*yptrans10

```
ytrans50<-ytrans25*yptrans10
ytrans51<-ytrans13*yptrans10
ytrans52<-ytrans26*yptrans10
ytrans53<-ytrans7*yptrans10
ytrans54<-ytrans27*yptrans10
ytrans55<-ytrans14*yptrans10
ytrans56<-ytrans28*yptrans10
ytrans57<-ytrans3*yptrans10
ytrans58<-ytrans29*yptrans10
ytrans59<-ytrans15*yptrans10
ytrans60<-ytrans30*yptrans10
ytrans61<-ytrans8*yptrans10
ytrans62<-ytrans31*yptrans10
ytrans63<-ytrans16*yptrans10
ytrans64<-ytrans32*yptrans10

ytotal2<-ytrans2
ytotal4<-ytotal2+ytrans3+ytrans4
ytotal6<-ytotal4+ytrans5+ytrans6+ytrans7+ytrans8
ytotal8<-
ytotal6+ytrans9+ytrans10+ytrans11+ytrans12+ytrans13+ytrans14+ytra
ns15+ytrans16
ytotal10<-
ytotal8+ytrans17+ytrans18+ytrans19+ytrans20+ytrans21+ytrans22+ytr
ans23+ytrans24+ytrans25+ytrans26+ytrans27+ytrans28+ytrans29+ytra
ns30+ytrans31+ytrans32
ytotal12<-
ytotal10+ytrans33+ytrans34+ytrans35+ytrans36+ytrans37+ytrans38+yt
rans39+ytrans40+ytrans41+ytrans42+ytrans43+ytrans44+ytrans45+ytr
ans46+ytrans47+ytrans48+ytrans49+ytrans50+ytrans51+ytrans52+ytra
ns53+ytrans54+ytrans55+ytrans56+ytrans57+ytrans58+ytrans59+ytran
s60+ytrans61+ytrans62+ytrans63+ytrans64

#Transmission 3b

zptrans0<-trans0*(zpopulation0/100)
zptrans2<-zptrans0*(zpopulation2/100)
zptrans4<-zptrans0*(zpopulation4/100)
zptrans6<-zptrans0*(zpopulation6/100)
zptrans8<-zptrans0*(zpopulation8/100)
zptrans10<-zptrans0*(zpopulation10/100)

zpopulation0<-99
zpopulation2<-99-ztotal2
zpopulation4<-99-ztotal4
zpopulation6<-99-ztotal6
zpopulation8<-99-ztotal8
zpopulation10<-99-ztotal10
```

```
ztrans1<-cowclincure3b+cowclincure3c
ztrans2<-zptrans0*ztrans1
ztrans3<-ztrans2*zptrans2
ztrans4<-zptrans2*ztrans1
ztrans5<-zptrans4*ztrans1
ztrans6<-ztrans4*zptrans4
ztrans7<-ztrans2*zptrans4
ztrans8<-ztrans3*zptrans4
ztrans9<-zptrans6*ztrans1
ztrans10<-ztrans5*zptrans6
ztrans11<-ztrans4*zptrans6
ztrans12<-ztrans6*zptrans6
ztrans13<-ztrans2*zptrans6
ztrans14<-ztrans7*zptrans6
ztrans15<-ztrans3*zptrans6
ztrans16<-ztrans8*zptrans6
ztrans17<-zptrans8*ztrans1
ztrans18<-ztrans9*zptrans8
ztrans19<-ztrans5*zptrans8
ztrans20<-ztrans10*zptrans8
ztrans21<-ztrans4*zptrans8
ztrans22<-ztrans11*zptrans8
ztrans23<-ztrans6*zptrans8
ztrans24<-ztrans12*zptrans8
ztrans25<-ztrans2*zptrans8
ztrans26<-ztrans13*zptrans8
ztrans27<-ztrans7*zptrans8
ztrans28<-ztrans14*zptrans8
ztrans29<-ztrans3*zptrans8
ztrans30<-ztrans15*zptrans8
ztrans31<-ztrans8*zptrans8
ztrans32<-ztrans16*zptrans8
ztrans33<-zptrans10*ztrans1
ztrans34<-ztrans17*zptrans10
ztrans35<-ztrans9*zptrans10
ztrans36<-ztrans18*zptrans10
ztrans37<-ztrans5*zptrans10
ztrans38<-ztrans19*zptrans10
ztrans39<-ztrans10*zptrans10
ztrans40<-ztrans20*zptrans10
ztrans41<-ztrans4*zptrans10
ztrans42<-ztrans21*zptrans10
ztrans43<-ztrans11*zptrans10
ztrans44<-ztrans22*zptrans10
ztrans45<-ztrans6*zptrans10
ztrans46<-ztrans23*zptrans10
ztrans47<-ztrans12*zptrans10
ztrans48<-ztrans24*zptrans10
ztrans49<-ztrans2*zptrans10
```

```
ztrans50<-ztrans25*zptrans10
ztrans51<-ztrans13*zptrans10
ztrans52<-ztrans26*zptrans10
ztrans53<-ztrans7*zptrans10
ztrans54<-ztrans27*zptrans10
ztrans55<-ztrans14*zptrans10
ztrans56<-ztrans28*zptrans10
ztrans57<-ztrans3*zptrans10
ztrans58<-ztrans29*zptrans10
ztrans59<-ztrans15*zptrans10
ztrans60<-ztrans30*zptrans10
ztrans61<-ztrans8*zptrans10
ztrans62<-ztrans31*zptrans10
ztrans63<-ztrans16*zptrans10
ztrans64<-ztrans32*zptrans10

ztotal2<-ztrans2
ztotal4<-ztotal2+ztrans3+ztrans4
ztotal6<-ztotal4+ztrans5+ztrans6+ztrans7+ztrans8
ztotal8<-
ztotal6+ztrans9+ztrans10+ztrans11+ztrans12+ztrans13+ztrans14+ztran
s15+ztrans16
ztotal10<-
ztotal8+ztrans17+ztrans18+ztrans19+ztrans20+ztrans21+ztrans22+ztra
ns23+ztrans24+ztrans25+ztrans26+ztrans27+ztrans28+ztrans29+ztrans
30+ztrans31+ztrans32
ztotal12<-
ztotal10+ztrans33+ztrans34+ztrans35+ztrans36+ztrans37+ztrans38+ztr
ans39+ztrans40+ztrans41+ztrans42+ztrans43+ztrans44+ztrans45+ztran
s46+ztrans47+ztrans48+ztrans49+ztrans50+ztrans51+ztrans52+ztrans5
3+ztrans54+ztrans55+ztrans56+ztrans57+ztrans58+ztrans59+ztrans60+
ztrans61+ztrans62+ztrans63+ztrans64

#Transmission 4b

rptrans0<-trans0*(rpopulation0/100)
rptrans2<-rptrans0*(rpopulation2/100)
rptrans4<-rptrans0*(rpopulation4/100)
rptrans6<-rptrans0*(rpopulation6/100)
rptrans8<-rptrans0*(rpopulation8/100)
rptrans10<-rptrans0*(rpopulation10/100)

rpopulation0<-99
rpopulation2<-99-rtotal2
rpopulation4<-99-rtotal4
rpopulation6<-99-rtotal6
rpopulation8<-99-rtotal8
rpopulation10<-99-rtotal10
```

rtrans1<-cowclincure4b+cowclincure4c
rtrans2<-rptrans0*rtrans1
rtrans3<-rtrans2*rptrans2
rtrans4<-rptrans2*rtrans1
rtrans5<-rptrans4*rtrans1
rtrans6<-rtrans4*rptrans4
rtrans7<-rtrans2*rptrans4
rtrans8<-rtrans3*rptrans4
rtrans9<-rptrans6*rtrans1
rtrans10<-rtrans5*rptrans6
rtrans11<-rtrans4*rptrans6
rtrans12<-rtrans6*rptrans6
rtrans13<-rtrans2*rptrans6
rtrans14<-rtrans7*rptrans6
rtrans15<-rtrans3*rptrans6
rtrans16<-rtrans8*rptrans6
rtrans17<-rptrans8*rtrans1
rtrans18<-rtrans9*rptrans8
rtrans19<-rtrans5*rptrans8
rtrans20<-rtrans10*rptrans8
rtrans21<-rtrans4*rptrans8
rtrans22<-rtrans11*rptrans8
rtrans23<-rtrans6*rptrans8
rtrans24<-rtrans12*rptrans8
rtrans25<-rtrans2*rptrans8
rtrans26<-rtrans13*rptrans8
rtrans27<-rtrans7*rptrans8
rtrans28<-rtrans14*rptrans8
rtrans29<-rtrans3*rptrans8
rtrans30<-rtrans15*rptrans8
rtrans31<-rtrans8*rptrans8
rtrans32<-rtrans16*rptrans8
rtrans33<-rptrans10*rtrans1
rtrans34<-rtrans17*rptrans10
rtrans35<-rtrans9*rptrans10
rtrans36<-rtrans18*rptrans10
rtrans37<-rtrans5*rptrans10
rtrans38<-rtrans19*rptrans10
rtrans39<-rtrans10*rptrans10
rtrans40<-rtrans20*rptrans10
rtrans41<-rtrans4*rptrans10
rtrans42<-rtrans21*rptrans10
rtrans43<-rtrans11*rptrans10
rtrans44<-rtrans22*rptrans10
rtrans45<-rtrans6*rptrans10
rtrans46<-rtrans23*rptrans10
rtrans47<-rtrans12*rptrans10
rtrans48<-rtrans24*rptrans10
rtrans49<-rtrans2*rptrans10

```
rtrans50<-rtrans25*rptrans10
rtrans51<-rtrans13*rptrans10
rtrans52<-rtrans26*rptrans10
rtrans53<-rtrans7*rptrans10
rtrans54<-rtrans27*rptrans10
rtrans55<-rtrans14*rptrans10
rtrans56<-rtrans28*rptrans10
rtrans57<-rtrans3*rptrans10
rtrans58<-rtrans29*rptrans10
rtrans59<-rtrans15*rptrans10
rtrans60<-rtrans30*rptrans10
rtrans61<-rtrans8*rptrans10
rtrans62<-rtrans31*rptrans10
rtrans63<-rtrans16*rptrans10
rtrans64<-rtrans32*rptrans10

rtotal2<-rtrans2
rtotal4<-rtotal2+rtrans3+rtrans4
rtotal6<-rtotal4+rtrans5+rtrans6+rtrans7+rtrans8
rtotal8<-
rtotal6+rtrans9+rtrans10+rtrans11+rtrans12+rtrans13+rtrans14+rtrans
15+rtrans16
rtotal10<-
rtotal8+rtrans17+rtrans18+rtrans19+rtrans20+rtrans21+rtrans22+rtran
s23+rtrans24+rtrans25+rtrans26+rtrans27+rtrans28+rtrans29+rtrans3
0+rtrans31+rtrans32
rtotal12<-
rtotal10+rtrans33+rtrans34+rtrans35+rtrans36+rtrans37+rtrans38+rtra
ns39+rtrans40+rtrans41+rtrans42+rtrans43+rtrans44+rtrans45+rtrans
46+rtrans47+rtrans48+rtrans49+rtrans50+rtrans51+rtrans52+rtrans53
+rtrans54+rtrans55+rtrans56+rtrans57+rtrans58+rtrans59+rtrans60+rt
rans61+rtrans62+rtrans63+rtrans64

#Transmission 5b

gptrans0<-trans0*(gpopulation0/100)
gptrans2<-gptrans0*(gpopulation2/100)
gptrans4<-gptrans0*(gpopulation4/100)
gptrans6<-gptrans0*(gpopulation6/100)
gptrans8<-gptrans0*(gpopulation8/100)
gptrans10<-gptrans0*(gpopulation10/100)

gpopulation0<-99
gpopulation2<-99-gtotal2
gpopulation4<-99-gtotal4
gpopulation6<-99-gtotal6
gpopulation8<-99-gtotal8
gpopulation10<-99-gtotal10
```

gtrans1<-cowclincure5b+cowclincure5c
gtrans2<-gptrans0*gtrans1
gtrans3<-gtrans2*gptrans2
gtrans4<-gptrans2*gtrans1
gtrans5<-gptrans4*gtrans1
gtrans6<-gtrans4*gptrans4
gtrans7<-gtrans2*gptrans4
gtrans8<-gtrans3*gptrans4
gtrans9<-gptrans6*gtrans1
gtrans10<-gtrans5*gptrans6
gtrans11<-gtrans4*gptrans6
gtrans12<-gtrans6*gptrans6
gtrans13<-gtrans2*gptrans6
gtrans14<-gtrans7*gptrans6
gtrans15<-gtrans3*gptrans6
gtrans16<-gtrans8*gptrans6
gtrans17<-gptrans8*gtrans1
gtrans18<-gtrans9*gptrans8
gtrans19<-gtrans5*gptrans8
gtrans20<-gtrans10*gptrans8
gtrans21<-gtrans4*gptrans8
gtrans22<-gtrans11*gptrans8
gtrans23<-gtrans6*gptrans8
gtrans24<-gtrans12*gptrans8
gtrans25<-gtrans2*gptrans8
gtrans26<-gtrans13*gptrans8
gtrans27<-gtrans7*gptrans8
gtrans28<-gtrans14*gptrans8
gtrans29<-gtrans3*gptrans8
gtrans30<-gtrans15*gptrans8
gtrans31<-gtrans8*gptrans8
gtrans32<-gtrans16*gptrans8
gtrans33<-gptrans10*gtrans1
gtrans34<-gtrans17*gptrans10
gtrans35<-gtrans9*gptrans10
gtrans36<-gtrans18*gptrans10
gtrans37<-gtrans5*gptrans10
gtrans38<-gtrans19*gptrans10
gtrans39<-gtrans10*gptrans10
gtrans40<-gtrans20*gptrans10
gtrans41<-gtrans4*gptrans10
gtrans42<-gtrans21*gptrans10
gtrans43<-gtrans11*gptrans10
gtrans44<-gtrans22*gptrans10
gtrans45<-gtrans6*gptrans10
gtrans46<-gtrans23*gptrans10
gtrans47<-gtrans12*gptrans10
gtrans48<-gtrans24*gptrans10
gtrans49<-gtrans2*gptrans10

```
gtrans50<-gtrans25*gptrans10
gtrans51<-gtrans13*gptrans10
gtrans52<-gtrans26*gptrans10
gtrans53<-gtrans7*gptrans10
gtrans54<-gtrans27*gptrans10
gtrans55<-gtrans14*gptrans10
gtrans56<-gtrans28*gptrans10
gtrans57<-gtrans3*gptrans10
gtrans58<-gtrans29*gptrans10
gtrans59<-gtrans15*gptrans10
gtrans60<-gtrans30*gptrans10
gtrans61<-gtrans8*gptrans10
gtrans62<-gtrans31*gptrans10
gtrans63<-gtrans16*gptrans10
gtrans64<-gtrans32*gptrans10

gtotal2<-gtrans2
gtotal4<-gtotal2+gtrans3+gtrans4
gtotal6<-gtotal4+gtrans5+gtrans6+gtrans7+gtrans8
gtotal8<-
gtotal6+gtrans9+gtrans10+gtrans11+gtrans12+gtrans13+gtrans14+gtran
s15+gtrans16
gtotal10<-
gtotal8+gtrans17+gtrans18+gtrans19+gtrans20+gtrans21+gtrans22+gtra
ns23+gtrans24+gtrans25+gtrans26+gtrans27+gtrans28+gtrans29+gtran
s30+gtrans31+gtrans32
gtotal12<-
gtotal10+gtrans33+gtrans34+gtrans35+gtrans36+gtrans37+gtrans38+gt
rans39+gtrans40+gtrans41+gtrans42+gtrans43+gtrans44+gtrans45+gtra
ns46+gtrans47+gtrans48+gtrans49+gtrans50+gtrans51+gtrans52+gtran
s53+gtrans54+gtrans55+gtrans56+gtrans57+gtrans58+gtrans59+gtrans
60+gtrans61+gtrans62+gtrans63+gtrans64

totalcosts1<-
cull1acosts+endlactcosts1a+xcostcull1c+xcostofendlactation1c+ycostofen
dlactation1c+ycostcull1c+cull1bcosts+endlactcosts1b+costofdeath1+cost
ofdryoffsurvive1+costofdryoffcull1+costofcull1d+endlactcost1d+xcostcul
l1d+xcostofendlactation1d+ycostcull1d+ycostofendlactation1d+cull1ecos
ts+endlactcosts1e+costofdeath1c+costofdryoffsurvive1c+costofdryoffcull
1c+costofcull1f+endlactcost1f+cull1hcosts+cull1gcosts

totalcosts2<-
cull2acosts+endlactcosts2a+xcostcull2c+xcostofendlactation2c+ycostofen
dlactation2c+ycostcull2c+cull2bcosts+endlactcosts2b+costofdeath2+cost
ofdryoffsurvive2+costofdryoffcull2+costofcull2d+endlactcost2d+xcostcul
l2d+xcostofendlactation2d+ycostcull2d+ycostofendlactation2d+cull2ecos
ts+endlactcosts2e+costofdeath2c+costofdryoffsurvive2c+costofdryoffcull
2c+costofcull2f+endlactcost2f+cull2hcosts+cull2gcosts
```

```
totalcosts3<-
cull3acosts+endlactcosts3a+xcostcull3c+xcostofendlactation3c+ycostofen
dlactation3c+ycostcull3c+cull3bcosts+endlactcosts3b+costofdeath3+cost
ofdryoffsurvive3+costofdryoffcull3+costofcull3d+endlactcost3d+xcostcul
l3d+xcostofendlactation3d+ycostcull3d+ycostofendlactation3d+cull3ecos
ts+endlactcosts3e+costofdeath3c+costofdryoffsurvive3c+costofdryoffcull
3c+costofcull3f+endlactcost3f+cull3hcosts+cull3gcosts

totalcosts4<-
cull4acosts+endlactcosts4a+xcostcull4c+xcostofendlactation4c+ycostofen
dlactation4c+ycostcull4c+cull4bcosts+endlactcosts4b+costofdeath4+cost
ofdryoffsurvive4+costofdryoffcull4+costofcull4d+endlactcost4d+xcostcul
l4d+xcostofendlactation4d+ycostcull4d+ycostofendlactation4d+cull4ecos
ts+endlactcosts4e+costofdeath4c+costofdryoffsurvive4c+costofdryoffcull
4c+costofcull4f+endlactcost4f+cull4hcosts+cull4gcosts

totalcosts5<-
cull5acosts+endlactcosts5a+xcostcull5c+xcostofendlactation5c+ycostofen
dlactation5c+ycostcull5c+cull5bcosts+endlactcosts5b+costofdeath5+cost
ofdryoffsurvive5+costofdryoffcull5+costofcull5d+endlactcost5d+xcostcul
l5d+xcostofendlactation5d+ycostcull5d+ycostofendlactation5d+cull5ecos
ts+endlactcosts5e+costofdeath5c+costofdryoffsurvive5c+costofdryoffcull
5c+costofcull5f+endlactcost5f+cull5hcosts+cull5gcosts

totalcostplustransmission1<-totalcosts1+(totalcosts1*(total12+xtotal12))

totalcostplustransmission2<-
totalcosts2+(totalcosts2*(btotal12+ytotal12))

totalcostplustransmission3<-
totalcosts3+(totalcosts3*(ctotal12+ztotal12))

totalcostplustransmission4<-
totalcosts4+(totalcosts4*(dtotal12+rtotal12))

totalcostplustransmission5<-
totalcosts5+(totalcosts5*(etotal12+gtotal12))

}
```

Appendix 2

Example of WinBUGS code for cost-effectiveness model from Chapter 5

```
#----MODEL Definition----------

model
{
# Level 1 definition
for(i in 1:N) {
CMDPx[i] ~ dnorm(mu[i],tau)
mu[i]<- a[i] + b[i] + c[i]

a[i]<- beta[1] * cons[i]
+ beta[2] * D0.CMDP12MR[i]    #Day 0 CMDP rate
+ beta[3] * v7220i_1[i]        #DC cubicles cleaned twice daily
+ beta[4] * v7220i_2[i]
+ beta[5] * v7620i_1[i]        #DC rations formulated by qualified nutritionist
+ beta[6] * v7620i_2[i]
+ beta[7] * v7860i_1[i]        #DCT selected at cow level
+ beta[8] * v7860i_2[i]
+ beta[9] * v7880i_1[i]        #AB and non-AB DCT considered for low scc cows
+ beta[10] * v7880i_2[i]
+ beta[11] * v8015i_1[i]       #Cows calve in individual calving pens
b[i]<- beta[12] * v8015i_2[i]
+ beta[13] * v8135i_1[i]       #Straw yards should be completely mucked out at least
monthly
+ beta[14] * v8135i_2[i]
+ beta[15] * v8715i_1[i]       #Calves must only be allowed to suckle their own dam
+ beta[16] * v8715i_2[i]
+ beta[17] * v7815i_1[i]
+ beta[18] * v7815i_2[i]
+ beta[19] * v8735i_1[i]       #Cows should be first milked within 24hrs of calving
+ beta[20] * v8735i_2[i]
+ beta[21] * v7640i_1[i]
c[i]<- beta[22] * v7640i_2[i]
+ beta[23] * v7680i_1[i]       #Calcium and Magnesium should be balanced to
prevent MF
+ beta[24] * v7680i_2[i]
+ beta[25] * v7171i_1[i]       #Cubilces should be designed so >90% cows lie in
them right
+ beta[26] * v7171i_2[i]
+ beta[27] * v7310i_1[i]
+ beta[28] * v7310i_2[i]
+ beta[29] * v7830i_1[i]       #Cows must not be dried off whilst foot trimming
+ beta[30] * v7830i_2[i]
+ beta[31] * v7355i_1[i]
+ beta[32] * v7355i_2[i]
+ beta[33] * v7225i_1[i]       #Clean bedding should be applied at least daily (DC)
+ beta[34] * v7225i_2[i]
+ beta[35] * v7115i_1[i]       #Max no. days cows dried off before calving <70
+ beta[36] * v7115i_2[i]
+ beta[37] * graze_2_rest_4_1[i]      #G2R4
+ beta[38] * graze_2_rest_4_2[i]

}
```

```
# Higher level definitions
# Priors for fixed effects
for (k in 1:38) { beta[k] ~ dflat() }
# Priors for random terms
tau ~ dgamma(0.001000,0.001000)
sigma2 <- 1/tau

for (j in 1: P) {

cmcost[j] ~ dnorm(313, 0.00009803)I(0, )     #cost of a case of CM (Green et al 2009)

#cost benefit analysis of cleaning cubicles twice daily
cleancubicleseffect[j] <- y[j] * (beta[3]/100)   #predicted effect of clean cubicles on
CMDP
cleancubiclescost1[j] <- 250              #cost of using instslling calving pens (£)
cleancubiclescost2[j] <- 500
cleancubiclescost3[j] <- 750
cleancubiclescost4[j] <- 1000
cleancubiclessaving[j] <- (cmcost[j] * cleancubicleseffect[j]) * 10   #Savings made/yr
for 120 cow herd
inbCLEANCUBICLES1[j] <- cleancubiclessaving[j] + cleancubiclescost1[j]   #INB (£)
inbCLEANCUBICLES2[j] <- cleancubiclessaving[j] + cleancubiclescost2[j]
inbCLEANCUBICLES3[j] <- cleancubiclessaving[j] + cleancubiclescost3[j]
inbCLEANCUBICLES4[j] <- cleancubiclessaving[j] + cleancubiclescost4[j]
p500.cleancubicles1[j]<-step(-(inbCLEANCUBICLES1[j]+500))       #probability of
saving £500 after 1 year
p500.cleancubicles2[j]<-step(-(inbCLEANCUBICLES2[j]+500))
p500.cleancubicles3[j]<-step(-(inbCLEANCUBICLES3[j]+500))
p500.cleancubicles4[j]<-step(-(inbCLEANCUBICLES4[j]+500))
p1000.cleancubicles1[j]<-step(-(inbCLEANCUBICLES1[j]+1000))
p1000.cleancubicles2[j]<-step(-(inbCLEANCUBICLES2[j]+1000))
p1000.cleancubicles3[j]<-step(-(inbCLEANCUBICLES3[j]+1000))
p1000.cleancubicles4[j]<-step(-(inbCLEANCUBICLES4[j]+1000))

#cost benefit analysis of ration
rationeffect[j] <- y[j] * (beta[5]/100)            #predicted effect of ration on CMDP
rationcost1[j] <- 250                              #cost of ration (£)
rationcost2[j] <- 500
rationcost3[j] <- 1000
rationcost4[j] <- 2000
rationsaving[j] <- (cmcost[j] * rationeffect[j]) * 10   #Savings made/yr for 120 cow herd
inbRATION1[j] <- rationsaving[j] + rationcost1[j]                    #INB (£)
inbRATION2[j] <- rationsaving[j] + rationcost2[j]                    #INB (£)
inbRATION3[j] <- rationsaving[j] + rationcost3[j]                    #INB (£) (
inbRATION4[j] <- rationsaving[j] + rationcost4[j]                    #INB (£) (negative
means saving money)
p1000.ration1[j]<-step(-(inbRATION1[j]+1000)) #probability of saving £1000 after 1
year
p1000.ration2[j]<-step(-(inbRATION2[j]+1000))
p1000.ration3[j]<-step(-(inbRATION3[j]+1000))
p1000.ration4[j]<-step(-(inbRATION4[j]+1000))


}
```

Appendix 3

EDP Interventions investigated in Chapter 5

Alleyways, loafing and feed areas should be scraped at least twice daily. (dry cows)

Straw yards should be cleaned out completely at least once per month. (dry cows)

As a general principle the environment of dry cows should be managed at least as well as for milking cows.

There should be a bedded lying area of 1.25sq.m. Per 1000 litres of milk per cow (herd annual milk yield) (dry cows)

Calves must only be allowed to suckle their own mother to prevent the possible transfer of pathogens in milk between cows.

Alleyways, loafing and feed areas should be scraped at least twice daily. (calving cows)

Straw yards should be cleaned out completely at least once per month. (calving cows)

New, clean, dry straw should be put in yards or pens at least once daily. (calving cows)

You must monitor indices describing udder health in conjunction with the attending veterinary surgeon.

Dry cow therapy must be administered hygienically, as detailed in the standard operating procedure provided with the training materials.

Cows are sometimes or always dried off during the milking process.

Cows must be observed for signs of disease at least every 6 hours for the first 24hrs, to ensure early detection of mastitis (or any other disease).

New clean, dry straw should be put in the yards at least once daily. (dry cows)

Cows sometimes have access to the same lying area (e.g. Loafing paddock, paddock near the farm or sheltered area) for more than two continuous weeks. (dry cows)

At least 250kg of straw per cow should be used to bed cows per month housed (~1.5 tonnes straw per dry cow per winter). (dry cows)

Cows are sometimes on the same pasture, paddock or field for two or more weeks. (dry cows)

There should be 15sq.m. Per cow, whether cows calve in pens or yards.

You must monitor mastitis indices at least every three months.

If limited space is available, priority should be given to the space allowances for transition cows and bedding frequency should be increased. (dry cows)

Heifers must be kept in clean, dry environmental conditions at all times.

Calves must be fed 3 litres colostrum in the first 6 hours of life to minimize the risk of general disease.

Milk yield should be reduced to less than 15 litres by the time of drying off, and preferably to less than 10 litres.

You should monitor mastitis indices on a monthly basis.

Mixing maiden heifers and dry cows should be avoided since this has been associated with an increased risk of mastitis after calving.

Clean bedding material should be applied at least once daily for organic bedding. (dry cows)

An aseptic milk sample must be collected from every case of clinical mastitis.

Cows sometimes return to a grazing, loafing or rest area within 4 weeks after it has last been used by cattle. (dry cows)

An aseptic treatment procedure and partial insertion of the intramammary tube into the teat end must be used (as for dry cow therapy administration).

Cows should be milked for the first time within 24 hours of calving.

The success of mastitis treatments must be monitored (in consultation with the attending veterinary surgeon) by monitoring cow scc in the months after treatment.

Cows should be dried off in the parlour, (but not during milking) since this gives best access for udder preparation.

Dry cow therapy should be selected at the cow level (a suitable product for each cow) in consultation with the attending veterinary surgeon.

Both antibiotic and non-antibiotic approaches should be considered for low scc cows.

Pens must be cleaned out between each cow calving.

Each quarter should be stripped within 4 hours of calving to check for mastitis.

There should be a separate transition cow group from approximately 3 weeks before calving.

Clinical mastitis incidence per quarter and per cow (indices to monitor)

Dung, soiling and wet bedding should be removed at least twice per day from dry cow cubicles. (dry cows)

Sometimes cows have to share calving pens or there are insufficient pens to allow them to be cleaned out between calvings.

There should be water trough space of >10cm per cow for all cows at all stages of the production cycle, including availability in the yards before and after milking.

Quarters must be fore-milked at each milking to look for milk changes (clots, watery, changes in colour).

You must move to a different field or move feeders if severe poaching of the land and/or gateways occurs. (dry cows)

There must be good ventilation, but without draughts in all dry cow housing.

New, clean sand should be put in yards or pens at least daily (aim to get cows onto a straw bed during calving).

A minimum of 10 milk samples must be cultured and the incidence of specific pathogens monitored in conjunction with a veterinary advisor.

Responses to treatment. (indices to monitor)

Drying off must be abrupt; that is, cows should not be milked once daily.

The calf should be removed from the cow within 24 hrs of birth after ensuring colostrum has been fed.

The high scc cow decision support tool should be used in consultation with the attending veterinary surgeon to decide the best course of action for each cow.

Drying agents should be used to improve the dryness of the cubicle beds. (dry cows)

All early dry period cows should have an appropriate dry cow mineral supplement.

In-line filters (if present) must be checked after each cow is milked.

There must be at least 2sq.m. loafing space/cow. (dry cows)

Inorganic bedding materials should be used wherever possible. (dry cows)

Surface flooding or severe poaching sometimes occurs at pasture. (dry cows)

A cmt (california mastitis test) test should be carried out on all quarters of each cow within 7 days of calving.

You should never exceed a stocking density of 100 cows/acre/day in a two week period. (dry cows)

Vitamin E - 1200 iu /cow/day (dry cows)

Heifers must have clean legs, udders and tails at all times.

All clinical cases of mastitis must be treated with antibiotics.

Significant pooling of liquid in housing, feeding and/or loafing areas occurs.

Straw, sawdust or paper products should be stored under a waterproof cover and kept dry at all times.

You should consider an extended antibiotic therapy regime. (treatment of high scc cows)

There should be at least 0.6m feedspace per cow in total for access to forage, concentrate or complete diet portions of the cows' feed. (dry cows)

There must be good ventilation but without draughts in all calving cow housing.

Calcium and magnesium should be balanced to prevent milk fever, whether calcium restriction or DCAB manipulation are used.

Cows with milk yields that have dropped below 5 litres should be dried off immediately.

Pre-milking teat disinfection must be carried out.

You should take a pre-treatment sample. (treatment of high scc cows)

20 to 30 seconds must elapse after application of pre-milking teat disinfection, before teats are dried.

There should be a brisket board in the cubicles at a distance of approximately 75% of the cubicle length (1.82m) to ensure that at least 90% of the dry cows dung into the passageway. (dry cows)

Cows should calve in individual pens rather than yards.

The yards or pens should have a base with sand on top of hardcore or concrete. (calving cows)

However many of the following items are performed, they must be done in this order: wash and dry teats, foremilk, pre-milking teat disinfection, dry teats with individual towels.

A CMT should be used to assess milk from quarters when in doubt over the presence of mastitis.

A J5 vaccination protocol could be used if the herd is suffering from uncontrollable severe coliform mastitis.

You should differentiate infected from uninfected cows using scc records from the current lactation.

The base of the straw yard should have excellent drainage, possibly with sand on top of hardcore or concrete. (dry cows)

There must be good ventilation, but without draughts in all milking cow housing.

Each quarter must be foremilked to detect mastitis.

Sufficient bedding should be used to keep surface conditions dry but also to retain cow comfort. (dry cows)

There should be at least 3sq.m. Per cow. (dry cows)

Individual cow somatic cell counts and trends. (indices to monitor)

Collecting yards must be scraped before or after every milking.

Dry cow rations should be formulated by a suitably qualified nutritional advisor.

All cases of clinical mastitis must be recorded according to a defined protocol.

Concrete floors must be grooved where and floors must be non-slip in all areas. (calving cows)

A non- steroidal anti-inflammatory drug should be used. (treatment of grade 2 cases)

Exit to parlour must be stress-free (no operator pressure or poor design features such as excessive slopes or bends).

Bedding should be spread evenly. (dry cows)

Ideally the dry period should be between 42 and 70 days in length.

Cubicles should be designed such that at least 90% of dry cows will lie in them correctly at all times. (dry cows)

The milking staff must assess cows for dullness, depression, anorexia.

Cows must not be dried off when foot-trimming.

Ideally the dry period should be between 42 and 70 days in length.

New bedding should be spread evenly. (calving cows)

Appendix 4

EL Interventions investigated in Chapter 6

Liners must be changed at least every 2500 milkings or 6 monthly (whichever occurs first) - unless the manufacturer specifies otherwise.

Clusters must be applied within 1 minute of the end of teat preparation.

There should be less than 5% of cows with moderate/severe teat end damage (hyperkeratosis).

An aseptic milk sample must be collected from every case of clinical mastitis.

Collecting yards must be scraped before or after every milking.

Each quarter must be foremilked to detect mastitis.

A six monthly machine test must be carried out by an independent, suitably qualified technician to ISO standard.

However many of the following items are performed, they must be done in this order: wash and dry teats, foremilk, pre-milking teat disinfection, dry teats with individual towels.

Quarters must be fore-milked at each milking to look for milk changes (clots, watery, changes in colour).

Pre-milking teat disinfection must be carried out.

An aseptic treatment procedure and partial insertion of the intramammary tube into the teat end must be used (as for dry cow therapy administration).

Cows with clinical mastitis and high scc must be milked last to stop the spread of infection to other cows.

20 to 30 seconds must elapse after application of pre-milking teat disinfection, before teats are dried.

There should be water trough space of >10cm per cow for all cows at all stages of the production cycle, including availability in the yards before and after milking.

There must be a clean yard on exit, which is scraped before and during milking if necessary.

You must monitor mastitis indices at least every three months.

You must monitor indices describing udder health in conjunction with the attending veterinary surgeon.

The clusters must be squarely aligned and balanced centrally under all cows.

Hot disinfectant should be used to clean clusters that become dirty during milking.

You should avoid returning cows to any one grazing, loafing or rest area for at least 4 weeks after it has been used by cattle. (milking cows)

Hot disinfectant must be used to wash clusters after milking a cow with clinical mastitis or a high somatic cell count, whether or not a separate cluster is used and, where possible, the plant back to the recording jar/meter must also be back-flushed with hot disinfectant.

The routine should take around 1 minute from start of preparation to putting units on.

Calves must be fed 3 litres colostrum in the first 6 hours of life to minimize the risk of general disease.

Damp bales should be discarded or at least used for the animals at lowest risk, such as youngstock.

Dump clusters/lines/buckets should be tested as a part of the plant assessment and included in a dynamic test.

Alleyways, loafing and feeding areas must be scraped out at least twice daily. (milking cows)

The success of mastitis treatments must be monitored (in consultation with the attending veterinary surgeon) by monitoring cow scc in the months after treatment.

There must be good ventilation, but without draughts in all milking cow housing.

There should be sufficient grip and grooving of concrete in all areas to prevent the risk of slipping and injury.

You should avoid letting cows have access to any one lying area (for example loafing paddocks near to the farm or sheltered areas) for more than two continuous weeks. (milking cows)

Dump bucket/line cluster liners must be changed when parlour liners are changed – and should be changed more frequently if necessary.

You should actively manage gateways/walkways by using bark, hardcore, shavings etc to minimize the risk of poaching. (milking cows)

A minimum of 10 milk samples must be cultured and the incidence of specific pathogens monitored in conjunction with a veterinary advisor.

All high scc cows (as a guide >200,000 cells/ml for two of the last three months) should be clearly marked (using tail tape, leg bands, sprays etc), so that care can be taken to avoid their milk contaminating hands or other cows through splashes or aerosols.

As a second best to the above, cows with clinical mastitis and high somatic cell counts should at least be milked with a separate cluster (this cluster should not be used to milk fresh calved cows or cows with milk out of the tank for reasons other than mastitis).

All wet areas must be dried with clean paper/laundered towel, with one clean / fresh part used per teat.

Straw, sawdust or paper products should be stored under a waterproof cover and kept dry at all times.

A rapid kill disinfection product must be used. (pre-milking teat disinfection)

Straw yards should be cleaned out completely at least once per month. (milking cows)

The acr removal flow rate should be checked at six monthly intervals by a suitably trained technician.

A wash with hot water and disinfectant should be carried out after every milking.

When a house is re-bedded after cleaning out, the environment must be totally clean, preferably disinfected and copious amounts of bedding used to ensure the cows do not become dirty. (milking cows)

There should be a bedded lying area of 1.25 sq.m. Per 1000 litres of milk per cow (herd annual milk yield). For example, an 8,000 litre cow needs

approximately 10 sq.m., whilst a 10,000 litre cow needs 12.5 sq.m. (milking cows)

You should rotate the use of routes and gateways wherever possible should poaching occur. (milking cows)

Cases which are doubtful but that have an increased cmt reading (or conductivity) must be treated.

You should group cows with a high scc and cows with clinical cases of mastitis separately to the main herd and milk them last at each milking.

Cows should always have access to water (not be denied access for more than 1 hour in a 24 hour period).

Clean bedding material must be applied at least once daily for organic bedding. (milking cows)

Significant pooling of liquid in housing, feeding and/or loafing areas occurs.

Clinical mastitis incidence per quarter and per cow (indices to monitor)

All clinical cases of mastitis must be treated with antibiotics.

You should monitor mastitis indices on a monthly basis.

If limited space is available, priority should be given to the space allowances for the high yielding cows and bedding frequency should be increased.

The high scc cow decision support tool should be used in consultation with the attending veterinary surgeon to decide the best course of action for each cow.

The milking machine should be washed with hot water and a full disinfection cycle, following the manufacturers recommendations, after every milking.

Responses to treatment. (indices to monitor)

You should avoid having cows on the same pasture, paddock or field for more than two continuous weeks. (milking cows)

Significant poaching of pastures, gateways, walkways, shelter or feed areas sometimes occurs.

Air bleed holes must remain open and clear throughout the milking process.

You must maintain excellent housing conditions (as for winter) if cows have access to housed lying areas during the grazing months. (milking cows)

Sufficient bedding must be used to keep surface conditions dry and also retain cow comfort. (milking cows)

You must show due diligence with milk withdrawal when using off-label products by using the standard milk withdrawal period (at least 7 days) and then also testing the milk to ensure freedom from antibiotic residues before allowing it back into the bulk tank.

Fresh food should be provided after each milking to encourage the cows to stand for >30 minutes after milking and to prevent access to the lying area.

The herd should have a written farm policy for biosecurity made in consultation with the attending veterinary surgeon.

As a second best measure, you should at least group cows with clinical mastitis separately to the main herd.

Hands and gloves should be washed and dried during milking if they become dirty.

A CMT should be used to assess milk from quarters when in doubt over the presence of mastitis.

Cows must not be over-milked.

Cows are sometimes on the same pasture, paddock or field for two or more weeks. (dry cows)

There should be well designed yards and alleys that minimise the risk of slipping and injury.

The herd should be closed, with barriers to outside animals and people.

You must move to a different field if severe poaching of the land and/or gateways occurs. (milking cows)

A static and dynamic machine test must be performed by an independent qualified technician if a new parlour or extension is fitted.

You must ensure good fly control for all lactating cows and heifers through the summer period when flies are expected or apparent.

You should take a pre-treatment sample. (treatment of high scc cows)

Cows sometimes have to wait more than one hour to be milked.

Drying agents could be used to improve the dryness of cubicle beds, but they are not clinically proven to reduce mastitis. (milking cows)

The base of the straw yard should have excellent drainage, possibly with sand on top of hardcore or concrete. (milking cows)

There should be at least 0.6m feedspace per cow in total for access to forage, concentrate or complete diet portions of the cows' feed. (milking cows)

The straw for bedding should be unchopped. (milking cows)

Dry straw only should be harvested or purchased. Prior to bedding, straw should contain no more than 15% moisture and this can be checked using a moisture meter if in doubt.

If teats are dirty they must be washed up to base of the udder with warm potable water.

In-line filters (if present) must be checked after each cow is milked.

Inorganic bedding materials should be used wherever possible. (milking cows)

You could use ‘off-label’ approaches to treatment in consultation with the attending veterinary surgeon.

Clusters that become dirty during milking must be washed using potable (ie water of drinking quality) water.

The scrapers must work sufficiently often to keep alleyways clean. (milking cows)

There must be access to ad lib water in the post milking yard.

Affected quarters must be stripped out thoroughly.

Selenium - 3.6 mg /cow/day (dry cows)

There should be 5% more cubicles than cows for each group. (milking cows)

There should be a brisket board in the cubicles at a distance of approximately 75% of the cubicle length (but should be adjustable) to

ensure that at least 90% of the cows dung into the passageway. (milking cows)

The milking staff must assess cows for dullness, depression, anorexia.

Foremilking should be into a strip cup or carried out with great care to avoid the spread of infection.

A non- steroidal anti-inflammatory drug should used. (treatment of grade 3 cases)

Cubicle partitions must be safe and in good condition and unlikely to cause teat or udder injury. (milking cows)

You must have sufficient pasture drainage to never allow surface flooding or severe poaching. (milking cows)

Water troughs must not be sited in the bedded area, and must be surrounded by a clean, well-drained surface in the loafing or feed areas. (milking cows)

New, clean, dry straw should be put in yards or pens at least once daily. (calving cows)

Pre-milking teat disinfection should be applied with a cup rather than a spray.

Copper 11 mg/kg dm in diet (milking cows)

Dogs should not be used to move cows, when cows are housed.

A non- steroidal anti-inflammatory drug should be used. (treatment of grade 2 cases)

There should be less than 5% of cows with liner slip.

At least 250kg of straw per cow should be used to bed cows per month housed (approximately 1.5 tonnes straw per milking cow per winter). (milking cows)

Some cows show signs of discomfort during milking.

The cow must be cmt negative for 3 consecutive days if purchased in early lactation. (cows being bought)

cubicles should be designed such that at least 90% cows will lie in them correctly, at all times. (milking cows)

Alleyways, loafing and feed areas should be scraped at least twice daily. (dry cows)

In general, the highest flow rate acr setting at removal should be used that allows effective milk out, to minimize the time clusters are on the cows.

Cows sometimes have access to the same lying area (e.g. Loafing paddock, paddock near the farm or sheltered area) for more than two continuous weeks. (dry cows)

There must be a minimum of at least 2sq.m./cow. (loafing space for milking cows)

The milking staff must look at/feel the udder for signs of inflammation (heat, swelling, redness, pain).

Less than 5% cows should leak milk while waiting to be milked.

Vitamin E - 550 iu / cow / day (milking cows)

There must be at least as many cubicles as cows for each group. (milking cows)

Selenium 0.3 mg/kg dm in diet (milking cows)

There should be less than 2% of cows with other teat lesions.

A licensed antibiotic product must be used for treatment according to datasheet recommendations.

Collecting yards should have sufficient drainage to prevent excessive pooling of liquid and footbaths should not be used just before milking.

Grade three cases should be treated in close consultation with the attending veterinary surgeon.

Collecting yards should have sufficient grip and grooving to prevent the risk of slipping and injury.

Zinc 50 mg/kg dm in diet (milking cows)

During milking, the vacuum should not drop by more than 2kpa when one more cluster than the number of milking staff is open.

You should consider an extended antibiotic therapy regime. (treatment of high scc cows)

You must follow the manufacturer's recommendations regarding the wash such as the quantity/temperature of water required and the types/concentrations/frequency of chemicals used.

Clean bedding material must be applied at least once every other day for inorganic bedding. (milking cows)

Exit to parlour must be stress-free (no operator pressure or poor design features such as excessive slopes or bends).

Dogs should be used with extreme care to move cows.

Pooling of liquid in the post milking yard sometimes occurs.

Cows with clinical mastitis must be milked to a dump line where possible.