Cow-specific treatment of clinical mastitis: An economic approach

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ABSTRACT

Under Dutch circumstances, most clinical mastitis (CM) cases of cows on dairy farms are treated with a standard intramammary antimicrobial treatment. Several antimicrobial treatments are available for CM, differing in antimicrobial compound, route of application, duration, and cost. Because cow factors (e.g., parity, stage of lactation, and somatic cell count history) and the causal pathogen influence the probability of cure, cow-specific treatment of CM is often recommended. The objective of this study was to determine if cow-specific treatment of CM is economically beneficial. Using a stochastic Monte Carlo simulation model, 20,000 CM cases were simulated. These CM cases were caused by *Streptococcus uberis* and *Streptococcus dysgalactiae* (40%), *Staphylococcus aureus* (30%), or *Escherichia coli* (30%). For each simulated CM case, the consequences of using different antimicrobial treatment regimens (standard 3-d intramammary, extended 5-d intramammary, combination 3-d intramammary + systemic, combination 3-d intramammary + systemic + 1-d nonsteroidal antiinflammatory drugs, and combination extended 5-d intramammary + systemic) were simulated simultaneously. Finally, total costs of the 5 antimicrobial treatment regimens were compared. Some inputs for the model were based on literature information and assumptions made by the authors were used if no information was available. Bacteriological cure for each individual cow depended on the antimicrobial treatment regimen, the causal pathogen, and the cow factors parity, stage of lactation, somatic cell count history, CM history, and whether the cow was systemically ill. Total costs for each case depended on treatment costs for the initial CM case (including costs for antibiotics, milk withdrawal, and labor), treatment costs for follow-up CM cases, costs for milk production losses, and costs for culling. Average total costs for CM

using the 5 treatments were (US) \$224, \$247, \$253, \$260, and \$275, respectively. Average probabilities of bacteriological cure for the 5 treatments were 0.53, 0.65, 0.65, 0.68, and 0.75, respectively. For all different simulated CM cases, the standard 3-d intramammary antimicrobial treatment had the lowest total costs. The benefits of lower costs for milk production losses and culling for cases treated with the intensive treatments did not outweigh the higher treatment costs. The stochastic model was developed using information from the literature and assumptions made by the authors. Using these information sources resulted in a difference in effectiveness of different antimicrobial treatments for CM. Based on our assumptions, cow-specific treatment of CM was not economically beneficial.

Key words: clinical mastitis, antimicrobial treatment, economics, dairy cow

INTRODUCTION

Mastitis is one of the most frequently occurring and costly diseases in dairy cows (e.g., Halasa et al., 2007). Most mild clinical mastitis (CM) cases are treated with a 3-d intramammary treatment. However, several antimicrobial treatment regimens are available for CM, differing in antimicrobial compound, route of application, duration, probability of cure, and costs (e.g., Barkema et al., 2006). Other treatment options are to use nonsteroidal antiinflammatory drugs (NSAID) in combination with an antimicrobial treatment (McDougall et al., 2009) or immediate culling (Bar et al., 2008a). The probability of cure depends highly on the causal pathogen of CM (e.g., McDougall et al., 2007; Bradley and Green, 2009). The probability of cure is determined by the treatment regimen and the causal pathogen, but several cow factors also influence the success of treatment. For instance, Sol et al. (2000) and Barkema et al. (2006) mentioned that the probability of cure of *Staphylococcus aureus* CM depends, for instance, on the cow factors SCC and parity.

On an increasing number of dairy farms, information on cow factors that may influence the probability of cure is available automatically via management programs. A farmer has to consider all information sources

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Table 1. Probabilities used to determine the parity of the cow, whether the cow with clinical mastitis was systemically ill, and whether the clinical mastitis case is a repeated case, given the causal pathogen of clinical mastitis

Causal pathogen	Parity		Systemically ill		Repeated case	
	1	≥ 2	Yes	No	Yes	No
<i>Streptococci</i>	0.19	0.81	0.10	0.90	0.10	0.90
<i>Staphylococcus aureus</i>	0.18	0.82	0.06	0.94	0.12	0.88
<i>Escherichia coli</i>	0.15	0.85	0.31	0.69	0.05	0.95

when making treatment decisions for a cow with CM. Because people can only use a maximum number of information sources to make the optimal decision (Miller, 1956), making the optimal decision for treatment of CM based on all available information sources is very difficult. Combining information on several treatment options and all cure-influencing cow factors in an automated decision support model would be useful to support farmers in their decisions on the optimal CM treatment. Bar et al. (2008b) presented a dynamic programming model to support farmers in making CM treatment decisions. In their model, however, it was not possible to choose between different antimicrobial treatment regimens for individual cows.

The importance of optimizing the choice of CM treatment is stressed frequently (Barkema et al., 2006; Bar et al., 2008b; Steeneveld et al., 2009). However, before developing a computerized decision support model for treatment of CM, we must determine whether optimizing the choice of treatment is worthwhile. The optimal CM treatment is often measured in terms of clinical or bacteriological cure. Barkema et al. (2006), however, mentioned that dairy farming is an economic enterprise and therefore the real measure of cure should be the cost-benefit of treatment. So far, no study has determined whether making cow-specific CM treatment decisions is economically beneficial. The overall objective of this study was to determine if cow-specific treatment of CM is economically beneficial.

MATERIALS AND METHODS

Model Development

A stochastic Monte Carlo simulation model, at cow level, was built to calculate the costs of CM cases treated with different treatment regimens using Microsoft Excel with @Risk add-in software (2002; Palisade Corp., Newfield, NY). Model outcomes were generated in 3 steps. First, each iteration (20,000 in total) during the simulation process yielded a specific cow with CM. In the second step, treating the simulated CM case was simulated using 6 defined treatment regimens (5 different antimicrobial treatment regimens and im-

mediate culling). The third step involved calculation of the associated total costs for CM under each of the 6 treatment regimens. All discrete events and variability with regard to the modeled CM cases under the 6 different treatment regimens were triggered stochastically using random numbers drawn from relevant distributions. These distributions were based on knowledge of the model domain, information from the literature and, if no other information was available, on assumptions made by the authors.

Simulation of a Cow with CM

The causal pathogen of the CM case was determined using a discrete probability distribution. In our model, the CM case could be caused by streptococci (*Streptococcus uberis* and *Streptococcus dysgalactiae*; probability = 0.40), *Staphylococcus aureus* (probability = 0.30) or *Escherichia coli* (probability = 0.30). This pathogen distribution was based on results of Barkema et al. (1998) and Olde Riekerink et al. (2007). The length of the calving interval of the cow with CM was determined with a pert probability distribution with a minimum of 336 d, a most likely value of 410 d, and a maximum of 556 d (CRV, 2009). Subsequently, using a dry period of 60 d, the length of lactation was 60 d shorter than the calving interval. The parity of the cow (heifer or older cow), whether the cow was systemically ill, and whether the CM case was a repeated case were determined with discrete probability distributions, where probabilities were dependent on the causal pathogen. The month in milk of CM (1, 2, 3, ..., ≥ 8) was determined with a discrete probability distribution, where probabilities were dependent on the causal pathogen and parity. When the month in milk was determined, a uniform probability distribution was used to determine the exact day of CM occurrence in that specific month in milk. The 305-d milk production of the cow with CM was modeled assuming a normal distribution. A mean 305-d milk production for heifers and older cows of 7,434 and 8,666 kg, respectively, was used (CRV, 2009). The daily milk production at the moment of CM and the remaining milk production after the CM case

Table 2. Probabilities used to determine the month in milk, given the parity of the cow and the causal pathogen of clinical mastitis

Causal pathogen	Parity 1 (month in milk)								Parity ≥2 (month in milk)							
	1	2	3	4	5	6	7	≥8	1	2	3	4	5	6	7	≥8
Streptococci	0.60	0.13	0.08	0.02	0.05	0.05	0.02	0.05	0.25	0.16	0.16	0.10	0.08	0.06	0.07	0.12
<i>Staphylococcus aureus</i>	0.38	0.10	0.12	0.08	0.11	0.07	0.01	0.13	0.38	0.13	0.15	0.12	0.08	0.08	0.06	0.14
<i>Escherichia coli</i>	0.36	0.16	0.11	0.09	0.03	0.06	0.07	0.12	0.26	0.18	0.14	0.12	0.10	0.08	0.04	0.08

were estimated using the Wood lactation curve (Wood, 1967). The most recent SCC measurement before the CM case depended on the causal pathogen and the parity of the cow. The most recent SCC measurement (categorized into <200,000, 200,000 to 500,000, and >500,000 cells/mL) was determined using a discrete probability distribution.

Probability distributions to determine the parity, month in milk, most recent SCC, and whether the cow with CM was systemically ill were based on data as used by Steeneveld et al. (2009). The probabilities to determine whether the CM case was a repeated case were based on Döpfer et al. (1999) and Swinkels et al. (2005a,b). All of these probabilities are presented in Tables 1, 2, and 3.

Simulation of Follow-Up of Treatment Regimens for CM

For each simulated CM case, the follow-up using different antimicrobial treatment regimens was simulated simultaneously. In total, 5 antimicrobial treatment regimens were defined, differing in route of application [3-d intramammary with antimicrobials (IMM3); 5-d intramammary with antimicrobials (IMM5); 3-d intramammary + systemic with antimicrobials (IMM3_S); 3-d intramammary + systemic with antimicrobials + 1-d NSAID (IMM3_S_NSAID); and 5-d intramammary + systemic with antimicrobials (IMM5_S)], costs, milk withdrawal period, and total treatment time (Table 4). The follow-up of the antimicrobial treatment regimens is presented in Figure 1.

Treatment of the initial CM case (CM1) could result in complete cure (bacteriological + clinical cure),

no cure (no bacteriological cure + no clinical cure), or clinical cure but no bacteriological cure (Figure 1). To determine this cure status, it was first determined whether CM1 was cured bacteriologically after antimicrobial treatment.

To make the probability of bacteriological cure cow-specific, maximum probabilities of bacteriological cure were first determined for each causal pathogen treated with each of the defined antimicrobial treatment regimens. Probability of bacteriological cure was highest (maximum) for a heifer, not systemically ill, in the first 60 DIM, with a most recent SCC <200,000 cells/mL, and no CM history (Table 4). Because such maximum probabilities of bacteriological cure were not available in the literature, values from the following sources were adapted: McDougall (1998), Sol et al. (2000), McDougall (2003), Oliver et al. (2003), Wraight (2003), Sérieys et al. (2005), McDougall et al. (2007), and Bradley and Green (2009). Literature information on the probability of bacteriological cure was limited for the intensive antimicrobial treatment regimens. Therefore, assumptions made by the authors were used to fill in all remaining maximum probabilities of bacteriological cure (Table 4). Subsequently, compared with the defined maximum probabilities of bacteriological cure, lower probabilities were assumed for older cows, for cows >60 DIM, for systemically ill cows, for cows with most recent SCC between 200,000 and 500,000 cells/mL, for cows with most recent SCC >500,000 cells/mL, and for cows with a repeated CM case (Table 5). Information from the peer-reviewed literature and assumptions made by the authors were used to determine the effect of cow factors on the probability of bacteriological cure (Table 5). A cow-specific probability of bacteriological cure was cal-

Table 3. Probabilities used to determine the most recent SCC measurement, given the parity of the cow and the causal pathogen of clinical mastitis

Causal pathogen	Parity 1 SCC (× 1,000 cells/mL)			Parity ≥2 SCC (× 1,000 cells/mL)		
	<200	200–500	>500	<200	200–500	>500
Streptococci	0.34	0.22	0.44	0.41	0.17	0.42
<i>Staphylococcus aureus</i>	0.40	0.25	0.35	0.35	0.20	0.45
<i>Escherichia coli</i>	0.84	0.08	0.08	0.70	0.12	0.18

Table 4. Characteristics of 5 defined clinical mastitis (CM) antimicrobial treatment regimens

Characteristic	Antimicrobial treatment regimen				
	IMM3	IMM5	IMM3_S	IMM3_S_NSAID	IMM5_S
Application and duration (d)	Intramammary (3)	Intramammary (5)	Intramammary (3) + systemic (3)	Intramammary (3) + systemic (3) + nonsteroidal antiinflammatory drug (1)	Intramammary (5) + systemic (3)
Total cost of antibiotics (\$)	19	32	57	69	70
Milk withdrawal (d)	5	7	5	5	7
Total treatment time ¹ (min)	42	62	45	48	65
Probability of bacteriological cure ²					
<i>Streptococcus dysgalactiae</i> or <i>uberis</i>	0.70 ³	0.80 ⁴	0.80 ⁵	0.83 ⁵	0.90 ⁵
<i>Staphylococcus aureus</i>	0.40 ⁶	0.60 ⁷	0.60 ⁵	0.63 ⁵	0.70 ⁵
<i>Escherichia coli</i>	0.80 ⁸	0.80 ⁵	0.80 ⁵	0.80 ⁵	0.80 ⁵
Probability of clinical cure for bacteriologically noncured CM cases	0.80 ⁵	0.80 ⁵	0.80 ⁵	0.80 ⁵	0.80 ⁵

¹Includes time for treatment and time for milk withdrawal.

²Probability of bacteriological cure assumed for heifers, not systemically ill, <60 DIM, with SCC <200,000 cells/mL, and no previous clinical mastitis.

³Adapted from McDougall (1998); McDougall (2003); Oliver et al. (2003); Wraight (2003); Sérieys et al. (2005); McDougall et al. (2007); Bradley and Green (2009).

⁴Adapted from Oliver et al. (2003).

⁵Estimated by the authors.

⁶Adapted from Sol et al. (2000); McDougall (2003); Wraight (2003); Sérieys et al. (2005); McDougall et al. (2007); Bradley and Green (2009).

⁷Adapted from Sol et al. (2000).

⁸Adapted from Sérieys et al. (2005); Bradley and Green (2009).

Figure 1. Schematic representation of the simulation model for antimicrobial treatment of a clinical mastitis (CM) case (bact. = bacteriological, clin. = clinical).

culated for each simulated cow with CM treated with each of the 5 defined antimicrobial treatment regimens using the defined maximum probability of bacteriological cure and the defined effects of the cow factors on

the probability of bacteriological cure. The cow-specific probability of bacteriological cure ($P_{Bact.cure}$) was calculated with the following equation, using a logit formula:

$$P_{Bact.cure} = \frac{1}{\left\{ 1 + \text{Exp} \left[-1 \times \left(\ln \left(\frac{C_{max}}{1 - C_{max}} \right) + \ln \left(\frac{C_{parity}}{C_{max}} \right) + \ln \left(\frac{C_{Sys}}{C_{max}} \right) + \ln \left(\frac{C_{DIM}}{C_{max}} \right) + \ln \left(\frac{C_{SCC}}{C_{max}} \right) + \ln \left(\frac{C_R}{C_{max}} \right) \right) \right] \right\}},$$

where C_{max} is the maximum probability of bacteriological cure for the combination of causal pathogen and treatment regimen (Table 4), and C_{parity} , C_{Sys} , C_{DIM} , C_{SCC} , and C_R are the maximum probability of bacteriological cure (Table 4) minus the effect of the cow factors (parity, systemically ill, DIM, most recent SCC, and repeated CM) on the probability of bacteriological cure (Table 5).

Subsequently, we determined whether the CM case was cured bacteriologically, or not, using a discrete probability distribution. Each bacteriologically cured CM case was assumed to be cured clinically as well. A discrete probability distribution was used to determine whether nonbacteriological cured CM cases were cured clinically or not. These probabilities of clinical cure are presented in Table 4.

Completely noncured CM cases received an extended treatment with the initial treatment regimen. Nonbacteriologically but clinically cured CM cases could have clinical flare-up cases (CM2 and CM3). These clinical flare-up cases were caused by the same pathogen as CM1 and were again treated with the initial treatment regimen. In addition, the follow-up of the extended treatment and the treatment of CM2 and CM3 were simulated (Figure 1). The follow-up was simulated using discrete probability distributions; the probabilities are presented in Table 5.

A cow with a completely noncured CM case after an extended treatment could die or the quarter of the cow could be dried off. For cows with dried-off quarters, we determined whether this cow was culled in the remainder of the lactation (Table 5). A cow that cured completely had a probability of being culled, which depended on whether the CM case was the first, second, or third case (Table 5). A cow with a nonbacteriologically but clinically cured CM case had a probability of being culled, a probability of getting a clinical flare-up, and a probability of reaching the end of lactation. The probability of being culled increased with the number of CM cases (Table 5). The probabilities of being culled were 0.10 higher when the cow with CM was systemically ill.

A pert distribution was used to determine the day of occurrence of the potential first and second clinical flare-up cases. The minimum interval between clinical (flare-up) cases was 14 d, the most likely interval between clinical flare-up cases was 30 d, and the last day of occurrence of a clinical flare-up was the last day of lactation. For CM2 and CM3, the daily milk produc-

tion at the day of occurrence (using the Wood lactation curve), the most recent SCC measurement, and whether the cow was systemically ill were determined again. It was assumed that a cow not cured bacteriologically after CM3 was culled 7 d after the day of treatment. For all other culled cows, the day of culling was in the remainder of lactation and was determined with a uniform probability distribution.

Calculation of Costs

The total costs for the defined CM treatment regimens included costs for treatment of CM1 (including antimicrobials, discarded milk and labor), costs for treatment of follow-up treatments (for extended treatments and treatments of clinical flare-up cases, including costs for antimicrobials, discarded milk and labor), costs for milk production losses and costs for culling. The original calculations were made in Euros and converted to US dollars using an exchange rate of 1.2725 (<http://www.x-rates.com/calculator.html>; accessed Sep. 13, 2010). All costs presented herein are in US dollars.

Costs for antimicrobials for all defined treatment regimens are presented in Table 4. Total costs of discarded milk were determined by daily milk production on the day of CM (estimated with Wood's lactation curve), milk withdrawal time (Table 4), and the economic value of discarded milk (Table 5). Total labor costs were determined by treatment time (for treating and milk withdrawal; Table 4) and the hourly cost of labor (Table 5).

Total costs for milk production loss were determined by the remaining milk production after the CM case (estimated with Wood's lactation curve), the percentage of milk production loss per month after CM, and the economic value of milk production loss (Table 5). The percentage of milk production loss per month after CM depended on the causal pathogen (Gröhn et al., 2004; Schukken et al., 2009), parity (Gröhn et al., 2004; Hagnestam et al., 2007; Schukken et al., 2009), month after CM (Schukken et al., 2009), whether the cow was systemically ill, and whether the cow was cured bacteriologically (Table 5). Milk production losses ranged from 6% (mo 1) to 1% (mo ≥ 8) per month after CM for bacteriologically cured CM cases caused by streptococci in heifers that were not systemically ill. An additional milk production loss per month after CM was added for CM caused by *Staph. aureus* and *E. coli*, for CM in older

Table 5. Values and source of parameters used in the simulation model for different antimicrobial treatment regimens for clinical mastitis (CM)

Input parameters for simulation treatment of CM	Value	Source
Decrease in probability of bacteriological cure ¹		Expertise
Parity ≥ 2	0.10	
DIM ≥ 60	0.10	
Systemically ill	0.20	
SCC 200,000–500,000 cells/mL	0.10	
SCC >500,000 cells/mL	0.20	
Repeated case	0.20	
Probability of being culled for bacteriologically noncured CM cases		Adapted from Bar et al. (2008a)
Initial CM case	0.16	
First clinical flare-up case	0.20	
Probability of being culled for completely cured CM cases		Adapted from Bar et al. (2008a)
Initial CM case	0.05	
First clinical flare-up case	0.15	
Second clinical flare-up case	0.25	
Probability of mortality for nonclinical cured CM cases	0.05	Adapted from Bar et al. (2008a)
Probability of drying-off quarter for nonclinical cured CM cases	0.95	Expertise
Probability of being culled for cows with dried-off quarters	0.33	Expertise
Increase in all culling probabilities when cow with CM is systemically ill	0.10	Expertise
Probability of clinical flare-up for bacteriologically noncured CM cases		Swinkels et al. (2005b); Swinkels et al. (2005a); Döpfer et al. (1999)
<i>Streptococcus dysgalactiae</i> or <i>uberis</i>	0.10	
<i>Staphylococcus aureus</i>	0.12	
<i>Escherichia coli</i>	0.05	
Increase in milk production losses per month in lactation ² (%)		
<i>Staphylococcus aureus</i>	2	Adapted from Gröhn et al. (2004); Hagnestam et al. (2007); Schukken et al. (2009)
<i>Escherichia coli</i>	4	
Parity ≥ 2	5	
Systemically ill	5	
Bacteriologically noncured	5	
Economic input parameters		
Economic value discarded milk (\$/kg)	0.22	
Economic value milk production losses (\$/kg)	0.15	Huijps et al. (2008)
Labor costs (\$/h)	23	Huijps et al. (2008)
Culling costs (\$)	Retention pay-off	Huijps et al. (2008)
		Houben et al. (1994); Van der Walle (2004)

¹Compared with a heifer, not systemically ill, <60 DIM, with somatic cell count <200,000 cells/mL, and no previous clinical mastitis.

²Compared with a bacteriologically cured CM case caused by streptococci in heifers that were not systemically ill.

cows, for bacteriologically noncured CM cases, and for systemically ill cows (Table 5). Cows with a dried-off quarter had a total 15% milk production loss in the remainder of lactation. After a clinical flare-up case, milk production loss decreased by the same amount as after CM1 (Schukken et al., 2009). In the current study, a percentage milk production loss per month after CM was needed for a combination of cow factors. Because estimates on milk production losses were given in kilograms in most studies, we needed to adapt the values from the literature to percentages.

Culling costs were determined for culled cows and expressed using retention pay-off (**RPO**). The RPO values were calculated using a stochastic model developed by Houben et al. (1994). The model outcomes were updated by Van der Walle (2004) using values for prices and production level from the year 2003. With this model, culling costs were based on the specific cow factors parity, month of lactation, pregnancy status, and production level. For example, the culling costs

for a pregnant cow in her second lactation with a very high production level were \$975, whereas those for a nonpregnant heifer with a very low production level were \$146.

Validation and Sensitivity Analysis

Because data were not available for external validation of the model, an internal validation was performed. A large number of inputs were compared with the output to check the consistency and the credibility of the model output.

A sensitivity analysis was performed to verify the values of the input parameters and to assess the effect of varying the input values on the outcome total costs of the treatment regimen. Values for input variables in the sensitivity analysis were based on information in the literature. Assumptions made by the authors were used if no information in the literature was found. The sensitivity analysis was performed on pathogen distri-

Table 6. Average noneconomic output of the Monte Carlo simulation model

Item	Antimicrobial treatment regimen ¹				
	IMM3	IMM5	IMM3_S	IMM3_S_NSAID	IMM5_S
Probability of bacteriological cure for CM1 ²					
<i>Streptococcus dysgalactiae</i> or <i>uberis</i>	0.60	0.73	0.73	0.76	0.86
<i>Staphylococcus aureus</i>	0.22	0.47	0.47	0.50	0.60
<i>Escherichia coli</i>	0.74	0.74	0.74	0.74	0.74
Overall	0.53	0.65	0.65	0.68	0.75
Probability of clinical cure for CM1 ²					
<i>Streptococcus dysgalactiae</i> or <i>uberis</i>	0.92	0.95	0.95	0.96	0.97
<i>Staphylococcus aureus</i>	0.84	0.89	0.89	0.90	0.91
<i>Escherichia coli</i>	0.94	0.94	0.94	0.94	0.94
Overall	0.90	0.93	0.93	0.93	0.95
Overall probability of bacteriological cure for CM2 and CM3 ³	0.44	0.57	0.57	0.61	0.68
Culled cows (%)	12	10	10	9	8
Milk production losses (%)	7	6	6	6	6
Extended treatments (%)	10	7	7	5	3
CM2 and CM3 ³ (%)	4	3	3	2	2

¹IMM3 = standard 3-d intramammary treatment with antimicrobials; IMM5 = extended 5-d intramammary treatment with antimicrobials; IMM3_S = 3-d standard intramammary + systemic treatment with antimicrobials; IMM3_S_NSAID = standard 3-d intramammary + systemic treatment with antimicrobials + 1-d nonsteroidal antiinflammatory drug; and IMM5_S = extended 5-d intramammary + systemic treatment with antimicrobials.

²Treatment of the initial clinical mastitis (CM) case.

³Treatment of the clinical flare-up cases.

bution, probability of culling, percentage milk production losses, probabilities of bacteriological cure, costs for culling, costs for labor, costs for milk production losses, and costs for milk withdrawal.

RESULTS

The outcome of treatment-specific parameters under default circumstances is presented in Table 6. On average, the overall probability of bacteriological cure for treatment of CM1 with IMM3, IMM5, IMM3_S, IMM3_S_NSAID, and IMM5_S was 0.53, 0.65, 0.65, 0.68, and 0.75, respectively. On average, the overall probability of clinical cure for treatment of CM1 with IMM3, IMM5, IMM3_S, IMM3_S_NSAID, and IMM5_S was 0.90, 0.93, 0.93, 0.93, and 0.95, respectively. Intensive antimicrobial treatment regimens resulted in fewer culled cows, fewer CM cases with an extended treatment, and fewer clinical flare-up cases. The total amount of milk production losses due to CM was approximately the same for all 5 antimicrobial treatment regimens.

On average, total costs for a CM case treated with IMM3 were \$224 (Table 7), and consisted of costs for the initial treatment (\$66), follow-up treatments (\$9), milk production losses (\$95), and culling (\$54). The total costs of CM treated with the intensive antimicrobial treatments were \$247, \$253, \$260, and \$275 for IMM5, IMM3_S, IMM3_S_NSAID, and IMM5_S, respectively. With increasing intensity of the antibiotic treatment regimen, the costs for milk production losses and culling decreased. These benefits of the intensive

antimicrobial treatment regimens did not, however, outweigh the increasing costs for the initial treatment (costs for antibiotics, milk withdrawal, and labor). For instance, compared with IMM3, the average benefits of IMM5 were \$9 (\$4 for less milk production loss and \$5 for less culling), whereas the average extra costs were \$32 (\$13 for antibiotics, \$12 for milk withdrawal, and \$7 for labor). In Table 7, the variability in outcomes is shown using 5th and 95th percentiles. The range in outcomes was smaller for the intensive antimicrobial treatment regimens.

The causal pathogen and several cow characteristics influenced the total costs of CM treated with different treatment regimens (Table 8). On average, the total costs of a CM case caused by streptococci and treated with IMM3 was \$196, whereas the total costs of a *Staph. aureus* CM case treated with IMM3 was \$255. The costs of CM increased with increasing daily milk production at the moment of CM, increasing relative production value, increasing parity number, and decreasing month in milk. In addition, for repeated CM cases and CM cases in systemically ill cows, the costs were higher than for nonrepeated cases and those in cows that were not systemically ill, respectively. Antimicrobial treatment of CM with IMM3 resulted in the lowest total costs for all causal pathogens and for all cow characteristics, with one exception: immediate culling resulted in the lowest total costs for cows with a low relative production value (<80).

The association between total average costs and the probability of bacteriological cure is presented in Figure 2. Treatment of all simulated CM cases with IMM3

Table 7. Average total costs (\$) for the 6 clinical mastitis treatment regimens, including costs for the different cost factors (5th and 95th percentiles given between parentheses)

Cost (\$)	Treatment regimen ¹					
	IMM3	IMM5	IMM3_S	IMM3_S_NSAID	IMM5_S	Culling
Treatment CM1 ²						
Antibiotics	19	32	57	69	70	0
Milk withdrawal	31	43	31	31	43	0
	(11; 42)	(13; 60)	(11; 42)	(11; 42)	(13; 60)	
Labor	17	24	18	18	25	0
Treatment CM2 and CM3 ³	9	9	10	9	8	0
	(0; 70)	(0; 97)	(0; 111)	(0; 115)	(0; 111)	
Milk production losses	95	91	90	89	87	0
	(25; 192)	(24; 185)	(23; 185)	(24; 181)	(24; 153)	
Culling	53	48	47	44	42	708
	(0; 545)	(0; 484)	(0; 486)	(0; 445)	(0; 281)	(193; 1,224)
Total costs	224	247	253	260	275	708
	(79; 714)	(103; 720)	(116; 722)	(127; 714)	(140; 702)	(193; 1,224)

¹IMM3 = standard 3-d intramammary treatment with antimicrobials; IMM5 = extended 5-d intramammary treatment with antimicrobials; IMM3_S = 3-d standard intramammary + systemic treatment with antimicrobials; IMM3_S_NSAID = standard 3-d intramammary + systemic treatment with antimicrobials + 1-d nonsteroidal antiinflammatory drug; and IMM5_S = extended 5-d intramammary + systemic treatment with antimicrobials.

²Initial clinical mastitis (CM) case of the cow.

³Costs for antibiotics, milk withdrawal, and labor of the clinical flare-up cases.

resulted in the lowest total average costs but also in the lowest probability of bacteriological cure (0.53; Figure 2). The total costs and the probability of cure increased with the intensive antimicrobial treatments. Treatment regimens included on the least-cost frontier resemble those that were the most cost-effective. Because treatment with IMM3_S resulted in higher costs but the same probability of cure as treatment with IMM5, the IMM3_S treatment was not cost-effective and thus not included on the least-cost frontier. Total costs and probability of cure are also presented for an *E. coli* CM case, a *Staph. aureus* CM case, a CM case with a low probability of cure (older cow, >60 DIM, SCC >500,000 cells/mL, a previous CM case, and systemically ill), and for a CM case with a high probability of cure (heifer, <60 DIM, SCC <200,000 cell/mL, no previous CM, and not systemically ill) (Figure 2). Treatment with IMM3 resulted in the lowest total costs for these specific cows. The difference in total average costs between the antimicrobial treatment regimens was smaller for a cow with *Staph. aureus* CM than for a cow with a high probability of cure.

Results of the sensitivity analysis are given in Tables 9 and 10. The pathogen distribution, the probability of culling a cow, the amount of milk production losses, the costs for culling, the costs for milk production losses, costs for discarded milk, and costs for labor influenced the total costs for CM treated with different treatment regimens. For instance, increasing the economic value of milk by \$0.06 increased the costs of CM treated with IMM3 by \$50. Treatment of CM with IMM3 resulted

in the lowest total costs for all situations presented in Table 9.

Increasing probabilities of bacteriological cure resulted in lower costs for CM for all defined antimicrobial treatment regimens, whereas decreasing probabilities of bacteriological cure resulted in higher costs for CM (Table 10). By increasing the probability of bacteriological cure of streptococcal CM by 0.10 for all defined antimicrobial treatment regimens, the total costs of CM treated with IMM3 decreased by \$9 compared with the default situation. By increasing the probability of bacteriological cure of *Staph. aureus* and *E. coli* CM by 0.10 for all defined treatment regimens, the total costs of CM treated with IMM3 decreased by \$10 and \$9 compared with the default situation, respectively. By increasing the probability of bacteriological cure of the intensive antimicrobial treatment regimens (IMM5, IMM3_S, IMM3_S_NSAID, and IMM5_S) by 0.10, treatment of CM with IMM5 resulted in the same total costs as treatment with IMM3.

DISCUSSION

In this study, total average costs for a CM case treated with IMM3 were \$224 (Table 7) and consisted of costs for the initial treatment (\$66), follow-up treatments (\$9), milk production losses (\$95), and culling (\$54). The total costs increased with the more intensive antibiotic treatment regimens. Compared with IMM3, treating with the intensive antibiotic treatment regimens resulted in benefits (Table 7) resulting from fewer

Table 8. Average total costs (\$) for the 6 treatment regimens for all cow characteristics

Total costs (\$)	Treatment regimen ¹					
	IMM3	IMM5	IMM3_S	IMM3_S_NSAID	IMM5_S	Culling
Overall	224	247	253	260	275	708
Causal pathogen						
<i>Streptococcus dysgalactiae</i> or <i>uberis</i>	196	220	227	235	246	700
<i>Staphylococcus aureus</i>	255	260	263	275	286	694
<i>Escherichia coli</i>	230	271	280	288	309	737
Daily milk production (kg)						
<20	140	155	173	192	177	450
20–25	164	185	192	202	207	542
25–30	178	202	216	227	235	533
30–35	193	219	227	235	255	524
35–40	224	251	255	268	284	681
>40	284	308	309	317	331	958
Systemically ill						
No	213	234	239	249	262	706
Yes	293	326	340	346	364	714
Previous clinical mastitis						
No	223	247	253	263	277	711
Yes	234	252	253	257	272	694
Parity						
1	157	181	193	201	216	308
≥2	238	262	267	276	290	795
SCC (× 1,000 cells/mL)						
<200	220	251	255	263	281	705
200–500	221	241	251	262	272	694
>500	232	247	256	265	275	716
Relative production value ²						
<80	121	146	162	174	190	120
80–90	155	181	187	197	215	271
90–100	199	223	232	242	256	550
100–110	237	261	266	275	288	784
110–120	270	288	290	302	316	966
>120	302	328	298	327	330	1,176
Month in milk						
1	257	282	288	298	313	837
2	261	286	284	298	313	781
3	241	267	269	276	289	743
4	227	243	253	265	279	678
5	192	218	227	238	253	617
6	178	199	214	224	228	561
7	159	185	192	201	211	576
≥8	154	173	185	181	209	552

¹IMM3 = standard 3-d intramammary treatment with antimicrobials; IMM5 = extended 5-d intramammary treatment with antimicrobials; IMM3_S = 3-d standard intramammary + systemic treatment with antimicrobials; IMM3_S_NSAID = standard 3-d intramammary + systemic treatment with antimicrobials + 1-d nonsteroidal antiinflammatory drug; and IMM5_S = extended 5-d intramammary + systemic treatment with antimicrobials.

²Represents index for 305-d milk production. A cow with a 305-d milk production of 8,500 kg has a relative production value of 100.

follow-up treatments, less milk production loss, and less culling (Table 6). These benefits did not, however, outweigh the extra treatment costs (costs for antibiotics, milk withdrawal, and labor; Table 7). Additionally, for all different cow characteristics (Table 8 and Figure 2) and under different circumstances (Table 9), treatment of CM with IMM3 always resulted in the lowest total

costs. For all different cow characteristics, the benefits of the intensive antibiotic treatment regimens on decreased costs for follow-up treatments, milk production losses, and culling did not outweigh the extra treatment costs for the initial CM case. Based on our assumptions, cow-specific treatment of CM was not economically beneficial.

Figure 2. Average total costs for each antimicrobial treatment regimen with their associated average probability of bacteriological cure for different cows (IMM3 = standard 3-d intramammary treatment with antimicrobials; IMM5 = extended 5-d intramammary treatment with antimicrobials; IMM3_S = 3-d standard intramammary + systemic treatment with antimicrobials; IMM3_S_NSAID = standard 3-d intramammary + systemic treatment with antimicrobials + 1-d nonsteroidal antiinflammatory drug; and IMM5_S = extended 5-d intramammary + systemic treatment with antimicrobials). The lines resemble the least-cost frontier of treatment for the different clinical mastitis cases. *E. coli* = *Escherichia coli*; *S. aureus* = *Staphylococcus aureus*.

Results of the current study are highly influenced by the assumptions used; therefore, the results will not be applicable to all farm situations. Because of a lack of detailed information, as was needed for our model, several assumptions had to be made. These assumptions included the pathogen distribution used, the probabilities of cure and culling used, and an assumption that all defined treatments were effective against both gram-positive and gram-negative pathogens. The pathogen distribution used, with the high probability of *Staph. aureus*, might not reflect reality for non-Dutch farms. All probabilities of cure used in the current simulation model were based as much as possible on information in the peer-reviewed literature. Although many clinical trials on treatment of CM have been performed (e.g., Sérieys et al., 2005; McDougall et al., 2007; Bradley and Green, 2009), detailed information on the probability of cure necessary for the current simulation model was not available in literature. Pathogen-specific probabilities of bacteriological and clinical cure were available for treatment with IMM3 (e.g., McDougall, 1998, 2003; Wraight, 2003), but pathogen-specific probabilities of cure were only reported in 3 studies for the more intensive antibiotic treatment regimens (Sol et al., 2000; Oliver et al., 2003; Taponen et al., 2003). Moreover, it was necessary to adapt available average probabilities

of cure to maximum probabilities of cure because cow-specific probabilities were needed for the simulations. In addition, estimates on the effect of cow factors on the probability of cure were necessary. Although some studies indicated that cow factors influenced the probability of cure (Sol et al., 2000; Bradley and Green, 2009), usable estimates on the effects were not available. Assumptions made by the authors were used to determine all missing probabilities of cure, to adapt all average probabilities to maximum probabilities of cure, and to determine the effect of cow factors on the probability of cure. A lot of uncertainty existed about the used probabilities of cure, and thus the sensitivity analysis was important to verify our estimates.

The probabilities of bacteriological cure used influenced the total costs of CM. Higher probabilities of cure resulted in lower costs for CM. Increasing or decreasing the probabilities of bacteriological cure, however, did not result in lower total costs for the intensive antibiotic treatment regimens than for the standard antibiotic treatment regimen (Table 10). Increasing the probability of bacteriological cure for IMM5 by 0.10 resulted in equal total costs (\$224) for treatment with IMM3 and IMM5 (Table 10). This implies that the benefits of treating with IMM5 almost outweighed the extra treatment costs. Therefore, the difference in probability

Table 9. Sensitivity of the total costs (\$) of clinical mastitis (CM) treated with 6 treatment regimens for different input values

Item	Value	Default	Treatment regimen ¹					
			IMM3	IMM5	IMM3_S	IMM3_S_NSAID	IMM5_S	Culling
Default situation			224	247	253	260	275	708
Pathogen distribution (streptococci; <i>Staphylococcus aureus</i> ; <i>Escherichia coli</i>)	0.60; 0.20; 0.20	0.40; 0.30; 0.30	219	239	249	255	265	708
	0.20; 0.60; 0.20	0.40; 0.30; 0.30	234	253	258	267	285	708
	0.20; 0.20; 0.60	0.40; 0.30; 0.30	234	252	261	275	291	708
Probability of culling for bacteriologically noncured CM cases	0.21; 0.25 ²	0.16; 0.20 ²	237	255	261	270	279	708
	0.11; 0.15 ²	0.16; 0.20 ²	218	243	249	261	279	708
Probability of culling for completely cured CM cases	0	0.05; 0.15; 0.25 ³	211	227	232	242	255	708
Milk production losses per month in lactation (%)	6–30 ⁴	1–25 ⁴	260	279	288	302	314	708
	1–20 ⁴	1–25 ⁴	187	209	216	229	243	708
Costs of culling (\$)	RPO ⁵ +100	RPO	239	260	265	276	284	839
	RPO –100	RPO	210	228	238	244	265	579
Economic value of milk (\$/kg)	0.21 ⁶ ; 0.28 ⁷	0.15 ⁶ ; 0.22 ⁷	274	295	302	312	326	708
	0.09 ⁶ ; 0.16 ⁷	0.15 ⁶ ; 0.22 ⁷	176	191	202	218	228	708
Costs of labor (\$/h)	0	23	214	227	235	248	252	708
	12	23	215	232	232	255	265	708

¹IMM3 = standard 3-d intramammary treatment with antimicrobials; IMM5 = extended 5-d intramammary treatment with antimicrobials; IMM3_S = 3-d standard intramammary + systemic treatment with antimicrobials; IMM3_S_NSAID = standard 3-d intramammary + systemic treatment with antimicrobials + 1-d nonsteroidal antiinflammatory drug; and IMM5_S = extended 5-d intramammary + systemic treatment with antimicrobials.

²Dependent on culling due to the first clinical mastitis case or due to the first clinical flare-up case.

³Dependent on culling due to the first clinical mastitis case, due to the first clinical flare-up case, or due to the second clinical flare-up case.

⁴Dependent on the causal pathogen, parity, month after CM case, whether cow is systemically ill, and whether CM is cured bacteriologically.

⁵Retention pay-off.

⁶Economic value for milk production losses.

⁷Economic value for discarded milk.

Table 10. Sensitivity of the total costs (\$) of clinical mastitis (CM) treated with 5 different treatment regimens for input values on probability of bacteriological cure

Total cost (\$)	Change in probability of bacteriological cure	Antibiotic treatment regimen ¹				
		IMM3	IMM5	IMM3_S	IMM3_S_NSAID	IMM5_S
Default probability of bacteriological cure ²						
<i>Streptococcus dysgalactiae</i> or <i>uberis</i>		0.70	0.80	0.80	0.83	0.90
<i>Staphylococcus aureus</i>		0.40	0.60	0.60	0.63	0.70
<i>Escherichia coli</i>		0.80	0.80	0.80	0.80	0.80
Default situation		224	247	253	260	275
Probability of bacteriological cure of streptococcal CM	+0.10	215	234	243	255	310
	−0.10	225	241	251	262	277
Probability of bacteriological cure of <i>Staphylococcus aureus</i> CM	+0.10	214	241	247	249	268
	−0.10	224	247	256	265	279
Probability of bacteriological cure of <i>Escherichia coli</i> CM	+0.10	215	235	242	255	265
	−0.10	228	244	255	263	279
Probability of bacteriological cure of IMM5, IMM3_S, IMM3_S_NSAID, and IMM5_S ²	+0.05	224	235	242	255	262
	+0.10	224	224	234	246	298
	−0.05	224	249	263	267	281
	−0.10	224	262	274	280	294

¹IMM3 = standard 3-d intramammary treatment with antimicrobials; IMM5 = extended 5-d intramammary treatment with antimicrobials; IMM3_S = 3-d standard intramammary + systemic treatment with antimicrobials; IMM3_S_NSAID = standard 3-d intramammary + systemic treatment with antimicrobials + 1-d nonsteroidal antiinflammatory drug; and IMM5_S = extended 5-d intramammary + systemic treatment with antimicrobials.

²Probability of bacteriological cure assumed for heifers, not systemically ill, <60 DIM, with SCC <200,000 cells/mL, and no previous clinical mastitis.

of bacteriological cure between the defined treatment regimens influences whether cow-specific treatment is economically beneficial. Using our defined values on the probabilities of bacteriological and clinical cure, cow-specific treatment of CM is not economically beneficial. Nevertheless, this conclusion may change when results of future clinical trials on intensive antibiotic treatment regimens yield much higher probabilities of cure.

To determine if cow-specific treatment of CM is economically beneficial, treatment regimens that were used by Dutch dairy farmers were defined. In addition, Dutch economic values were used; for instance, on costs for culling, discarding milk, and labor. Other studies using Dutch input values also estimated the costs for CM cases treated with standard treatment regimens (Huijps et al., 2008; Halasa et al., 2009). The costs for a CM case of \$224 were lower than the \$267 found by Huijps et al. (2008). This was especially due to the probability of culling used in the current model, which was based on whether the CM case was the first case in the lactation or a follow-up case (Bar et al., 2008a), whether the cow was systemically ill, and the cure status. The costs for CM caused by streptococci, *Staph. aureus*, and *E. coli* of \$196, \$253, and \$239, respectively (Table 8) are in agreement with estimates found by Halasa et al. (2009). Milk production losses and culling contribute greatly to the total costs of CM (Table 7), as was also found by Huijps et al. (2008) and Halasa et al. (2009). In other countries, the costs for culling, discarding milk, and labor are different. Including dif-

ferent economic input values influenced the total costs for CM, as was found in the results from the sensitivity analysis. Varying these economic input values did not, however, influence the result that treating CM with IMM3 resulted in the lowest total costs. To adapt the model to other countries, country-specific economic input values are needed.

Including culling in the current model was difficult. Culling is a decision of the dairy farmer and several factors are involved: not only udder health status, but also factors such as milk production, reproduction status (e.g., Lehenbauer and Oltjen, 1998), the milk quota situation of the farm, and the availability of replacement heifers play a role in the decision to cull a cow. Including all these factors is very difficult and was not included in our study.

The costs of culling make a substantial contribution to the total costs of CM and influence the amount of benefits of the intensive antibiotic treatment regimens (Table 7). The costs of culling were based on the RPO value of the cow, and this value represents the amount of money that should be spent in trying to keep the cow in case of health problems (e.g., Groenendaal et al., 2004). The RPO value of a cow varies between farms and estimations are difficult to make. The results of the sensitivity analysis demonstrate, however, that increasing or decreasing the costs of culling a cow did not result in lower costs for the intensive antibiotic treatment regimens than for the standard antibiotic treatment regimen. Average total costs for immediate culling of a

cow with CM were \$708. This value was much higher than the average total costs for the 5 antimicrobial treatment regimens (Table 7); therefore, immediate culling of a cow with CM is unprofitable.

It would be interesting to include a no-treatment scenario in our model. We decided not to include this scenario for 2 reasons. First, in the Netherlands, almost all CM cases are treated with antimicrobials. Nontreatment of CM cases is very rare, and therefore including this scenario does not reflect reality for Dutch farms. Second, very detailed information was needed for our model; for instance, for the bacteriological cure. Few reports exist on leaving CM cases untreated (Guterbock et al., 1993; Roberson et al., 2004); therefore, for the authors (and other experts), it was very difficult to give cure estimates for the no-treatment scenario, and thus we decided not to include it. We expect that including the no-treatment scenario based on best guesses would not reflect reality and could result in erroneous conclusions.

Benefits of CM treatment also include prevention of mastitis in other cows on the farm. Halasa et al. (2009) mentioned the importance of transmission of pathogens for the costs of CM. van den Borne et al. (2010) showed that lactational treatment of contagious subclinical mastitis seems economically beneficial in dairy herds that implement management measures to decrease the transmission of contagious mastitis pathogens such as *Staph. aureus*. The intensive antibiotic treatment regimens resulted in higher probabilities of bacteriological cure than did the standard treatment regimen (Table 6), and these intensive treatment regimens will therefore prevent more new CM cases in other cows than would the standard treatment regimen. It is expected that also including these benefits will favor the intensive antibiotic treatment regimens more. To include these benefits, the within-herd dynamics of infection must be included and development of a herd-level model would be necessary. The model developed in our study simulated single CM cases, and it was not possible to properly include within-herd dynamics of infection.

Dairy farmers do not always make cost-effective decisions, and factors other than the costs influence mastitis management decisions (Valeeva et al., 2007). For specific cows with CM, farmers will prefer a treatment that results in the highest probability of cure instead of the lowest total cost. Making these decisions will not result in a cost-effective decision, but for some farmers a cured cow is more important. For some specific CM cases, the extra amount of money needed to reach a higher probability of cure is small. For instance, treating with IMM5 instead of IMM3 for a *Staph. aureus* CM will result in an additional \$5, but the probability of cure will increase by 0.25 (Figure 2). This implies

that using the intensive antibiotic treatments for *Staph. aureus* CM is more economically beneficial than for CM cases caused by other pathogens. Bacteriological culture results are available too late; therefore, the choice of treatment needs to be made before knowing the causal pathogen. Several models, however, were developed that can aid in diagnosis of the causal pathogen (Jones and Ward, 1990; Heald et al., 2000; de Haas et al., 2004; Steeneveld et al., 2009).

Recently, promising results have been presented about on-farm culture systems to determine the causal pathogen of CM (Lago et al., 2009; Keefe et al., 2010). For mild or moderate CM cases, no difference in probability of cure (Keefe et al., 2010), CM recurrence, SCC, milk production, or culling (Lago et al., 2009) was observed between CM cases treated immediately and cases treated 24 h after detection. It would be very interesting to evaluate the use of these on-farm diagnostic tests economically. Stochastic simulation would be a suitable tool to do so. Compared with the current model, the model structure would be different: all possible outcomes of on-farm bacteriological culture would have to be included, including major and minor pathogens and bacteriological negative outcomes.

With increasing automation on dairy farms, the possibilities for automated individual cow management have increased. Automated decision support on choice of CM treatment for individual cows is an example of automated individual cow management. To determine whether it is worthwhile to include choice of treatment in decision support models, we need to determine if choosing different antibiotic treatment for different cows is economically beneficial. Because of the cow-specific probabilities of cure, we expected that cow-specific treatment would be economically beneficial. Based on our assumptions, however, cow-specific treatment of CM was not economically beneficial.

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