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Bioeconomic modeling of lactational antimicrobial treatment of new bovine subclinical intramammary infections caused by contagious pathogens

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ABSTRACT

This study determined the direct and indirect epidemiologic and economic effects of lactational treatment of new bovine subclinical intramammary infections (IMI) caused by contagious pathogens using an existing bioeconomic model. The dynamic and stochastic model simulated the dynamics of *Staphylococcus aureus*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, and *Escherichia coli* during lactation and the dry period in a 100-cow dairy herd during 1 quota year. Input parameters on cure were obtained from recent Dutch field data. The costs of clinical IMI, subclinical IMI, and intervention were calculated into the combined total annual net costs of IMI per herd. The cost effectiveness of 4 scenarios with lactational intervention was determined; scenarios included no intervention, treatment after 1 mo of infection, treatment after 2 mo of infection, and treatment after 1 mo of infection and culling of uncured cows after 2 mo of infection. Model behavior was observed for variation in parameter input values. Compared with no lactational intervention, lactational intervention of new subclinical IMI resulted in fewer clinical flare ups, less transmission within the herd, and much lower combined total annual net costs of IMI in dairy herds. Antimicrobial treatment of IMI after 1 mo of infection and culling of uncured cows after 2 mo of infection resulted in the lowest costs, whereas treatment after 2 mo of infection was associated with the highest costs between the scenarios with intervention. Changing the probability of cure resulted in a nonlinear change in the cumulative incidence of IMI cases and associated costs. Lactational treatment was able to prevent IMI epidemics in dairy herds at high transmission rates of *Strep. uberis*, *Strep. dysgalactiae,* and *E. coli*. Lactational treatment did not limit the spread of *Staph. aureus* at high transmission rates, although the associated costs were lower compared with no intervention. To improve udder health in a dairy herd, lactational treatment of contagious subclinical IMI must therefore be preceded by management measures that lower the transmission rate. Lactational treatment of environmental subclinical IMI seemed less cost effective. Detection of subclinical IMI needs improvement to be able to most effectively treat subclinical IMI caused by contagious pathogens during lactation.
Key words: subclinical mastitis, antimicrobial treatment, stochastic economic model, transmission

INTRODUCTION

Subclinical mastitis in cows may cause production losses (Reksen et al., 2007; Whist et al., 2007, 2009), increased SCC, and higher probabilities of clinical flare ups and culling (Reksen et al., 2006; Whist et al., 2007, 2009). Moreover, subclinical mastitis can spread to other healthy cows (Zadoks et al., 2001, 2002), causing additional losses in those cows. Consequently, subclinical mastitis results in considerable economic losses in dairy herds worldwide (Halasa et al., 2007).

After diagnosis with bacteriological culture, antimicrobial treatment of subclinical mastitis during lactation is suggested to improve udder health in the dairy herd (Barkema et al., 2006). Bacteriological cure of subclinical mastitis is affected by treatment factors (Barkema et al., 2006), cow characteristics (Sol et al., 1997; Deluyker et al., 2005; Sandgren et al., 2008), and strain type (Sol et al., 1997; Dingwell et al., 2006; van den Borne et al., 2010a). Cure of subclinical mastitis after antimicrobial treatment may contribute to decreased probabilities of clinical flare ups and culling, reduced SCC and milk loss within the treated cows (direct effects), and a reduced transmission within the herd, preventing additional losses in other cows (indirect effects; Barkema et al., 2006). Economic modeling of antimicrobial treatment of subclinical mastitis during lactation, using deterministic (Swinkels et al., 2005a,b) and stochastic (Steeneveld et al., 2007) models, revealed that treatment of subclinical mastitis may be beneficial for some cows, depending on the economic value and the probability of

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cure of the cow. However, only chronic cases were evaluated in these static models, whereas early treatment of subclinical mastitis tends to improve bacteriological cure (van den Borne et al., 2010b). Furthermore, transmission of pathogens was taken into account at the cow level but not at the herd level. The reduction of infected cows through lactational treatment, combined with an increasing number of susceptible cows or other aspects of transmission dynamics, were not modeled in these previous studies.

Using a deterministic dynamic simulation model, Barlow et al. (2009) identified antimicrobial treatment to have positive indirect effects caused by reduced IMI transmission within dairy herds with low to moderate transmission rates. The positive indirect effects disappeared when transmission rates were high because recovered (and thus susceptible) quarters rapidly became infected again. The authors therefore suggested that treatment of subclinical IMI during lactation had to be preceded by management practices that decrease transmission of IMI within the herd (e.g., segregation, culling of infected cows, or postmilking teat disinfection) to have positive indirect effects. However, no economic evaluation of lactational treatment of pathogen-specific subclinical IMI was carried out in that study. Also, the imperfect detection of IMI was not modeled, whereas it may have epidemiological and economic consequences. Consequently, a further exploration of the economic efficacy of antimicrobial treatment of subclinical IMI during lactation seemed warranted.

The objective of this study was to investigate the direct and indirect epidemiologic and economic effects of early lactational antimicrobial treatment of contagious subclinical mastitis with the use of a bioeconomic simulation model.

MATERIALS AND METHODS

Model Description

The bioeconomic model used in this study is a previously described stochastic and dynamic simulation model with some modifications to evaluate lactational intervention of subclinical mastitis during 1 quota year. The model simulates the dynamics of pathogen-specific IMI within dairy herds during lactation (Halasa et al., 2009b) and the dry period (Halasa et al., 2010). At each time period, a cow was either free of IMI (and considered susceptible) or infected. When infected, the subclinical state was distinguished from the clinical state. The model was written in Mathematica 6.0 (Wolfram Research, Champaign, IL). In brief, the dynamics of *Staphylococcus aureus*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, and *Escherichia coli* were simulated at cow level using a discrete event model in a dairy herd with initial 100 cows in a milk quota system. Each time period in the model was 2 wk (Halasa et al., 2009b, 2010). Reed-Frost models were used to model IMI dynamics of contagious pathogens (i.e., *Staph. aureus*, *Strep. uberis*, and *Strep. dysgalactiae*) during the lactation (Zadoks et al., 2001, 2002), and a Greenwood model was used to model IMI dynamics of *E. coli* (Barkema et al., 1998). Transmission dynamics in a Reed-Frost model depend on the number of infectious individuals, where risk of infection increases with increased number of infectious individuals (Becker, 1989). Transmission in the Greenwood model is independent of the number of infectious individuals (Becker, 1989). The environment was considered an infectious individual that was always present (Halasa et al., 2009b). Greenwood models for all 4 pathogens were assumed to represent IMI dynamics during the dry period (Halasa et al., 2010). Dry cow therapy was applied to every cow at drying off. Clinical IMI cases were assumed to be treated with antibiotics for 3 d during lactation and the dry period, whereas no antimicrobial treatment was assumed for subclinical IMI cows. After 3 d of antibiotic treatment of a clinical cow, the cow could recover based on pathogen-specific probabilities of cure or it could persist as a subclinical IMI cow until the end of that time period. A subclinical IMI cow could recover based on pathogen-specific probabilities of spontaneous cure, flare up as a clinical IMI cow, or persist as a subclinical IMI cow to the next time period. Lactational intervention of subclinical IMI cows was added in the current study.

During lactation, the probability of acquiring an IMI was determined at the beginning of each time period, based on the number of pathogen-specific IMI cows in the previous time period, the number of susceptible cows, and a pathogen-specific transmission rate (Table 1). For *E. coli* IMI, a constant probability of infection during lactation was used, based on the cumulative incidence of *E. coli* IMI per 14 cow-days at risk. During the dry period, the probability of new IMI per 14 cow-days at risk and the cure of existing IMI at dry off following antimicrobial treatment were based on the literature (Halasa et al., 2010).

Cows were culled with a certain probability at each time step because of clinical IMI, subclinical IMI, or other reasons (Halasa et al., 2009b) and were replaced by heifers based on the need for new animals to fill the milk quota (Houben et al., 1994; Østergaard et al., 2005). A replacement heifer entered the herd when the production deficiency of the herd was more than the average production of a replacement heifer (Halasa et al., 2009b). Milk losses attributed to IMI were calculated as follows (Halasa et al., 2009b). The actual milk production was calculated for each lactating cow during

Table 1. Force of infection and probabilities of spontaneous cure and cure after antimicrobial treatment for 4 pathogens per 14 d at risk[1]

Parameter	Value	Lower limit	Upper limit
Staphylococcus aureus			
Transmission rate	0.25		
Spontaneous cure rate	0.09		
Cure rate after treatment	0.61	0.47	0.75
Streptococcus uberis			
Transmission rate	0.21		
Spontaneous cure rate	0.20		
Cure rate after treatment	0.65	0.46	0.85
Streptococcus dysgalactiae			
Transmission rate	0.21		
Spontaneous cure rate	0.16		
Cure rate after treatment	0.79	0.61	0.97
Escherichia coli			
Cumulative incidence	0.002		
Spontaneous cure rate	0.31		
Cure rate after treatment	1.00	1.00	1.00

[1]The lower and upper limits were used to study model behavior.

each time period in the model. Consequently, the herd actual milk production was calculated based on the actual milk production of the lactating cows while including the effects of culling and IMI (Gröhn et al., 2004; Halasa et al., 2009a). Similarly, an expected optimal herd milk production was calculated without culling and IMI production effects. This was used to estimate the kilograms of milk that should be produced per time period to fulfill the herd-level milk quota by the end of the quota year. The calculated difference between the actual and the expected herd-level milk production at each time period was used to decide on the introduction of replacement heifers, similar to how the milk quota was filled by replacement heifers for culled cows.

Modeling Intervention Scenarios

Three scenarios of lactational subclinical IMI interventions were modeled and compared with a default scenario (without lactational subclinical IMI intervention). In scenario 1, a susceptible cow that was subclinically infected for 2 consecutive time periods (i.e., 1 mo) received antimicrobial treatment at the beginning of the third time period. In scenario 2, a susceptible cow that was subclinically infected for 4 consecutive time periods (i.e., 2 mo) received antimicrobial therapy at the beginning of the fifth time period. Scenario 3 was similar to scenario 1, but if the treated cow remained subclinically infected for 2 more consecutive time periods after treatment, the cow was culled at the end of the fourth time period. Scenarios 1 and 2 simulated antimicrobial treatment at different duration of IMI, whereas scenario 3 simulated early treatment of IMI combined with culling of cows that did not show bacteriological cure. These scenarios were selected to mimic treatment timing of a recently conducted randomized field trial (van den Borne et al., 2010b).

The pathogen-specific spontaneous cure per 14 d and the pathogen-specific probability of cure after antimicrobial treatment of subclinical IMI cows were obtained from recent Dutch field data (van den Borne et al., 2010b) and are presented in Table 1. Probabilities of spontaneous cure were recalculated per 14 d, assuming a constant rate of cure throughout the month after detection. In the default scenario, subclinical IMI cows were subjected to the pathogen-specific spontaneous cure rate at each time period. In the intervention scenarios, IMI cows were subjected to the pathogen-specific spontaneous cure rates at each time period, except for the time period of antimicrobial therapy, in which they were subjected to the pathogen-specific probability of cure after 3 d of antimicrobial therapy (Table 1). A similar probability of cure after antimicrobial treatment of the selected subclinical IMI cows was modeled for scenarios 1 and 2 to investigate the effect of delayed treatment on IMI transmission. Cows were again subjected to the pathogen-specific spontaneous cure rates in case they did not recover and persisted as subclinical IMI cows. Subclinical IMI cows were treated with antibiotics for 3 d in case they flared up to clinical IMI, resulting in a pathogen-specific cure rate as described (Halasa et al., 2009b). Then, they did not fall under the lactational subclinical IMI intervention.

Economic Analysis

Costs of lactational intervention were calculated as 1) the costs of culturing 4 quarters to diagnose IMI per subclinical IMI cow (€19/cow laboratory costs; www.gddeventer.com) and 10 min labor time (based on au-

thors' experience), 2) the labor costs to apply the antibiotics (which was the labor time multiplied by a labor wage), 3) the costs of antibiotics per treated subclinical IMI cow, and 4) the costs of milk withdrawal for 6 d after antimicrobial therapy, which was calculated as the costs of a replacement heifer to produce the withdrawn milk, similar to the way the milk loss for clinical and subclinical IMI was calculated (Halasa et al., 2009b). Input values on antibiotics, labor wage, and labor time were according to Halasa et al. (2009b).

Costs of clinical and subclinical IMI during lactation were calculated as follows (Halasa et al., 2009b). The sum of the costs of milk yield loss attributed to clinical IMI, costs of culling (the sum of the retention pay off values of the culled cows), costs of veterinary service, and costs of labor and antibiotics minus the saved costs, which is attributed to lower feed costs (Halasa et al., 2009b), were calculated into the annual net costs of clinical IMI caused by the 4 simulated IMI pathogens. The annual net costs of subclinical IMI caused by the 4 IMI pathogens was calculated as the sum of the costs of milk yield loss attributed to subclinical IMI, costs of culling, and the bulk tank SCC penalty, minus the saved costs of feed. The costs of a clinical case during the early or late dry period consisted of the costs of antibiotics for 3 d and the labor time to apply the antibiotics.

The combined total annual net costs of IMI caused by the 4 simulated IMI pathogens were calculated as the sum of the annual net costs of clinical and subclinical IMI and the intervention costs per scenario. Costs were presented in Euros as average and in 5th and 95th percentiles to represent the economic variation. The cumulative incidences of IMI events and the combined total annual net costs of IMI between scenarios 1, 2, and 3 and the default scenario were compared to determine the effectiveness of early treatment of contagious subclinical IMI during lactation.

Parameter Input Variation

The model assumed perfect overall sensitivity of the test system (i.e., composite SCC and bacteriological culturing) to identify new IMI in the 3 scenarios with lactational treatment, which is similar to the model study of Barlow et al. (2009). However, the sensitivity is not 100% in dairy practice (Sanford et al., 2006), but lower and unknown. Hence, a probability of detection of 25, 50, and 75% was assumed to identify and treat subclinical IMI cows in scenario 1 in separate model runs. To observe model behavior to variation in cure probabilities, the probability of cure after antimicrobial treatment for all 4 pathogens was varied simultaneously according to the 95% confidence interval observed in the field (van den Borne et al., 2010b; Table 1). The effect of extended antimicrobial treatment duration for subclinical IMI cows in scenario 1 was also investigated. Antimicrobial treatment was assumed to be 6 d and would hypothetically result in a higher cure of IMI, which was assumed to be 80% for all pathogens except for *E. coli*, which had a probability of cure of 100% (van den Borne et al., 2010b). In these model runs, milk withdrawal would extend to 9 d and costs of medicines and labor time to treat a selected subclinical IMI cow would double. In scenario 2, additionally, the probability of cure after antimicrobial treatment of subclinical *Staph. aureus* IMI cows was reduced to 45.8% according to field observations (van den Borne et al., 2010b). Finally, model behavior analysis was also conducted for scenario 1 by changing the pathogen-specific transmission rate parameter one at a time in separate model runs by 1/2, 2/3, 1, 1 1/4, 1 1/2, and 2 times the default value (Table 1). This was replicated for *Staph. aureus* in the default scenario without treatment to determine whether antimicrobial treatment of subclinical *Staph. aureus* IMI at different transmission rates is economically beneficial. Changes to economic input values in the model were not evaluated because initial model runs identified costs of detection and treatment of IMI to be relatively low compared with the direct and indirect economic benefits.

Model Run and Stabilization

The model was run for 2 quota years, starting with the same endemic herd situation per model run to ensure a stable infection process over time (Halasa et al., 2009b). The rate of pathogen-specific IMI at the end of the second quota year was used to start a new model run for 2 quota years to be used for epidemiologic and economic assessment. The epidemiologic and economic output from the second quota year only was used to conduct the assessment per scenario to simulate the effect of the applied intervention in the herd and not the initial herd status (Østergaard et al., 2005). The model was replicated until the change in the combined total annual net costs of IMI changed by $<2\%$, which was the case using at least 3,000 iterations. The model was iterated 1,000 times when observing model behavior for different transmission rates.

RESULTS

Intervention Scenarios

Herd performance not related to IMI (e.g., replacements rates, milk production, number of dry cows) is described elsewhere (Halasa et al., 2009b, 2010) and

Table 2. Average, median, and 5th and 95th percentiles of 3,000 iterations of the annual cumulative incidence of clinical and subclinical IMI cases in 4 scenarios[1] with lactational subclinical IMI intervention in a 100-cow dairy herd[2]

		Clinical		Subclinical			
Scenario	Total	Subtotal	Originated from flare up	Subtotal	Treated	Cured after treatment	Culled
Default							
Average	78	37	21	41	—	—	—
Median	73	34	—	38	—	—	—
5th and 95th percentiles	9–168	7–77	—	2–93	—	—	—
1							
Average	27	15	5	12	8	6	—
Median	20	12	—	8	—	—	—
5th and 95th percentiles	6–69	4–33	—	1–37	—	—	—
2							
Average	45	23	11	22	8	5	—
Median	34	19	—	16	—	—	—
5th and 95th percentiles	8–114	5–52	—	1–64	—	—	—
3							
Average	18	11	3	7	5	3	1
Median	15	10	—	5	—	—	—
5th and 95th percentiles	6–42	4–22	—	1–21	—	—	—

[1]Scenarios: default = no intervention; 1 = treatment after 1 mo of infection; 2 = treatment after 2 mo of infection; 3 = treatment after 1 mo of infection and culling of uncured cows after 2 mo of infection.

[2]The median and 5th and 95th percentiles of subtotals do not add up because they can originate from different iterations but were presented to represent the variation in IMI occurrence.

did not differ between model scenarios. The annual cumulative incidences of IMI per model scenario of lactational intervention of subclinical IMI are presented in Table 2. In the default scenario, without lactational treatment, the median cumulative incidence of total IMI was 73, whereas in the scenarios with lactational treatment, the median cumulative incidences of total IMI cases were considerably lower: 20, 34, and 15 for scenarios 1, 2, and 3, respectively. The median cumulative incidences of treated IMI were similar in scenarios 1 and 2, but occurrence of clinical and subclinical IMI was higher when subclinical IMI was treated after 2 mo of infection compared with treatment after 1 mo of infection. The median cumulative incidence of IMI cows that were culled because of intervention (scenario 3) was 1 and resulted in a lower median cumulative incidence of subclinical IMI to be treated and in fewer clinical and subclinical IMI cases compared with scenario 1. Variation in IMI occurrence was lower in the 3 scenarios with lactational treatment compared with the default scenario without treatment (Table 2).

Antimicrobial treatment of subclinical IMI after 1 mo of infection resulted in lower probabilities of clinical IMI flare ups compared with the default scenario and scenario 2 (lactational treatment after 2 mo of infection). In the default scenario without lactational intervention, 57% (21/37) of clinical IMI resulted from subclinical infections, whereas in scenarios 1, 2, and 3, average proportions of clinical IMI resulting from flare ups were 33% (5/15), 48% (11/23), and 27% (3/11), respectively (Table 2).

Average costs associated with IMI for the 4 scenarios are presented in Table 3 and represent the costs of clinical IMI during lactation and the dry period, the costs of subclinical IMI during lactation, and the costs of subclinical IMI intervention. The average combined total annual net costs of IMI in the default scenario (no treatment of subclinical IMI) were €9,060 and varied widely: the 5th and 95th percentiles were €1,088 and €19,827, respectively. Average combined total annual net costs of IMI were €5,084, €2,979, and €5,741 lower in scenarios 1, 2 and 3, respectively, compared with the default scenario without lactational subclinical IMI intervention. Moreover, less variation in combined total annual net costs of IMI was observed in the scenarios with treatment. Comparing the scenarios with lactational intervention, average costs of clinical and subclinical IMI were the lowest when uncured cows from treatment after 1 mo of infection were culled after the second month of infection (scenario 3) and were the highest when antibiotics were administered after 2 mo of infection (scenario 2). Costs of subclinical IMI intervention were relatively similar among scenarios 1, 2, and 3. In scenarios 1 and 2 (treatment after 1 or 2 mo of infection), costs of subclinical IMI intervention consisted mainly of treatment costs of IMI cows (i.e., labor and antibiotics). In scenario 3, with treatment and culling, costs of subclinical IMI intervention were mainly attributed to culling. Annual culling costs attributed to intervention were on average €613 in this scenario, but the 95th percentile was €2,511, indicating high associated culling costs in some situations. Costs

Table 3. Average annual costs (5th and 95th percentiles) of intervention of new subclinical IMI during lactation for 4 scenarios[1] in a 100-cow dairy herd[2]

	Scenario			
Cost-benefit factor (€)	Default	1	2	3
Costs of subclinical IMI during lactation	3,899 (0–9,558)	918 (0–3,018)	1,911 (0–5,535)	479 (0–1,510)
Milk loss	210 (9–488)	49 (3–148)	102 (6–290)	25 (2–77)
Culling	3,892 (0–9,543)	916 (0–3,013)	1,908 (0–5,525)	478 (0–1,507)
Saved costs	203 (9–470)	47 (3–143)	98 (5–280)	24 (2–74)
Costs of subclinical IMI intervention	—	1,006 (0–3,120)	988 (0–2,995)	1,317 (0–4,553)
Bacteriological culture	—	185 (0–569)	181 (0–547)	219 (0–656)
Labor	—	305 (0–936)	298 (0–900)	180 (0–540)
Milk withdrawal	—	178 (0–586)	178 (0–552)	104 (0–340)
Antibiotics	—	339 (0–1,040)	331 (0–1,000)	200 (0–600)
Culling	—	—	—	613 (0–2,511)
Costs of clinical IMI during lactation	5,056 (759–10,789)	2,008 (422–4,786)	3,115 (590–7,498)	1,493 (338–3,278)
Milk loss	1,083 (166–2,334)	412 (103–994)	662 (133–1,617)	291 (86–631)
Antibiotics	1,477 (280–3,080)	588 (160–1,320)	901 (200–2,080)	434 (160–880)
Veterinary services	277 (53–578)	110 (30–248)	169 (38–390)	81 (30–165)
Labor	1,330 (252–2,772)	529 (144–1,188)	811 (180–1,872)	391 (144–792)
Culling	1,934 (0–4,520)	767 (0–2,009)	1,211 (0–3,516)	576 (0–1,507)
Saved costs	1,044 (160–2,251)	398 (99–958)	638 (128–1,559)	280 (83–609)
Costs of clinical IMI during dry period	105 (0–304)	44 (0–152)	66 (0–228)	29 (0–152)
Combined total net costs of IMI	9,060 (1,088–19,827)	3,976 (673–10,218)	6,081 (878–15,624)	3,319 (670–8,673)

[1]Scenarios: default = no intervention; 1 = treatment after 1 mo of infection; 2 = treatment after 2 mo of infection; 3 = treatment after 1 mo of infection and culling of uncured cows after 2 mo of infection.

[2]The 5th and 95th percentiles do not add up because they can originate from different iterations but were presented to represent the variation in costs.

of bacteriological culturing and milk withdrawal were relatively low in the 3 scenarios with treatment compared with the total costs of lactational intervention of subclinical IMI. Average costs of clinical IMI during the dry period were lower in the scenarios with lactational treatment compared with the default scenario.

Parameter Input Variation

Cure Rates. The model was sensitive to variation in cure rate estimates. A lower median cumulative incidence of total IMI was observed in the situation with high probability of bacteriological cure compared with the situation with low probability (Table 4). The average proportion of clinical IMI resulting from flare ups was 33% (4/12) when cure probabilities were high, whereas the average proportion of clinical IMI resulting from flare ups was 42% (8/19) when cure probabilities were low. Compared with the default probability of cure in scenario 1, the average combined total annual net costs of IMI were €911 lower when cure probabilities were high, whereas the combined total annual net costs of IMI were on average €1,502 higher when cure probabilities were low.

Occurrence of IMI was higher when in scenario 2 (treatment after 2 mo of infection) the probability of cure of *Staph. aureus* was decreased to 45.8%. The median cumulative incidences of total, clinical, and

Table 4. Median cumulative incidence of annual clinical and subclinical IMI cases and the average combined total annual net costs of IMI in a 100-cow dairy herd after lactational treatment of subclinical IMI after 1 mo of infection (scenario 1) with default, low, and high probabilities of cure[1]

	Probability of cure		
Cumulative incidence of IMI cases	Default	Low	High
Total	20	26	16
Clinical	12	15	11
Originated from flare ups	3	5	2
Subclinical	8	11	6
Treated	5	8	4
Cured after treatment	4	4	3
Combined total net costs of IMI (€)	3,976	5,478	3,065

[1]See Table 1.

subclinical IMI cases were 44, 22, and 21, respectively. The average cumulative incidence of clinical IMI cases resulting from flare ups was 13 (50% of total clinical IMI cases), whereas the median cumulative incidence of cured IMI after treatment was 4 out of 7. The average combined total annual net costs of IMI were €7,363.

Increasing the duration of treatment to 6 d resulted in similar annual intervention costs (i.e., €1,133) compared with the same scenario with 3-d treatment duration (scenario 1; Table 3). Costs of bacteriological culture, labor, milk withdrawal, and antibiotics were €120, €396, €177, and €440, respectively. Because of increased cure probabilities, transmission of IMI was lower compared with scenario 1 (Table 2). The median cumulative incidences of total, clinical, and subclinical IMI were 16, 10, and 6, respectively. The average cumulative incidence of clinical IMI cases resulting from flare ups was 3 (25% of total clinical IMI), and the median cumulative incidence of treated subclinical IMI cases was 4, of which 3 cured. The average combined total annual net costs of IMI were €3,373 in this analysis.

Transmission. The bioeconomic model was sensitive to changes in *Staph. aureus* transmission rate (Figure 1). Treatment after 1 mo of infection was not able to limit the spread of infection within the dairy herd for high *Staph. aureus* transmission rates, although IMI cases and associated costs were lower compared with the default scenario. At the *Staph. aureus* transmission rate of 1 1/2 times the default, 130 total IMI cases were observed for scenario 1 with treatment, whereas 321 total IMI cases were observed for the default scenario without treatment. Both situations resulted in extreme associated losses. At the *Staph. aureus* transmission rate of 2 times the default, the model became instable because all cows became infected in both the default scenario and scenario 1. Treatment of subclinical *Staph. aureus* IMI was also economically beneficial at low transmission rates because lower combined total annual net costs of IMI were observed in the scenario with treatment compared with the scenario without treatment, but the difference between the scenarios became smaller (Figure 1). Decreasing the *Staph. aureus* transmission rate at high values in the default scenario without treatment resulted in a similar decrease in IMI cases and associated costs compared with the scenario with treatment of subclinical IMI. Treatment of *Strep. uberis*, *Strep. dysgalactiae*, and *E. coli* after 1 mo of infection at each force of infection value was economically profitable because the median cumulative incidence of total IMI cases and the average combined total annual net costs of IMI were always lower than in the situation without treatment with 1 times the default force of infection for all 4 pathogens.

IMI Detection. Fewer subclinical IMI cases were selected for treatment when sensitivity of IMI detection decreased. Subsequently, this resulted in an increasing cumulative incidence of clinical and subclinical IMI cases in the dairy herd (Table 5). The average combined total annual net costs of IMI increased with decreasing overall sensitivity of IMI detection but were still lower than the combined total annual net costs of IMI in the default scenario without treatment (Table 3).

DISCUSSION

The direct and indirect effects of lactational intervention of subclinical IMI, as observed by Barlow et al. (2009) in a deterministic model, were further investigated in the current study using a stochastic simulation model. This stochastic model included the economics of pathogen-specific IMI dynamics and was used to assess the epidemiologic and economic efficiency in 3 scenarios with lactational intervention of new subclinical IMI. Based on a 100% sensitive method to detect subclinical IMI, all 3 scenarios with lactational intervention of contagious pathogens resulted in lower costs of IMI compared with the default scenario without intervention. Treatment of subclinical IMI after 1 mo of infection in combination with culling of noncured IMI cows after 2 mo of infection resulted in the lowest cumulative incidence of IMI cases and associated costs. Compared with this scenario, more IMI transmission occurred in the treatment scenarios without culling as observed by a higher cumulative incidence of IMI cases, resulting in more associated costs of IMI. Postponing treatment of contagious pathogens for 1 mo resulted in more IMI transmission and higher IMI-associated costs within dairy herds.

Relatively little quantitative knowledge exists on transmission of contagious IMI within dairy herds. The pathogen-specific transmission parameter estimates from the current model were obtained from the 3 herds studied by Zadoks et al. (2001, 2002). Model behavior according to different transmission rates was determined because differences in IMI transmission may be expected between dairy herds because of differences in strains and mastitis management. The model was highly sensitive to variation in the *Staph. aureus* transmission rate, both in the default scenario without lactational treatment and in scenario 1 with treatment after 1 mo of infection. Importantly, lactational treatment was economically beneficial at all *Staph. aureus* transmission rates, but the economic difference between treatment and no treatment became smaller with lower transmission rates. The model with lactational treatment after 1 mo of infection (scenario 1) was less

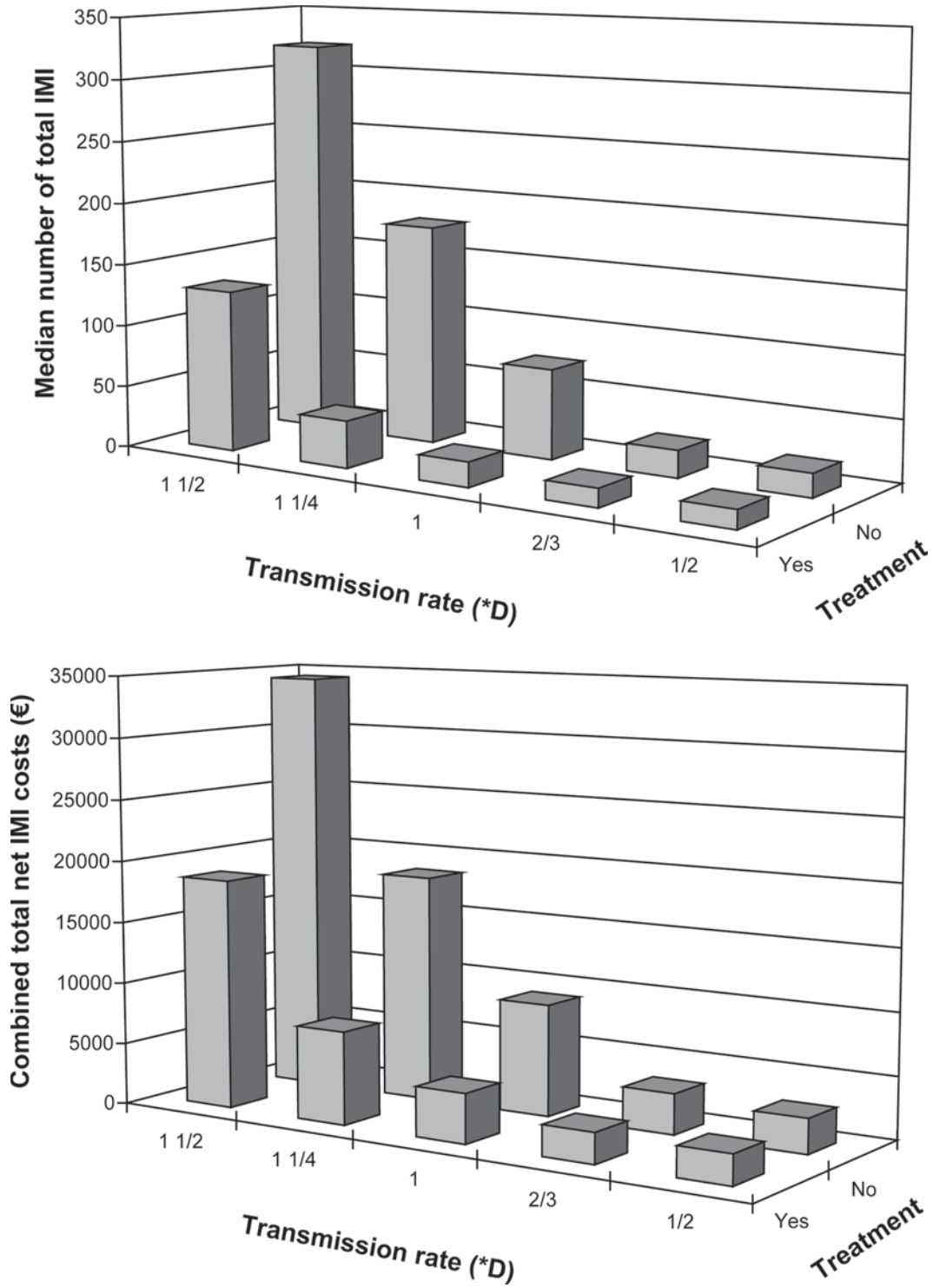

Figure 1. Median annual cumulative incidence of total IMI cases (top) and associated average combined total annual net costs of IMI (bottom) in a 100-cow dairy herd with 1/2, 2/3, 1, 1 1/4, and 1 1/2 times the default (D) *Staphylococcus aureus* transmission rate for the default scenario without lactational treatment and scenario 1 with treatment after 1 mo of infection. The model estimates of 2 times the default *Staph. aureus* transmission rate are not presented because all cows within the herd became infected, resulting in unstable models in both scenarios.

Table 5. Median cumulative incidence of annual IMI cases and the average total annual net costs of IMI for scenario 1 (treatment after 1 mo of infection) with 100 (default), 75, 50, and 25% probability of IMI detection in a 100-cow dairy herd

Cumulative incidence of IMI cases	Probability of IMI detection (%)			
	100	75	50	25
Total	20	27	39	50
Clinical	12	15	20	25
Originated from flare ups	3	5	9	12
Subclinical	8	12	18	25
Treated	5	6	6	4
Cured after treatment	4	4	4	2
Combined total net costs of IMI (€)	3,976	5,042	6,459	7,221

sensitive to changes in streptococci transmission rates and to changes in the cumulative incidence of *E. coli*. Barlow et al. (2009) identified lactational treatment to have the largest beneficial indirect effects at the herd level when IMI transmission was low to moderate. Our study identified lactational treatment to be economically efficient for all *Staph. aureus* transmission rates because IMI-associated costs were always lower compared with the default scenario without treatment. However, lactational treatment of subclinical IMI was not able to prevent within-herd epidemics of *Staph. aureus* IMI for high transmission rates, and lowering the transmission rate in the default scenario without treatment had a similar decreasing effect compared with the scenario with lactational treatment of subclinical IMI. Antimicrobial treatment of subclinical mastitis IMI must therefore be preceded by management measures to decrease the transmission rate within dairy herds (e.g., culling or segregation of IMI cows or post milking teat disinfection) as suggested (Barlow et al., 2009).

In previous economic evaluations of lactational treatment of subclinical IMI using deterministic (Swinkels et al., 2005a,b) and stochastic models (Steeneveld et al., 2007), it was identified that antimicrobial treatment of chronic subclinical IMI was beneficial for some cows, depending on certain cow and herd characteristics and the economic value of the cow. For example, antimicrobial treatment of subclinical *Strep. uberis* IMI seemed economically beneficial for cows with a high retention pay off (e.g., primiparous cows in early lactation) in dairy herds with a high transmission rate, whereas treatment seemed detrimental for cows with a low retention pay off in dairy herds with a low transmission rate (Steeneveld et al., 2007). Recent research could not identify cow factors to be related to bacteriological cure of new subclinical IMI, and early treatment tended to improve bacteriological cure (van den Borne et al., 2010b). Therefore, the economic calculations by Swinkels et al. (2005a,b) and Steeneveld et al. (2007) may not apply for new subclinical IMI cases as modeled in the current study. Additionally, nonlinear IMI dynamics were shown to cause indirect effects within dairy herds in the model study of Barlow et al. (2009) as well as in the current study. We conclude that lactational intervention of new subclinical IMI can reduce IMI-associated costs at the herd level more then previously estimated.

The model was sensitive to changes in the cure rate of subclinical IMI after antimicrobial treatment during lactation. Median total IMI occurrence was 4 IMI cases lower and 6 IMI cases higher when the default cure probabilities for scenario 1 were adjusted to high and low probabilities of cure. The combined total annual net costs of IMI changed accordingly but remained lower than the default scenario without lactational treatment. More transmission was observed with higher associated costs of IMI when *Staph. aureus* cure rates were adjusted down in scenario 2. This stresses the importance of early intervention of subclinical IMI (Barkema et al., 2006; van den Borne et al., 2010b). Additionally, increased treatment duration seemed to outweigh the initial extra costs of treatment (antimicrobials and labor) if higher probabilities of cure are achieved, followed by lower IMI transmission within the herd. Although the probabilities of cure were hypothetical in these model runs, cure rates of 80% were observed previously (Deluyker et al., 2005).

The bioeconomic model that was used to study the direct and indirect effects of lactational intervention of subclinical IMI simplifies reality, as any other simulation model. Contagious transmission of *Staph. aureus*, *Strep. uberis*, and *Strep. dysgalactiae* was modeled (Zadoks et al., 2001, 2002), whereas *E. coli* was assumed to be of environmental origin (Barkema et al., 1998). However, at strain level, some strains may behave contagious and some environmental within the same pathogen specie (Zadoks et al., 2000, 2003). To reflect dairy herds with environmental IMI problems, transmission rates of contagious pathogens were set to 0 while the cumulative incidence of *E. coli* was increased. The model showed

similar cumulative incidences of IMI cases and slightly higher associated costs in the models with lactational treatment of environmental subclinical IMI compared with a model without lactational intervention (results not shown). This was the consequence of the absence of contagious transmission and the low clinical flare up rate of *E. coli* (Halasa et al., 2009b). It suggests that lactational treatment of subclinical IMI is not economically efficient when caused by environmental strains of pathogens with a low clinical flare up. Other management measures (e.g., improvement of the hygiene within the herd) should be implemented to control subclinical IMI from environmental origin. Strain typing of pathogens would be needed to discriminate contagious *Staph. aureus*, *Strep. uberis*, and *Strep. dysgalactiae* strains from strains originating from the environment.

Blanket dry cow therapy was applied in all 4 scenarios with or without lactational intervention of subclinical IMI. The effects of other dry cow intervention strategies were the subject of a separate study (Halasa et al., 2010). Cows did not receive lactational treatment of subclinical IMI in that study because this is not common practice in the Netherlands. It is difficult to predict the epidemiological and economic effects of lactational treatment when blanket dry cow therapy is not applied because of the nonlinear relationships in the model. However, the ranking of the scenarios would most likely not change because cost-effectiveness of various dry cow interventions were rather similar in the study of Halasa et al. (2010), indicating little effect on the number of infected animals within the herd.

Our model approach differed from Barlow et al. (2009), who modeled IMI dynamics using an SIR model at quarter level and differentiated susceptible quarters without a previous infection (S) from recovered and susceptible (R) quarters because a higher susceptibility to infection was observed in recovered quarters (Zadoks et al., 2001, 2002). In our study, an SIS model approach was applied at cow level with differentiation of the infectious state (I) in a clinical and a subclinical state. Our model underestimates the costs of clinical IMI and transmission of pathogens within the herd because multiple quarters within a cow can be infected. However, we believe that the differentiation between subclinical and clinical IMI is more appropriate for economic evaluations because milk losses and risks of culling are higher in the clinical state (Halasa et al., 2007). Moreover, we chose to model IMI dynamics at the cow level because economic decisions, such as treatment or culling of IMI cows, are generally made at the cow level. Nevertheless, the herd-level IMI dynamics were very similar in both models, indicating the potential to improve udder health in dairy herds with lactational treatment of subclinical IMI.

Currently, there is no 100% sensitive method available to validly identify new subclinical IMI in the field. New subclinical IMI cows may be identified by whole-herd culturing, but whole-herd samplings are labor intensive and costly. Composite SCC are commonly used in dairy practice as a first indication of subclinical IMI (Schukken et al., 2003), and milk samples are subsequently taken from high SCC cows to identify subclinical IMI (van den Borne et al., 2010b). Sensitivity of bacteriological culturing of subclinical IMI at the end of lactation was estimated to be 62 and 95%, using latent class models, for major and all pathogens, respectively, and ranged from 41 to 100% (Sanford et al., 2006). However, performing multiple tests in series (i.e., culturing of high SCC cows) results in a decreased (and yet unknown) sensitivity (Dohoo et al., 2003). A sensitivity analysis on IMI detection was therefore conducted in this study to evaluate its effect on IMI dynamics and economic efficiency. Increasing the number of false-negative IMI (i.e., decreasing the sensitivity) decreased the proportion of treated cases, as expected. This consequently resulted in an increased transmission of IMI within the herd with higher associated costs. Detection of IMI in the field has to improve to contribute to lower IMI-associated costs after lactational treatment of contagious subclinical IMI in dairy herds.

CONCLUSIONS

Lactational intervention with antimicrobials of new cases of contagious subclinical IMI resulted in fewer clinical flare ups and less transmission of pathogens within dairy herds using a stochastic and dynamic bioeconomic simulation model. Costs associated with IMI were the lowest when uncured cows were culled after treatment and the highest when no intervention was applied. Antimicrobial treatment of contagious new subclinical IMI may be an economically beneficial option to improve udder health in dairy herds that implement practices to reduce transmission rates of contagious pathogens. Detection of IMI needs to be optimized in the field before lactational intervention strategies can be most effectively applied in dairy herds.

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