

Economic and epidemiological impact of different intervention strategies for subclinical and clinical mastitis

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ABSTRACT

The objective of this study was to evaluate and compare different combinations of intervention strategies for contagious or opportunistic subclinical and clinical intramammary infections (IMI). We simulated two different Danish dairy cattle herds with ten different intervention strategies focusing on cow-specific treatment or culling, including three baseline strategies without subclinical interventions. In one herd, the main causative pathogen of IMI was *Staphylococcus (S.) aureus*. In the other herd, *Streptococcus (St.) agalactiae* was the main causative agent. For both herds, we investigated costs and effectiveness of all ten intervention strategies. Intervention strategies consisted of measures against clinical and subclinical IMI, with baselines given by purely clinical intervention strategies. Our results showed that strategies including subclinical interventions were more cost-effective than the respective baseline strategies. Increase in income and reduction of IMI cases came at the cost of increased antibiotic usage and an increased culling rate in relation to IMI. However, there were differences between the herds. In the *St. agalactiae* herd, the clinical intervention strategy did not seem to have a big impact on income and number of cases. However, intervention strategies which included cow-specific clinical interventions led to a higher income and lower number of cases in the *S. aureus* herd. The results show that intervention strategies including interventions against contagious or opportunistic clinical and subclinical IMI can be highly cost-effective, but should be herd-specific.

1. Introduction

Mastitis, or intramammary infection (IMI), causes considerable economic losses for many dairy cattle farms (e.g., Halasa et al., 2007). Costs for IMI arise from both treatment of cases and replacement of prematurely culled animals, as well as, indirectly, from production losses (e.g., Halasa et al., 2007). Production losses occur as a response to the inflammation, for both clinical (Gröhn et al., 2004; Hertl et al., 2014) and subclinical mastitis (Hortet et al., 1999; Halasa et al., 2009a). Consequently, there is a multitude of studies investigating the economic effects of clinical (e.g., Bar et al., 2008; Hagnestam-Nielsen and Østergaard, 2009) and subclinical IMI (e.g. Halasa et al., 2009b; Huijps et al., 2008). However, only a few studies explicitly investigated

the economic effects of intervention against clinical (Halasa, 2012) or subclinical IMI (e.g., Swinkels et al., 2005a; Steeneveld et al., 2007; van den Borne et al., 2010a), mainly focusing on treatment with antibiotics. Moreover, interventions for IMI are typically investigated separately for clinical or subclinical cases, albeit clinical and subclinical IMI could be considered as correlated issues. Reducing the number of infected quarters through treatment of subclinical cases should also lead to fewer flared up clinical cases (see, e.g., van den Borne et al., 2010a). In the case of contagious transmission, a good intervention strategy for clinical IMI can be expected to decrease IMI transmission (e.g., Steeneveld et al., 2011), thereby also leading to fewer subclinical cases. It is therefore not immediately clear how intervention strategies for subclinical or clinical IMI may interact. To our knowledge, there are no

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previous studies investigating the economic effects of interventions for subclinical and clinical IMI combined. Furthermore, the usual investigated intervention strategies are antibiotic treatments. Although culling could also be considered as an active and deliberate intervention for IMI, it is commonly only regarded as an unwanted measure that has to be taken as a consequence of IMI (Halasa and Hogeveen, 2018) and studied in the context of optimal replacement times (e.g., Heikkilä et al., 2012; Cha et al., 2014). Consumer awareness regarding antimicrobial resistance and its connection with antibiotic usage in food animals is rising (Ruegg, 2003). Thus, while antibiotics are important to control and prevent IMI, prudent use of antibiotics is essential. A combined cow-specific approach of culling or treating animals with subclinical IMI may therefore be sensible. For instance, low producing cows could be culled instead of treated if they are diagnosed with contagious subclinical IMI. This would minimize the risk of pathogen spread to healthy herd mates and reduce additional antibiotics usage, while still improving herd health. Still, the economic effects of such a strategy must be investigated. The aim of this simulation study was to evaluate intervention strategies for subclinical IMI, combined with different intervention strategies for clinical IMI, caused by contagious or opportunistic (both contagious and environmental) IMI causing pathogens. For this purpose, two different Danish dairy herds with 200 cows including cow- and strain-specific IMI transmission were simulated. In one herd, IMI cases were mainly caused by contagious *Staphylococcus* (*S.*) *aureus*, while they were mainly caused by opportunistic *Streptococcus* (*St.*) *agalactiae* in the other herd. These pathogens were chosen as they are of major concern both in Denmark and in other countries. For these herds, several subclinical and clinical intervention strategies were combined and farm economics, antibiotic usage, culling, and epidemiological parameters were compared.

2. Materials and methods

2.1. Herd and transmission model

The MiCull (Mastitis-iCull) model, version 3.0 was used in this study. The original MiCull version 1.0 was described in detail in Gussmann et al. (2018b); MiCull version 2.0 includes only intervention strategies for clinical IMI (Gussmann et al., 2019). The presented version 3.0 additionally includes intervention strategies for subclinical IMI, as described below. The model was programmed and all simulations were run in the statistical computing software R version 3.2.2 “Fire Safety” (R Core Team, 2015). Figures were made using the package ggplot2 (Wickham, 2009).

2.2. Herd model

The model is a stochastic mechanistic population model that simulates a Danish dairy herd with 200 cows in daily time steps (Gussmann et al., 2018b). All animals belong to one of five compartments (calves, heifers, lactating cows, dry cows, calving cows), and move on to the next compartment after a stochastically determined

number of days. Lactation (milk, protein, and fat) and somatic cell count (SCC) curves are estimated for all cows based on Græsbøll et al. (2016) and adjusted for IMI, i.e. increased SCC (Schepers et al., 1997; Wilson et al., 1997) and decreased milk yield (Hortet et al., 1999; Gröhn et al., 2004). Once a month, milk yield and SCC are recorded, and the expected future average production (FAP) of a cow is estimated as described by Græsbøll et al. (2017). If a cow is treated with antibiotics, the milk is withdrawn and discarded during treatment and for six days afterwards. Feeding of lactating cows depends on the produced milk.

2.3. Transmission framework

The model simulates IMI spread in a dairy herd at quarter level (Gussmann et al., 2018b). It currently includes five pathogen strains: a contagious *S. aureus*, 2 types of *Streptococcus uberis*, which was either contagious or environmental, *St. agalactiae* with contagious and environmental elements at the same time (opportunistic), and environmental *Escherichia coli*. Heifers are exempt from dynamic transmission and have a probability of already being infected at calving. For lactating cows, the infection probability for every non-infected quarter is calculated every day. This probability depends on the active pathogen strains, the susceptibility, and, for contagious pathogens, on the number of infected quarters. Transmission of *St. agalactiae* has an environmental and a contagious part (Gussmann et al., 2018b). The susceptibility is relative to previously uninfected primiparous cows and is determined by risk factors such as parity or previous IMI (Zadoks et al., 2001). A newly infected quarter can appear as either a subclinical or a clinical case, depending on a pathogen-specific probability (Halasa et al., 2009b). Clinical quarters are treated with a 3-day intramammary treatment. After treatment has ended, the quarter will either recover to susceptible with a cow-specific probability, or return to subclinical (Steenefeld et al., 2011). Subclinical quarters have daily pathogen-specific probabilities for spontaneous recovery (return to susceptible) or for flare up (become clinical).

Before a cow with a clinical IMI during lactation or a high SCC (200,000 or higher) at one of the last three monthly recordings is dried off, a test of a pooled milk sample by polymerase chain reaction (PCR) will be simulated (sensitivity and specificity are given in Table 1). If the test result is positive, the cow receives dry cow treatment, otherwise it will be dried off without dry cow treatment. New IMI and spontaneous recovery can occur during the whole dry period (Halasa et al., 2010). However, infection probabilities are simulated to be lower for cows with dry cow treatment, and they are independent of the number of infected quarters (Halasa et al., 2009c). Clinical cases (flared up and newly infected) can only occur in the first or last week of the dry period. If a cow becomes clinical in the first week, it will receive dry cow treatment.

2.4. Culling

Cows are assessed for culling once a week, if the total number of

Table 1

Model parameters for the main causative pathogens (*S. aureus* in Herd 1 or *St. agalactiae* in Herd 2) for lactating cows. The given rates and probabilities are used daily.

Parameter	Description	Value		Reference
		Herd 1	Herd 2	
Transmission rate	Rate for susceptible quarters to enter infected state	0.0009	0.003	Fitted values
Probability of clinical state	Probability for a quarter to enter clinical state upon infection	0.17	0.01	See Table S1
Flare up probability	Probability for a subclinical quarter to become clinical	0.0081	0.0005	See Table S1
Spontaneous recovery probability	Probability for a subclinical quarter to become susceptible (without treatment)	0.0064	0.0022	See Table S1
Recovery probability	Probability for a clinical quarter to become susceptible after treatment	0.4	0.7	See Table S1
Test sensitivity	Test sensitivity for PCR (used at dry off)	0.908		Mahmmod et al. (2013)
Test specificity	Test specificity for PCR (used at dry off)	0.988		Mahmmod et al. (2013)
Probability to identify pathogen	Probability to identify causative pathogen by PCR	0.85		Taponen et al. (2009)

Table 2

Prices in EUR used in the model to calculate income (positive values) and costs (negative values).

	Price	Reference
1 kg protein	5.8132	www.arla.dk , September 2017
1 kg fat	4.1519	www.arla.dk , September 2017
Handling of 1 kg milk	−0.0134	www.arla.dk , September 2017
Costs of a heifer	−1000	Assumed market value
Slaughter value per cow	483	Kudahl et al. (2007)
Feeding		
Per calf per day	−0.0026	Kirkeby et al. (2016)
Per heifer/dry cow per day	−0.9311	Kirkeby et al. (2016)
Per energy corrected milk	−0.1947	Kirkeby et al. (2016)
Treatment (per day)	−11.10	Michael Farre (SEGES, Aarhus, Denmark, personal communication)
Opportunity cost (per case per day)	−6.66	Halasa et al. (2009b); Michael Farre (SEGES, Aarhus, Denmark, personal communication)
Dry cow treatment	−9.60	Michael Farre (SEGES, Aarhus, Denmark, personal communication)
Bacterial culture	−12	Michael Farre (SEGES, Aarhus, Denmark, personal communication)
PCR	−13.3	Michael Farre (SEGES, Aarhus, Denmark, personal communication)

cows in the herd exceeds the target count of 200 dairy animals (Kirkeby et al., 2016; Gussmann et al., 2018b). Parity, reproduction status, low milk yield, high SCC, and previous cases of clinical IMI are weighted, and the cows with the highest weights are culled. Involuntary culling, i.e. culling for other reasons such as, e.g., lameness, happens with a certain probability and is prioritized over voluntary culling (Kirkeby et al., 2016). Culling costs include the market value of a new heifer and the slaughter value of the culled cow (see Table 2).

2.5. Intervention strategies for IMI

For this study, two different Danish dairy cattle herds were simulated. In both herds, the primary pathogen contained a contagious element; however, the transmission mode and parameters differed. In one herd, the majority of IMI cases were caused by purely contagious *S. aureus* (Herd 1), while opportunistic *St. agalactiae* (Herd 2) caused most subclinical cases in the second herd. Intervention measures included antibiotic intramammary treatment, testing by polymerase chain reaction (PCR), and culling, and they were aimed at both clinical and subclinical cases. For the strategies, clinical and subclinical intervention measures were combined with three baseline strategies (only clinical intervention measures).

2.5.1. Clinical IMI: Indifferent treatment for all cases (Basic3)

In the default intervention, all clinical cases receive a 3-day intramammary treatment.

2.5.2. Clinical IMI: testing before treatment (Before50)

A milk sample of every new clinical quarter is sent for testing by PCR. After one day, test results are returned and used to calculate an expected recovery probability, which depends on the causative pathogen (85% probability for correct identification, see Table 1), history of IMI, parity, days in milk (DIM), and SCC at the last milk recording (Steenneveld et al., 2011). For unidentified pathogens, recovery probability is a mean base cure probability (see Table 1). Cows with a recovery probability below 50% are culled; all other cases are treated.

2.5.3. Clinical IMI: culling with exceptions (notCullTop)

Similarly to the Before50 strategy, cows with a recovery probability below 75% are culled. However, as described above, the FAP is calculated for all cows and those in the top 25% according to FAP are always treated (i.e., these cows are not culled).

2.5.4. Subclinical IMI: Test, treat and cull (TestTreatCull)

In this strategy, cows with a high SCC (> 200,000) in two consecutive milk recordings are tested by PCR. Test results return after one day and positive quarters receive 3-day intramammary treatment. After one month, quarters are re-tested and cows are culled, if the test is

positive. Intervention against clinical IMI is Basic3. Results for this subclinical measure are only shown in combination with clinical intervention Basic3.

2.5.5. Subclinical IMI: treatment with exceptions (CullBottom)

Cows with a high SCC in two consecutive milk recordings are tested by PCR and test results return after one day. Positively tested cows are culled if they are in the bottom 25% according to FAP, otherwise the respective quarter is treated for three days. This strategy is combined with each of the intervention strategies against clinical IMI (CullBottom & Basic3, CullBottom & Before50, CullBottom & notCullTop).

2.5.6. Subclinical IMI: cow-specific treatment (TreatTopLonger)

Similarly to CullBottom, cows with a high SCC in two consecutive milk recordings are tested by PCR and test results return after one day. Positively tested cows are culled if they are in the bottom 25% according to FAP, otherwise the respective quarter is treated. Treatment lasts for five days, if the cow is in the top 25% according to FAP, or three days otherwise. This strategy is combined with each of the intervention strategies against clinical IMI (TreatTopLonger & Basic3, TreatTopLonger & Before50, TreatTopLonger & notCullTop).

2.6. Simulations and model output

We simulated the presented strategies for five years with a preceding five year burn-in period. The three clinical intervention strategies without added subclinical intervention serve as baseline strategies. 500 iterations per strategy ensured stable results that described the effects of the strategies rather than the initial parameter values (Gussmann et al., 2018b).

In the simulated five year period, the following economic and epidemiological model outputs were collected: income from milk (depending on fat and protein prices, a fee for milk handling, and a bonus or penalty for the bulk tank SCC), IMI related costs (testing, lactational and dry cow treatment, opportunity costs including extra time spent on cows with clinical IMI, culling), other costs (feed, culling with a high SCC or history of IMI), number of subclinical cases (susceptible or clinical quarters entering subclinical state, including infected quarters of heifers at first calving), number of clinical cases (susceptible or subclinical quarters entering clinical state), number of treatment days (e.g., three treatment days for a 3-day treatment), and number of culled cows (culling as IMI intervention or with a high SCC or history of IMI). The gross income for the farm was calculated by subtracting the mentioned costs from the income from milk, while additional expenses (e.g., costs for other diseases, other costs related to cattle, buildings, and machinery) were not considered. Model output is presented as rounded median values of the annual arithmetic mean over five simulated years (including the 5th and 95th percentiles). All IMI cases are counted at

Table 3

Values used in the sensitivity analyses, default values (Tables 1 and 2) are marked by *.

Sensitivity analysis	Values				
Base cure probability (Herd 1)	0.2	0.4*	0.6		
Base cure probability (Herd 2)	0.5	0.7*	0.8		
Environmental part in <i>St. agalactiae</i> transmission	0.1*	0.25	0.5	0.75	0.9
Milk price					
Price for 1 kg protein/1 kg fat in EUR	5.25 / 3.75	5.51 / 3.94	5.66 / 4.04	5.81 / 4.15*	5.92 / 4.23
Additional costs for culling in EUR	0*	250	500	1000	

quarter level. Prices are given in Table 2.

2.7. Sensitivity analyses

Sensitivity analyses were performed for base cure probability after lactational treatment; fat and protein prices in Denmark in 2017 (www.arla.dk/om-arla/ejere/arlapis/2017); and culling costs (Table 3). For *St. agalactiae* (Herd 2), which is modelled as an opportunistic pathogen with contagious and environmental elements, an additional sensitivity analysis for the environmental part in transmission was conducted (Table 3).

3. Results

An overview of all results can be found in Table 4. Input values for sensitivity analyses are given in Table 3. In Herd 1, where the main problem was *S. aureus* IMI, the baseline strategy Basic3 yielded a median yearly income of €187,666, with a median of 42 clinical and of 136 subclinical cases per year. There were 123 treatment days per year and 16 cows per year culled in relation to IMI (median values). The other two baseline strategies Before50 and notCullTop led to a higher median yearly income (about €197,000) and lower median yearly number of cases (clinical and subclinical), with substantially fewer

treatment days and more cows culled in relation to IMI (Table 4). All strategies with intervention against subclinical IMI could further improve the median yearly income and reduce the number of cases. Combined with Basic3, the strategies TestTreatCull, CullBottom, and TreatTopLonger led to comparable yearly numbers of clinical (27 in median) and subclinical (120–122 in median) cases. Among these three strategies, TestTreatCull yielded the lowest median yearly income (€198,418) with the other two strategies yielding about €2000 (CullBottom) and €2500 (TreatTopLonger) more per year (median values). The median yearly numbers of treatment days were higher than in the baseline strategies, ranging from 149 (CullBottom) to 193 treatment days (TestTreatCull). The median yearly number of culled cows was 23 with strategy TestTreatCull and 45 and 43 with strategies CullBottom and TreatTopLonger, respectively. When the strategies CullBottom and TreatTopLonger were combined with one of the other two baseline strategies Before50 and notCullTop, the median yearly income was between €204,000 and €206,000. Median yearly numbers of clinical cases ranged from 14 to 16 and from 83 to 87 for subclinical cases. There were more treatment days (around 40) than in the respective baseline strategies (median yearly numbers), but less than with Basic3. The median yearly number of cows culled in relation to IMI was higher than that in the baseline strategies, but lower than in the CullBottom and TreatTopLonger strategies when combined with Basic3. In Herd 2,

Table 4

Median model output (with 5th and 95th percentiles) of 500 iterations for a herd with 200 dairy cows, simulated over 5 years: income in € (income from milk minus costs related to IMI and for feeding), number of clinical IMI cases, number of subclinical IMI cases, number of treatment days, and number of culled cows (due to IMI intervention, or with a high SCC or history of IMI).

Strategy	Gross income		Clinical IMI cases		Subclinical IMI cases		Treatment days		Culled cows	
Herd 1 (<i>S. aureus</i>)										
Basic3	187,666	(173,363; 202,147)	42	(33; 51)	136	(121; 161)	123	(95; 151)	16	(12; 20)
TestTreatCull ^a	198,418	(185,806; 213,398)	27	(11; 33)	120	(75; 133)	193	(118; 226)	23	(10; 29)
CullBottom ^a	200,491	(187,248; 215,304)	27	(11; 33)	122	(74; 135)	149	(77; 177)	45	(28; 52)
TreatTopLonger ^a	201,029	(188,613; 214,898)	27	(11; 33)	122	(74; 135)	158	(85; 189)	43	(30; 52)
Before50	196,995	(181,427; 211,492)	30	(15; 38)	111	(75; 130)	47	(36; 64)	24	(10; 29)
CullBottom ^b	206,342	(192,801; 218,478)	14	(10; 27)	83	(71; 120)	86	(67; 115)	34	(26; 51)
TreatTopLonger ^b	205,975	(193,335; 218,272)	14	(10; 27)	84	(71; 118)	92	(71; 127)	35	(26; 51)
notCullTop	196,704	(182,197; 213,318)	32	(14; 39)	113	(72; 127)	32	(12; 43)	29	(16; 34)
CullBottom ^c	205,383	(192,057; 216,535)	16	(10; 30)	87	(71; 123)	76	(48; 108)	40	(30; 54)
TreatTopLonger ^c	204,240	(191,357; 217,887)	15	(10; 29)	85	(71; 122)	79	(54; 121)	39	(29; 53)
Herd 2 (<i>St. agalactiae</i>)										
Basic3	155,170	(135,863; 176,596)	21	(17; 30)	130	(110; 164)	62	(50; 87)	22	(17; 27)
TestTreatCull ^a	200,176	(188,232; 211,562)	13	(11; 16)	96	(86; 107)	149	(130; 169)	17	(14; 21)
CullBottom ^a	200,333	(188,264; 214,044)	13	(10; 16)	97	(87; 107)	107	(92; 124)	39	(33; 45)
TreatTopLonger ^a	200,494	(188,813; 211,936)	13	(10; 16)	96	(86; 107)	115	(97; 136)	38	(31; 46)
Before50	157,690	(137,244; 178,725)	21	(17; 30)	126	(108; 162)	50	(40; 73)	24	(19; 29)
CullBottom ^b	200,286	(187,645; 212,006)	13	(10; 16)	96	(87; 107)	104	(88; 120)	39	(34; 47)
TreatTopLonger ^b	200,367	(189,299; 211,525)	13	(10; 16)	96	(87; 106)	112	(96; 132)	39	(34; 45)
notCullTop	158,885	(138,046; 181,690)	20	(16; 25)	121	(105; 145)	18	(12; 25)	31	(25; 37)
CullBottom ^c	199,748	(188,168; 211,576)	13	(10; 16)	94	(85; 104)	82	(66; 98)	42	(35; 48)
TreatTopLonger ^c	199,649	(187,233; 212,443)	13	(10; 15)	94	(84; 103)	89	(73; 106)	42	(35; 48)

Subclinical measures: Test TreatCull (Test after two consecutive high SCC, treat positive cows, cull after one month if not recovered), CullBottom (similar to TestTreatCull, but low producing cows are culled instead of treated for subclinical IMI), TreatTopLonger (similar to CullBottom, but additionally high producing cows are treated for 5 instead of 3 days).

^a Intervention strategies combined with Basic3 (3-day treatment).

^b Intervention strategies combined with Before50 (testing before treatment, cull cows with low recovery probability).

^c Intervention strategies combined with notCullTop (similar to Before50, but high producing cows are not culled).

where *St. agalactiae* IMI was the main problem, the median yearly income with the baseline strategies was much lower than in Herd 1 (€155,170 with Basic3). The median yearly number of clinical cases was 20 (notCullTop) or 21, and the median yearly number of subclinical cases was between 121 and 130. There were 62 treatment days with Basic3 and 18 treatment days with notCullTop (median yearly values). Conversely, a median number of 22 (Basic3) and 31 (notCullTop) cows were culled per year in relation to IMI.

With all other strategies, the median yearly income was around €200,000, there were a median of 13 clinical cases and of 94–97 subclinical cases per year. The median yearly number of treatment days was higher than in the baseline strategies, ranging from 149 (TestTreatCull) down to 82 (CullBottom & notCullTop). Similarly, more cows were culled in relation to IMI (between 38 and 42 in median), with the exception of strategy TestTreatCull, where the number was reduced to 17. Sensitivity analysis for the base cure probability after lactational treatment showed that the yearly income increased and the number of cases decreased (both clinical and subclinical) with increasing cure probability. In Herd 1 (*S. aureus*), this trend was most visible when the clinical intervention was Basic3 and least visible when it was Before50 (Fig. 1). In Herd 2 (*St. agalactiae*), the trend was less visible, but more dependent on the subclinical than the clinical intervention (Fig. 2). An increase of the environmental part of *St. agalactiae* transmission led to a slight decrease in income and increase in the number of subclinical cases (results not shown). Sensitivity analysis on the fat and protein prices showed a high dependency of the yearly income on the milk price for all strategies, with median values ranging from €109,000 to €187,000 for baseline strategy Basic3 in Herd 1. Differences between strategies were similar, independent of the milk price (results not shown). Sensitivity analysis of culling costs showed a decrease in income for increased costs. Reduction in the yearly income was higher in strategies where more cows were culled (Fig. 3).

4. Discussion

The objective of this study was to evaluate different combinations of intervention strategies for clinical and subclinical IMI of contagious or opportunistic origin, as these are of major concern in dairy cattle herds. *S. aureus* was chosen as a contagious pathogen of major concern in many countries, while *St. agalactiae* was chosen because its prevalence in Denmark has increased from under 2% to approximately 5.5% in 2017 (Farre, 2017), which led to concerns in the dairy industry. For that purpose, three clinical and three subclinical strategies were combined. Altogether, ten different strategies were presented for two different herds, one with a *S. aureus* problem (Herd 1) and another with a *St. agalactiae* problem (Herd 2). Three of those were baseline strategies, i.e. strategies without intervention for subclinical IMI. In all strategies, clinical cases were treated with intramammary antibiotic injections for three days or culled, though there was no reactive culling in the baseline strategy Basic3. Interventions for subclinical mastitis consisted of testing, 3-day intramammary treatment, and reactive culling of persistently infected cows (TestTreatCull). The other subclinical strategies reflected cow-specific control measures. Low producing cows could be subjected to reactive culling instead of treatment (3 CullBottom and 3 TreatTopLonger strategies), and high producing cows could be treated for five instead of three days, if they were tested positive for subclinical IMI (all TreatTopLonger strategies). The production levels of the cows were incorporated into the strategies, as a previous study has shown that it was a determinant for antimicrobial treatment for mastitis (Gussmann et al., 2018a).

Model results showed that adding intervention measures against subclinical IMI to a clinical intervention strategy led to a higher yearly income and both fewer clinical and fewer subclinical cases (Table 4). The increase in yearly income was especially noticeable in Herd 2, where most subclinical cases were caused by *St. agalactiae*. In this herd, the income range (5th to 95th percentile) over the 500 iterations did not overlap. As *St. agalactiae* is mostly associated with subclinical IMI

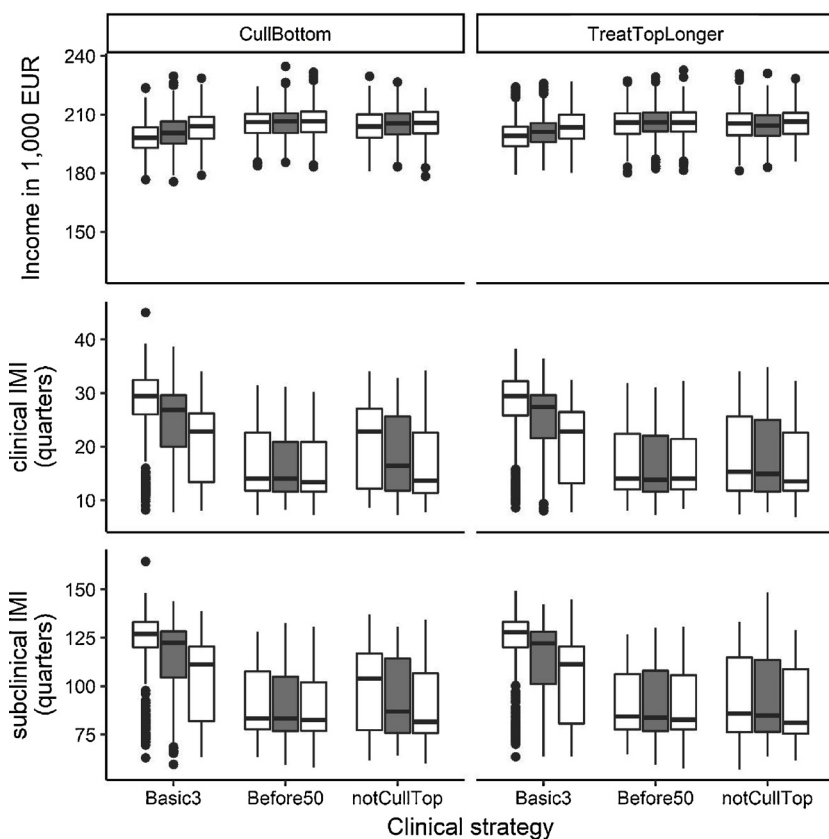


Fig. 1. Results of the sensitivity analysis for the base cure probabilities (values are 0.2, 0.4 and 0.6 from left to right) in Herd 1 (*S. aureus*). The box plots show the mean annual income (income from milk minus costs for feed, culling, dry cow treatment, and IMI intervention), mean annual number of clinical IMI cases, and of subclinical IMI cases. The subclinical intervention measure is shown at the top (CullBottom – test after two consecutive high SCC, treat positive quarters or cull if it is a low producing cow, cull not recovered cases after one month; TreatTopLonger – as CullBottom, but high producing cows are treated for 5 instead of 3 days), while the clinical intervention is shown on the x-axis (Basic3 – 3-day treatment; Before 50 – testing before treatment, cull cows with low recovery probability; notCullTop – similar to Before50, but high producing cows are not culled). Results with default values are marked in gray.

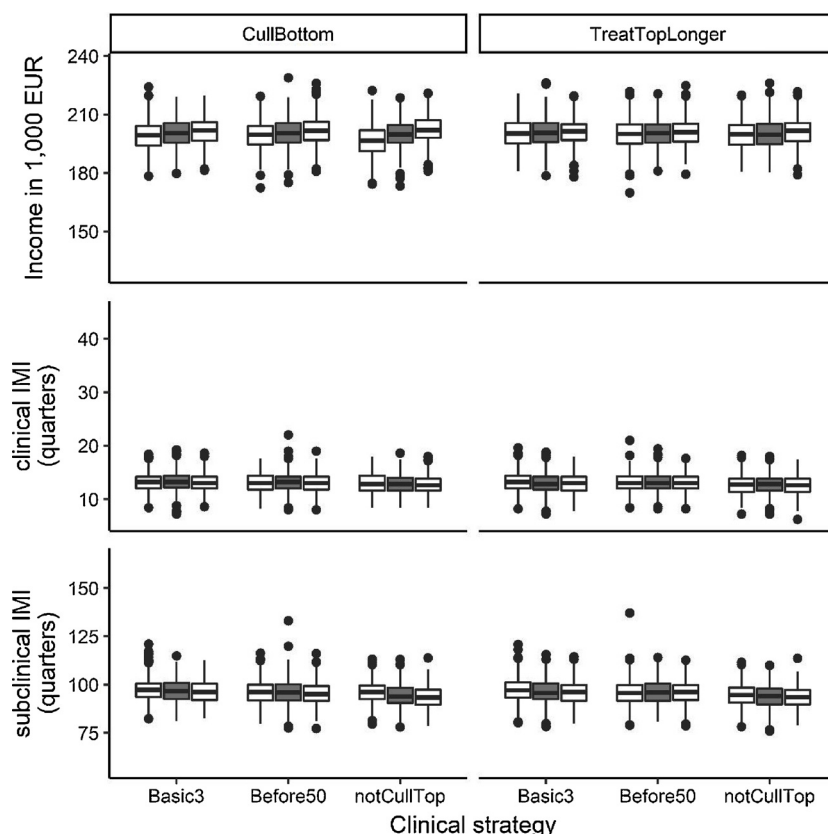


Fig. 2. Results of the sensitivity analysis for the base cure probabilities (values are 0.5, 0.7 and 0.8 from left to right) in Herd 2 (*St. agalactiae*). The box plots show the mean annual income (income from milk minus costs for feed, culling, dry cow treatment, and IMI intervention), mean annual number of clinical IMI cases, and of subclinical IMI cases. The subclinical intervention measure is shown at the top (CullBottom – test after two consecutive high SCC, treat positive quarters or cull if it is a low producing cow, cull not recovered cases after one month; TreatTopLonger – as CullBottom, but high producing cows are treated for 5 instead of 3 days), while the clinical intervention is shown on the x-axis (Basic3 – 3-day treatment; Before50 – testing before treatment, cull cows with low recovery probability; notCullTop – similar to Before50, but high producing cows are not culled). Results with default values are marked in gray.

(Keefe, 1997), intervention measures for subclinical IMI could be expected to be more effective than interventions for clinical IMI, so the increase in income is not so surprising. These findings are in general consistent with earlier studies that have shown that interventions for contagious subclinical IMI could be cost-effective (e.g., van den Borne et al., 2010a). However, our results suggest additionally, that altering clinical intervention on top of adding subclinical interventions could in some cases lead to an even higher yearly income, while further reducing the number of IMI cases (Herd 1, Table 4). If clinical cases are rare, as in Herd 2, the clinical intervention strategy does not seem to be important, if an intervention strategy for subclinical IMI is in place (Herd 2, Table 4). This illustrates that it is important to make herd-specific decisions, taking the clinical manifestation of the causative pathogen into account when choosing an intervention strategy in the herd. Schukken et al. (2012) also pointed out that herd-specific decisions are important for control and prevention of IMI.

Intervention for subclinical IMI lost a bit in effectiveness when the environmental part of transmission of opportunistic *St. agalactiae* was

higher in sensitivity analysis, but the differences between Herd 1 and 2 were more pronounced. The difference between the two herds was also visible in the sensitivity analysis on the base cure probability. In Herd 1, sensitivity to the cure probability seemed to be more dependent on the clinical part of the intervention strategy (Fig. 1). Contrarily, changing the subclinical part of the intervention strategy had a greater influence on results in Herd 2 (Fig. 2). This further emphasizes the importance of herd-specific decisions.

In both herds, the most cost-effective strategies included intervention measures for subclinical IMI and there were several strategies that seemed similarly cost-effective in terms of yearly income and number of IMI cases. The expenses that were not considered in the model (e.g., costs for other diseases, buildings or machinery) were assumed to be independent of IMI and therefore the same in all scenarios, not changing the results. The difference between these strategies could be seen in the number of treatment days and culled cows. Generally, changing the clinical intervention could reduce antibiotic usage at the cost of an increased number of culled cows (compare, e.g., CullBottom & Before50

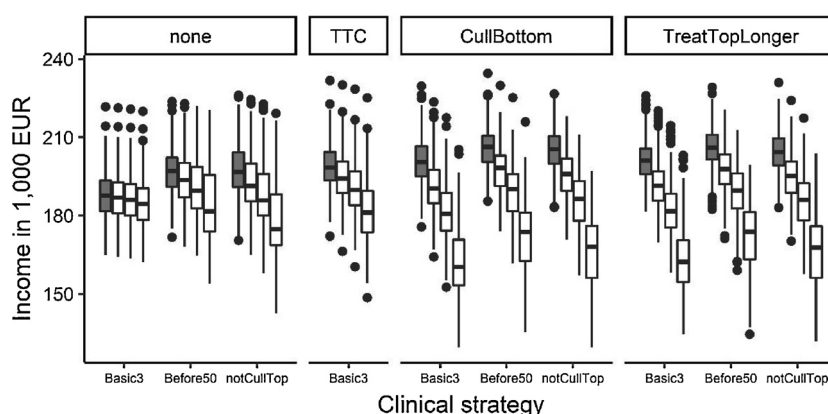


Fig. 3. Results of the sensitivity analysis for culling prices (values are EUR 1000, 1250, 1500 and 2000 from left to right) in Herd 1 (*S. aureus*). The box plots show the mean annual income (income from milk minus costs for feed, culling, dry cow treatment, and IMI intervention). The subclinical intervention measure is shown at the top (TTC – test after two consecutive high SCC, treat positive quarters, cull not recovered cases after one month; CullBottom – similar to TestTreatCull, but low producing cows are culled instead of treated; TreatTopLonger – as CullBottom, but high producing cows are treated for 5 instead of 3 days), while the clinical intervention is shown on the x-axis (Basic3 – 3-day treatment; Before50 – testing before treatment, cull cows with low recovery probability; notCullTop – similar to Before50, but high producing cows are not culled). Results with default values are marked in gray.

and CullBottom & notCullTop, Table 4). The same trend could be seen when comparing strategy TestTreatCull with one of the other sub-clinical strategies. Changing subclinical intervention from CullBottom to TreatTopLonger did not seem to affect the number of culled cows, but slightly increased treatment days. Strategies including TreatTopLonger may therefore not be ideal. Nevertheless, the results show that cost-effective strategies still come with a certain price: increased antibiotics usage or reduced longevity. The farmer will have to decide which kind of costs he or she can best justify for their farm; the “best” strategy depends therefore on the specific herd. A possibility to partly avoid this particular dilemma could be to reduce IMI transmission rates in the herd through rigorous hygienic or biosecurity measures (Lam et al., 1996). This would lead to a reduced IMI incidence, while also reducing both treatment days and the number of cows culled in relation to IMI (results not shown). However, there are few studies investigating cost-effectiveness of hygienic measures (e.g., Huijps et al., 2010), so it remains unclear if the increase in income from milk would compensate for the costs of implementing a comprehensive hygiene strategy.

In this study, we did not change prices over time. That may be unrealistic, but it simplifies comparison of different intervention strategies, as extra noise is removed. Sensitivity analysis of culling costs and milk prices showed that both have a substantial influence on the yearly income (Fig. 3). However, the implications differ; while an increased milk price led to a higher income in all strategies, the extent to which higher culling costs lowered the yearly income depended on the intervention strategy. Therefore, culling costs should be taken into account upon choosing an intervention strategy, too.

The presented strategies included strict culling rules and led to a high number of culled cows. However, the culling rules for subclinical IMI concentrated on removing persistently infected or low producing cows. As a previous study showed that in some Danish herds a high milk production could be a determinant for antimicrobial treatment (Gussmann et al., 2018a), it does not seem so farfetched that farmers may be willing to consider culling low producing cows. This would also conform to a study by Vaarst et al. (2006), where farmers were willing to adopt culling strategies that fit into their goal for the herd. The strict culling rules also affect the usual culling procedure in the model, as we simulated a closed herd where replacement heifers had to be reared on-farm. In a real herd, where other, non-voluntary culling occurs, e.g. due to other diseases, a strict culling strategy in relation to IMI may be challenging to implement. Furthermore, there is an ethical aspect to consider: strict culling rules may reduce longevity and thus impede animal welfare (Bruijn et al., 2013). In this study, however, we focussed on the economic and epidemiological effects of IMI interventions, and we leave it to future studies to investigate how general culling dynamics are influenced by strict culling rules for IMI.

It should be kept in mind that this study used a modelling approach to investigate different intervention strategies. The results depend on the model parameters, e.g., transmission and cure rates, and on the modelled herd structures. These are likely to differ to a certain degree in real herds. Therefore, a field study to validate the results would be ideal, but also costly and time-consuming. However, in the absence of such a field study, the trends found in the results are clear and supported by the conducted sensitivity analysis. The differences in cost-efficiency could be explained and were far from marginal, allowing the strong belief that the results of the model are trustworthy.

5. Conclusions

We investigated different combinations of cow-specific intervention strategies against contagious or opportunistic clinical IMI and sub-clinical IMI in two situations; in a herd with *S. aureus* as the main causative pathogen, and in another herd with *St. agalactiae* as the main causative pathogen. Intervention measures generally led to an increased number of culled animals or higher intake of antibiotics. We demonstrated that intervention strategies against both subclinical and

clinical IMI, including cow-specific treatment and culling decisions, could reduce IMI incidence and thereby increase the farm's yearly income in the long term. In addition, the optimal intervention strategy was dependent on the main causative pathogen within the herd, illustrating that control of IMI must be herd-specific.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.prevetmed.2019.03.001>.

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